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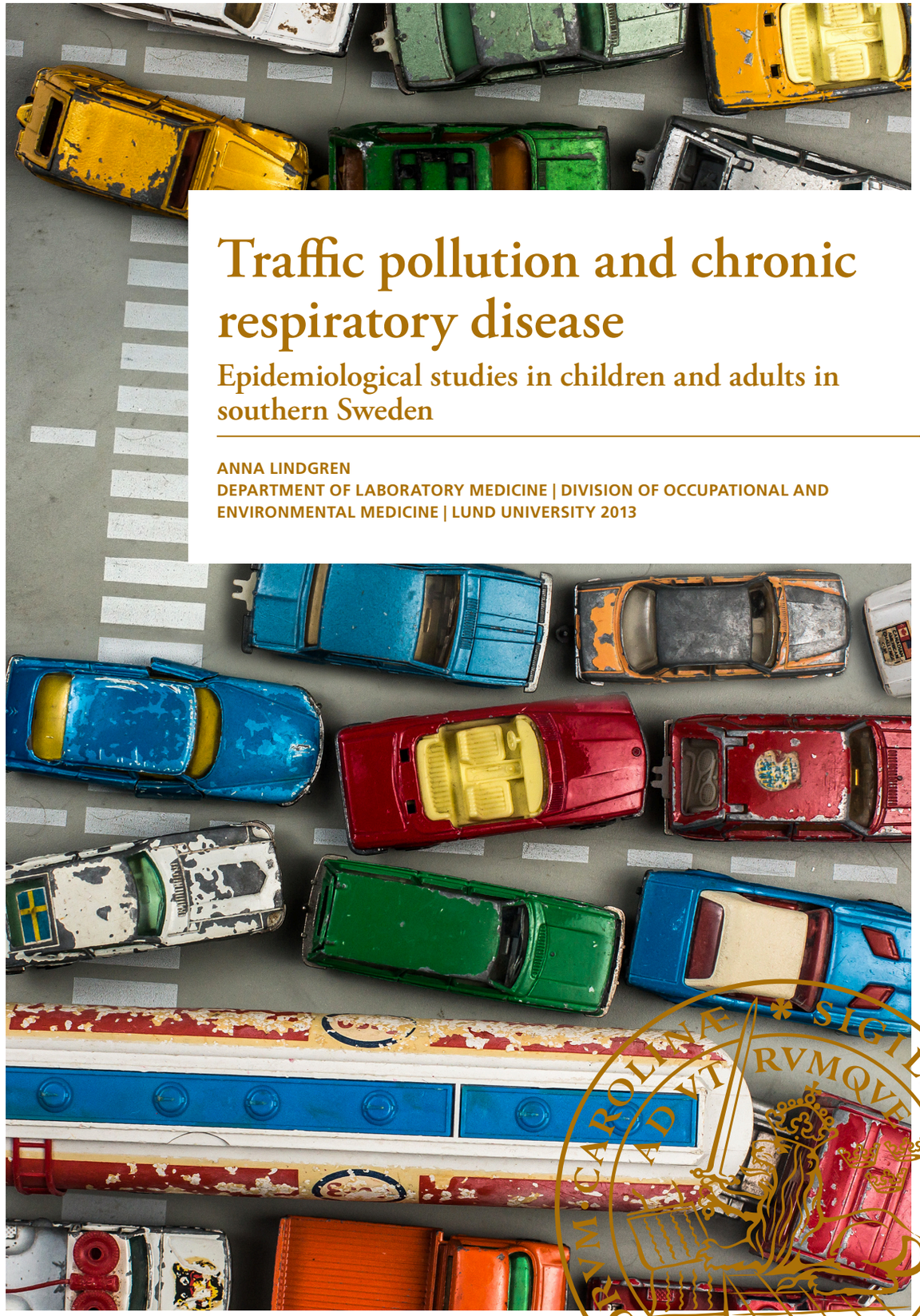

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Epidemiological studies in children and adults in southern Sweden

ANNA LINDGREN
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Traffic pollution and chronic respiratory disease

Epidemiological studies in children and adults in southern Sweden

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Title and subtitle Traffic pollution and chronic respiratory disease. Epidemiological studies in children and adults in southern Sweden.

Abstract

This thesis investigate if long-term exposure to traffic pollution is a risk factor for development of chronic respiratory disease and allergy in adults and children in southern Sweden (Scania).

Information about health was obtained from surveys and health care registers. Traffic pollution exposure was estimated by traffic intensity and levels of NO_x at residential addresses, which were obtained by GIS-based methods.

Paper 1 found that adults living close to dense traffic had higher prevalence of asthma and COPD. *Paper 2* found that adults living close to dense traffic had higher prevalence of allergic asthma, allergic rhinitis and eczema but not non-allergic asthma or rhinitis. *Paper 3* found that asthma in adults was associated with dense traffic at the home location but not traffic at the work location, daily time spent outdoor in traffic or a combined exposure estimate. *Paper 4* found that growing up close to dense traffic was not associated with higher incidence of asthma medication, asthma diagnosis, obstructive bronchitis diagnosis or bronchiolitis diagnosis, in children 0-6 years.

In conclusion, living close to dense traffic was associated with prevalence of asthma, COPD, allergic rhinitis and eczema, in adults, but not with incidence of asthma or other obstructive respiratory disease in young children.

Key words Asthma, COPD, Air pollution, Traffic,NOx, Epidemiology

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List of papers

1) Lindgren A, Stroh E, Montnémery P, Nihlén U, Jakobsson K, Axmon A. Traffic-related air pollution associated with prevalence of asthma and COPD/chronic bronchitis. A cross-sectional study in Southern Sweden. International Journal of Health Geographics. 2009;8:2.

2) Lindgren A, Stroh E, Nihlén U, Montnémery P, Axmon A, Jakobsson K. Traffic exposure associated with allergic asthma and allergic rhinitis in adults. A cross-sectional study in southern Sweden. International Journal of Health Geographics.2009;8:25.

3) Lindgren A, Björk J, Stroh E, Jakobsson K. Adult asthma and traffic exposure at residential address, workplace address, and self-reported daily time outdoor in traffic: A two-stage case-control study. BMC Public Health. 2010; 10:716

4) Lindgren A, Stroh E, Björk J, Jakobsson K. Asthma incidence in children growing up close to traffic: A registry-based birth cohort in southern Sweden. Environmental Health. 2013; 12:91 (Epub ahead of print).

Aims

The objective of this thesis was to investigate if long-term exposure to traffic-related air pollution (traffic pollution) is a risk factor for development of chronic obstructive respiratory disease, in a region with NO_2 levels below the WHO-guidelines.

The specific aims were to investigate:

1) Is exposure to traffic pollution associated with prevalence of asthma and COPD (Chronic Obstructive Pulmonary Disease)/chronic bronchitis in adults? (Paper 1).
2) How are subtypes of asthma and rhinitis in adults affected? Is there a difference between how prevalence of allergic and non-allergic subtypes are associated with exposure to traffic pollution? (Paper 2).
3) Is there any association between traffic pollution and prevalence of asthma and asthma symptoms in adults in occupationally active age? We wanted to investigate 1) separate associations with traffic pollution at residence, workplace, and daily time in traffic, and 2) if combining the exposures, i.e. accounting for total exposure, would strengthen the association between traffic and asthma (Paper 3).
4) Is long-term exposure to traffic pollution associated with incidence of asthma and other obstructive respiratory disease in children 0-6 years? (Paper 4).

1 Introduction

1.1 The traffic pollution hypothesis

The prevalence of asthma and allergy increased sharply during the 20th century, especially in the so called "westernized countries" (Western Europe, US, Australia, New Zealand etc.) almost evolving into an "asthma epidemic" [1]. In Sweden, the prevalence of asthma rose from 2% in the 1970s to 5% in the 1980s and 8% in the middle of the 1990s [2, 3]. During the 2000s the asthma prevalence seems to have reached a plateau, at least in Sweden [3]. However, allergic sensitization is still rising in Swedish children [4] and adults [5]. The increase in allergy has given rise to a lot of speculation on the reason behind the increase, and it has been fairly well established that the increase is real and not only due to changed diagnostic habits [6]. One early observation, was a tendency to more allergy in urban than in rural areas [7], why urban air pollution has been considered as a possible cause.

During the period 1980-2000, when allergic disease increased markedly, most monitored background air pollutants decreased substantially in the "westernized" countries due to stricter air pollution regulations [8, 9]. This has been hold as an argument that urban air pollution in general is unlikely to be the cause. However, at the same time the number of cars increased substantially during this time period and despite the decrease of background air pollution, local exposure to car exhaust has increased [10-12]. A hypothesis is thus that this "modern" type of air pollution from traffic is the cause of the increase in asthma and allergy [13].

Etiologic research is complicated not only because traffic pollution is a complex mixture of many different pollutants, not all which are measured, but also because asthma, COPD and rhinitis are heterogeneous diseases consisting of potentially many subtypes [14-16]. Contributing to the difficulties of investigating the relationship between air pollution and disease, is also that air pollution strongly correlates with urban living, making it difficult to separate the effects from traffic pollution from the effects of other urban lifestyle factors.

Epidemiologic studies are the only way to assess long-term effects of traffic exhaust on populations, but this is dependent on exposure assessment methods which can be used on a wide population scale. Monitor stations are sparsely distributed geographically and do not capture the full spatial variation of air pollution from traffic. In recent years, Geographical Information Systems (GIS) has been used to

assess exposure to traffic pollution, e.g. by measuring distance from residence to roads or modeling air pollution concentrations from nearby emission sources. This possibility of higher spatial resolution of exposure assessment has been necessary for the ability to detect long-term effects of traffic on chronic respiratory disease.

It has been known for a long time that traffic pollution can trigger asthma attacks in asthmatics, but there is now increasing evidence that it also contributes to the initial development of asthma disease [17] and possibly also to COPD [18] and allergies [19].

1.2 Traffic pollution

Air pollution is a mixture of particles (solid and liquid materials) and gases in the air. Air pollution mixtures differ in time and space but in general, urban outdoor air pollution has shifted from being dominated by coal-burning to being dominated by traffic-related pollutions. Air pollution from traffic includes both traffic exhaust (CO, $PM_{0.1}$, NO) and non-exhaust traffic pollution (such as PM_{10} from road dust and wear from tire and breaks). The traffic pollution can also be further divided into the primarily emitted pollutants (NO, CO, $PM_{0.1}$) and secondary formed pollutants ($PM_{2.5}$, O_3, NO_2).

1.2.1 Particles

Particles are small solid or liquid material in the air and is usually measured by mass with consideration to size. Particle mass (PM) is measured as PM_{10}, $PM_{2,5}$ or $PM_{0,1}$ with an aerodynamic diameter of <10μm, <2,5μm and <0,1μm respectively. Ultrafine particle ($PM_{0,1}$) are not routinely measured, but are considered important for health effects. The size of the particles influence how they are deposited in the airways. Larger particles are deposited higher in the respiratory tract, while smaller particles can penetrate deeper down to the alveolar region [20]. Particles with the same size can have completely different chemical composition. Particles less than 1 μm are generated by gas-to particle and coagulation processes, while larger particles are mainly mechanically generated [21]. Examples of PM_{10} are wear from tires, sand dust and sea spray. $PM_{2.5}$ may consist of nitrates and sulphates secondary formed from traffic exhaust, while $PM_{0,1}$ are primarily generated in fresh traffic exhaust [22].

The size of PM also determines the spatial distribution and dispersion in outdoor air. $PM_{2.5}$ generally has a homogenous spread over a city [23], even if levels are slightly higher close to traffic due to the traffic accumulation mode fraction (0.1-1 μm) [24]. PM_{10} partly has a homogenous background value due to long-range transport but also a spatially variable component generated locally in street canyons from road dust, tire

wear etc. Ultrafine particle ($PM_{0,1}$) have high local number concentrations close to traffic, but quickly coagulates to larger particles away from traffic [24].

1.2.2 Gases

Nitrogen Oxides

Nitrogen oxides (NO_x = NO, NO_2) are produced during combustion in the presence of air (since air contains N_2 and O_2), especially during high temperatures. Road traffic is the dominating source of outdoor NO_x but other combustion processes contribute to considerable amounts (e.g. shipping) and some amounts are also generated by natural processes such as lightning. The primary pollutant from gasoline engines is NO, which react with O_3 to form NO_2.

In the presence of sunlight, NO_2 is converted back to NO and O_3, and usually an equilibrium is rapidly established [25]. Diesel engines have a higher proportion of directly emitted NO_2 [11]. Nitrogen Dioxide (NO_2) is a water non-soluble gas which can penetrate deep into the lungs and is toxic per se in high concentrations.

The total concentration of outdoor NO_x is usually measured as an indicator of the presence of local exhaust from traffic. The concentrations of NO_x are highest in street canyons and rapidly decrease with increasing distance from the street, to obtain background values within approximately 150m [26]. How well NO_x estimates traffic pollution depends on the presence of other NO_x sources such as other outdoor combustion sources, or indoor sources (such as gas ovens).

The correlation between NO_x and different air pollutants thus depends on measurement site. Kerbside street location, NO_x usually has a high correlation with $PM_{0.1}$[24, 27], CO [28] and sometimes a good correlation with PM_{10} [29].

Carbon monoxide, Ozone, Sulphur dioxide

Carbon monoxide (CO) is a directly emitted pollutant from incomplete combustion of carbon-based fuels.

CO has a high local correlation with NO when measured close to a freeway [28]. A study in Italy found indications that traffic pollution in highly polluted areas can contribute to as high levels of CO in blood as average smoking [30].

Ozone (O_3) is a highly reactive secondary pollutant, which at ground-level is formed by precursors of NO_2 and Volatile Organic Compounds (VOC) in the presence of sunlight [25]. Since ozone is consumed in the conversion of NO to NO_2, ozone concentrations are usually lower in urban areas than in surrounding sub-urban areas [25] and often have a negative correlation with NO_x. Sulphur Dioxide (SO_2) is produced from sulphate-containing fuels, which has greatly been decreased due to regulations and removal of sulphur from fuels. In Sweden road traffic constituted

0.5% of the total SO_2 emissions in 2010. The SO_2-emissions today are mainly from shipping and industries, which use residual oil containing sulphur. SO_2 concentrations can thus not be expected to correlate with road traffic.

1.2.3 Current WHO guidelines

When assessing the Air Quality Guidelines, the World Health Organisation has done a pure health based evaluation of the evidence for a certain limit. This can be contrasted to EU and national regulations which often set their limits taking societal and economic interests into account.

To estimate health effects from separate traffic pollutants can be difficult since they occur in a mixture. The current guidelines are based on scientific evidence of a safe limit for each pollutant *per se*. If NO_2 instead is regarded as a proxy for traffic-related pollution there is evidence for health effects at exposure levels below the current guidelines [25]. A recent updated review of the scientific evidence for health effects from air pollution also recommend that several of the WHO-guidelines should be revised toward lower values [31].

Table 1.
Current WHO Air Quality Guidelines [25].

Pollutant	Concentration	Averaging Period
Particulate matter ($PM_{2.5}$)	10 µg/m^3 25 µg/m^3	1 year 24 hour
Particulate matter (PM_{10})	20 µg/m^3 50 µg/m^3	1 year 24 hour
Ozone (O_3)	100 µg/m^3	8 hour
Nitrogen dioxide (NO_2)	40 µg/m^3 200 µg/m^3	1 year 1 hour
Sulphur dioxide (SO_2)	20 µg/m^3 500 µg/m^3	24 hour 10 minute

1.3 Different types of epidemiological air pollution studies

1.3.1 Temporal aggregation: Short-term and long-term studies

Epidemiological studies on air pollution are traditionally divided into short-term studies, assessing the acute effects of day-to day-variations in air pollution levels, and long-term studies, assessing the health effect of living for years in areas with high levels of air pollution. This division is reflected in WHO's air pollution guidelines, which have separate short-term and long-term limits.

Short-term studies usually compare daily variations in air pollution levels. These studies have shown that on days with high air pollution levels, there is a higher number of hospital visits and deaths due to respiratory diseases. This type of study has been conducted for a very long time, and acute respiratory effects have also been known for long. One of the more famous examples is the London Fog in 1952 when high levels of air pollution, due to coal use and a few days with inversion, caused extremely high levels of SO_2 but also of particles. This is believed to have caused 4000-12 000 excess deaths during two months [32, 33]. In the aftermath, this led to stronger air pollution legislation such as the introduction of the British Clean Air Act in 1956 [34]. Similar findings can be seen today - although levels of PM generally are much lower, mortality and morbidity can still be increased during days with high air pollution levels. During the China Olympics, measures were taken to reduce the levels of air pollution, and the number of asthma hospital visits dropped to 52% of the usual number [35].

Long-term studies, comparing annual mean levels of pollution to assess the long-term effects from exposure to air pollution, begun as early as the 60s [36]. However it was not until the early 1990s, when several epidemiological studies reported long-term effects on mortality from unexpectedly low concentrations of PM [22], that it started to be acknowledged that air pollution also have long-term effects on health. These early studies used monitor stations to compare cities with high levels of air pollution with cities with lower levels of air pollution. One of the most classic long-term studies is the Harvard Six Cities study, which showed a 26% higher mortality rate in cities with higher air pollution levels [37]. Long-term effects are not only accumulated short-term effects on mortality but it is also believed that air pollution gives chronic disease development of both respiratory and cardiovascular diseases [31].

1.3.2 Spatial aggregation: Area level and individual level studies

Air pollution studies, especially long-term studies, are often divided into "area-level" studies which uses monitor stations to compare the background air pollution levels between larger areas or cities and the more recent "individual level" studies, comparing the local gradients of air pollution exposure between smaller areas or peoples' residences etc.

"Area level exposure" studies

During the 90s there was still little evidence that long-term exposure to traffic pollution could contribute to asthma incidence [38, 39]. Comparing the asthma prevalence between cities with high levels of air pollution and cities with lower levels of air pollution gave mixed results [25, 38]. Most early studies did not have individual information on population characteristics (so called "ecological" studies) while other collected detailed information from questionnaires and thus could adjust for risk factors such as smoking on an individual level ("semi-individual studies" [40]). However, the problem remained with both types of studies; air pollution measurements were only made on area level, poorly reflecting the true spatial variation of air pollutants.

For short-term studies, which rely on temporal contrasts, area level exposure assessment has been less of a limitation since monitor stations have a high resolution in time.

"Individual level exposure" studies

For long-term studies, it was first during 2000s that the computer development gave possibilities to model exposure to traffic pollution on a more detailed individual level. With the introduction of GIS, addresses could be geocoded and linked to databases of road locations and other emissions sources. Although community-level "between area"-studies, still show no association with asthma incidence [38], more recent studies with detailed exposure assessment have indicated that within-city variation of traffic pollution is associated with asthma incidence [17].

Some short-time studies have measured individual exposure by personal air pollution monitoring, which has been in limited use due to its cost. Modeled data give short-term studies the possibility of detailed individual assessment for larger populations. This combination of high resolution in time with high resolution in space may further advance the knowledge on exact which concentrations that triggers acute health effects. While background monitor stations give daily or hourly variations in background ambient air (where concentrations never get very high), or at few urban hotspots, the daily variations in air pollution at "hot spots" can now be modeled for larger populations.

1.3.3 Air pollution exposure assessment in epidemiological studies

Exposure assessment of traffic pollution, in epidemiological studies, is usually based on either data from monitoring stations, individual monitoring, self-reported data or modeled exposures.

Monitoring stations. Many municipalities have monitoring stations for air pollution assessment at city level but these are sparsely distributed and usually placed in urban backgrounds or at roof level at a few selected "hot spots" with high traffic. At the regional level, rural background stations may sometimes also exist. These monitor stations have a good resolution in time, measuring hourly variations in air pollutions, but a poor resolution in space since most cities have only a few stations. When assessing population exposure, all individuals living within a few kilometers of a monitor are usually assigned the same air pollution concentration. This may be a reasonable assumption for more homogenously spread pollutants such as $PM_{2.5}$, but gives a poor prediction of individual exposure of traffic pollutants such as NO_x, which vary on small spatial distances [23]. It may also be a reasonable assumption for short-term studies, which is more dependent on time contrasts in pollution concentrations, than for long-term studies which are more dependent on the spatial contrasts. The main advantage is that data from monitor stations are readily available in most cities and can thus be used for exposure assessment without further collection of exposure data.

Individual monitoring. Façade measurements outside people's front door or personal samplers that people carry on their clothes during a few weeks have been employed in a few studies and is often seen as the golden standard for individual exposure assessment [41]. However, to conduct individual monitoring is expensive and is thus limiting the measurements to smaller study groups during shorter time periods. There may also be difficulties with compliance and selection bias, since only selected populations will volunteer to carry monitors for a prolonged time period [41]. If the purpose is to assess exposure to traffic pollution, there will also be confounding from indoor sources of NO_2 and particles. Façade or other stationary measurements can be a good proxy for outdoor sources of NO_x and PM, such as road traffic, but have the disadvantage of not capturing personal exposure during commuting time or other daily exposure to traffic away from home, and it does not account for the incomplete penetration of outdoor pollution to the indoor environment [42]. An advantage with both types of individual monitoring is that certain types of monitoring devices can provide information on personal "peak concentrations" to traffic pollution which may be especially valuable for studies of acute effects.

Self-reported data. Survey data has been employed in a large number of studies and is a relatively cheap and easy way of individual exposure assessment. Simple questions such as: "Do you live close to a major road?" have been found to be associated with asthma [43]. However, the subjectivity in self-reported data makes it susceptible to bias. Especially of concern is the risk of awareness bias, i.e. that people may be more

aware of and hence over-report exposures that are known to be connected with their disease [43-45]. Since air pollution is a well known risk factor for respiratory symptoms, this could give a false positive relation between self-reported respiratory disease and self-reported high traffic exposure [43]. There is also often selection bias in response for self-reported data, i.e. that certain groups of people answer the survey to a higher extent. In Scania it has been shown that women, individuals with high education and individuals born in Sweden are overrepresented among responders [46].

Modeled exposure. Modeling techniques have been increasingly used for estimating population exposure to air pollution in epidemiological studies. Using geographically referenced data, a spatial air pollution surface can be created by GIS or other modeling tools. This spatial surface can then be linked to geocoded addresses for use in epidemiological studies. The modeling methods differs widely in complexity, from simple distance-based methods, considering only distance to monitor stations or roads, to the use of complex dispersion models based on detailed data on emission sources and dispersion factors [47].The advantage of modeled data is that it is the only relatively cheap way to get objective individual exposure estimates for large populations. However, the quality of modeled data can be expected to vary greatly depending on quality of input data and the validity of the model employed. Validation studies, comparing modeled and measured data are therefore of importance. It has been pointed out that many studies use the same data for building as for validating the model, something which is likely to give an overestimation of the model performance [48, 49].

1.4 Current evidence from epidemiological studies

This section gives a brief summary of the current evidence of health effects of outdoor air pollution on chronic respiratory disease and allergy. The overall evidence for health effects from the most common air pollutants has been reviewed by WHO 2006 [25] and revised 2013[31].

Evidence of short-term effects

Time-series studies, using register data, have shown increased number of hospital visits and deaths due to respiratory causes, during days with high air pollution levels or after some lag period [25, 31]. The associations between NO_2 and respiratory admissions are most consistent among children and older adults (≥ 65 years age) for all respiratory diagnoses, and for all age groups for asthma admissions [31]. Effects have also been seen on allergic rhinitis outpatient visits [50, 51]. Acute effects have been seen even at current levels of air pollution in Sweden, with increased frequency

of severe asthma, and increased number of acute hospital visits for asthma and respiratory diseases on days with high air pollution levels [52, 53] .

Panel studies, evaluating smaller study groups by symptom diaries or other symptoms measurements, have shown that asthma symptoms and cough can be triggered by air pollution [31]. There is less evidence that COPD exacerbation can get triggered by high air pollution concentration [54].

Evidence of long-term effects

Asthma. Recent reviews conclude there is an overall association between asthma in children and traffic-related air pollution [11]. For adults, fewer studies have been conducted and the role of traffic pollution in adult onset asthma is less conclusive [55]. Traffic pollution has been associated with asthma incidence in both children [56] and adults in Sweden [57, 58].

COPD/Chronic bronchitis. A recent review condude that there is suggestive but not conclusive evidence that traffic pollution causes COPD [59, 60]. Few cohort studies have been conducted and most studies rely on hospital admission or doctor's diagnosis of COPD rather than on spirometry definitions. A study in Copenhagen found that first ever hospitalization with COPD was associated with long-term air pollution level [61] .

Lung function. There is strong evidence that both background levels of air pollution and local levels of air pollution decrease lung function growth in children and adolescents [18]. There are few studies on adults, and existing studies are mainly cross-sectional [18]. One longitudinal study has shown that a reduction of PM decreases the decline in lung function [62] .

*Allergic sensitization, allergic rhinitis and atopic eczema.*The effects of long-term exposure to traffic on development of allergic disease such as sensitization, atopic eczema and allergic rhinitis is overall inconclusive [11] even if many individual studies have found traffic pollution linked to sensitization (especially to inhalation allergens) [63-65], allergic rhinitis [63, 66], and prevalence of atopic eczema [63, 67, 68]. A recent meta-analysis of five European birth cohorts did not find evidence of sensitization (specific IgE) in relation to traffic [69]. A few studies in Sweden have however found an association with sensitization in children [4, 64, 70].

Evidence in experimental human studies

Experimental studies of real-world exposures support the epidemiological data on acute effects [11]. For asthmatics walking along Oxford street, lung function has been shown to be impaired compared to walking in Hyde Park [71]. Chamber studies, exposing people to specific pollutants or pollutant mixtures under controlled circumstances, have also provided evidence of acute effects but at much higher levels, i.e. small effects on increased airway hyperresponsiveness from NO_2 can be seen at 200µg/m^3 among mild asthmatics, and from 1900 µg/m^3 among healthy adults [25,

31] It has also been shown that nasal instillation of diesel particles can enhance allergic response to allergens [72].

2 The current studies

2.1 Material and methods

2.1.1 Study area

The study area was the county of Scania, the southern part of Sweden, which has a population of 1.2 million of Sweden's total population of 9.5 million, and 115 inhabitants/km^2 (data from 2012 [73]) and a land area of approximately 11 350 km^2). The largest city in the region is Malmö with a population of 307 207 [73]. A large part of the population in Scania is living on the west coast, and most road traffic from Europe to Sweden and Norway passes this area. A more detailed description of some of the cities in the area can be found in an article by Stroh et al [74].

The air pollution levels for NO_2 are generally well below the WHO-guidelines, at least when measured by monitoring stations. Although pollutant levels in the region are low in a European context, they are higher than in the remainder of Sweden, due to long-range transport of pollutants from the continent and extensive harbor and ferry traffic. Malmö has the highest level of air pollution in the area, however, Trelleborg and Helsingborg have extensive harbor- and ferry traffic and therefore also relatively high air pollution levels.

Previous studies have found that immigrants, and children residing in areas with low income, has a higher exposure to NO_2 in Malmö [74, 75], but that the relation between socio-economy and NO_2 differs between municipalities [74].

2.1.2 Study population

Paper 1 and 2 are based on a cross-sectional survey in 2000 (n=9319, age 18-77 years, response rate=78%), within former Malmöhus county, which is the western part of Scania. The population was randomly sampled in Malmö and 10 of its surrounding municipalities (Lund, Burlöv Landskrona, Kävlinge, Lomma, Staffanstorp, Eslöv, Höör, Hörby, and Svalöv). The study population originated from two different study populations, with 5039 subjects (response rate: 71%) from a new random selection, and 4280 subjects (response rate: 87%) who constituted a follow-up group from a previous survey in 1992.

Paper 3 is based on two cross-sectional surveys, one in 2004 (n=24819, age 18-80, response rate=59%) and the second in 2005 (n=2856, age 18-65, response rate=86%). The first was a public health survey covering the entire Scania. The sampling was stratified on age, sex and geographical area; the 29 municipalities were divided into 62 geographical strata, with equal number randomly sampled in each stratum independent of population size, in order to increase the statistical power in some smaller administrative areas. The second survey (2005) was sent to all asthma cases from the first survey (2004) which had agreed to participate in further studies, and to controls randomly sampled from the first survey (1:3), frequency matched on sex but not on geographical area.

Paper 4 is a birth cohort in Scania. The study was limited in time to children born from July 2005, when individual level medication data was first available. All children were followed to the end of 2011.

To identify the birth cohort, the identity number of all children born by mothers living in Malmö, Svedala, Vellinge and Trelleborg during July 2005-2010, were retrieved from the Perinatal Revision South (PNS)-registry. The PNS registry has 100% coverage of visits on obstetric and peri/prenatal units in the county. Out of 28 037 children identified in the PNS-registry, 875 were not found in the Scania population registry and thus excluded, since they were not registered as living in the region during childhood. Outcome data was available for all children found in the Scania population registry (n= 27 162), by linkage to the Scania Health Care Registry (SHCR) and the Swedish Prescribed Drug Register. Geographical coordinates of the children's registered address (during the year of birth) was available for 26 128 children. Most of the missing geocodes belonged to children born in December, whose late birth date lead to addresses not being registered during their year of birth. Geocodes were also retrieved for all subsequent years, until the end of 2010. Finally, covariate information from questionnaires routinely distributed at Child Health Care centers was available for 7898 children, which formed the main study cohort.

2.1.3 Geocoding

Traffic exposure assessment was obtained by the use of GIS to link geographical coordinates for people's residential address to traffic exposure data. For residential address (paper 1-4), geocodes were obtained by linking each individual's unique 10-digit personal identity codes to a registry containing the geographical coordinates of nationally registered residential address. This assigned individuals a position at their real estate. In paper 3, occupational addresses were obtained in one of the surveys, and geocoded by their address.

2.1.4 Exposure measures

Exposure to traffic was assessed using three different types of proxies (Figure 1).

1. Self-reported exposures to traffic. This was obtained from surveys (Paper 1-3).
2. Traffic intensity on the heaviest road within a certain radius. GIS-based registers from The Swedish National Road Database provided information about traffic intensity for all major roads in the county (Paper 1-4).
3. Modeled exposure to NO_x, which is a commonly used indicator for traffic pollution. In the present studies, we made use of a GIS-based emission database for nitrogen oxides (NO_x and NO_2) which has been developed and validated for southern Sweden. Annual mean concentrations of NO_x were modeled in a grid with a spatial resolution of 250x250m (Paper 1-3), as well as 100x100m (Paper 4).

