Asthma in school age:
prevalence, incidence and remission in relation to environmental determinants

The Obstructive Lung Disease in Northern Sweden (OLIN) Studies, Thesis XI

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Abstract

Background

In the past half-century, the prevalence of asthma among children and adolescents has risen and asthma has become an important public health challenge in Sweden as well as in many other countries, necessitating further studies on this complex disease and its risk factor pattern. The studies included in this thesis aimed to investigate the clinical expression of childhood asthma over time, to describe the determinants of new-onset and remission of asthma, and to evaluate possible environmental risk factors in northern Sweden.

Methods

As the result of a repeated questionnaire survey among primary school children aged 7-8 years in three municipalities in the north of Sweden, two pediatric cohorts were formed, one in 1996 (n=3430) and one in 2006 (n=2585). The cohort created in 1996 was followed annually until the age of 19 years. Skin prick testing was performed on children in both cohorts. Lung function and bronchial hyperreactivity testing were carried out in children with asthma in the first cohort. The study participation and retention rates were very high in both cohorts. Among children in the second cohort living in Luleå, the home addresses were assigned to coordinates in a geographical information system (GIS) to evaluate the impact on respiratory health of living near roads with much traffic, which was measured as the number of vehicles daily. We used a validated reported diagnosis of asthma and International Study of Asthma and Allergies in Childhood (ISAAC) questions were incorporated into the questionnaire. A cross-sectional study of children of the same age ten years apart, longitudinal studies on asthma incidence and remission as well as a cross-sectional study on vehicle traffic were performed.

Results

While children aged 7-8 years in 2006 more often had a physician-diagnosed asthma compared to children of the same age in 1996 (7.4% vs 5.7%, $p<0.001$), they had less asthma symptoms, especially severe symptoms. In parallel, a more beneficial environment and a more intense treatment with inhaled corticosteroids (ICS) were observed. The explanation for this change in clinical expression probably includes also an increased awareness and diagnosing of asthma. From age 12 years to age 19 years, the cumulative

incidence of physician-diagnosed asthma was 7.2% and of current wheeze 22.0%. The risk of new-onset asthma in adolescence was increased among girls, sensitized and those with heredity for asthma. Smoking and home dampness increased the risk for incident wheeze. The risk for both incident asthma and wheeze was inversely related to number of siblings. Among children with current asthma at age 7-8 years, 21% were in remission, 38% had periodic asthma and 41% had persistent asthma at a follow-up at age 19 years. Subjects in remission and with periodic asthma had significantly less airway obstruction and showed less bronchial hyperreactivity compared to subjects with persistent asthma. The probability of asthma remission from childhood to early adulthood was significantly increased by absence of allergic sensitization, male gender and a low asthma severity scoring at age 7-8 years. Sensitization to furred animals was more important as a determinant of both incidence and remission than sensitization to pollen. Living close to roads with high traffic flows, especially with heavy vehicles, was associated with an increased risk for current wheeze. Stratified analyses showed that the effect of traffic on asthma and wheeze was restricted to non-sensitized subjects.

Conclusion

Asthma onset in adolescence was more common among girls and remission was more common among boys. Children sensitized to furred animals and children with a more severe asthma were risk groups for persistence of asthma. Environmental factors such as smoking and dampness were associated to onset of asthma symptoms during adolescence, and vehicle traffic was associated with asthma symptoms among children also in a small city with relatively low traffic flows. Preventive measures like smoking reduction programs, improvement of damp housing conditions and separation of areas where many children live from heavily trafficked roads could prove to be beneficial.

Sammanfattning på svenska

Bakgrund

Sedan mitten av 1900-talet har astma blivit allt vanligare och är nu ett av de största folkhälsoproblemen bland barn och tonåringar i västvärlden. Senare tids forskning tyder på att astmasjukdomen är mer komplicerad än man tidigare trott. Målsättningen med studierna i denna avhandling var att undersöka hur astmans kliniska bild förändrats över tid, att beskriva orsakerna till nyinsjuknande i och tillfrisknande från astma samt att studera hur vägtrafiken påverkar barns hälsa i norra Sverige.

