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Safe air below EU air quality limit?

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Studies of respiratory disease using primary health care data, with Case-Crossover study design

Tahir Taj

LUND
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Abstract

Ambient air pollution has been linked with a number of adverse respiratory health outcomes. Earlier studies have shown that population exposure to ambient air pollution increases visits to emergency rooms and hospital admissions due to respiratory complaints. Exposure in vulnerable populations has also been shown to increase mortality risks. However, there is a need to better evaluate exposure-response to more mild and moderate respiratory diseases. The aim of this thesis was to explore the acute and long-term effects of air pollution on mild, moderate and severe respiratory diseases in an area where criteria pollutant levels are generally well below or close to current air quality limits. Air pollution levels throughout the study period from 2005 till 2010 remained well within WHO and EU guidelines All four studies are of case-crossover design. Papers I, II and IV have the total number of primary health care (PHC) visits due to asthma whereas in Paper III all visits regarding respiratory ailments to PHCs, inpatient admissions, and emergency visits were analysed. In Paper II, first visit due to asthma during the study period were analysed. In all four papers, urban background air pollution monitor data was used from the year 2005 till 2010. In Paper II, a geographic information system (GIS) based dispersion model together with an emission database was used to model long-term concentrations of NO_2 at the PHC clinic. Air pollution levels throughout the study period from 2005 till 2010 remained well within WHO and EU guidelines. Correlation between different air pollution monitoring stations within the same municipality was moderate to strong. In all our studies, we found an increase in the risk of PHC asthma visits with an increase in NO_2 levels. We did not found any statistically significant increases for inpatient admissions or emergency room visits due to respiratory illnesses. There was weak evidence for short-term associations between air pollution and asthma may to depend on background air pollution levels. In conclusion, the air does not seem to be entirely safe below the EU air quality limit

Key words:

Air Pollution, Asthma, Primary Health Care, Health Care Register data

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Studies of respiratory disease using primary health care data, with Case Crossover study design

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To my Father
Taj Muhammad Khan

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List of Abbreviation's

PHC	Primary Health Care
ICD-10	International Statistical Classification of Diseases and Related Health Problems, tenth revision
PM	Particulate matter
CP	Coarse Particle
NO_2	Nitrogen dioxide
O_3	Ozone
SO_2	Sulphur dioxide
SMHI	Swedish Meteorological and Hydrological Institute
GLM	Generalized linear model
DLNM	Distributed lag non-linear model
CI	Confidence interval (95% if not stated otherwise)
OR	Odds ratio
RR	Relative risk
WHO	World Health Organization
EU	European Union
PHCC	Primary Health Care Centre

Introduction

Air pollution is one of the most serious environmental risks causing strong negative impacts on human health. The Global Burden of Disease (GBD) study reported that air pollution is the main cause of environment-related deaths worldwide and estimates that 5.5 million premature deaths occurred globally in 2013 (Brauer et al., 2016; Collaborators et al., 2015). Among these, two thirds of the deaths have been attributed to outdoor air pollution (3.3 million premature deaths) (Lelieveld, Evans, Fnais, Giannadaki, & Pozzer, 2015). Air pollution and health research covering many decades has shown strong evidence of adverse health outcomes in relation to both morbidity and mortality. These outcomes primarily regard the health of cardiovascular (Meo & Suraya, 2015) and respiratory systems (Kurt, Zhang, & Pinkerton, 2016).

Evidence on the impact of human activities on air pollution goes back to 100 B.C, Ice core data shows that during the time of the Roman empire in 100 B.C, human activites led to the emission of a large amount of methane (Sapart et al., 2012) due to the burning of wood for metallurgical purposes (Irabien, Cearreta, & Urteaga, 2012) and domesticated animals were the main sources of emissions. Increases in methane during that time has also been attributed to the Han dynasty in China who expanded rice fields which contained methane producing bacteria (X. Q. Li, Dodson, Zhou, & Zhou, 2009). Evidence that this rise in air pollution was affecting people can also be found in the literature of that time. A famous Roman Empire poet, Horatius (65 B.C. – 8 A.D.) expressed his dislike of marble buildings becoming smudged by smoke in his poems (Flaccus, 2012). Evidence shows that the Romans acknowledged the problem of air pollution and tried to rectify it. In one instance, cheese making factories were advised to move out of the city so that the smoke emitted from them did not affect the local population. The first law regulating air pollution was also introduced by the Romans in which it was stated that “polluting air is not allowed” (Makra & Brimblecombe, 2004).

In modern times, the effects of air pollution on health came into focus after “The Great London Smog” of 1952 (Davis, 2002). During the winter of 1952, a weather condition known as an anticyclone occurred over London resulting in a temperature inversion that trapped cold air under warm air (Office, 2015).

Londoners burned more coal than usual to keep warm. The coal burned was of a low grade high in sulphur resulting in increased sulphur dioxide in exhausts. Increased air pollution production and the prevailing weather condition preventing dispersion of the pollution and resulted in very high levels of exposure causing an adverse health impact. Starting on 5th of December, and within four days, 150,000 Londoners needed hospitalization and over 12,000 died (M. L. Bell & Davis, 2001). This extreme event raised awareness among people and policy makers leading to the formulation of stricter measures to regulate air pollution. This lead to the Clean Air Act 1956 (Wyatt, 1958). Among many other steps taken, was one to relocate power stations to rural areas reminding us of the Roman relocation of cheeses factories.

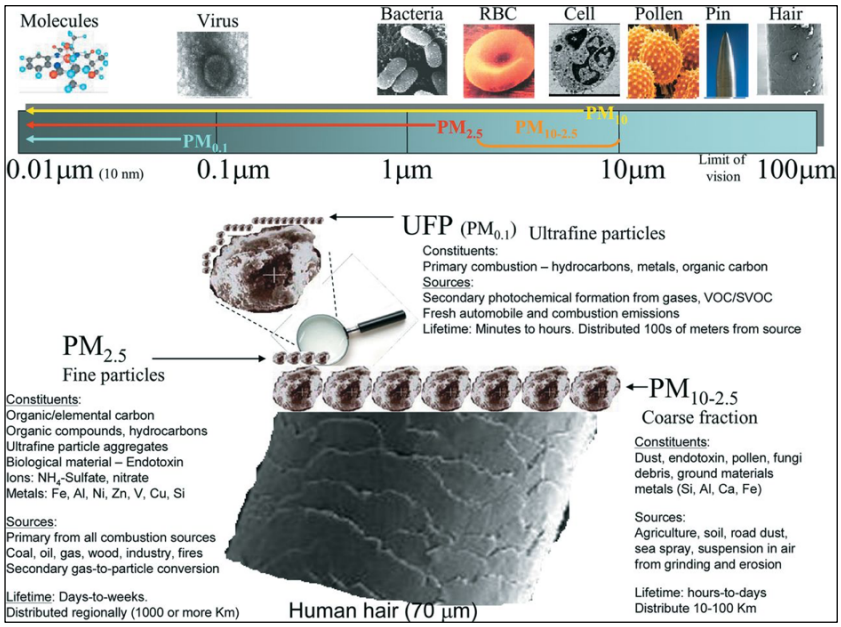

Figure 1 Size, sources and composition of PM air pollution RBC, red blood cell; SVOC, semi-volatile organic carbons; UFP, ultra-fine particles; VOC, volatile organic carbons The fine and ultrafine particles are of particular interest, since these particles can reach the periphery of the human airways and initiate oxidative stress and inflammation (Brook, 2008).

Subsequent to the severe situation in London mentioned above, the importance of air pollution in regard to public health is increasingly being understood. Several studies have found a link between increased air pollution and mortality and morbidity. The purpose of this thesis is to investigate the effects of low levels of air pollution on respiratory health. This thesis includes

investigations into outdoor air pollution exposure to the public and studying its health impact upon mainly respiratory health.

Particulate matter PM

Particulate matter (PM) is the single most important air pollutant in regard to effects on health. PM is a complex mixture of materials in solid or liquid states with different sized particles having diverse physical and chemical characteristics and suspended in the atmosphere.

PM can comprise a broad range of materials and are emitted from various sources. Broadly speaking, these sources can be divided into two types; biogenic or natural and anthropogenic or man-made sources. Biogenic aerosols include spores, pollen and volatile organic compounds emitted by soil and vegetation but sea spray is by far their major source. Sea spray aerosol has both organic and inorganic matter know as sea salt. Sea salt is mainly composed of sodium chloride with traces of magnesium and sulphate. Sea-spray particles range in size from one micrometer up to a few micrometers. In areas near coastal regions, sea salt made up of 80% of particulate mass (O'Dowd et al., 2004). (Putaud et al., 2004). Manders et al. (2010) (Ceburnis et al. 2006). Anthropogenic sources mainly come from fuel combustion such as fossil and biofuels in power plants, different industries, vehicles and other settings (Kelly & Fussell, 2012).

PM sizes range from a few nanometres, ultra-fine, that can only be seen through an electron microscope, to 0.1 to 2.5 μm fine particles and particles as large as 100 μm visible to the naked eye know as coarse particles (Stern, 2014). The size of a particle along with its chemical composition is an important parameter in determining its effect on the environment in general and human health specifically (Kim, Kabir, & Kabir, 2015). Large particles (>10 to 20 μm), when inhaled, are trapped in the nose and larynx mainly via impaction. Other smaller hygroscopic particles are also trapped in the nasal passage (Kolanjiyil & Kleinstreuer, 2016). Particles smaller than 10 μm can pass through the nasal passage and the nasopharynx to lower airways, i.e. the tracheobronchial region. Sedimentation is the most common mechanism due to reduced air speed in the airway (Feng, Xu, & Haghnegahdar, 2016). Particles smaller than 0.5 μm can reach to the lower lung alveolar region. Air speed in this area is nearly static and particles randomly land on alveolar membranes (Heyder, Gebhart, Rudolf, Schiller, & Stahlhofen, 1986).

Nitrogen dioxide (NO_2)

Nitrogen gas (N2) is the most abundant pure element on earth, comprising approximately 78% of Earth's atmosphere (Jones, 2016). The reaction between N2 and oxygen (O2) produces nitrogen oxides (NOx = NO + NO_2) and requires very high temperatures (Gaston, Drazen, Loscalzo, & Stamler, 1994). Nitrogen oxides are converted to NO_2 and the main pathway is through reaction with atmospheric ozone. Nitrogen dioxide (NO_2) is nasty smelling reddish brown colour gas and a component of urban air pollution. In nature, reactions such as high temperatures after lightning, natural forest fires and volcano can cause NO_2 production but all these causes combined results less than 1% of NO_2 levels (Akimoto, 2003). Burning of fossil fuels: coal, oil, and gas are major sources of nitrogen dioxide. Motor vehicle exhaust accounts for 80% of urban NO_2 levels (Fenger, 1999). Other main sources are power and heating plants and the manufacturing industry. NO_2 is removed from the atmosphere mainly by reacting with a OH radical producing nitric acid (HNO_3), and deposition (Gaston et al., 1994).