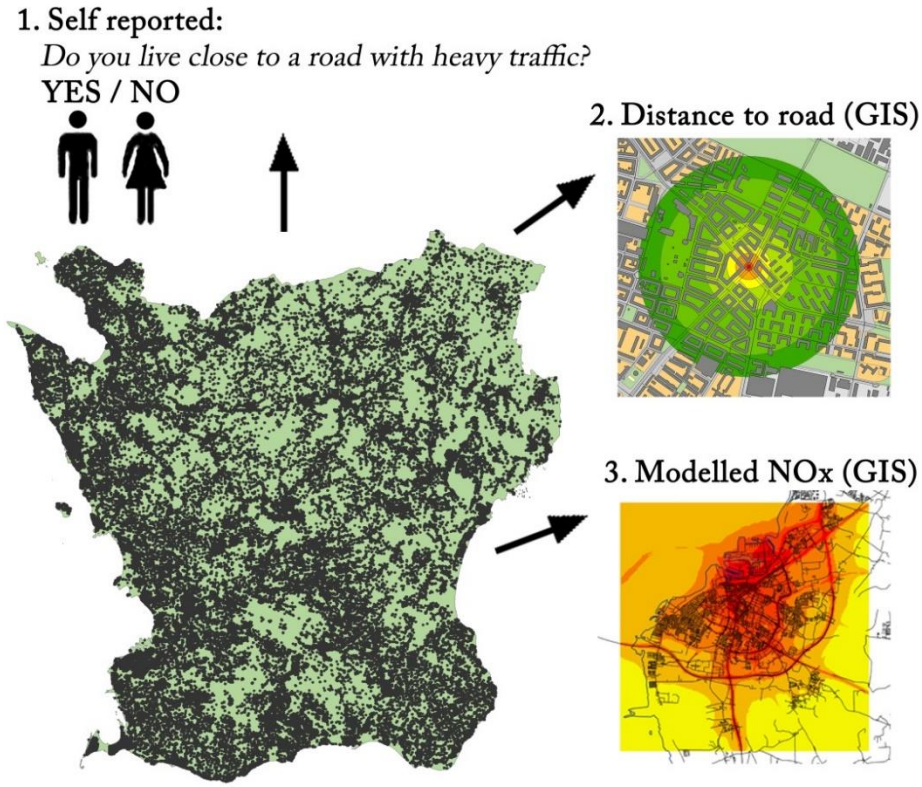

Figure 1.
Exposure measures used in the studies.

Emission database and dispersion modeling of NO_x.

Annual mean concentrations of NO_x were acquired from an emission database (EDB), originally based on the year 2001 but updated regularly, which has been extensively described in previous studies [76, 77]. Emission sources included in the database are: road traffic, shipping, aviation, railroad, industries and larger energy and heat producers, small scale heating, working machines, working vehicles, and working tools. Meteorological data were also included. A modified Gaussian dispersion model (AERMOD) was used for dispersion calculations; a flat two-dimensional model which did not adjust for effects of street canyons or other terrain, but which did take the height of the emission sources into consideration. Background values of NO_x were also added to the modeled values. Concentrations of NO_x were modeled as annual means on a grid with a spatial resolution of 250 × 250 m (Paper 1-3) and 100x100m (Paper 4). Bilinear interpolation was used to adjust individual exposure with weighted values of neighboring area concentrations [78].

Validation of the EDB has been done by comparing modeled NO_2 with 100x100m-resolution with measured facade measurements during one week (Spearman's $r=0.8$, $p<0.01$) [79].

2.1.5 Health measures

Questionnaires

The first three studies (Paper 1-3) relied on questionnaires for outcome data and confounder information, and the fourth study (Paper 4) relied on questionnaires for confounder information. Only the second questionnaire in paper 3 (sent in 2005), was designed with the specific purpose of investigating effects from traffic exposure. The other questionnaires were originally distributed for other purposes.

Paper 1 and 2 are based on a cross-sectional survey distributed in 2000. The questionnaire focused on respiratory disease, and was originally distributed with the purpose of studying prevalence of respiratory disease, symptoms, comorbidity and determinants. An English translation of the questionnaire has been published elsewhere [80]. The questions about upper respiratory tract disease and symptoms were designed for the specific study, while questions about lower respiratory tract disease and symptoms were based on a validated questionnaire used in the OLIN (Obstructive Lung Disease in Northern Sweden) studies [81].

Paper 3 is based on two cross-sectional surveys, one in 2004 and the second in 2005. The public health questionnaire (2004) had a broad purpose of investigating health and risk factors for population health in Scania. The second survey (2005) was distributed with the specific purpose to estimate effects of traffic pollution and other environmental factors. A supplemental file published together with paper 3, contains the original Swedish questionnaires with English translations [82]. A study of the

representativity of responders in a previous public health-survey in the same region found that women, individuals with high education and individuals born in Sweden were overrepresented among participants [46].

Paper 4 used questionnaires distributed at Child Health Care-centers (CHC) to obtain covariate information. The questionnaire was handed out to parents during the child's 8 month checkup. The questionnaire had been validated and translated from Swedish into five different languages: Albanian, Arabic, English, Serbo-Croatian, and Somali. The CHC-questionnaires were originally distributed as part of the "Child Health and living conditions study" in Malmö, Svedala, Vellinge and Trelleborg [83]. The CHC-center visits cover almost 100% of the children in the country [83], however, there may be selection in which CHC-centers that participated in the study. Moreover, questionnaires were not handed out on all visits [84].

Registry-based data

Paper 4 used registry-based outcome data. In addition to hospital data (which is commonly used) we also had access to primary health care data and data from the Prescribed Drug Register. Few countries have access to primary health care or drug registers for the entire population. The main advantage with registry-based data is that it decreases the risk of recall and awareness bias, and if the coverage is good, also decreases the risk of selection bias.

The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register includes all drugs dispensed at pharmacies in Sweden, since July 2005 linked to personal identity numbers [85]. The registry is maintained by the National Board of Health and Welfare. All dispensed prescribed drugs at the pharmacies are registered, with a very small number of incorrect or incomplete registrations of ID. The population coverage with correct patient identities is 99.7%.

The registry contains data on all dispensed prescriptions in ambulatory care. Over-the-counter (OTC) medications and drugs used at inpatient settings are not included. Medication data are classified according to the Anatomical Therapeutic Chemical Classification System (ATC) [86].

The Scania Health Care Registry (SHCR)

In Sweden, all healthcare consultations are recorded in county-specific databases. The SHCR holds details for primary health care, and hospital based in- and outpatient care for Scania. Each consultation generates data entries that are transferred to SHCR and which constitute the basis for reimbursement to the healthcare providers. The hospital care has a good coverage and validity for diagnostic codes [87, 88]. However, for primary care, the number of consultations with diagnostic codes is less complete. The diagnostic codes from public care are transferred to SHCR, but have some

missing registration of diagnostic codes due to incomplete journal entries. For private health care providers, consultation events, but not diagnostic codes, are transferred to SHCR. In paper 4, diagnostic codes were available for 96.5% of the hospital visits, and for 50.2% of the primary care visits. Among the latter, 70.2% of public primary care visits had diagnostic codes, while codes were completely missing for private primary care visits. The proportion of private primary care was 27.8% of total primary care visits.

2.2 Method description for the individual papers

2.2.1 Paper 1.

Title: **Traffic-related air pollution associated with prevalence of asthma and COPD/chronic bronchitis. A cross-sectional study in Southern Sweden.**

Study aim: To examine if exposure to traffic pollution is associated with prevalence of asthma and COPD/chronic bronchitis in adults

Study population: This paper was based on a cross-sectional respiratory survey in 2000, (n=9319 age 18-77, response rate=78%) , within the western part of Scania. The population was randomly sampled in Malmö and 10 of its surrounding municipalities.

Outcome measures: A postal questionnaire was used to investigate the following outcomes.

1. Diagnosis of asthma. *"Have you been diagnosed by a doctor as having asthma?"*
2. Diagnosis of COPD/Chronic bronchitis/Emphysema. *"Have you been diagnosed by a doctor as having chronic bronchitis, emphysema, or COPD?".*
3. Asthma symptoms during the last 12 months. *"Have you had asthma symptoms during the last 12 months, i.e. intermittent breathlessness or attacks of breathlessness? The symptoms may exist with or without cough or wheezing."*
4. Chronic bronchitis symptoms. *"Have you had periods of at least three months where you brought up phlegm when coughing on most days?", and if so, "Have you had such periods during at least two successive years?".* Both questions had to be answered with "yes", to be classified as having chronic bronchitis symptoms.

Exposure data:

1. Self-reported data, *"Do you live close to a road with heavy traffic? Yes/No".*
2. GIS modeled traffic intensity on the heaviest road within 100m, at residential address.
3. Dispersion-modeled concentrations of NOx (250x250 m grid) , at residential address.

Statistics: Multiple logistic regression was used to assess the relation between exposure data and outcomes, OR:s were adjusted for age sex and smoking. Socio-Economic Indices (SEI) and occupational exposure (coded as ALOHA Job Exposure Matrix (ALOHA JEM) [89]) were also considered as confounders but did not change the effect estimates more than 10% and were not included in the final models.

2.2.2 Paper 2.

Title: **Traffic exposure associated with allergic asthma and allergic rhinitis in adults. A cross-sectional study in southern Sweden.**

Study aim: To examine if there was a difference between how subtypes of asthma and rhinits were affected by traffic pollution.

Study population: same as for paper 1.

Outcome measures: Asthma, rhinitis and eczema were investigated using the survey questions specified in figure 2.

Exposure data:

1. Self-reported data *"Do you live close to a road with heavy traffic? Yes/No.".*
2. GIS modeled traffic intensity on the heaviest road within 100m, at residential address.
3. Dispersion-modeled concentrations of NO_x (250x250 m grid), at residential address.

Statistics: Multiple logistic regression was used for the analyses, and OR:s were adjusted for age, sex and smoking. SEI and occupational exposure (ALOHA JEM) were also considered as confounders but did not change the effect estimates more than 10% and were not included in the final models.

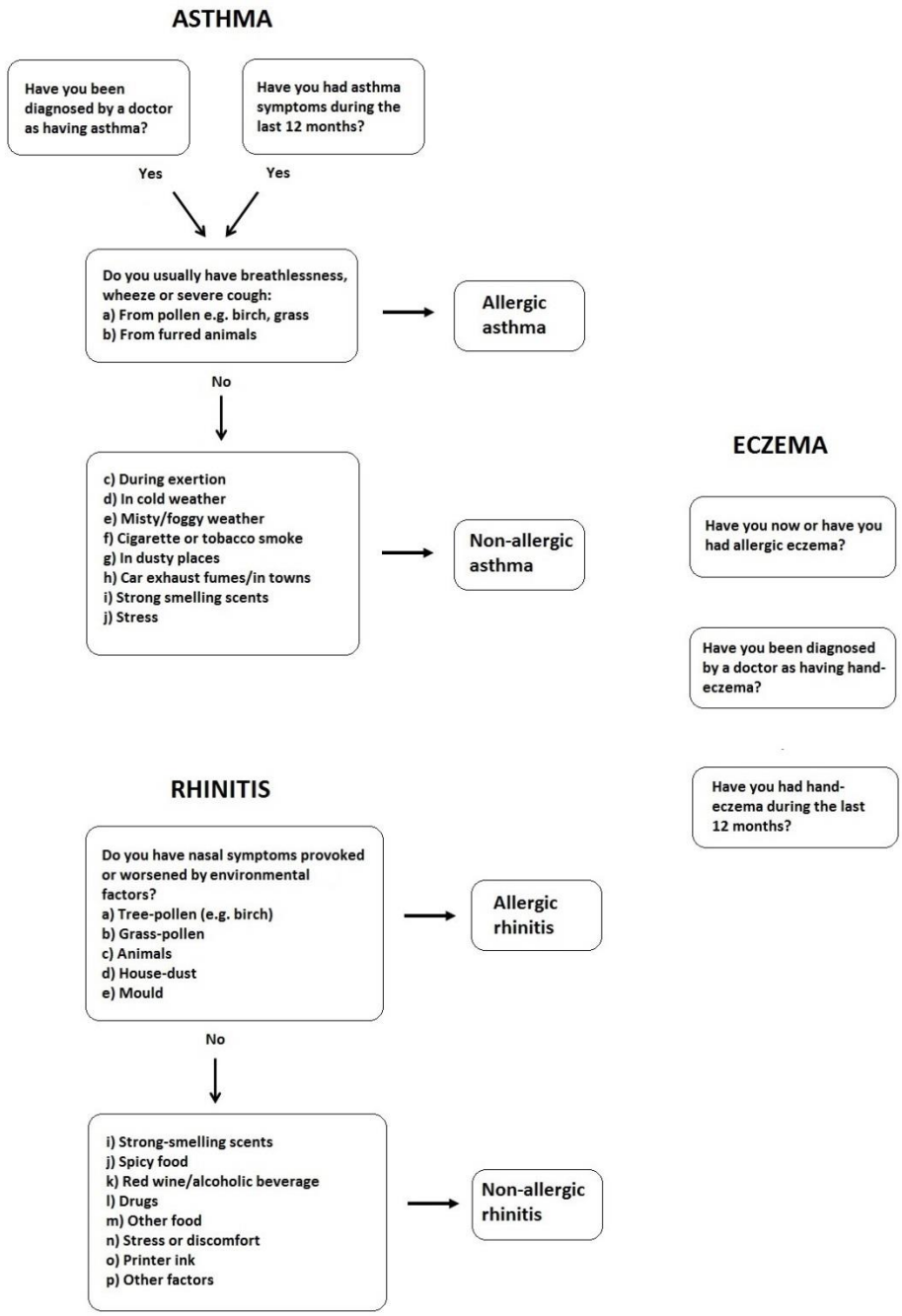

Figure 2.
Outcome definitions for paper 2.

2.2.3 Paper 3.

Title: **Adult asthma and traffic exposure at residential address, workplace address, and self-reported daily time outdoor in traffic: A two-stage case-control study.**

Study aim: The aim was to investigate the association between traffic pollution and prevalence of asthma and asthma symptoms in adults in occupationally active age. We investigated 1) separate associations with traffic at residence, workplace, and daily time in traffic, and 2) if combining the exposures, i.e. accounting for total exposure, would strengthen the association between traffic and asthma.

Study population: This study is based on two cross-sectional surveys, one in 2004 (n=24819, age 18-80, response rate=59%, however, we restricted our analysis to age 18-65, n = 22693) and the second in 2005 (n=2856, age 18-65, response rate = 86%). The first was a public health survey covering entire Scania. The sampling was stratified on age, sex and geographical area; with 29 municipalities divided into 62 geographical stratum, with equal number randomly sampled in each stratum (independent on population size), in order to increase the statistical power in some smaller administrative areas. The second survey (2005) was sent to all asthma cases from the first survey (2004) which had agreed to participate in further studies, and to controls randomly sampled from the first survey (1:3), frequency matched on sex but not on geographical area.

Outcome measures: The following survey questions were used as outcome measures.

1. Asthma prevalence. *"Do you have asthma?"* The answers: *"No"*, *"Yes, but not symptoms"*, *"Yes, minor symptoms"*, *"Yes, severe symptoms"* were dichotomized into *"Yes"* (All three "Yes-answers") or *"No"*. This question was only present in the first survey.
2. Asthma symptoms during the last 12 months. *"Have you had asthma symptoms during the last 12 months, i.e. intermittent breathlessness or attacks of breathlessness?"*. This question was available in the second survey.
3. Self-reported doctor's diagnosis of asthma was also analyzed for those with this information available in the second survey *"Have you been diagnosed by a doctor as having asthma?"*.

Exposure data:

1. GIS modeled traffic intensity on the heaviest road within 50, 100, 250 m, at residential and occupational address.
2. Dispersion-modeled concentrations of NO_x (250x250 m grid), at residential and occupational address.
3. Self-reported data. "*What is the traffic intensity on the street outside work/school (within a distance of 50m)*","*What is the traffic intensity on heaviest road you*

can see from any window in your apartment? (within a distance of 50m)", and *"How much time do you on average spend outdoor in traffic every day? (in cars, buses, bike, walking on streets etc)"* and *"How long time does it take for you to transport to work/school?"*.

4. Total exposure. Total exposure was calculated as ((Total time - time at work - time in traffic)*NO_x at home address) + (time at work*NO_x at workplace address) + (time in traffic*C). The constant C representing the hypothesized average NO_x-dose from time in traffic was varied between 30 and 300.

Statistics: Effect estimates were obtained as Odds Ratios (OR:s), by multiple logistic regression. Potential confounders present in both the first and the second survey were adjusted for (sex, age, smoking, Body Mass Index (BMI), SEI-codes and self-reported "exposure to chemicals, dust, or fumes at work"). Potential confounders from the second survey (indoor dampness, smell of mould, condensation on inside of windows, specific work-exposures assessed by self-reported exposure to dust, motor exhaust or chemicals (assessed as separate questions) and by coding self-reported occupation to ALOHA JEM) were also considered for inclusion in the model but did not change the estimate more than 10% and were not included in the final models.

2.2.4 Paper 4.

Title: **Asthma incidence in children growing up close to traffic. A birth cohort in southern Sweden.**

Study aim: Is long-term exposure to traffic pollution associated with incidence of asthma and other obstructive respiratory disease in children 0-6 years?

Study population: We investigated a birth cohort in southern Sweden, consisting of N=26 128 children with outcome and exposure data (born July 2005-2010). Of these children, N=7898 had additional covariate information. The cohort was followed to the end of 2011. Covariate information was obtained from questionnaires distributed to parents at Child Health Care-centre visits, eight months after birth.

Outcome measures: Outcome data were obtained from registry data on dispensed asthma medication (the Swedish Prescribed Drug Register), and hospital and primary health care data with diagnostic codes (The Scania Health Care Register).

As primary outcomes we used (from the Swedish Prescribed Drug Register):

1. Incidence of first ever dispensed inhaled β2-agonist
2. Incidence of third year with dispensed inhaled β2-agonist
3. Incidence of first ever dispensed inhaled corticosteroid
4. Incidence of third year with dispensed inhaled corticosteroid

The secondary outcomes were primary diagnoses of (from The Scania Health Care Register):

1. Bronchiolitis (J210, J218, J219)
2. Obstructive bronchitis (J200-J209, J22-P)
3. Asthma (J450- J459, J45-P, J469)

The diagnostic codes are based on a Swedish version of the ICD10-system, and a simplified primary health care version KSH97-P

Exposure data:

1. GIS modeled traffic intensity on the heaviest road within 100m, at residential address.
2. Dispersion-modeled concentrations of NO_x (100x100 m grid), at residential address.

Statistics: Cox proportional hazards regression was used. The model was adjusted for sex, environmental tobacco smoke (ETS), breastfeeding, parental allergy, parental origin, parental education and year of birth. Covariates were selected by pre-screening and stepwise selection, variables considered but not selected for inclusion were birth weight, smoking during pregnancy, mold at home, furred pets at home, problems to pay bills, and type of housing.

2.3 Results and comments: Paper 1-4

Paper 1. We found asthma and COPD to be associated with traffic at residential address among adults, in southern Sweden, an area with relatively low levels of air pollution. Overall, residential traffic was associated with a higher prevalence of both asthma diagnosis and asthma symptoms during the last 12 months, as well as COPD diagnosis and chronic bronchitis symptoms. Traffic intensity on the heaviest road within 100m showed effects at a traffic intensity of ≥6 cars/min (8640 cars/day). Effects of NO_x were seen in the highest exposure quintile of annual average >19µg/m^3, but only in Malmö, not in the region outside. That traffic pollution does not only increase asthma symptoms but also asthma incidence has considerable evidence in children [11] and is observed in several recent longitudinal studies in adults, however not consistently [11]. Long-term effects of traffic on COPD have been less studied, but some studies have found traffic to increase the incidence of COPD/chronic bronchitis and some has not [59]. None of these studies reported a greater effect in smokers, which was possibly indicated in our study although not statistically significant.

Paper 2. We found only current asthma and rhinitis triggered by allergic factors, not current asthma and rhinits triggered by other factors, to be associated with traffic exposure. We also found an association between traffic exposure and eczema. Many studies have found that traffic causes allergic disease or allergic sensitization, but there are also many studies finding no association. The results are very interesting since allergic sensitization is still increasing in Swedish children [4, 90] and adults [5], but asthma prevalence and symptoms of rhinitis and eczema seems to have reached a plateau for both children [4, 90] and adults [3]. Allergic sensitization has been associated with traffic in some Swedish studies [4, 64]. The fact that allergic sensitization has increased without a rise in total symptoms of asthma, rhinitis or eczema might depend on concurrent decrease in daily smoking [4]. For example, in southern Sweden, daily smoking has dropped from 37% to 17% in men, and 28 to 18% in women between 1980 and 2003 [91]. It has been suggested that there is an ongoing switch to more allergic subtypes of asthma and rhinitis [90]. Finally, it should be noted that our study only investigated trigger-related allergic and non-allergic disease, and did not address other non-allergic chronic respiratory symptoms from the upper respiratory tract, such as permanent nasal symptoms and yellow nasal discharge, which have previously been related to self-reported traffic in the area [92].

Paper 3. Our results shows that asthma prevalence was associated with high traffic exposure at the residential address but no significant associations were found with traffic exposure at work-address or with daily time spent outdoor in traffic. A stronger association was not seen when considering total traffic exposure compared to only residential traffic. The fact that total traffic did not give a stronger estimate is likely to reflect that work-address or time spent in traffic did not show single associations with asthma (although effects were indicated in the highest exposure categories) and that residential and occupational traffic exposure were correlated. Another likely cause for the lesser effect from traffic at work-address may be that the geocoding, although assigned at exact address, still may be imprecise at work-address compared to residential address since work-place buildings may be large, and people relocated to other addresses part of their working time. It is also possible that migrational bias affects residential address less than work address or other daily activities. It was however difficult to assess the independent effects of the different exposures since residential and occupational exposures were largely associated and there was low power for stratification. The associations between residential traffic exposure and asthma in this study confirm the results in paper 1 and 2. However, the effect estimates for residential traffic were slightly higher in the second survey. This rises a question of selection bias. The overall participation rate in the first survey was 59%, while the second survey had a response rate of 86% and was only sent to respondents from the first survey which had agreed to be contacted again. It is known from previous public health surveys that the response rate depends on socioeconomic and geographical strata [46].

Paper 4. We found no association between growing up close to traffic, and asthma incidence or incidence of other chronic obstructive respiratory disease, in children 0-6 years in southern Sweden. On the contrary, there was a lower prevalence of all outcomes except obstructive bronchitis, in these children. Overall, the literature clearly supports an association between asthma incidence and traffic exposure. However, most reviews have not made any distinction on age of onset. We believe that there is much larger support for asthma incidence in older children and much less support for asthma incidence in young children. We therefore think that our results may reflect this and that if this cohort is followed to older age there may be an association between traffic and allergic asthma (which is more common in children ≥3 years). It is also possible that there is no effects on asthma onset in this region with its very low levels of exposure, but that higher levels of air pollution would have shown an association with the outcomes in this study. We believe that our objective registry outcome data is a big advantage in this study, since almost all other studies rely on self-reported data which may cause an awareness bias. However, the registry based outcomes may still be susceptible to other form of biases. The higher prevalence of asthma in those with low traffic exposure suggests that we have not adjusted for all important population factors. The validity of dispense of asthma medication from the Swedish Prescribed Drug Registry as a proxy for asthma and other obstructive respiratory disease was recently investigated. For pre-schoolers (age 0-4.5 years), a dispense of ≥2 inhaled corticosteroids, leukotriene receptor antagonists, or combinations of inhaled corticosteroids and B2-agonists, with at least two weeks gap between dispense, gave a positive predicitive value (PPV) of 75% for asthma. Of children that did not fulfill the asthma criteria, 18% were defined as having obstructive bronchitis and 7% as having been given asthma medication for other reasons such as cough or upper respiratory tract infections [93]. This strengthens our use of dispensed asthma medication as a good proxy for asthma and other obstructive respiratory disease.

2.4 Methodological discussion

2.4.1 Is traffic a cause of allergic asthma?

Traffic pollution was associated with allergic asthma in paper 2 but not with non-allergic asthma. The cross-sectional study design and lack of information on disease onset was a major limitation since we could not establish if traffic pollution causes childhood or adult disease, induces sensitization to allergens, leads to manifest disease among already allergic individuals or only acts as a direct or adjuvant trigger, all roles which have been suggested in the literature [94].

Is sensitization an intermediate variable in the effects of traffic on asthma?

This question has major analytical implications since many asthma studies actually often adjust for atopy or allergic factors despite their position in the causal chain, which formally excludes them from being a confounder [95]. Often the problem discussed concerns residual confounding, more seldom the problem with overadjustment (i.e. that when adjusting for risk factors that are only intermediary variables, studies may partly adjust away the effects) [95]. The heterogeneity in confounder control, where some studies adjust for sensitization and some do not, may be one factor contributing to inconclusive results in reviews of the effects between air pollution and asthma.

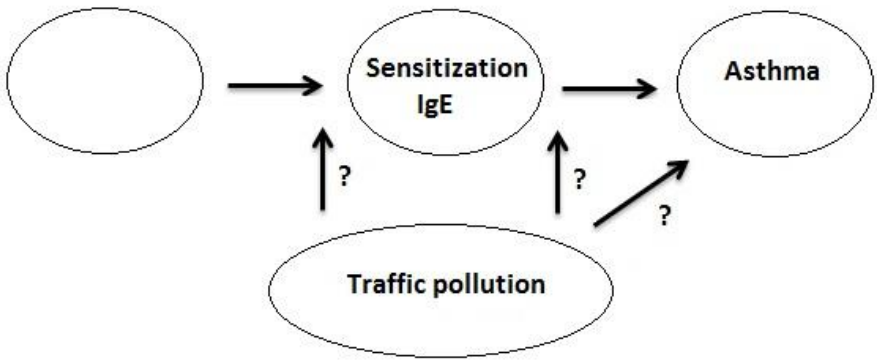

Figure 3.
Traffic pollution has been suggested both to induce sensitization, lead to disease among already sensitized as well as trigging existing asthma.

What elements that are independent risk factors can only be answered in longitudinal studies (establishing temporal associations). Cross-sectional studies, especially if containing both intermediary and end-point variables, however play an important role in the search for hypotheses to guide decisions for both longitudinal and experimental studies, since these studies cannot be optimally designed to account for more than a few factors. In our studies, the lack of intermediary endpoints, such as specific IgE is a limitation. Simple questions such as presence of atopic eczema in childhood may also give important etiological information in cross-sectional studies.

In paper 4 we could longitudinally follow a birth cohort population, and the lack of effect on chronic respiratory symptoms in early age (which mainly reflect non-allergic obstructive symptoms) may be consistent with the theory that traffic pollution would cause primarily allergic asthma. This cohort should be followed further longitudinally – if traffic exposure turns out to be associated with persistent or later-onset childhood asthma in these children, this could support an association with primarily allergic asthma, even if we lack specific IgE.

Relative risks /OR:s do not generally determine biologically susceptible groups

A problem (well known) in epidemiology is the tradition of testing interaction terms (or effect modification) in terms of relative effects while biological interaction in practice more often means an increase in absolute effects [96]. Since the absolute risk of asthma is higher in many subgroups such as smokers or atopics, if the relative effect due to traffic was the same for atopics as non-atopics, the absolute increase in number of cases due to traffic needs to be much larger in the atopic group. A larger OR in the atopic group means there is a larger both relative and absolute effect in that group but a larger OR in the non-atopic group only means that there is a larger relative effect. This is sometimes interpreted as "inconsistency" in the hypothesis that atopics are more sensitive to traffic.

A recent review of the effects of traffic and asthma [55] compared the effects for atopic vs non-atopics and noted that the effect of air pollution on asthma seemed stronger in atopics in two studies [57, 97] and in non-atopics in the third [98]. However, the study with stronger effect in non-atopics (the association between 10 ug/m^3 NO_2 and asthma incidence was OR= 1.57 for non-atopics, and OR= 1.31 for atopics) had an overall OR of 4.21 for the risk of asthma incidence in atopics compared to non-atopics. It is thus very likely that if absolute effects had been estimated and tested for, there had been a larger absolute risk in all three studies for atopics.

For the research on effects of air pollution on asthma and allergy to progress, it is important that all studies investigating susceptibility in subgroups should report also interactions in absolute risk estimates, to make it possible to compare literature in a sensical way.

The problem is also illustrated in Paper 1, when stratifying the effects of traffic on COPD for smokers vs non-smokers. By looking at the crude prevalence, there seems to be a much higher absolute increase with increasing traffic for smokers, but what is actually statistically tested is only interaction on an OR-scale (mulplicative scale), which is non-significant. However, a test for interaction on an additive scale had been more proper in this case [96, 99].

A calculation of relative excess risk due to interaction is a commonly used measure of additive interaction [99]; in the example from our study, a calculation of relative excess risk (RERI) without adjustment for confounders, gives a significant relative excess risk of COPD due to additive interaction between smoking and having a road with traffic intensity ≥10/cars min within 100m, RERI= 1.60 (Table 2). Similarly, the attributable proportion (AP) due to interaction between smoking and traffic intensity is also significant, but not the synergy index which was also calculated. Depending on what measure had been used, interaction between smoking and traffic thus could have turned out statistically significant in paper 1 if interaction had been tested on an additive scale.

Table 2.
If there is no additive interaction are RERI and AP equal to 0 and S is equal to 1.

Estimations of additive interaction: combined exposure to tobacco and traffic			
Measure	Estimate	Lower CI	Upper CI
RERI	1,604	0,227	2,981
AP	0,505	0,222	0,789
S	3,813	0,874	16,639

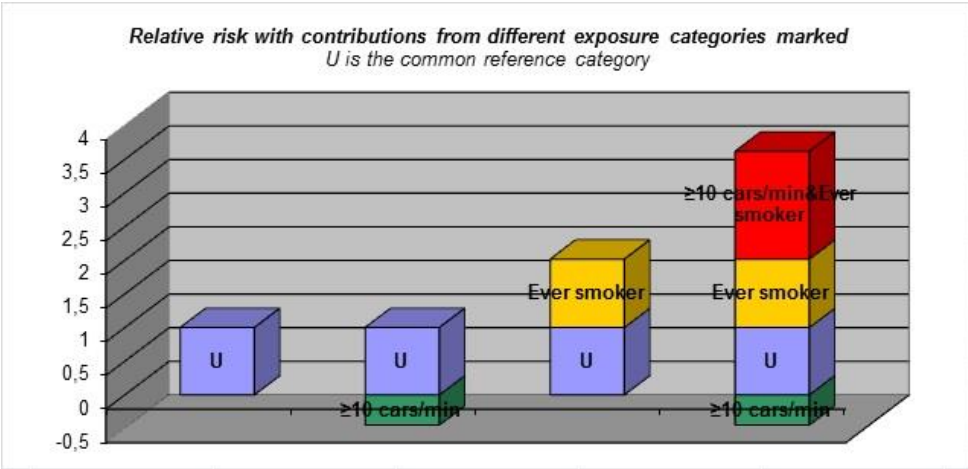

Figure 4.
Relative risk contributions from smoking, traffic and their interaction.

2.4.2 What factors prevented optimal confounder control?

In paper 4, there was a lower risk of asthma among those living close to traffic. This raises the question of potential unmeasured residual confounding factors. The question also remains if the positive results in Paper 1-3 could be due to confounding. I here discuss some of the problems inherent in air pollution epidemiology, investigating long-term effects, which were also encountered in the present studies and which prevented optimal confounder control.