Metodik

Studierna i denna avhandling baserades på frågeformulär som fylldes i av föräldrarna till skolbarn i åldern 7-8 år i tre kommuner i Norrbotten 1996 (n=3430) respektive 2006 (n=2585). Två barnkohorter skapades därigenom och kohorten från 1996 följdes upp årligen till 19 års ålder. Frågeformuläret kompletterades med objektiva undersökningar som pricktest, bronkreaktivitetstest och lungfunktionsmätning. Deltagandet var högt i båda kohorterna vid den första undersökningen och vid uppföljningarna av den första kohorten. För att studera hur barns luftvägshälsa påverkas av exponering för trafikavgaser studerades de barn som ingick i den andra kohorten och bodde i Luleå. Barnens hemadresser koordinatsattes i ett geografiskt informationssystem (GIS) där avståndet till närliggande vägar kunde mätas. Trafik mättes som antal fordon per dag. Frågan om läkardiagnosticerad astma är validerad och ISAAC-studiens frågor inkluderades i formuläret för att underlätta jämförelser med andra länder. Studierna innefattar en upprepad tvärsnittsundersökning av 7- och 8-åringar med 10 års mellanrum, en tvärsnittsundersökning av trafikavgaser som riskfaktor för astmasymtom och astma och longitudinella studier av incidens och remission samt relaterade faktorer.

Resultat

Barn som var 7-8 år gamla 2006 hade oftare läkardiagnosticerad astma men mindre astmasymtom, speciellt svårare symtom, jämfört med barn i samma ålder 1996 (7,4% respektive 5,7%, $p<0,001$). Parallellt förbättrades omgivningsmiljön och medicineringen med inhalationskortison ökade. Sannolikt har även synen på astmadiagnosen förändrats och medvetenheten om sjukdomen ökat. Risken för nyinsjuknande i astma är ökad för flickor i tonåren, för sensibiliserade och för de med ärftlighet för sjukdomen.

Rökning och fukt i inomhusmiljön ökade risken för astmasymtom (pip och väs i bröstet). Risken för nyinsjuknande i både astma och astmasymtom var omvänt proportionerlig till antalet syskon. Den kumulativa incidensen från 12 till 19 års ålder var 7,2% för läkardiagnosticerad astma och 22,0% för astmasymtom. Remission från astma var vanligare hos pojkar, hos icke-sensibiliserade och hos de med en mildare astmasjukdom. Bland barn med astma vid 7-8 års ålder gick 21% i remission, 38% hade astma periodvis och 41% hade persisterande astma fram till 19 års ålder. Barn i remission eller med periodvis astma hade mindre luftvägsobstruktion och lägre bronkiell reaktivitet jämfört med barn med persisterande astma. Sensibilisering mot pälsdjur var viktigare än mot pollen för både astmaincidens och -remission. Fordonstrafik i närheten av bostaden, särskilt tung trafik, var associerad med ökade astmasymtom (pip och väs i bröstet). Stratifierade analyser visade att effekten av trafik på astma och astmasymtom endast kunde observeras hos icke-sensibiliserade barn.

Slutsats

Flickor och sensibiliserade (särskilt mot pälsdjur) hade störst risk för nyinsjuknande och persistens av astma under tonåren. Miljöfaktorer som rökning och fukt i inomhusmiljön var associerade med nyinsjuknande i astmasymtom bland tonåringar och fordonstrafik var associerat med astmasymtom bland barn även i en relativt liten stad med låga trafikflöden. Att förebygga exponering för tobaksrök, fuktskador i hemmet och att placera bostäder långt från intensivt trafikerade vägar kan vara en möjlig väg att minska astmaförekomsten bland barn.