Ozone O_3

Ozone O_3 is an allotrope of oxygen. O_3 is a colourless, odourless gas. Ozone in stratospheric, 12 to 25 km above the earth and protects the earth from harmful UV-light (Parson, 2003). The ozone produced at ground level is called tropospheric ozone and is a secondary pollutant formed via a series of photochemical reactions between oxides of nitrogen (NOx) and volatile organic compounds (VOC). Ground level ozone has distinct seasonal and diurnal patterns with higher concentrations in the summer and in the afternoons. When nitrogen dioxide (NO_2) is exposed to sunlight it splits into nitric oxide (NO) and an unstable form of oxygen (O) which reacts with oxygen (O_2) to form ground-level ozone (O_3) (Brune et al., 2016).

Sulfur dioxide (SO_2)

Sulphur dioxide is a pungent smelling colourless gas. The main sources of SO_2 include the combustion of coal (poor quality contains a high level of sulphur),

oil, and gasoline, and in the oxidation of naturally occurring sulphur gasses as well as naturally in volcanic eruptions. However close to 99% of SO_2 comes from human sources. SO_2 is highly soluble in water and reacts readily with other substances to form harmful compounds such as sulphuric acid (H2SO4), sulphurous acid (H2SO3) and sulphate particles. SO_2 is also a major component in acidic rain (Boubel, Vallero, Fox, Turner, & Stern, 2013).

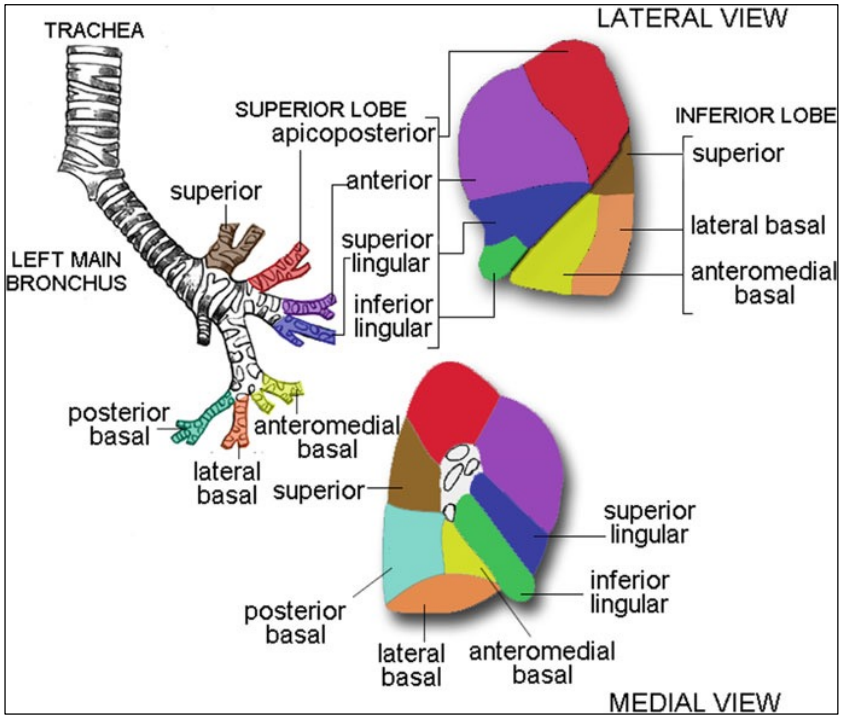

Fig. 2 Left segmental bronchi and its attachment to the left lung segments (Tu, Inthavong, & Ahmadi, 2012)

Asthma

Asthma is a chronic inflammatory disease of the small airways with allergic and non-allergic phenotypes. To fully understand how small airways are affected, it is important to have knowledge of lung anatomy (Roche, 1998). The lung is a complex structure of tubes which continue to divide as they become smaller and finally end at the alveoli (air sacks). Anatomically, large tubes are very different from smaller ones. The main difference, which is relevant in relation to asthma, is that large tubes contain cartilaginous rings along with smooth muscles which prevent them from collapsing. However, in smaller airways this cartilaginous ring is not present and only a layer of smooth

muscle is present to maintain structural integrity (Agur & Dalley, 2009). When smooth muscles contract in these small airways known as bronchi and bronchioles, it results in decreasing the lumen of the small airways, increased airway resistance. This diminishes the flow of air into the lungs. When the lung is exposed to an irritant such as an allergen, an inflammatory reaction is triggered resulting in an increased number of inflammatory cells (such as eosinophils, neutrophils, and mast cells) in bronchioles causing a swelling of walls or oedematous changes. Another change which occurs over time is that the smooth muscle in small airways increases in size. The exact reason for this is still not known but two possible explanations may be muscle contraction and muscle hypertrophy. Along with this, there is also an increased production of mucus causing a plugging of the airways resulting in coughing, wheezing, and shortness of breath (Jeffery, 2001). However, all these changes are reversible and in between attacks airways appear normal. There is a list of environmental exposures that can act as allergens such as pollen, moulds, animal dander and insect irritants. Also, irritants such as the pollutants, gas, diesel fumes, chlorine and other chemicals leading to asthmatic symptoms (Etzel, 2003).

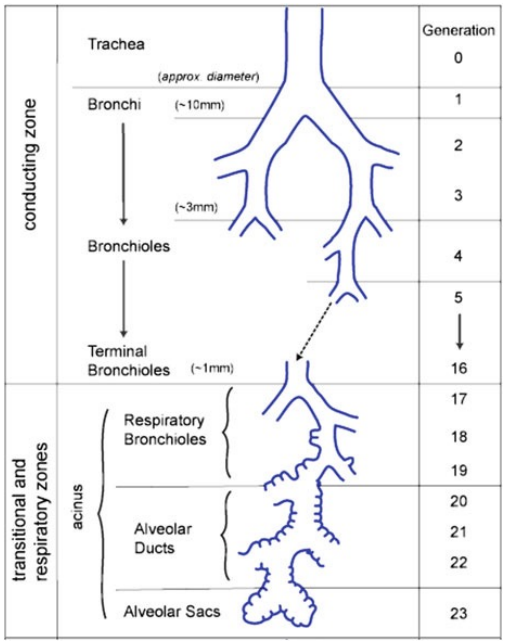

Fig. 3 Schematic of the airway generations in the human adult lung. On average, a total of21–25 generations are found between the trachea and the alveoli. (Tu et al., 2012)

Air pollutants exposure and asthma

Air pollutants are studied extensively in conjunction with the association to asthma (Andersen et al., 2007; Michelle L Bell et al; Bennett et al., 2007, Liu, 2002). The pollutants for which there is strong evidence of having a significant impact on asthmatics are SO_2, NO_2, O_3, PM (both $PM_{2.5–10}$ and $PM_{0.5–2.5}$). There is also a strong indication that second-hand tobacco smoke, smoke from burning biomass fuel indoors and bioaerosols cause asthmatic symptoms (Gilmour, Jaakkola, London, Nel, & Rogers, 2006).

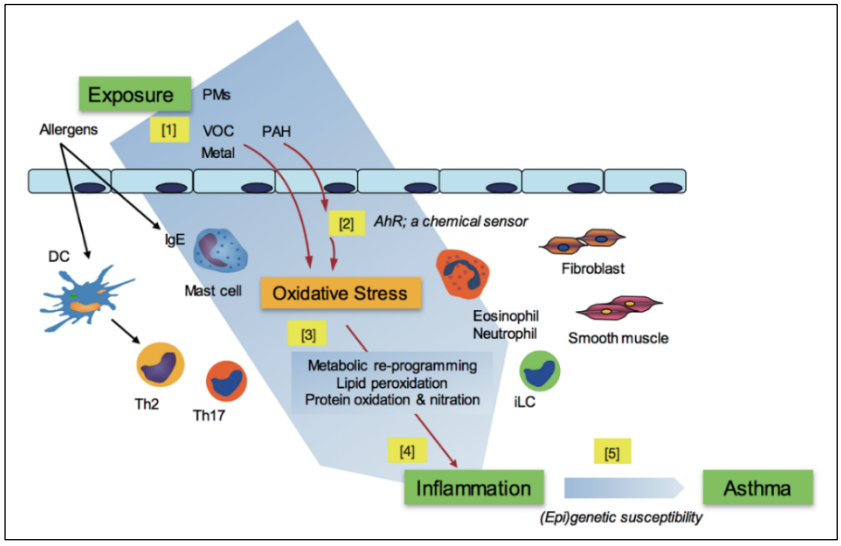

Figure 4 A mechanistic model of the exposure disease relationship illustrating a sequential event originating from the exposure to the development of asthma. This model encompasses the major events known to be involved in asthma, including activation of pulmonary resident cells, including epithelium, fibroblasts and airway smooth muscle cells, as well as of those immune regulatory cell types, including dendritic cells (DCs), Th2, Th17, mast cells, granulocytes (eosinophils and neutrophils) and innate type lymphoid cells (iLCs).(Huang, Zhang, Qiu, & Chung, 2014)

Particulate Matter and Asthma Pathophysiological mechanism

Particulate matter as both coarse mode PM ($PM_{2.5–10}$ μm) and fine mode PM ($PM_{0.5–2.5}$ μm) is a major cause of asthma exacerbation and wheezing. There are several pathophysiological mechanisms studied in chamber exposure, epidemiological and other laboratory studies. The metal component of PM has

been shown to cause airway inflammation in exposure studies mainly $PM_{2.5}$ component (Schaumann et al., 2004). Both animals, in vitro and human studies, have revealed that exposure to diesel exhaust particles (DEP) present in vehicular PM trigger eosinophilic inflammation TH2-type (Hernandez et al., 2012; Hernandez et al., 2013). Human exposure studies have shown that nasal challenge of DEP causes an IgE-mediated response (Diaz-Sanchez, Tsien, Fleming, & Saxon, 1997). Low-level diesel exposure in healthy human volunteers has also resulted in non-specific airway reactivity, an increase in neutrophil count inflammatory cytokines IL-6 and IL-8 in the brachial-alveolar fluid, mast cells and neutrophil, ICAM-1, VCAM-1 and IL-13 in bronchial tissue (Salvi et al., 2000). Bacterial endotoxin, which can be part of coarse and fine mode PM of both outdoor and indoor dust can both cause and prevent asthma. Early life exposure has been shown to be a protective development of IgE responses to allergens termed as the hygiene hypothesis (Liu, 2002). However increased exposure to endotoxin has also be shown to exacerbate symptoms of acute airway diseases (Cândida Rizzo et al., 1997).

