Exposure to air pollution during pregnancy and health risks for mother and child

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Abstract

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We did not find any consistent associations between air pollution and birth outcomes, whereas an increased prevalence of gestational diabetes and preeclampsia with increasing NO_x exposure was observed. We did also find that the risk of developing T1D increased if the mother had lived in areas of elevated levels of NO_x during third trimester or ozone during second trimester. Our studies suggest that air pollution during pregnancy might be a health risk for mother and child, even at levels below current air quality guidelines.

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Raise a million filters and the rain will not be clean, until the longing for it be refined in deep confession.

Leonard Cohen Book of Mercy

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Abstract

We had in the present thesis the unique possibility to use, in a socio-economically relatively homogenous population, high quality registry information on a population-based birth cohort (84 039 births during the period 1999-2005) in Scania (Skåne), the most Southern county of Sweden. The aim of the thesis was to investigate whether exposure to air pollution, in an area of low-levels exposures, during different periods of the pregnancy was associated with birth outcomes, pregnancy complications and risk of the child to develop type I diabetes (T1D). For all outcomes air pollution was assessed as nitrogen oxides (NO_x) and traffic exposure. For T1D we also assessed the association with exposures to ozone.

We did not find any consistent associations between air pollution and birth outcomes, whereas an increased prevalence of gestational diabetes and preeclampsia with increasing NO_x exposure was observed. We did also find that the risk of developing T1D increased if the mother had lived in areas of elevated levels of NO_x during third trimester or ozone during second trimester. Our studies suggest that air pollution during pregnancy might be a health risk for mother and child, even at levels below current air quality guidelines.

List of papers

I. **Malmqvist E**, Rignell-Hydbom A, Tinnerberg H, Björk J, Stroh E, Jakobsson K, Rittner R, Rylander L. Maternal exposure to air pollution and birth outcomes. Environmental Health Perspective 2011;119:553-8.

II. **Malmqvist E**, Jakobsson K, Tinnerberg H, Rignell-Hydbom A, Rylander L. Gestational diabetes and preeclampsia in association with air pollution at levels below current air quality guidelines. Environmental Health Perspective 2013;121:488-93.

III. **Malmqvist E**, Olsson D, Hagenbjörk-Gustafsson A, Forsberg B, Mattisson K, Stroh E, Strömgren M, Swietlicki E, Rylander L, Hoek G, Tinnerberg H, Modig L. Assessing ozone exposure for long term epidemiological studies (submitted).

IV. **Malmqvist E**, Elding-Larsson H, Rignell-Hydbom A, Ivarsson SA, Tinnerberg H, Stroh E, Rittner R, Jakobsson K, Swietlicki E, Rylander L. Maternal exposure to air pollution and the risk among the offspring for the development of type 1 diabetes. (manuscript)

Abbreviations

BMI	Body Mass Index
BVOCs	Biogenic Volatile Organic Compounds
CI	Confidence Interval
CO	Carbon Monoxide
CO_2	Carbon Dioxide
DiPiS	Diabetes prediction in Scania
EDB	Emission Database
GIS	Geographical Information System
HEI	Health Effect Institute
HLA	Human Leukocyte Antigen
IVL	Swedish Environmental Research Institute
IUGR	Intrauterine growth retardation
LBW	Low Birth Weight
LUR	Land Use Regression
NO_x	Nitrogen Oxides
NO	Nitrogen monoxide
NO_2	Nitrogen Dioxide
O_3	Ozone
O_2	Oxygen
OR	Odds Ratio
PAH	Polycyclic Aromatic Hydrocarbon
PM	Particulate Matter
$PM_{0.1}$	Particulate matter < 0.1 μm in aerodynamic diameter
$PM_{2.5}$	Particulate matter < 2.5 μm in aerodynamic diameter
PM_{10}	Particulate matter < 10 μm in aerodynamic diameter
PTB	Preterm Birth
R^2	Squared Correlation coefficient
SES	Socio Economic Status
SGA	Small for Gestational Age
SMBR	Swedish Medical Birth Registry
SMHI	Swedish Meteorological and Hydrological Institute
SO_2	Sulphur Dioxide
T1D	Type 1 Diabetes
VOCs	Volatile Organic Compounds
WHO	World Health Organisation

Aim

The aim of our birth cohort studies, in an area of low-level exposures to air pollutions, was to investigate if exposure to air pollution during different periods of the pregnancy was associated with:

i. birth outcomes; preterm birth [PTB], low birth weight [LBW], and small for gestational age [SGA]),
ii. pregnancy complications (gestational diabetes and preeclampsia), and
iii. risk of the child to develop type I diabetes (T1D).

For all outcomes air pollution was measured as Nitrogen oxides (NO_x) and traffic exposure. For T1D we also assessed the association with exposures to ozone.

Populärvetenskaplig sammanfattning

Luftföroreningar har i många studier visat sig skada vår hälsa. Även om risken för den enskilda individen kan vara relativt liten så kan omfattningen av hälsoeffekterna bli stora eftersom det är så många som exponeras. Tidigare har man huvudsakligen sett effekter på andningsorganen men under de senare åren har man även börjat se effekter som sträcker sig bortom våra andningsorgan. Framförallt det senaste decenniet har många studier på både djur och människor indikerat att luftföroreningar under graviditeten kan påverka fostret. De flesta studierna har undersökt om risken ökar för att barnet föds för litet eller för tidigt. Ett fåtal studier har även undersökt om mamman har en ökad risk för havandeskapsförgiftning (preeklampsi) ifall hon utsatts för högre halter av luftföroreningar. De flesta studierna är gjorda i områden med relativt höga halter av luftföroreningar som Los Angeles och dessa har sett luftföroreningseffekter på såväl fostret som mamman.

I Sverige har vi jämförelsevis ganska låga halter av luftföroreningar, men i vissa områden kan dessa halter vara något förhöjda. Ett sådant område är Skåne där det passerar mycket trafik på både vägar och hav. Hamnar och områden i de största städerna där mycket trafik passerar är de mest förorenade, men halterna i Skåne ligger ändå runt rådande luftkvalitetsnormer. Ur ett sådant perspektiv är det intressant att studera om det finns effekter av luftföroreningar även vid våra halter eftersom det kan ge en indikation på att luftkvalitetsnormerna måste sänkas.

Denna avhandling baseras på studier där alla mammor som födde barn i Skåne mellan 1999 och 2005 inkluderades. Vi modellerade varje kvinnas halter av kväveoxider (som är ett mått på förbränning av bland annat bensin) vid bostadsadressen. Dessutom räknade vi ut hur mycket trafik som körde utanför kvinnans bostadsadress. Vi studerade även halterna av ozon i Malmöområdet och i en av studierna så använde vi ozon som exponeringsmått. Med hjälp av geokodad information och personnummer kunde vi koppla information från födelseregister och diabetesregister till exponeringen för luftföroreningar för varje kvinna.

När vi hade varje kvinnas exponering för luftföroreningar och hälsoutfall från register kunde vi räkna ut om det var en högre förekomst av sjukdomarna i de områden som hade högst halter av luftföroreningar. Med hjälp av registerdata kunde vi dessutom ta hänsyn till andra kända riskfaktorer för sjukdomarna som exempelvis antal tidigare födda barn, rökning, ålder m.m.

Vi fann inga tydliga samband mellan luftföroreningar och födelseutfall. Däremot var förekomsten av havandeskapsförgiftning och graviditetsdiabetes högre om kvinnan bodde i områden med högre luftföroreningshalter. Dessutom fick barnen oftare Typ1 diabetes om de exponerats under fosterlivet för högre halter av luftföroreningar. Dessa resultat stod sig även om vi tog hänsyn till andra kända riskfaktorer. Våra studier visar således att exponering för luftföroreningar under graviditeten kan vara en risk för både mamman och barnet även vid halter som ligger under rådande luftkvalitetsnormer.

Part 1 Background

I durst not laugh for fear of opening my lips and receiving the bad air.

William Shakespeare.

Introduction

The history of air pollution, as we think of it today, arises from the human combustion processes. The smoke from the fires probably made our ancestors cough in their caves. When populations of humans grew and villages became larger and larger and when wood became scarce, humans turned to coal and peat for heating and cooking. With industrialisation came metal smelters and industries providing the air with their own mix of toxic substances. The smoke ridden cities were not always seen as a health threat but led to artistic inspiration for Molière and Dickens. The workers saw the smoke of the chimneys as a symbol for prosperity and food on the tables. Even if readings from Greek philosophers quote the annoyance of air pollution it was not until the 20th century that air pollution became a publicly known health risk [1]. During the London fog event in early December 1952, the levels of particles were ten times the normal levels of those days and hundred times the levels in London of today. The reasons behind this event was cold weather leading to a lot of coal burning and stagnant weather conditions getting the air trapped over the city [2]. People actually choked to death out on the streets. The event led to 12 000 excess death [2] and even more hospital admissions and public awareness of the health effects grew [1].