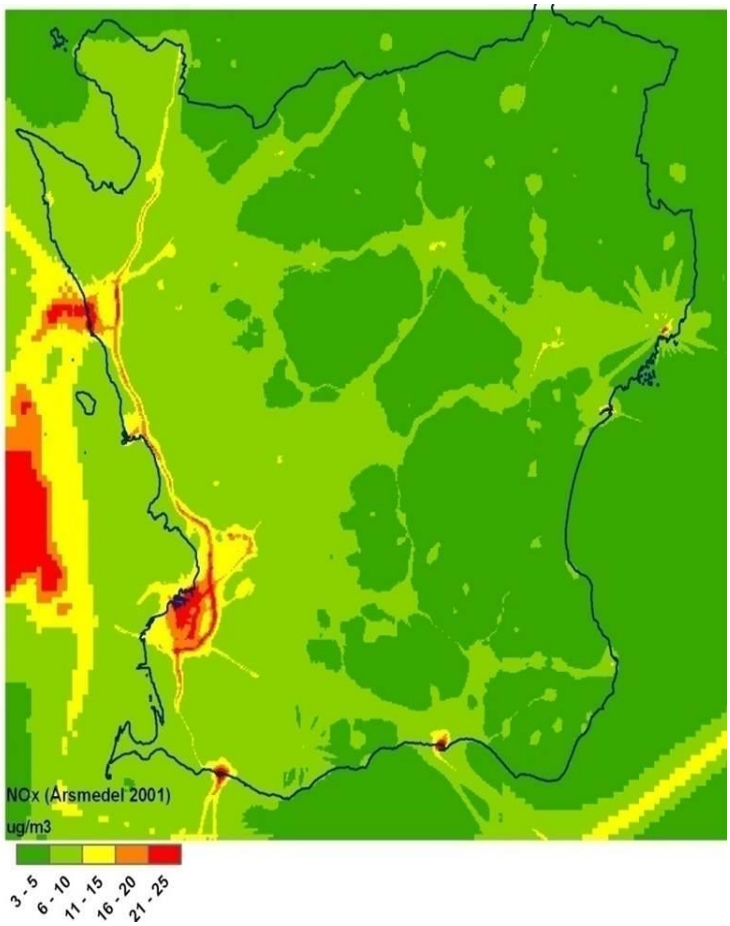

Figure 5.
High levels of NO_x (red) is mainly found in Malmö in Scania. On the lefthand side is Copenhagen (Denmark) in red, and some ferry traffic is visible in yellow.

Traffic pollution correlates with urban living

Exposure to air pollution from traffic highly correlates with living in cities, which means there is always a risk that effects of air pollution is confounded by other factors related to urban living. Even if collecting and adjusting for urban risk factors such as differences in smoking rates or occupation, unmeasured factors may remain. Common strategies to avoid this is study restriction to selected populations, post-stratification, that is to look separately at effects within in different areas (Paper 1), or statistical adjustment for different baseline risks within different communities (by dummy variables for urban versus rural, or by random effects in a multi-level paradigm).

However, to adjust statistically for urban-rural differences there must be comparable exposure ranges between the areas. When not, differences in baseline risk between cities because of different traffic exposure cannot be separated from differences in risk due to other factors. In our studies exposure distributions were very unbalanced. Basically, comparing high with low exposure means comparing Malmö with remaining area in paper 1. In paper 3 there is also a resulting "Urban versus Rural" comparison (figure 6) with potentially unmeasured confounding which can't be accounted for by analytical methods.

The consequences of potential unmeasured confounding, in the presence of unbalanced data, is not only that risk factors may cause a false positive effect. It is equally likely that risk factors may cancel each other out or even reverse the association, a special case of confounding known as Simpson's paradox [100].

That different baseline risks in city versus countryside may cancel out the effects of air pollution is not at all unlikely, since almost all ecological studies on asthma have failed to find any between-city associations with traffic pollution [101]. The inability to geographically stratify data in Paper 3 (since most municipalities had no high levels of traffic) to assess within-city effects, is thus a major limitation.

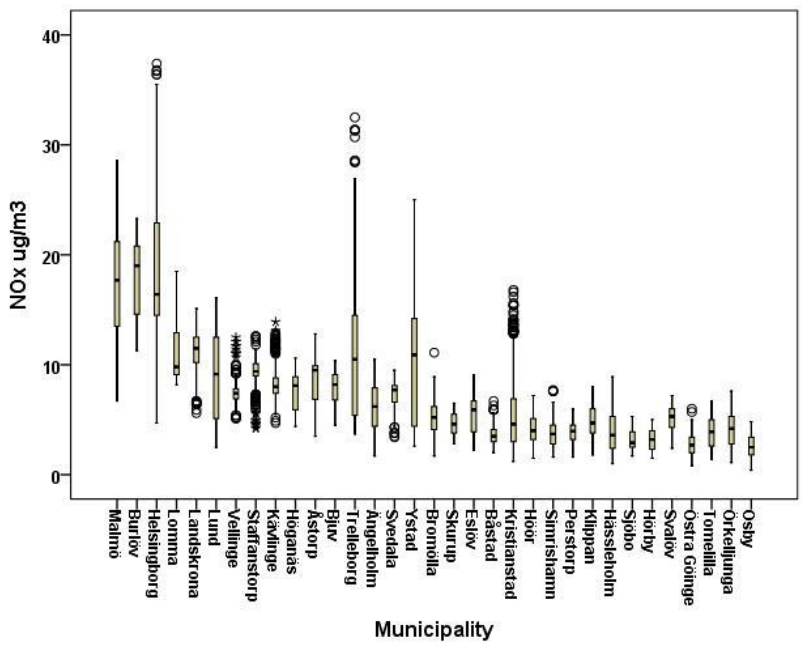

Figure 6.
NO_x distribution in the study population (Paper 3), sorted by population density in the municipality. Comparing the asthma prevalence for high NO_x vs low NO_x exposure basically means comparing individuals from Malmö with a reference category consisting of subjects from sparsely populated areas

Limited power because high levels of traffic exposure is rare

This problem is illustrated in Paper 3, which had a large total number of participants but still low statistical power. The power is mainly determined by the number of subjects in the group with least subjects (e.g. the number with high traffic exposure). The lack of power due to relatively few with high traffic exposure means that data cannot be stratified into relevant subgroups (even for factors which do have comparable exposure range) and analyses are restricted to looking at main effects. There is not enough power to test statistical interactions, and adjustments for more than single confounders are not particularly meaningful since multi-way tables quickly obtains null cells. In Paper 3, the rich data cannot entirely be utilized and the uncertainty shows off in wide confidence intervals.

Although the problem is exaggerated in paper 3 (Table 3) due to oversampling of small communities with low levels of air pollution in addition to generally low levels of pollution in Sweden, this is also a problem in many large European studies (like ECRHS [102] and SAPALDIA) which descriptively report subgroups but do not have power enough to test differences [97]. It has been acknowledged that most cohorts are initially started for other purposes and are not optimally designed for traffic-related air pollution [23].

Table 3.
Exposure distribution in Paper 3. Most participants had no heavy road nearby.

Residential address		1st Survey (2004)	2nd Survey (2005)
		n	n
Traffic intensity on heaviest road <50 m	No heavy road	18878	2100
	<2 cars/min	4514	472
	2-6 cars/min	1917	216
	6-10 cars/min	358	34
	≥10 cars/min	253	36

Unbalanced or rare exposure is only a problem when using a random study design and can easily be solved with biased sampling. The main advantage with tools like the emissiondatabase for NO_x is that in further studies balanced design can very easily be achieved at design stage, something which has not previously been possible with the same detail. Future studies should consider to ensure comparable exposure ranges in relevant subgroups such as socioeconomic groups (which can be obtained by register data) and oversample subjects in exposure ranges where effects previously have been

seen. It has been suggested that the efficiency can be improved in this type of studies by using two-phase designs [103].

2.4.3 How could other types of bias have affected the studies?

Self-selection and coverage selection bias in registry-based data

The Swedish prescribed drug register, despite its name, contains only information on dispensed drugs, and prescription date for dispensed drugs. No information is available of prescribed drugs that never has been dispensed. There is a lot of factors beyond the need for a certain drug that could affect the actual dispense, a conceptual framework has been provided by Weitoft et al (figure 6) [104].

The results in Paper 4, which indicates less dispense of asthma medication among children with parents with poor economy, raises the question if children in poor families do not get access to asthma treatment to the same extent as children in more well-off families.

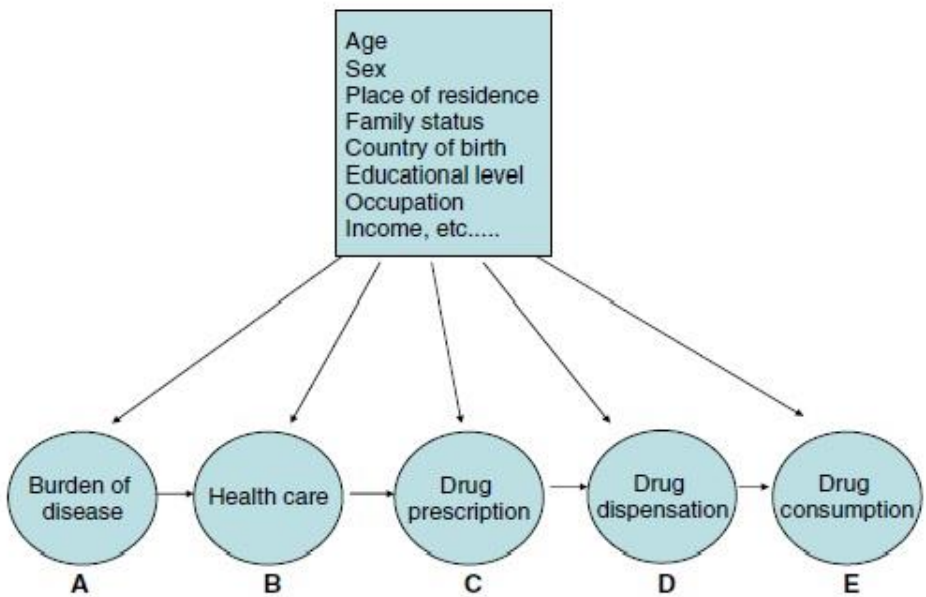

Figure 7.
A conceptual framework for investigating the relation between socioeconomic and demographic variables and drug use (Weitoft et. al. 2008)

There has been many studies linking low socio-economic status with higher drug use, but this is mainly because the disease burden is higher for those with low socio-economic status [104, 105]. At the same time, factors may be working in opposite

direction, since people with low socio-economic status may not seek health care or purchase drugs, because of the cost.

In Sweden there is a ceiling on the total amount that a patient pays during a 12-month period for pharmaceuticals, and health-care fees are low. A Swedish study, controlling for health status, identified three possible main explanations for a socio-economic gradient in drug utilization; doctor's prescription behavior, affordability and compliance [106]. In that study, high drug use was linked to high education level, but not linked to economic means after controlling for health status, so they conclude that doctor's prescription behavior and compliance are the main factors and that a good "patient-doctor" match in term of high socio-economic status, might be an important factor for the tendency of doctors to prescribe medication.

It is a difficult task to fully disentangle the potential extent of a selection bias caused by socio-economic status, since this would require access to not only dispensed and prescribed data, but one also would need to know the true disease status to account for different health-seeking behavior. This can only be available from outreaching studies. In absence of this kind of data, it may be equally important (as for self-reported data), that register studies adjusts for socio-economic status. Although the prescribed drug register may have "self-selection" bias due to different health seeking behavior and different drug dispense rate (in addition to"doctor's prescription bias"), which may differentially affect the dispense rate of different population groups, the coverage of the register is nearly 100%, which excludes selection bias due to bad coverage. This is a unique strength, since it actually covers principally all drugs that have ever been dispensed since 2005, in all population groups in Sweden.

The primary health care register data may suffer from coverage selection bias, since the number of visits with diagnostic codes on average was only 50.2% and also varied between health care centers, with private centers reporting 0% of the diagnostic codes. Since private visits may be related to both individual socio-economic status and the primary care center's neighborhood status - which may correlate with air pollution levels - a selection bias could exist. Future studies should obtain individual level information also on visits which did not get a diagnostic code, to better be able to investigate possible coverage selection bias in the primary health care data.

Finally it should be mentioned that a major advantage of register data in general, but especially of the prescribed drug register data (since it has complete coverage) is that it excludes recall bias and reduces awareness bias. The ability to exclude recall bias is especially important to avoid that long-term effects are confounded by current symptoms, something which may be the case in cohort studies with long time periods between follow-ups, when people might have forgotten symptoms if they don't currently have them. It has been shown in Sweden that adults with mild asthma tend to underreport their asthma compared to those with more severe asthma [107].

Migrational exposure misclassification and migrational selection bias

It is a major problem in cross-sectional studies (Paper 1- 3) that migrational bias can be expected to dilute the effects of traffic pollution and bias effects towards null, or even bias the effects away from null if there is differential misclassification. One study in northern Sweden did not find any differential misclassification in peoples migrational pattern [108], however this may not be generalizable to Scania.

In Paper 4, the risk of exposure misclassification due to migration is largely eliminated, since people are censored when they moved. Since people are censored, however, it is important to investigate that no bias instead is introduced due to this censoring. In a Dutch study, it was shown that migrants are healthier than permanent residents. However, when socioeconomic variables are controlled for, migrants appear to be less healthy, with the exception of the younger age groups [109]. In Sweden, it has also been shown that migrants across municipalities have lower mortality than non-migrants, a difference however that is not consistent after considering educational level. Among those with low education, non-migrants had the lowest mortality [110, 111]. Overall it is clear that moving may reflect socio-economic ability. There can therefore be an expected selection towards lower socio-economic status for those non-censored in higher ages. This is also the case for data in Paper 4; Out of children age 6 at study end that had never moved, 66.4% had a parent with >12 years education, compared to 74.5% of the children age 6 which had moved. This is not likely to be a major cause of bias in the study since we adjusted for education, but the above mentioned studies indicate that some differences in health status between migrants and non-migrants may remain after adjustment for socio-economic status. A strength is therefore that we also had information on NO_x exposure each year even after people had moved, and could make complementary analyses without censoring on migration.

In conclusion, the potential selection mechanisms due to migration may be important to keep in mind especially when expecting that the effect from traffic on asthma can be different in different age groups. Further analyses of how migration is related to air pollution levels in Scania would be of interest to investigate if censoring on migration could be a potential source of bias.

Other exposure misclassification bias

We used traffic intensity at the heaviest road within 100m, and dispersion-modeled concentrations of NO_x, at residential addresses, as exposure measures in all studies and consistently found associations with adult asthma (Paper 1-3) but not with asthma in children. Assuming that traffic is a true risk factor for asthma in adults, the results strengthens that our exposure measures were good enough for use in studies estimating effects of traffic pollution in low-dose areas. A validation study of out emission database have shown good agreement between modeled outdoor levels of NO_2 and façade measurements during one week (Spearman's $r=0.8$ and $p<0.01$),

which further strengthens the validity of modeled NO_x as exposure measure, even if it showed poorer agreement with personal exposure [79].

In paper 3, we estimated traffic intensity and NO_x not only at residential address, but also at occupational address, and self-reported time spent in traffic was also considered, but no association with asthma was seen except for traffic exposure at residential address. A combined estimate did not give stronger association with asthma. Validation studies including modeled levels of NO_2 at occupational address, in addition to modeled NO_2 at residential address, have had mixed results. In Scania, this did not improve the agreement with measured personal exposure [79], but in a study conducted in Stockholm it did markedly improve the agreement [112].

Most consistent effects were seen for high traffic intensity within 50 or 100m, which may speak in favor of this exposure proxy. However, the exposure measures were not comparable in our studies, since they differed in many aspects. The performance of NO_x as a proxy may depend on a number of modeling choices, such as the spatial resolution, the emission sources included in the modeling (e.g. only road traffic or total emission sources). There are no certain answers to what are the best chocies in this regard, since it is not known if air pollution exposure from road traffic is most detrimental or if other combustion sources such as industries, shipping are equally important. Optimal spatial resolution may also depend on a number of other factors, such as the geocoding accuracy. Misclassification of exposure may in best case only lead to reduced power, but could also lead to bias in the effect estimates [113].

It should be noted that depending on how the exposure proxies are constructed, not only exposure but also reference categories may change. In paper 3, it is possible that unmeasured urban-rural confounding was stronger when accounting for total exposure since we were then comparing more pronounced rural living (not only living but also working within low levels of air pollution) with more pronounced urban living.

In conclusion, if we assume that the associations found in Paper 1-3 are due to a true effect, it seems that both traffic intensity at residential address and modeled NO_x (250x250m) at residential address are good enough measures to find effect on chronic respiratory disease in a low-dose area. However, the effects of NO_x were mainly statistically non-significant and future studies may consider to model only NO_x from traffic sources.

3 Conclusions

Associations between traffic and prevalence of asthma, COPD and allergic rhinitis in adults were found in an area with background levels of air pollution below the current WHO-guidelines. This indicates that the guidelines do not provide safe levels to protect against adverse effects on chronic respiratory disease in adults.

Traffic pollution was associated with current allergic asthma and allergic rhinitis, but not with asthma or rhinitis triggered by non-allergic factors. An association was also seen with prevalence of hand-eczema last 12 months. The results in this study suggest that traffic is related to allergic disease in adults.

Asthma in adults was associated with traffic at home-address but not with traffic at work-address, daily time spent outdoor in traffic, or a combined exposure estimate. This is likely to partly reflect the larger uncertainties when estimating non-residential exposure, but it may also reflect that residential exposure is the most influential exposure determinant for adults.

Growing up close to dense traffic was not associated with increased incidence of asthma medication, or incidence of asthma diagnosis, obstructive bronchitis diagnosis, or bronchiolitis diagnosis, in children 0-6 years. This may reflect that early wheeze is mainly virus-associated, and may have other causes than traffic, in contrast to asthma in older childhood years, which has more often been associated with traffic.

3.1 What have we learned for future studies?

Traffic intensity on heaviest road within 100m, and modeled NO_x, both seems to be good enough measures to find effect on chronic respiratory disease in a low-dose area. However, the effects of NO_x were mainly statistically non-significant. Future studies should consider to model only NO_x from traffic sources.

It is important to ensure at the design stage that enough contrast in traffic exposure is obtained not only in the study as a whole, but also in different subgroups. This is important to be able to optimally control for confounding and to be able to investigate effect modification between subgroups. Since high traffic exposure is rare in Scania a random study design will often give low power for testing hypotheses regarding traffic exposure.

Comparisons of the effect of traffic on allergic vs non-allergic asthma and other subgroups should not be reported/tested as relative risks (OR:s) if they do not have the same reference group, but rather focus on differences and interactions in absolute terms.

The main advantage with register data is the avoidance of recall bias which may otherwise confound short-term with long-term effects, and the decrease in awareness bias which may otherwise give false positive effects. However, adjusting for socio-economic status to avoid bias may be equally important in register-studies as in studies based on self-reported data. More information on socio-economic status and other covariates should be collected from register data to be able to utilize all of the outcome register data in Scania and not have analyses limited to groups with questionnaire data.

Socio-economic selection may also emerge due to censoring on migration. Movers should therefore preferably not be censored but be followed with yearly updated exposure estimates for both NO_x and road traffic.

4 Sammanfattning på svenska

Samband mellan exponering för trafikrelaterade luftföroreningar i Skåne och förekomst av kronisk luftvägssjukdom och allergi

Det har länge varit känt att förhöjda halter av luftföroreningar från trafik kan förvärra luftvägssymtom och ge upphov till ökat antal sjukhusinläggningar på grund av astma och kronisk obstruktiv lungsjukdom(KOL). Mer omtvistat har varit om trafikens luftföroreningar också är en direkt orsak till att dessa sjukdomar uppkommer. Ett problem när man vill studera långtidseffekter av trafik har tidigare varit att hitta bra exponeringsmått på individnivå. Det är numera lättare, eftersom man med geografiska informationssystem (GIS) har fått verktyg för att kunna hantera stora datamänger som varierar i tid och rum, och kan knyta dessa data till hälsodata för stora befolkningsgrupper.

Våra studier har haft till syfte att undersöka om boende nära trafik är en riskfaktor för övre/nedre kronisk luftvägssjukdom och allergi bland barn och vuxna i Skåne, som är ett område med förhållandevis låga halter av luftföroreningar, sett ur ett internationellt perspektiv.

Förekomsten av astma och andra luftvägssjukdomar bland vuxna kartlades genom enkätstudier, Två av avhandlingens delarbeten är baserade på en enkät som år 2000 hade sänt till 9319 personer, 18-77 år gamla, som var bosatta i sydvästra Skåne. I ett tredje delarbete används både den stora skånska folkhälsoenkät som år 2004 besvarades av 24819 personer, 18-80 år gamla, och ett urval av 2856 personer med och utan astma, som 2005 besvarade en kompletterande enkät.

I det fjärde delarbetet, som handlar om obstruktiva luftvägssjukdomar bland barn 0-6 år, studerades 26128 barn från Malmö och tre närliggande kommuner. Uppgifter om luftvägssjukdom hämtades dels från vårdregister från primärvård och sjukhusvård (diagnoser), dels från läkemedelsregistret (användning av astmamediciner). För 7898 barn fanns dessutom uppgifter från en barnhälsoenkät från BVC-besök vid 8 månaders ålder.

Studiedeltagarnas personnummer används för att koppla ihop enkät- och registerinformation med information om var bostaden var belägen. Med hjälp av GIS kunde vi sedan koppla bostadskoordinater till den svenska vägdatabasen, som innehåller uppgifter om koordinater och trafikintensitet för alla större vägar, och till en skånsk emissionsdatabas för kväveoxider (NO_x, en indikator för trafikens luftföroreningar).

Vuxna i Skåne, som bodde nära starkt trafikerad väg (≥8640 bilar/dygn), hade oftare astma och KOL jämfört med dem som inte var exponerade för trafik vid bostaden. Effekt sågs tydligt vid halter av NO_x som var > 19µg/m^3. Vi studerade olika undertyper av astma och näsbesvär, och fann att det främst var de som hade allergisk astma och allergiska näsbesvär som utlöstes av pollen eller pälsdjur som påverkades av trafik. Vi hittade också ett samband mellan exponering för trafikens luftföroreningar och förekomst av eksem.

Vi undersökte även om trafikens luftföroreningar vid arbetsplatsen och under pendlingsresor och annan tid i trafik också var associerade med astma. Vi fann dock inga säkerställda samband. Det kan delvis förklaras av att osäkerheten var större för dessa exponeringsmått, men det kan också vara så att tiden då man vistas i bostaden har störst betydelse för graden av exponering för trafikavgaser.

Barn som under perioden 2005-2010 föddes och växte upp i sydvästra Skåne, och som bodde nära starkt trafikerade vägar eller i områden med höga halter NO_x, hade inte högre risk för att få astma eller andra luftvägsbesvär jämfört med barn som inte växte upp nära trafik. Att ingen effekt av trafikens luftföroreningar sågs för barn kan bero på att astmatiska besvär/ besvär med trånga luftrör i tidiga barnaår oftast beror på virusinfektioner. Det kan vara så att luftföroreningar från trafik kanske inte har så stor effekt på denna typ av besvär vid de halter – i internationellt perspektiv ganska låga – som finns i vårt land. Andra vetenskapliga studier har dock visat på en koppling mellan trafik och utveckling av astmatiska besvär bland barn. Det är därför angeläget att fortsätta att följa dessa barn under uppväxttiden, för att se om de möjligen får en ökad risk för astma när de kommer upp i skolåldern.

Sammanfattningsvis har vi i dessa studier visat att vuxna i Skåne, som bor nära trafikerade vägar och i områden med högre halter av luftföroreningar från trafik oftare har allergisk astma, allergiska näsbesvär och KOL samt eksem, jämfört med dem som är mindre exponerade för trafikens luftföroreningar. Däremot fann vi inte att sådana luftföroreningar var en riskfaktor för astma eller andra besvär med trånga luftrör hos barn 0-6 år gamla, som bodde i Malmö med omnejd.

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Paper I

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Traffic-related air pollution associated with prevalence of asthma and COPD/chronic bronchitis. A cross-sectional study in Southern Sweden

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Abstract

Background: There is growing evidence that air pollution from traffic has adverse long-term effects on chronic respiratory disease in children, but there are few studies and more inconclusive results in adults. We examined associations between residential traffic and asthma and COPD in adults in southern Sweden. A postal questionnaire in 2000 (n = 9319, 18–77 years) provided disease status, and self-reported exposure to traffic. A Geographical Information System (GIS) was used to link geocoded residential addresses to a Swedish road database and an emission database for NOx.

Results: Living within 100 m of a road with >10 cars/minute (compared with having no heavy road within this distance) was associated with prevalence of asthma diagnosis (OR = 1.40, 95% CI = 1.04–1.89), and COPD diagnosis (OR = 1.64, 95%CI = 1.11–2.4), as well as asthma and chronic bronchitis symptoms. Self-reported traffic exposure was associated with asthma diagnosis and COPD diagnosis, and with asthma symptoms. Annual average NOx was associated with COPD diagnosis and symptoms of asthma and chronic bronchitis.

Conclusion: Living close to traffic was associated with prevalence of asthma diagnosis, COPD diagnosis, and symptoms of asthma and bronchitis. This indicates that traffic-related air pollution has both long-term and short-term effects on chronic respiratory disease in adults, even in a region with overall low levels of air pollution.

Background

Traffic-related air pollution is well known to have short-term effects on chronic respiratory disease, exacerbating symptoms and increasing hospital admissions for respiratory causes [1]. Strong effects on symptoms have also been observed in areas with relatively low background pollution [2]. Long-term effects have been disputed, but there is growing evidence that traffic-related air pollution is related, at least among children, to asthma incidence [3-7], decreased lung function development [8,9], and incidence of bronchitic symptoms [4,10].

In adults, studies of long-term effects from traffic-related air pollution have been few, and recent studies have found both positive [11-15] and negative [16-18] associations with asthma, as well as positive [16,19,20] and negative [13,14] associations with COPD. Overall, chronic respiratory disease in adults is heterogenous and involves major exposures, such as personal smoking and occupational exposure, which do not directly affect children. This larger variety of risk factors may complicate research and contribute to inconclusive results in adults.

Self-reported living close to traffic has been associated with prevalence of asthma, but not COPD, among adults in southern Sweden [14]. However, self-reports could be severely biased if people are more aware of (and hence over-report) exposures that are known to be potentially connected to disease, and may not be trustworthy if used as the only exposure estimate [21].

One way of obtaining objective exposure estimates is the use of Geographical Information Systems (GIS) to combine geocoded population data with external traffic exposure data, such as road networks and modeled or monitored traffic pollutants. Since the concentrations of many traffic pollutants decline to background levels within 30–200 m of a road, the level of spatial aggregation may be just as important as the type of proxy when estimating exposure [22,23]. Some studies have found that adverse effects on respiratory disease are best captured with simple variables of traffic density and proximity to roads [24], rather than more complex models of specific pollutants, which are difficult to model with a high resolution. However, air pollutant models do have a number of advantages; for example, they can account for total traffic density, and can also be validated against real measurements, providing more specific estimates of the level of pollution at which adverse effects from traffic can be seen.

In the present study, we made use of a high quality GIS-modeled pollutant database for nitrogen oxides (NO_x and NO_2) which has been developed and validated for southern Sweden [25]. The high spatial variability of NO_x ($NO+NO_2$), with traffic as the dominating source, makes it a better proxy for exposure to traffic at the local level, compared with pollutants such as $PM_{2.5}$ which have a more geographically homogenous spread [26]. We also used GIS-based road data and self-reported living close to heavy traffic as proxies for exposure.

Study aim

The aim of this study was to investigate the association between traffic-related air pollution and asthma and COPD in adults. The outcomes investigated were prevalence of; 1) asthma diagnosis 2) COPD diagnosis 3) asthma symptoms last 12 months, and 4) chronic bronchitis symptoms, in relation to residential traffic exposure.

Methods

Study area

The study area was the most southwestern part of Sweden (figure 1), the most populated part of the county of Scania. The study area contains 840 000 of Sweden's total population of 8.9 million, and has a population density of 170 inhabitants per km^2 (data from 2000). The majority of the population live in six of the communities, the largest of which is Malmö, the third largest city in Sweden, with a population of 260 000. A detailed regional description has previously been given [27]. In the geographical stratification of the present study, "Malmö" refers strictly to the city boundaries of Malmö, not the larger municipality.

The climate in the region is homogenous. Although pollutant levels in the region are low in an European context, they are higher than in the remainder of Sweden [28], due to long-range transport of pollutants from the continent and extensive harbor and ferry traffic.

Study population & questionnaire

In 2000, a questionnaire was sent to a total of 11933 individuals aged 18–77, of whom 9319 (78%) answered. The study population originated from two different study populations, with 5039 (response rate: 71%) from a new random selection, and 4280 (response rate: 87%) constituting a follow-up group from an earlier selection [29].

The questionnaire dealt with respiratory symptoms, potential confounders such as smoking habits and occupation, and exposures such as living close to a road with heavy traffic [29]. An external exposure assessment was also obtained by geocoding the residential addresses (as of 2000) of both respondents and non-respondents. This was achieved by linking each individual's unique 10-digit personal identity codes to a registry containing the geographical coordinates of all residential addresses.

Non-respondents had a higher mean of NO_x than respondents; 14.7 $\mu g/m^3$ versus 13.5 $\mu g/m^3$. To a large extent this was due to a lower response rate in the more polluted city of Malmö (73% vs. 80% in the remaining region).

Outcome measures

The following outcomes were investigated, as obtained by the postal questionnaires:

• *Diagnosis of asthma*. "Have you been diagnosed by a doctor as having asthma?"

Figure 1
Study area. Malmö is the largest city in the study region, which comprises the southwestern part of Sweden.

• *Diagnosis of COPD/CBE (Chronic Bronchitis Emphysema)*. "Have you been diagnosed by a doctor as having chronic bronchitis, emphysema, or COPD?"

• *Asthma symptoms during the last 12 months*. "Have you had asthma symptoms during the last 12 months, i.e. intermittent breathlessness or attacks of breathlessness? The symptoms may exist with or without cough or wheezing."

• *Chronic bronchitis symptoms*. "Have you had periods of at least three months where you brought up phlegm when coughing on most days?", and if so, "Have you had such periods during at least two successive years?"

The questionnaire has been published previously [29]. No information regarding year of disease onset was available.

Exposure assessment

Exposure to traffic-related air pollution was assessed at each participant's residential address in 2000, using three different proxies:

1. Self-reported exposure to traffic. This was obtained from the survey. Exposure was defined as a positive answer to the question "*Do you live close to a road with heavy traffic?*"

2. Traffic intensity on the heaviest road within 100 m. GIS-based registers from *The Swedish National Road Database* [30] provided information about traffic intensity for all major roads in the county (figure 2). To assess exposure to traffic, we identified the road with the heaviest traffic intensity within 100 m of the residence. Traffic intensity was categorized as 0–1 cars/min, 2–5 cars/min, 6–10 cars/min, and >10 cars/min, based upon 24-hour mean levels.

3. Modeled exposure to NO_x (figure 3). Annual mean concentrations of NO_x were acquired from a pollutant database, based on the year 2001 [25,31]. Emission sources included in the model were: road traffic, shipping, aviation, railroad, industries and larger energy and heat producers, small scale heating, working machines, working vehicles, and working tools. Meteorological data were also included. A modified Gaussian dispersion model (AERMOD) was used for dispersion calculations; a flat two-dimensional model which did not adjust for effects of street canyons or other terrain, but which did take the height of the emission sources into consideration. Concentrations of NO_x were modeled as annual means on a grid with a spatial resolution of 250 × 250 m. Bilinear interpolation was used to adjust individual exposure with weighted values of neighboring area concentrations. Concentrations modeled with this spatial resolution have been validated and found to have a high correlation with measured values in the region [25,31].

Statistics

A categorical classification of NO_x was used in order to allow analysis of non-linear associations with outcomes. To determine the category limits, the subjects (n = 9274) were divided into NO_x-quintiles. The five exposure groups used were 0–8 μg/m^3, 8–11 μg/m^3, 11–14 μg/m^3, 14–19 μg/m^3, and >19 μg/m^3.

For all measures of exposure, subgroup analyses were made for Malmö and the remaining region. Relative risk was not estimated in exposure groups with fewer than 50 individuals. As few individuals in Malmö had a low exposure to NO_x, the middle exposure group was used as the reference category for NO_x, in Malmö. Because of this, NO_x was also used as a continuous variable for trend analysis using logistic regression. A p-value < 0.05 was regarded as evidence of a trend. Stratified analyses were performed for sex, age, smoking, geographical region (Malmö vs. remaining region), and study population (new random selection vs. follow-up group). Sensitivity analyses of the associations with traffic were also performed by restricting the groups to those with asthma but not COPD, and COPD but not asthma, to exclude confounding by comorbidity. This process was also followed for symptoms.

