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Short-term and Long-term Exposure to Air pollution and Stroke risk

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Short-term and Long-term Exposure to Air pollution and Stroke risk

Exploring methodological aspects

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Papers

I.   Stroh E, Oudin A, Gustafsson S, Pilesjö P, Harrie L, Strömberg U, Jakobsson K. Are associations between socio-economic characteristics and exposure to air pollution a question of study area size? An example from Scania, Sweden
International Journal of Health Geographics, 2005 4:30

II.   Oudin A, Björk J, Strömberg U. Efficiency of two-phase methods with focus on a planned population-based case-control study on air pollution and stroke
Environmental Health, 2007 6:34

III. Oudin A, Stroh E, Strömberg U, Jakobsson K, Björk J. Long-term exposure to air pollution and hospital admissions for ischemic stroke. A register-based case-control study using modelled NO_x as exposure proxy
BMC Public Health 2009, 9:301

IV.   Oudin A, Strömberg U, Jakobsson K, Stroh E, Björk J. Estimation of short-term effects of air pollution on stroke hospital admissions in southern Sweden.
Accepted for publication in Neuroepidemiology

V.   Oudin A, Strömberg U, Lindgren A, Norrving B, Pessah-Rasmussen H, Stroh E, Jakobsson K, Björk J. Long-term exposure to air pollution and hospital admissions for ischemic stroke - An updated two-phase case-control study on the main effects and effect modifications.
To be submitted

Abbreviations

CO	Carbon Monoxide
CI	Confidence Interval
CVD	Cardiovascular disease
EM	Expectation-maximization algorithm
GIS	Geographical Information Systems
GDP	Gross Domestic Product
HNO_3	Nitric Acid
ML	Maximum likelihood
MI	Myocaridal Infarction
NO_x	Nitrogen Oxides including NO_2 (Nitrogen dioxide)
OR	Odds ratio
O_3	Ozone
PM	Particulate matter
PM_{10}	Particulate matter with an aerodynamic diameter less than 10 μm
$PM_{2.5}$	Particulate matter with an aerodynamic diameter less than 2.5 μm
RR	Relative Risk
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SO_2	Sulfur dioxide
WHO	World Health Organization

"We learn more by looking for the answer to a question and not finding it than we do from learning the answer itself." Lloyd Alexander

"We don't see things as they are, we see them as we are." Anaïs Nin

I dedicate this thesis to my family, and especially to Pappa, for always being so curious about my research and perhaps not always getting the best of answers from me.

Contents

Aims

Cardiovascular disease (CVD) is a class of disorders affecting the heart and blood vessels. CVD is the most common cause of death throughout the world. One of the most common diseases among CVD is *cerebro*vascular disease, which is a disease of the blood vessels supplying the brain: stroke being the most common disorder.

Stroke is the single somatic disease that requires the largest number of days of care at Swedish hospitals and the total cost to society has been estimated to be about 0.5% of the Swedish GDP. Beside the traditional risk factors (smoking, hypertension, diabetes mellitus, atrial fibrillation, physical inactivity and poor socio-economic conditions), air pollution is becoming an acknowledged risk factor for stroke, especially regarding its acute effects. Chronic effects of air pollution in relation to stroke are less well documented than acute effects, possibly due to the methodological challenges of assessing long-term health effects of air pollution. Some of these challenges can be overcome by using so called two-phase methods, where registry-data for a large sample is combined with more detailed data for a subsample, but further studies are required to determine the extent to which they can be used and their limitations.

The implementation of measures to improve outdoor air quality and reduce the concentrations of pollutants has led to decreased mortality (Clancy et al. 2002; Laden et al. 2006). Given the considerable health burden caused by stroke and the fact that air pollution affects the total population, it is important from a public health perspective to investigate the extent of the association between air pollution and stroke in a setting where pollution levels are generally lower than present day air quality guidelines.

The specific aims of this thesis were:

1. to investigate the association between long-term exposure (chronic effects) to air pollution and the incidence of stroke in Scania (southernmost part of Sweden) (Papers III & V);
2. to investigate the association between short-term exposure (acute effects) to air pollution and the incidence of stroke in Scania (Paper IV);
3. to elucidate a possible association between socio-economic status and air pollution in Scania, and to investigate whether such associations depend on geographic level or type of socio-economic index (Paper I);
4. to generalise a specific two-phase method so as to be applicable in settings with area-level polytomous exposure variables obtained from an exposure database (Paper II);
5. to examine the strengths and limitations of various two-phase methods (Paper II and thesis frame);
6. to compare two different approaches to the analysis of acute exposure effects (Paper IV and thesis frame).

Thesis at a glance

	Objective	Type of study	Method of analysis	Main findings/conclusions
Paper 1	To investigate the correlation between socio-economy and outdoor air pollution	A descriptive cross-sectional study	Weighted correlation analysis	Strong associations were found and the type of associations depended heavily on the area resolution used, and the socio-economic index used
Paper II	To investigate the performance of different two-phase methods in a setting where first-phase data were available on group-level	A simulated two-phase case-control study	Two-phase logistic regression analysis of simulated data in twelve strata	An iterative method in which area-level exposure data were taken into account performed best with respect to efficiency
Paper III	To investigate whether long-term exposure to air pollution increases the risk of being admitted to hospital with ischemic stroke.	Two-phase case-control design, the entire population acted as controls in the first phase.	Two-phase logistic regression analysis	No evidence was found of an association between modelled levels of NOx as a marker of air pollution, and hospital admissions for ischemic stroke in the study area, where pollution levels are rather low.
Paper IV	To investigate whether acute exposure to air pollution affects hospital admissions for ischemic and hemorrhagic stroke. To compare two methods for evaluating acute exposure effects	Time series analysis and time-stratified case-crossover analysis	Poisson regression and conditional logistic regression	An increase in risk of ischemic stroke was observed when levels of PM10 were above 30 µg/m3, and a decrease in risk when temperatures were above 16°C. The two approaches yielded similar effect estimates.
Paper V	The same as Paper III and to investigate whether NOx modifies the effect of any of the known risk factors for stroke, using an improved study design	A two-phase study employing questionnaires	Two-phase logistic regression analysis	No evidence was found of an association between NOx and ischemic stroke. There was no clear evidence of effect modification.

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Introduction

Cerebrovascular disease

Stroke is the most common disorder in the group of diseases referred to as cerebrovascular disease. Strokes may be ischemic, meaning an infarct in the brain, or hemorrhagic, which implies an accumulation of blood in the skull vault. According to the World Health Organization (WHO), 5.7 out of 17.1 million deaths in 2004 resulting from CVD were due to cerebrovascular disease, and 7.2 million were due to coronary heart disease. The WHO estimated that by the year 2030, 23.6 million people will die worldwide from CVD each year.

In Sweden, the incidence of first-time strokes is 200-300/100,000 inhabitants per year (Norrving et al. 2006). Of all the strokes in Sweden, about 85% are ischemic strokes and 10% are hemorrhagic strokes. The remaining 5% are subarachnoid hemorrhage and are not studied in this work. The one month mortality rate after stroke is about 15-20%, and after five years 50-60% (Norrving et al. 2006), which makes stroke the third most common cause of death after myocardial infarction (MI) and cancer.

With nearly a million hospitalisation days per year, stroke is the single somatic disease that requires the largest number of hospitalisation days in Sweden. Moreover, considerable resources in terms of special housing and home-help services are often required for those who have suffered a stroke. The total cost to the community has been estimated to be at least SEK 14 billion per year, corresponding to about 0.5% of the GDP.

Risk factors

The risk factors can vary between the different subtypes of stroke (Harmsen et al. 1990), but age is the dominant risk factor; the risk roughly doubling with each decade of life (Goldstein et al. 2009). Stroke is equally common among men and women, although the average age at diagnosis is in general five years lower for men (Peltonen et al. 2000). This can be compared with ischemic heart disease, where 2/3 of the patients are men and 1/3 women. The average age at diagnosis of male stroke patients in Sweden in 2007 was 73.6 years, and for women 78.3 years.

Hypertension, smoking and diabetes mellitus (hereafter denoted diabetes) have been identified as three major risk factors (Harmsen et al. 1990; Asplund 2003; Goldstein et al. 2009). Atrial fibrillation is also an important risk factor (Wolf et al. 1987; Harmsen et al. 1990), while it has been shown that moderate physical activity significantly decreases the risk of stroke (Wannamethee and Shaper 1992). If a parent has had a stroke, the risk is significantly increased (Kiely et al. 1993). Many of the risk factors are partly hereditary but there is a hereditary component in stroke risk that remains after taking those risk factors into account (Asplund 2003). Several reports in the literature on genetic epidemiology link different polymorphisms to an increased risk of stroke(Hassan and Markus 2000).

There is a clear socio-economic gradient, where the unemployed, those with unqualified jobs and a lower level of education are overrepresented (Peltonen et al. 2000). Some of the differences seen between different socio-economic groups are due to known risk factors such as smoking, poor eating habits and too little exercise (Cox et al. 2006). Results from a Swedish study indicated that not only the incidence, but also the survival of the patients was dependent on socio-economic status (Peltonen et al. 2000).

Interest in the effects of environmental risk factors has increased recently. Both acute (short-term) and chronic (long-term) exposure to air pollution have been described as risk factors for stroke (Wellenius et al. 2005; Kettunen et al. 2007; Miller et al. 2007; Lisabeth et al. 2008). Neighborhood socioeconomic environment has been observed to influence coronary heart disease at the individual level (Sundquist et al. 2004). The possibility of such an association to stroke has, to the author's knowledge, not been investigated. Noise is a potential, but rather undocumented risk factor for stroke, however long-term exposure to road traffic noise has been observed to increase the risk of MI (Selander et al. 2009). Moreover, an increased risk of hypertension (a strong risk factor for stroke) has been linked to airport noise (Jarup et al. 2007) and to road traffic noise (Bodin et al. 2009). In another study it was observed that associations between cardiovascular mortality and long-term exposure to black smoke and traffic intensity were insensitive to adjustment for traffic noise (Beelen et al. 2009). Hard water, which is rich in minerals such as calcium and magnesium, has been observed to be inversely related to the risk of CVD in several studies and reviews (Allwright et al. 1974; Neri et al. 1985; Nerbrand et al. 1992), but the evidence are not clear, as other studies have failed to show an association (Yang 1998; Maheswaran et al. 1999; Rosenlund et al. 2005). However, low magnesium intake has been reported to increase stroke risk and cardiovascular mortality in two extensive reviews (Monarca et al. 2006; Catling et al. 2008).

Temperature has also been suggested to be a risk factor for stroke, but the results presented in the literature are inconsistent. Evidence of a seasonal variation in stroke occurrence has been presented, although the month in which stroke rate peaks differs between the studies (Shinkawa et al. 1990; Oberg et al. 2000). Cold climate has been suggested to be a risk factor for stroke (Azevedo et al. 1994), and for mortality following stroke (Sheth et al. 1999; Hong et al. 2003), and to be associated with increased levels of markers for inflammation and blood coagulation (Schneider et al. 2008). Increased temperature has also been observed to increase stroke admissions (Low et al. 2006), while no association

was found between stroke occurrence and outside temperature in other studies (Woo and Nicholls 1991; Michelozzi et al. 2006; Michelozzi et al. 2009).

Characteristics of air pollution

Air pollution is not a static phenomenon, but differs in time and space. Air pollutants can be grouped into two types: gases, which are characterised by their chemical composition, and particulate matter (PM) which is characterised by its physical properties, usually mass, size (aerodynamic diameter) and number.

Gases

The most common gaseous air pollutants are sulphur dioxide (SO_2), nitrogen oxides (NO_x), carbon monoxide (CO) and ozone (O_3) (Chen et al. 2007).

Nitrogen oxides are gases containing nitrogen and oxygen in varying combinations (NO_2, NO and N_2O), and these are typically formed in combustion processes, for example, motor vehicles, heating plants and industry. NO_x are therefore considered to be a good proxy for air pollution generated by traffic (WHO 2003).

The levels of SO_2 have steadily decreased in Sweden since the 1960s although the levels during the 2000s have been fairly constant. The decrease is for example due to the transmission from oil and coal with high sulphuric contents to natural gas and oil that is low in sulphuric content. CO is formed by incomplete combustion of carbon-containing compounds, and is therefore a component of motor vehicle exhaust.