The lethal effects of air pollution led to a change in fuels for heating, and coal were often replaced by gas and coke. Levels of pollutants went down, but at the same time, the automobiles became more and more common, highways and suburbia was built and with it the launch of a new dimension of air pollution with a chemically reactive cocktail of gases and particles. However, the overall air quality in London and other places has dramatically improved, while the industrialization of the developing world has sometimes history repeating itself with an increasing burden of air pollution. The improvement of air pollution is due to public pressure on governments and behind lays research into the field of toxicology and environmental health [1].

Air pollutants

Air pollution can be both *anthropogenic*, which means it is caused by humans, and *biogenic*, which means that it is caused by the rest of nature. In cases of volcanic eruption or Saharan dust winds the biogenic contribution to air pollution can be dominant [3]. In most areas, this area included, the anthropogenic sources to air pollutants are clearly dominant [3] and thus will be in focus. Occupational exposure to air pollution can be detrimental for the individual but the number of people exposed are limited [3]. In this thesis we have focused on population exposure to ambient air pollution. Although point sources, such as industry, can release a cocktail of air toxics in the air such as heavy metals or Volatile Organic Compounds (VOCs), the majority of the air pollution that the general population is exposed to in our study area is combustion related primary and secondary aerosols. The present thesis will focus on combustion related exposure.

If combustions, in for example vehicles or heating plants, would operate to full completion of the fuel and if we used ideal fuels, air pollution would be minimized. However, the current technology and fuel markets are far from there yet. Instead as a result of incomplete combustion a large number of air pollutants such as carbon dioxide (CO_2), carbon monoxide (CO), black carbon, hydrocarbons, particulate matter (PM), nitrogen oxides (NO_x), formaldehyde, benzene, 1.3 butadiene and metals are released. Furthermore secondary by-products such as ozone (O_3), nitrates and organic and inorganic acids are formed [3]. Particles, even called particulate matter, are divided into different sizes, Particulate matter < 10 µm in aerodynamic diameter (PM10), Particulate matter < 2.5 µm in aerodynamic diameter (PM2.5) and Particulate matter < 0.1 µm in aerodynamic diameter (PM0.1). The latter is often refered to as ultrafine particles.

Distance decay

The largest emitter of combustion related aerosols are, in most areas, traffic. Most air pollutants, with the exception of secondary pollutants, are in the highest concentration near the source of pollutants, such as the tailpipe of a car, after that they can react with other aerosols in the air, deposit to the ground or be transported with winds further away from the source. How far away from the source most of this dilution occur is called the distance-decay and is dependent on pollutants and wind direction. Ultrafine particles, black carbon and CO decrease with 60-80% 100m downwind from a busy highway [4] whereas nitrogen dioxide (NO_2) greatest decrease occur within 200m [5]. On the upwind side of the road, on the other hand, the greatest decrease could vary between 300-1500m for NO_2 [5, 6] and 800m for ultrafine particles [7]. NO_x is also sometimes considered a proxy for

$PM_{2,5}$. $PM_{2,5,}$ however, have a less sharp distance-decay gradient and do not greatly decrease until 300-500m from highways [8].

Air pollutants in our studies

To capture the spatial and temporal variation in combustion related air pollutants we have in the present thesis focused on exposure assessment for the following air pollutants; NO_x (which is the sum of nitrogen monoxide (NO) and NO_2) and ozone. We have also used a more general traffic intensity measure. We did not investigate direct effects of PM and SO_2. However, NO_x has been seen as a good proxy for ultrafine particles, which is the smallest and probably most detrimental fraction of PM [3]. For sulphur dioxide (SO_2), levels in the studied area are well below current air quality guidelines and the local contribution to SO_2 is small and largely attributed to ships and thus hard to capture in spatial exposure assessment.

NO_x

NO_x is, as previously mentioned, the sum of NO and NO_2 commonly derived from incomplete combustion. There are only air quality guidelines for NO_2. NO_2 is the most common of the forms -as soon as NO has reacted with the oxygen in the air it oxidise into NO_2. Thus, the proportion of the ratio between NO and NO_2 vary with distance from the source. As previously mentioned, NO_x and NO_2 are common proxies for general air pollution and ultrafine particles but also for black carbon and polycyclic hydrocarbons [3]. The most important source in Europe for NO_2 is traffic. The spatial distribution of NO_2 varies highly and is largely dependent on traffic; therefore careful consideration of exposure assessment is even more crucial for NO_2 than for the more homogeneously distributed $PM_{2.5}$ and PM_{10}. The health effects of NO_x and NO_2 should until further evidence of independent effects, represent the mixture of traffic-related air pollutants [3].

Ozone

Ozone is present in the stratosphere but also in the troposphere (ground level up to 10km) where it can be detrimental to health. Ground level ozone [hereafter referred to as ozone] is a secondary pollutant and is formed through chemical reactions including mainly $NO_{x,}$ and VOCs, collectively called *ozone precursors*, in the presence of sunlight. The photo stationary-state equation describes the equilibrium reaction of $NO + O_3 \leftrightarrow NO_2 + O_2$. However, the ozone processes are not only affected by NO_x. During the growing season plants emit highly reactive hydrocarbons so called Biogenic VOCs [hereafter referred to as BVOCs], such as isoprene or terpenes, especially when temperatures are higher [9]. These BVOCs can increase ozone formation. However, in the Scandinavian region it is common with certain tree types that emit BVOCs that could have an opposite effect and decrease levels of ozone through ozonolysis (i.e. ozone causing the breakage of

molecules thru oxidation) [10]. This is especially common in areas with a lot of Betula (birch trees) which have highly reactive terpenes [11].

We illustrate the basic principles of the ozone formations in the following figure 1.

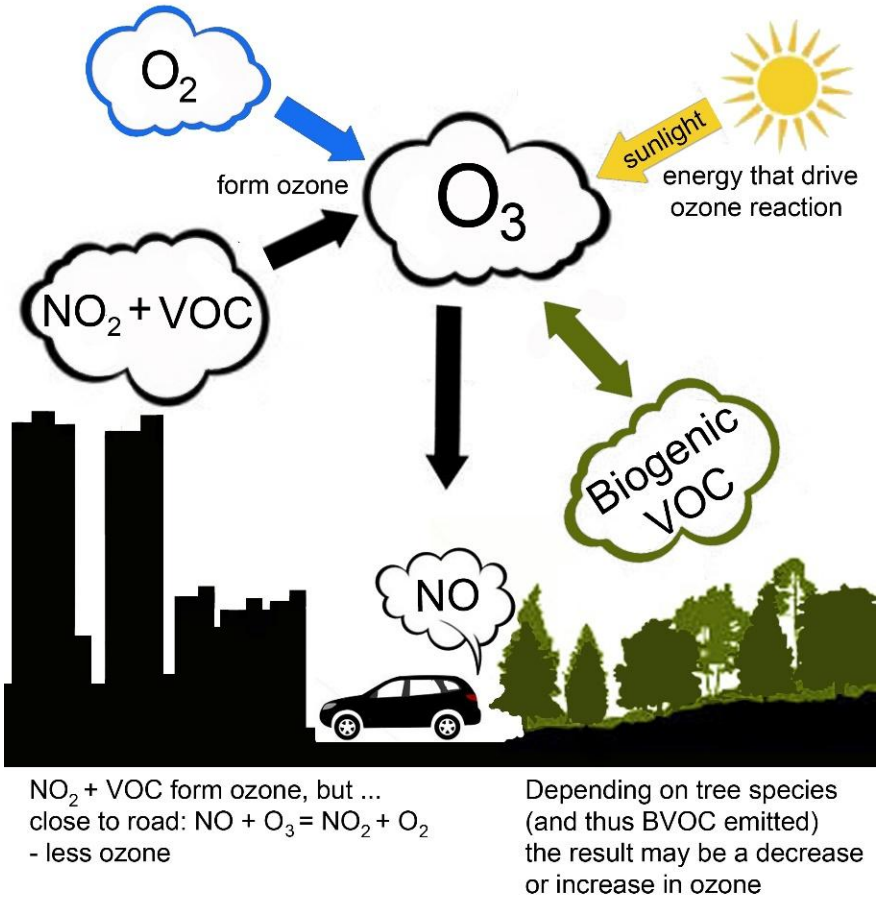

Figure 1
Basic principles of ozone formation with NO_x and VOCs.

Previous studies have focused on the development of more precise exposure assessment models for primary pollutants such as NO_x. Less focus has been put on developing models for long term ozone exposure, even if the health risks of ozone exposure is considered at least as serious [12, 13]. This stated, there was an obvious and important need to investigate the spatial variation of ozone on the local scale to make it possible to study the long term health effects of ozone.

Health effects

Several studies have shown a convincing link between mortality and increased levels of air pollution. The most well-known study is the Six Cities study from Harvard, where cities with high levels of air pollution had a 26% increased risk for mortality [13]. The state of knowledge about health effects of air pollution has recently been reviewed and it has been concluded that there is an increased risk of cardiovascular and respiratory morbidity and mortality even after adjustment for several confounders such as socioeconomic status and traffic noise [3]. Furthermore, air pollution effects on risks for several other outcomes in Sweden and Europe such as lung cancer and impaired lung function have been found recently [14, 15].

In the following sections the air pollution effects on the outcomes investigated in the present thesis will be reviewed.