Relative risk was estimated using Odds Ratios (ORs) with 95% Confidence Intervals (CI). Odds Ratios and tests of trends were obtained by binary logistic regression, using version 13.0 of SPSS.

Sex, age (seven categories), and smoking (smokers/ex-smokers vs. non-smokers) are known risk factors for asthma, and were therefore adjusted for in the model. Socio-Economic Indices (SEI codes, based on occupational status [32]) and occupational exposure (ALOHA JEM [33]) were tested as confounders, using the "change-in-estimate" method [34], where a change in the OR of 10% would have motivated an inclusion in the model.

Neither occupational exposure nor Socio-Economic Indices fulfilled the predetermined confounder criteria, or had any noticeable impact on the risk estimates, and were thus not included in the model.

Results

A description of the study population in terms sex, age, and smoking, along with the associations with the outcomes, is presented in table 1.

Association with self-reported living close to traffic

Asthma diagnosis and asthma symptoms in the last 12 months were associated with self-reported traffic exposure

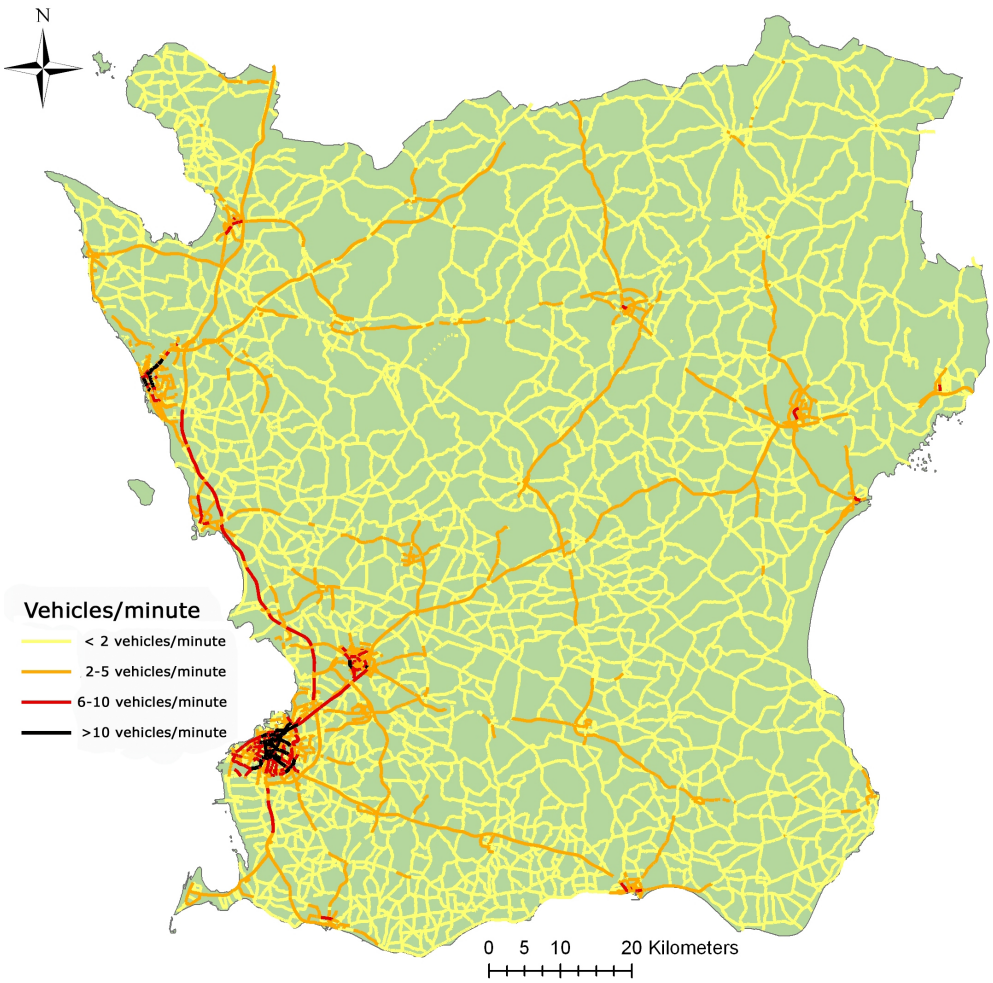

Figure 2
Regional road network. Data from the Swedish National Road Network. No heavy road means that no registered road was available in the database, but local traffic could exist. The traffic intensity categories of (0–1, 2–5, 6–10, >10) cars/min corresponds to daily mean traffic counts of (0–2880, 2880–8640, 8640–14400, >14400) cars/day.

(table 2). These results were consistent in a geographical stratification (tables 3, 4).

COPD diagnosis was associated with self-reported traffic exposure, both for the whole region (table 5) and when geographically stratified (table 6). Chronic bronchitis symptoms were not associated with self-reported traffic exposure (tables 5, 7).

Association with traffic intensity on heaviest road within 100 m

Asthma diagnosis and asthma symptoms were associated with traffic intensity (table 2), with higher prevalence of

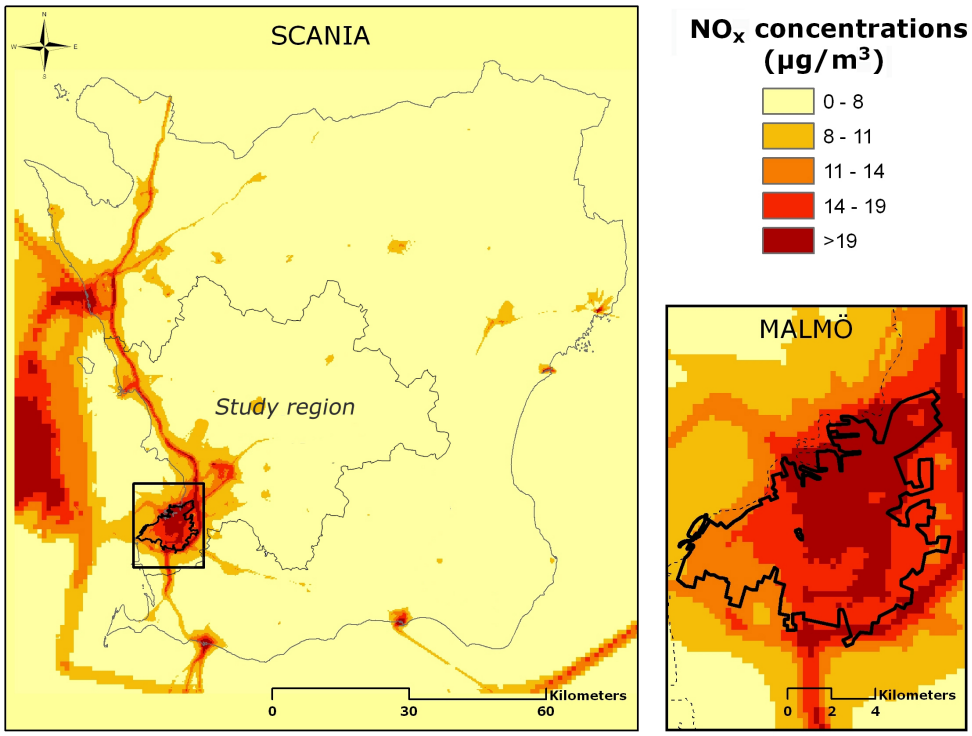

Figure 3
Modeled levels of NO_x Dispersion modeled annual average of NO_x, modeled with a resolution of 250 × 250 m.

asthma symptoms among those living next to a road with at least 6 cars/minute, and higher prevalence of asthma diagnosis among those exposed to at least 10 cars/minute, compared with the group having no road within 100 m. The effects seemed consistent, although statistically non-significant, across geographical region (tables 3, 4).

COPD and chronic bronchitis symptoms were associated with traffic intensity (table 5). However, when stratified geographically, the effect estimates indicated that chronic bronchitis symptoms were not associated with traffic intensity in Malmö (table 7).

Association with NO_x at residential address

Asthma symptoms, but not asthma diagnosis, were associated with NO_x in the trend tests (table 2). However, effects were only seen in the highest quintile of >19 µg/m³. A geographical stratification showed that it was only in Malmö that high exposure was associated with asthma; no association was found in the region outside (tables 3, 4).

COPD diagnosis and chronic bronchitis symptoms were associated with NO_x(table 5). After geographical stratification, associations were seen only in Malmö, and not in the region outside (tables 6, 7).

Stratification by smoking, sex, age, response group, and restricted analysis

In a stratified analysis, the effects of traffic exposure were more pronounced for smokers than for non-smokers, for both COPD (table 8) and bronchitis symptoms (data not shown). A test for interaction, however, showed no significance except for the interaction between smoking and road within 100 m for chronic bronchitis symptoms (p =

Table 1: Description of study population. Disease prevalence in relation to sex, age, and smoking.

		n	Diagnosed asthma	Asthma symptoms	Diagnosed COPD	Chronic b. symptoms
Sex	Men	4341	258(5.9%)	429(9.9%)	172(4.0%)	308(7.1%)
	Women	4975	428(8.6%)	686(13.8%)	243(4.9%)	327(6.6%)
Ever smoker	No	4306	291(6.8%)	431(10.0%)	118(2.7%)	217(5.0%)
	Yes	5010	395(7.9%)	684(13.7%)	297(5.9%)	418(8.3%)
Age	18–19	135	15(11.1%)	23(17%)	3(2.2%)	9(6.7%)
	20–29	1062	110(10.4%)	141(13.3%)	19(1.8%)	41(3.9%)
	30–39	2045	158(7.7%)	246(12.0%)	61(3.0%)	108(5.3%)
	40–49	1887	112(5.9%)	217(11.5%)	69(3.7%)	101(5.4%)
	50–59	2123	142(6.7%)	237(11.2%)	106(5.0%)	185(8.7%)
	60–69	1586	113(7.1%)	178(11.2%)	115(7.3%)	139(8.8%)
	70–77	478	36(7.5%)	73(15.3%)	42(8.8%)	52(10.9%)

0.023). Asthma showed no indications of effect modification by smoking.

No effect modifications were seen when the data were stratified by sex, age, or sample group (new participants vs. follow-up group). Restriction of analysis to asthmatics without COPD, and to those with COPD without asthma, was performed for both diagnoses and symptoms. The results showed similar effects in the restricted and non-restricted groups. The overlaps between the different disease outcome definitions are presented in table 9.

Discussion

Overall, residential traffic was associated with a higher prevalence of both asthma diagnosis and asthma symptoms in the last 12 months, as well as COPD diagnosis and chronic bronchitis symptoms. Traffic intensity on the heaviest road within 100 m showed effects at a traffic intensity of >6 cars/min. Effects from NO_x were seen in the highest exposure quintile of >19 μg/m³, but only in Malmö, not in the region outside.

Discussion of exposure assessment

The major strength of this study was the use of three different proxies of exposure, which may have different intrinsic strengths and weaknesses. The strengths of the NO_x model are firstly that it reflects total traffic density in the area, and secondly the fact that the dispersion model has been validated, with a resolution of 250 × 250 m showing a high correlation with measured background concentrations [25]. Nevertheless, street-level concentrations may vary on a much smaller scale. High peak concentrations are often found in so-called "street canyons" in urban areas, where pollutants are trapped between high buildings [23]. Since the dispersion model did not take account of this kind of accumulation effect, the true expo-

Table 2: Asthma diagnosis and asthma symptoms in relation to traffic.

		Asthma Diagnosis			Asthma Symptoms		
		n	n (%)	OR [a]	n	n (%)	OR [a],
Heavy traffic	No	6041	400(6.6%)	1.00	6041	668(11.1%)	1.00
	Yes	3275	286(8.7%)	1.28(1.09–1.50)	3275	447(13.6%)	1.22(1.07–1.39)
Heaviest road within <100 m	no heavy road	3755	269(7.2%)	1.00	3755	419(11.2%)	1.00
	<2 cars/min	2235	149(6.7%)	0.92(0.75–1.13)	2235	263(11.8%)	1.05(0.89–1.24)
	2–5 cars/min	1820	134(7.4%)	1.00(0.81–1.25)	1820	216(11.9%)	1.06(0.89–1.26)
	6–10 cars/min	886	69(7.8%)	1.05(0.79–1.38)	886	126(14.2%)	1.25(1.01–1.55)
	>10 cars/min	578	61(10.6%)	1.40(1.04–1.89)	578	85(14.7%)	1.29(1.00–1.67)
NO_x (μg/m³)	0–8	1855	140(7.5%)	1.00	1855	217(11.7%)	1.00
	8–11	1855	146(7.9%)	1.04(0.82–1.32)	1855	213(11.5%)	0.97(0.80–1.19)
	11–14	1855	124(6.7%)	0.85(0.66–1.09)	1855	208(11.2%)	0.94(0.77–1.15)
	14–19	1858	115(6.2%)	0.77(0.60–1.00)	1858	206(11.1%)	0.90(0.74–1.11)
	>19	1851	157(8.5%)	1.05(0.83–1.34)	1851	265(14.3%)	1.21(0.99–1.46)
			p-trend	0.84		p-trend	0.026

[a] Adjusted for age, sex, and smoking. [OR(95%CI)].

Table 3: Geographical stratification. Asthma diagnosis in the city of Malmö and the area outside.

		Malmö			Region outside Malmö		
		n	Asthma diagnosis	OR [a]	n	Asthma diagnosis	OR [a]
Heavy traffic	No	1767	109(6.2%)	1.00	4178	283(6.8%)	1.00
	Yes	1877	161(8.6%)	1.35(1.05–1.75)	1343	119(8.9%)	1.28(1.02–1.61)
Heaviest road within <100 m	no heavy road	586	40(6.8%)	1.00	3124	224(7.2%)	1.00
	<2 cars/min	1021	66(6.5%)	0.95(0.63–1.43)	1193	82(6.9%)	0.95(0.73–1.23)
	2–5 cars/min	837	57(6.8%)	0.99(0.65–1.51)	961	75(7.8%)	1.07(0.81–1.40)
	6–10 cars/min	663	50(7.5%)	1.12(0.72–1.72)	212	19(9.0%)	1.21(0.74–1.99)
	>10 cars/min	537	57(10.6%)	1.50(0.98–2.31)	31	2	-
NO_x (μg/m^3)	0–8	13	1	-	1824	138(7.6%)	1.00
	8–11	46	5	-	1792	138(7.7%)	1.01(0.79–1.30)
	11–14	562	39(6.9%)	1.00	1268	83(6.5%)	0.81(0.61–1.08)
	14–19	1325	76(5.7%)	0.79(0.53–1.18)	510	37(7.3%)	0.93(0.64–1.36)
	>19	1698	149(8.8%)	1.18(0.81–1.71)	127	6(4.7%)	0.58(0.25–1.34)
			p-trend	0.044		p-trend	0.079

[a] Adjusted for age, sex, and smoking. [OR(95%CI)].

sure among people living in these surroundings might have been underestimated. This may partly explain why effects from NO_x were seen in the urban city of Malmö but not in the surrounding area.

The proportion of NO_x that originates from traffic is also dependent on geographical area. In urban areas of southern Sweden, local traffic contributes approximately 50–60% of total NO_x, while in the countryside such traffic is responsible for only 10–30% of total NO_x (S. Gustafsson, personal communication, 2007-10-17). This difference was also reported by the SAPALDIA study, which found that local traffic accounted for the majority of NO_x in urban but not rural areas [35]. This indicates that our model of NO_x is a good proxy for exposure to traffic-related air pollution in an urban area, but may not be sensitive enough to capture individual risk in the countryside, where traffic contributes to a lower proportion of total concentrations.

Self-reported living close to a road with heavy traffic, and traffic intensity on the heaviest road within 100 m, are simple proxies; they do not reflect, for example, whether someone lives at a junction. Still, they have the advantage that they are less limited by aggregation in space than the NO_x model. In the present study, both of these variables

Table 4: Geographical stratification. Asthma symptoms in the city of Malmö and the region outside.

		Malmö			Region outside Malmö		
		n	Asthma symptoms	OR [a]	n	Asthma symptoms	OR [a]
Heavy traffic	No	1767	209(11.8%)	1.00	4178	449(10.7%)	1.00
	Yes	1877	263(14.0%)	1.17(0.96–1.43)	1343	178(13.3%)	1.23(1.02–1.49)
Heaviest road within <100 m	No heavy road	586	74(12.6%)	1.00	3124	342(10.9%)	1.00
	<2 cars/min	1021	119(11.7%)	0.93(0.68–1.26)	1193	142(11.9%)	1.09(0.88–1.34)
	2–5 cars/min	837	101(12.1%)	0.97(0.70–1.33)	961	112(11.7%)	1.06(0.84–1.33)
	6–10 cars/min	663	97(14.6%)	1.17(0.85–1.63)	212	29(13.7%)	1.24(0.82–1.87)
	>10 cars/min	537	81(15.1%)	1.19(0.84–1.68)	31	2	-
NO_x (μg/m^3)	0–8	13	1	-	1824	215(11.8%)	1.00
	8–11	46	6	-	1792	205(11.4%)	0.96(0.79–1.18)
	11–14	562	65(11.6%)	1.00	1268	142(11.2%)	0.93(0.74–1.16)
	14–19	1325	146(11.0%)	0.90(0.66–1.23)	510	57(11.2%)	0.95(0.69–1.29)
	>19	1698	254(15.0%)	1.28(0.95–1.72)	127	8(6.3%)	0.50(0.24–1.04)
			p-trend	0.002		p-trend	0.344

[a] Adjusted for age, sex, and smoking. [OR (95%CI)].

Table 5: COPD diagnosis and chronic bronchitis symptoms in relation to traffic.

		COPD Diagnosis			Chronic bronchitis symptoms		
		n	n, (%)	OR [a]	n	n, (%)	OR [a]
Heavy traffic	No	6041	243(4.0%)	1.00	6041	401(6.6%)	1.00
	Yes	3275	172(5.3%)	1.36(1.10–1.67)	3275	234(7.1%)	1.11(0.94–1.31)
Heaviest road within <100 m	no heavy road	3755	153(4.1%)	1.00	3755	222(5.9%)	1.00
	<2 cars/min	2235	95(4.3%)	1.04(0.80–1.35)	2235	159(7.1%)	1.21(0.98–1.50)
	2–5 cars/min	1820	71(3.9%)	0.96(0.72–1.28)	1820	137(7.5%)	1.30(1.04–1.62)
	6–10 cars/min	886	60(6.8%)	1.57(1.15–2.14)	886	67(7.6%)	1.24(0.93–1.65)
	>10 cars/min	578	34(5.9%)	1.64(1.11–2.41)	578	48(8.3%)	1.53(1.10–2.13)
NO_x ($\mu g/m^3$)	0–8	1855	74(4.0%)	1.00	1855	110(5.9%)	1.00
	8–11	1855	68(3.7%)	0.89(0.63–1.24)	1855	118(6.4%)	1.05(0.81–1.38)
	11–14	1855	87(4.7%)	1.19(0.86–1.64)	1855	121(6.5%)	1.12(0.86–1.46)
	14–19	1858	83(4.5%)	1.03(0.74–1.42)	1858	122(6.6%)	1.06(0.81–1.39)
	>19	1851	101(5.5%)	1.43(1.04–1.95)	1851	162(8.8%)	1.55(1.21–2.00)
			p-trend	0.010		p-trend	<0.0001

[a] Adjusted for age, sex, and smoking. [OR(95%CI)].

showed fairly consistent associations, at least with asthma, despite large differences in the level of NO_x that they corresponded to in Malmö and the region outside (table 10); this may indicate that adverse effects from traffic pollutants are mainly seen in close proximity to traffic. High traffic intensity, however, may not only correlate with high total number of vehicles, but also with a higher proportion of heavy vehicles, an additional factor which could affect the outcome, since diesel exhaust from heavy vehicles might have more adverse respiratory effects [36].

It should be noted that the distribution of exposure is not comparable between the proxies. While NO_x was divided into quintiles, with 20% in the highest exposure category, only 6% of the population lay in the highest traffic intensity category. Thus, the different proxies are complementary rather than comparable in this study.

One limitation of all three proxies of exposure was that traffic-related air pollution was only estimated by residential address. Lack of individual data about work address and time spent commuting could have biased the expo-

Table 6: Geographical stratification. COPD diagnosis in Malmö and the region outside.

		Malmö			Region outside Malmö		
		n	COPD	OR [a]	n	COPD	OR [a]
Heavy traffic	No	1767	85(4.8%)	1.00	4178	152(3.6%)	1.00
	Yes	1877	103(5.5%)	1.24(0.92–1.67)	1343	69(5.1%)	1.47(1.09–1.97)
Heaviest road within <100 m	no heavy road	586	28(4.8%)	1.00	3124	124(4.0%)	1.00
	<2 cars/min	1021	44(4.3%)	0.89(0.55–146)	1193	49(4.1%)	1.06(0.75–1.49)
	2–5 cars/min	837	35(4.2%)	0.89(0.53–1.48)	961	35(3.6%)	0.93(0.64–1.37)
	6–10 cars/min	663	50(7.5%)	1.53(0.95–2.48)	212	10(4.7%)	1.20(0.62–2.35)
	>10 cars/min	537	31(5.8%)	1.34(0.79–2.28)	31	3	-
NO_x ($\mu g/m^3$)	0–8	13	0	-	1824	72(3.9%)	1.00
	8–11	46	2	-	1792	66(3.7%)	0.90(0.64–1.27)
	11–14	562	27(4.8%)	1.00	1268	60(4.7%)	1.26(0.89–1.80)
	14–19	1325	64(4.8%)	0.94(0.59–1.49)	510	18(3.5%)	0.91(0.54–1.55)
	>19	1698	95(5.6%)	1.23(0.79–1.92)	127	5(3.9%)	1.19(0.47–3.02)
			p-trend	0.142		p-trend	0.421

[a] Adjusted for age, sex, and smoking. [OR (95%CI)].

Table 7: Geographical stratification. Chronic bronchitis symptoms in the city of Malmö and the area outside.

		Malmö			Region outside Malmö		
		n	Chronic b. symptoms	OR [a]	n	Chronic b. symptoms	OR [a]
Heavy traffic	No	1767	150(8.5%)	1.00	4178	246(5.9%)	1.00
	Yes	1877	140(7.5%)	0.91(0.71–1.16)	1343	92(6.9%)	1.20(0.94–1.54)
Heaviest road within <100 m	no heavy road	586	43(7.3%)	1.00	3124	179(5.7%)	1.00
	<2 cars/min	1021	89(8.7%)	1.21(0.83–1.77)	1193	68(5.7%)	1.00(0.75–1.34)
	2–5 cars/min	837	66(7.9%)	1.10(0.73–1.64)	961	69(7.2%)	1.30(0.98–1.74)
	6–10 cars/min	663	47(7.1%)	0.94(0.61–1.45)	212	19(9.0%)	1.63(0.99–2.69)
	>10 cars/min	537	45(8.4%)	1.22(0.78–1.89)	31	3	-
NO_x ($\mu g/m^3$)	0–8	13	0	-	1824	109(6.0%)	1.00
	8–11	46	4	-	1792	113(6.3%)	1.04(0.79–1.37)
	11–14	562	35(6.2%)	1.00	1268	84(6.6%)	1.17(0.87–1.57)
	14–19	1325	96(7.2%)	1.13(0.76–1.70)	510	26(5.1%)	0.88(0.57–1.37)
	>19	1698	155(9.1%)	1.57(1.06–2.30)	127	6(4.7%)	0.86(0.37–2.01)
			p-trend	0.017		p-trend	0.541

[a] Adjusted for age, sex, and smoking. [OR(95%CI)].

sure assessments, particularly for people living in areas with low exposure to traffic-related air pollution, where individual differences in daily activities outside the residential area translate to a large proportion of total exposure [37]. In Los Angeles, 1 h commuting/day contributes approximately 10–50% of people's daily exposure to ultrafine particles from traffic [38]. While only 20% of the working population living in Malmö commute to work outside Malmö, the majority of the population in smaller municipalities in the remaining region commute to work outside their own municipality [39].

Another limitation was the cross-sectional nature of the study; we had no information about disease onset or years living at current address, making it hard to establish a temporal relationship between cause and effect. However, since asthma and COPD are known to be exacerbated by traffic-related air pollution, subjects with disease may have been more likely to move away from traffic, rather than towards it, and so a migrational bias would mainly be expected to dilute the effects.

Table 8: Stratification on smoking. COPD diagnosis in relation to traffic among smokers/ex-smokers and non-smokers.

		Smokers/ex-smokers			Non-smokers		
		n	COPD D	OR [a]	n	COPD D	OR [a]
Heavy traffic	No	3149	167(5.3%)	1.00	2892	76(2.6%)	1.00
	Yes	1861	130(7.0%)	1.43(1.13–1.82)	1414	42(3.0%)	1.19(0.81–1.76)
Heaviest road within <100 m	no heavy road	1951	104(5.3%)	1.00	1804	49(2.7%)	1.00
	<2 cars/min	1185	67(5.7%)	1.06(0.77–1.45)	1050	28(2.7%)	0.99(0.62–1.59)
	2–5 cars/min	992	52(5.2%)	0.99(0.70–1.40)	828	19(2.3%)	0.88(0.51–1.51)
	6–10 cars/min	522	44(8.4%)	1.56(1.08–2.26)	364	16(4.4%)	1.64(0.92–2.94)
	>10 cars/min	344	28(8.1%)	1.84(1.18–2.86)	234	6(2.6%)	1.15(0.48–2.75)
NO_x ($\mu g/m^3$)	0–8	969	47(4.9%)	1.00	886	27(3.0%)	1.00
	8–11	971	47(4.8%)	0.96(0.63–1.46)	884	21(2.4%)	0.77(0.43–1.37)
	11–14	945	63(6.7%)	1.35(0.92–2.00)	910	24(2.6%)	0.92(0.52–1.61)
	14–19	1037	60(5.8%)	1.14(0.92–2.00)	821	23(2.8%)	0.85(0.48–1.50)
	>19	1072	78(7.3%)	1.61(1.11–2.35)	779	23(3.0%)	1.12(0.63–1.98)
Test för Interaction	Heavy traffic*eversmoker			p = 0.47			
	Heaviestroad100 m*eversmoker			p = 0.89			
	NOx*eversmoker			p = 0.83			

[a] Adjusted for age and sex. [OR(95%CI)].

Table 9: Description of overlap between the different reported disease outcomes. Percentage within row. The first row shows that 70% of those with asthma diagnosis had asthma symptoms, 20% of those with asthma diagnosis had COPD diagnosis, and 21% of those with asthma diagnosis had chronic bronchitis symptoms.

	Total n	Asthma diagnosis n (%)	Asthma symptoms n (%)	COPD diagnosis n (%)	Chronic b. Symptoms (n %)
Asthma diagnosis	686	-	483 (70%)	139 (20%)	145 (21%)
Asthma symptoms	1115	483 (43%)	-	219 (20%)	277 (25%)
COPD diagnosis	415	139 (34%)	219 (53%)	-	152 (37%)
Chronic bronchitis symptoms	635	145 (23%)	277 (44%)	152 (24%)	-

Discussion of potential confounding

Areas with high levels of exposure to traffic-related air pollution were mainly located in the city of Malmö (table 4 and figure 2), while low exposure was found in more sparsely populated areas. It is a well recognized problem that the different exposure levels in rural and urban environments are also accompanied by large differences in lifestyle factors, and even if confounders are controlled for, unmeasured factors may remain. Since NO_x was limited by its spatial resolution, it is also the measure that was most susceptible to ecological bias. The lack of association seen with NO_x, in the region outside Malmö might thus reflect that the individual risk from traffic is being overridden by some other factor correlating with low exposure levels. The existence of independent risk factors correlating with low exposure is given some support by a Swedish study which found a tendency to higher adult asthma incidence in rural areas, after adjustment for exposure to traffic [11].

The most important risk factors from a validity standpoint, however, are factors that could correlate with high exposure to traffic-related air pollution, and thus cause a false positive relationship, such as socio-economic and occupational risk factors. However, the present study, which used individual-level data, found no confounding effects for either socio-economic status or occupational exposure. A recently developed and validated JEM was used to adjust for occupational exposure [33]. In a JEM, people are assigned the statistically average level of exposure in their occupation; this is an aggregated form of exposure assessment that can suffer from misclassification bias, although non-differential to disease. Since we only had information on the participants' current occupations, we cannot rule out the possibility of a "healthy worker effect". Lack of information about occupational history may be a limitation, especially in relation to the prevalence of COPD/chronic bronchitis.

Results discussion

Although asthma and COPD have many risk factors in common and often coexist in clinical settings, and there is some evidence that asthma may be a risk factor for the development of COPD [40], they are distinct conditions, with differing clinical course and pathological features. Thus, inconsistencies between studies in the relation between air pollution and asthma/COPD could depend both on the presence of different competing risk factors,

Table 10: Relation between the exposure proxies and modeled NO_x ($\mu g/m^3$) as a continuous variable.

		Malmö NO_x				Region outside Malmö NO_x			
		n	Mean	SD	Median	n	Mean	SD	Median
Heavy traffic	No	1507	18.0	3.1	17.4	4502	10.2	3.5	9.6
	Yes	1772	19.6	3.2	19.6	1495	12.1	4.5	11.4
Heaviest road within <100 m	no heavy road	488	17.6	3.4	17.2	3267	10.1	3.4	9.6
	<2 cars/min	855	18.0	2.9	17.8	1380	9.8	4.3	8.1
	2–5 cars/min	746	18.9	3.3	19.4	1074	12.6	3.8	11.5
	6–10 cars/min	627	18.1	2.8	17.4	259	13.8	2.3	14.03
	>10 cars/min	561	21.9	2.0	22.0	17	19.2	4.4	21.6
NO_x ($\mu g/m^3$)	0–8	13	6.8	1.3	6.8	1824	6.7	1.1	6.8
	8–11	46	10.4	0.8	9.6	1792	9.9	0.8	10.0
	11–14	562	13.5	0.7	13.7	1268	12.8	1.0	12.7
	14–19	1325	16.7	1.3	15.9	510	15.7	1.2	15.3
	>19	1698	21.7	1.3	21.5	127	21.9	3.8	21.2
	Total	3644	18.4	3.6	18.5	5521	10.31	3.6	10.04

and on geographically different pollution mixtures acting on different regions of the respiratory tract. It is therefore important to consider local pollution characteristics as thoroughly as possible (tables 11, 12). When using traffic intensity or self-reported traffic exposure as a proxy, there is a lack of knowledge of the exact pollution compounds that this exposure represents. One known characteristic of traffic-related pollution in the study region is a large amount of wear particles from road-tire interaction. These particles have been shown to be potent inducers of local inflammation [41,42], and their levels are high in the Scandinavian countries due to the use of traction sand and studded tires.

Although levels of traffic pollution in Sweden are lower than those found in most other countries, the results for asthma are basically supported by some European studies with higher exposure levels. An Italian study reported an association between symptom exaggeration of adult asthma and NO_2 exposure levels [12], and the Swiss SAPALDIA study observed an increase of asthma-related symptoms, although not current asthma, in relation to NO_2 [43]. The European ECRHS study found a positive association between NO_2 (modeled with a resolution of 1 km) and asthma incidence, but effect estimates seemed very heterogenous among the Swedish centers (although overall heterogeneity tested was non-significant). [15]. Most relevantly, a Swedish study found a non-significant tendency to increased asthma incidence among adults living close to traffic flows, and measured NO_2 levels comparable to those found in the present study [11]. Another study of asthma symptoms in Sweden found a significant but weak relation to NO_2 [44], although a stronger relation was found with self-reported measures of traffic. The findings in the present study, support the existence of a relation between exposure to traffic-related air pollution and asthma in adults at relatively low levels of traffic-related air pollution.