Sunlight, together with nitrogen oxides and hydrocarbons, can create ozone. Ozone is widely dispersed, whereas the other gases (SO_2, CO and NO_x) tend to remain in close proximity to their emission sources. As can be seen from Figure 1 and Eq. 1, the relationship between NO_2 and ozone can be inverse.

$$NO + O_3 \rightarrow NO_2 + O_2 \qquad\qquad (1)$$
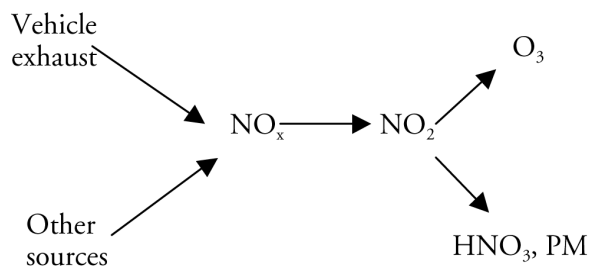
Figure 1. Simplified illustration of the emission of NO_x and the formation of other substances, including particles and ozone.

Particulate matter

PM consists of tiny particles of solids or liquids, suspended in the air. Particles are divided into different classes, depending on their aerodynamic diameter: large particles (> 10 µm) and inhalable particles (< 10 µm).

The inhalable particles can be further divided into three subcategories: coarse particles (2.5-10 µm), fine particles (0.1-2.5 µm) and ultrafine particles (< 0.1 µm). PM_{10} and $PM_{2.5}$ denote particles with an aerodynamic diameter of less than 10 µm and 2.5 µm, respectively. Consequently, $PM_{2.5}$ is included in PM_{10}. An approximation of the distribution of particles in ambient air can be seen in Figure 2, and their size in relation to other objects in Figure 3. The composition of particulate air pollution differs in time and geography. For example, the ratio between PM_{10} and $PM_{2.5}$ differs substantially between sites and countries (Querol et al. 2004).
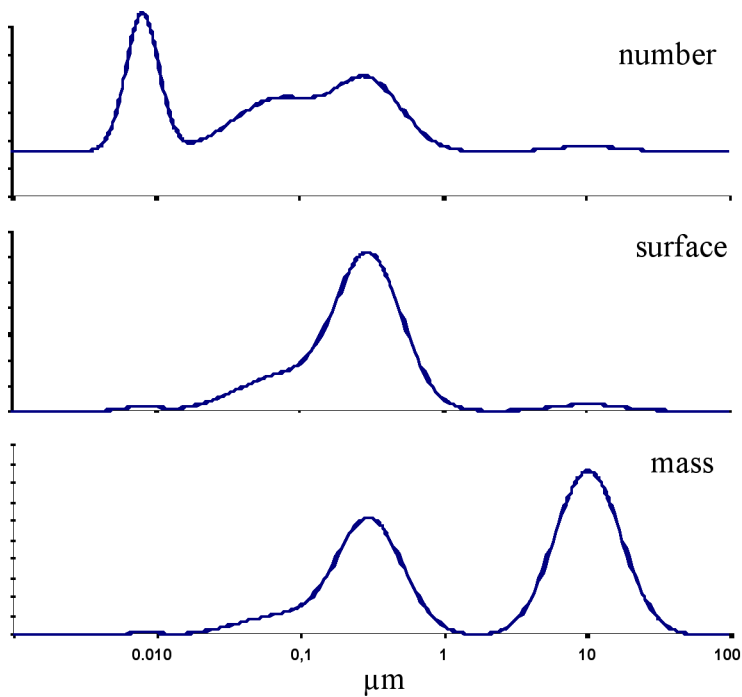
Figure 2. Simplified and idealized size distribution of athmosperic aerosol particles with respect to particle diameter and three different physical quantities. Source: Helsingborgs miljökontor.
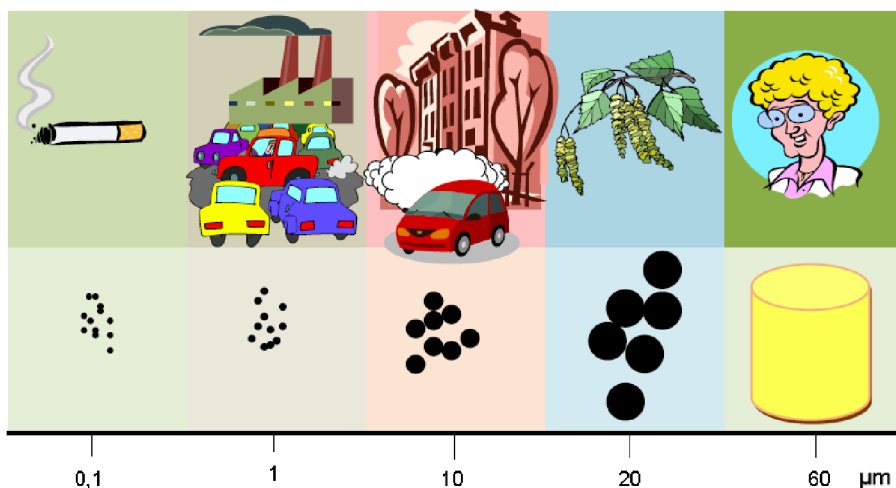
Figure 3. Illustration of the size of particles in relation to a human hair. Source: Helsingborgs miljökontor

The study area – Scania

Scania is the southernmost county of Sweden, located close to Denmark and the European continent (Figure 4). It covers 11 350 km², or 2% of the total area of Sweden. The number of inhabitants in Scania is approximately 1.2 million (year 2008), which is 13% of the total Swedish population (Statistics Sweden 2009). The main city in Scania is Malmö with about 290 000 inhabitants (year 2008).

According to the European mortality database, the age-standardised death rate resulting from cerebrovascular disease is 44 per 100,000 inhabitants and year in Sweden, compared with 120 per 100,000 in the EU. The stroke prevalence in Scania is similar to that of Sweden overall, but the age- and sex- adjusted stroke risk varies between geographical areas in Scania (Figure 5). Moreover, smoking prevalence also varies geographically in Scania (Figure 6), which is an indicator of different composition in population regarding for example socio-economy.

The pollutant levels in Scania are generally higher than in the rest of Sweden, although relatively low in an international perspective (WHO 2005). The high amount of traffic to and through Scania together with the closeness to the city of Copenhagen, and the continent, and an often westerly wind contribute to the air pollution in the region. There is a clear eastern-western gradient regarding NO_x pollution levels in Scania (Figure 4). A large proportion of the PM_{10} concentrations in Scania stems from long-way transport, yielding less geographical contrasts in concentrations but contrasts in time. The WHO air quality guidelines from year 2006 regarding PM_{10} recommend

that the mean daily level should not exceed 50 μg/m³ and that the annual mean should be less than 20 μg/m³. The annual mean urban background PM_{10} (measured in Malmö: Figure 4) between the years 2001 and 2005 ranged between 15.9 and 21.6 μg/m³, while the rural background (measured in Vavihill: Figure 4) ranged between 13.8 and 18.6 μg/m³ during the same years. The daily mean urban background PM_{10} concentration was above 50 μg/m³ at about 3% (50 out of 1826) of the days during the same period. The urban background $PM_{2.5}$ annual mean during the years 2001-2005 ranged between 10.0 and 12.0 μg/m³. Regarding NO_2, the annual mean should be below 40 μg/m³ according to the WHO guidelines. The NO_x annual mean for the ischemic stroke cases in Paper III was 12.8 μg/m³. The air quality guidelines given by WHO can thus be assumed to be met for a large majority of the population of Scania.
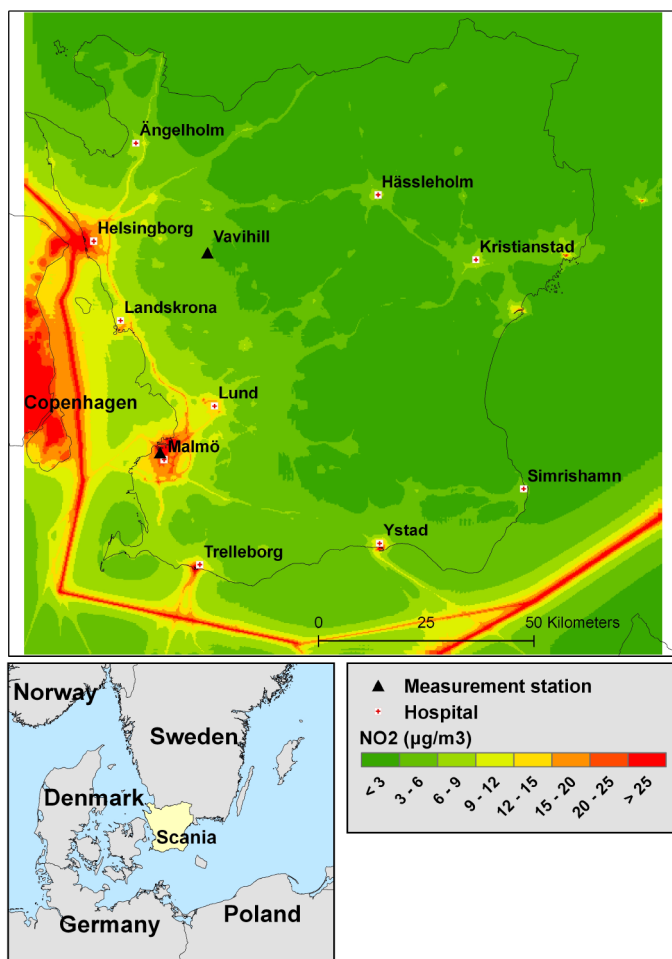

Figure 4. Northern Europe and annual mean NO_x concentrations in Scania year 2003. The 10 hospitals reporting stroke cases to *Riks-stroke* and the two measuring stations of Malmö and Vavihill.

Health effects of air pollution

The effects of air pollution on health were first scientifically acknowledged after the Belgium Meuse Valley incident in 1930 when a thick fog, lasting five days, in a heavily industrialized area led to hundreds of people suffering from respiratory symptoms and 60 deaths during the following three days (Nemery et al. 2001). Another famous incident was the London Fog in December 1952, which was caused by extraordinary weather conditions combined with the burning of large amounts of coal due to cold weather, and was estimated to have led to 4,000 extra deaths. (Logan 1953) The number of extra deaths has later been re-estimated to be nearly 12,000. (Bell and Davis 2001)

Since then, extensive research has been conducted on the health effects of air pollution. For example, it has been estimated that urban particulate air pollution was responsible for 800,000 extra deaths worldwide in the year 2000, due to lung cancer, respiratory diseases and CVD (Cohen et al. 2005). In a Swedish study, it was estimated that particulate air pollution from long-range transport causes about 3,500 deaths annually (Forsberg et al. 2005). The literature on air pollution and health was summarized and the known health effects of several different pollutants reviewed in an extensive paper (Brunekreef and Holgate 2002). In the short summary of the literature presented here, attention will be devoted to CVD and, more specifically, cerebrovascular disease.

An extensive review of the literature on pollution and CVD concluded that there is evidence of effects due to both short-term and long-term air pollution exposure on CVD, and that studies on short-term effects are more numerous than those on long-term effects (Brook et al. 2004). Regarding chronic exposure, individual-level associations were observed in an early study on the association between air pollution and mortality across the USA (Dockery et al. 1993). Later, a relation between long-term exposure to fine-particulate air pollution and cardiovascular mortality was observed in a large study (Pope et al. 2004). In that study, an association between pollution and ischemic heart disease, cardiac dysrhythmia and heart failure was observed, but no clear evidence of an association between pollution and cerebrovascular mortality was found, with a Relative Risk (RR) associated with a 10 $\mu g/m^3$ increase in PM_{10} of 1.02 (95% Confidence Interval (CI): 0.95-1.10). Two studies were conducted in the UK, one in which mortality resulting from stroke was observed to be associated with living near main roads (used as a proxy for long-term exposure to air pollution), and another in a small area, where stroke mortality was observed to be associated with outdoor levels of NO_x, PM_{10} and CO. For example, the mortality rate following stroke was 37% higher in the quintile exposed to the highest levels of NO_x ($\geq 57.7 \mu g/m^3$) than in the quintile exposed to the lowest levels (49.6 $\mu g/m^3$) (Maheswaran and Elliott 2003; Maheswaran et al. 2005). In a cohort study conducted in Norway between the years 1972 and 1998, it was reported that a 10 $\mu g/m^3$ increase in NO_x level at the study subject's home address between 1974 and 1978 led to an increase in the relative risk of dying from ischemic heart disease during follow-up of 1.08 (95% CI: 1.03-1.12), and from cerebrovascular disease of 1.04 (95% CI: 0.94-1.15) (Nafstad et al. 2004). Another large cohort study

was conducted in the USA in which the effects of long-term exposure to $PM_{2.5}$ on cardiovascular events in women were investigated (Miller et al. 2007). In that study, a 10 µg/m^3 increase in $PM_{2.5}$ was found to be associated with cardiovascular events, with a hazard ratio of 1.24 (95% CI: 1.09 to 1.41), and with cerebrovascular events, with a hazard ratio of 1.35 (95% CI: 1.08 to 1.68). Recently, a 10 µg/m^3 increase in $PM_{2.5}$ was found to be associated with cerebrovascular mortality in a Dutch study, with a RR of 1.62 (95% CI: 1.07 to 2.44) (Beelen et al. 2009).