Birth outcomes

In the past decade or two, epidemiological studies linking registry data, such as birth certificates, with exposure based on monitoring data has resulted in a body of evidence of air pollution's harmful effects on foetal development [16]. Birth outcomes included low birth weight (LBW<2500g at birth) and small for gestational age (SGA), and prematurity (PTB<37 weeks completed gestation) [16]. Early studies in China [17] and the Czech Republic [18] identified effects of particles and SO_2 as being associated with adverse birth outcomes, with most of the pollutants coming from coal heating or industry. Studies have also observed reductions in birth weight from indoor biomass burning for cooking in rural Guatemala [19] and Zimbabwe [20]. In recent years most studies are performed in areas with traffic as the major source of pollutants. Several studies have shown, although not consistently, that air pollution is a risk factor for preterm births and altered foetal growth, especially in high-exposure areas [21-23]. The inconclusive results are largely depending on definition of outcome [16], region, socioeconomic status, duration of exposure [24] and air pollution exposure assessments [25, 26].

As previously described, there are several studies that have shown that air pollution might be a risk factor for foetal growth restriction and gestational length. It has, nevertheless, been clearly stated that future research on air pollution and birth outcomes must confirm that observed air pollution effects on birth weights, prematurity, and SGA are genuine, causal, and not attributable to confounding factors and to investigate whether the effect also remains in low-exposure areas [16, 22, 27]. Further, it has been suggested that gender differences in sensitivity to air pollution and related birth outcomes needs to be investigated [28].

Gestational complications

Some recent studies have reported air pollution effects on risks of preeclampsia, a severe condition for both mother and foetus [23, 26, 29, 30], whereas one reported no association [31] and one inconclusive findings [32]. Three studies have reported associations between air pollutants and gestational hypertension (a risk factor and early symptom of preeclampsia) [32-34].

Gestational diabetes mellitus is defined as glucose intolerance that begins or is first recognized during pregnancy [35]. Gestational diabetes has been linked to negative health effects both for the mother and the newborn [35]. Previous studies have reported associations between air pollution and type 2 diabetes [36-39]. Pregnancy is a condition with an increased susceptibility to glucose intolerance [35], and accordingly pregnant women might be a group susceptible to potential air pollution effects on the incidence of diabetes. To our knowledge, there has been only one previous study of air pollution and gestational diabetes, which reported no association [40] but this study used a relatively crude exposure assessment (proximity to road or distance weighted traffic density). Preeclampsia and other pregnancy complications have been identified as priority research areas relating to air pollution and reproductive effects [27].

Type1 Diabetes

Mehers and Gillespie suggest that T1D occur from the action of environmental factors in genetically predisposed individuals [41]. Hathout et al. [42, 43] have given the first indications that air pollution may be an environmental risk factor for T1D. The possible biological mechanisms linking air pollution to autoimmunity disorders, such as T1D has been discussed [44]. If air pollution can influence the immune system and trigger other hypersensitivity disorders, such as allergy, it is according to the author an indication that more research in the field of autoimmunity and air pollution is needed [44].

Biological plausibility

As air pollution is a mix of gases and particles in the air with different characteristics, they will deposit differently in our respiratory regions and beyond. Even though the majority of the inhaled air pollution is exhaled, it is well known that larger particles between PM_{10} and $PM_{2.5}$ can deposit in the upper part of the respiratory region, however most of them are coughed up or sneezed out. Smaller particles than $PM_{2.5}$ could penetrate further down in our lungs and ultrafine particles (and gases) could even pass the alveolar system into our bloodstream. One of the hypothesized mechanisms when it has entered the blood stream is

oxidative stress [45]. Particles from vehicles has high oxidative potential [46] and the ambient concentration of ozone can increase the toxicity of particles [47].

Air quality guidelines

Different air quality guidelines have been set up as a preventive measure for health among the general population (Table 1). The pollutants included are NO_2, SO_2, $PM_{2.5}$, PM_{10} and ozone.

Table 1.
Current Air Quality Guidelines

Pollutant	**Current WHO Air Quality Guidelines (2006) Concentration (µg/m^3)**	**Averaging Period**	**EU Directive 2008/50/EC Concentration (µg/m^3)**	**Averaging Period**
Particulate matter ($PM_{2.5}$)	10 25	1 year 24 hours	25	1 year
Particulate matter (PM_{10})	20 50	1 year 24 hours	40 50	1 year 24 hours
Nitrogen dioxide (NO_2)	40 200	1 year 1 hour	40 200	1 year 1 hour
Sulphur dioxide (SO_2)	20 500	24 hours 10 minutes	125 350	24 hours 1 hour
Ozone (O_3)	100	8 hours	120	8 hours

The current limits are set based on the review by WHO [48] of the current state of knowledge in 2005. However, it should be stated that since then, new evidence have emerged with associations of health effects at levels below current guidelines [3]. New air quality guidelines have been suggested for black carbon, which would be beneficial not only for public health but also to mitigate short lived climate pollutants. As for ozone a long term (summer) mean target has been proposed. Regarding NO_2, a lower guideline value has been proposed [3].

Air pollution modelling

Exposure assessment is a challenge in epidemiological studies and health effect estimates might be incorrect when predicted exposure is different from true exposure [49]. To assess exposure two important aspects need to be considered,

- Exposure to air pollution depend on the variability of concentration of air pollutants at different times and places
- People move around in different times and places [50].

In order to capture individuals exposure to air pollutants, the assessment can be done with *direct* or *indirect methods*.

Direct methods

In the direct methods the individual's exposure are monitored by personal portable monitors or by collection of biomarkers of pollutants. In a large dataset this would however be both costly and labour intensive. Another inherent problem with biomarkers is to define the toxin and time period of relevance. Since air pollution is a complex mixture of particles and gases, it would be hard to define the specific toxin of interest based on current knowledge. There is no consensus today in the field of an appropriate biomarker for ambient air pollution Some Polycyclic Aromatic Hydrocarbons (PAHs) has been suggested, measured as hydroxylated PAH metabolites in urine or by DNA adducts. With PAHs as biomarkers comes the inherent problem of source contribution from dietary versus inhaled dose and if measured in urine biomarkers will only reflect short time exposure [16].

Indirect methods

Due to the limitations with direct methods, indirect methods are commonly used to assess individuals' exposure to air pollution. The principle is to know where a person spends time and combine with information of pollutants at that place. We will now present some indirect methods, and discuss the method´s limitations in assessing pollutants in places where there are no direct measurements. The challenges in capturing the time-activity pattern of the individuals will be described elsewhere.

Nearest station approach

In order to follow air quality guidelines the levels of air pollutants are monitored by local, regional or country-level authorities. The individual´s exposure is based on measurements at the nearest monitoring station. Geographical Information

Systems (GIS) is often used to assess the nearest station given the individual's location and the location of the monitor. The method assumes that all individuals residing in the area surrounding the monitoring station experience the same pollution levels. This method has it's limitation by ignoring the spatial variation of air pollutants [50]. The extent of this problem varies by study design, pollutants and density of the monitoring stations.

Proximity based

The proximity based models are the simplest method by assuming that nearness to sources, such as roads, proxies for exposure. This model can be combined with road type and traffic density [51].

Interpolation models

The previous method can be improved by interpolation with for example distance-weighted traffic density. But these models assume that stations and pollutants are evenly distributed, which they seldom are. Kriging is a somehow more sophisticated model that allows the selection of monitors to vary from point to point based on the structure of data. In co-kriging other predictor variables such as elevation can be entered to affect this selection. However, for kriging and co-kriging to function properly there needs to be enough monitoring stations [50].

Land Use Regression

In recent years the increasingly popular land use regression (LUR) models have been developed in large parts of Europe thru the ESCAPE-project [52]. LUR use a least-squares regression model based on monitoring data and exogenous independent variables to explain the spatial variation of pollution levels [51].

The data on pollution levels can be collected both from already existing monitoring data and by special sampling campaigns. The existing monitoring data can be rich in time (with hourly collection of some pollutants) but only collected at limited number of fixed locations. If data are collected by specific measurement campaigns [51], on the other hand, measurements might be performed only during a few weeks and then used for a whole or many years [26].

LUR tries to explain the spatial variation of pollutant concentration by creating explanatory variables using GIS layers such as road, land use and population data in buffers around the place where the measurements have been conducted [50]. Theoretically, these variables represent emission sources for the pollutant of interest. The explanatory variables are then entered into a statistical programme using regression models to find the variables that can explain most of its variation. This equation of variables is then applied using GIS to calculate the pollution concentration at locations of the individuals [50]. Hoek et al. did a thorough

review of LUR models and found most R^2 to be around 0.6-0.7 for models on NO_2 [53]. An uncertainty regarding this is that the evaluation of the LUR model is often built on the same data as the model [54].

Dispersion models

Dispersion models often rely on a Gaussian plume equation and uses data on emissions, meteorology and pollution concentrations to estimate spatial distribution of pollutant concentrations [51]. Data on pollution concentration at monitored background concentrations in the studied area are used for calibrating the model. Meteorological data provide information on wind speed and wind direction, temperature and solar radiation. Simplified atmospheric chemistry, diffusion and transport are also inserted in the model. Emissions are often divided into stationary and mobile (line) sources [51]. The dispersion model have the advantage of incorporating both the spatial and temporal variation without need of extensive monitoring but are costly and requires highly trained personnel within both computer programming and GIS [51].