Ozone O_3 and Asthma Pathophysiological mechanism

How ozone aggravates asthma symptoms is not very clear, however there are several mechanisms studied in various exposure studies. Exposure to ozone has been shown to cause decrements in lung function through the nociceptive response; exposure alters pain (C-fibre) mediated in function lung and at the same time causing neutrophilic, inflammation (Passannante et al., 1998). Increased BMI and female gender may also be additional risk factors for increased lung function response to O_3 (Bennett et al., 2007). Exposure to O_3 also attracts dendritic and macrophages as well as increased airway permeability and bronchial reactivity. O_3 exposure increased IL-1 and IL-8 levels, expression of TLR4 in bronchial airways (Hollingsworth et al., 2010).

Sulfur dioxide SO_2 and Asthma Pathophysiological mechanism

SO_2 is a highly irritant gas and acts as a very potent broncho-constrictor in asthmatics (Horstman, Seal, Folinsbee, Ives, & Roger, 1988). Even at a very low dose it can cause a significant decrease in FEV1 by as much as 60% (Peden, 1997) within two to five minutes. Response to exposure is decreased by nasal breathing due to nasal absorption of gas and nasal comorbidities causing a decrease in nasal breathing increase response. The response is also

increased by exercise due to increasing the amount of SO_2 delivered to the bronchial airway (Folinsbee, 2000). Recovery after acute exposure can take up to 30 minutes.

Nitrogen dioxide NO_2 and Asthma Pathophysiological mechanism

Table 1: Acute Pathophysiological effects of pollutants which impact asthma

Physiologic effect	**O_3**	**PM**	**NO_2**	**SO_2**
Airway inflammation	++++	+++	++	+
Airway reactivity	+	+	+	+++
Allergen reactivity	+++	++++	+	+
Nociceptive decrease in lung function	++++	+	+	+

* + shows strength of association

Exposure to NO_2 can cause both acute and chronic changes in lung function by directly affecting inflammatory response. In vitro studies, exposure to NO_2 resulted in increased production of inflammatory cytokines by epithelial cells. Exposure to healthy volunteers has caused increased numbers of polymorphonuclear leukocytes (PMNs) in the airway (Frampton et al., 2002). NO_2 also augments late phase cellular responses of asthmatics to allergens alike O_3 (Barck, Lundahl, Hallden, & Bylin, 2005).

Epidemiological evidence

Particulate Matter and Asthma

Exposure to PM has been associated with morbidity and mortality in patients with asthma in numerous epidemiological studies. Very strong epidemiological evidence is available from different parts of the world that analyses both short and long-term exposure to PM with adverse respiratory health outcomes and in young, middle and old age groups.

Short-term epidemiological studies reported positive associations between mortality and respiratory hospital admissions; coarse particles and cardiovascular (Atkinson et al., 2001; Chen, Goldberg, & Villeneuve, 2008),

respiratory (Fajersztajn, Saldiva, Pereira, Leite, & Buehler, 2017) or total mortality (Meister, Johansson, & Forsberg, 2012; Ostro et al., 2011).

Studies linking the impact of PM exposure with morbidity have mainly analysed health care utilization data, i.e. emergency visits and inpatient admission. A nationwide study in the United States found a positive association of $PM_{2.5}$ with asthma. Increasing $PM_{2.5}$ concentration significantly increased the asthma risk in central cities (OR: 1.050, 95% CI, 1.01-1.09) and in outer ring suburban counties (OR: 1.04, 95% CI, 1.00-1.08) (T. Li & Lin, 2014). European birth cohort studies found a significant association of $PM_{2.5}$ and asthma in the young population (Brauer et al., 2007; Gehring et al., 2010; Morgenstern et al., 2007). A research study from Hong Kong (Qiu et al., 2012) found positive associations between coarse PM and hospital admissions due to all cause respiratory illness, asthma, and COPD. Also, several studies have found a worsening of symptoms such as wheezing and dyspnea in asthmatics after exposure to outdoor PM. A study from California found decreased FEV1% predicted (−0.51, −0.79 to −0.23) and FEF (−0.66, −1.07 to −0.24) among asthmatics (Vempilly et al., 2013). Research linking PM exposure with asthma incidence has not been very conclusive. In one Canadian study, living close to large roads was associated with children developing asthma (Clark et al., 2015), however, a meta-analysis by (Anderson, Favarato, & Atkinson, 2013a) found no association.

Ozone and Asthma

Epidemiological evidence associating outdoor O_3 exposure with adverse respiratory health outcomes, especially asthma, has increased over the last decade. Several recent studies have found an association to O_3 with asthma-related emergency visits, hospital admissions and worsening symptoms. A systematic review concluded that ozone increases the risk of hospital admissions due to asthma in children. The review included 12 prospective studies (Lilian Tzivian, 2011). In another study from Japan, long-term exposure to O_3 was associated with worsening asthma symptoms among adults. Results were robust even after controlling for sex, age, body mass index, education, smoking and use of inhaled corticosteroids (Jacquemin et al., 2011). Despite increasing evidence suggesting that O_3 worsens asthma symptoms, research associating ozone with the incidence of asthma has been negative. In a systematic meta-analysis of multi-community asthma prevalence studies, researchers found that ozone had no effect on asthma prevalence (Anderson, Favarato, & Atkinson, 2013b).

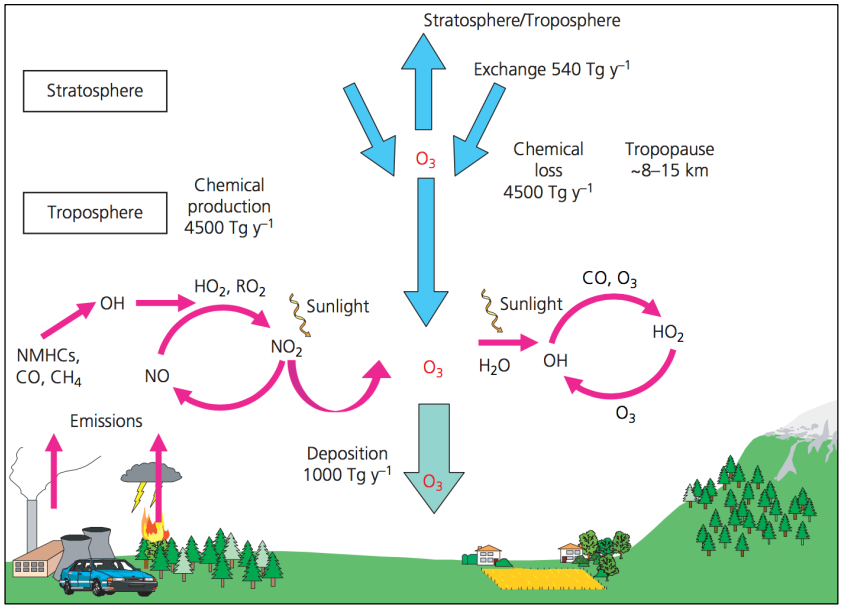

Figure 5 A schematic view of the sources and sinks of O_3 in the troposphere. Annual global fluxes of O_3 calculated using a global chemistry–transport model have been included to show the magnitudes of the individual terms. These fluxes include stratosphere to troposphere exchange, chemical production and loss in the troposphere and the deposition flux to terrestrial and marine surfaces. Data source: IPCC Fourth Assessment Report Working Group I Repo**rt "The Physical Science Basis**. (Fowler et al., 2008)

NO_2 and Asthma

Strong epidemiological evidence suggests an effect of NO_2 on asthma-related hospital admissions and emergency room visits. The California Environmental Protection Agency Air Resources Board (CARB, 2007) report in 2007; WHO in a 2005 global update of air quality guidelines and an EPA report in 2008 all reported positive associations with short-term exposure to NO_2 and asthma-related emergency visits and hospital admissions. The effect was stronger among children and in the age group above 65 years of age. A meta-analysis performed by (Andersen, Wahlin, Raaschou-Nielsen, Scheike, & Loft, 2007) also concluded that asthma-related hospital admissions increased 1.37% (95%

CI: 0.59–2.15) among all ages and 2.92% (95% CI: 1.15–4.72) among children for a 24-hour average NO_2. Publications reporting increased health care utilization due to asthma with single pollutant associations are (Michelle L Bell, Levy, & Lin, 2007; Colais et al., 2008; Giovannini, Sala, Riva, & Radaelli, 2010; Halonen et al., 2008; Jalaludin, Khalaj, Sheppeard, & Morgan, 2008; Samoli, Nastos, Paliatsos, Katsouyanni, & Priftis, 2011; Szyszkowicz, 2008; Ueda, Nitta, & Odajima, 2010; Villeneuve, Chen, Rowe, & Coates, 2007). Also, (Halonen et al., 2008) reported NO_2 as an independent predictor of emergency room visits in children due to asthma in Finland and (Iskandar et al., 2011) in Copenhagen. The long-term effects of exposure on the incidence of asthma is uncertain. Two metaanalyses by (Anderson et al., 2013b) were unsuccessful to find a relationship between NO_2 and the prevalence of asthma. However, living close to a major road and asthma in highly susceptible populations was rather weakly associated.

SO_2 and Asthma

The short-term effects of SO_2 on aggravating asthma symptoms in children was shown in a multicity study by (Schildcrout et al., 2006). Another study by (Canova et al., 2010) found a decline in lung function among asthmatic adults after short-term exposure. Hospital admissions among children were reported in several studies. An increase of 1.3% visits was found in (Lee, Wong, & Lau, 2006) and a 6% increase was reported by (Samoli et al., 2011) after a 10-unit increase in SO_2. Another study from Hong Kong by Kong (Ko et al., 2007) reported a non-significant association. Many studies analysing associations in adult age groups have reported inconclusive results (Andersen et al., 2007; Michelle L Bell et al., 2007; Ko et al., 2007; Tsai, Cheng, Chiu, Wu, & Yang, 2006; Yang, Chen, Chen, & Kuo, 2007). Evidence suggesting SO_2 and emergency room visits for asthma is inconclusive, as there were mixed results in multi-pollutant models.