Regarding the short-term effects of air pollutants on stroke rate, numerous studies have been carried out, yielding both positive and negative findings. The effects of several different pollutants are often investigated in such studies, different exposure windows are used and the outcome may be either mortality or hospital admission. A schematic overview over that research area can be found in Paper IV, Supplementary File 1. In summary, there is rather strong evidence of an association between particulate air pollution and both cerebrovascular mortality (Hong, Lee, Kim, Ha et al. 2002; Hong, Lee, Kim and Kwon 2002; Kan et al. 2003; Kim et al. 2003; Kettunen et al. 2007) and cerebrovascular hospital admissions (Wordley et al. 1997; Tsai et al. 2003; Wellenius et al. 2005; Dominici et al. 2006; Low et al. 2006; Lisabeth et al. 2008).

During recent years, much attention has been devoted to the role of particulate matter in air pollution and its effects on health (WHO 2003; WHO 2004; Pope and Dockery 2006). For example, it has been reported that ultrafine and fine particles are the most harmful to health (Ibald-Mulli et al. 2004). Unpublished results from London suggest that the total particle number (dominantly particles with a diameter less than 1 µm) is mainly responsible for cardiovascular mortality and admissions for CVD.

NO_x are not in itself regarded as especially harmful to health, but is considered a good indicator of other pollutants, mainly those arising from traffic. In the Copenhagen urban area (Figure 4) measurements of NO_x levels have been shown to correlate with total particle number at an urban background site (r = 0.83) and at a near-city monitoring site (r = 0.78), indicating a common traffic source (Ketzel et al. 2004). Concentrations of NO_x can be expected to be reasonably well correlated with concentration of particles with an aerodynamic diameter less than 1 µm.
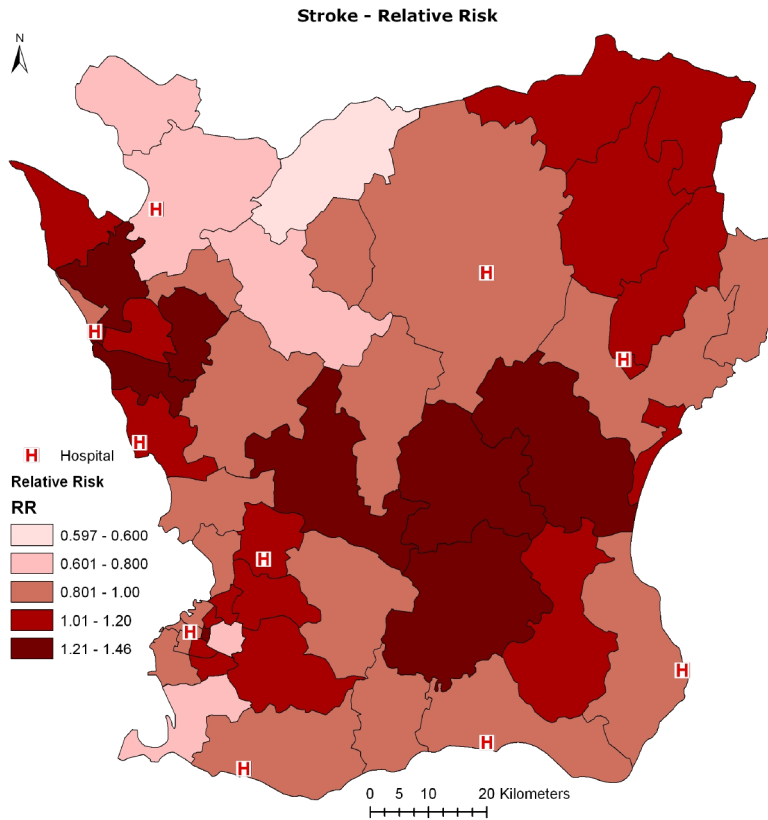
Figure 5. Stroke rates across municipalities in Scania.

Deposition

The health effects of particulate air pollution depend on the extent to which the particles are inhaled and deposited in the airways and the lungs. Moreover, the potential health effects are dependent on where in the respiratory tract (head airways, lung airways or alveolar region) the particles deposit.

The deposition of particulate air pollution in the respiratory system have been observed to vary between individuals (Löndahl et al. 2008), although clear differences in deposition for example with respect to age are not evident (Kim and Jaques 2005). The probability of deposition is dependent on a large number of factors, for example the shape of the particles (Lippmann 1990). Furthermore, particle water absorption influence particle deposition in the body (Löndahl et al. 2007; Löndahl et al. 2008). A high breathing frequency increase deposition of particles > 1 μm whereas a low breathing

frequency favours deposition of particles < 1 μm (Kim and Jaques 2004), whereas total particle deposition increase when exercising (Löndahl et al. 2007). Moreover, a substantially higher proportion of the particles resulting from heavy traffic will be deposited in the lungs than particles generated from the combustion of biomass (Löndahl 2009).
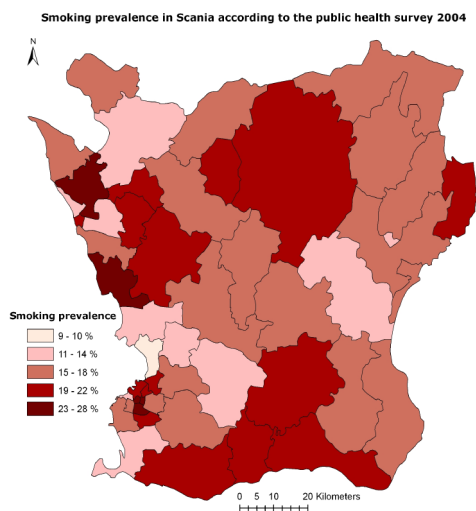
Figure 6. Smoking prevalence across municipalities in Scania.

Potential mechanisms

In this section a short review of potential mechanisms linking air pollution to CVD will be given; a much more extensive review can be found in Ljungmans Doctoral Thesis (2009). A simplified account of potential mechanisms is presented in Figure 7.

Results from experimental studies on humans and animals, as well as observational studies, have suggested several plausible mechanisms linking air pollution to CVD (Brook et al. 2004). There is substantial evidence that inflammation plays a role, as a link has been reported between air pollution and atherosclerosis (Libby et al. 2002; Sun et al. 2005), and also directly to CVD (Pearson et al. 2003; Libby 2006). Results from a study on short-term exposure to particulate air pollution indicated that inhalation is associated with biological responses in pulmonary cells, and that specific components in particulate air pollution may be responsible for different mechanisms (Clarke et al. 2000). In experimental studies on humans in air pollution exposure chambers associations between diesel exhaust and increased inflammatory responses in the airways as well as vascular dysfunction have been reported (Salvi et al. 2000; Mills et al. 2005). Short-term exposure to air pollution has been found to increase markers of inflamma-

tion in peripheral blood, and to lead to endothelial dysfunction at least 24 hours after exposure (Tornqvist et al. 2007). Exposure to particulate air pollution in both humans and animals has been shown to cause inflammation and destabilisation of atherosclerotic plaque (van Eeden and Hogg 2002), and to cause sequestration of red blood cells (Seaton et al. 1999). Associations have been observed between long-term exposure to particulate air pollution and increased levels of fibrinogen, platelets, white blood cells and permanent pulmonary damage (Souza et al. 1998; Schwartz 2001). Air pollution has also been observed to increase plasma viscosity and to be associated with acute arterial vasoconstriction, and increased blood pressure (Peters et al. 1997; Ibald-Mulli et al. 2001; Brook et al. 2002; Urch et al. 2005; Bartoli et al. 2009). Moreover, air pollution has been suggested to cause oxidative stress (Kelly 2003; Risom et al. 2005), which is a risk factor for CVD (Dhalla et al. 2000; Papaharalambus and Griendling 2007).

Another potential pathway between air pollution and CVD is arrhythmia (Peters et al. 2000; Hoek et al. 2001). Decreased heart rate variability (which is a strong indicator of cardiac function) has been suggested as a potential pathway in several studies (Pope et al. 1999; Gold et al. 2000; Devlin et al. 2003). Ultrafine particles may cause alveolar inflammation and enter the bloodstream through the alveoli (Seaton et al. 1995; Nemmar et al. 2002), although no clear evidence was found in other studies (Mills et al. 2006). Mechanisms causing CVD resulting from PM_{10} exposure have been summarised to be inflammation, oxidative stress, coagulation, endothelial function and haemodynamic responses (Kannan et al. 2006).
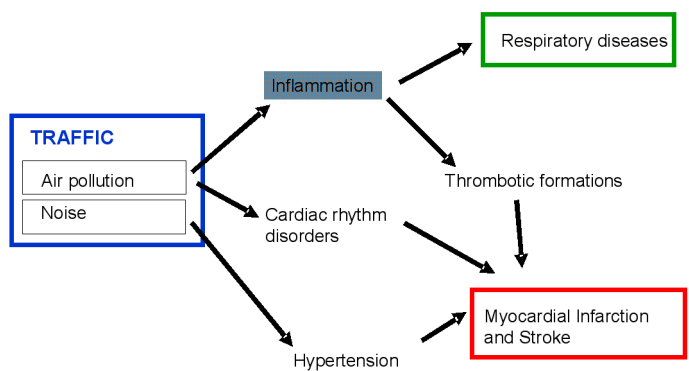

Figure 7. A simplified illustration of mechanisms between air pollution and health outcomes.

Potential effect modifiers

Are certain subgroups of the population more susceptible than others to the potential effects of air pollution on stroke, and how could this affect the already known risk

factors? An effect modifier is a factor that modifies the effect of the potential causal factor(s) under study. If for example men and women are differently influenced by an exposure with respect to a certain outcome, gender is an effect modifier on the association between the outcome and the exposure. There is a growing consensus that men and women should be analysed separately in most epidemiological contexts.

Evidence has been presented for effects of air pollution to increase with age (Gouveia and Fletcher 2000), and for pollution to lead to increased hospital admissions for respiratory and cardiovascular disease among those aged 65 or older (Wong et al. 2002). Moreover, the effect of PM_{10} on stroke mortality was reported to be highest in the oldest age category (>75 years) in another study (Zeka et al. 2006). Moreover, it is not likely that the risk model is independent on age, since the baseline risk heavily increases with age.

The effect of particulate air pollution on cardiopulmonary mortality has been reported to be greater in non-smokers and in people with a low level of education (Pope et al. 2002). It has also been reported that sex, smoking and level of education modify the association between long-term exposure to air pollution and fatal MI (Rosenlund et al. 2006). An increased effect of $PM_{2.5}$ on subclinical atherosclerosis has been observed in never-smokers (Künzli et al. 2005). Moreover, the effect of smoking on the risk of stroke has been observed to differ between age groups, and between men and women (Shinton and Beevers 1989). Evidence that air pollution has a greater effect on mortality in areas with high socio-economic conditions makes socio-economic status another potential effect modifier (Gouveia and Fletcher 2000).

There is increasing support that exposure to air pollution increases the risk of diabetes (Brook et al. 2008; Bhatnagar 2009). Furthermore, there is evidence that diabetes and hypertension modify the effect of particulate air pollution on levels of markers of inflammation (Dubowsky et al. 2006; O'Neill et al. 2006). In another study, diabetes was observed to modify the effect of air pollution on cardiovascular emergency admissions; diabetic patients being substantially more susceptible (Pereira et al. 2008). The risk of death due to air pollution was higher in diabetes patients than in the general population (Bateson and Schwartz 2004). Enhanced PM_{10} levels have been suggested to cause oxidative stress, leading to CVD in patients with diabetes (Liu et al. 2007).