The dispersion model will never be better than the emission data inserted into the model. The spatial and temporal resolutions of the pollutants can be used using different time and grid cells, depending on the study design and resources. In larger cities this model can be improved by taking the street canyons into account, giving a better prediction in areas with buildings that block the passage of pollutants by using a street-canyon model OSPM (Operational Street Pollution Model) developed by the Danish National Environmental Research Institute (DMU).

In addition to the above mentioned, different hybrid models of methods are used and models with more advanced methods of incorporating the temporal variation by for example inserting meteorology in the models.

Epidemiological considerations

Long term and short term studies

Time is an important policy question when it comes to health effects of air pollution [55]. Study design affects how exposure can be related to the health outcomes and can typically be divided into time-series, and cohort studies. Time-series focus on temporal variability of exposure and cohort studies use individual-level data and focus on spatial variability of exposure [49]. Long term health effects are estimated by following longitudinal cohorts and analysing the contribution of the geographical variation of exposure adjusting for individual risk factors associated with exposure and disease [56]. Short term health effects are

done by examining associations between daily counts of death (or disease) and daily pollutants recorded at monitoring stations and they are often referred to as time series studies [56]. Lately the time series studies have been enhanced by accounting for the spatial variation and individual risk factors by using a case-crossover method [57].

There is a discrepancy between health effects estimates of air pollution on a short term (days to weeks) and long term (years or decades) [58]. Generally long term health effect estimates are larger than those of short term health effects, even after adjusting for individual risk factors [58]. A possible explanation is the cumulative exposure effects in long term exposure studies which might increase sensitivity in highly exposed subgroups [56]. Time-series studies assumes that exposure effects are acute and acting within days or a few weeks at most. But for many birth outcomes, the more appropriate scale may be months or trimesters [16]. It might also be hard to find the appropriate exposure window to look for short term effects if not looking at a specific birth defect due to lack of toxicological information [16]. In a cohort study (long term) on the other hand, there must be enough inherent spatial variability in the exposure aspect to make a study worthwhile [49].

Confounders

Vandenbroucke et al. explains that confounding literally means confusion of effects. They further describe that if a study finds an association between an exposure and a risk for disease there might be another explanation behind. That factor could be another risk factor (directly or indirectly) for the disease associated with the exposure. [59].

Sheppard et al. explains some of the specific forms of confounding and exposure measurement errors in cohort studies of air pollution effects. Although mainly focusing on mortality, a lot can be applied to other health outcomes. The author clearly points out the need to adjust for individual risk factors, such as smoking habits. The underlying reason is that long-term exposure to ambient air pollution is just one of several known risk factors. There are as well socio-demographic variables that could potentially contribute to spatial confounding [49].

Confounding bias in studies on pregnancy-related health effects of air pollution is more of a problem in long term studies than in time series studies. Time series studies might have to adjust for seasonal patterns due to weather but this can be calculated if birth date is available. Long term studies might have confounding problems related to maternal behaviour (e.g. low socioeconomic status communities that also tend to have higher air pollution levels). But these confounding problems might be adjusted for by proxies such as age, education, race/ethnicity, parity, prenatal care which might be available in public records. Furthermore, some sub-populations may be more susceptible to air pollutant

effects, such as individuals with a poorer diet, smoking, or poorer health. In a Los Angeles study, they observed that traffic-related air pollution exposure disproportionately affected low-income and disadvantaged neighbourhoods resulting in the highest odds of preterm birth for disadvantage subgroups [16].

Part 2 Materials and methods

The internal combustion engine, one of the greatest technological advancements in history, has an unfortunate downside, namely air pollution (…)

Cuthbert Soup, A Whole Nother Story

Study area

The study was carried out in Scania (Skåne), the most southern county in Sweden (Figure 2). Sweden's third largest city (Malmö; ~ 260,000 inhabitants) is located in Scania, and the county is compared with the rest of the country densely populated, with approximately 1.2 million people living within 11,000 km^2.

Figure 2
Study area in paper I, II and IV

Because of its proximity to the European continent and the Danish capital, Copenhagen, a great deal of cargo is transported to, from, and through this region by road, rail, and water, resulting in high levels of emissions relative to other parts of Sweden, especially in the western part. Although the air pollution levels vary considerably within the county, they are generally below the present WHO air quality guidelines for NO_2, PM_{10}, and O_3 [48, 60]. The mean exposure level of NO_x in the study area was 16.4 μg/m^3 during 1999–2005. In table 2 we give a view of the level of other air pollutants.

Table 2
Summary statistics of air pollution (all monitoring stations, hourly resolution) Scania, 2005

Variable	Minimum	Median	Maximum	Mean ± SD
PM_{10}	3.74	15.77	58.27	18.03 ± 9,25
$PM_{2.5}$	5.30	9.39	38.35	11.14 ± 5,85
NO_2	4.51	16.04	36.36	16.82 ± 6,54
Ozone	10.12	55.01	90.29	53.77 ± 16,7
SO_2	1.23	3.04	12.74	3.34 ± 1.623

The study population

The information about the study population in this thesis was obtained from registry data. In Papers I and II we included all singleton deliveries (81,110) in Scania during the period 1999-2005, which was obtained via linkages with the Swedish Medical Birth Registry (SMBR) covering almost all (98–99%) infants born in Sweden (Socialstyrelsen 2002). In Paper IV we also included multiple births which gave a total of 84 039 births.

Air pollution models in our studies

In this thesis we have in Papers I, II and IV used traffic intensity at nearest road within 100 or 200m buffers around residency which is a proximity based and rather crude model of traffic pollutants. It is built on data from the Swedish Road Administration.

We have in Papers I, II and IV used modelled individually assessed exposure to NO_x at residency with a spatial resolution of 500*500m grid cells with an hourly resolution aggregated to trimester specific exposure using a dispersion model. The emission sources in the emission database can be divided into eight categories [61].

1. Data on road traffic (such as vehicle types, fuel types, traffic intensity, speed limits) from the Swedish Road Administration and local municipalities.
2. Shipping (such as type of ships, ship construction, temporal and spatial patterns) manually collected for each harbour by Gustafsson et al. (2006).
3. Aviation, only emissions below 3000 ft. (912 m) from yearly environment reports produced by the Scandinavian airports during the year of 2001 were included.
4. Railroads (most rail traffic is electrified in Sweden, with the exception of some cargo transport and a few lines)
5. Industries and major energy and heat producers (such as height of chimney, chemical composition of discharge, exhaust gas temperature) from the national database "EMIR" (Emission Register administrated by Sweden's county administration).
6. Small-scale heating including the area's 150,000 residential heating appliances (70 000 oil burners, 67 000 small fireplaces and 13 000 wood or pellet heaters) with some indirect measures of frequency of usage from the National Rescue Agency's chimney register (2001).
7. Construction machinery (several vehicles, tools and machines used for construction or industrial applications including farming) most information originates from a report published by IVL, 'Swedish Environmental Research Institute' [62].
8. Since the emissions from Zealand, Denmark are quite high and since westerly winds are dominant in this area, these concentrations must be included. Information regarding the emissions was gathered from an investigation by SMHI (Swedish Meteorological and Hydrological Institute) in 2000.

The dispersion program used in these studies is ENVIMAN, which has been developed by OPSIS AB (Opsis, 2006). ENVIMAN is a combination of a Gaussian dispersion model AERMOD provided by the U.S. Environmental Protection Agency [63] and a street-canyon model OSPM However, building heights could not be included in the modelling due to lack of data. Meteorological data is also included in the modelling (such as temperature, radiation, wind speed and direction) collected from SMHI. In a study by Stroh et al. [64] modelled residential levels were compared to measured levels at same facades during one week with good agreement (r_s=0.8, p> 0.001). Modelled mean levels of NO_x for year 2005 are illustrated in figure 3.