For COPD, a German study restricted to women found that COPD as defined by the GOLD criteria was 1.79 times more likely (95% CI 1.06–3.02) for those living less than 100 m from a road with 10 000 cars/day, than for those living farther away [19]. This is in agreement with our results, which found effects for living less than 100 m from a road with 6 cars/min (8 640 cars/day).

The European ECRHS study found that new onset of chronic bronchitis, as defined by chronic phlegm, was related among females to both self-reported traffic inten-

Table 11: Urban background. Descriptive data of regional air pollution at a monitoring station in Malmö. Annual mean concentrations of traffic-related pollutants measured at Rådhuset Malmö 1980–2006. Data source: IVL Swedish Environmental Research Institute Ltd. http://www.ivl.se/miljo/

Year	SO_2 (μg/m³)	NO_2 (μg/m³)	O_3 (μg/m³)	PM_{10} (μg/m³)	$PM_{2.5}$ (μg/m³)
1980*	49				
1981	50				
1982	43				
1983	33,1				
1984	22,9	42			
1985	20,3	39			
1986	16,7	31			
1987	20,3	32			
1988	13	30.5			
1989	12	26.9	46		
1990	9	21.3	39		
1991	8	19.6	41		
1992	7	22.4	43		
1993	8	25.6	40		
1994	6	21.4	43		
1995	6	22	50		
1996	8	24.6	50	17.4	
1997	5	26.2	48	17.6	
1998	4	21.8	47	15.2	
1999	4	23.5	50	15.8	12.6
2000	2	22.9	49	16.5	13.5
2001	2	21.1	46	18.7	12
2002	2	20.3	52	18.1	11.5
2003	3	20.8	49	21.6	13.7
2004	3	19.5	54	15.9	10
2005	4	20.6	49	17.5	11.1
2006	3	19.3	52	18.2	12.3

Table 12: Rural background. Descriptive data of regional air pollution at a monitoring station in a rural area. Annual mean concentrations of traffic-related pollutants measured at Vavihill 1985–2006. Data source: IVL Swedish Environmental Research Institute Ltd. http://www.ivl.se/miljo/

Year	SO_2 (μg/m^3)	NO_2 (μg/m^3)	O_3 (μg/m^3)	PM_{10} (μg/m^3)	$PM_{2.5}$ (μg/m^3)
1985	5.14	2.36	60.2		
1986		2.27	59.9		
1987	5.47	2.11	55.1		
1988	3.90	1.84	57.7		
1989	3.93	2.66	56.5		
1990	2.98	2.36	55.0		
1991	2.64	2.08	51.3		
1992	2.06	1.72	56.0		
1993	1.70	1.98	57.4		
1994	1.17	1.78	58.6		
1995	1.35	1.92	59.3		
1996	1.31	1.77	63.0		
1997	0.67	2.05	58.8		
1998	0.74	1.87	54.6		
1999	0.55	1.66	59.1		
2000	0.45	1.70	57.6	16.0	
2001	0.42	1.37	60.2	15.4	
2002	0.37	1.39	66.6	16.3	
2003	0.52	1.54	62.9	18.6	
2004	0.37	1.48	58.5	13.8	
2005	0.49	1.47	61.0	15.2	
2006	0.50	1.59	64.3	17.3	

sity (constant traffic vs. none, OR = 1.86; 95% CI 1.24 to 2.77) and home outdoor NO_2 (OR = 50 μg/m^3 vs. 20 μg/m^3 = 2.71; 95% CI 1.03 to 7.16) [20]. The higher levels of NO_2 seen in the ECRHS study may partly stem from truly higher concentrations, but may also have been affected by the use of home outdoor measurements, which are better than our models at capturing locally high peak exposures. Other studies have suggested an effect modification for sex, with women being at higher risk, but this was not observed in our study. Our results did indicate effect modification by smoking, but tests for interaction were mainly non-significant. No interaction with smoking was found in any of the abovementioned studies of the effects of air pollution on prevalence/incidence of COPD in adults.

Overall, our results show that traffic-related air pollution is associated with the prevalence of COPD/chronic bronchitis in adults, but there is still a need for further investigation of the reasons behind the inconsistencies seen when the data were stratified by region.

Conclusion

Residential traffic is associated with both current symptoms and prevalence of diagnosis of asthma and COPD/chronic bronchitis, among adults in southern Sweden. This may indicate that traffic has not only short-term but also long-term effects on adult chronic respiratory disease, even in a region with low overall levels of traffic pollution.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AL: Conducted the statistical analyses and wrote the main part of the manuscript. ES: Performed GIS analyses and wrote part of the manuscript. PM: Designed and conducted the survey and made revisions on drafts. UN: Designed and conducted the survey and made revisions on drafts. KJ: Designed the study and made revisions on drafts. AA: Wrote part of the manuscript and made major revisions of drafts. All authors read and approved the final manuscript.

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Paper II

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Research

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Traffic exposure associated with allergic asthma and allergic rhinitis in adults. A cross-sectional study in southern Sweden

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Abstract

Background: There is conflicting evidence that traffic-related air pollution is a risk factor for allergic conditions. Few studies have investigated this in adults. In adults, a high proportion of asthma, rhinitis and eczema is triggered by non-allergic factors. We investigated traffic as a risk factor for allergic versus non-allergic asthma and rhinitis, and eczema, in adults.

A questionnaire from 2000 (n = 9319, 18–77 years) provided individual data about disease outcome and self-reported traffic exposure. Additional exposure assessments were obtained using Geographical Informations Systems (GIS). Residential addresses were linked to the national Swedish Road Database and to a pollutant database with modelled annual means of NO_x (Nitrogen Oxids).

Results: Living within 100 m from a road with a traffic intensity of >10 cars/min (24 hour mean) was associated with prevalence of current asthma reported to be triggered by allergic factors (OR = 1.83, 95% CI = 1.23–2.72) and with allergic rhinitis (OR = 1.30, 95%CI = (1.05–1.61). No relation was seen with asthma or rhinitis triggered by other factors. Living within 100 m of a road with >10 cars/min was also associated with hand-eczema during the last 12 months (OR = 1.63, 95% CI = 1.19–2.23), but not with allergic eczema or diagnosed hand-eczema. Consistent results were seen using self-reported traffic, but the associations with NO_x were less consistent.

Conclusion: Exposure to traffic was associated with a higher prevalence of allergic asthma and allergic rhinitis, but not with asthma or rhinitis triggered by non-allergic factors. This difference was suggested by the overall pattern, but only clear using GIS-measured traffic intensity as a proxy for traffic exposure. An association was also found with hand-eczema during the last 12 months. We suggest that asthma and rhinitis should not be treated as homogenous groups when estimating effects from traffic in adults.

Background

There has been a significant increase in chronic respiratory diseases and allergy during the last decades. Air pollution from traffic has been one proposed risk factor. There is now evidence for long-term negative effects on lung function development [1], asthma [2], and COPD [3,4], but effects on allergic rhinitis and atopic dermatitis have remained unclear, even if a recent cohort study in children supports adverse effects [5].

An increased risk of asthma, allergic rhinitis, and eczema in individuals with a susceptibility for allergy (atopy) is well established [6], and it has been suggested that traffic pollution would increase or induce sensitivity for allergens in atopic individuals [7]. Support for this "sensitisation theory" stems mainly from laboratory studies [7], while epidemiologic studies estimating long-term effects on allergic conditions have shown conflicting results [8].

Traffic pollutions may potentiate allergic reactions in different ways [9]:

1) By attaching to the surface of e.g. pollen grains, air pollutants can change their morphology and enhance allergenic potential. 2) by inducing inflammation, which increases epithelial permeability, pollutants overcome the mucosal barrier and facilitate the allergen-induced inflammatory responses 3) diesel exhaust emissions increases immunoglobulin E synthesis, the dominating immune response in atopic subjects. Experimental studies have also shown that exposure to traffic-related air pollution can cause trans-epidermal water-loss [10] and decreased skin wheal response [11], in patients with atopic dermatitis.

Allergic symptoms often arise in childhood, and a majority of epidemiologic studies investigating effects from traffic on asthma, rhinitis and eczema have focused on children. In adults, a higher proportion of these diseases is triggered by non-allergic factors, than in children. Especially asthma is a heterogeneous condition in adults, and it has been suggested that asthma should not be used as a homogenous disease concept [12].

The present article is motivated by a previous study where we found asthma and COPD to be associated with traffic-related air pollution [13]. The present study investigates if both allergic and non-allergic subgroups of asthma are affected by traffic, and we also investigate the effect on allergic versus non-allergic rhinitis and eczema, in adults. GIS was used to complement self-reported traffic with external road data and a pollutant database for NO_x, objective indicators for traffic-related air pollution at a local level.

Materials and methods

Study area

The study area was the south western part of the county of Scania, Sweden. The study area has a population of 840000 out of Sweden's total population of 8.9 millions, and a population density of 170 inhabitants/km^2 (data from 2000). The majority of the population is living in six of the municipalities, the largest of which is Malmö, the third largest city in Sweden, with a population of 260000. A detailed description of the study area has previously been given [14]. In the geographical stratification of the present study, "Malmö" refers strictly to the city boundaries of Malmö, not the larger municipality.

Although pollutant levels in the region are low in an European context, they are higher than in most other parts of Sweden [15], due to a relatively higher population density, long-range transport of pollutants from the continent, and more extensive road- harbour- and ferry traffic.

Study population, Questionnaire and Geocoding

In 2000, a questionnaire was sent to a total of 11 933 randomly selected individuals aged 18–77 and 9 319 (78%) answered [13]. The study population originated from two different study populations, 5039 individuals (response rate 71%) from a new random selection, and 4280 individuals (response rate 87%) constituting a follow-up group from an earlier selection [16]. The questionnaire was focused on respiratory symptoms, but also contained information about eczema, smoking habits, occupation, and self-reported living close to traffic. The full questionnaire has been published previously [16]. Residential addresses were geocoded by linking each individual's unique 10-digit personal identity code to a registry containing geographical coordinates of all residential addresses. For non-responder analysis, see earlier publications [13,16].

Outcome measures

Asthma, rhinitis and eczema were investigated using the questions specified in figure 1.

Current asthma was defined as self-reported physician diagnosed asthma in combination with asthma-symptoms last 12 months. This combination of questions has been validated in Sweden and showed a high specificity for asthma [17].

Subgroups of allergic versus non-allergic current asthma and rhinitis were defined by a question about what specific factors that usually triggered symptoms.

Exposure assessment

Exposure to traffic was assessed at each participant's residential address in 2000, using three different proxies:

1. Self-reported exposure to traffic. This was obtained from the questionnaire. Exposure was defined as a positive answer to the question "*Do you live close to a road with heavy traffic?*".

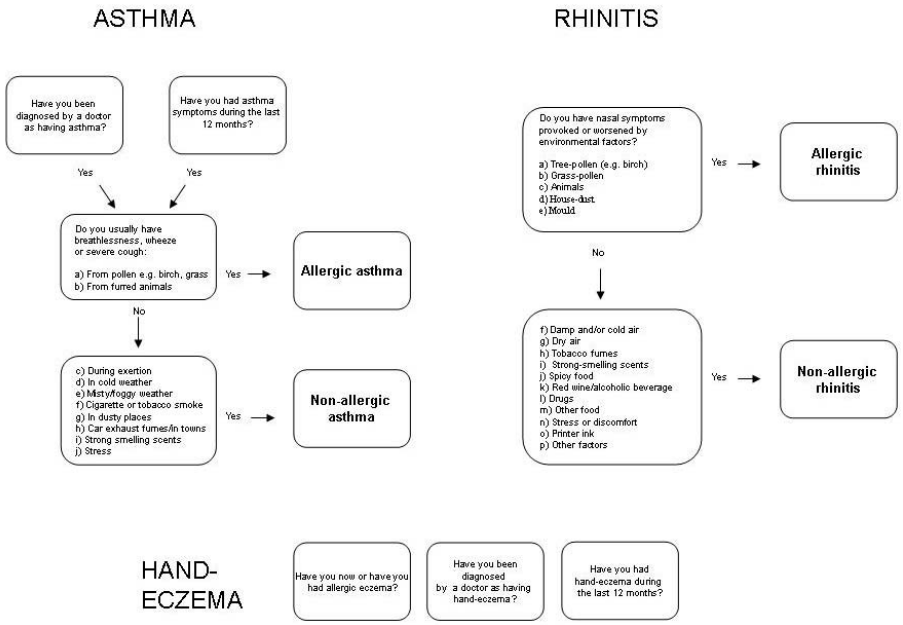

Figure 1
Disease outcome definitions.

2. Distance to roads with specified traffic intensity. GIS-based registers from *The Swedish National Road Database* [18] contained information about traffic intensity for all major roads in the county. To assess exposure to traffic, the individual was assigned the road with the heaviest traffic intensity within a radius of 100 m from residence. Traffic intensity was categorized as <2 cars/min, 2–5 cars/min, 6–10 cars/min and >10 cars/min, based upon annual 24 hour mean levels.

3. Modelled exposure to NO_x. Annual mean concentrations of NO_x were obtained from a GIS-based pollutant database for Scania based on the year 2001 [19]. Emission sources included in the model were: road traffic, shipping, aviation, railroad, industries and larger energy and heat producers, small scale heating, working machines, working vehicles and working tools. Meteorological data were also included. For dispersion calculations, a modified Gaussian dispersion model (AERMOD) was used, which is a flat two-dimensional model not adjusting for effects of street canyons or terrain, but taking the height of the emission sources into consideration. Concentrations of NO_x were modelled as annual mean in a grid with a spatial resolution of 250 × 250 m. Bilinear interpolation was used to adjust individual exposure (based upon the individuals residence) with weighted values of neighbouring grid cells concentrations. Modelled concentrations with this spatial resolution have been validated and found to have a high correlation with measured values in the region [20-22].

Potential confounders

For respiratory diseases, self-reported occupations were coded according to the European classification system ISCO-88 (COM), and the European job exposure matrix (JEM), ALOHA [23]. For eczema, a classification system based on risk occupations specifically for eczema was used [24]. Occupations were also coded according to the socio-economic indices (SEI-codes) officially used by Statistics Sweden [25].

Statistics

Relative risk was estimated using Odds Ratios (OR:s) with 95% Confidence Intervals (CI). These were obtained by binary logistic regression, using SPSS, version 13.0. Sex, age and smoking (smokers and ex-smokers vs. non-smokers) were adjusted for in the model.

Occupational exposure and socio-economic status were tested as potential confounders. A predetermined change-in-estimate criteria of 10% would have motivated an inclusion in the model [26], but this was not fulfilled, neither was there any minor noticeable changes in estimate, why occupational exposure and socio-economic status were excluded from the model.

Odds ratios were not estimated in exposure groups with fewer than 50 individuals.

A categorical classification of NO_x was used to be able to analyse non-linear associations between exposure to NO_x and outcomes. To determine the category limits, the observations were merged and divided into NO_x-quintiles. The five exposure groups used were 0–8 μg/m³, 8–11 μg/m³, 11–14 μg/m³, 14–19 μg/m³, and above 19 μg/m³ .

NO_x was also used as a continuous variable for trend analysis using logistic regression. A p-value < 0.05 was regarded as evidence of a trend.

Since areas with high exposure to traffic mainly were located in the city of Malmö, a geographical stratification (Malmö versus region outside Malmö) was done to exclude confounding from direct urban-rural comparison, when comparing high and low exposure.

We also investigated potential effect modification by stratified analysis on sex and smoking (current, former, never smoker).

In addition to current asthma, physician diagnosed asthma and asthma symptoms last 12 months were assessed separately in allergic vs non-allergic subgroups, to increase comparability with the previous study [13]. 72 of those with physician diagnosed asthma and 68 of those with asthma symptoms during the last 12 months had not reported any triggers and were therefore missing in the analysis.

Results

Description of the relation between disease outcomes and covariates are given in table 1.

For description of reported triggers see additional file 1: Description of overlap between reported triggers of asthma and rhinitis.

In a stratified analysis, we found no evidence of effect modification by sex or smoking for any of the outcomes, although the power was also low to test for interaction.

Asthma triggered by pollen or furred animals

Current asthma with symptoms reported to be triggered by pollen or furred animals, here defined as allergic asthma, was associated with self-reported traffic exposure and GIS-measured traffic intensity on heaviest road within 100 m, but not with modelled concentrations of NO_x (table 2).

A geographical stratification showed increased prevalence in association with NO_x, in Malmö, but not in the region outside (table 3). The association with self-reported traffic and GIS-measured traffic intensity seemed consistent across study area.

Separate assessment of asthma diagnosis and asthma symptoms during the last 12 months, triggered by allergic factors, showed the same patterns of associations with traffic as allergic current asthma (See additional file 2: Allergic vs. non-allergic physician-diagnosed asthma and asthma symptoms last 12 months).

Table 1: Descriptives of study population, and disease prevalence in relation to sex, age, and smoking.

			Current asthma		Rhinitis		Eczema		
		Total n	Allergic	Non-allergic	Allergic	Non-allergic	Allergic eczema	Diagnosis of Hand-eczema	Hand-eczema last 12 months
Sex	Men	4341	106(2.4%)	57(1.3%)	800(18.4%)	266(6.1%)	326(7.5%)	171 (3.9%)	195 (4.5%)
	Women	4975	218(4.4%)	91(1.8%)	1064(21.4%)	339(8.0%)	813(16.3%)	430 (8.6%)	401 (8.1%)
Ever smoker	No	4306	143(3.3%)	53(1.2%)	941(21.9%)	254(5.9%)	504(11.7%)	245 (5.7%)	248 (5.8%)
	Yes	5010	181(3.6%)	95(1.9%)	923(18.4%)	351(7.0%)	635(12.7%)	356 (7.1%)	348 (6.9%)
Age	18–19	135	5(5.2%)	7(5.2%)	31(23%)	4(3.0%)	28(20.7%)	5 (3.7%)	3 (2.2%)
	20–29	1062	52(4.9%)	19(1.8%)	284(26.7%)	53(5.0%)	230(21.7%)	59 (5.6%)	80 (7.5%)
	30–39	2045	92(4.5%)	21(1.0%)	520(25.4%)	106(5.2%)	306(15.0%)	141 (6.9%)	166 (8.1%)
	40–49	1887	61(3.2%)	24(1.3%)	407(21.6%)	118(6.3%)	236(12.5%)	131 (6.9%)	132 (7.0%)
	50–59	2123	62(2.9%)	31(1.5%)	344(16.2%)	166(7.8%)	207(9.8%)	151 (7.1%)	134 (6.3%)
	60–69	1586	38(2.4%)	33(2.1%)	21813.7%)	122(7.7%)	112(7.1%)	94 (5.9%)	71 (4.5%)
	70–77	478	14(2.9%)	13(2.7%)	60(12.6%)	36(7.5%)	20(4.2%)	20 (4.2%)	10 (2.1%)

Asthma triggered by other factors

Current asthma triggered by non-allergic factor, was not associated with any of the exposure metrics (table 2).

A geographical stratification found no indications of effect modification by study area (table 4). Separate assessment of asthma diagnosis and asthma symptoms during the last 12 months, triggered by non- allergic factors, showed no association with traffic (See additional file 2: Allergic vs. non-allergic physician-diagnosed asthma and asthma symptoms last 12 months).

Rhinitis triggered by pollen, furred animals, house dust or mould

Rhinitis triggered by pollen, animals, house dust or mould, was associated with all measures (table 5). A geographical stratification found no indications of effect modification by study area.

Rhinitis triggered by other factors

Rhinitis triggered by non-allergic factors was not associated with self-reported traffic or GIS-measured traffic intensity, but showed a relation with modelled concentrations of NO_x (table 5). A geographical stratification found no indication of effect modification by study area.

Eczema

Self-reported allergic eczema was significantly associated with self-reported living close to a road with heavy traffic, and showed non-significant tendencies to a relation with the other measures. Self-reported physician diagnosed hand-eczema showed weak, but statistically non-significant, associations with traffic, while hand-eczema during the last 12 months showed a significant relation with self-reported living close to a road with heavy traffic and GIS-measured traffic intensity within 100 m, but not with modelled concentrations of NO_x (table 6).

A geographical stratification found no indications of effect modification by study area for allergic eczema, but some inconsistencies across study area for diagnosed hand-eczema and hand-eczema last 12 months. These inconsistencies were seen for all three measures but showed no consistent pattern (data not shown).

Discussion

This study found traffic to be associated with higher prevalence of allergic asthma and allergic rhinitis, but not with non-allergic asthma and only with NO_x for non-allergic rhinitis. The difference between allergic and non-allergic outcomes was suggested by overall pattern, but only clear using GIS-measured traffic intensity as a proxy for traffic exposure. An increased prevalence in relation to traffic was also seen on hand-eczema during the last 12 months.

Study strengths and limitations

An important strength of the study was the use of three different proxies for exposure to traffic with high-quality of road- and emission data, and detailed questions of respiratory symptoms, which allowed for a distinction

Table 2: Current asthma in relation to traffic.

		Current asthma Allergic[a]			Non-allergic[b]		
		n[c]	n, %	Adj OR[d]	n[c]	n, %	Adj OR[d]
Heavy traffic	No	5441	187(3.4%)	1.00	5341	87(1.6%	1.00
	Yes	2881	137(4.8%)	1.32(1.05–1.66)	2805	61(2.2%)	1.28(0.92–1.79)
Heaviest road radie <100 m	no heavy road	3371	117(3.5%)	1.00	3316	62(1.9%)	1.00
	<2 cars/min	2014	79(3.9%)	1.13(0.84–1.51)	1966	31(1.6%)	0.82(0.53–1.28)
	2–5 cars/min	1608	54(3.4%)	0.96(0.69–1.33)	1584	30(1.9%)	0.98(0.63–1.53)
	6–10 cars/min	781	37(4.7%)	1.34(0.92–1.96)	759	15(2.0%)	0.95(0.54–1.69)
	>10 cars/min	511	35(6.8%)	1.83(1.23–2.72)	485	9(1.9%)	0.96(0.47–1.96)
NOx (ug/m3)	0–8	1665	68(4.1%)	1.00	1624	27(1.7%)	1.00
	8–11	1669	70(4.2%)	1.04(0.74–1.46)	1630	31(1.9%)	1.13(0.67–1.91)
	11–14	1661	52(3.1%)	0.74(0.51–1.07)	1641	32(2.0%)	1.15(0.69–1.94)
	14–19	1674	51(3.0%)	0.73(0.50–1.05)	1655	32(1.9%)	1.05(0.62–1.76)
	>19	1616	81(5.0%)	1.15(0.82–1.61)	1560	25(1.6%)	0.91(0.52–1.58)
			p-trend	0.669		p-trend	0.553

[a] Asthma triggered by pollen or furred animals
[b]Asthma triggered by other factors
[c] Individuals with non-allergic current asthma were excluded from the analysis of allergic current asthma in relation to traffic, and vice versa.
[d] OR:s, 95% CI. Adjusted for age, sex and smoking

Table 3: Geographical stratification.

		Current asthma, allergic[a] Malmö			Region outside Malmö		
		n[b]	n, %	Adj OR[c]	n[b]	n, %	Adj OR[c]
Heavy traffic	No	1586	55(3.5%)	1.00	3768	128(3.4%)	1.00
	Yes	1641	76(4.6%)	1.22(0.85–1.75)	1189	57(4.8%)	1.38(1.00–1.91)
Heaviest road radie <100 m (cars/min)	No road	517	16(3.1%)	1.00	2815	100(3.6%)	1.00
	<2	917	32(3.5%)	1.15(0.62–2.12)	1077	46(4.3%)	1.19(0.83–1.71)
	2–5	740	25(3.4%)	1.08(0.57–2.05)	847	27(3.2%)	0.89(0.58–1.37)
	6–10	581	26(4.5%)	1.49(0.79–2.82)	189	11(5.8%)	1.66(0.87–3.18)
	>10	472	32(6.8%)	1.96(1.05–3.66)	29	1	-
NOx (ug/m3)	0–8	12	0	-	1635	67(4.1%)	1.00
	8–11	43	4	-	1612	65(4.0%)	0.99(0.70–1.41)
	11–14	499	13(2.6%)	1.00	1138	38(3.3%)	0.79(0.52–1.19)
	14–19	1197	36(3.0%)	1.12(0.59–2.14)	457	14(3.1%)	0.74(0.41–1.33)
	>19	1476	78(5.3%)	1.78(0.97–3.27)	115	1(0.9%)	0.20(0.03–1.43)
			p-trend	0.019		p-trend	0.029

Current allergic asthma in the city of Malmö and the region outside.

[a] Asthma triggered by pollen or furred animals

[b] Individuals with non-allergic current asthma were excluded from the analysis of allergic current asthma in relation to traffic.

[c] OR:s, 95% CI, Adjusted for age, sex and smoking

between allergic and non-allergic subjects. Symptoms triggered by pollen or furred animals can probably be seen as highly specific for allergy. However, "symptoms triggered by other factors" is a heterogenous grouping, and these results should be interpreted with caution. It should be noted that only trigger-dependent symptoms were analysed in this study, not non-allergic chronic respiratory symptoms which are not dependent on triggers.

Self-report of allergic triggers has shown moderate association with skin prick-test [27], but this association does not necessarily reflect the validity of self-report, but also reflects that not all which show positive prick-test have actual symptoms of their allergy. While about 40% of the western population have elevated levels of IgE to common environmental allergens, only about 7% express their atopy as asthma [28]. Since air pollution might exert effects either in sensitization or in later manifestation of disease, biological markers should be related to reports and tests of actual symptoms. Our study strongly indicates that allergic asthma and allergic rhinitis are affected by traffic in adults, but the lack of biological markers and objective symptom testing is a limitation.

A limitation was also the cross-sectional study design, which makes it difficult to assess if pollution is associated with the onset of allergy or only trigger an existing allergic disease.

We had no possibility to properly assess retrospective exposure. We therefore focused on current asthma since symptoms last 12 months are in agreement with estimated exposure, and ever doctor's diagnosis exclude asthmatic symptoms not specific of asthma.

Even if the additional separate association with ever diagnosis of asthma indicates long-term effects, there is a possibility of recall-bias, where those with current symptoms are more likely to remember being diagnosed, which would bias these effects away from null. On the other hand, since asthma and rhinitis could be triggered by traffic pollution, those with respiratory symptoms are also likely to be affected by migrational bias, which would rather bias both the effects of diagnosis and current symptoms towards null.

The traffic exposure measures have been more thoroughly discussed in a related article [13]. Self-reported traffic mainly showed consistent, although less pronounced results compared with using GIS-measured traffic intensity. The GIS-based road proxy has the advantage to not be limited by spatial aggregation, but is a simple proxy for exposure, only considering the heaviest road within a certain radius. Modelled levels of NO_x on the other hand, takes total traffic density into account, but had the disadvantage to be the measure with the lowest spatial resolution, and may therefore be most sensitive for ecological bias. The finding that associations with NO_x for allergic asthma were only seen in Malmö, may indicate unmeasured confounding and/or that NO_x is not a good proxy of traffic-related air pollution outside urban areas, something we have discussed in a previous article where we analysed asthma as a homogenous group [13].

Table 4: Geographical stratification. Current non-allergic asthma in the city of Malmö and the region outside.

		Current asthma, non-allergic[a] Malmö			Region outside Malmö		
		n[b]	n, %	Adj OR[c]	n[b]	n, %	Adj OR[c]
Heavy Traffic	No	1557	26(1.7%)	1.00	3700	60(1.6%)	1.00
	Yes	1599	34(2.1%)	1.31(0.78–2.21)	1159	27(2.3%)	1.37(0.86–2.17)
Heaviest road radie <100 m (cars/min)	No heavy road	512	11(2.1%)	1.00	2766	51(1.8%)	1.00
	<2 cars/min	902	17(1.9%)	0.88(0.41–1.89)	1045	14(1.3%)	0.73(0.40–1.33)
	2–5 cars/min	726	11(1.5%)	0.73(0.31–1.70)	839	19(2.3%)	1.17(0.68–2.00)
	6–10 cars/min	567	12(2.1%)	0.94(0.41–2.17)	181	3(1.7%)	0.82(0.25–2.66)
	>10 cars/min	449	9(2.0%)	1.00(0.41–2.46)	28	0	-
NOx (ug/m3)	0–8	12	0	-	1595	27(1.7%)	1.00
	8–11	39	0	-	1578	31(2.0%)	1.15(0.68–1.95)
	11–14	501	15(3.0%)	1.00	1117	17(1.5%)	0.86(0.46–1.59)
	14–19	1181	20(1.7%)	0.51(0.26–1.02)	455	12(2.6%)	1.50(0.75–3.00)
	>19	1423	25(1.8%)	0.58(0.30–1.12)	114	0(0%)	-
			p-trend	0.501		p-trend	0.677

[a]Asthma triggered by other factors
[b] Individuals with allergic current asthma were excluded from the analysis of non-allergic current asthma in relation to traffic.
[c] OR:s, 95% CI, Adjusted for age, sex and smoking

Discussion of main results and comparison with other studies

There was a clear relation between exposure to traffic and asthma triggered by pollen or furred animals, but not with asthma triggered by other factors. This result seems to be supported by a Swedish study which found that an increased incidence of adult asthma associated with increase in NO_2only occurred among atopics [29]. The Swedish cities in the RHINE-study however, found no interaction between asthma and NO_2 using hay-fever as a proxy for atopy [30]. The ECRHS-study also found no interaction with atopy for the relation between traffic and adult asthma incidence [31], and no relation between traffic and sensitization [32]. The Swiss SAPALDIA study found traffic to be related to allergic sensitization to pollen in skin prick-test, but not with asthma symptoms, at baseline [33]. In the recently published follow-up, those with atopy at baseline seemed to have a higher incidence of asthma in relation to traffic, although there was not enough power for statistical confirmation [34]. A German study found neither increase of asthma or allergic sensitization living at self-reported busy roads [35]. Comparison with our study is complicated by the fact that atopy could both act as effect-modifier and mediator to disease. None of the abovementioned studies have directly related traffic to allergic asthma.

Consistent with the results for asthma, rhinitis due to pollen or furred animals were affected by traffic, but not rhinitis triggered by other factors, which showed an association with NO_x, but no convincing overall trend toward a relation with traffic. There is previous weak epidemiologic support for an effect from traffic on allergic rhinitis in adults. The Swiss SAPALDIA study in 2000 found living close to busy roads not to be associated with allergic rhinitis [33]. In Germany, living close to extremely or considerably busy roads has been associated with an marginally increased risk of allergic rhinitis (OR = 1.16 (0.94–1.42) [35]. An Italian study in adults found outdoor NO_2 exposure to be associated with significantly increased prevalence of allergic rhinitis in the Mediterranean region (OR = 1.38; 95% CI 1.12 to 1.69), but not in the subcontinental region, and concluded that climate interacts with effects of NO_2 outdoor exposure [36]. Our results strengthens previous very weak evidence for associations between traffic and self-reported allergic rhinitis in adults, but it should be noted that the specific question we used for definition of allergic rhinitis differs from what has been used in other studies.