The effect modifiers investigated in Papers III-V are given in Table 1. Effect modification by the area of residence, urban or rural, was studied (Paper III) and in the following study (Papers IV & V), the effect of residing in a major city was studied. This was done more in terms of a sensitivity analysis, rather than to investigate whether this actually modified the effect, therefore this variable was not included in Table 1.

Table 1. Effect modifications tested in Paper II-V

	Effect modifiers
Paper III	Age, sex, birth country
Paper IV	Age, sex, smoking warm/cold season
Paper V	Age, sex and NOx*

* The effect modifications between NOx and the major risk factors smoking, regular exercise, diabetes, hypertension and arrhythmia and also education, marital status and birth country were tested for.

Epidemiological methods

Exposure

An emission database containing information on approximately 24,000 emission sources in Scania was used for the exposure assessments (Papers I & III-V). The emission database was developed as part of a project within the Swedish National Air Pollution and Health Effects Programme. The emission sources included in the database are roads and shipping routes, industrial plants, heating plants, domestic wood burning, farming, large construction sites, etc. The database also includes information on temporal variations on an hourly, daily and monthly basis. Together with information on meteorology and with dispersion modelling, a geographical information system (GIS) the data can be used to model the NO_2 and NO_x levels at high resolution in both time and in space (Gustafsson 2007). Distant sources of air pollutants are not included in the database, but an average contribution of 2.5-3 $\mu g/m^3$ was added to the modelled NO_x concentrations to account for long-range sources. As the residential coordinates of nearly all the inhabitants of Scania (>99%) is known, their outdoor residential NO_2 and NO_x levels could be estimated. The modelled annual mean values were compared with measurements from monitoring stations, yielding a correlation coefficient of 0.69. Validation of the model is ongoing, and the focus in a present study is on validation of short-term NO_x modelling, for example, weekly averages.

In Paper I, where the annual mean value of NO_2 at the residential address was modelled, in detail describes the modelling of NO_2. The spatial resolution in that study was 250 x 250 m. The spatial resolution in the studies described in Papers III and V (where annual mean value of NO_x was modelled) was 500 x 500 m. In Paper IV, effects of short-term exposure to air pollution on stroke risk were the subject of interest, and the annual mean was thus not an appropriate measure of exposure. Instead, the hourly NO_x concentration was modelled, and aggregated to give daily mean values, again with a spatial resolution of 500 x 500 m. Important to note is that the modelled concentrations in Papers I and III-V thus in a sense are ecological exposures measures, since all persons residing in the same grid cell share assessed exposure. However, the resolution in space is fine, and the exposure measures are hereafter referred to as individual-level exposures.

Apart from the modelled NO_x values, data collected from two monitoring sites were used in Paper IV. From the monitoring site in the city of Malmö (Figure 4), data were

obtained on mean hourly ozone, mean daily PM_{10}, reflecting urban background levels, and mean daily temperature. From the monitoring site at Vavihill, 60 km north of Malmö (Figure 4), hourly values of the ozone level were obtained, reflecting rural background levels. The hourly ozone measurements were aggregated to give daily means from midnight to midnight. The ozone data used in the analysis of Paper IV was the rural background levels, due to less missing data in that measurement series. The correlation between the urban and rural background ozone measurements was found to be high for the years 2001 to 2005 on days where neither value was missing (N = 1772), Spearman's correlation, r_s = 0.78 and Pearson correlation, r = 0.76 (Figure 8). An overview of the exposure measures in the different studies is given in Table 2.

Table 2. Schematic overview of exposure data.

Type of exposure data	Describes what	Used where
Annual mean levels of NOx modelled at residential address*	Used to assess geographical contrasts. The contrasts in time are small.	Paper I*, Paper III and Paper V
Daily mean levels of NOx modelled at residential address*	Used to assess geographical contrasts and daily variations in exposure.	Paper IV
Measured levels of PM10 and ozone	Contrasts in time, not in geography since one measuring station is used to account for exposure for an entire county.	Paper IV

*The NOx-concentration is modelled in a grid with cell size (resolution) 250 x 250 meters in Paper I, and 500 x 500 meters in Paper III to V.
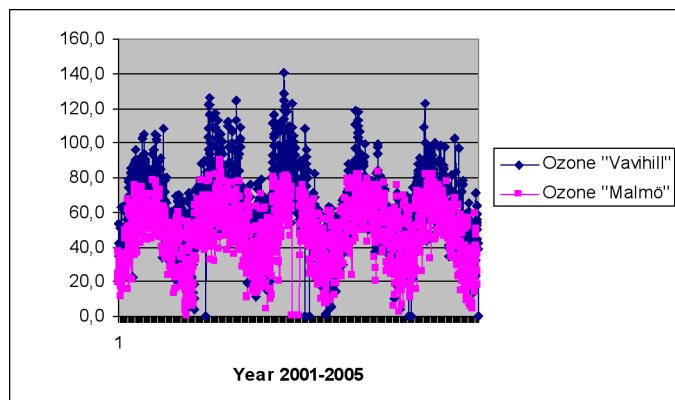
Figure 8. Ozone daily mean levels according to two monitoring stations in Scania, one in "Vavihill", representing rural background levels and one in "Malmö", representing urban background levels.

Strategies for assessment of air pollution exposure in epidemiologic studies

Different types of exposure data have been applied for assessment of air pollution exposure in this work. The type of variations in exposure that is of interest determines what type of exposure data are appropriate.

In Papers I, III and V modelled levels of air pollution (NO_2 or NO_x) at the residential address (or more exactly, in the grid cell where the address was located) of each study subject were aggregated to annual mean concentrations, describing geographical contrasts in exposure. Contrasts in time are not described by such an exposure measure. The nature of the data yield daily variation in levels at a certain location depending on day of the week and meteorology. Moreover, emission factors for vehicles change over the years and were incorporated in the modelling. However, due to aggregation in time, the annual means over the study period at a certain location are fairly constant.

To describe contrasts in time, data from measuring stations and modelled daily mean levels were used (Paper IV). By using only one measuring station for each exposure variable (Malmö for PM_{10} and temperature, Vavihill for ozone; Figure 4) geographical contrasts by those exposures were not available; the exposure contrasts were instead given in time. The modelled daily mean levels of NO_x provided contrasts both in time and space since modelling was carried out for each person, at their residential address.

The outdoor air pollution at a person's residential address may not reflect that subject's actual exposure. There is some ambiguity in terminology, but herafter the difference between a person's "true" exposure and their exposure estimated by the different approaches accounted for above is denoted *exposure measurement error*. Three components of exposure measurement error in studies on the acute health effects of air pollution has been defined (Zeger et al. 2000): 1) the error due to aggregation of exposure, 2) differences between average personal exposure and the true ambient level, and 3) the difference between the true and the measured ambient level. In studies on the long-term effects of air pollution, where levels of air pollution are modelled at a certain area, the third type can be expressed as the difference between modelled and true ambient concentrations, and another component of the error, 4) the error caused by people migrating, can be added.

Potential sources of exposure measurement error due to outdoor-indoor differences are for example smoking, which increase the particle levels indoors. We could adjust for personal smoking, but not for environmental tobacco smoke from partners. Similarly, we could not adjust for use of gas stove, which increase indoor NO_x. Other factors that might affect personal exposure to air pollution are occupational exposure and exposure while commuting to and from work (McKone et al. 2008). A person is often exposed to more air pollution while in transport than when at home or at work. According to a public health survey from 2004 in Scania, around 20% of the working population spend more than an hour commuting every work-day. However, the results of a recent, yet unpublished study conducted at our department suggest that taking commuting time or workplace exposure into account does not improve exposure assessment in terms of strengthening the effect estimates associated with asthma symptoms. This may reflect larger uncertainties when estimating exposure during commuting or at occupational address, but may also reflect that residence is still the major long-term exposure determinant in adults.

Another source of exposure measurement error is uncertainty/error in assessing the time of the stroke (Lokken et al. 2009). This was considered to be an unlikely problem

in the studies presented here, due to the high quality of the register data. However, in the study where acute effects are investigated (Paper IV), information regarding what time of the day the event occurred would have reduced exposure measurement error. Factors influencing deposition in the respiratory tract, i.e. related to respiratory diseases and CVD could be considered another source of exposure error, which (just like time-activity patterns) may be non-differential. In studies where only first-time strokes are assessed, this bias is partly reduced.

Another way of assessing personal exposure to air pollution is for each subject to carry a personal monitoring device. Health effects of air pollution are typically rather small on an individual level, and a large number of subjects is usually required in epidemiological studies to obtain enough statistical power to detect an association. Therefore, it is often not feasible for each person to carry a personal monitoring device in large studies. Personal exposure thus has to be estimated, leading to exposure measurement error. Although modelled exposure is not optimal, in studies with large sample sizes, of long duration, and diverse outcomes and exposures, modelled individual exposure might be preferable to other approaches (Gilliland et al. 2005).

Registers

Every person living in Sweden can be identified through a unique personal identification number, which includes date of birth. The sex of the person can also be determined from this number.

The Regional Health Care Authority of Scania (*Region Skåne*) has access to the residential coordinates (in the coordinate system RT90 2.5 gon W) of each person in Scania. Statistics Sweden is an administrative agency that produces statistical data and manages the Swedish system for official statistics. Statistics Sweden has access to, among other things, information on educational level, marital status, country of birth and income on all Swedish citizens. Each person can be identified in these registers by their personal identification number. Statistics Sweden provided datasets containing information for each person resident in Scania on education, country of birth, year of birth and gender, from which the personal identification number and the residential coordinates had been removed for ethical reasons. These data were used in the study described in Paper I, and for the first-phase controls described in Paper III. Scania was divided into a grid with a resolution of 250 x 250 m, and information was given for each person regarding which grid cell their residence was located in. The grid cell information allowed levels of NO_2 or NO_x to be modelled for each person.

Data were obtained from *Region Skåne* on the coordinates of the residences of the stroke patients described in Paper III, and for all the study subjects described in Papers IV and V. Data on educational level, marital status and birth country were obtained

from Statistics Sweden. Data on income were not used as income has limitations as a measure of socio-economic status for women (Hogstedt et al. 2009).

The Swedish Stroke Register

The aim of the Swedish Stroke Register, *Riks-stroke*, is to improve stroke care. Data are collected in the register from the time the stroke occurred, during hospital stay and at a follow-up examination after three months. All hospitals in Sweden that have an emergency ward and which admit stroke patients for care participate in the scheme. In Scania, 10 hospitals participated during the period 2001 to 2005 (Figure 4). In 2006, the hospitals at Ystad and Simrishamn started reporting their stroke cases together, so there are now 9 hospitals in Scania reporting their stroke cases to Riks-stroke.

Initially, data were obtained from *Riks-stroke* on all stroke cases registered during the years 2001-2005; data were later obtained on cases that occurred during 2006. The data files from *Riks-stroke* contained the variables type of stroke (ischemic, hemorrhagic or subarachnoid hemorrhage), the date the stroke occurred, the date the patient was admitted to hospital, the use of medication for hypertension, smoking and diabetes.

Two-phase design

The general concept of a two-phase design is that some variables (first-phase variables) are available for all, or nearly all, of the study subjects, while some other variables (second-phase variables) are available only for a subsample of the subjects. For example, consider a case-control study, where age, sex and residential address are known for all subjects. For those who choose to participate in the study, another set of variables may become available, for example, smoking or occupational history. The subjects for whom first-phase variables are available are denoted first-phase subjects, and the subjects for whom second-phase variables are available are correspondingly denoted second-phase subjects. The idea with two-phase studies is to combine data from the first and second phase. A common approach in epidemiology is to analyse the data from the second-phase subjects only, and to ignore first-phase subjects as some data are missing. This approach has been shown to lead to bias and a considerable loss of efficiency (Shinton R. Beevers 1989).

Second-phase data can either be collected for variables other than those that are available in the first phase (for example, for confounder assessment) or can be aimed at improved assessment of crude or error-prone first-phase variables. Two-phase studies are often more efficient than traditional designs, and may account for bias resulting from varying participation rates, or varying sampling fractions. In a two-phase design, it is possible to adjust for participation bias or selection bias and to reduce the standard

errors in the parameter estimates by incorporating the data from the first-phase subjects into the data analysis.