Sweden Health Care system

The Swedish health care system is a tax-financed, comprehensive, publically managed decentralized health care system. Sweden is divided into 26 administratively independent provinces. Both financing and delivery of health care services is the responsibility of counties. Each county council finances its

health care using collected income tax, grants from central government, the social insurance system and payment from patients when they seek health care. Sweden spends 11.0% of GDP for health care which is comparable to other Nordic countries, or in per capita terms, Sweden spent $4,904 per capita in 2013. The government spends 84% on health care (4169 USD) and the rest comes from the private sector ($735). A visit to a specialist costs 200-300 SEK and hospital stays cost SEK 80 per day. The cost for a visit to primary health care varies from between SEK 100 and 300 ($13–40) depending on the county council. However, there is an annual ceiling for hospital care between SEK 900-1100.For dispensed prescribed medication, the ceiling is SEK 2,000. Once the payment ceiling is reached, the rest of the payments are made by the state government. For children, all types of health care including dental care are entirely free of charge.

Primary health care

Primary health care (PHC) is also known as basic health and medical care. In Sweden, there are 1200 Primary Health Care centres with one to 20 general practitioners (GPs) per PHC. Along with GPs, the PHC team includes nurses, social workers, psychologists, and physiotherapists. They provide diagnoses and treatment for most common illness and if judged necessary, will refer patients to specialist care for further treatment. Since the 1990s, there has been a shift in health care delivery from inpatient to PHCs with a policy of having shorter hospital stays and early diagnoses to focus on care and treatment close to home. As a result, hospital beds per 1,000 persons has decreased from 11.9 to 2.7 resulting in increased PHC visits. On average, every citizen consults a GP three times per year and close to 70% of this consultation is in PHC clinics. PHCs provide health care to both adults and children for non-urgent or non-life-threatening medical problems. PHCs also provide preventive health care through vaccination programs and other preventive services. The physicians at PHC clinics typically decide if a patient should be referred to a specialist clinic or if the patient should be treated at the PHC clinic.

The personal identity number (PIN)

The history of the Swedish population register starts way back in the 17th century when the church at that time started to collect and organize vital population statistics. The system introduced back then has evolved over time into a total population register (TPR). The main component of the TPR, vital

for research, is a ten-digit unique personal identification number (PIN) and was introduced in 1947.Every individual who resides in Sweden is assigned ten-digit unique PIN. The first six digits correspond to the birthday, and digits seven to nine are a serial number, odd for male and even for female with the last or tenth digit being check digit for verification of birth and the previous three digit numbers. The PIN is used extensively in Swedish in public administration, population statistics, migration, taxation, education, passports, income, and social security. It is very important in health care as it helps to trace individuals in various health care registers such as Patient Register (with inpatient and outpatient data), Cancer Register, Cause of Death Register, Medical Birth Register, and e.g. the National surveillance system for infectious diseases. It also helps to avoid duplication error and provide reliable data for research purposes

Case-Crossover Study Design

The case-crossover study design is a relatively new epidemiological study design proposed by Maclure in 1991(Maclure, 1991). It is a modified version of a matched case-control design where each participant is his or her own control during the study period. At the conclusion of the study, distribution of exposure is compared between the two groups. The case-crossover design was proposed to study the acute transient effect of sporadic exposure. It compares exposures at index times, when the exposure triggered an event, with exposures at referent times, a time when an event is not triggered. For example, air pollution exposure levels days prior to health care visits or medicine prescribed, or hospital admission also known as index time or the case period, are compared to exposure levels during the control period or referent time selected during the specified time or strata. This technique reduces confounding of time-invariant characteristics of study participants such as age, gender, ethnicity other behaviour which remains constant over time. However, there are several challenges while performing case-crossover studies. Selection of exposure requires careful consideration of the exposure window conditions and should match the case window. Also, the selection of the length of the case and control windows requires special consideration and should be selected in accordance with the outcome. As the exposure is often assessed after the outcome, information bias caused by the inaccurate recall of the exposure can be a challenge in case-crossover studies. However, in air pollution studies,

exposure levels are measured prior to the event and hence there is no risk of recall bias. Another challenge while performing case-crossover studies using air pollution data is trends and seasonality in the air pollution over time. Case-crossover design is based on the assumption that the exposure distribution is stationary, which is not the case in air pollution levels which fluctuate over time and have distinct trends and seasonal patterns. By matching the day of the week and season, case-crossover study control for these confounding by design. Another kind of bias which can be introduced in the case-crossover study is Overlap bias. This is the result of selecting non-separated strata to partition the event in a case-crossover study. Overlap bias was first identified by Lumley and levy, they also have shown that this is usually small, however, its magnitude and direction cannot be predicted without prior knowledge of exposure.

Time Series Study Design

A Time series is an ecological study design widely used in environmental epidemiology. It analyses the association between the varying over time daily counts of health care events such as hospital visits and inpatient admissions, with air pollution and weather exposure. Time series data is recorded at regular time intervals and the main unit of analysis is the event count of each day - however, not necessarily daily levels. Annual, monthly, or hourly time series can also be analysed. Time series data is generally analysed using a Generalized linear model (GLM) with parametric splines and Generalized additive models (GAM) with nonparametric spines.

Time Series and Case-crossover design comparison

There are several factors influencing the selection of study design. These are mainly the research question and the availability of data. While deciding between a case-crossover and time series, several important aspects need to be considered. Both designs use different methods to control for trends and seasonality in data. Time series use a statistical adjustment smooth function whereas a case-crossover adjusts by design using sampling technique. Case-crossover by design provides computation convenience shown by Lu and Zeger. They argued that case-crossover using conditional logistic regression is equal to time series analysis when there is a common exposure (Lu, Symons, Geyh, & Zeger, 2008). Case-crossover by design can assess effect modification

across population whereas a time series cannot since in time series events are aggregated over time and individual risk information is not available.

Knowledge Gap

Primary health care and air pollution studies

Prior studies conducted to investigate the association between air pollution and adverse health outcomes (as explained in above section), have used emergency visits data, inpatient hospital admissions and mortality data. All three of these types of health care contact represent a more severe form of the disease condition, and hence evidence focusing on air pollution effects on mild and moderate disease outcomes has by and large been missing. The first point of health care contact is primary health care clinics, and patients often have mild and moderate symptoms or are exhibiting the initial phase of disease symptoms. There were very few studies published prior to our work looking at this important association, and those published before and during the last four years lack good quality population data on primary health care visits. Three studies published in Japan looked at PHC visits due to asthma and air pollution, but all three of them only analysed night time PHC visits and most likely sampled acute asthma attacks and hence missed patients with mild and moderate symptoms (Yamazaki, Shima, Ando, & Nitta, 2009; Yamazaki et al., 2014, 2015). Also, another study conducted in Chile looked at the association of O_3 exposure to PHC visits due to asthma among patients under the age of 15. A large population-based study from London, UK did include a large number of PHC clinics, but in the London study, the main outcome was different from our studies (Hajat et al., 2001). They analysed health care visits due to upper respiratory illness.

Investigations in populations exposed at levels below current air quality guidelines

Air pollutants have a very low threshold, and exposure below current WHO and EU guidelines does not ensure safety and can still cause harmful health effects. Current EU guidelines on outdoor air pollutants are considerably higher than the health care based recommendation (Brunekreef et al., 2012). Therefore, there was a need for further research in areas where air pollution levels are well within EU guidelines. Air pollution levels in the study area of all four papers were well within WHO, European guidelines or other regional and country level guidelines for air pollution. These studies will help to

understand the adverse impact on health of low-level air pollution on respiratory health.

Combined effect of long-time and short-time exposure

In the past, air pollution research studies either looked at short-term effects or long-term effects of air pollution on respiratory health. However, no prior study to our knowledge has studied how the short-term effects of different types of air pollution are modified by long-term air pollution levels. The answer to this research question is important to understand, i.e. whether the burden of air pollution attributable to exacerbations of asthma is due to air pollution increasing the pool of subjects with asthma or related to the triggering of asthma the attack.

Metrics other than 24-hr means

Historically, outdoor air pollution and health risks have been studied using daily mean levels of pollutants. Since the air pollution levels are not constant during the day, fluctuations in exposure levels during the day are not studied by using the daily mean. There is a need to study other air pollution metrics more sensitive to daily pollutant level variation to better understand the health effects.

Aim

The overall aim of the thesis was to explore the short-term effects of air pollution on mild, moderate and severe respiratory diseases in an area where criteria pollutant levels are generally well below or close to present air quality limits.

Specific Aims

1. To investigate the relationship between ambient air pollution and primary health care visits due to asthma.
2. To investigate the association of living in high versus low long-term air pollution areas and responses to a short-term rise in air pollution levels.
3. To investigate the relationship between ambient air pollution and respiratory health in primary health care, inpatient and emergency care visits.
4. To analyse the sensitivity of using different air pollutants and metrics for the above-mentioned aim one. Metrics relate to time (peaks, day/night, commuting hours). Pollutants are PM_{10}, $PM_{2.5}$, coarse particles ($PM_{10-2.5}$), NOx, and ozone.

Material and Methods

Overall study design

Each study encompassed different study designs and selection of health outcomes as well as exposures to investigate specific study aims.

Study Area

All studies were performed using different municipalities located in Scania County. Scania is the southernmost Swedish county and comprises 33 municipalities with a population of over 1.3 million. The total area of Scania is 11,027 km^2. It is primarily urban county with over 90% of the population living in urban and semi-urban areas. The population is concentrated on the west coast which faces Denmark. Its four main cities and their populations are Malmö 313,000, Helsingborg 133,000 and Lund 114,000 and Kristianstad 81,000.

Study population

Scania Primary Health Care register

In Scania, health care registers, along with data relating to inpatient and emergency visits, also include records of primary health care visits. The register coverage is close to 100% of all cases of individuals seeking health care in the region incentivised by the reimbursements made to the clinics.