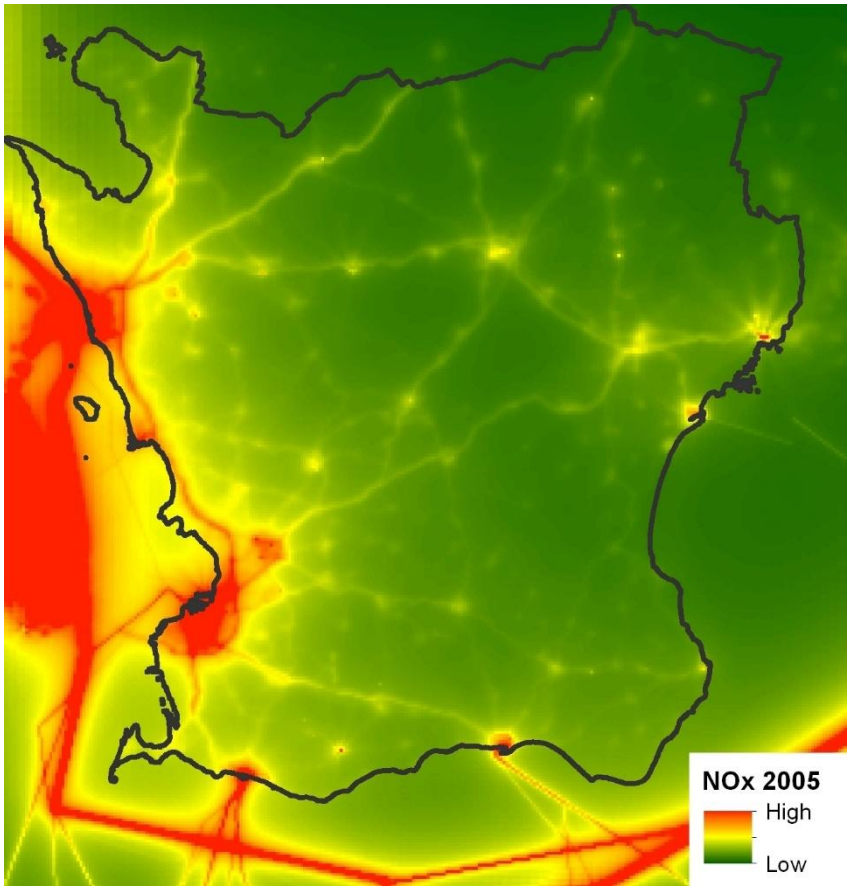

Figure 3
Modelled mean levels of NO_x for 2005

Based on results from Paper III, on the small spatial variation and poor model fit in our study area, we decided to use a nearest station approach in Paper IV to assess ozone exposure. We used measurements of ozone from 30 monitoring stations (figure 4) collected by local municipalities and reported to the Swedish Environmental Research Institute (IVL) were data was retrieved. All individuals were assessed with measurements using the nearest station approach. If the nearest station had missing data the individual were assessed to the next nearest station or the third nearest station. We excluded data if there was more than 10% missing data or if an individual lived further away from a station than 32 km according to the EPA recommendations [65]. The mean distance to stations used in the model was 8.5 km.

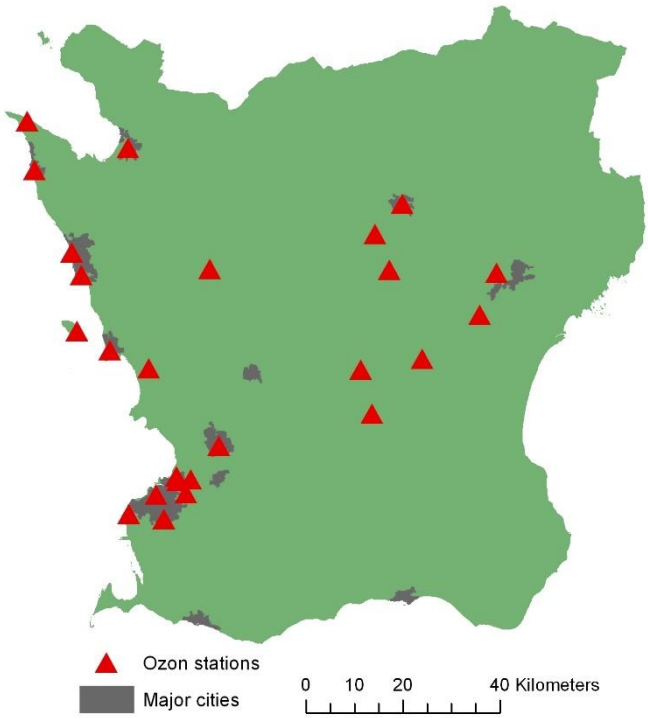

Figure 4
Ozone monitoring stations used in Paper IV.

Exposure assessment

As in most epidemiological studies we used residency as a proxy for total exposure. Each Swedish resident has a unique 10-digit personal identification code that can in this area be linked to the centre coordinate of her or his location of residence (updated yearly). The residential coordinates were used to calculate exposure. In addition the personal identification codes were the link between calculated exposure and information about outcomes and confounders in the registries used. A woman could have lived at multiple locations, if she moved during pregnancy, and thus different trimester-specific exposure. Since we lacked information on exact timing of the move, we thus conducted sensitivity analyses with women who had not moved during pregnancy.

Outcomes

In Paper I we analysed the associations between air pollution and the following birth outcomes; LBW, birth weight, PTB and SGA. We further analysed if there were any gender differences in effects. Information about the outcomes and confounders was obtained from the SMBR and Perinatal Revision Syd (PRS -a birth registry covering Scania).

In Paper II we analysed the associations between air pollution and the following pregnancy complications; preeclampsia and gestational diabetes. Information about these outcomes and confounders was obtained from the SMBR and PRS. Almost all pregnant women visit the maternal health care centres where blood pressure and proteinuria are measured at each visit. Preeclampsia-diagnosis is based on systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg (measured twice with at least 6 hr. between) and proteinuria > 0.3 g/day after 20 weeks of gestation. The diagnostic criterion for severe preeclampsia is blood pressure ≥ 160/110 mmHg or proteinuria ≥ 5 g/day. Furthermore, in the study area, an oral glucose tolerance test is routinely performed during pregnancy week 28 to screen for gestational diabetes. All pregnant women are offered the test and the participation rate is approximately 93% [66]. Gestational diabetes is diagnosed based on plasma glucose > 10 mmol/L 2 hr after oral administration of 75 g of glucose. If results indicate impaired glucose tolerance (plasma glucose 8.6–9.9 mmol/L), the test is repeated within a week.

In Paper IV the study design was a case-control study and in case control studies, investigators compare exposure between people with a certain disease (cases) and people without a certain disease (controls). Cases and controls should be collected wisely to represent a cross-section of a population, the cases are usually all with the disease in that population and controls is usually a small fraction that should represent the same population as the cases [59]. All children born 1999-2005 diagnosed with T1D have been registered in local diabetes quality registries; Skånestudien and Better Diabetes Diagnostics. In total, 344 children born 1999 to 2005 were diagnosed with T1D. In addition, all children born in Scania from September 2000 to August 2004 were offered screening for genetic risk of T1D at birth in the DiPiS-project [Diabetes prediction in Scania]. The Human Leukocyte Antigen [HLA] system is linked to the immune system, one or both of the susceptibility gene types is present in 90-95 % of young children developing T1D, whereas the protective gene type is present in less than 0.1% of T1D cases [41, 67]. 74% of children born during 2000-2004 were HLA-typed in the DiPiS-project. From the DiPiS cohort three children without T1D were randomly selected for each case matched for HLA genotype and who had never had

antibodies strongly connected with future development of disease. In the analyses we had 944 controls. Information on possible confounding factors was obtained from SMBR.

Statistics

All associations between exposure to air pollution and dichotomized health outcomes in Papers I and II were examinedusing logistic regression models. The birth weight in Paper I was also analysed as a continuous variable in linear regression models. We used IBM SPSS Statistics, (IBM Inc., Chicago, IL, USA) for Papers I and II. Due to the matched design in Paper IV we used conditional logistic regression models in LogXact (Cytel Studios, Cambridge MA). In addition to unadjusted analyses we also adjusted for potential confounders. Moreover, the robustness of the results was evaluated by sensitivity analyses including specific subgroups (for details see the orginal Papers). The results were presented as Odds Ratios (OR), which is the ratio of the odds of a disease occurring in one group to the odds of it occurring in another groupIn Paper III, multiple linear regression models was used to identify geographical variables that could explain the variation in measured levels of Ozone at different sites. For detailed description of predictor variables, model development and model validation, see Paper III.

Part 3 Results and Discussions

Remember when atmospheric pollutants were romantically called stardust?

Lane Olinghouse

Paper 1 – Birth outcomes

Results and main findings

We did not observe any consistent effects of our exposures on the risk of being born with a low birth weight. We did find an association between newborns that were SGA and maternal exposure to NO_x in unadjusted analyses or partly adjusted analyses, those results did not remain statistically significant after adjusting for all potential confounders. In the crude analysis, for the highest exposure quartile of NO_x compared with the lowest category, the OR was 1.37 (95% CI, 1.28–1.47). For traffic density, comparing the category with > 10 cars/min with the reference category, the OR was 1.26 (95% CI, 1.14–1.40) in the crude analysis. After adjusting for all confounders, no statistically significant results remained, with ORs of 1.07 (95% CI, 0.99–1.15) and 1.04 (95% CI, 0.93–1.15), respectively. This stated, a small exception was that we observed a statistically significant, but fairly small risk, in the fully adjusted models comparing highest to lowest NO_x-quartiles, for SGA for newborn girls (OR = 1.12; 95% CI, 1.01–1.24), and in a sub-analysis including only mothers who had not changed residency during pregnancy. The risk of PTB was lower in the three higher NO_x- exposure quartiles compared to the reference category. The unadjusted and adjusted odds ratios varied between 0.85 and 0.91.