Abbreviations

ATS	American Thoracic Society
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
EAACI	European Academy of Allergology and Clinical Immunology
GIS	Geographical Information System
GNI	Gross National Income
HR	Hazard Ratio
ICS	Inhaled Corticosteroids
ISAAC	The International Study of Asthma and Allergies in Childhood
km	kilometer
MCh	Methacholine
NO_x	Nitrogen Oxides
OLIN	Obstructive Lung Disease in Northern Sweden studies
OPC	OLIN Pediatric Cohort
OR	Odds Ratio
PM	Particulate Matter
RCT	Randomized Controlled Trial
SPT	Skin Prick Test
SO_x	Sulphur Oxides
TH_2	T-helper cell 2
UK	United Kingdom
U.S.	United States

Original Papers

I **Andersson M**, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. The clinical expression of asthma in schoolchildren has changed between 1996 and 2006. *Pediatr Allergy Immunol* 2010: 21: 859-866.

II **Andersson M**, Modig L, Hedman L, Forsberg B, Rönmark E. Heavy vehicle traffic is related to wheeze among schoolchildren: a population-based study in an area with low traffic flows. *Environmental Health* 2011, 10:91.

III **Andersson M**, Hedman L, Bjerg A, Lundbäck B, Forsberg B, Rönmark E. Persistence and remission of asthma followed from 7 to 19 years of age. (under revision)

IV Hedman L, **Andersson M**, Forsberg B, Lundbäck B, Rönmark E. Incidence of wheeze and asthma in adolescence in relation to environmental factors. (in manuscript)

 The Papers are referred to by their Roman numerals.

Introduction

Asthmatic disease has been described since antiquity. Symptoms of asthma were documented in Chinese writings and a pharaonic pharmacopedia as early as the very beginning of the historic era[1]. In the *Corpus Hippocraticum*, a milestone of early Western medicine, the Greek word "asthma" was used to describe the symptom of panting and not as a reference to a specific disease entity, perhaps not that erroneously after all[1, 2]. Still, asthma and allergies are contemporary diagnoses more than probably any other condition as the number of affected people has grown enormously over the course of the 20th century, ultimately earning the label of an "asthma epidemic". Epidemiological studies have enabled us not only to monitor the rising numbers and identify the connection between asthma and allergic conditions such as hay fever and eczema, but also to recognize other groups of people exhibiting similar symptoms but related to non-allergic factors, like physical exercise, cold temperatures and certain occupational and environmental exposures. However, as our knowledge of asthma has increased, it has become clear that the factors governing it are highly complex[3, 4].

Nowadays, asthma and allergies are unquestionably the most common non-communicable diseases among children and adolescents in the affluent world, which has lead to the theory of "a westernized lifestyle" as the underlying explanation. Suggestions of the key lifestyle factors responsible for the increased prevalence of asthma vary; overly clean housing conditions and decreased exposure to microbial agents in utero or early in life, changing infection patterns, exposure to air pollution, changes in physical activity and changes in diet are among them. A number of risk factors have been identified and recently the proposal that asthma consists of several separate or only partly interlinked diseases has attracted much interest[2, 5].

It is a mystery why such a rapid change in the frequency of asthma has taken place. Unfortunately, this thesis does not completely unravel it but rather forms one part of an ongoing worldwide study of asthma in childhood. It seems likely that in antiquity, or indeed at the beginning of the 20th century, a person with asthma only shared his or her ailments with a minority of today's asthmatics in Sweden. As what asthma is seems to continuously change over time and by location, ongoing investigation of the prevalence, onset and recovery are necessary not only for proper healthcare planning but also to identify preventive or interventive measures. In addition, we specifically evaluated if the risk of asthma in children was affected by

exposure to traffic exhaust in a small town setting, as has been reported previously for several traffic intense metropolitan areas.