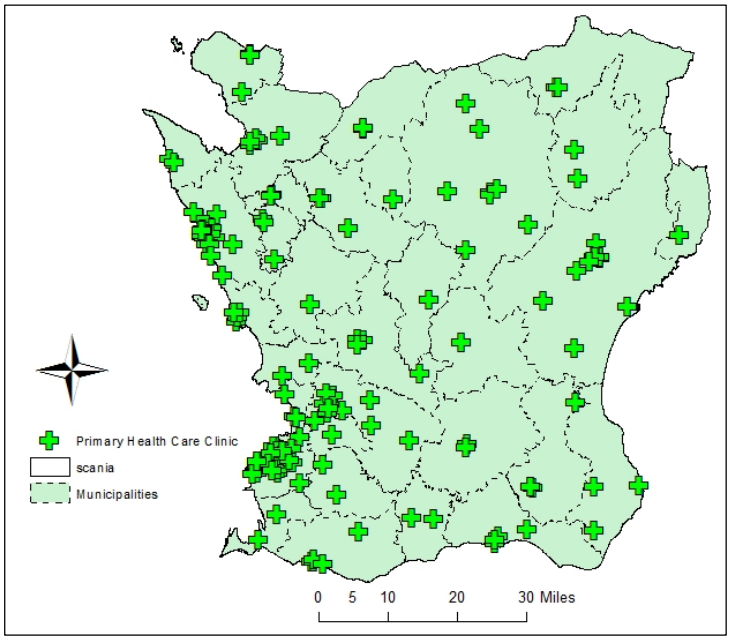

Figure 6 Location of Primary health care clinics in Scania

Study of outdoor air pollution exposure and PHC asthma visits (Paper I)

This was a case-crossover study using primary health care (PHC) visits data from six selected municipalities in Scania: Malmö, Lund, Vellinge, Burlöv, Staffanstorp and Lomma. PHC visits due to asthma were identified using the International classification of disease code ICD-10 J-45 and the Swedish translation of ICD-10 J45-p in between 2005 and 2010 from the Scania Health Care Register. Asthma visits from 19 PHC centres in selected municipalities were included in this study. Health care visits to PHCs for residents with registered addresses outside of the municipalities were excluded from the study as well as visits to private PHCs (17%) due to missing diagnoses. In total, 68,872 PHC visits due to asthma were identified during the study period.

Study of long and short term air pollution exposure and asthma (Paper II)

The study was performed in Scania County. Primary health care records from 2007 to 2010 were extracted from the main dataset using ICD 10 codes for asthma illness (J45 codes) and a Swedish translation of ICD 10 codes (J45-p). Each Scania resident in the health care register was followed from the year 2005 till 2010 and first visits of the participant in our dataset were included in the study. A total of 20,909 first-asthma visits during the study period for individuals living in Scania were extracted for 123 primary health care centres (PHCCs). For all PHCCs, geographical coordinates were obtained to find the nearest air pollution monitoring station.

Study of Short-term associations between air pollution concentrations and respiratory health; comparing PHC visits, hospital admissions and ER visits in a multi-municipality study (Paper III)

For this study, five municipalities were selected from Scania based on population size and availability of exposure data. The five selected municipalities were Malmö, Helsingborg, Lund, Landskrona and Trelleborg. All consultation for respiratory outcomes during the study period 2005 till 2010 were extracted from the Scania Health Care Register using ICD-10 codes. The ICD-10 J-codes and the Swedish translation of ICD10-J (J00-J99) codes were used to identify the respiratory illness. To ensure diagnostic reliability, visits were limited to patients above five years of age, since the diagnosis of respiratory health problems at a young age may not be accurate. All respiratory health care visits were categorized into three categories.

Primary Health care visits

All visits to primary health care clinics in the study area with the ICD-10 J-code and were categorized as emergency visits, i.e. not pre-booked, were identified. The number of PHC clinics was; 17 in Malmö, six in Lund, eight

in Helsingborg, three in Landskrona, and two in Trelleborg. There was a total of 81,019 PHC visits during the study period.

Emergency department visits

Visits to the emergency room at a hospital where the diagnosis was respiratory illness (J-code). There were 38,217 emergency room visits in the selected study population during the study period.

Inpatient hospital admission

All hospital admissions which were doctor diagnosed as respiratory illness (J-code), and were not pre-planned, were also included in the study. Final inpatient hospital admissions analysed were 25,271

Alternative air pollution metrics & their associations with primary health care visits due to asthma; a study from Malmö, Sweden (Paper IV)

Malmö Municipality was selected for Paper IV. Malmö is the southernmost municipality in Scania. It has a population of over 300,000 individuals and is the third most populated city in Sweden. Due to its geographical location, Malmö serves as a connection hub between Europe and rest of Sweden via rail and road links. Beside rail and road links, Malmö also has an active industrial harbour. It also has a very diverse population with close to half of its inhabitants having a foreign background. and 14% are foreign nationals. Visits to PHCs related to asthma (J45) for the study period were identified from the Swedish Health Care Register database using the International classification of disease IC-10.

PHC visits labelled as emergency visits, i.e. visits without prior appointment were included for the analysis. In total, 5,941 asthma visits between 2005 and 2010, with an average of 3.2 visits per day were analysed. To further study association with different age group, visits were categorized into age groups 0 to 5, 6 to 25, 26 to 60 and 60 plus

Exposure assessment

Exposure assessment Paper I

For outdoor air pollution exposure assessment, six urban background monitoring stations were used. Three in Malmö at Rådhuset, Rosengård and Hemparken station, two in Lund and one in Burlov. Hourly values of PM_{10}, $PM_{2.5}$, Ozone (O_3), Nitrogen dioxide (NO_2) and Sulphur dioxide (SO_2) were obtained for the period January 1st, 2005 to December 31st, 2010 from the Swedish Environmental Research Institute (SMHI). The daily mean was calculated using hourly data. Information on meteorological variables such as daily levels of temperature, humidity, precipitation, wind speed, wind direction and barometric pressure were obtained from the Swedish Meteorological and Hydrological Institute (SMHI).

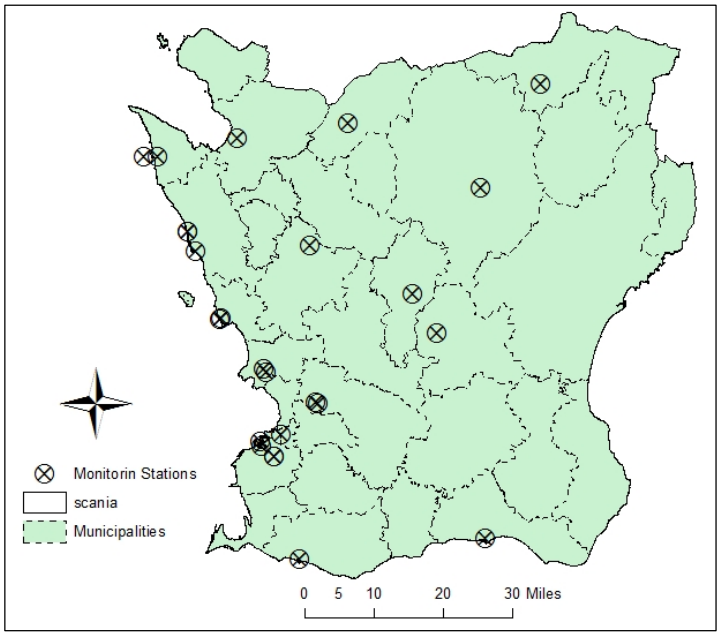

Figure 7 Location of urban background air pollution monitoring stations in Scania

Exposure assessment Paper II

Nitrogen dioxide (NO_2) was used as a proxy for air pollution exposure. Hourly values from 21 air pollution monitoring stations in different parts of Scania were obtained from SMHI. Geographical coordinates were obtained for all monitoring stations. Air pollution levels at PHCCs were assigned based on the proximity to the air pollution station. For better exposure assessment, PHCCs with air pollution stations with over a 20-km radius were excluded from the study (22 PHC asthma visits = 6,384). For short-term air pollution exposure, average NO_2 levels during the same day and three days prior to visits were assigned. For long term exposure, average NO_2 levels two years prior to the visit were used. A GIS-based dispersion model together with an emission database was used to model long-term concentrations of NO_2 at the PHCC.

Exposure assessment Paper III

For Paper III, urban background air pollution for PM_{10}, Ozone (O_3) and Nitrogen dioxide (NO_2) for the period January 1st, 2005 to December 31st, 2010 were used. Air pollution levels obtained from 11 monitoring stations were included within each municipality; three in Malmö, two in each Lund, Helsingborg, and Landskrona and one in Trelleborg. For all five, PM_{10} and NO_2 data was available whereas O_3 was missing in Trelleborg Municipality. To avoid exposure misclassification, health visits by patients residing in a municipality other than where health care was sought were excluded from the final analysis. Daily meteorological data for temperature and humidity was also included for the study area.

Exposure assessment Paper IV

For exposure, the Malmö Rådhuset Urban background air pollution monitoring station was used. The Rådhuset monitoring station is situated in a government building on a rooftop at 20 meters above the ground. Hourly measurement of PM_{10} using Tapered Element Oscillating Microbalance, Series 1400AB method, NO_2 using Eco Physics CLD 700 AL chemiluminescence instrument and O_3 using Thermo Environmental Instruments Model 49C were measured. To investigate the exposure of different air pollution metrics on asthma visits, temporal metrics of daily pollutant concentrations were created using hourly data. For each pollutant, daily one-hour maximum value, daily one-hour

minimum value, daily eight-hour maximum average, and the 24-hourly average were calculated. Further, three more metrics were calculated that are sensitive to human activity during working days. These were commuting hours (07:00–10:00 and 16:00–19:00), a daytime average (08:00–19:00) and a night-time average (24:00–06:00). Meteorological data for temperature, humidity, rainfall, wind speed and wind direction for the Malmö area from IVL for stations was also obtained.

Statistical analysis

Study design

The case-crossover study design was used to investigate the association between exposure and adverse health outcomes. Case-crossover design was selected based on the simplicity of analysis, as PHC visits data is interrupted with no visits over the weekend and on public holidays. This method by design adjusted for confounder which remains constant over time such as gender, ethnicity and other behaviours. This design also adjusts for seasonality and time trend if the control days are selected appropriately. Case-crossover compares the exposure period just prior to the health care visits with days matched control during the calendar month or 28 days long non-over-lapping strata.

Statistical Model

We combined the case-crossover analyses with a distributed lag non-linear model (DLNM) (Gasparrini, Armstrong, & Kenward, 2010), lag structures of an average 0-2 days, 0-3, 0-7 as well as 0-15 days. The first model built was unadjusted with only main exposure as a covariate. In the second model, variable for temperature and humidity were introduced with smooth function (natural cubic splines) with three degrees of freedom. In a subsequent model, the remaining pollutants were introduced in the model one by one. Results were presented for 10-μg/m3 increases in the pollutant level. A number of models check were performed to assess the robustness of the analysis. Residual deviance was plotted versus fitted values, checking R2 and calculating AIC.