There was a higher prevalence of allergic eczema and hand-eczema in relation to heavy traffic, but this was only significant for self-reported hand-eczema during the last 12 months. It had been desirable to make a distinction between atopic dermatitis and contact eczema, but this distinction has low validity in questionnaires without clinical examination or validated differential questions, such as debut of hand-eczema in childhood or presence of nickel allergy [37]. Occupational exposure is a major risk factor for hand-eczema, but was not found to be a confounder with the present assessment of risk occupations. Since Sweden has a largely segregated labour market in

Table 5: Rhinitis in relation to traffic.

		Rhinitis Allergic rhinitis[a]			Non-allergic rhinitis[b]		
		n[c]	n, %	Adj OR[d]	n[c]	n, %	Adj OR[d]
Heavy traffic	No	5641	1154(20.5%)	1.00	4887	400(8.2%)	1.00
	Yes	3070	710(23.1%)	1.13(1.01–1.26)	2565	205(8.0%)	0.99(0.83–1.18)
Heaviest road radie <100 m	no heavy road	3523	715(20.3%)	1.00	3040	232(7.6%)	1.00
	<2 cars/min	2087	421(20.2%)	0.99(0.87–1.14)	1814	148(8.2%)	1.08(0.87–1.34)
	2–5 cars/min	1684	373(22.1%)	1.11(0.96–1.28)	1447	136(9.4%)	1.27(1.01–1.58)
	6–10 cars/min	835	201(24.1%)	1.27(1.06–1.53)	685	51(7.4%)	0.96(0.70–1.32)
	>10 cars/min	544	143(26.3%)	1.30(1.05–1.61)	435	34(7.8%)	1.07(0.73–1.56)
NOx (ug/m3)	0–8	1759	329(18.7%)	1.00	1526	96(6.3%)	1.00
	8–11	1729	391(22.6%)	1.30(1.10–1.53)	1464	126(8.6%)	1.39(1.05–1.83)
	11–14	1731	368(21.3%)	1.16(0.98–1.38)	1487	124(8.3%)	1.37(1.04–1.80)
	14–19	1721	347(20.2%)	1.14(0.96–1.35)	1511	137(9.1%)	1.47(1.12–1.93)
	>19	1733	418(24.1%)	1.33(1.13–1.57)	1433	118(8.2%)	1.37(1.03–1.81)
			p-trend	0.006		p-trend	0.057

[a] Rhinitis triggered by pollen, furred animals, house-dust or mould
[b]Rhinitis triggered by other factors
[c] Individuals with non-allergic rhinitis were excluded from the analysis of allergic rhinitis in relation to traffic, and vice versa.
[d] OR:s, 95% CI. Adjusted for age, sex and smoking

respect of gender [38], adjustment for sex and age may partly adjust for risk occupation. Few epidemiological studies have investigated the effect from traffic on atopic dermatitis. A previous cross-sectional study in southern Sweden in 1992, related to this study, found self-reported traffic to be associated with allergic eczema (OR = 1.45, 95% CI 1.28–1.66), but this seems to be the only evidence of effects of traffic on eczema in adults. In children, a few studies have indicated long-term effects on atopic dermatitis [5,39,40]. To our knowledge, no epidemiologic study has previously studied effects from traffic on hand-eczema.

In conclusion, the present study of a randomly selected adult population found that allergic asthma and allergic rhinitis are associated with traffic-related air pollution, but not non-allergic asthma or rhinitis. This result suggests that asthma and rhinitis should be divided into allergic and non-allergic conditions when investigating effects from traffic pollution in adults. However, the cross-sec-

Table 6: Eczema in relation to traffic.

		Self-reported allergic eczema			Diagnosed hand-eczema		Hand-eczema last 12 months	
		n	n, %	Adj OR[a]	n, %	Adj OR[a]	n, %	Adj OR[a]
Heavy traffic	No	6041	681(11.3%)	1.00	373(6.2%)	1.00	345(5.7%)	1.00
	Yes	3275	458(14.0%)	1.16(1.02–1.32)	228(7.0%)	1.12(0.94–1.33)	251(7.7%)	1.32(1.12–1.57)
Heaviest road radie <100 m	no heavy road	3755	442(11.8%)	1.00	228(6.1%)	1.00	221(5.9%)	1.00
	<2 cars/min	2235	262(11.7%)	0.99(0.84–1.17)	148(6.6%)	1.10(0.89–1.37)	135(6.0%)	1.04(0.83–1.29)
	2–5 cars/min	1820	226(12.4%)	1.04(0.87–1.24)	116(6.4%)	1.08(0.86–1.37)	117(6.4%)	1.11(0.88–1.40)
	6–10 cars/min	886	119(13.4%)	1.15(0.92–1.43)	64(7.2%)	1.20(0.90–1.61)	65(7.3%)	1.29(0.97–1.72)
	>10 cars/min	578	84(14.5%)	1.08(0.83–1.40)	45(7.8%)	1.35(0.96–1.89)	56(9.7%)	1.63(1.19–2.23)
NOx (ug/m3)	0–8	1855	209(11.3%)	1.00	108(5.8%)	1.00	111(6.0%)	1.00
	8–11	1855	206(11.1%)	0.99(0.80–1.22)	124(6.7%)	1.15(0.88–1.50)	108(5.8%)	0.97(0.74–1.28)
	11–14	1855	251(13.5%)	1.19(0.98–1.46)	124(6.7%)	1.17(0.90–1.53)	131(7.1%)	1.20(0.92–1.56)
	14–19	1858	225(12.1%)	1.09(0.89–1.33)	123(6.6%)	1.15(0.88–1.50)	117(6.3%)	1.08(0.83–1.42)
	>19	1851	242(13.1%)	1.06(0.87–1.30)	122(6.6%)	1.16(0.89–1.52)	127(6.9%)	1.13(0.86–1.47)
			p-trend	0.44	p-trend	0.52	p-trend	0.357

[a] OR:s, 95% CI, Adjusted for age, sex and smoking

tional design is a severe limitation of this study, and longitudinal studies in adults are needed to investigate if the effects for allergic versus non-allergic chronic respiratory disease reflects adult onset disease. Potential biological mechanisms can also not be explained in our epidemiological study, which lacked biological markers, but the indications of effects on eczema are interesting and either indicate that adverse effects from traffic on allergic disease are not limited to the respiratory tract, or that exposure to traffic have negative effects on the skin which are not related to allergic disease.

Conclusion

This study found that exposure to traffic is associated with a higher prevalence of allergic asthma and allergic rhinitis, but not with asthma or rhinitis triggered by non-allergic factors. This difference was suggested by the overall pattern, but only clear using GIS-measured traffic intensity as a proxy for traffic exposure. An association was also found with hand-eczema. We suggest that asthma and rhinitis should not be treated as homogenous groups when estimating effects from traffic in adults.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AL: Decided the content of the article, conducted the statistical analyses and wrote the main part of the manuscript. ES: Performed GIS analyses and wrote part of the manuscript. UN: Designed and conducted the survey and made revisions on draft. PM: Designed and conducted the survey and made revisions on draft. AA: Made revisions on draft. KJ: Made major revisions on draft. All authors read and approved the final manuscript.

Additional material

Additional file 1

Description of overlap between reported triggers of asthma and rhinitis.

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[http://www.biomedcentral.com/content/supplementary/1476-072X-8-25-S1.pdf]

Additional file 2

Allergic vs. non-allergic physician-diagnosed asthma and asthma symptoms last 12 months.

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[http://www.biomedcentral.com/content/supplementary/1476-072X-8-25-S2.pdf]

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Paper III

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RESEARCH ARTICLE Open Access

Adult asthma and traffic exposure at residential address, workplace address, and self-reported daily time outdoor in traffic: A two-stage case-control study

Anna Lindgren*, Jonas Björk, Emilie Stroh, Kristina Jakobsson

Abstract

Background: Most epidemiologic studies use traffic at residential address as a surrogate for total traffic exposure when investigating effects of traffic on respiratory health. This study used GIS (Geographical Information Systems) to estimate traffic exposure, not only on residential, but also on workplace address, in addition to survey questions on time spent in traffic during commuting or other daily activities.
The aim was to investigate 1) if there is an association between traffic exposure and prevalence of adult asthma and asthma symptoms, and 2) if so, does this association become stronger using more complete traffic exposure information.

Methods: This study was conducted in two stages: A first cross-sectional survey in Southern Sweden 2004 (n = 24819, 18-80 years, response rate 59%) was followed by a case-control study in 2005 to obtain more detailed exposure and confounder information (n = 2856, asthmatics and controls (1:3), 86% response rate). In the first survey, only residential address was known. In the second survey, questions about workplace addresses and daily time spent in traffic were also included. Residential and workplace addresses were geocoded and linked with GIS to road data and dispersion modelled outdoor concentrations of NO_x (annual mean, 250 × 250 m resolution).

Results: Living within 50 m of a road (measured by GIS) with traffic intensity of >10 cars/minute (compared with no road within this distance) was associated with an increased prevalence of asthma, (OR = 1.8, 95% CI = (1.1-2.8), and with asthma symptoms last 12 months. No statistically significant effects were seen for traffic exposure at workplace address, daily time spent in traffic, or commuting time to work, after adjustment for confounders.
A combined total exposure estimate did not give a stronger association with asthma prevalence or asthma symptoms.

Conclusions: Traffic exposure at close proximity to residential address showed association with asthma prevalence and asthma symptoms last 12 months, among adults in southern Sweden. The associations were not stronger when accounting for total traffic exposure. This could reflect exposure misclassfication at workplace address and for other daily time in traffic, but also that residential address remains the main determinant for traffic exposure among adults.

Background

That air pollution can trigger asthma symptoms is well known [1], and there is increasing evidence that traffic also induces asthma incidence in both children [2] and adults [3-6]. This increasing evidence from epidemiological studies has been parallel with and probably dependent on the development of long-term exposure measures of traffic with a geographically high spatial resolution, which capture contrasts in exposure better than data from air pollution monitor stations only [7].

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Although the exposure models for traffic have becomes better in recent years, most studies still estimate only exposure to traffic at residential address, even if a large proportion of traffic exposure, especially for adults, is commuting time, and workplace exposure [8]. The misclassification from using residential exposure as a proxy for total exposure can be expected to distort the true risk estimates, and reduce the power to detect an effect [9]. While personal sampling exposure studies can estimate the relationship between traffic and respiratory symptoms in short-term studies, this is expensive and not feasible for longer time periods or larger populations. It can also be a disadvantage to measure concentrations of a specific pollutant from all sources, rather than the effects of a specific exposure source (i.e traffic) with its complex mixture. It has been suggested that geographical informations systems (GIS) should be used for dynamic, 24 h- modelling of long-term exposure from traffic [10], and this has been done in simulation studies [11], but empirical epidemiological studies linking this to health effects have been rare [12,13].

This is to our knowledge the first study on asthma and traffic to use GIS to estimate traffic exposure, not only at residential address, but also on workplace address and with self-reported information on commuting time to work or other outdoor activity in traffic. Traffic intensity and modelled outdoor NO_x was used as proxies for local traffic-related air pollution, rather than exposure to NO_x per se (which also comes from indoor sources like gas stoves). The aim was to investigate the association between traffic exposure and prevalence of asthma and asthma symptoms in adults in occupationally active age. We investigated 1) separate associations with traffic at residence, workplace, and daily time in traffic, and 2) if combining the exposures, i.e. accounting for total exposure, would strengthen the association between traffic and asthma.

Methods

Study area &sampling

This study was conducted in two stages (figure 1): A first large sample study was followed by nested sampling of a subgroup of asthma cases and controls for more detailed exposure assessment and confounder information.

The first study was a cross-sectional public health survey (Additional files 1, 2) conducted in Scania (southern Sweden) in 2004 (N = 24 819; 59% participation rate, age 18-80 years, however, we restricted our analysis to age 18-65 (n = 22693). The sampling was stratified by age, sex and geographical area, with equal number of subjects randomly sampled in each strata, independent on population size in order to increase the statistical power in some smaller administrative areas [14]. Thus, the descriptive data in the study are only representative for the entire Scania region in a weighted analysis. The survey had a broad public health purpose.

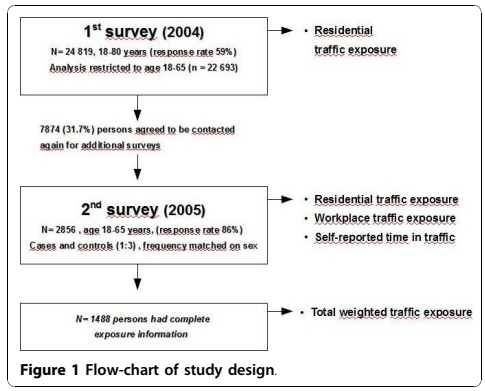

Figure 1 Flow-chart of study design.

The sampling frame for the second survey (Additional files 3, 4) was those in the public health survey who had agreed to participate in additional studies (7874 persons, 31.7% of the participants in the first survey) and were in occupationally active age (18-65). The second survey was sent in 2005 to all eligible asthmatics and to controls (1:3, frequency matched on sex). The final case-control study included 2856 respondents (86% response rate), 705 asthmatics and the rest controls. The questions in this survey were focused on traffic exposures, housing conditions and occupational factors including information on workplace address.

The study was conducted in accordance with the Helsinki Declaration. No animals were used in the study and human subjects participated only after informed consent. Ethical permission for the study was obtained from the Regional Ethics Review Boards, Lund, Sweden. Reference number: dnr 387/2004.

Geocoding

In the first survey, residential addresses for all participants were geocoded. For those participating in the second survey, workplace addresses were also geocoded. At residential address, geocoding was achieved by linking each individual's unique 10-digit personal identity codes to a registry containing the geographical coordinates of nationally registered residential address. This assigned individuals a position in the centre of their real estate.

Workplace addresses were obtained by self-report in the survey, and individuals were manually geocoded to this address, which is more accurate positioning than applying the centre of the real estate.

Exposure assessment

All geocoded addresses were linked to GIS-based registers from the Swedish National Road Database, containing information about traffic intensity on all major roads in the county, for the year 2004. To assess exposure to traffic, we identified the road with the heaviest traffic intensity within 100 m of the residence. Traffic intensity was categorized as 0-1 cars/min, 2-5 cars/min, 6-10 cars/min, and >10 cars/min, based upon 24-hour mean levels.

All geocoded addresses were also linked to modelled concentrations of NO_x based on a validated emission database based on year 2001 [15,16]. The exposure information for NO_x is thus extrapolated from 2001. Emission sources included were: road traffic, shipping, aviation, railroad, industries and larger energy and heat producers, small scale heating, working machines, working vehicles and working tools. Meterological data were also included. A dispersion model (AERMOD) was used for dispersion calculation of annual mean concentrations $\mu g/m^3$, within a 250 × 250 m grid, using bilinear interpolation. A detailed description and discussion of exposure assessment methods has been published previously [17].

In addition to GIS-estimated exposure, questions about traffic at residential address, traffic at workplace address and time spent in traffic were present in the second survey.

In total, the following exposures were investigated:

- *Residential address.*

GIS measured traffic intensity on the heaviest road within 50, 100, 250 m

GIS-modelled exposure to NO_x

Survey question: "What is the traffic intensity on the heaviest road you can see from any window in your apartment? (within a distance of 50 m)"

- *Workplace address.*

GIS measured traffic intensity on the heaviest road within 50, 100, 250 m

GIS-modelled exposure to NO_x

Survey question:" What is the traffic intensity on the street outside your work/school? (within a distance of 50 m)"

- *Daily activities*

Survey questions: "How much time do you on average spend outdoor in traffic every day? (in cars, buses, bike, walking on streets etc)?" and "How long time does it take for you to transport to work/school?"

- Total exposure. N = 1488 people had complete exposure information (geocoded residential and workplace address, reported time spent in traffic and reported percentage of full time work) and were thus used for calculation of total exposure.

Total exposure.was calculated as ((Total time - time at work - time in traffic)*NO_x at home address) + (time at work*NO_x at workplace address) + (time in traffic*C). The constant C representing the hypothesized average NO_x-dose from time in traffic was varied between 30 and 300, since concentrations of fresh exhaust emissions like NO can be many times higher in curbside intense traffic, compared with background levels [18]. NO_x at residential and workplace addresses were estimated by the GIS-modelling. Time in traffic was estimated from the survey question "How much time do you on average spend outdoor in traffic every day?". Time at work was estimated by reported percentage of full-time (40 h/week) occupation.

Categorisations of variables were chosen to be comparable with previous study in the area [17] and for the GIS-measures to be comparable with the self-reported questions. Information on years of living at current address was available.

Outcome measures

The following questions were investigated, as obtained from the postal questionnaires:

- *Asthma prevalence.* "Do you have asthma?" The potential answers "No" "Yes, but no symptoms" "Yes, minor symptoms" "Yes, severe symptoms" were dichotomized to "No" and "Yes " (all three "Yes"-answers were categorized as "Yes"). This question was used in the first survey.
- *Asthma Symptoms during the last 12 months.* Have you had asthma symptoms during the last 12 months, i.e. intermittent breathlessness or attacks of breathlessness? This question was only used in the second survey.

Information about doctor's diagnosis of asthma and use of asthma medication was also available in the second survey.

Statistical analyses

Univariate analyses of the association of asthma with the different traffic measures were performed. Analyses were

also made restricted to those with asthma diagnosis, those with severe and minor symptoms, those with asthma medication (dichotomized as "no" versus "yes", where yes included both "yes, when needed" and "yes, regularly") and those which had been living >5 years at current address.

Associations between asthma and total exposure to NO_x were also estimated. Traffic exposure was categorised into quantiles and effect estimates from total exposure was compared with effect estimates from quantiles based on the single-variate exposures. It could then be assessed if the association got stronger by reclassification of the same individuals according to complete exposure information. Odds Ratios (ORs) with 95% Confidence Intervals (CI) were estimated by binary logistic regression, using version 17.0 of SPSS.

Confounders which were known risk factors and present in both first and second survey were adjusted for (table 1). Adjusting for Socio-Economic Index (SEI) based on occupational status [19] and Body Mass Index (BMI) increased the effect estimates, while additional adjustment for the other confounders in table 1 did not change the estimates noticeably (below 10%), but these were still included in the model. Potential confounder variables from the second survey (damp, smell of mould, condensate on inside of window, more detailed work-exposure assessment by self-reported exposure to dust, motor exhaust or chemicals as separate entities, or by coding self-reported occupation to the ALOHA Job-Exposure-Matrix (JEM), showing probabilistic exposure to dust, gases or fumes [20]), did not noticeably change the estimate further and were not adjusted for.

Results

Description of study population, selection, and exposure

Descriptive data for the study population are given in table 1. White-collar workers were more willing than blue-collar workers to participate in further studies. This was more pronounced among non-asthmatics than asthmatics. Those with high residential traffic exposure were also more willing to participate in additional studies than those with low residential traffic exposure. This difference was more pronounced among asthmatics than non-asthmatics.

In the second survey, there was an increased proportion of white-collar workers and decreased proportion of blue-collar workers answering the second survey, compared to the first survey. In the second survey, there was also a slightly higher response rate among those exposed to >19 $\mu g/m^3$ NO_x , but this was not dependent on asthma status.

Description of overlap between the different traffic exposures can be seen in table 2. Residential exposure to NOx was predictive of exposure at workplace address, but less predictive of time spent outdoor in traffic. Pearson correlation between NO_x (continous) at residential and workplace address was 0.5 ($p < 0.001$). The modelled concentrations of NO_x ($\mu g/m^3$) at residential address were: (1^{st} -3^{rd} quartile = 4.4-13), (min-max = 0.4-37), and at workplace address: (1^{st} -3^{rd} quartile = 7.1-18), (min-max = 0.8-42).

The distribution of NO_x at residential address differed between the different municipalities, with almost all in the high exposure range living in the major municipality Malmö (figure 2).

The distribution of working hours for the subjects included in the analysis of total traffic exposure was (40 hours week was considered 100% of full time): 43 persons reported working more than 100%, 984 persons worked 100%, 270 persons worked 75 to 100%, 144 persons worked 50 to 75%, and 47 persons worked less than 50%. Of those reporting asthma symptoms, 85% also reported that they used asthma medication regularly or when needed (table 3).

Residential traffic

Living within 50 m of a road with a traffic intensity of >10 cars/min according to GIS showed increased asthma prevalence compared to having no road within this distance (table 4). High traffic intensity within 50 and 100 m was associated with asthma symptoms last 12 months (table 4)

No associations were seen with traffic intensity within 250 m or with annual mean of NO_x.

Traffic exposure at workplace address

No effects on asthma prevalence were seen in association with traffic at workplace address (table 5) although asthma symptoms last 12 months showed a tendency to higher prevalence with high exposure to traffic.

Traffic exposure during daily activities

No effects on asthma were seen from self-reported daily time spent in traffic or commuting time to and through work, after adjustment for confounders (adjusted estimates in table 5), although time spent in traffic showed an unadjusted association with asthma symptoms, 1-2 h in traffic (OR = 1.4 (1.0-1.9)) and >2 h in traffic (OR = 1.8(1.3-2.4)) compared to 0-30 min in traffic.

Accounting for total traffic exposure

Combining traffic exposure at residential address, with workplace address and self-reported daily time spent in traffic did not increase the association with asthma (table 6).

Adjusting the association between asthma and traffic intensity at residential address (within 100 m), for traffic intensity at work-address(within 100 m), and daily time

Table 1 Descriptive data from the 1st and 2nd survey

		The 1st survey (2004)			Non-cases stratified on exposure		The 2nd survey (2005)			Non-cases stratified on exposure	
		Cases n (%)	Non-cases n (%)	OR	NOx <19	NOx >19	Cases n (%)	Non-cases n (%)	OR	NOx <19 μ/m³	NOx <19 μ/m³
Sex	Male	865 (40.4)	8726 (45.4)	1.0	7876 (45.5)	850 (44.9)	272 (39.0)	843 (39.0)	1.0	764 (39.3)	79 (36.6)
	Female	1275 (59.6)	10494 (54.6)	1.2 (1.1-1.3)	9449 (54.5)	1045 (55.1)	426 (61.0)	1317 (61.0)	1.0 (0.84-1.2)	1180 (60.7)	137 (63.4)
Age	18-24	282 (13.2)	2119 (11.0)	1.0	1867(10.8)	252 (13.3)	69 (9.9)	216 (10.0)	1.0	186 (9.6)	30 (13.9)
(5 Groups)	25-34	454 (21.2)	3521 (18.3)	0.97 (0.83-1.1)	2937 (17.0)	584 (30.8)	142 (20.3)	435 (20.1)	1.0 (0.73-1.4)	364 (18.7)	71 (32.9)
	35-44	395 (18.5)	4341 (22.6)	0.68 (0.58-0.80)	3980 (23.0)	361 (19.1)	139 (19.9)	470 (21.8)	0.93 (0.67-1.3)	436 (22.4)	34 (15.7)
	45-54	460 (21.5)	4276 (22.2)	0.81 (0.69-0.95)	3937 (22.7)	339 (17.9)	154 (22.1)	461 (21.3)	1.0 (0.75-1.5)	419 (21.6)	42 (19.4)
	55-65	549 (25.7)	4963 (25.8)	0.83 (0.71-0.97)	4604 (26.6)	359 (18.9)	194 (27.8)	578 (26.8)	1.1 (0.77-1.4)	539 (27.7)	39 (18.1)
Smoking	No	1630 (76.6)	14890 (77.9)	1.0	13556 (78.6)	1334 (70.7)	530 (76.3)	1690 (78.6)	1.0	1534 (79.2)	156 (72.6)
	Yes, sometimes	131 (6.2)	984 (5.1)	1.0 (0.92-1.2)	836 (4.8)	148 (7.8)	34 (4.9)	99 (4.6)	1.2(0.92-1.4)	84 (4.3)	15 (7.0)
	Daily	367 (17.2)	3250 (17.0)	1.2 (1.0-1.5)	2846 (16.5)	404 (21.4)	131 (18.8)	362 (16.8)	1.1(0.73-1.6)	318 (16.4)	44 (20.5)
BMI	< 25	1001 (48.4)	10325 (55.0)	1.0	9228 (54.5)	1097 (59.3)	315 (46.3)	1193 (56.2)	1.0	1066 (55.7)	127 (60.8)
	Overweight	740 (35.8)	6399 (34.1)	1.2 (1.1-1.3)	5821 (34.4)	578 (31.2)	264 (38.8)	676 (31.9)	1.5 (1.2-1.8)	614 (32.1)	62 (29.7)
	Fat	327 (15.8)	2057 (11.0)	1.6 (1.4-1.9)	1881 (11.1)	176 (9.5)	102 (15.0)	253 (11.9)	1.5 (1.2-2.0)	233 (12.2)	20 (9.6)
SEI	Professionals, etc	234 (11.8)	2333(12.9)	1.0	2132 (13.1)	201 (11.3)	81 (12.6)	307(14.9)	1.0	278 (15.0)	29 (14.3)
	Intermediate non-manual	340 (17.1)	3366 (18.7)	1.0 (0.85-1.2)	3086 (19.0)	280 (15.8)	124 (19.3)	436(21.2)	1.1(0.79-1.5)	399 (21.5)	37 (18.2)
	Assistant non-manual	187 (9.4)	1735 (9.6)	1.1 (0.88-1.3)	1559 (9.6)	176 (9.9)	71 (11.0)	188(9.1)	1.4 (0.99-2.1)	175 (9.4)	13 (6.4)
	Skilled workers	245 (12.3)	2359 (13.1)	1.0 (0.86-1.3)	2171 (13.3)	188 (10.6)	72 (11.2)	251(12.2)	1.1(0.76-1.6)	226 (12.2)	25 (12.3)
	Unskilled workers	334 (16.8)	3150 (17.5)	1.1 (0.89-1.3)	2854 (17.5)	296 (16.7)	100 (15.5)	287(13.9)	1.3 (0.95-1.8)	252 (13.6)	35 (17.2)
	Self-employed (non-prof.)	107 (5.4)	1275 (7.1)	0.8 (0.66-1.1)	1177 (7.2)	98 (5.5)	38 (5.9)	155(7.5)	0.93 (0.60-1.4)	145 (7.8)	10 (4.9)
	Disability pensioners	192 (9.7)	1042 (5.8)	1.8 (1.5-2.3)	927 (5.7)	115 (6.5)	66(10.2)	131(6.4)	1.9(1.3-2.8)	117 (6.3)	14 (6.9)
	Unemployed	139 (7.0)	1073 (5.9)	1.3 (1.0-1.6)	893 (5.5)	180 (10.2)	32(5.0)	107(5.2)	1.1 (0.71-1.8)	91 (4.9)	16 (7.9)
	Students	210 (10.6)	1702 (9.4)	1.2 (1.0-1.5)	1464 (9.0)	238 (13.4)	60(9.3)	197(9.6)	1.2(0.79-1.7)	173 (9.3)	24 (11.8)
Exposure to chemicals, dust, or fumes at work	Never	909 (61.7)	8876 (62.7)	1.0	8054 (62.4)	91 (62.3)	333 (65.7)	1085 (66.9)	1.0	988 (67.1)	97 (65.1)
	More seldom	303 (20.6)	2731 (19.3)	1.0 (0.86-1.2)	2511 (19.5)	30 (20.5)	101 (19.9)	282 (17.4)	0.97 (0.68-1.4)	256 (17.4)	26 (17.4)
	Few days/week	94 (6.4)	946 (6.7)	0.97 (0.78.-1.2)	872 (6.8)	8 (5.5)	28 (5.5)	103 (6.4)	0.89 (0.57-1.4)	91 (6.2)	12 (8.1)
	Every day	168 (11.4)	1597 (11.3)	1.1 (0.95-1.2)	1468 (11.4)	17 (11.6)	45 (8.9)	152 (9.4)	1.2 (0.90-1.5)	138 (9.4)	14 (9.4)

Table 2 Description of joint exposures

The 2nd survey		NO_x at workplace address (μg/m3)						Time outdoor in traffic/day (self-reported)				
		total	0-8	8-11	11-14	14-19	> 19	Total	0-30 min	30-1 h	1-2 h	> 2 h
NO_x at residential address (μg/m3)	0-8	770	412 (53.5%)	78 (10.1%)	132 (17.1%)	60(7.8%)	88 (11.4%)	770	159 (20.6%)	306 (39.7%)	188 (24.4%)	117 (15.2%)
	8-11	210	30 (14.3%)	44 (21.0%)	59 (28.1%)	32 (15.2%)	45 (21.4%)	210	34 (16.2%)	87 (41.4%)	55 (26.2%)	34 (16.2%)
	11-14	210	13(6.2%)	15(7.1%)	102 (48.6%)	26 (12.4%)	54 (25.7%)	210	41 (19.5%)	88 (41.9%)	65 (31.0%)	16(7.6%)
	14-19	161	4(2.5%)	7(4.3%)	38 (23.6%)	39 (24.2%)	73 (45.3%)	161	29 (18.0%)	65 (40.4%)	41 (25.5%)	26 (16.1%)
	> 19	137	9(6.6%)	4(2.9%)	18 (13.1%)	26 (19.0%)	80 (58.4%)	137	20 (14.6%)	53 (38.7%)	37 (27.0%)	27 (19.7%)

Percentage within row total. Exposure to residential traffic was predictive of exposure at workplace address, but less predictive of time spent outdoor in traffic. The first row shows that of those who live at a residential address with 0-8 ug NOx/m^3, 53.5% also have a workplace address with 0-8 ug NOx/m^3 and 20.6% spend 0-30 min outdoor in traffic/day.

spent in traffic, with and without adjustment for other confounders, did not change the estimate at residence noticeably (< 10%).

Similarly, associations with traffic intensity at workplace address (within 100 m) and time spent in traffic, were robust to adjustment for other traffic exposures.

Restricted analyses

The effects on asthma prevalence from traffic were stronger and statistically significant when limiting to people living on their current address >5 years (data not shown). Restricting the analysis to asthma cases which also had doctors diagnosis of asthma did not significantly alter the estimates. Restricting the analyses to subgroups of asthmatics who had answered "Yes, minor symptoms" or "Yes, severe symptoms" (compared to "No asthma") did not significantly alter the estimates. Use of asthma medication was associated with having a road with a traffic intensity of >10 cars/min, within 50 m (adj. OR = 3.24(1.39-7.58) and within 100 m (adj. OR = 2.07(1.01-4.27) of residence, compared to having no road within the same distance, but use of asthma medication was not associated with the other traffic exposures.

Discussion

Living in close proximity to traffic was associated with increased prevalence of asthma and asthma symptoms last 12 months. No statistically significant effects were seen from traffic exposure at workplace address, daily time spent in traffic, or commuting time to work, after adjustment for potential confounders. A combined exposure estimate did not give higher association with asthma.

Discussion of exposure assessment

This is to our knowledge the first epidemiological study on asthma to use GIS not only to estimate traffic at residential address but also at workplace address and with information about commuting time to work or other outdoor time in traffic. However, while this more complete exposure information could be expected to strengthen any association with asthma, this was not found in this study.

A potential reason that no significant adverse effect was seen on workplace address could be if misclassification of exposure, due to invalid geocoding, was larger for workplace address. Since geocoding for the workplace address was made for the exact address, the geocoding technique in itself is not likely to be the reason for no association. However, if the study subjects are not stationary at their work location, or the company address might refer to larger commercial areas or buildings there might be little association between the personal exposure and the outdoor-indoor levels for that location. Exposure estimates at the residential addresses might on the other hand have inaccuracies due to imprecise geocoding since individuals are positioned at the centre of their real estates. In urban areas there might therefore be substantial misplacement for individuals living in large family-housing, or for large estates with vast land areas in the rural areas. It is well known that geocoding error generally gives conservative estimates [21], as does exposure misclassification in general if not related to disease.

It should be noted that effects of traffic on asthma symptoms were indicated at workplace addresses, but the effect estimates were lower than at residential address, and not statistically significant.