Background

Asthma in childhood – a global concern

Asthma is the fourth most common cause for the loss of disability adjusted life years (DALYs) in the age group of 10-14 years globally[6]. The prevalence of asthma and wheeze in the last 12 months (i.e., current wheeze, a commonly used indicator of asthma in childhood) varies tremendously across the globe, but also within countries or even within cities, suggesting that non-genetic etiologic factors are important[7-9]. In 1998, phase I of the International Study on Asthma and Allergies in Childhood (ISAAC) reported that the United Kingdom had one of the highest symptom prevalences: 32% of adolescents reported current wheeze[10]. In contrast, a study from Ethiopia reported that only 1.7% of 10-19 year old children and young adults were affected[11]. In the third phase of the ISAAC survey at the beginning of the new millennium, the prevalence of current wheeze among children aged 6-7 years ranged from 2.4% in Jodhpur (India) to 37.6% in Costa Rica[7]. In northern Sweden in 2006, the prevalence of wheezing in the last 12 months was 13% and the prevalence of physician-diagnosed asthma was about 7%[12].

Asthma is common in many high-income countries, where despite the ready availability of effective medication, there is still a risk of a severe or fatal asthmatic reaction. More commonly, asthma symptoms lead to hospitalization, school absenteeism, parental work absenteeism and restrictions of normal childhood activities[13, 14]. On the other hand, asthma seems to be more severe in less affluent parts of the world[7].

The definition of asthma

Asthma is often regarded as a single disease entity. In fact, asthma is a heterogeneous syndrome characterized by chronic airway inflammation, bronchial hyperresponsiveness and variable airflow obstruction. Common symptoms are recurrent episodes of chest wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning[15]. There is however no comprehensive clinical definition of asthma. The diagnosis is most often based on the patient's history and the clinical examination. Lung function measurements, reversibility and bronchial challenge testing may sometimes confirm the diagnosis.

In asthma epidemiology, a questionnaire-based classification is often the most feasible approach. A self-reported physician-diagnosis of asthma may be highly specific, i.e., identifying only those children that definitely have

asthma[16]. Wheezing or other symptoms of asthma are less specific but may be more sensitive, i.e., a larger proportion of all children with asthma may be identified. In the absence of a validated report of physician-diagnosed asthma or pediatric clinical examination, wheezing is probably the best indicator for classifying schoolchildren in epidemiological studies of asthma[17]. Wheezing in the last 12 months is also a key component of the ISAAC core questions[18].

The concept of asthma *phenotypes* has become increasingly important as the demands for individually customized treatments and more accurate methods to assess the prognosis have increased[2, 5]. Asthma phenotypes can be defined as the observable features of different groups of children with asthma, although *phenotype* is often used in a very vague sense[19]. Different phenotypes may have different risk factor patterns, clinical expression, prognosis, and treatment responses. For example, because children with asthma may or may not experience worsened symptoms upon exposure to certain allergens, this could be regarded as a two clinical phenotypes.

In epidemiology, the distinction between allergic and non-allergic asthma was recognized more than 60 years ago. The risk factor patterns for allergic and non-allergic asthma differ. Environmental factors such as tobacco smoke and dampness at home are mainly associated with non-allergic asthma[16]. However, childhood asthma phenotypes may also be separated by age of onset[20] and symptoms, e.g., wheezy bronchitis caused by respiratory infections in early childhood[21]. Another possible classification is by severity, including symptom reports, treatment and objective measurements, e.g., of lung function and bronchial hyperresponsiveness[19]. These asthma or wheezing phenotypes probably represent separate or only partially linked underlying diseases[2, 5, 20].

Determinants of childhood asthma and wheeze

Allergic conditions and sensitization

Allergic sensitization[22, 23], allergic rhinitis[24-26] and eczema[24, 27], have been identified as predictors of the onset of asthma in adolescence. Absence of allergic sensitization has been related to an increased probability of remission[28-31]. Allergic sensitization is a stronger risk factor for asthma among schoolchildren and young adults than later in life. However, the importance of sensitization and atopic conditions as asthma risk factors may have been overemphasized. For example, many children with asthma are non-sensitized[32].