Statistical software and packages used

PostgreSQL 9.1.3 relational database software was used for selecting health care visits from the main data (PostgreSQL, 2017). PostgreSQL provided flexibility to sample and subsample data using various constraints and selecting health care visits accurately for hypothesis testing. In Paper II, PostgreSQL was also used to identify first asthma visits and calculating short and long-term NO_2 levels for each visit. Statistical analysis was performed using the statistical software R version 2.16 (Computing, 2017) and the model

was constructed using the dlnm statistical package (Gasparrini et al., 2010). In Paper III, pooled estimates for all five cities were created by using fixed-effect meta-analyses. R package MVMETA (Gasparrini, Armstrong, & Kenward, 2012) was used to perform pooled analyses. In Paper IV, descriptive figures were plotted using R package open-air (Ropkins & Carslaw, 2012).

Material and Method individual paper

Paper I

Title: Air pollution is associated with primary health care visits for asthma in Sweden: A case-crossover design with a distributed lag non-linear model

Aim: To investigate the association between PHC visits and daily levels of air pollution in Scania, Southern Sweden.

Study population: Six municipalities Malmö, Lund, Vellinge, Burlöv, Staffanstorp and Lomma. The combined area of the municipalities is around 1000 km2 and the population over half a million.

Exposure data: Hourly values of PM_{10}, $PM_{2.5}$, Ozone (O_3), Nitrogen dioxide (NO_2) and Sulphur dioxide (SO_2) from six urban background monitoring stations. Three stations in Malmö at Rådhuset, Rosengård and Hemparken station, one in Burlov and two in Lund from January 1st, 2005 to December 31st, 2010.

Outcome: All PHC visits between 2005 and 2010 from 19 PHC clinics in Malmö, six in Lund, and one each in Lomma, Staffanstorp, Vellinge, and Burlöv. Visits with a primary diagnosis of asthma using the ICD-10 codes J-45 and J45-P (Swedish translation of ICD Codes) and used in the final analysis.

Study design: The analysis was performed using a case-crossover design with a 28-day fixed time strata. Single and multi-pollutant model (model adjusted for other pollutants) was constructed using distributed lag nonlinear models (Gasparrini et al., 2010) with 3df smooth functions for weather variables (temperature, humidity and precipitation).

Paper II

Title: Short-term fluctuations in air pollution and asthma in Scania, Sweden. Is the association modified by long-term concentrations?

Aim: To assess whether individuals living in areas with higher long-term air pollution levels respond differently to a short-term increase in air pollution concentrations than those living in areas with lower long-term air pollution concentrations.

Study population: The study was performed in the southernmost county of Sweden, Scania, which comprises 33 municipalities with a total population of about 1.25 million people.

Exposure data: For short-term air pollution exposure (same day and three days prior to the visit) assessment, hourly values of nitrogen dioxide (NO_2), from 21 air pollution monitoring stations in different parts of Scania were used. To assign long-term exposure, a GIS-based dispersion model together with an emission database was used to model long-term concentrations (two years prior to the visit) of NO_2 at the PHCC.

Outcome: From the Primary health care register, a total of 13,880 first asthma visits for 88 primary health care clinics (PHCCs) from 2007 to 2010 were obtained using ICD 10 codes for asthma illness (J45 codes) and a Swedish translation of ICD 10 codes (J45-p).

Study design: A time stratified case-crossover study design was used for each visit; four bi-directional control periods matched by day of the week were calculated, two control periods prior to the visit and two after, using the same air pollution monitoring station.

Paper III

Title: Short-term associations between air pollution concentrations and respiratory health; comparing primary health care visits, hospital admissions and emergency room visits in a multi-municipality study

Aim: To investigate the impact of air pollution levels on overall respiratory health by studying PHC visits, inpatient and emergency room visits simultaneously in a multi-municipality setting.

Study population: Five municipalities from Scania were selected based on population size and availability of exposure data. The municipalities were Malmö, Helsingborg, Lund, Landskrona and Trelleborg.

Exposure data: The daily mean values of PM_{10}, Ozone (O_3) and Nitrogen dioxide (NO_2) were obtained for the period January 1st, 2005 to December 31st, 2010 from 11 monitoring stations within each municipality. Three stations were in Malmö, two each in Lund, Helsingborg and Landskrona and one in Trelleborg.

Outcome: Using the International Classification of Diseases, Revision 10 (ICD-10), and the Swedish translation of ICD-10, health care visits for adverse respiratory outcomes during the study period (2005-2010) were identified. All respiratory health care visits were categorized into three categories; primary health care visits, emergency room visits and inpatient hospital admissions. There were a total of 81,019 PHC visits, 25,271 inpatient admissions and 38,217 emergency room visits related to respiratory illness during the study period.

Study design: We combined the case-crossover analyses with a distributed lag non-linear model (DLNM). Lag structures of 0-2 days as well as 0-15 days were used. Pooled estimates for all five cities were obtained by pooling the municipality-specific estimates using fixed effects meta-analyses.

Paper IV

Title: Alternative air pollution metrics & their associations with primary health care visits due to asthma; a study from Malmö, Sweden

Aim: To investigate the effects of the alternate air pollution metrics approach to studying air pollution effects on respiratory health in an urban setting.

Study population: This study was conducted in Malmö, the most populated city in Scania. It has a population of over 340,000 and is the third most populated city in Sweden. Malmö is a hub of rail and road transport connecting rest of the Sweden to Europe via Øresund Bridge.

Exposure data: Hourly ambient concentrations of PM_{10}, NO_2, and O_3 were obtained from the Malmö Rådhuset urban background air pollution monitoring stations. Using hourly data, temporal metrics of daily pollutant concentrations were made: a daily 1-hour maximum, daily 8-hour maximum average, a 24-hour average, an average of commuting hours (07:00–10:00 and 16:00–19:00), a day-time average (08:00–19:00) and a night-time average (24:00–06:00).

Outcome: Daily count of asthma visits to PHCs using ICD-10 diagnostic code for asthma (J45) were identified. In total 5,941 asthma visits to PHCs between 2005 and 2010 were included in the study. For further analysis, visits were categorized based on gender and age groups 0 to 5, 6 to 25, 26 to 60 and 60 plus.

Study design: The case-crossover design with a distributed lag non-linear model (DLNM) was selected because the outcome data for PHC visits was not uniformly distributed over a week. Calendar month, non-overlapping strata was selected to prevent overlap bias and control days were matched by the day of the week.

Results and comments

Air pollution Exposure Levels Paper I

Air pollution levels throughout the study period from 2005 till 2010 remained well within WHO and EU guidelines. The only time when hourly pollutant levels exceeded the guidelines were the first few hours of 1st January each year. This can be attributed to the use of fireworks for New Year's Eve celebrations. Daily mean levels of pollutants at the urban background monitoring station Malmö Rädhuset during the study period was, PM_{10} 16.4 µ g/m3 (SD; 7.9), $PM_{2.5}$ 11.9 µ g/m3 (SD; 7.1), coarse particles 4.5 µ g/m3 (SD; 3.9), O_3 51.2 µ g/m3 (SD; 17.4), NO 3.9 µ g/m3 (SD; 4.3), NO_2 18.4 µ g/m3 (SD; 7.8), NOx 21.5 µ g/m3 (SD; 10.4), SO_2 2.3 µ g/m3 (SD; 1.9). There was a strong seasonal pattern in pollutant levels during the year. NO_2 levels were higher in winter as compare to summer whereas the O_3 trend was the opposite; higher during the summer and lower during the winter. For PM_{10}, there was not a clear seasonal pattern, however, there was a strong association with wind direction. Higher PM_{10} and $PM_{2.5}$ corresponded with a south-eastward wind direction. Both PM_{10} and NO_2 were higher during the daytime with two distinct peaks with the first correlating with morning commuting time and second after office hours. Ozone, in contrast, was higher during the night hours as compared to day time.

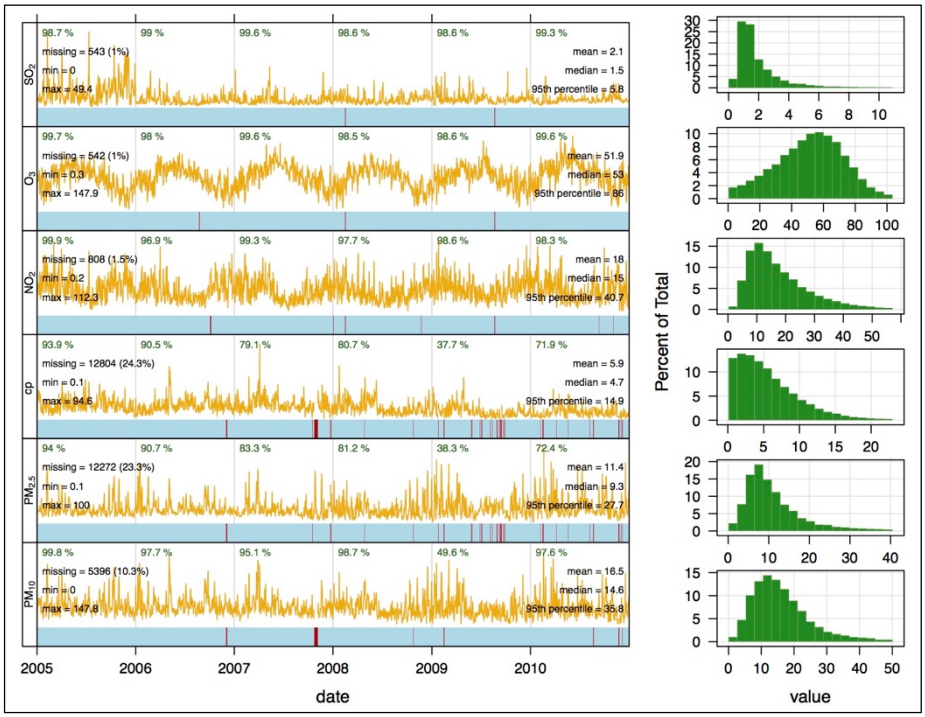

Figure 8: Air pollution summary plot Malmö Rädhuset urban background monitoring station year 2005-2010

Correlations between pollutants Paper I ~ IV

The correlation between different air pollution monitoring stations within the same municipality were moderate to strong. Strong positive correlations were observed between PM_{10} and $PM_{2.5}$ (rs 0.86; p>0.01) and between PM_{10} and coarse particle $PM_{2.5–10}$, (rs 0.46; p>0.01). A moderate negative correlation was seen between O_3 and NO_2 (rs -0.59, p>0.01). Air pollutant levels between different municipalities showed a weak correlation; the correlation between PM_{10} and NO_2 (0.54 to 0.16) between PM_{10} and NO_2 (0.54 to 0.16) whereas a negative correlation was observed between O_3 and NO_2 (range between -0.37 to – 0.55). Correlations between different air pollutants metrics were calculated for Paper IV. There was a strong correlation for overlapping metrics such as

daytime with commuting time and rather weak to negative correlation between daytime with night time.