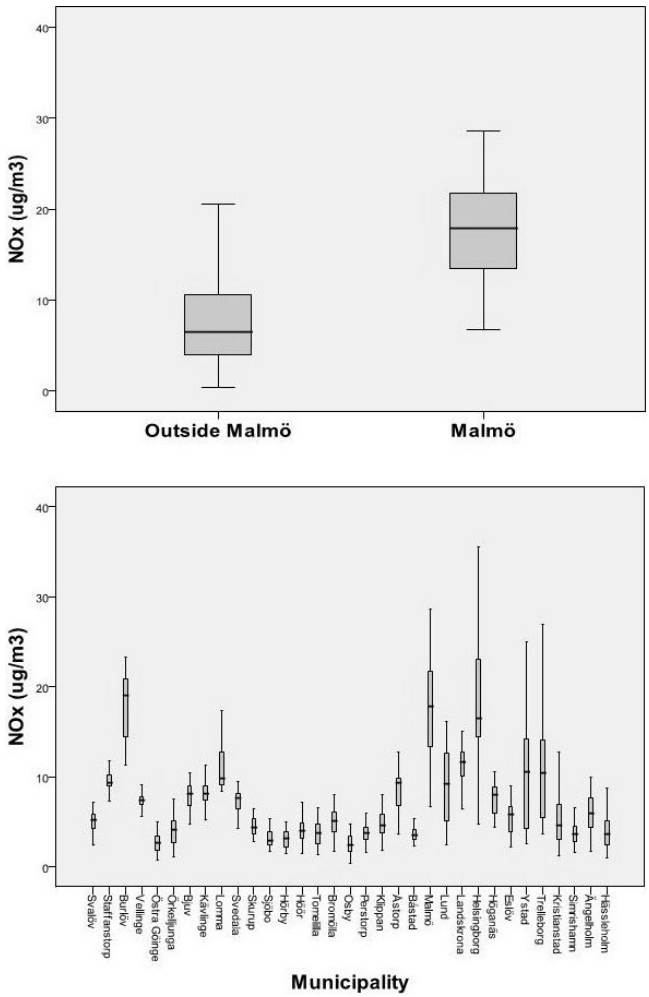

Figure 2 Exposure distribution of NO_x at residence, a) among people living in the major municipality Malmö (n = 3408 persons) vs outside (n = 19285 persons) and b) in all the 33 municipalities separately.

Table 3 Use of asthma medication

			Asthma medication			
			No	Yes, when needed	Yes, regularly	Total
Asthmatic symptoms	NO	Count	2253	81	45	2379
		%	94.7%	3.4%	1.9%	100.0%
	YES	Count	68	185	200	453
		%	15.0%	40.8%	44.2%	100.0%

Of those who reported asthmatic symptoms last 12 months did 85% also report using asthma medication regularly or when needed.

Table 4 Asthma and traffic at residential address

Residential Address		The 1st survey (2004)			The 2nd survey (2005)				
		n	Asthma n (%)	Asthma (OR)[1]	n	Asthma n (%)	Asthma (OR)[1]	Asthma symptoms n (%)	Asthma symtoms (OR)[1]
Self-report Heaviest road <50 m	0-1 cars/min	-	-	-	445	105 (23.6)	1.0	71(16.0)	1.0
	< 2 cars/min	-	-	-	1512	339 (22.4)	1.10 (0.81-1.5)	216(14.4)	0.95 (0.66-1.4)
	2-5 cars/min	-	-	-	410	113 (27.6)	1.17 (0.80-1.7)	81(19.9)	1.2 (0.76-1.8)
	6-10 cars/min	-	-	-	203	56 (27.6)	1.20 (0.74-2.0)	34(17.0)	0.79 (0.42-1.5)
	> 10 cars/min	-	-	-	258	76 (29.5)	1.5 (0.94-2.3)	48(18.5)	1.2 (0.72-2.1)
GIS Heaviest road <50 m	no heavy road	15584	1542 (9.9)	1.0	2100	494 (23.5)	1.0	316 (15.1)	1.0
	< 2 cars/min	3691	375 (10.2)	1.0 (0.90-1.2)	472	121 (25.6)	1.2 (0.89-1.6)	79 (16.8)	1.1 (0.81-1.6)
	2-5 cars/min	1555	159 (10.2)	0.95 (0.76-1.2)	216	61 (28.2)	1.2 (0.79-1.7)	39 (18.1)	1.1 (0.71-1.8)
	6-10 cars/min	307	35 (11.4)	1.0 (0.65-1.6)	34	10 (29.4)	1.0 (0.33-3.2)	7(20.6)	1.4 (0.39-5.1)
	> 10 cars/min	223	29 (13.0)	1.8 (1.1-2.8)	36	12 (33.3)	2.3 (0.99-5.2)	12 (33.3)	4.6 (2.0-10.6)
GIS Heaviest road <100 m	no heavy road	10875	1062 (9.8)	1.0	1461	330 (22.6)	1.0	215 (14.7)	1.0
	< 2 cars/min	5741	589 (10.3)	1.1 (0.92-1.2)	744	197 (26.5)	1.4 (1.1-1.7)	128 (17.4)	1.2 (0.92-1.7)
	2-5 cars/min	3309	327 (9.9)	0.96 (0.81-1.1)	462	121 (26.2)	1.2 (0.88-1.6)	75 (16.3)	1.1 (0.80-1.7)
	6-10 cars/min	894	101 (11.3)	1.2 (0.92-1.6)	119	29 (24.4)	1.4 (0.82-2.3)	14 (11.8)	0.81 (0.38-1.7)
	> 10 cars/min	541	61 (11.3)	1.3 (0.95-1.8)	72	21 (29.2)	1.6 (0.82-3.2)	21 (29.2)	2.7 (1.3-5.5)
GIS Heaviest road <250 m	no heavy road	4412	429 (9.7)	1.0	590	136 (23.1)	1.0	84 (14.2)	1.0
	< 2 cars/min	7079	698 (9.9)	1.0 (0.86-1.2)	904	225 (24.9)	1.1 (0.85-1.5)	147 (16.4)	1.1 (0.7-1.5)
	2-5 cars/min	6297	636 (10.1)	0.96 (0.82-1.1)	870	220 (25.3)	1.1 (0.83-1.5)	139 (16.1)	1.0 (0.7-1.4)
	6-10 cars/min	2100	222 (10.6)	1.1 (0.86-1.3)	298	68 (22.8)	1.2 (0.77-1.7)	42 (14.1)	1.0 (0.6-1.9)
	> 10 cars/min	1472	155 (10.5)	0.98 (0.76-1.3)	196	49 (25.0)	0.8 (0.51-1.4)	41 (20.7)	1.1 (0.6-1.9)
GIS NOx ($\mu g/m^3$) (250 × 250 m)	0-8	11273	1111 (9.9)	1.0	1508	376 (24.9)	1.0	240 (16.0)	1.0
	8-11	3133	300 (9.6)	0.94 (0.79-1.1)	371	78 (21.0)	0.79 (0.56-1.1)	45 (12.3)	1.0 (0.74-1.49)
	11-14	2496	256 (10.3)	1.1 (0.93-1.3)	388	90 (23.2)	1.2 (0.86-1.6)	57 (14.8)	0.97 (0.68-1.39)
	14-19	2319	229 (9.9)	0.84 (0.69-1.0)	298	77 (25.8)	1.0 (0.73-1.5)	55 (18.4)	0.99 (0.60-1.6)
	> 19	2139	244 (11.4)	1.1 (0.93-1.4)	293	77 (26.3)	1.1 (077)	56 (19.1)	1.1 (0.60-1.9)

[1]Adjusted for age, sex, BMI, socio-economy, smoking, and occupational exposure. [OR(95%CI)]

Since the associations between traffic-related air pollution and asthma generally shows distance-dependent relationship with strongest effects on asthma from living within 50 m of roads, and with sharp decline of many air pollutants within 30-150 m, a modelled resolution on NO_x of 250 × 250 m might be too low to detect any effects from traffic. This must be weighted against the fact that a higher spatial resolution may not be meaningful considering the likely location uncertainty of workplace address.

Table 5 Asthma and traffic at workplace address and during daily activities

The 2nd survey						
WORKPLACE ADDRESS		**n**	**Asthma n (%)**	**Asthma (OR)[1]**	**Asthma Symptoms. n (%)**	**Asthma Symptoms (OR)[1]**
Self-reported Heaviest road <50 m	0-1 cars/min	601	144 (24.0)	1.0	80 (13.4)	1.0
	2-5 cars/min	571	132 (23.1)	1.1 (0.80-1.5)	79 (14.0)	0.95 (0.66-1.4)
	6-10 cars/min	351	75 (21.4)	1.2 (0.79-1.7)	49 (14.0)	1.2 (0.76-1.8)
	> 10 cars/min	606	147 (24.3)	1.2 (0.73-1.9)	96 (15.9)	0.79 (0.42-1.5)
	Workplace varies	214	50 (23.4)	1.5 (0.93-2.7)	34 (16.0)	1.2 (0.72-2.1)
GIS Heaviest road <50 m	no heavy road	161	36 (22.4)	1.0	21 (13.2)	1.0
	< 2 cars/min	267	61 (22.8)	1.0 (0.62-1.7)	34 (12.7)	1.1 (0.55-2.1)
	2-5 cars/min	673	149 (22.1)	0.91 (0.57-1.4)	94 (14.0)	1.2 (0.65-2.1)
	6-10 cars/min	407	83 (20.4)	0.92 (0.56-1.5)	45 (11.1)	1.1 (0.58-2.0)
	> 10 cars/min	326	78 (23.9)	1.0 (0.62-1.7)	51 (15.7)	1.4 (0.72-2.6)
GIS Heaviest road <100 m	no heavy road	527	126 (23.9)	1.0	74 (14.1)	1.0
	< 2 cars/min	327	76 (23.2)	0.88 (0.61-1.3)	41 (12.5)	0.79 (0.49-1.3)
	2-5 cars/min	509	102 (20.0)	0.85 (0.61-1.2)	67 (13.2)	0.97 (0.65-1.5)
	6-10 cars/min	277	58 (20.9)	0.98 (0.66-1.5)	35 (12.7)	1.2 (0.74-1.9)
	> 10 cars/min	194	45 (23.2)	0.99 (0.63-1.5)	28 (14.5)	1.2 (0.72-2.1)
GIS Heaviest road <250 m	no heavy road	161	36 (22.4)	1.0	21 (13.2)	1.0
	< 2 cars/min	267	61 (22.8)	1.0 (0.62-1.8)	34 (12.7)	1.1 (0.55-2.1)
	2-5 cars/min	673	149 (22.1)	0.91 (0.57-1.4)	94 (14.0)	1.2 (0.65-2.1)
	6-10 cars/min	407	83 (20.4)	0.92 (0.56-1.5)	45 (11.1)	1.1 (0.58-2.0)
	> 10 cars/min	326	78 (23.9)	1.0 (0.62-1.7)	51 (15.7)	1.4 (0.72-2.6)
GIS NO_x ($\mu g/m^{3)}$ (250 × 250 m)	0-8	558	129 (23.1)	1.0	70 (12.6)	1.0
	8-11	163	34 (20.9)	0.88 (0.55-1.4)	23 (14.1)	1.1 (0.65-2.0)
	11-14	455	94 (20.7)	0.91 (0.65-1.3)	56 (12.4)	0.99 (0.64-1.5)
	14-19	227	48 (21.1)	1.0 (0.68-1.5)	27 (11.9)	1.2 (0.71-2.0)
	> 19	431	102 (23.7)	0.98 (0.70-1.4)	69 (16.1)	1.3 (0.88-2.0)
DAILY ACTIVITIES		**n**	**Asthma n (%)**	**Asthma (OR)[1]**	**Asthma symptoms n (%)**	**Asthma Symptoms n (%)**
Time outdoor in traffic/day	0-30 min	622	134 (21.5)	1.0	79 (12.8)	1.0
	30 min-1 h	1066	248 (23.3)	1.1 (0.8-1.4)	159 (15.1)	1.2 (0.83-1.7)
	1-2 h	715	194 (27.1)	1.1 (0.8-1.5)	121 (17.0)	1.4 (0.91-2.0)
	> 2 h	453	121 (26.7)	1.0 (0.7-1.4)	92 (20.4)	1.3 (0.83-2.0)
Commuting time to work	< 15 min	881	211 (24.0)	1.0	117 (13.4)	1.0
	15-30 min	915	207 (22.6)	0.90 (0.70-1.1)	140 (15.4)	1.1 (0.84-1.5)
	30 min-1 h	408	99 (24.3)	1.0 (0.73-1.4)	60 (14.8)	1.2 (0.78-1.7)
	> 1 h	129	29 (22.5)	0.77 (0.45-1.33)	18 (14.2)	0.92 (0.47-1.8)

[1]Adjusted for age, sex, BMI, socio-economy, smoking, and occupational exposure. [OR(95%CI)]

An effect from daily time spent in traffic on asthma symptoms was indicated in unadjusted estimates, but not after adjustment for confounders. Exposure studies and simulations studies have shown that personal NO_x dose *per se* is only marginally influenced by commuting time [11], but if NO_x is seen as a proxy for NO and ultrafine particles, or other pipe-exhausts, the contribution from time in traffic outdoor at street-level i.e in congested traffic, may be many times higher and very influential of total exposure. In this study we regarded NO_x as a proxy for traffic pollution and treated use of gas stove as a potential confounder rather than exposure. When calculating the contribution of "time in traffic" to total exposure, we let the "dosecontribution" vary between 30 $\mu g/m^3$ and a more extreme scenario of 300 $\mu g/m^3$, but this did not give a stronger association with asthma, although some of the asthma cases were moved from the lowest to a higher exposure category.

The major source of exposure misclassification may be the cross-sectional study character, especially for asthma

Table 6 Total traffic exposure

The 2nd survey						
COMBINED EXPOSURE	**n**	**Asthma, n (%)**	**Asthma, n (%)**	**Asthma OR[1]**	**Asthma symptoms, n (%)**	**Asthma symptoms (OR)[1]**
Total exposure[2] *C = 30*	1st	298	72(24.2%)	1.00	41(13.8%)	1.00
	2nd	298	68(22.8%)	0.90 (0.61-1.35)	32(10.8%)	0.70(0.41-1.18)
	3rd	297	59(19.9%)	0.76 (0.51-1.15)	43(14.5%)	1.09(0.67-1.77)
	4th	298	65(21.8%)	0.87 (0.58-1.31)	41(13.8%)	1.09(0.66-1.79)
	5th	297	70(23.6%)	0.96 (0.64-1.44)	48(16.2%)	1.28(0.79-2.08)
Total exposure[2] *C = 300*	1st	298	67(22.5%)	1.00	35(11.8%)	1.00
	2nd	298	67/22.5%)	1.02 (0.68-1.53)	35(11.8%)	1.06(0.63-1.79)
	3rd	297	69(23.2%)	1.00 (0.66-1.50)	48(16.2%)	1.50(0.91-2.48)
	4th	298	65(21.8%)	0.88 (0.58-1.34)	45(15.2%)	1.33(0.79-2.21)
	5th	297	66(22.2%)	0.88 (0.58-1.33)	42(14.1%)	1.18(0.71-1.99)
Residential + workplace Address[2]	1st	298	73(24.5%)	1.00	41(13.8%)	1.00
	2nd	298	69(23.2%)	0.91 (0.61-1.35)	36(12.1%)	0.89(0.53-1.47)
	3rd	297	54(18.2%)	0.64 (0.42-0.97)	36(12.2%)	0.87(0.52-1.44)
	4th	298	69(23.2%)	0.98 (0.66-1.46)	46(15.5%)	1.31(0.81-2.12)
	5th	297	69(23.2%)	0.94 (0.63-1.41)	46(15.5%)	1.27(0.78-2.07)
Workplace Address	1st	298	74(24.8%)	1.00	40(13.5%)	1.00
	2nd	298	64(21.5%)	0.81 (0.54-1.22)	41(13.8%)	1.12(0.68-1.85)
	3rd	297	66(22.2%)	0.87 (0.58-1.31)	41(13.8%)	1.11(0.67-1.85)
	4th	298	67/22.5%)	0.92 (0.62-1.37)	40(13.5%)	1.14(0.70-1.88)
	5th	297	63(21.2%)	0.77 (0.51-1.16)	43(14.6%)	1.19(0.72-1.96)
Residential Address	1st	298	71(23.8%)	1.00	41(13.8%)	1.00
	2nd	298	70(23.5%)	0.90 (0.60-1.34)	35(11.8%)	0.80(0.48-1.33)
	3rd	297	58(19.5%)	0.78 (0.52-1.18)	41(13.9%)	1.08(0.66-1.75)
	4th	298	66(22.1%)	0.91 (0.60-1.36)	40(13.4%)	1.09(0.66-1.80)
	5th	297	69(23.2%)	0.96 (0.64-1.44)	48(16.2%)	1.31(0.81-2.13)

[1]Adjusted for age, sex, BMI, socio-economy, smoking, and occupational exposure. [OR(95%CI)]. [2] Total exposure assessment (residential address + workplace address + time in traffic) is explained in methods section. The estimate based on only residential + workplace address is also time-weighted. C is the exposure dose time in traffic is hypothesized to contribute.

The association between traffic and asthma is not stronger when combining total exposure compared to using only residential exposure. Using quantiles, i.e holding the number of individuals fixed in each category, the changes in estimates reflects individuals moving between the low/high categories depending on what exposures (residential address, workplace address, time outdoor in traffic) that are combined to estimate high vs low traffic exposure.

prevalence, which showed an increased association with traffic when analysis was restricted to subjects which had been living at least 5 years at current address. Although asthma may start in adult age, most asthma begin in childhood [22], hence, a cross-sectional study in adults may poorly reflect retrospective exposure. This however should less affect the results for asthma symptoms last 12 months, a condition which is better related to current exposure, but may have different etiology and be affected differently by air pollution [23].

Since air pollution is well known to trigger symptoms [1,23], (even if it is less certain if it contributes to the development of asthma), asthmatics may be more likely to move away from than towards traffic. Therefore a migrational bias is most likely to decrease the effects on asthma prevalence and asthma symptoms. It is also likely that the large proportion (44%) who regularly used asthma medication further would diminish the association between traffic and asthma symptoms, especially since people living closing to roads had a higher prevalence of asthma medication. In conclusion, cross-sectional studies need to be confirmed by prospective studies, not only to establish the casual link, but also to measure the true burden of disease from traffic.

Since this study was conducted in an area with low levels of air pollution in a European perspective, high exposure to traffic was rare and the study was slightly underpowered to estimate effects from residential traffic at traffic levels which has previously shown to be related to effects. This also hindered any further analysis of effect modifications by other risk factors than traffic. Pooling of exposure groups would not help since only the highest exposure groups showed a relation to traffic, thus pooling would severely dilute the effects.

Discussion of potential confounding and selection bias

A strength of the study was the large number of potential confounder information which was collected, such

as BMI [24], occupational exposure [25], and presence of indoor dampness and mould [26], which are known risk factors for adult asthma and often associated with socio-economic status of the neighbourhood. Socio-economic status (SEI), with the classification system used in this study, has in Sweden shown an association with asthma incidence in recent years [27]. Confounder adjustment slightly increased the effect estimates for residential address, suggesting that competing risk factors sometimes dilute the effects from traffic, something we have previously suggested [17]. A weakness was that we did not have more detailed data on triggers for asthmatic symptoms, since we previously have observed a association between traffic and asthma triggered by pollen and furred animals, but not with asthma triggered by other factors [28]. Degree of confounding (measured or unmeasured) is not likely to be directly generalizable between studies since the association between covariates such as socio-economic status and air pollution (NO_x) has been shown to be reversed depending on area in Scania [29]. Confounding is better controlled for with respect to asthma symptoms than to asthma prevalence in this study, since we had information about current but not past exposure to risk factors.

The effect estimates for residential traffic were stronger in the case-control study than in the first survey, indicating potential selection bias. In previous public health surveys in the region it has been shown that the response rate is dependent on geographical strata [30]. It is thus not unlikely that selection bias can have occurred, however the objective exposure assessments used in this study is a true advantage. Ideally, since this study was sampled on geographical strata, an analysis conditional on geographical stratum might have increased the validity. This was however not possible since exposure ranges were not comparable between the different stratas/communities (figure 2). This also excluded the possibility to use a dummy variable for urban/rural areas to adjust for potential residual urban-rural confounding. It should be noted that accounting for total traffic exposure could further have strengthened any residual urban-rural confounding by comparing people who are both working and living in rural environments, with people who are both working and living in urban environments.

Results discussion

To our knowledge, all previous studies on adult asthma prevalence have only estimated traffic exposure at residential address. A previous cross-sectional study in southern Sweden found asthma triggered by allergic factors to be associated with high traffic intensity within 100 m of residence, and with modelled NO_x > 19 μg/m^3 [17,28]. A cross-sectional study in northern Sweden found that asthmatic symptoms increased significantly with modelled NO_2-concentrations and self-reported heavy vehicles outside the kitchen window [31]. A Swedish case-control study found measured home outdoor NO_2 (min-max: 0-29 μg/m^3) to be associated with asthma incidence among atopics [5]. The Swedish cities in the Nordic Rhine study found modelled NO_2 to be associated with incident asthma (OR = 1.5, 95% CI 1.0-2.4, per 10 μg/m^3) (min-max: 3.3-46 μg/m^3) [6].

A few European cohort studies have supported that traffic pollution increases asthma incidence in adults: The ECRHS study found an association between modelled NO_2 and increased asthma incidence (OR 1.4; 95% CI 1.0-2.0, per 10 μg/m^3) [3], The SAPALDIA study found that asthma incidence was associated with modelled change in TPM_{10}, hazard ratio (1.3, 95%CI: 1.1 - 1.6 per 1 μg/m^3 change) [4]

The results from other Swedish studies support that asthma symptoms are affected at relatively low levels of air pollution. Cohort studies in adults, although still few, also supports that the association between traffic exposure and asthma prevalence observed in this cross-sectional study may reflect a true increase in asthma incidence when living close to traffic.

However, if the most recent studies support the association between air pollution and asthma, the relation with asthma incidence is not fully settled and there are also a few recent negative studies in adults [32,33], and some cohorts in children [34].

There are two studies in children which have investigated the effects of traffic at both home and school, on asthma. McConnell et al found an increased hazard ratio when combining traffic-related pollutants at school-and residential address, on new-onset asthma, compared to the independent effects [12]. The other study by Kim et al make a reservation that the study was not designed for independent assessment of exposure at school- and residential address, and the sample size was insufficient to properly do so, but they report that they found a slight attenuation of effects on current asthma from residential traffic pollution when adding both residential and school exposure in the same model [13].

In our study, effects at workplace address in the highest exposure categories were statistically insignificant partly because lack of power to confirm small effect estimates. Further studies in areas where high levels of air pollution is rare, should consider to strongly oversample exposed subjects in relevant exposure ranges and population groups.

However, the lack of power can not explain that the association did not get stronger for total exposure. Alhough our lack of statistically significant association with traffic at workplace address and time spent in

traffic may be due to misclassification of exposure, it may also indicate that residence is still the most influential exposure determinant of traffic exposure among adults.

Conclusions

Living within 50 m of a road with high traffic intensity was associated with higher prevalence of asthma and asthma symptoms last 12 months. No statistically significant effects were seen from traffic exposure at work-address, daily time spent in traffic, or commuting time to and through work. A combined total exposure estimate did not give a stronger association with asthma prevalence or asthma symptoms.

Additional material

Additional file 1: Survey1_2004_Swedish original. The Swedish original questionnaire for the first survey (2004).

Additional file 2: Survey1_2004_English translation. English translation of the first survey questionnaire (2004).

Additional file 3: Survey2_2005_Swedish orginal. The Swedish original questionnaire for the second survey (2005).

Additional file 4: Survey2_2005_English translation. English translation of the second survey questionnaire (2005).

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Authors' contributions

AL wrote the main part part of the manuscript and conducted the statistical analyses. ES provided GIS-data and made revisions on draft. JB and KJ designed and conducted the surveys and made revisions on drafts. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Asthma incidence in children growing up close to traffic: a registry-based birth cohort

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Asthma incidence in children growing up close to traffic: a registry-based birth cohort

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Abstract

Background

Recent reviews conclude an association between traffic-related pollution and incidence of asthma in children, but not all studies agree. Studies have almost exclusively relied on parental-reported symptoms or parental-reported diagnoses of asthma and wheeze. Our aim was to investigate if traffic exposure is associated with higher incidence of early onset asthma, using registry-based outcome data.

Methods

We investigated a birth cohort in southern Sweden, consisting of N = 26 128 children with outcome and exposure data (born July 2005–2010). Of these children, N = 7898 had additional covariate information. The cohort was followed to the end of 2011.

Traffic intensity, and dispersion-modeled concentrations of NO_X (100x100 m grid), at residential addresses, were linked with registry data on dispensed asthma medication (the Swedish Prescribed Drug Register), and hospital and primary health care diagnoses of bronchiolitis, obstructive bronchitis and asthma (The Scania Health Care Register).

Covariate information was obtained from questionnaires distributed to parents at Child Health Care-centre visits, eight months after birth. Cox proportional hazards regression was used for the statistical analyses.

Results

Living in close proximity to a road with ≥8640 cars/day (compared to 0–8640 cars/day), was not associated with higher incidence of first purchase of inhaled β_2-agonist (adjusted hazard ratio (adj.HR) = 0.9, 95% CI: 0.8-1.0); third year purchase of inhaled β_2-agonist (adj.HR = 0.7, 95% CI: 0.6-0.9); bronchiolitis (adj.HR = 0.7, 95% CI: 0.6-0.9), obstructive bronchitis (adj.HR = 1.0, 95% CI: 0.9-1.2), or asthma (adj.HR = 0.7, 95% CI: 0.6- 0.9). Similar results were found for inhaled corticosteroids, and in relation to NO_X.

Conclusions

Traffic-related exposure was not associated with higher incidence of asthma medication, or diagnoses of asthma, bronchiolitis, or obstructive bronchitis, in children 0–6 years in southern Sweden. This may depend on the low levels of traffic pollution in the area, mainly well below the WHO-guideline for NO_2.

Keywords

Air pollution, Asthma, Bronchitis, Children, Environmental, Epidemiology, GIS, Nitrogen oxides, Roadway proximity, Traffic

Background

It is well known that traffic-related air pollution can trigger asthma symptoms in children and adults [1]. There is also increasing evidence that long-term exposure to traffic exhaust increases the incidence of asthma development in children. Recent reviews conclude that living close to a major road is associated with higher asthma incidence in children, although there is not evidence to conclude a casual relation [2,3].

Asthmatic symptoms in children, sometimes termed “wheeze”, or “obstructive respiratory symptoms”, has diverse etiology. Before the age of 3 years, asthmatic symptoms are mainly due to respiratory virus infections, while after 3 years, asthma due to allergic sensitization is more often the cause [4]. Early asthmatic symptoms, “wheeze”, to some degree predict later asthma [5]. Traffic has been connected to both early [6,7], and late childhood asthma incidence [8-12].

For children, asthmatic symptoms, “wheeze”, are not clinically distinct disease entities, but rather clinically similar wheezing symptoms which becomes classified according to age and other characteristics. Bronchiolitis is a diagnosis of wheeze, mainly used for infants. Obstructive bronchitis is a diagnosis used for single episodes of wheezing symptoms for children mainly younger than 3 years, when nothing speaks for allergic etiology. Asthma is a diagnosis often used for a third episode of wheezing symptoms, or for a first episode when the child is older, the parents are known to be allergic, or the child has had atopic eczema which speaks for an allergic heredity [13]. The above statement refers to common diagnostic practice in Sweden, but practice may differ between countries.

The first line of treatment for obstructive wheezing symptoms is inhaled β_2-agonists, which is prescribed for all of the mentioned diagnoses, and give immediate relief by dilating the

airways. Inhaled corticosteroids, which has a more preventive anti-inflammatory effect, is prescribed as an additional medication for treatment of repeated wheeze or wheeze with suspected allergic component and is considered more specific for asthma. Some studies have used inhaled β_2-agonists/corticosteroids as a proxy for asthma incidence [14,15].

Studies on long-term effects of traffic on asthma, however, have traditionally relied on parental-reports of wheeze or parental-reports on diagnosis of asthma. Clinical asthma examinations cannot be performed in small children due to compliance difficulties [16], and have not been performed in cohort studies on traffic pollution and asthma incidence in older children either, probably because of the cost and effort required which would result in a small sample size. Due to the risk of awareness bias in parental-reported data [17], and the risk of overestimation of effects in small samples [18], there is a need for registry-based studies which can have both objective outcome data and a larger sample size.

The Swedish Prescribed Drug Register has a complete (99.7%) coverage of individual-level dispensed medication for all individuals living in Sweden, and dispensed asthma medication will in this study be used as a proxy variable for incidence of asthma. We also used diagnosis of bronchiolitis, obstructive bronchitis, and asthma, from the Scania Health Care Register (SHCR), which covers inpatient and outpatient care in the region, from hospitals as well as primary health care centers. However, the SHCR has less complete coverage and will therefore be used as a secondary outcome. This is the first study to use dispensed medication to estimate long-term effects from traffic-related exposure on asthma, and only one study has used hospital and primary health care registries for this purpose before [8].

The overall study aim was to investigate if children growing up close to high traffic intensity, or high levels of nitrogen oxides (NO_X), are at higher risk of developing asthma, or other obstructive respiratory disease, “wheezing”, in early childhood.

Methods

Study area

Scania is the southernmost county of Sweden, with a population of 1 243 329, in year 2010 [19]. Children born in Scania, whose mothers were registered as living in the municipalities Malmö, Svedala, Vellinge or Trelleborg were included, since survey data with covariate information were available from Child Health Care centers (CHC) in this area. Malmö is the major municipality in the county, 298 963 inhabitants, with a large socio-economically disadvantaged immigrant population, 30.2% foreign born. Previous studies have found that immigrants,and children residing in areas with low income, has a higher exposure to NO_2 in Malmö [20,21].

Malmö has the highest level of air pollution in the area. Although pollutant levels in the region are low in a European context (Additional file 1), they are higher than in most of Sweden, due to long-range transport of pollutants from the continent and extensive harbor and ferry traffic.

Selection of study population

A flow-chart of the study population selection is displayed in Figure 1. The study was limited in time to children born from July 2005, since individual level medication data is only available since then. All children were followed to the end of 2011.

Figure 1 Selection of study population.

To identify a birth cohort, we retrospectively retrieved the identity number of all children born by mothers living in Malmö, Svedala, Vellinge and Trelleborg during July 2005–2010, from the Perinatal Revision South (PNS)-registry. The PNS registry has a 100% coverage of visits on obstetric and peri/prenatal units in the county. Out of 28 037 children identified in the PNS-register, 875 were not found in the Scania population registry and thus excluded, since they were not registered as living in the region during childhood. Outcome data was available for all children found in the Scania population registry (n = 27 162), by linkage to the SHCR and the Swedish Prescribed Drug Register. Geographical coordinates (geocodes) for registered birth year address was available for 26 128 children, for which exposure was assessed. Most of the missing geocodes belonged to children born in December, whose late birth date probably lead to addresses not being registered during year of birth. Geocodes were retrieved for birth year and subsequent years for each child, until the end of 2010. Finally, covariate information from questionnaires routinely distributed at Child Health Care centers was available for 7898 children, which formed the main study cohort.

Ethical permission

This study was approved by the Lund University Ethical Committee (registration no. 2011/468). No formal informed consent was required, but the study was advertised in the local newspaper and information was distributed to Child Health Care centers, allowing parents to request that their children not be included in it. No such request was raised.