Such a two-phase analysis was described for a case-control study where a dichotomous exposure and disease status is known for all subjects, but the evaluation of a covariate is desired by selecting a subsample of the subjects (White 1982). For multiplicative models, the method described by White was generalised to include both multiple exposure categories and several covariates (Cain and Breslow 1988). This was done using a pseudo-maximum-likelihood approach to estimate parameters in a two-phase design. For multiplicative risk models, the log-odds ratio for the combined first- and second-phase data (1+2) for exposure category i ($i > 0$) compared with the reference exposure category ($i = 0$), can be estimated with adjustments for confounders in the following way:

$$(2)$$

$$\log(\hat{OR}_i^{1+2}) = \log(\hat{OR}_i^{1;unadj}) + \log(\hat{OR}_i^{2;adj}) - \log(\hat{OR}_i^{2;unadj})$$

$$\mathrm{var}[\log(\hat{OR}_i^{1+2})] = \mathrm{var}[\log(\hat{OR}_i^{1;unadj})] + \mathrm{var}[\log(\hat{OR}_i^{2;adj})] - \mathrm{var}[\log(\hat{OR}_i^{2;unadj})]$$

However, the method proposed by Cain and Breslow cannot be directly generalised for the assessment of non-multiplicative joint effects between first- and second-phase variables. The above equations were reformulated in an intuitive way in order to use them for study planning purposes (Hanley et al. 2005). The iterative expectation-maximization (EM) algorithm was introduced for the computation of maximum likelihood (ML) estimates in cases of missing data (Dempster et al. 1977). The use of the EM algorithm was later proposed for effect estimation in two-phase case-control studies (Wacholder and Weinberg 1994). Their approach yields valid joint effect estimates between the first- and second-phase variables with both multiplicative and non-multiplicative models. If first-phase data are available on individual level, and contextual effects are present, a mixed model allowing for residual random effects within areas would also be an appropriate method (Wong and Mason 1985). Bayesian hierarchical models can be used, for example, to model responses to exposure varying by area (Richardson and Best 2003).

Exposure information on group level (ecological data) is frequently available in the field of occupational/environmental epidemiology. Ecological data can very seldom be used to infer individual associations, the so-called ecological fallacy (Robinson 2009). Two-phase analysis can be used to increase precision and to reduce bias in settings where first-phase data are partially or purely ecological (Strömberg and Björk 2004; Jackson et al. 2006; Wakefield and Haneuse 2008). Other methods of dealing with settings where some of the data are ecological, to avoid the ecological fallacy, were presented in a recent paper (Wakefield 2009). The hybrid design is another way of combining ecological and individual data (Haneuse and Wakefield 2007; Haneuse and Wakefield 2008). In another study, maximum likelihood estimates were obtained for a combined model of area-level data on disease status, exposure and covariables in the first phase, and indi-

vidual data on these variables for a subsample in the second phase (Jackson et al. 2006). Their method was later further explored, with respect to evaluate effects (both individual and contextual), and interaction effects (Jackson et al. 2009). The EM algorithm has also been used to obtain ML estimates from the additive-multiplicative regression model for the exposure-disease association on the individual level in a situation where disease status, group affiliation (e.g. occupational group or residential area), and general covariates such as age, and sex were known individually for all subjects in the first phase (Strömberg and Björk 2004). The association between the first-phase exposure variable given by population estimates of the exposure probability in each group/area and the individual risk of disease could be assumed to be linear conditional on other covariates in the model (Bouyer and Hemon 1993). Second-phase data provided individual-level exposure data, which were assumed to be dichotomous, but no further covariates were taken into account. When available, the second-phase (individual-level) exposure data were used to replace the first-phase (ecological-level) exposure data in the analysis (Strömberg and Björk 2004). However, to obtain bias-free estimates with such replacements, area affiliation and ecological-level variables should not have any contextual effects. If contextual effects were present and first-phase data are on group-level, the model described by Jackson and colleagues would probably be more appropriate. (Jackson et al. 2006; Jackson et al. 2009) Paper II in this thesis describes a generalisation of the scenario described by Strömberg and Björk to include polytomous exposure variables and a confounding factor.

Studying short-term health effects of air pollution

Time series studies are performed when exposure varies over time, and when the purpose of the study is to investigate the acute effects of exposure, for example, hospital admissions in association with daily variations in air pollution. Traditionally, time series analysis, for example Poisson regression, has been used to analyse these types of data, but during recent years the case-crossover design has been applied by many researchers.

The case-crossover design corresponds to a case-control study where each case is its own control. In an epidemiological context, for example, one can compare the exposure of a person on the day before the disease occurred with the exposure on another randomly chosen day, i.e. the control day. Data are then analysed with conditional logistic regression. Due to the fact that each person is their own control, the design has built-in control for confounding factors, which is intuitively attractive. The way in which control days are chosen is important to avoid bias, and the pros and cons of several control selection methods have been debated (Greenland 1996; Lumley and Levy 2000; Levy et al. 2001; Janes et al. 2005; Janes et al. 2005; Whitaker et al. 2007). The time-strati-

fied control selection explained in Paper IV seems to have many advantages (Janes et al. 2005; Janes et al. 2005; Whitaker et al. 2007).

Two different types of exposure data can be present in these types of studies: shared or individual exposure data. The literature is not consistent regarding whether a case-crossover design is a suitable substitute for the traditional time series analysis when data are shared between individuals. The case-crossover design and the time series analysis have been observed to yield similar effect estimates (Schwartz 2004), but in a simulation study, it was convincingly demonstrated that the use of the case-crossover approach is limited: the methods were either biased or a special case of other, more flexible methods (Whitaker et al. 2007). A design corresponding to the time-stratified case-crossover design can be implemented by using Poisson regression with dummy variables for time (Lu and Zeger 2006; Whitaker et al. 2007). Poisson regression is more flexible than case-crossover approaches since it easily can adjust for overdispersion, model fit can be checked and it is more flexible in terms of modelling time trends or seasonality (Whitaker et al. 2007). The precision can be expected to be lower in a case-crossover design than in a time series analysis since control time is sampled in the case-crossover design whereas time series analysis uses all day-by-day data on exposure fluctuations.

When exposure is modelled or measured individually for each person in the study, the traditional time series analysis can no longer be applied to model the risk. The case-crossover design can then provide an attractive alternative, provided that certain criteria regarding the choice of control day are met, and that there are no strong time trends regarding exposure or risk of disease.

Further bias considerations

Besides information bias stemming from exposure measurement error, selection bias due to the incomplete registration coverage can occur. Registration coverage is a term describing the proportion of cases occurring in a population that are registered in a particular register, such as *Riks-stroke*. If the registration coverage were to differ substantially between the hospitals reporting to *Riks-stroke*, and with respect to exposure, substantial selection bias could occur, especially in Papers III and V, where long-term exposure to air pollution was studied. If for example registration coverage were higher in the most polluted areas, there would then be an unrepresentatively high proportion of highly polluted cases, leading to a bias away from the null.

In its annual report, the committee for *Riks-stroke* estimates the registration coverage of the hospitals that report to the register. Estimates of coverage have previously been based on the expected number of stroke patients in each hospital admission area. However, this method has limitations, since differences in stroke rates between regions will not be accounted for. Moreover, in densely populated areas like Scania, where there are several hospitals, the hospital admission area may not be well defined. A specific individual could be admitted to a hospital outside the assumed admission area. Thus, the coverage estimated by the method described above, could exceed 100% (Table 3). Starting from 2007, the registration coverage has been calculated based on the number

of first-time strokes registered in *Riks-stroke* in relation to the number of registered first-time strokes in the national in-patient register. The total coverage calculated according to the previous method varied from 84% in 2001 to 93% in 2006. With the new method, the total coverage in 2007 was estimated to be 85.5%, thus lower in average than the values obtained with the previous method in 2001-2006 (Table 3). Although the estimated coverage is high, if the coverage were to be highly correlated with NO_x levels, bias may occur in studies where geographical areas are compared. Matching cases and controls on hospital admission area would have decreased the potential bias due to differences in registration between hospitals. However, given that exposure to air pollution in Scania is rather uniform (Figure 4) such matching would probably reduce the power to detect associations.

Table 3. For each of the 10 hospitals in Scania, the estimated population of year 2006 to 2007 and the Riks-stroke coverage calculated according to the old and new method. An overall coverage is also calculated, weighted on population size.

Hospital	Estimated population in thousands in hospital admission area[1,2]	Coverage year 2006 according to previous method.[1]	Coverage year 2007 according to new method.[1]
UMAS (Malmö)	274	103	90
Lund	246	74	78
Helsingborg	161	108	91
Kristianstad	103	108	86
Ystad3	60	88	-
Simrishamn3	33	77	-
Ystad/Simrishamn3	93	-	85
Landskrona	53	61	72
Trelleborg	90	68	88
Hässleholm	70	80	78
Ängelholm	92	100	94
Total	1151	93	86

[1] Information gathered from http://www.riks-stroke.org/content/analyser/Rapport06.pdf
[2] Information gathered from http://www.riks-stroke.org/content/analyser/Rapport07.pdf
[3] Between 2006 and 2007, the hospitals Ystad and Simrishamn were merged together.

Residual confounding is another potential source of bias in Papers III and V, where risks are compared between areas. By using the two-phase approach we controlled for the risk factors that were available on individual level. It should be stressed that in this work, other sources of personal exposure to air pollution than the exposure assessed by modelled or measured levels is considered to be exposure measurement error, not a confounding factor.

When comparing populations in urban areas with populations in rural areas, the populations will probably differ in several respects. Adjusting for confounding factors can account for a large part of the variance that stems from differences in age, educa-

tional level, smoking habits, etc. However, it is not certain that the effect of, for example, having a low level of education is similar in both urban and rural areas. Moreover, the exposure measurement error may differ substantially between urban and rural areas, due to modelling and other sources of exposure (Stroh et al. 2007). Restricting the analysis to only urban or rural areas is one way of limiting the consequences of such differences. Another is to investigate statistically whether the effect differs in urban and rural areas (test for effect modification).

An established way of accounting for random geographical fluctuations, especially in area-level studies, is to incorporate spatial correlation structures into the analysis. Figure 4 seems to suggest substantial variations in risk between different municipalities in Scania. However, the municipality risk estimates in the fully adjusted model in Papers III and V did not indicate any conspicuous geographical clusterings in risk. Therefore we refrained from incorporating such spatial correlation structures.

Through *Riks-stroke*, high-quality data were obtained on stroke occurrence. Access to this kind of register is highly valuable for epidemiologists, especially regarding improving the precision in the time of the event and precision in diagnosis, which is recorded more accurately than in cause-of-death registers, or in in-patient registers, that are often used in epidemiological studies. Moreover, *Riks-stroke* provided valuable information regarding the known risk-factors (and potential confounders) hypertension, diabetes and smoking. However, the data contained in those types of registers are primarily not intended for epidemiological research. For example, the amount of data in *Riks-stroke* regarding risk factors is small, whereas the data on follow-up parameters are extensive. Moreover, as mentioned above, although the aim is to record all strokes in an area, the consequences in epidemiological research can be serious if, for example, registration coverage varies geographically or temporally, whereas this is perhaps of less importance when evaluating hospital care, for example.

In the study presented in Paper V, data from three different stroke registers were combined, namely *Riks-stroke* and the Malmö and Lund hospital stroke registers (Figure 9). Only in-patients are recorded in *Riks-stroke*, whereas the Malmö and Lund registers also include patients who were not admitted to hospital. Although this difference is likely to cause little or no bias in this particular study, it is an example of a difficulty encountered when combining registers.
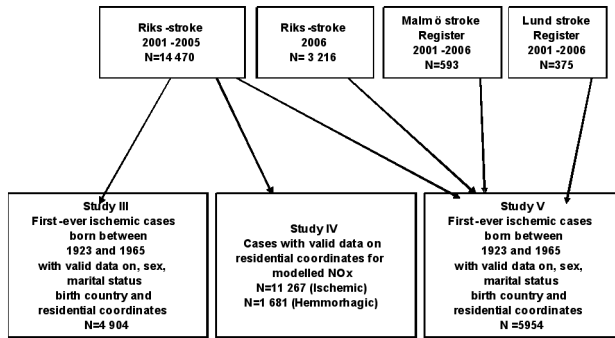
Figure 9. Flow-chart describing cases, registers and inclusion criterias for Papers III-V.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

The STROBE initiative, is aimed at improving the reporting of observational studies, and an extensive document including guidelines was presented in 2007 (Vandenbroucke et al. 2007). The studies described in Papers III-V were carried out with many of the STROBE recommendations in mind. For example, one of the STROBE suggestions employed in this work was to define the objectives of the study by carefully specifying the populations, exposures and outcomes. Furthermore, the controls were stratified by exposure in the descriptive tables given in Papers III and V.