Heredity and genetics

Parental asthma is a well-established risk factor for the prevalence[33] and incidence of childhood asthma[22, 25], especially early onset[34]. The findings regarding heredity and asthma remission are not unequivocal[31, 35, 36]. Asthma in the family may not only represent an inherited genetic predisposition but also environmental or social conditions shared by family members. Recently, the number of studies on the genome and asthma susceptibility has increased and several associated loci have been identified[37]. Epigenetic modification by methylation has also been discussed as a component in the heredity of asthma[37]. The susceptibility to environmental risk factors for asthma may vary with genetic predisposition[38]. Thus, different phenotypes of asthma may have different genetic origins. For example, in Sweden, a difference in the risk of asthma due to vehicle exhaust exposure was attributed to genetic polymorphism[39].

Air pollution

During the 20th century, rapidly increasing vehicle fleets led to a worsening of the traffic situation in many cities. Even though advancements in combustion technology have enabled more effective fuel processing, traffic-related air pollutants have become an important global health topic. In most urban areas, traffic emissions are responsible for most of the air pollution. Industrial pollutants might also contribute in some areas, but mostly only affect background pollutant levels. Two of the earliest and most well-known studies on the association between air pollution and respiratory health are the US Six Cities Study[40] and the Children's Health Study of Southern California[41-43]. In the Six Cities Study, over 20,000 children and adults in six communities were followed prospectively, while in the Children's Health Study, school children from 12 communities, selected to represent a range of

exposures, were studied, also prospectively. To date, epidemiological studies of air pollution and asthma in children have almost exclusively focused on metropolitan areas in Europe and the U.S.[44-54], either at home or at school[42]. In contrast, childhood asthma and air pollution has been less well studied in developing countries[55, 56] and rural parts of the Western world.

Vehicle exhaust is a mixture of gases and particles. Combustion bi-products, e.g., particulate matter (PM) of different size[57], NO_x[58], SO_x[59] and ozone[60], have been associated with childhood respiratory health, and NO_X has been used as a marker of traffic exposure in some studies[46, 54, 58]. Probably, not a single but several components or the interacting mixture as a whole are responsible for the negative effect on the human airways. Airway oxidative stress caused by, for e.g., diesel exhaust, has been linked to asthma and suggested as the causal mechanism. However, this pathway has not yet been fully elucidated[61-63].

Exposure to traffic-related air pollution has been linked to the prevalence and incidence of childhood asthma[42, 46, 64, 65] as well as respiratory symptoms[43, 54] in a number of studies. Air pollution has also been suggested to be responsible for both an increase in hospital visits and school absenteeism among children[66, 67]. However, it is not clear if air pollution exposure contributed to the past increase in asthma[3, 68, 69], and well-designed studies have also found weak or no association[69, 70]. For unbiased results, proper exposure assessment is as important as correct classification of the outcomes[71]. Objective exposure classification may involve objectively measuring traffic intensity or distance to the nearest road[42], but also more novel methods like land-use regression[72].

Indoor environment

The indoor environment is partly determined by outdoor air pollutant concentrations and ventilation mechanisms, but there are also specific indoor determinant factors. Although not always defined in the same way, dampness in buildings has been consistently associated with asthma in children[73-75]. Chlorinated swimming pool attendance has also been related to childhood asthma[76], but the results are not conclusive[77]. Another possible indoor factor is exposure to biomass combustion particles that are emitted from indoor cooking and heating. Indoor biomass combustion and lack of proper ventilation, which is common in many parts of the world, may affect childhood respiratory health[78].