Asthma medication

The Swedish Prescribed Drug Register includes all drugs dispensed at pharmacies in Sweden, since July 2005 linked to personal identity numbers [22]. The registry is maintained by the National Board of Health and Welfare. All expedited drugs on the pharmacies are registered, with a very small number of incorrect or incomplete registrations of ID. The population coverage with correct patient identities is 99.7% [23].

The registry contains data on all dispensed prescriptions in ambulatory care. Over-the-counter (OTC) medications and drugs used at in-patients settings are not included. Medication data are classified according to the Anatomical Therapeutic Chemical (ATC) Classification System [24].

The Pharmaceutical Benefit Scheme, which is mainly tax financed, covers the main costs for drugs in ambulatory care in Sweden. There is a ceiling on the total amount that a patient pays during a 12-month period for subsidized pharmaceuticals (2013: SEK 2200, €252). The drug costs of children younger than 18 years, living in the same household, are counted together.

We obtained information on medications prescribed for obstructive airways disease (ATC-code R03). The outcomes used were dispensed prescription of inhaled β_2-agonist (ATC-codes: R03AC, R03AK04, R03AK06, R03AK07), and inhaled corticosteroids (ATC-codes: R03BA, R03AK06, R03AK07). Drugs with code R03AK06 and R03AK07 are combinations of β_2-agonists and corticosteroids and therefore occur in both outcomes.

As primary outcomes we used:

1) Incidence of first ever dispensed inhaled β_2-agonist
2) Incidence of third year with dispensed inhaled β_2-agonist
3) Incidence of first ever dispensed inhaled corticosteroid
4) Incidence of third year with dispensed inhaled corticosteroid

First dispensed medication was seen as a proxy for incidence of obstructive respiratory disease, but may reflect primarily transient disease. Third year with dispensed medication was seen as a proxy for more persistent disease. The three years were not necessarily consecutive years.

Diagnoses of bronchiolitis, obstructive bronchitis, and asthma

In Sweden, all healthcare consultations are recorded in county-specific databases. The SHCR holds details for primary health care, and hospital based in- and outpatient care for Scania. In Sweden, all patients are registered to a general primary care practice. However, patients are not obliged to attend primary care before seeing a specialist, although that is the most common procedure [25].

Each consultation generates data entries that are transferred to SHCR and which constitute the basis for reimbursement to the healthcare providers. The hospital care has a good coverage and validity for diagnostic codes [25,26]. However, for primary care, the number of consultations with diagnostic codes is less complete. The diagnostic codes from public care are transferred to SHCR, but have some missing registration of diagnostic codes due to incomplete journal entries. For private health care providers, consultation events, but not diagnostic codes, are transferred to SHCR. Private care makes up approximately 30% of all primary care in Scania [25].

The number of visits that lacked diagnostic codes was only provided on overall level for the children in this study, not individual level.

The hospital-based health care uses a Swedish version of the diagnostic ICD-10 system, ICD-10-SE, and the primary health care uses a simplified version, KSH97-P. As secondary outcomes we used diagnostic codes from SHCR, including hospital-based as well as primary health care. Visits are often given multiple diagnostic codes, but we included only the primary diagnostic code.

The secondary outcomes were primary diagnoses of:

1) bronchiolitis (J210, J218, J219),
2) obstructive bronchitis (J200-J209, J22-P)
3) asthma (J450- J459, J45-P, J469)

Exposure assessment

Geocodes for the children's officially registered residential addresses were retrieved from the population registry, for each year from birth until the end of 2010. Individuals are positioned at the center coordinate of their residence.

Traffic intensity

A Geographical Information System based registry, from the Swedish National Road Database, provided data on traffic intensity in all major roads in the county. To assess exposure to traffic, we identified the road with the heaviest traffic intensity within 100 m of the residence. Traffic intensity was categorized as "no road", "road with 0–2880 cars/day", "2880–8640 cars/day"," 8640–14400 cars/day", and " ≥14400 cars/day", based upon daily (24-hour) mean levels.

The traffic intensity categories were merged into a dichotomous variable, "0-8640 cars/day" (including children with "no road") and "≥8640 cars/day", to obtain enough power, since not enough cases lived in the highest exposure category to assess it separately. The classification was based upon results from previous studies in the same geographical region, which found a higher prevalence of asthma among adults living within 100 m of roads with ≥8640 cars/day [27,28]. Separate analyses were done in relation to traffic intensity for: 1) birth address exposure 2) birth address exposure, with children censored when/if they moved during time at risk.

Modeled concentrations of NO_x

Concentrations of NO_X (NO_2 + NO) at each child's residential address, were modeled as annual means for each calendar year 2005–2010, with a spatial resolution of 100x100 m. Concentrations were obtained from an emission database (EDB) for NO_X, previously described in detail [20]. The emission sources included were: road traffic, shipping, aviation, railroads, industries and larger energy and heat producers, small-scale heating, working machineries, working vehicles and working tools. Background levels of NO_X due to transport of pollutants from the continent, were also included, based on data from rural background monitor stations, and meteorological factors were incorporated. For dispersion calculations, the EDB was combined with a modified Gaussian two-dimensional dispersion model (AERMOD). Bilinear interpolation was applied. Validation of the EDB showed satisfying agreement between modeled and measured concentrations of NO_2 (Spearman's r = 0.8) [29].

Separate NO_X -analyses were done for: 1) birth address exposure 2) birth address exposure, with children censored when/if they moved during time at risk, and 3) mean NO_X during all years at risk (excluding 2011 for which geocodes were not available). The mean NO_X during time at risk was only assessed for those never moving outside the study area during time at risk. Since time at risk differ with outcome, the number with modeled mean NO_X during time at risk, also vary depending on outcome.

We used a categorical classification of NO_X , since previous studies in the same geographical region have indicated non-linear relationship between NO_X and asthma [27,28]. We based our categories on exposure contrasts (≤15, 15–25 and >25 $\mu g/m^3$), rather than on the distribution of NO_X among the population.

Covariate information

The final cohort for the main analysis included 7898 children born in the region, whose parents had answered a CHC center questionnaire 8 months after birth. The questionnaire was handed out to parents in Malmö, Svedala, Vellinge and Trelleborg, in conjunction with their children's 8 month checkup at the CHC centers [30]. The questionnaire had been validated and translated from Swedish into five different languages: Albanian, Arabic, English, Serbo-Croatian, and Somali. The response rate varied between years but was approximately 65% of handed out questionnaires [30].

Variables considered for inclusion in the multivariable models were: sex, birth weight, smoking during pregnancy, environmental tobacco smoke (ETS), mold at home, parental allergy, furred pets at home, breastfeeding, parental origin, parental education, problems to pay bills, and type of housing, and birth year.

Statistical analysis

All statistical analyses were performed using SAS, version 9.3. Survival analysis was performed because of different lengths of follow-up of the children. We used two different censoring variables: 1) children were censored at year of study end (2011), or 2) children were censored when they moved from their original birth address, or at year of study end (2011).

Descriptive Kaplan-Meier survival curves, with numbers at risk, were displayed for all outcomes. The proportional hazard assumptions for exposure and outcome were checked graphically by log(−log(survival))-curves. We then reported unadjusted Cox proportional hazards-ratios (Cox PH) between exposure and outcomes.

We used prescreening of variables in combination with a stepwise Cox PH-procedure, to select covariates to include in the final multivariable models. We performed the same selection procedure for all outcomes in relation to traffic intensity, to find the most important predictors. Any variable staying in any of the outcome models, was included in all the models, for model consistency. Traffic intensity was forced to remain in the model in each step. The following steps were done:

1. Univariable prescreening of all covariates in Table 1, except city. Any variable with a univariate p-value < 0.2 for the HR between the covariate and the outcome, was selected to next step.

Table 1 Description of the main cohort, n = 7898

		N (%)	HR (95% CI)[a] 1st purchase, inhaled β_2-agonist
Sex	Girl	3784 (49)	1.0
	Boy	3996 (51)	1.3 (1.2-1.5)
	Missing	118	
Birth weight	2500-4000 (normal)	6079 (78)	1.0
	500-2499 (low)	301 (4)	1.1 (0.9-1.5)
	4001-6500 (high)	1396 (18)	1.1 (1.0-1.3)
	Missing	122	
Smoking during pregnancy	No	7275 (94)	1.0
	Yes	499 (6)	1.2 (1.0-1.5)
	Missing	124	
Environmental tobacco smoke	No	6591 (85)	1.0
	Yes	1177 (15)	1.2 (1.1-1.4)
	Missing	130	
Breastfeeding	≥8 months	3920 (56)	1.0
	<8 months	2807 (40)	1.2 (1.1-1.3)
	Never breastfed	278 (4)	1.3 (1.0-1.6)
	Missing	893	
Parental allergy	No	3177 (46)	1.0
	Yes	3751 (54)	1.2 (1.1-1.4)
	Missing	970	
Furred pets at home	No	5790 (75)	1.0
	Yes	1922 (25)	1.0 (0.9-1.1)
	Missing	186	
Mold at home	No	7326 (95)	1.0
	Yes	386 (5)	1.0 (0.8-1.3)
	Missing	186	
Problems to pay bills	Never or seldom	7361 (96)	1.0
	Yes, >6 months/year	348 (5)	0.8 (0.6-1.0)
	Missing	189	
Swedish Parents	Yes, both Swedish	4811 (62)	1.0
	One foreign	1290 (17)	0.9 (0.8-1.1)
	Both foreign	1689 (22)	0.8 (0.7-1.0)
	Missing	108	
Highest education any parent	>12 years	5612 (73)	1.0
	9-12 years	1792 (23)	1.1 (1.0-1.3)
	≤ 9 years	297 (4)	1.1 (0.8-1.4)
	Missing	197	
Type of housing	Owned house	2783 (36)	1.0
	Tenant-owned apartment	2242 (29)	0.9 (0.8-1.0)
	Rented apartment	2616 (34)	0.9 (0.8-1.1)
	Other	101 (1)	0.7 (0.4-1.1)
	Missing	156	
City	Vellinge	449 (6)	1.0
	Svedala	664 (8)	0.9 (0.7-1.2)
	Trelleborg	611 (8)	1.1 (0.8-1.4)
	Malmö	6134 (78)	0.8 (0.6-1.0)
	Missing	40	
Birth year	2005	1066 (14)	1.0
	2006	2395 (30)	1.1 (0.9-1.3)
	2007	1664 (21)	1.0 (0.8-1.2)
	2008	2179 (28)	1.0 (0.9-1.2)
	2009	594 (8)	1.2 (0.9-1.5)

[a] Unadjusted.

2. All the selected variables were included into a multivariable Cox model, together with traffic intensity which was forced to stay in the model. Backward selection was performed, with significance level for staying (Slstay) = 0.1.

3. Starting with an initial model including the variables selected from step 2. Forward selection was performed, with significance level for entry (Slentry) =0.2, to consider for inclusion the variables initially not selected at step 1.

4. Starting with the model selected from step 3. Finetuning was done by stepwise selection-Slentry/Slstay 0.05. The variables selected to be included in the final multivariable models were: Sex, ETS, breastfeeding, parental allergy, parental origin, parental education and year of birth.

Since all selected covariates approximately fulfilled the PH-assumption, we used the Cox PH model for the final multivariable analyses, to assess the incidence of asthma medication and diagnoses in relation to traffic-related exposures. Multivariable analyses presented do not include children with missing values for any of the variables included.

We also performed sensitivity analyses: we analyzed the unadjusted relation between traffic-related exposure and outcomes, for all children with complete information on exposure and outcome (n = 26 128). For the main cohort (n = 7898), we separately estimated effects for Malmö vs. the remaining study area, to see if results were consistent across geographical regions. We also performed an analysis excluding children born 2006, the year when most children had high traffic exposure. Finally, we performed analyses restricted to children with high socio-economic status (n = 3464), here defined as children whose parents fulfilled all the following criteria; never problems to pay bills, at least one parent with >12 years education, and both parents born in Sweden. The question about ability to pay bills was here not dichotomized as in the main analysis, but instead a finer original classification was used, where “never problems to pay bills” was separated from “seldom problems to pay bills”.

The hazard ratios (HR) in all analyses were displayed with 95% confidence intervals (CI).

Results

Covariate description

Population characteristics, and incidence of inhaled β_2-agonists in relation to these characteristics, are displayed in Table 1. Most of the risk factors included in the multivariable analyses, were more common in proximity to roads with low traffic intensity (parental allergy, ETS, no or little breastfeeding, short parental education). Male sex of the child was associated with high traffic intensity. Parental origin, and year of birth had no consistent relation to traffic, but a large proportion of the children with high traffic intensity and high NO_X were born in 2006.

Exposure description

The percentage of the study population living ≤100 m from a traffic intensity of 0–8640 cars/day at birth address was 73.8%, compared to 26.2% with traffic intensity of ≥ 8640 cars/day at birth address. We classified modeled NO_X levels into ≤15, 15–25 and >25 $\mu g/m^3$.

For exposure at birth address, the percentage of the population living in respective category was 34%, 57% and 9%. Mean NO_X at birth year was 17 $\mu g/m^3$, and the percentile distribution was 9.2, 11.8, 17.6, 21.1, and 24.6 $\mu g/m^3$ (10th, 25th, 50th, 75th, and 90th percentile). Min, Max = (6.1, 45.9) $\mu g/m^3$. The distribution of NO_X by traffic intensity, is displayed in Figure 2.

Figure 2 Distribution of modeled annual mean NO_x at birth address, by traffic intensity (n = 7895). Upper and lower borders of boxplots represent the 75th and 25th percentiles and the bold line is the median. The whiskers extend to the minimum and maximum of the NO_x-concentrations.

Missing outcome data and Kaplan-Meier survival curves

Diagnostic codes were available for 97% of the hospital visits, and for 50% of the primary care visits. Among the latter, 70% of public primary care visits had diagnostic codes, while codes were completely missing for private primary care visits. The proportion of private primary care was 28% of total primary care visits.

Kaplan Meier survival curves, and life table data, showed that most of the incidence of first dispensed asthma medication and diagnoses, occurred in age 1–2 years (Additional file 1: Table S5 and Additional file 2). The oldest children were followed to age 6 years.

Incidence of dispensed medication

Incidence of purchased inhaled β_2-agonist, and inhaled corticosteroids, was lower for children living close to a road with ≥8640 cars/day (compared to 0–8640 cars/day) at birth address (Table 2). Both first and third year purchase was associated with a lower traffic intensity, in some cases significantly so. Similar results were observed in relation to NO_X. The results were consistent for children who never moved during time at risk, for mean NO_X during time at risk, and both before and after adjustment for covariates (Table 2, and Additional file 1).

Table 2 Adjusted HR (95% CI) for asthma medication and diagnoses, in relation to traffic-related exposure, n = 7898

	Inhaled asthma medication[a]				Diagnoses[a]		
	β_2-agonist 1st purchase	β_2-agonist 3rd year	Corticosteroid 1st purchase	Corticosteroid 3rd year	Bronchiolitis	Obstructive bronchitis	Asthma
Heaviest road ≤100 m, birth address [b]							
0-8640 cars/day	1.0	1.0	1.0	1.0	1.0	1.0	1.0
≥8640 cars/day	0.9 (0.8-1.0)	0.7 (0.6- 0.9)	0.8 (0.7-0.9)	0.8 (0.6-1.0)	0.7 (0.6-0.9)	1.0 (0.9-1.2)	0.7 (0.6- 0.9)
Heaviest road ≤100 m, never moved [b]							
0-8640 cars/day	1.0	1.0	1.0	1.0	1.0	1.0	1.0
≥8640 cars/day	0.9 (0.7-1.0)	0.7 (0.5-1.0)	0.8 (0.6-0.9)	0.9 (0.6-1.2)	0.7 (0.6-0.9)	1.0 (0.8-1.2)	0.7 (0.6-0.9)
NO_X, birth address [c]							
≤15 μg/m^3	1.0	1.0	1.0	1.0	1.0	1.0	1.0
15-25	0.8 (0.7-1.0)	0.7 (0.5-0.8)	0.8 (0.7-0.9)	0.7 (0.5-0.9)	0.6 (0.5-0.8)	1.1 (0.9-1.3)	0.8 (0.7-0.9)
>25	0.7 (0.6-0.9)	0.6 (0.4-0.8)	0.7 (0.5-0.9)	0.6 (0.4-0.8)	0.5 (0.4-0.8)	1.1 (0.8-1.4)	0.7 (0.5-0.9)
NO_X, never moved [c]							
≤15 μg/m^3	1.0	1.0	1.0	1.0	1.0	1.0	1.0
15-25	0.8 (0.7-1.0)	0.6 (0.4-0.8)	0.8 (0.7-0.9)	0.6 (0.4-0.8)	0.6 (0.5-0.8)	1.1 (0.9-1.3)	0.8 (0.7-0.9)
>25	0.8 (0.6-1.0)	0.5 (0.3-0.9)	0.6 (0.5-0.8)	0.5 (0.3-0.9)	0.5 (0.4-0.8)	1.1 (0.8-1.5)	0.7 (0.5-0.9)
NO_X, lifetime mean [d]							
≤15 μg/m^3	1.0	1.0	1.0	1.0	1.0	1.0	1.0
15-25	0.8 (0.7-0.9)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.5-0.8)	0.9 (0.8-1.1)	0.7 (0.6-0.9)
>25	0.8 (0.6-1.1)	0.5 (0.3-0.9)	0.6 (0.5-0.9)	0.5 (0.3-0.9)	0.7 (0.5-1.0)	1.0 (0.7-1.3)	0.7 (0.5-1.0)

[a]adjusted for sex, ETS, breastfeeding, parental allergy, parental origin, parental education, and year of birth.
[b] n = 6007 children had complete covariate information and traffic exposure assessments.
[c] n = 6005 children had complete covariate information and modeled NO_X concentrations.
[d]number of children with complete covariate information and modeled mean NO_X during time at risk varies between n = 5194-5248 depending on outcome.

Incidence of bronchiolitis, obstructive bronchitis and asthma

There was a significantly lower incidence of diagnoses of bronchiolitis, and asthma, but not obstructive bronchitis, among children living close to a road with ≥8640 cars/day (compared to 0–8640 cars/day) at birth address (Table 2). Similar results were observed in relation to NO_X. The results were consistent for children who never moved during time at risk, and for mean NO_X during time at risk. The results were consistent before and after adjustment for covariates, except the HR for obstructive bronchitis, which diminished with adjustment (Table 2, and Additional file 1).

Sensitivity analyses

An analysis of all children for which outcome and exposure data was available (n = 26 128), unadjusted for any factors, showed that traffic-related exposure was statistically significantly associated with a lower incidence of all outcomes except obstructive bronchitis, for which the HR was not significantly different from 1 (Additional file 1).

For the main cohort (children with covariate information, n = 7898), we stratified our analyses separately for Malmö vs. the remaining region, and the results were largely consistent across the regions (data not shown). The results were also consistent when excluding children born 2006. Finally, we performed an analysis restricted to children with high socio-economic status (n = 3464) and the results for this subgroup were similar to the results for the main cohort (Additional file 1).

Discussion

There was no increased purchase of asthma medication or diagnosis of bronchiolitis, obstructive bronchitis or asthma among children 0–6 years, growing up close to a road with high traffic intensity, or high levels of NO_X. On the contrary, there was a lower incidence for all outcomes except obstructive bronchitis, among these children. This indicates that traffic-related exposure is not a risk factor for early onset asthma/wheeze in children in southern Sweden.

Strengths and limitations

A strength of the study was the register-based outcome data with complete coverage of dispensed medication, which prevents potential awareness bias due to parental-reported outcomes. There are still some possibilities of selection bias due to questionnaire data in this study, since the confounder information was only available through CHC-questionnaires, which is likely to have lead to a selection towards high socio-economic status among those who answered the CHC-questionnaire. A potential limitation was that the drug register only includes dispensed medication. The observed lower incidence of medication among children in households with bad economy or with immigrant parents in the present study, raise a suspicion they cannot afford to dispense prescribed medication (or do not get diagnosed in the first place), to the same degree as the children in households with good economy. A previous study in Swedish children found low socio-economic status to be related to higher incidence of late onset wheeze, when based on self-reported data of diagnosis or wheeze [31]. However, a recent Swedish study did not find income to be a predictor for dispense of drugs, after controlling for health status, but there was higher prescription rate toward people with

high education [32]. However, since we had individual level data on socio-economic status we could address this by adjustment and restriction on different socio-economic indices, which did not affect the result, and thus this is not a likely source of bias for the results in our study. Another limitation was that a non-negligible percentage of the health care visit data lacked diagnostic codes, which could possibly cause a bias which we cannot account for. This is also why we treated it as a secondary outcome only, which supports the results from the medication data, but cannot be fully trusted on its own.

That the results for the larger study population were the same as for the cohort with questionnaire information strengthens that there is a higher incidence of wheeze in areas with low traffic pollution in the region. It is implausible that air pollution would be "protecting" against asthma, and the results therefore speaks for the presence of unmeasured risk factors, or different health-seeking behavior, in areas with low traffic pollution.

Another strength was the exposure data in this study. Residential addresses for each year since birth were known, which exclude a migration bias which could otherwise be expected to dilute the effects. We also had validated high quality exposure data for NO_x, modeled with a high resolution, which further minimize the risk of other exposure misclassification biases which could be expected to dilute the effects.

The levels of modeled NO_X at children's home address in this study were low compared to other studies, despite the high resolution of the grid, which can be expected to increase the exposure range [33]. Since different studies use different measures of traffic exposure, complicating comparisons, we also provide a table with background levels of air pollution in the region, to give a picture of the exposure situation in the area (Additional file 1).

We believe the quality of exposure data are better than most other studies which have found a relation between traffic and wheeze, we therefore see it as unlikely that poor quality of exposure data would be the cause of the negative findings in our study.

Comparison with other studies

Recent reviews conclude that there is, overall, evidence for a relation between long-term exposure to traffic and asthma incidence in children [2,3]. However, not all individual studies agree, and little differentiation has been made in reviews according to age of asthma onset. We think there is more evidence for an association with persistent wheeze and later onset asthma, than with early onset asthma/wheeze. At least in the studies in the Nordic countries which is where the exposure situation is similar to our study. A cohort study in Norway had similar finding to our study, with a negative association between NO_2 and early onset asthma (RR = 0.8, 95% CI: 0.6-1.0) [34]. However, late onset asthma ($\geq$4 years age), had a positive but non-significant association with NO_2. A Swedish cohort study also found no association between NO_X and transient early wheeze before 2 years age (OR = 0.8, 95% CI: 0.5-1.4), but a positive association with persistent wheeze [35], and a positive association with asthma onset at age 12 [10].

Some studies outside the Nordic countries have found associations between traffic-related exposures and incidence of wheeze or early asthma [6,7], but others have not [36,37]. In a Dutch birth cohort, NO_2 was not associated with incident asthma at age 2, but was associated with asthma incidence in older age [9].

In contrast, cohort studies in older children seems to have found more consistent results for traffic-related exposure to be associated with asthma incidence [9-12]. Clark et al. 2010 used hospital and primary care diagnosis records, and found a relation between NO_2 and asthma incidence already at ages 3–4 years [8]. However, this study had more restrictive case definition of asthma compared to our study, reflecting more severe or persistent asthma.

It should be noted that numerous studies with positive associations between traffic-related exposure and asthma incidence are still statistically insignificant [3]. These studies have in reviews still been interpreted as contributing evidence for a relation between traffic-related exposure and asthma. Our study on the contrary, was based on large numbers and can thus rule out positive effects with high statistical certainty. However, confounding can never be fully excluded. We also want to point out that the exposure levels in our study were lower than most other studies, something which could also explain the lack of effect.

We think that our study together with the results from previous studies in the Nordic countries, suggests that traffic exposure, at the levels observed, either is not a risk factor for incidence of early onset wheeze or asthma, or that the effects may be so small that they are easily overridden by other risk factors. However, the situation may be different in countries with higher exposure to traffic pollution. Also, it should be kept in mind the results from our study does not exclude effects on late-onset asthma in children, or wheeze that persists into older age. This cohort should be followed up in later age to investigate the relation between traffic and later-onset of childhood asthma, or persistent wheeze continuing into older age.

Conclusions

We found no association between growing up close to traffic and higher incidence of dispensed asthma medication, diagnosis of bronchiolitis, obstructive bronchitis or asthma, in children 0–6 years in southern Sweden. This indicates that traffic-related exposure is not a risk factor for early onset asthma, or “wheeze”, in southern Sweden, something which may depend on the low levels of traffic-related air pollution in the area.

Abbreviations

adj.HR, adjusted Hazard Ratio; ATC, Anatomical Therapeutic Chemical Classification System; CHC-centers, Child Health Care centers; CI, Confidence interval; Cox PH, Cox proportional hazards; EDB, Emission database; HR, Hazard ratio; ETS, Environmental tobacco smoke; NO_X, Nitrogen oxides; PNS-registry, Perinatal Revision South-registry; SHCR, Scania Health Care Register; Slentry, Significance level for entry; Slstay, Significance level for staying

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

AL drafted the manuscript, conducted the statistical analyses, and did the main design of the study and interpretation of results. ES conducted exposure modeling, and did the main design

of the study and interpretation of results. JB participated in interpretation of results. KJ participated in the design of the study and in interpretation of results. All authors made revisions on drafts, and read and approved of the final manuscript.

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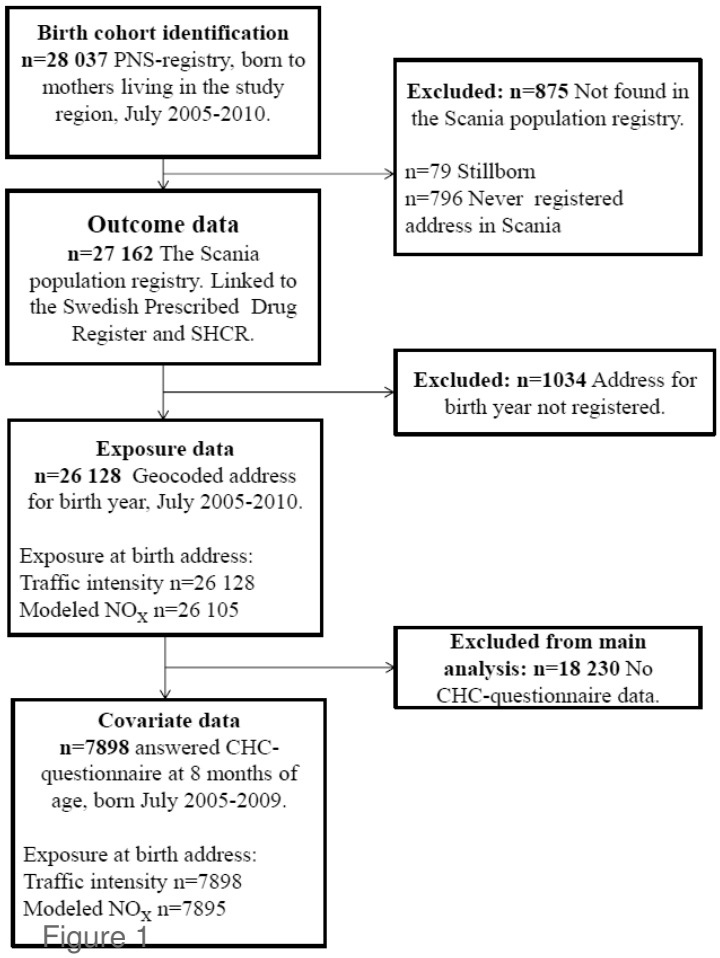
Additional files

Additional_file_1 as DOCX

Additional file 1 Table S1. Urban background. Descriptive data of regional air pollution at monitoring station in Malmö. **Table S2.** Unadjusted HR (95% CI) for asthma medication and diagnoses, in relation to traffic-related exposure, n = 7898. **Table S3.** Sensitivity analysis including all children with outcome and exposure data, n = 26128. **Table S4.** Sensitivity analysis of children with high socio-economic status [a], n = 3464. **Table S5.** Life table data.

Additional_file_2 as PDF

Additional file 2 Kaplan-Meier survival curves of asthma medication and diagnoses in relation to traffic intensity, with number at risk.


Birth cohort identification
n=28 037 PNS-registry, born to mothers living in the study region, July 2005-2010.
Excluded: n=875 Not found in the Scania population registry.
n=79 Stillborn
n=796 Never registered address in Scania
Outcome data
n=27 162 The Scania population registry. Linked to the Swedish Prescribed Drug Register and SHCR.
Excluded: n=1034 Address for birth year not registered.
Exposure data
n=26 128 Geocoded address for birth year, July 2005-2010.
Exposure at birth address:
Traffic intensity n=26 128
Modeled NO_X n=26 105
Excluded from main analysis: n=18 230 No CHC-questionnaire data.
Covariate data
n=7898 answered CHC-questionnaire at 8 months of age, born July 2005-2009.
Exposure at birth address:
Traffic intensity n=7898
Modeled NO_X n=7895
Figure 1

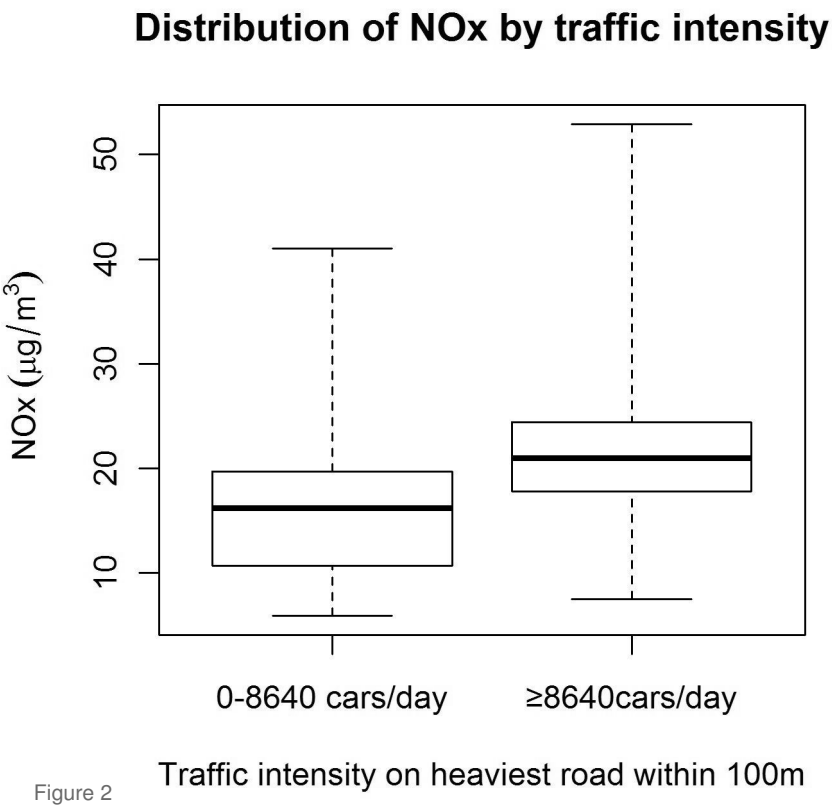

Distribution of NOx by traffic intensity
NOx (µg/m3)
10
20
30
40
50
0-8640 cars/day
≥8640cars/day
Traffic intensity on heaviest road within 100m

Figure 2

Additional files provided with this submission:

Additional file 1: 2001047612102441_add1.docx, 41K
http://www.ehjournal.net/imedia/1194722984111645/supp1.docx
Additional file 2: 2001047612102441_add2.pdf, 297K
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