Results and comments

Paper I

The study included all the residents of Scania (≈ 1.2 million), and modelled levels of residential outdoor NO_2 were used as a measure of individual exposure to air pollution. The main finding was that strong associations (measured with Spearman correlation coefficients) occur between indicators for socio-economic status and air pollution, but that the associations differ between the five cities studied. The association also differed depending on the indicator used for socio-economic status and on area level (city, cities together or region). The results may have different implications for epidemiological studies depending on how strongly associated socio-economic status is with the outcome. The slope of the curve was not calculated, but most associations were graphically illustrated in diagrams.

Paper II

Unbiased or marginally biased (<7%) effect estimates were obtained with all four methods; the method that uses only second-phase data, the method given by Eq.2 and the EM-methods with and without external first-phase group-level data. The efficiency of the EM method that takes first-phase register data into account was generally higher than that obtained with the other methods. However, that method relies on the assumption that the first-phase register data is non-erroneous. It would have been desirable to employ that application of the EM method in practice, but since first-phase exposure data was available on individual level and not on group-level this was beyond the scope of this thesis.

Paper III

No association was found between outdoor residential annual mean NO_x (as a marker for individual long-term exposure to air pollution) and hospital admissions for ischemic

stroke, using a two-phase approach. Adjustments for smoking, diabetes and hypertension did not have any substantial influence on the effect estimates. When adjusting for birth year, sex, country of birth and marital status, the odds ratio (OR) for a 10 µg/m³ increase in NO_x was 0.99 (95% CI: 0.95-1.02), p for trend = 0.44. Neither age nor sex was found to modify the effect. Evidence of effect modification resulting from smoking (p = 0.01) was seen in the second-phase data.

Exposure in the first-phase data were available on individual level, in contrast to the study scenarios presented in Paper II. The equations (Eq. 2) which do not use additional exposure data in the second phase, were used to analyse the two-phase data. (Breslow and Cain 1988; Cain and Breslow 1988) Paper III illustrates the advantage of two-phase methods in an empirical study. If we had relied only on the second-phase estimate, which is often employed in practice in epidemiological studies, the wrong conclusions could have been drawn due to selection bias of the controls.

Paper IV

In an area where urban background PM_{10}-concentrations exceeded the WHO air quality guidelines (daily average of 50 µg/m³) only about 3% of the days, a statistically significant effect on ischemic stroke hospital admissions was observed. The relative risk of suffering a stroke the day after being exposed to PM_{10} levels above 30 µg/m³, compared with PM_{10} levels below 15 µg/m³, was 1.13 (95% CI: 1.04-1.22).

Daily mean temperature also seemed to be associated with ischemic stroke; the highest quintile of temperatures (above 16°C), compared with the lowest quintile (below 2.5°C), yielded a RR of 0.88 (95% CI: 0.77-1.00). The effect estimates in the three temperature categories in between (2.5-16°C) were rather similar to those of the lowest category (below 2.5°C). There was no clear evidence that ozone or NO_x levels affected the risk of stroke. The time series analysis and the case-crossover analysis yielded similar results. The exposure contrasts between the index days and controls days for PM_{10} and temperature are illustrated in Table 4 and 5, indicating that pair-wise concordance is high and that the differences in exposure distribution are small. For example, the proportion of index days (excluding concordant pairs) with a temperature above 16°C is 6.7% (1.3 plus 5.4%)). For control days, the corresponding number is 7.5% (1.4 plus 6.1%) (Table 5).

Table 4. Distribution (percentages) of the matched index day-control day pairs from the case-crossover analysis with respect to PM_{10}-level. Ischemic stroke.

PM_{10} at control day (µg/m3)	PM_{10} at index day (µg/m3)		
	<15	15-<30	≥30
<15	19.8	20.3	2.7
15-<30	19.5	23.9	4.9
≥30	2.7	4.6	1.5

Table 5. Distribution (percentages) of the matched index day-control day pairs from the case-crossover analysis with respect to temperature-level. Ischemic stroke.

Temperature at control day (°C)	Temperature at index day (°C)				
	<2.5	2.5-<6.5	6.5-<12	12-<16	≥16
<2.5	11.3	6.2	2.1	0.1	0
2.5-<6.5	6.6	6.9	5.2	0.3	0
6.5-<12	2.3	5.2	8.0	5.1	1.3
12-<16	0	0.4	4.8	8.6	5.4
≥16	0	0	1.4	6.1	12.6

The results regarding PM_{10} and temperature in association with hemorrhagic stroke were similar to those of ischemic stroke, although more imprecise. No clear evidence was found of any associations between hemorrhagic stroke and levels of NO_x, PM_{10} and ozone, or temperature. Sex, age at diagnosis, residing in a major city, smoking and season did not appear to modify any of the effects on neither ischemic nor hemorrhagic stroke risk. Interestingly, the effects of exposure were generally slightly weaker when using single-pollutant models less than when using multi-pollutant models.

Both first-time (N = 8142) and recurrent (N = 2982) strokes were included in the study. To test whether the acute effect of particulate air pollution was different for those who did not have a history of stroke, the data were stratified by whether the stroke was a first-ever or a recurrent stroke. The OR associated with the highest level of PM_{10} (≥30 µg/m³) compared with the lowest level (<15 µg/m³), in first-ever strokes was 1.09 (95% CI: 1.00-1.19), and in recurrent strokes 1.23 (95% CI: 1.06-1.42). The results thus seem to suggest that the effect of short-term exposure to air pollution is stronger in those with a history of stroke.

The age distributions of those having first-ever strokes and recurrent strokes were surprisingly similar: the median age of men suffering their first-time stroke was 75 years, and for women 80 years, and for recurrent strokes 78 for men and 82 for women. The data were restricted to those born between 1923 and 1965 (N = 6684), thus excluding the most elderly and using the same age restriction as in Paper III and V, and restricted to those born before 1923 (N = 4521). The ORs were similar in the two subgroups, with an OR of 1.15 (95% CI: 1.05-1.26) in the group born 1923 to 1965 and 1.12 (0.99-1.26) in the group born before 1923.

The association observed between temperature and ischemic stroke was not an a priori hypothesis in this work. There are some support in the literature for a decrease in temperature to increase stroke risk (Azevedo et al. 1994; Hong et al. 2003; Chan et al. 2006), or markers for stroke risk (Schneider et al. 2008), but others did not observe an association (Rothwell et al. 1996; Michelozzi et al. 2006; Michelozzi et al. 2009). Moreover, increased temperature is a rather established risk factor for CVD in general (Koken et al. 2003; Schwartz et al. 2004). Interestingly, associations between air pollution and stroke only in the warm season in low-level areas has been reported several times (Villeneuve et al. 2006; Kettunen et al. 2007; Szyszkowicz 2008), while there was no tendency of an effect modified by season in this work. If the registration of stroke

cases was lower on warmer days, for example during the holidays, bias might have occurred. However, the results were adjusted for month, day and year which should take this kind of seasonal variation into account.

Although the correlation between PM_{10} and temperature was low (r_s = 0.19), the positive correlation might mean that there is an over-representation of days when the PM_{10} is high (high risk) and the temperature is high (low risk), perhaps leading to an smaller total PM_{10} effect than expected. In the single-pollutant model (where temperature is not adjusted for), the RR associated with PM_{10} above 30 µg/m³ was 1.09 (95% CI: 1.01-1.17). The proportion of days where PM_{10} concentrations were above 30 µg/m³ and the temperature was above 16 °C was 23% (36 out of 155), similar to the 20% (374 out of 1826) of the total number of days above 16 °C during the period. Moreover, adjusting the single-pollutant model for temperature, yields a RR associated with PM_{10} above 30 µg/m³ of 1.11 (95% CI: 1.03-1.19). In summary, the correlation between PM_{10} and temperature is likely of minor importance, at least for high levels (>30 µg/m³) of PM_{10}.

To test whether the decreased risk on days where the average daily temperature above 16 ° C was due to an increase during the very warmest days, an additional analysis was done. The highest temperature category was split at 19.5 ° C, resulting in a RR of 0.88 (95% CI: 0.78-1.01) in the category 16-<19.5 °C (N =249) and a RR of 0.84 (95% CI: 0.72-0.98) in the category ≥19 °C (N = 125). Only 7% (125 of 1826) days during the study period had a mean daily temperature above 19.5 ° C in Scania, therefore it was not feasible to further increase the cut-off temperature. When comparing the effects of temperature on stroke risk between different studies, it should be noted that the temperature distributions between the study areas differ. In Sweden and Scania the temperatures are rather low (mean daily level 9 ° C during the study period). The association between temperature and stroke might differ depending on the temperature span. It should be stressed that influenza and humidity was not adjusted for in the risk models in this study, perhaps biasing the temperature effect estimates.

Paper V

Despite using an new set of controls and an additional number of cases from two other stroke registers, no association was found between the annual mean level of NO_x at the residential address and hospital admissions for ischemic stroke. Tests for effect modifications between NO_x and known stroke risk factors: marital status, education, country of birth, diabetes, physical inactivity, hypertension, atrial fibrillation and smoking, revealed no statistically significant effect modifications. A tendency towards a modification of hypertension was seen, in that people exposed to higher levels of NO_x at home seemed to be slightly more affected by hypertension as a risk factor for ischemic stroke.

Interestingly, adjusting for geographical area has a substantial effect towards the null on the exposure effect estimates Aiming at improving precision and reducing registration bias, data from the Lund and Malmö separate stroke registers were incorporated. The effect estimates indicated a NO_x effect when not adjusted for geographical area, however, when adjustments were done the effect was close to null. A subanalysis restricted to Malmö also indicates a lack of a true effect.

Given that there is some evidence for the effect of air pollution to differ between age groups, a potential effect modification by age should perhaps have been investigated with a polytomous variable instead of a dichotomous. However, there were no tendencies of effect modification in Papers III-V with respect to age as a dichotomous variable. We also refrained from including data from patients of all ages in Papers III and V, since second-phase data were only available for those born between 1923 and 1965. Nevertheless, the first-phase estimates of those born before 1923 (the patients born after 1965 were very few) would have been of interest although competing risks are a problem in older populations.

Interestingly, socio-economy has been showed to influence not only the incidence, but also the survival of the patients (Peltonen et al. 2000), implying that the socio-economic status of the second-phase cases (who all survived their stroke) would be higher than that of the first-phase cases. Comparing Tables 1 and 2 in Paper V, the proportion with a high educational level (>12 years) was 15% among the first-phase cases and 17% among the second-phase cases. A similar tendency is observed regarding birth country. However, the differences are small and cannot be expected to have any influence on the conclusions of the study.

Discussion

Aim 1 & 2

The first and second aim of this work was to investigate whether acute or chronic exposure to air pollution increases the risk of stroke in Scania. No evidence was found of effects from long-term (chronic) exposure (Papers III & V) but there was some evidence that particulate air pollution had short-term (acute) effects on ischemic stroke admissions (Paper IV).

First-ever versus recurrent stroke and hospital admissions versus stroke mortality

An important difference between the studies on long-term effects (Papers III & V) and the study on short-term effects (Paper IV) is that the studies on long-term effects were carried out on an age-restricted population and included only first-ever strokes, whereas the study on short-term effects included patients of all ages and recurrent strokes.

Patients with a previous cardiovascular event or other diseases influencing the cardiovascular or respiratory system might be more susceptible to the effects of air pollution than people without a history of CVD (Sunyer et al. 2000; Bateson and Schwartz 2004; Ljungman 2009). A subanalysis in this work supports this theory, indicating that the short-term effect of PM_{10} on ischemic stroke hospital admissions was higher in patients with recurrent strokes than in patients first-ever strokes (RR = 1.23 versus RR = 1.09).

In most studies on stroke and long-term exposure to air pollution, mortality has been used as the outcome, and both first-ever and recurrent strokes are included (Maheswaran and Elliott 2003; Nafstad et al. 2004; Pope et al. 2004; Maheswaran et al. 2005). An exception is the study where women with a history of CVD were excluded, and where both stroke and mortality were studied (Miller et al. 2007). However, most of the effect on stroke events (which included both admissions and mortality) in that study seemed to stem from stroke mortality (Miller et al. 2007). In Papers III and V cases with a previous stroke were excluded, since such an event might lead to altered living conditions, for example by changing residential address. Exposure at the current residential address of individuals with a history of stroke may therefore not reflect their long-term exposure in the same way as for the general population. To investigate

whether patients with recurrent stroke are more sensitive to long-term exposure to air pollution than those without a previous stroke would therefore have required another type of exposure assessment than the outdoor annual mean at the residential address as proxy for long-term exposure (used in Papers III & V).