Discussions

Our study, finding no consistent evidence for any negative effects of air pollution on birth outcomes at comparably low exposure levels, clearly points out the need for good exposure estimates and careful control of possible confounding factors, especially those that are linked to socioeconomic and spatial gradients. Concerning PTB, we observed an opposite trend, suggesting that air pollution might have a small protective effect, which runs counter to earlier results. It might be the case that our air pollution levels underlie air pollution effects on PTB or due to some

unmeasured confounding. Although we had good data from SMBR and PRS on some other risk factors that could have confounded results such as maternal age, sex, smoking reported during early pregnancy and parity. We are not certain if the effect estimates would look different if we further investigated the role of socioeconomic status as confounder or effect modifier. We could not adjust for socio-economic variables such as maternal education or income was an inherent problem when interpreting the results in Paper I, even if Sweden is globally considered a relatively socio-economic homogeneous population. Populations of non-Nordic origin have in our study area been shown to live in more polluted areas, although this varies between cities in the study area [68]. It can thus not be denied that the interpretation of the results would have gained by a more robust measure of socio-economic status. In figure 5, we show how air pollution exposure varies with maternal country of origin.

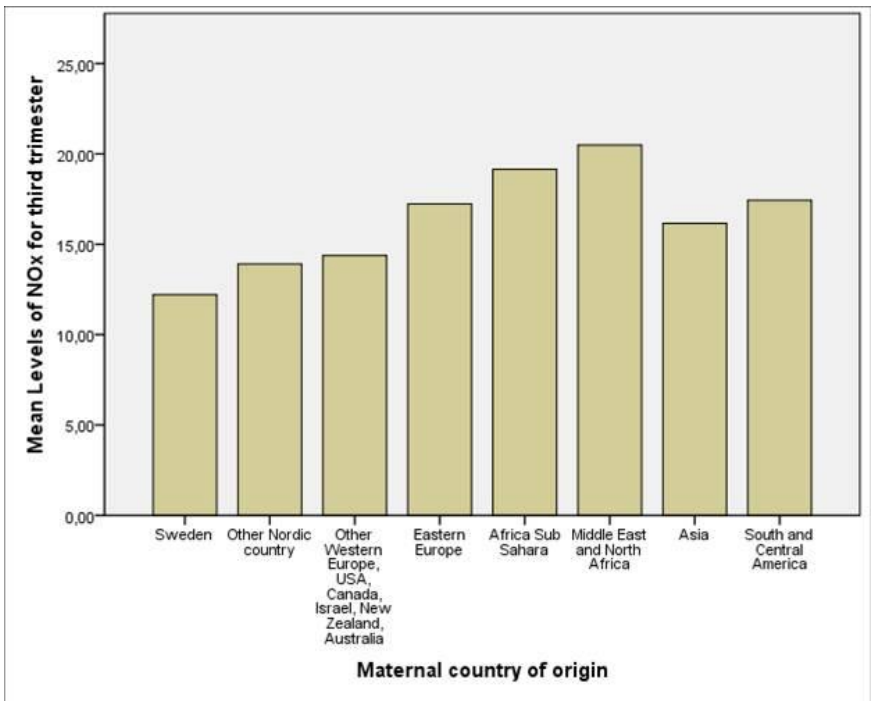

Figure 5
Air pollution by Maternal country of origin

The effect of ethnicity on the risk of having a newborn with reduced birth weight is well known [69, 70]. This has also been shown in this study area and the main explanation did not seem to be maternal physical size, but rather maternal psychosocial factors such as low social anchorage in some immigrant populations

[71]. Since exposure to air pollution is closely linked to urban-rural contrasts it needs to be mentioned that there might also be some unmeasured confounding related to this contrast.

Biological mechanisms

The biological plausibility behind air pollution effects on birth outcomes has been discussed. Pregnancy is a period of human development particularly susceptible to air pollution toxins due to high cell proliferation, organ development and the changing capabilities of foetal metabolism [72].

Paper II – Pregnancy complications

Results and main findings

The prevalence of gestational diabetes increased with each NO_x quartile, with an adjusted odds ratio (OR) of 1.69 (95% CI: 1.41, 2.03) for the highest (> 22.7 µg/m3) compared with the lowest quartile (2.5–8.9 µg/m3) of exposure during the second trimester. Also, an association between air pollution exposure and preeclampsia was observed. The adjusted OR for acquiring preeclampsia after exposure during the third trimester was 1.51 (1.32, 1.73) in the highest quartile of NO_x compared with the lowest. The associations remained when we adjusted for confounders and performed restricted analyses. For gestational diabetes the effect of air pollution seemed to be linear. An increased risk of mild preeclampsia seemed to be present already at low levels of air pollution whereas for severe preeclampsia an increased risk appeared at higher levels. Findings from the data suggested an association between traffic density at the nearest road within 200 m and gestational diabetes, although no obvious association between traffic density and preeclampsia was observed.

Discussions

Our outcome data is based on population-based registries using same criteria for disease. In this second paper we excluded cases which could have been misclassified due to diseases occurring prior to exposure (pre-pregnancy hypertension and diabetes). In Paper II we performed additional analyses within only urban or rural areas and results seemed robust. Thus, associations did not seem to be an effect of urban/rural setting. Thru linkage to SMBR and PRS we obtained information about some of the potential confounders. The confounders we could adjust for were individual factors such as maternal smoking during

different time windows of pregnancy, parity, mother's diabetic or hypertonic stage prior and during pregnancy, maternal age, BMI and maternal country of birth.

We could not adjust for socio-economic variables such as maternal education or income which has been associated with outcome [73, 74]. However, using proxies such as country of origin or smoking did not seem to largely confound our results. Two possible confounders not adjusted for are diet and physical activity for which we had no data. To what extent diet and physical activity is linked to exposure can only be hypothesised and thus the confounding effects of these factors.

The importance of this finding has been highlighted by Tillett [75]. Gestational diabetes and preeclampsia are pregnancy conditions with suspected links to systemic inflammation which can affect foetal and maternal morbidity and mortality. Although our study lacks individual socioeconomic data, the large sample size and individually modelled exposure estimates indicate a statistically significant relationship between gestational diabetes and preeclampsia and exposure to low levels of air pollution. The effects are comparable to those of other well-known risk factors such as obesity or being over 35 years of age. Tillett further states that this information could affect public health policy that addresses maternal health care (Tillett 2013).

Biological mechanisms

Many studies have seen air pollution effects on Type 2 Diabetes [39, 76]. Therefore, more studies have been conducted on the biological mechanism behind air pollution effects on etiologically similar Type 2 Diabetes than on gestational diabetes. Three major mechanisms has been suggested; first induction of systemic oxidative stress and inflammatory responses, secondly by direct effects of ultrafine particles or pollution constituents on the circulatory system and potentially distant organs and thirdly by changes in the autonomous nervous system function [76]. Pregnancy can be a time in life with an increased susceptibility to glucose intolerance [35], and consequently, pregnant women might, theoretically, be a group susceptible to potential air pollution effects on the incidence of diabetes.

The biological mechanisms behind preeclampsia are ambiguous [77]. Studies have shown that ischemic placenta and endothelial dysfunction play a role in development of the disease. Endothelial dysfunction can occur due to systemic inflammation, oxidative stress and cytokine release [78] all of which, as mentioned earlier has been related to exposure to air pollution.

Paper III – Ozone modelling

In Paper III we developed LUR models for ozone in and surrounding the largest city, Malmö, in the studied area and in and surrounding Umeå, a smaller city in the North of Sweden. This is illustrated in figure 6.

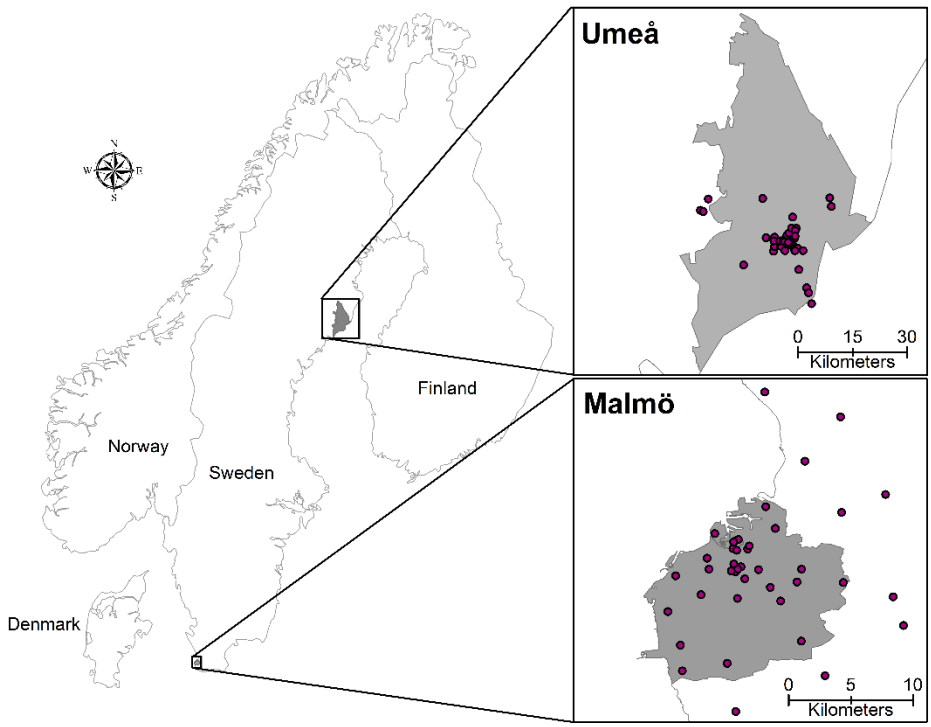

Figure 6
Study areas for Paper III and measurements sites.