Air pollution exposure and PHC visits Paper I ~ IV

The main aim of all the studies was in different ways to assess the risk of PHC visits with various air pollutants. In our analysis, we found a strong association with an increase in PHC visits with some pollutants despite very low levels during the study period. In all our studies, we found an increase in the risk of asthma visits in conjunction with an increase in NO_2 levels. In our first analysis, we observed a 5% (95% CI: 3.91–6.25%) increase in PHC visits due to asthma with every 10μgm−3 increase in NO_2 lag 0 to 15. In Paper II, short-term associations between PHC visits and NO_2 was seen both in the area with "high" levels of background air pollution levels (NO_2), with an RR of 1.09 (95% confidence interval (CI): 1.02– 1.17) and in the area with "low" background levels with an RR of 1.15 (95% CI: 1.08–1.23). In Paper III, a 10 μg/m3 increase in NO_2 resulted in point estimates indicating increased risk for PHC visits due to respiratory diseases in all five selected municipalities, however, the risk was statistically significant in Malmö (RR=1.019 (95% CI: 1.005 to 1.032). In Paper IV, both NO_2 and PM_{10} exposure resulted in increased PHC asthma visits. Other pollutants, ozone (studied in Paper I, III and IV), $PM_{2.5}$, coarse particle and SO_2 (analysed in Paper I) did not show any significant increases in PHC visits.

Air pollution risk Emergency and Inpatient Admission Paper III

In Paper III visits to all three health care centres were analysed for air pollution associations. We did not found any statistically significant increase in risk for PM_{10}, NO_2, and O_3 for inpatient admissions due to respiratory illness. For emergency room visits due to all types of respiratory complaints, there was a 2.52% increase (95% CI: 0.44 -4.64; table 4) for the lag of 0-2 in a multi-pollutant model with a 10 μg/m3 increase in PM_{10} for Helsingborg There was no increase in the four other municipalities in the study. Also, there was no

statistically significant increase in NO_2 and O_3 levels for either of the studied municipalities.

Long term and short term NO_2 exposure effect on asthma visits Paper II

In Paper II, the pooled odds ratios for PHCCs with long-term lower NO_2 levels were higher 1.15 (95% confidence interval (CI): 1.08–1.23), as compared to the pooled odds ratio for PHCCs with long-term higher NO_2 levels 1.09 (95% CI: 1.02– 1.17). However, the difference in RRs between the areas with low and high background levels was not statistically significant ($p = 0.13$), but the results indicate that those living in low air pollution areas may be affected more severely by short-term rises in air pollution levels.

Air pollution metrics and asthma risk Paper IV

The risk of health care visits related to asthma in conjunction with various air pollution metrics were analysed, as seen in our previous analysis. The NO_2 daily mean and different metrics showed a significantly increased risk of visits due to asthma after elevated exposure. NO_2 metrics commuting time, daily mean, one-hour and eight-hour maximum value was associated with an increased risk of visits due to asthma at ages 0-5 for Lag 3 and 4. PM_{10} daily mean levels in our previous studies have shown no significantly increased risk of asthma, but in Paper IV, for metrics commuting hours 4.31% (0.10% to 8.72%) one hour maximum 2.95% (0.16% to 5.83%) and night time was 5.73% (0.81% to 10.92%) resulting in an increase in asthma visits at lag 0-2. For ozone-like prior analysis, there was no increased risk of visits due to asthma. The risk remains insignificant for all metrics and in different age groups as well as among male and female patients.

General discussion

Asthma PHC visits low level air pollution

In all four studies, we found an association between an increased risk of asthma (Papers I, II and IV) or respiratory linked visits (Paper III) to PHCs with outdoor air pollutants. Although the level of air pollution in the study area was well below the recommended guidelines (WHO and EU), the increased risk was statistically significant. There are a number of prior studies published from low air pollution areas (Fusco et al., 2001; Middleton et al., 2008; Migliaretti, Dalmasso, & Gregori, 2007; Olmo et al., 2011) associating respiratory health with air pollution levels, but the main difference between studies included in this thesis and prior studies is the use of PHC data for outcomes. Studies referred to above-used inpatient admissions and emergency care visits which account for a more severe form of disease development whereas PHC visits data used in studies included in the thesis are more a reflection of mild and moderate symptoms. The most consistent risk increases were observed in conjunction with NO_2. One possible explanation for this association is that NO_2 is a good proxy for combustion-related air pollution and the main source of outdoor air pollution in the study area is emissions from automobiles. Associations observed in our studies were also different from prior studies in terms of lag structure. Previous air pollution and health studies looking at short-term effects of exposure found a significant increase with 0 to 3 days' lag. However, in our studies, increase association was seen for rather long lag periods. The main reason behind this change in risk is the behaviour associated with seeking health care which differs between PHC, inpatient, and emergency care. Unlike inpatient and emergency care, patients seeking health care at PHC clinics due to mild and moderate disease symptoms, patients take a longer time to seek health care. In the case of asthma and other common respiratory conditions, there is also a tendency to self-medicate or tolerate symptoms during the initial days of the disease. Whereas, emergency care and inpatient symptoms are more severe in nature and hence prompt urgent health care consultation.

Effect of long-term air pollution concentration and short term air pollution concentration and daily asthma visits

In Paper II, we studied how long-term air pollution concentration effects the association between short-term increases in air pollution concentration and daily asthma visits. We found this association to be stronger in areas with long-term low air pollution levels as compare to long-term high air pollution areas. Even though this difference in the association was not statistically significant, it is very interesting in understanding low-level air pollution effects on respiratory health. However, there numerous possible alternative explanations for our findings. First could be the demographic difference in populations. Older age groups or individuals more susceptible to respiratory illness may live in areas where air pollution is lower. This can occur over a period when those more susceptible to adverse health effects due to air pollution move to areas with cleaner air. There is no published evidence to support the above explanation, but this could be a plausible reason for our findings.

Air pollution and effect on PHC emergency and inpatient admission

In our analysis for Paper III, we investigated the association of outdoor air pollution with all three main types of health care contact; PHC, inpatient and emergency room. This is the first study which has included all three types of health care contact and compared results. We found an increase in PHC visits due to respiratory complaints after exposure to NO_2. This finding (1.85%, 95% CI: 0.52 to 3.20) in Malmö) was consistent with results of our first paper. The risk of inpatient admissions and emergency room visits was close to null and statistically insignificant for all five selected municipalities. Prior studies have found increases in hospital or inpatient admissions (Colucci, Veronesi, Roveda, Marangio, & Sansebastiano, 2006; Schwela, 2000) and emergency visits (Brand et al., 2016; Weichenthal et al., 2015; Zheng et al., 2015) in association with air pollution, however, in our setting we failed to find any increased risk for air pollution levels in the study area. One possible explanation for the lack of a statistically significant finding is a relatively small number of inpatient and emergency visits as compared to visits to PHCs. This

may have resulted in the lack of statistical power to find any association. This explanation was also applicable to the lack of association observed between air pollution and PHC visits in smaller municipalities. In analysing the difference in risk among the three types of health care contact, we did not find any statistically significant differences in risk. More robust large-scale population studies are required to examine this difference.

Air pollution metrics and asthma visits

In our fourth paper, the number of air pollution metrics were analysed in conjunction with asthma visits. Studying different air pollution metrics can help address exposure misclassification in outdoor air pollution studies. We found commuting, for a maximum of one-hour and night-time metrics of PM_{10} were strongly associated with PHC asthma visits. Prior studies analysing O_3 metrics found similar findings for one and eight-hour metrics exposure (M. L. Bell, Hobbs, & Ellis, 2005; Delfino, Zeiger, Seltzer, & Street, 1998). More studies with the rigorous analysis are required to study various air pollutant metrics with high etiological plausibility. Metrics which are more sensitive and account for in detail human activity patterns will also help assign exposure more accurately and hence decrease misclassification bias.

Risk difference among different age groups

One of the aims of the thesis work was to identify in the study if there are certain age group more vulnerable to air pollution effects than others. In the past, research has shown that children and younger age groups are more susceptible to various respiratory diseases after air pollution exposure. In Paper IV, a number of visits were further categorized based on different age groups. We observed an increase in visits related to asthma in the age group 0-5 with increased NO_2 daily mean exposure, commuting time daily one hour and eight-hour maximum levels at lag 3 and 4. This increase was comparable with prior studies. This increase in risk among young age group needs to be taken with main limitation, as a diagnosis of asthma at this age group is difficult and the risk of misdiagnosis is high (L. Tzivian, 2011). We also observed an increased risk of asthma in age group 26-60. There was a 3% increase in visits per 10-unit increase in PM_{10} at lag 1 and 2.

Methodological discussion

Strengths

Novelty of health outcome data Paper I-IV

The main strength of the studies performed for this thesis is utilization of unique outcome data, primary health care data. Sweden is among the very few countries where primary health care data is well organized. The population-based data on PHC visits are unusual in an international perspective. In Scania, municipal PHC data is collected and maintained by the county, with 100% coverage and regularly checked for validity. Close to 80% of the total health care consultation in our study population were at PHC clinics. PHC is typically the very first health care contact in seeking health care. PHC data represents data from the early phases of a disease and hence patients with more mild and moderate symptoms. There are only a few studies prior to one reported in this thesis utilizing PHC data. Prior studies utilizing PHC data had rather limited access (Hajat, Anderson, Atkinson, & Haines, 2002; Hajat et al., 2001), or only had access to night time visits (Yamazaki, Shima, Ando, & Nitta, 2009; Yamazaki et al., 2014, 2015). The PHC data provided us with the opportunity to study air pollution effects on mild and moderate symptoms of respiratory health.

PHC clinics, Emergency department visits and hospital admission in same study Paper III

In Paper III we analysed health outcome data from three different types of health care contacts, PHC, emergency room visits and inpatient admissions. This is the first study to our knowledge studying air pollution effects on respiratory health utilizing all three health data sources. This study helped to analyse mild-moderate and severe health effects of air pollution on respiratory health in the same population and compare their association.

Exposure assessment Paper I-IV

In all four studies, exposure was assigned using very good quality outdoor air pollution monitoring data. In all studies, measures were taken to improve exposure assessment. Air pollution monitoring data was of high quality, with a very small percentage of missing data, and validated by national institutes (IVL & SMHI). In Paper I, the six air pollution monitoring stations used were mainly located in a highly-populated section of the study area. In Paper II, 21 urban background air pollution were included to assigned air pollution levels to further improve exposure assessment and reduce exposure misclassification. A radius of 20 km was selected and PHC clinics situated outside a 20 km radius from a monitoring station were excluded from the study. In this study, the previously validated NO_2 model was used to assign long-term exposure. In Paper III and IV, exposure assessment was made utilizing all available air pollution station data. Missing air pollution data was very low in air pollution stations used for studies. In the paper, one missing data ranged from 1.2% for O_3 to 2.2% for NO_2, which was replaced with a mean of three before and three after the closest hours' air pollution levels available. In the other three studies missing data was omitted from final analysis.