Exposure measurement error

Exposure measurement error is an acknowledged problem in epidemiological studies intended to explore the health effects of air pollution, and must be considered in both short-term and long-term studies. In the study presented in Paper III, an attempt was made to quantify the bias caused by measurement error according to different components of exposure measurement error (Zeger et al. 2000). The error components for which the impact could be estimated did not seem to substantially influence the effect estimates, assuming moderate "true" effects (OR = 1.1). However, exposure measurement error would yield a greater bias if the true OR was greater than 1.1. Moreover, it is important to stress that a substantial bias caused by differences between actual personal exposure and ambient exposure could not be ruled out.

If the exposure measurement error differed between cases and controls (Papers III & V), bias can occur. Given that the cases are probably less healthy than the controls (as indicated by the distribution of, for example, diabetes, atrial fibrillation and hypertension), their behavioural pattern would probably also differ. If the nature of the difference is associated with exposure to air pollution, for example, the time spent out doors, the modelled outdoor concentration of NO_x may be differently applicable to cases and controls, which could result in a bias in either direction.

Interestingly, in Paper IV, the effects in the single-pollutant models were generally smaller than the effects of multi-pollutant models. Bias resulting from exposure measurement error becomes more unpredictable in multi-pollutant models than in single-pollutant models although the sign of the bias is not expected to change if the error (difference between ambient level and measured level) is not highly correlated between the pollutants (Zeger et al. 2000).

Pollutants

No associations were observed between NO_x, the pollutant that was modelled at the study subjects' residence, and admission for stroke (Papers III-V). NO_x exposure is not in itself regarded as especially harmful to health, but is considered a good indicator a good indicator for total other air pollutants, especially particle number in ambient air and thereby particles with an aerodynamic diameter less than 1 μm (Ketzel et al. 2004).

Recent research has given attention to health effects of fine and ultrafine particulate air pollution. If such effects were present on stroke hospital admissions an increased

effect by high NO_x concentrations should be present in this work, which they are not. This may indicate that modelled levels of NO_x are a less valid indicator for fine particulate air pollution than previously believed, or that exposure measurement error is present. If modelled annual mean of NO_x exposure is not a good indicator of other kinds of long-term exposure to air pollution, or if exposure measurement error caused substantial bias, there may still be chronic effects of exposure to air pollution in Scania, despite the negative results obtained in these studies (Papers III and V).

Regarding acute effects, there is support for $PM_{2.5}$ to increase the risk for stroke hospital admissions (Lisabeth et al. 2008). If the correlation between $PM_{2.5}$ and PM_{10} is high, the association observed between PM_{10} and ischemic stroke hospital admissions in Paper IV might be caused by a $PM_{2.5}$ effect. For year 2001, 306 days had at least one measurement of both PM_{10} and $PM_{2.5}$ in Malmö (Figure 4). The Spearman correlation coefficient between $PM_{2.5}$ and PM_{10} those days was high: $r_s = 0.86$, indicating that separating effects of PM_{10} and $PM_{2.5}$ can be difficult. However, the large number of missing measurements of $PM_{2.5}$ seen over the whole period made it difficult to investigate a potential overall effect of $PM_{2.5}$.

Confounding factors

Although the main risk factors were reasonably well adjusted for in Papers III and V, residual confounding must also be considered.

There is some evidence for noise to be a risk factor for hypertension (Jarup et al. 2007; Bodin et al. 2009), and MI (Selander et al. 2009). Especially road traffic noise is highly correlated with air pollution, and since hypertension is a risk factor for stroke, noise exposure could confound or modify an association between air pollution and stroke. In a preliminary analysis, using the same road traffic noise data base further described in by Bodin and colleagues the effect of noise exposure on ischemic stroke hospital admissions was investigated, but no evidence of an association was found. Daily variations in outdoor residential noise would probably not have a strong correlation with daily variations in air pollution and therefore not be a potential confounding factor in Paper IV. Given that geography is adjusted for, water hardness is not likely to cause any bias that would alter the conclusions presented in Papers III & V.

A random effect for parish was included in the models specified in Papers III and V, thereby allowing for variations in base-line risk across areas which could be due to contextual effects. However, introducing such an effect did not alter the risk estimates.

Studies on short-term exposure to air pollution and stroke have often adjusted for humidity and influenza (Supplementary File 1; Paper IV), but this was not done in the present work. Influenza has been stated an important confounder on the association between temperature and mortality (Gosling et al. 2009), and there is evidence for temperature to be negatively associated with cerebrovascular mortality after taking influenza into account (Langford and Bentham 1995). Although influenza probably af-

fects overall mortality and respiratory admissions/mortality, the association with stroke is less clear.

Registration bias

Registration coverage differs between the hospitals in Scania that report to *Riks-stroke* (Table 3). In total, during the years 2001 to 2005, when the studies in Papers III & IV were conducted, the total estimated coverage in *Riks-stroke* was about 87%, based on the expected number of strokes in a hospital admission area. When data for 2006 were included (Paper V), the coverage was 88%. However, if the coverage had been estimated based on the in-patient register (as was done starting in 2007), the coverage estimates would probably have been lower. Assuming that the true coverage was the same in 2006 and 2007, the method based on in-patient registers yields 8% lower coverage than the method used previously. This assumption yields an overall estimated coverage between 2001 and 2006 of about 81% (88% x (1-0.08)), meaning that about 20% of the stroke cases occurring in Scania during that period of time might not have been registered.

Whether this causes any bias depends on how the missing data are associated with exposure. If the coverage were higher in areas where air pollution is high, a bias away from the null might occur. However, a simple correlation analysis of the coverage (calculated based on in-patient registers) and the annual mean NO_x in the hospital admission area yields a correlation coefficient of $r_s = -0.02$. Moreover, in Paper III biased sampling was applied in a sensitivity analysis and the results were not altered, also indicating a lack of geographical bias.

By contrast, in Paper V, adjusting for municipality altered the effect estimates substantially towards the null, indicating a confounding effect due to location, perhaps caused by differences in registration coverage between hospitals. Consequently it seems as some kind of geographical bias was introduced in Paper V, perhaps by including the extra cases from Malmö and Lund. However, the distributions of cases and controls in Paper III and Paper V are similar (Table 6 and Table 7). This illustrates the significance of registration bias and the difficulty to predict it. Moreover, the sensitivity of large studies where high exposure is rare and exposure effects are small is stressed by the example. This is also an illustration of difficulties that might occur when different registers are merged. A dialogue between epidemiologists and those in charge of quality registers is of great importance for future epidemiological research, given the opportunities for epidemiological studies inherent in such registers. It is likely that in the future epidemiological studies based on the combination of data from different types of registers will be important, and it is therefore of great importance to address potential difficulties early.

Table 6. Proportion of cases in Paper III and Paper V according to the exposure categories of Paper III.

NO$_x$ (μg/m3)	First-phase cases Paper III N(%)	First-phase cases Paper V* N(%)	First-phase cases Paper V** N(%)
0-<10	1667 (33.9)	2008 (33.7)	2175 (33.3)
10-<20	1944 (39.6)	2368 (39.8)	2579 (39.5)
20-<30	1065 (21.7)	1295 (21.8)	1459 (22.3)
30-<60	228 (4.6)	283 (4.8)	323 (4.9)

* First-phase cases in Paper V are all non-missing with respect to education status.
** Including the cases with missing education information to improve comparability with Paper III.

Table 7. Proportion of controls in Paper III and Paper V according to the exposure categories of Paper III.

NO$_x$ (μg/m3)	First-phase controls Paper III N(%)	First-phase controls Paper V* N(%)	First-phase controls Paper V** N(%)
0-<10	197371 (35.4)	2401 (36.0)	2426 (35.7)
10-<20	221981 (39.9)	2653 (39.8)	2698 (39.8)
20-<30	110001 (19.7)	1358 (20.4)	1390 (20.4)
30-<60	27558 (4.9)	262 (3.9)	273 (4.0)

*The first-phase controls in Paper V are all non-missing with respect to education status.
** Including the controls with missing in education to improve comparability with Paper III.

Registration bias is probably of little practical issue of concern in the short-term study (Paper IV) since contrasts in time are studied and there are no clear (or very weak) time-trends with regard to exposure.

Previous studies and air pollution levels

Studies on both short-term and long-term associations between air pollution and stroke have often been conducted in areas where the levels of air pollution are higher than in the area studied here. Paper IV provided further evidence for effects of particulate air pollution on ischemic stroke hospital admissions, in a rather low level area.

The air pollution levels in two of the long-term exposure studies (that both observed strong associations with stroke in an area-level approach) were much higher than the levels in Scania, for example, the lowest and highest quintile group of NO$_x$ had an average of 47.6 μg/m³ and 61.9 μg/m³, respectively (Maheswaran and Elliott 2003; Maheswaran et al. 2005). Although the areas were small in those area-level studies, it is hazardous to infer individual-level relationships from area-level associations. Studies on long-term exposure to air pollution all typically apply group-level exposure measures, however with different spatial resolution (the spatial resolution in Paper III and V is for example 500 x 500 m). Such studies are therefore in a sense semi-ecological. If risk or exposure are time-varying in such studies, the effect estimates can be erroneous (Haneuse et al. 2007).

In two American studies on chronic effects, the mean value of $PM_{2.5}$ was 13.5 µg/m^3 (Miller et al. 2007) and 17.1 µg/m^3 (Pope et al. 2004), respectively, similar to our study area. Interestingly, the study with higher average $PM_{2.5}$ levels observed no association with cerebrovascular mortality (Pope et al. 2004) whereas the study with lower levels did observe associations with hospital admissions and mortality (Miller et al. 2007). In the Norwegian study that observed a modestly elevated but not statistical significant OR for cerebrovascular mortality (Nafstad et al. 2004), the air pollution levels were rather similar to Scanian levels, but the composition of air pollution has most likely changed substantially between the 1970s (Norwegian study) and the 2000s (our study).

In summary, there does not seem to be a clear pattern with respect to positive findings and levels of air pollution, especially not if the two area-level studies (Maheswaran and Elliott 2003; Maheswaran et al. 2005) are excluded.

Aim 3

The third aim of the work presented in this thesis was to explore whether socio-economic status was correlated to air pollution in Scania, and whether such associations differed depending on the geographic level (region or city) and on the marker of the index used to describe socio-economic status.

The Spearman correlation coefficients found in Paper I differed in sign and magnitude between geographical levels (city, cities together or region), between different cities, and depended on socio-economic index. Although highly statistical significant (p<0.0001), the correlation coefficients did not always indicate strong associations (r_s<0.3).

Paper I is an ecological study, in terms of the socio-economic indices used: i.e. the proportion of highly educated inhabitants and the proportion born in Sweden, in 1 x 1 km grid cells. The aim of this study was not to infer individual-level relationships, but to explore whether associations differed depending on which geographical area level was considered. Paper I provides an illustration of the ecological fallacy, i.e., that associations on one group level can not always be generalised to associations on another group level, or on the individual level.

Interest is growing in how one's neighbourhood can influence health. Characteristics of the neighbourhood could influence the risk of coronary heart disease, regardless of individual risk factors (Sundquist et al. 2004). For example, it has been observed that the inequality in social health is smaller in areas with more green space. (Mitchell and Popham 2008) In such studies, where contextual effects or area-level variables are of interest, it is important to define the area level in an appropriate way. The results of Paper I contribute to the knowledge guiding such decisions.

Aim 4 & 5

The fourth and fifth aims of this work were concerned with two-phase methods, namely, whether it is possible to generalise an existing method and apply it to a setting with a polytomous exposure variable and a confounding factor, and to outline the strengths and limitations of various two-phase designs.

The simulations presented in Paper II indicated that the EM-method which incorporated group-level data into the second-phase generally performed better than the other methods in terms of efficiency and standard deviation. In a setting where exposure is available on the group level in the first phase and where data on a confounding factor are collected in the second phase, the method will thus probably be preferable to the other methods with which it was compared. However, the nature of the method, employing an iterative algorithm (the EM algorithm), makes it somewhat impractical to implement in practice for most epidemiologists. Moreover, if there is more than one confounding factor or a large number of exposure categories this could result in unpredictable results due to few study subjects in some strata. However, the method does have the advantage of being able to deal with effect modifications for the combined two-phase estimates.