The models were based on 40 measurements using Ogawa diffusive sampler (Ogawa & Company, Pompano Beach, FL, USA) in each area during three different weeks spread out over a period from April to August 2012. GIS were used to generate variables to characterise the street, traffic load, land use and population density in different buffers around the coordinates of the measurement place. Regression analyses were used to find which variables best predicted variation in ozone concentrations from place to place.

In addition, we developed a temporal model for Malmö. For the temporal model, hourly data from 3 measurement stations that continuously measure levels of ozone by active UV- absorption were collected and aggregated into daily means

(21 daily measurements from each of the three stations). This data was collected from one urban background site and one traffic site in Malmö and one regional background site (situated 50 km north of Malmö). Meteorological data are collected from the Swedish Meteorological and Hydrological Institute [SMHI] site Heleneholm in Malmö. Regression analyses were used to find which variables best predicted variation in ozone concentrations from time to time.

Results and main findings

In the area surrounding Malmö [hereafter only referred to as Malmö] the variation of ozone varied between 59.9-83.1 µg/m^3 and in the area surrounding region Umeå [hereafter only referred to as Umeå] the ozone varied between 26.5-93.3 µg/m3. The measured levels by station type are illustrated in table 3.

Table 3
Ozone concentrations (µg/m^3) and number of stations by station type.

City	Site type	N	Mean	SD	Min	Max
Malmö	Regional background	7	69.1	5.9	60.4	79.0
	Urban background	15	66.7	3.2	59.9	73.0
	Traffic	18	68.4	8.0	60.0	83.1
Umeå	Regional background	5	54.9	18.3	27.5	93.3
	Urban background	23	52.5	14.2	29.4	71.8
	Traffic	12	49.3	13.5	26.5	69.7

For Malmö the LUR-model had an adjusted model R^2 of 0.39 and cross validation R^2 of 0.17. For Umeå the model had an adjusted model R^2 of 0.67 and cross validation adjusted R^2 of 0.48. When restricting the model to only including measuring sites from urban areas, the Malmö urban model had adjusted model R^2 of 0.51 (cross validation adjusted R^2 0.33) and the Umeå urban model had adjusted model R^2 of 0.81 (validation adjusted R^2 of 0.73).

The predictor variables with traffic went in the right direction of the scavenging effect of freshly emitted NO. Natural areas and urban green areas can have effect that goes in both directions. One explanation for a positive direction of effect can be the fact that green areas means absence of primary NO sources near the site. The role of BVOCs and its contributing or scavenging effect on ozone are largely depending on: meteorological factors, if there are high levels of ozone precursors such as NO_x present, as well as type of tree species and thus which kind of BVOCs are emitted [10, 11]. Residential land describes the urbanization around a site and

goes in the same direction as the scavenging effect of traffic. We have no explanation to why population density went in the opposite directions with positive direction of effects. The influence of the variables contributions to the model is described in Table 4.

Table 4
Predictor variable contribution to the models

Umeå		**Umeå urban**		**Malmö**		**Malmö urban**	
Predictor variables (buffer)	Adj R^2	Predictor variables (buffer)	Adj R^2	Predictor variables (buffer)	Adj R^2	Predictor variables (buffer)	Adj R^2
Traffic load (300)	0.44	Traffic load (300)	0.67	Low density residential areas (300)	0.19	Low density residential areas (100)	0.13
High density Residential areas (5000)	0.52	Natural areas (500)	0.75	Distance to sea	0.20	Urban green areas (100)	0.24
Natural areas (5000)	0.61	Population density (5000-1000)	0.79	Urban green areas (100)	0.26	Heavy traffic load (1000)	0.51
Urban green areas (500)	0.63	Population density (1000)	0.81	Traffic load (1000)	0.40		

To develop the temporal model for Malmö, hourly ozone data was aggregated into daily means during three weeks for two measurement stations in Malmö and one in a rural area outside Malmö. Using regression analyses we inserted meteorological variables into different temporal models and the one that performed best for all three stations was chosen.

Apparently, there were enough temporal variation, largely explained by mixing heights and radiation (vertical difference in temperature between 24 meters and 8 meters, net radiation and global radiation). For the urban background station the adjusted R2 was 0.54, for the traffic site the adjusted R2 was 0.61 and for the regional background site (situated 50 km from Malmö) adjusted R2 was 0.22. When validating the temporal model we used four randomly selected weeks between the years 2000 and 2012 and the model seems to works even in this extended time span with an adjusted validation R2 of 0.42.

This third study shows that it is possible to predict the spatial variability of levels of ozone, at least for Umeå and possibly in the urban areas of Malmö. The

temporal model showed that levels of ozone could be predicted by applying meteorological factors in a regression model.

Discussions

The contribution from the long distance transported ozone is a likely explanation for the relatively poor LUR-model fit in Malmö. Another possible explanation could be that the spatial variation of ozone was smaller in Malmö than in Umeå. It should also be noted, that our results should be put in the context of our cities being considerable small and levels of ozone precursors moderate.

There are several limitations in this study; firstly we validated our spatial models using leave one out cross validation. This is the most common validation for LUR-models and standardised in the ESCAPE project [52]. It should however be mentioned that this validation method has been criticised for overestimating the predictive ability of LUR-models [54].

The second possible caveat is the timing of measurements. We decided to measure simultaneously in spring, summer and autumn at both study sites. The two studied areas are situated quite geographically apart (1250 km) and seasons can vary substantially in time and it can be argued if we did capture any autumn trends in Malmö region.

Thirdly, it should also be noted that we used a standardized model, ESCAPE, which was originally developed for primary pollutants and do not capture fully the role of different BVOCs. A fourth possible limitation is that we use land use data from CORINE from 2000 and 2006 and it can be argued that the land use might not always be accurate for 2012. By visiting the sites to place and collect the samplers we could at least to some extent minimize this misclassification problem. Furthermore, as the formation of ozone is a photochemical reaction, variations in ozone concentrations can be expected throughout the year. The model will not be applicable for the winter season since this period was not studied, yet ozone levels is not of a health concern in this region during winter due to low solar radiation and thus low photochemical reactions.

The factors included in the temporal model seem to be factors that are important for local production of ozone such as solar radiation variables (net radiation and global radiation); rather than factors representing in transport of pollutants such as wind variables. This is also supported by the fact that the variables seems to predict better in the traffic site, with more of the scavenging effect of NO -that is solar dependent, than in the background site. This could of course also be due to the background site situated further from the meteorological station and thus affected by local weather patterns.

Paper IV – Type 1 Diabetes

Results and main findings

The main finding in our fourth study is that the risk of developing T1D increased if the mother had lived in areas of elevated levels of NO_x during third trimester or ozone during second trimester. For ozone exposure during the second trimester a statistically significant association with T1D was observed when the highest exposure quartile was compared with the reference category (OR 1.70, 95% CI 1.01 to 2.87). No significant associations were observed for ozone exposures during trimester 1 and trimester 2, although all ORs were above one. Regarding NOx exposure the ORs were above one for all three trimesters (1.36, 1.40 and 1.57, respectively) when we compared the highest exposure quartile with the reference category. However, it was only exposure during the third trimester that reached statistically significance. Traffic density was not associated with the risk of developing T1D.

Discussions

For Paper IV, little is known about environmental risk factors affecting T1D, we can therefore not judge if confounders have been fully adjusted for. We did perform some sensitivity analysis were we excluded cases that had a risk factor that could have influenced results such as maternal diabetes or smoking. In Paper IV our cases were based on a total population in Scania born 1999 to 2005. The controls, however, were based on a sample of the population born 2000 to 2004 that were included in DiPiS study, but participation rate were high (74%) which should limit this bias. Due to the study design and smaller population size we did not have the possibility to stratify into urban/rural areas. Special precaution should also be given the fact that we can't rule out that the air pollution effect is occurring during pregnancy and not during first years in life as at least NO_x-exposure should be similar if they had not moved residency.

In this study we additionally studied the effect of ozone exposure. Due to the small poor model fit for this area in Paper III we did not use a LUR-model. Instead it should be mentioned that we used a quite imprecise exposure assessment method by merely attributing measured levels at monitoring stations which can be situated quite far away from the location of residence. The error of this inprecise method should be weighted against the small spatial variation that we encountered in Paper III. We also used data from both passive and active samplings in the dataset, however previous studies have shown good agreements doing so with R^2 of 0.88-0.96 [79].

We were able to, in a population-based prospective study, for the first time; analyse the association of air pollution during pregnancy and risk of childhood development of T1D after controlling for the genetic risk of disease.

Biological mechanisms

T1D could be attributed to insufficient insulin production by the pancreatic beta cells. It is well known to often develop in genetically susceptible individuals, but the genetic inheritance is complex and does not show simple Mendelian traits [80]. It has been proposed that environmental factors could be the trigger in T1D by putting excess stress on pancreatic beta cells and sensitise them to the autoimmune attack [67] or even trigger the autoimmune response itself [81].