Diagnosis of Respiratory illness

One of the main advantages of using the Scania Health Care register data was the quality of diagnosis. There were many visits with a missing diagnosis but the cases where the diagnosis was available were of high quality. Both presented complaints, as well as comorbidity and was available from the dataset. The diagnosis was assigned by a medical doctor.

Study area

The studies were performed in Scania county which is very diverse in many ways, has a population that is primarily located in urban and semi-urban areas as opposed to rural areas. Moreover, Scania is very diverse with approximately 16% of the population being foreign born.

Limitation and Bias

Missing Diagnosis Private Healthcare clinics

The Health care Register data in Scania, on one hand, is unique and of very high quality with close to 100% coverage, but there are many challenges when using it for research purposes. The first main challenge was PHC visits to private health care clinics. In our study setting, 17% of all health visits were to private health care clinics. Private health care clinics, although they do record and provide information on health visits, do not report the diagnosis and hence all visits to these clinics had missing diagnoses presenting complaints and comorbidities. All visits to private clinics were excluded from the final analysis. This exclusion might have resulted in a selection bias and introduced bias into the study population based on socioeconomic status. But since the cost of PHC consultation is the same in both public and private clinics, it is reasonable to believe that the exclusion of private clinics would not limit the generalizability of the results.

Public Primary Health care clinics

The missing diagnoses were not only limited to private clinics. Close to 40% of all PHC visits lacked diagnoses. This is the main weakness in the studies performed for this thesis. Assuming that the missing diagnoses were completely random, such a large proportion would significantly decrease the precision of the estimates. This can be one of the explanations for rather weak and no statically significant associations in some of our analyses. We studied the pattern of missing diagnoses and if these missing diagnoses were of a certain pattern or association. There was no increase or decrease of missing diagnosis over the study period. Missing diagnoses were also not associated with gender or age of patient and municipality of residence. There was also no difference in missing diagnoses during different seasons of the year. Also, it is very unlikely that missing diagnoses were related to or caused by air pollution exposure level, therefore, it is most likely that a large number of missing diagnoses caused a bias towards the null and not away from it. Missing diagnoses were only a problem in PHC clinic data. For both emergency visits and inpatient admissions diagnoses were reported in close to 100% of the patients.

Primary health care scheduled visits

In a primary health care setting, a proportion of daily health care consultation can be pre-booked or pre-planned well in advance and therefore these visits cannot be associated with short-term exposure to air pollution. In Paper I we included all asthma visits regardless of whether they were classified as an emergency (least likely pre-planned visits) or non-emergency visits (more likely pre-planned visits). This is also possibly the reason behind the longer lag structure observed in Paper I. More likely, the bias caused by the inclusion of pre-scheduled visits is non-differential misclassification and thus bias the results towards the null. For Paper II, the first health care consultation which was not pre-booked was analysed. In Paper III and IV only primary health care visits labelled as emergency visits were included in the study. Primary health care clinics, unlike emergency care, only operate during working days and hence there is an increased probability that more patients will seek health care on the first working day after holidays. Since we used case-crossover design with control days selected matched by the day of the week, this potential confounder was adjusted by design.

Exposure misclassification Paper I to IV

Studying environmental exposure on disease outcome is very complex, mainly when assigning exposure to an individual, as environmental exposure takes place at a different location over time and hence it is very difficult to accurately estimate exposure for study participants. This inaccurate assessment of exposure results in misclassification of exposure which has been acknowledged as an inherent limitation of epidemiologic studies of the environment and health. In all four studies, special care was given to ensure exposure assessment is performed in the best way possible. However, exposure misclassification cannot be ruled out from air pollution studies using one or several air pollution monitoring stations to assign exposure to a population. This exposure misclassification results in decreased chances of identifying the health impacts of environmental agents in environmental studies. Exposure misclassification in our studies has most likely resulted in a non-differential misclassification causing a bias towards the null in our analysis.

In all four studies, we have taken several measures to improve exposure assessment and thus minimize exposure bias. In Paper I, six air pollution monitoring stations were used to assign exposure levels. All these stations were situated in the populated part of the city and hence better representative of exposure at both the residence and workplace. In Paper II, two different

mechanisms were used to assign exposure. For long-term exposure, a previously validated model data was used and for short-term exposure 21 air pollution monitoring stations situated in a different parts of the study area were included to further minimize exposure misclassification. All visits to PHCs where no air pollution monitoring was available within a 20-km radius were excluded from the final analysis. In Paper III, eleven monitoring stations situated in populated parts of the selected cities were included. For Paper IV, only one air pollution station was used. This was decided because of study objectives and to formulate different air pollution metrics. In Paper II to IV, to limit exposure misclassification, we also excluded individuals seeking health care outside their municipality in order to somewhat limit exposure misclassification.

As exposure was assigned based on the municipal address of patients (Papers I, II and IV) or the PHC municipality they visited (Paper II), the probability that these individuals spent most of the days in other municipalities is very high. Another source of exposure misclassification in ecological studies using one or several outdoor air pollution stations is that time study participants are exposed to indoor air pollution. According to some studies, urban populations spend as much as 80% of their daily time indoors and hence assigning outdoor exposure as the main cause of adverse health outcome can be misleading.

Pollen data

The association of pollen with asthma is well established (Krmpotic et al., 2011; Weiler et al., 2007). Several studies have shown that health care visits due to asthma increase during pollen season. Recently, studies have also shown interactions between pollen and air pollution (Bake, Viklund, & Olin, 2014). Studies have found that prior exposure to high levels of air pollution results in increased asthma symptoms (Barranco et al., 2012; Dales et al., 2004). Inclusion of pollen data would have improved exposure assessment, however, the case-crossover study design used studied the population in 28- day or monthly strata thus limiting possible bias caused by the pollen season.

Future research

Better exposure assessment

Exposure along with home also at work address

In studies included in the thesis, exposure was assigned based on the municipal address in Scania, i.e. people travelling within the county to different municipalities for work and study and spending most of their time there. For future studies using an occupational register, daytime exposure can be assigned at work or education address and thus improve exposure assessment. Hopefully it will be possible to model short-term associations with a high spatial resolution in the future

Cohort identified in health register

The quality of the health care register in Scania has improved significantly over the years and we have very good data quality covering more than 15 years. This provides a unique opportunity to study incident cases in the population. There is still no consensus on air pollution as a causal factor for incident asthma.

Using prescription data

Adverse health outcomes such as asthma, where the patient lives with a disease condition over a long period of time, educates patient in ways to know well before the time when symptoms will appear during a certain time of the year and ways to best manage them. Using dispensed medication data from the register can also help capture the complete health burden of disease and hence better quantify associations.

Interaction between air pollutants and pollen

There is a research gap in understanding the interaction between pollutants and pollen in real life settings. Pollen data is now available for study populations

and in the future, in air pollution studies using asthma as a health outcome, it would be advisable to use pollen data in these studies.

Conclusions

At relatively low-levels, ambient air pollution exposure was associated with primary health care visits due to asthma.

There was weak evidence that short-term associations between daily fluctuations in air pollution concentrations and primary health care visits for asthma differ depending on background air pollution levels.

Short-term elevations in NO_2, even at low levels, can increases the risk of visits to primary health care for respiratory symptoms but there was no increase in risk for inpatient admissions and emergency visits.

The risk of asthma differed with different air pollution metrics, this risk also varied among different age groups. Air pollution metrics might better reflect harmful air pollution properties as they are more sensitive to population mobility and thus might be important for epidemiological studies.

The results were inconclusive in smaller municipalities. For inpatient admissions and emergency room visits this may be due to study area size or to generally low levels of air pollution in the study area.

There was weak evidence for short-term associations between air pollution and asthma may to depend on background air pollution levels. In conclusion, the air does not seem to be entirely safe below the EU air quality limit

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List of papers

This thesis is based on four papers referred to by the following roman numbers:

I. **Taj T,** Jakobsson K, Stroh E, Oudin A. Air pollution is associated with primary health care visits for asthma in Sweden: A case–crossover design with a distributed lag non–linear model. Spat Spatiotemporal Epidemiology. 2016 :37–44

II. **Taj T,** Stroh E, Åström DO, Jakobsson K, Oudin A. Short-Term Fluctuations in Air Pollution and Asthma in Scania, Sweden. Is the Association Modified by Long-Term Concentrations? PLoS One. 2016 Nov 18;11

III. **Taj T,** Malmqvist E, Stroh E, Åström DO, Jakobsson K, Oudin A. Short-term associations between air pollution concentrations and respiratory health; comparing primary health care visits, hospital admissions and emergency department visits in a multi-municipality study. Submitted to International Journal of Environmental Research and Public Health in March 2017

IV. **Taj T,** Malmqvist E, Stroh E, Åström DO, Jakobsson K, Oudin A. Alternative air pollution metrics & their associations with primary health care visits due to asthma; a study from Malmö, Sweden. Manuscript form

Author's publications, not presented in this thesis

I. Oudin A, Richter JC, **Taj T**, Al-Nahar L, Jakobsson K Poor housing conditions in association with child health in a disadvantaged immigrant population: a cross-sectional study in Rosengård, Malmö, Sweden. BMJ Open. 2016 Jan 6

II. Kuklane K, Lundgren K, Gao C, Löndahl J, Hornyanszky ED, Östergren PO, Becker P, Samuels MC, Gooch P, Sternudd C, Albin M, **Taj T**, Malmqvist E, Swietlicki E, Olsson L, Persson K, Olsson JA, Kjellstrom T. Ebola: improving the design of protective clothing for emergency workers allows them to better cope with heat stress and help to contain the epidemic. Ann Occup Hyg. 2015 Mar;59(2)

III. Nafees AA, **Taj T**, Kadir MM, Fatmi Z, Lee K, Sathiakumar N. Indoor air pollution ($PM_{2.5}$) due to secondhand smoke in selected hospitality and entertainment venues of Karachi, Pakistan. Tob Control. 2012 Sep;21

IV. Ahmed J, **Taj T**, Shaikh S, Ali S. Factors associated with tobacco smoking among 6-10 grade school students in an urban Taluka of Sindh. J Coll Physicians Surg Pak. 2011 Nov

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