Although two-phase methods have been advocated some time now (the papers by Cain and Breslow were, for example, published in 1988), and new methodological papers are presented every year, practical use among epidemiologists is rare. New methods of adjusting for selection bias in case-control studies have been presented recently (Geneletti et al. 2009), but it is unclear to what extent they will be used in practice. Although the STROBE initiative, for example, has stressed the importance of reporting missing data in all stages of an epidemiological study, selection bias and missing data are likely to remain a major problem in many studies. Thus, the introduction of two-phase methods is desirable, and they must therefore be appealing and easy to use in practice.

Ecological data is often applied in epidemiological studies, and much recent research, including Paper II, has been focused on two-phase methods combining ecological data with individual-level data. In the Scandinavian countries including Sweden, detailed register information (available for all citizens) can provide individual-level first-phase data on many variables, such as age, sex and disease status. Incorporating group-level data on for example exposure is likely more common in countries where such registers are not available. However, an ecologic exposure measure can easily be imagined even here, in fact, the exposure measure applied in this work are in a sense ecologic measures, even though the resolution is fine with a grid cell size of 250 x 250 or 500 x 500 m. In a hypothetical exposure model, the one exposure concentration in each grid cell could be replaced with an exposure probability, yielding ecological data.

In the empirical studies presented here, exposure was considered to be on the individual level and several other individual-level variables were available in the first phase and individual-level data on several potential confounders were available also in the second phase, in contrast to the simple examples given in literature. Implementing the EM algorithm in such a scenario, would require some effort from a programming point

of view, which is a major drawback for epidemiologists not skilled in programming. The literature on the practical assessment of a two-phase effect modification in such a situation is, sparse. It is likely that the method presented by Cain and Breslow in 1988 can be generalised to settings with several individual variables in both phases, but further empirical examples or simulation studies are needed. Similarly, it is not clear from the literature whether the variance expression (given in Eq. 2) is valid for continuous exposure variables. A simulation study in which the validity of Eq. 2 is evaluated in a more complicated (and perhaps realistic) study situation, is desirable (with individual-level data in both the first and second phase), similar to that carried out by Jackson and colleagues in 2006 and 2009, who combined group-level and individual-level data, in order to evaluate contextual effects and interaction terms.

Aim 6

The sixth and last aim of this work was to compare time series analysis (Poisson regression) and the time-stratified case-crossover design for analysing the effects of short-term exposure to air pollution.

For the individual exposure series (modelled daily levels of NO_x at the residential address in Paper IV), the time-stratified case-crossover design was assumed the best method available since Poisson regression is adapted for shared data. However, it was uncertain how the performance of case-crossover approach was in situations where each case has an individual exposure value. Moreover, residual seasonality should be absent to yield bias-free estimates with the time-stratified case-crossover approach (Whitaker et al. 2007). Although the data revealed no evident temporal or seasonal trends at first glance, assuming that there must be no time trends in the exposure data is a rather strong assumption.

The first assumption was that Poisson regression would yield bias-free estimates (conditional on the model being checked). The second assumption was that if the case-crossover approach and the Poisson regression yielded similar (i.e. bias-free) estimates with the shared data series (where both approaches could be applied), that would indicate that the case-crossover would also yield bias-free estimates when exposure data was modelled uniquely for each person.

When comparing the risk estimates obtained with time series analysis with those given by conditional logistic regression analysis of the case-crossover approach (Tables 3 & 4 in Paper IV), it was seen that the risk estimates were similar. For example, comparing PM_{10} categories above 30 µg/m³ with levels below 15 µg/m³ on the previous day, using Poisson regression yielded a RR of 1.13 (95% CI: 1.04-1.22), and the logistic regression gave a value of OR = 1.14 (95% CI: 1.04-1.25). The effect estimates in the highest temperature category (>16°C) were a bit more different: a RR of 0.88 (95% CI: 0.77-1.00) compared with an OR of 0.80 (95% CI: 0.68-0.93). The CIs were as

expected slightly wider with the case-crossover approach. When comparing the estimates in Tables 3 & 4 in Paper IV, it should be noted that the NO_x variable is included in the model described in Table 4, thus the tables are not completely comparable. It should also be noted that the model specifications in the case-crossover analysis and the time series analysis are not completely identical regarding adjusting for time trends and seasonal trends.

Single-pollutant models are presented in Tables 3a and 4a in Paper IV, and are thus comparable with respect to what single exposure variable (pollutant or temperature) is modelled. The ischemic stroke estimates in Table 3a are rather similar to those in Table 4a, whereas the hemorrhagic stroke estimates are not as similar. However, the hemorrhagic stroke estimates were adjusted for overdispersion, perhaps causing the greater difference among the estimates for that type of stroke. A large part of the effects were close to one (both regarding hemorrhagic and ischemic stroke) and were consequently not ideal for comparison.

Although the NO_x concentrations were modelled individually, potential time trends and seasonal trends are likely similar to the measured (shared) data series. Thus, the similarity in the effects obtained with Poisson regression and the case-crossover approach probably indicates that there is no substantial bias in the NO_x estimates due to error stemming from modelling risk with the time-stratified case-crossover approach. In summary, the two approaches yielded similar results although the precision was slightly higher with the Poisson regression. Thus, the time-stratified case-crossover approach caused no substantial bias. This study provided empirical evidence that the time-stratified case-crossover design can be employed in a time series where exposure data are unique to each subject/patient).

Conclusions

- Group-level associations between socio-economy and air pollution are heterogeneous in Scania both with respect to area level and socio-economic index

- In a setting with non-erroneous group-level exposure data, the EM method benefits from incorporating such data in the first phase and can produce efficient estimates in a setting with a polytomous exposure variable and a confounding factor

- There was no support for an association between modelled annual mean NO_x at residential address (as a marker for long-term exposure to air pollution) and hospital admissions for ischemic stroke. However, it cannot be ruled out that exposure measurement error might have caused a bias towards the null.

- There was evidence for short-term associations between PM_{10} and hospital admissions for ischemic stroke

- There was evidence for a decreased risk of hospital admissions for ischemic stroke the day after the temperature was in the highest quintile (>16 °C)

- The practical use of two-phase methods was illustrated in Paper III and Paper V

- There was no clear evidence for effect modifications regarding known risk factors and air pollution on stroke risk neither in the studies on long-term exposure to air pollution or short-term exposure to air pollution

- Difficulties with registration bias were illustrated although high-quality register data were available

- The time-stratified case-crossover approach yielded similar effect estimates as the more established Poisson regression time series approach in the study setting.

Issues for Future Research

- Given that traffic-related noise and outdoor levels of traffic related air pollution (such as fine particles and NO_x) can be expected to be highly correlated, a study where both exposures are investigated and contrasts are available should be of high priority

- More research is urgent on how to 1) minimize exposure measurement error, and 2) estimate bias caused by it, mainly in studies on long-term exposure to air pollution, but also in studies on short-term exposure studies.

- It is desirable to investigate the performance of the two-phase method applied in Paper III in complex situations with for example a large number of both first-phase and second-phase variables. Both regarding main effects, effect modification and how to handle a continuous exposure.

- It should be further investigated what individuals are the most sensitive to health effects of air pollution in order to facilitate intervention strategies.

- It should also be further investigated what properties of air pollution that is the most harmful

- The role of temperature is not clear, especially the fact that increased temperature seem to increase risk of CVD (especially mortality), but for cerebrovascular disease there is some evidence pointing for the association to be reverse.

- Public health implications should be considered such as attributable fractions and effects on disability free life time expectancy.

Sammanfattning på svenska

Ungefär 30 000 människor drabbas av stroke varje år i Sverige. Det är en av de sjukdomar som flest dör av, och för de som överlever ger sjukdomen ofta allvarliga men för livet. Vissa beräkningar säger att sjukdomen kostar samhället så mycket som en halv procent av BNP. Det är alltså viktigt, både ur ett samhällsperspektiv och ur individens perspektiv, att undersöka faktorer som påverkar risken att få stroke. Det finns ett flertal kända riskfaktorer, till dem hör ärftlighet, rökning, diabetes, högt blodtryck, förmaksflimmer och brist på motion. Risk att få stroke är till stor del en klassfråga, risken att drabbas är högre bland arbetslösa, lågutbildade och låginkomsttagare.

På senare år har luftföroreningar uppmärksammats som ytterligare en riskfaktor för stroke. Man har visat att strokefrekvensen ökar den dag som halterna av luftföroreningar är höga och även ett par dagar efter. Det är mer osäkert om det även är så att risken ökar om man är bosatt i ett område där halterna är högre än genomsnittet. Man tror att det är så, men det är svårt att bevisa i en vetenskaplig studie, eftersom det finns många felkällor vid sådan forskning. Exempelvis kan bostadsområden skilja sig åt på många olika sätt förutom när det gäller halten av luftföroreningar, vilket kan försvåra jämförelser av risker mellan dessa områden. Det är även osäkert vilka halter av luftföroreningar som medför en riskökning. I Sverige har vi internationellt sett ganska låga halter av luftföroreningar.

I den här avhandlingen har effekterna på risk att få stroke i Skåne studerats. Studierna har gällt både akuta effekter och effekter av långtidsexponering. Även i Skåne är luftföroreningshalterna internationellt sett låga (även om de är högre än i Sverige i allmänhet) och de är väl kartlagda. Det finns en unik databas där alla emissioner (utsläpp) av luftföreningar är registrerade. Med hjälp av den och avancerade geografiska informationssystem kan man sen beräkna halterna av kväveoxider (bland annat kvävedioxid) i hela Skåne med en hög noggrannhet både i tid och rum. Kvävedioxid anses vara en bra indikator för luftföroreningar i allmänhet, särskilt de som orsakas av trafik.

I första artikeln i den här avhandlingen undersöktes samband mellan luftförorenings-halter (kvävedioxid) och klasstillhörighet i Skåne. Man såg att det fanns tydliga samband, men de var inte konsekventa. De varierade mellan olika städer och var beroende av om man tittade på hela Skåne eller på en enskild stad. Sambanden berodde också på vilket mått för klasstillhörighet man använde sig av.

I nästa arbete utvärderades olika metoder för att hantera information som saknas i den typ av studier som undersöker hälsoeffekter av till exempel miljörelaterade faktorer. Resultatet från den studien var att man kan tjäna på att ta in data från register på faktorer som man inte vet något om, även om registret inte ger exakt information utan bara sannolikheter.

I nästa del av avhandlingen (arbete 3), som syftade till att undersöka om luftföroreningar ökar risken att få stroke, hämtades information på stroke-fall som inträffat i Skåne under åren 2001-2006 från det nationella kvalitetsregistret för stroke-sjukvård, Riks-stroke. I Riks-stroke finns viss information på riskfaktorer. Information på hela Skånes befolkning, från 2003, som inkluderade ungefärlig bostadsadress (för att det inte skulle gå att identifiera enskilda individer), utbildningsnivå, kön, födelseår, inkomst och födelseland. Detta datamaterial användes som kontrollmaterial för att studera långtidseffekter genom att jämföra medelvärdet under ett år av luftföroreningshalter utanför bostaden med stroke-fallens medelvärde.

För att kunna kontrollera för kända riskfaktorer i analysen samlades data in från Folkhälsoenkäten 2004 på rökning, högt blodtryck och diabetes, variabler som också fanns i Riks-stroke. Genom att använda sig av de speciella metoder som utvärderats i arbete tre i kunde man sedan justera för dessa variabler i analysen. I nästa steg av studien skickades en enkät ut till människor som fått stroke, och till personer i befolkningen med motsvarande ålders- och könsfördelning som inte fått stroke. En rad frågor ställdes om boendemiljö, ärftlighet och livsstilsfaktorer. Sedan jämfördes halten av kvävedioxid (årsmedelvärde) vid bostaden mellan personer som fått och inte fått stroke, samtidigt som man kunde justera för kända riskfaktorer. I dessa båda studier sågs inget samband mellan halt av luftföroreningar vid bostaden och risk att få stroke.

I nästa studie undersöktes om det fanns ett samband mellan halter av luftföroreningar dagen, eller dagarna innan, en stroke inträffat och risk att få stroke. Där syntes ett tydligt samband, vid höga halter av inandningsbara partiklar i luften ökar strokerisken i befolkningen dagen efter.

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