Part 4 Discussion and conclusions

There's so much pollution in the air now that if it weren't for our lungs there'd be no place to put it all.

Robert Orben

General discussion

There are some limitations that have not been brought up in the previous chapter that are more general and will thus be discussed in this chapter.

Misclassification of exposure

Crucial for epidemiologic study design and inference is the scientific understanding of exposure and its sources of variation. Total exposure of air pollution is the sum of ambient and non-ambient sources. Ambient exposure is relevant for both indoor and outdoor exposure since ambient air enter the house due to infiltration [49]. The amount of time spent indoors varies with the population but the average time for an active adult in Europe is to spend 85-90% indoors, 7-9% in traffic and only 2-5% outdoors ([3, 82]. The time spent indoors is almost 100% for infants and other vulnerable groups. The majority of indoor exposure to air pollution, in an urban residency without gas ovens, smoking or solid fuel burning, arises from ambient air passing thru air exchange. [3]. The air exchange itself varies between buildings and pollutants. In the study area the gas appliances are sparse and the pollutants from heating somehow accounted for in the dispersion modelling. Passive smoking is of course detrimental but could not be accounted for in this thesis due to lack of data.

It is well known that exposures from workplaces and commuting vary between individuals to a larger extent than the exposure from ambient air pollution at a specific time and location, such as outside the individual's residency [3]. The contribution from other exposures will depend on the behaviour of the individual and their microenvironment. This is especially true for commuting which can contribute largely to the individual's total exposure. The rate of commuting exposure to total exposure depends on commuting mode and levels of pollutants in that area. If exposed directly to busy streets at bus stops, by walking or biking or

in vehicles with open windows or in tunnels the excess in exposure can be 20-30 µg/m^3 of $PM_{2.5}$ per time unit. If travelling in a modern car, bus or tram with intake air filtration the excess is negligible. Also air pollution at workplaces can be the largest source of exposure for an individual, but are limited to a specific, although not always small, subgroup of the population [3].

The important aspect of the time-activity pattern of the individual are, due to lack of data in epidemiological studies, often restricted to ambient exposure at individual's place of residence [49] [50].

We assessed exposure at the centre coordinate of the mother's residential property. This is in some cases not the exact location of residence. Some properties can be large, in the cases of agricultural properties and estate buildings covering larger areas. This is less of a problem in the dispersion modelling which interpolate levels of four grid cells surrounding the property. But in the case of traffic intensity at the nearest road within 100 or 200m there might be some cases with misclassification of exposure. Using the nearest station approach for ozone for Paper III assumes a very crude spatial resolution of ozone variations; this might not always be the true exposure.

The dispersion model incorporated a street canyon model, OSPM, but did not fully use its potential due to lack of data on building heights. This could mean that in some urban areas we under- or over-estimated true exposure. The number of streets with high and compact buildings is limited in the studied area and wind abundant which should minimize areas of poor air dispersion conditions. The individuals would also most likely already be classified in the highest or next highest exposure category. This should minimize this misclassification error.

Validation studies are performed to investigate how well the model perform compared to reality. When modelled levels are compared with measured levels; there are three important questions to be raised. Firstly, how well were the measured levels representing the study population, secondly were the duration of the measurement times representable and thirdly, were these measured levels already included in the model? Levels from our dispersion model have been compared with measured levels at 86 facades of participants in a week-long campaign in 2005-2006 [64]. Out of these 86 participants, 64 agreed to an additional week of façade measurements giving a total of 150 measurements and performed with an r_s of 0.8 and R^2 of 0.42. Meaning that the model performed well, in that sense that no indication of marked systematic differences was detected in the Bland-Altman plot $p<0.001$. The measured levels were not included in our dispersion model. In a previous validation study the modelled levels were compared to measured levels and had a good correlation R^2 of 0.69. Those measurement had however been used in the dispersion model for calibration [83]. In the LUR-model we used a validation technique Leave one out cross

validation which has been criticised for using measurements for validation that are already included in the model [54].

With this in mind we would like to acknowledge that there are also several strengths in these present epidemiological studies. In Scania, Sweden, unique personal identity codes, geocoded information on each individual's residence, an extensive dispersion model on NO_x, road traffic data, air pollution monitoring data, and high-quality information from population based registers have been used, using GIS and statistical software for linkage of data.

Generalizability

Previous chapters have focused on the validity of the papers included in this thesis. Of equal importance is the generalizability of the papers. The exposures studied are mainly combustion related and are occurring in most parts of the world, with a similar constitution of air pollutants. Fuel types and wear particles from the use of studded tyres might affect our air pollution mixture to a small extent. To the best of our knowledge, however, the generalizability of our studies is large. These studies have been conducted in a relatively low dose exposure area. Air pollution effects could therefore be even greater in more polluted areas.

Conclusions

- We did not find any consistent air pollution effects on birth outcomes; however socio economic factors could have influenced results.
- Our study showed an increased prevalence of gestational diabetes and preeclampsia with increasing NO_x exposure.
- The risk of developing T1D increased if the mother had lived in areas of elevated levels of NO_x during third trimester or ozone during second trimester.
- It was possible to predict high fractions of the spatial variability of levels of ozone, at least for Umeå and possibly in the urban areas of Malmö.
- The temporal model could predict high fractions of the temporal variation of ozone by applying meteorological factors in a regression model in Malmö.

Future studies

It seems that even though this thesis has touched upon some results regarding air pollution effects during pregnancy, more studies are clearly needed. Specifically, more studies on air pollution risks for foetal growth retardation are needed in low exposure areas where careful consideration of socioeconomic status is accounted for. In addition, more studies on pregnancy complications and T1D risks in regard to exposure to air pollution during pregnancy are clearly needed before our studies' suggested risks can be confirmed.

In an exposure assessment perspective, we are evidently in need of better knowledge of local ozone variation and especially the factors influencing this variation. One suggestion would be to study more deeply into different tree species release of BVOCs and how they influence ozone levels. More studies in different setting would be beneficial in natural areas, in urban green areas and of course in residential settings as the goal is to assess population exposure. To better capture ozone spatial variation, we need more measurements in diverse areas and during time periods not covered by Paper III.

Better knowledge about how the time-activity pattern of the individual affects the health effect results would be beneficial. In addition, more knowledge about what constituent in the pollutants from traffic that drives the health effect would be of outmost importance for policy-makers. Last but not least on the wish-list would of course a biomarker for exposure to air pollution be listed.

Implication for society

These present studies suggests that air pollution could be a risk for gestational diabetes and preeclampsia in the mothers and T1D in the children in an area with levels of pollutants generally below current air quality guidelines. The question remains if precautionary actions need to be taken for the pregnant women, on an individual level and/or governmental level. One simple answer would be to say that more studies in the field are needed, which is partly true. Before individual actions were to be given as advice to pregnant women, we need to carefully balance the risk versus the implication of such advice. The implication of such advice could lead to increased stress and restricted freedom of behaviour of these women.

On a governmental level, however, it should be put in a perspective that the precautionary principle allows for basing intervention on circumstantial evidence alone rather than on a definitive medical proof of harm. Ritz and Wilhelm

conclude that because, millions of women all over the world are exposed to air pollution at levels similar to or greater than the levels in the studies published the pre-cautionary principle should be applied [16]. Furthermore, as touched upon in the introduction of this thesis, increased risk for several other outcomes, such as impaired lung function and asthma have also been associated with air pollution at our levels [15, 84]. A new report from the Swedish Environmental Protection Agency suggests that a reduction of 1µg/m^3 of NO_2 in Stockholm, Sweden would generate a benefit for society with 168 million SEK per year when only considering fewer cases of asthma. A reduction of 1µg/m^3 is the exposure reduction that occurred in the inner city of Stockholm due to congestion charges which resulted in 15% decreased traffic [85].

On a European level the APHECOM studies have shown that exceeding WHO Air Quality Guidelines on $PM_{2.5}$ in 25 European cities with a total of 39 million inhabitants results in: 19,000 deaths (15,000 of them from cardiovascular diseases) and €31.5 billion in health and related costs every year [86]. It has been concluded at the international workshop *Saltsjöbaden V- taking international air pollution policies into the future* that special precautions to protect children and other vulnerable groups should be taken by appropriate authorities [87]. Current air quality standards in the EU or US do not always meet WHO air quality guidelines and the standards are in many areas violated [3].

In addition to be of a health benefit, strict implementation of air quality guidelines has cobenefits for climate change by reducing related emissions. The Saltsjöbaden workshop stressed the need of highlighting this link between climate and air quality. To reduce emissions of combustion related pollutants by reducing transport and energy will of course be beneficial even in a climate change perspective. One example is the black carbon particles which have an effect on both health and near-term climate purposes especially in Arctic and alpine regions [87]. But also climate change mitigation of reducing methane (also an ozone precursor) might help to abate harmful levels of (ground level) ozone[3].

This thesis adds to the new evidence that pregnant women might be a vulnerable group to air pollution, not only for the health of her child but for her own health as well. Current air quality guidelines do not necessarily protect pregnant women to the full extent.

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