Smoking

Prenatal exposure to tobacco smoke has been linked to asthma in children[79]. Similarly, environmental tobacco smoke exposure has been related to asthma severity, medication usage, asthma symptoms and peak-flow variability[80]. In adolescence, active smoking is also a possibility, and has been reported as a predictor of onset of asthma and asthma symptoms, especially among girls[22, 81] and non-allergic teenagers[82, 83]. Smokers additionally exposed to environmental tobacco smoke seem to be at the highest risk[84]. Cigarette smoking has been associated with persistence[30] and relapse[85] of asthma, but the previous studies on the effect of smoking on asthma remission are not univocal[31, 35, 86].

Socioeconomics

An association between asthma or wheeze in childhood and low household income has been demonstrated, but the reason is not fully understood[87-89]. Differences between socioeconomic groups, such as access to health care and life style factors, e.g., diet, physical exercise and smoking, are among the suggested explanations[87]. In the cross-sectional ISAAC study, gross national income (GNI) correlated to the prevalence of current symptoms of asthma in some countries but not in others.

Diet and weight

Preterm birth and low birth weight have been shown to be risk factors of asthma in children[79, 90] as well as in adults[91]. On the other hand, a higher BMI later in life has been linked to increased asthma prevalence and incidence both among adults and children, and especially among girls in adolescence[92, 93]. The reason for this is still unknown, but obesity may induce asthma symptoms by anatomical obstruction of the airways. Dietary factors could be protective, e.g., intake of vitamins and antioxidants, fatty acids, fruit and vegetables[94 95]. Whereas the evidence from prospective studies is not conclusive[96], a recent systematic review has reported that maternal intake of vitamins D and E has a protective effect and that children with asthma tend to have lower serum levels of vitamin A. It also described a protective effect of zinc, fruits, vegetables and a Mediterranean diet[97]. A recent publication from the OLIN studies reported that 8 out of 10 adolescents in our study area were vitamin D deficient during winter[98].

Breastfeeding has been demonstrated to protect from non-allergic childhood asthma[16, 99] and lower respiratory tract infections[100] in childhood but

breastfeeding has not been proven to be protective against allergic asthma and allergic sensitization[16, 101, 102].

Immunization and medication

Vaccination against tuberculosis, diphtheria, pertussis, poliomyelitis, tetanus and hemophilus influenzae b has not been associated with wheeze, eczema or asthma, and may even have a protective effect[103-108]. Fewer studies have reported associations between infections, e.g., measles, and a lower prevalence of sensitization and allergies[109]. The relations between infections, vaccinations and sensitization are not entirely clear[102, 110].

A number of studies have described an association between paracetamol use during pregnancy, in infancy or early childhood and later asthma[111-117]. The findings are equivocal[118] and the risk of confounding by early use of antipyretics because of early viral infections in children predisposed to asthma has not been dismissed. Early use of antibiotics has also been linked with childhood asthma[119]. However, as antibiotics use is probably higher in children with asthma, there is a risk that reverse causation may also explain this finding.

Gender

Among children, a higher prevalence of asthma and wheeze in boys has been consistently reported. However, during teenage, the boy-to-girl prevalence ratio switches from asthma being more common in boys to being more common among girls and women[24, 120-122]. Both an increased incidence[24, 25, 123] and a lower remission[30, 124, 125] of asthma in adolescent girls compared to boys have been reported. It has been suggested that this switch in male/female prevalence ratio is due to the hormonal changes of puberty influencing airway growth and inflammatory reaction patterns in gender-specific ways[126], but a recent study found no association with pubertal stages[125].

Time trends in prevalence

The ISAAC research program (International Study on Asthma and Allergies in Childhood) was launched in the early 1990s. It established a valid and standardized method for measuring the prevalence and severity of childhood asthma, rhinitis and eczema for international comparison[18]. Previous studies during the second half of the 20th century, mainly originating from the UK, Australia and New Zealand, had reported a large increase in asthma prevalence[3, 127, 128], which raised concern, especially as the severity seemed to increase as well[129]. Data from the repeated cross-sectional ISAAC phase I studies[130], collected after an average of seven years, revealed increases in the prevalence of wheezing in many low-prevalence centers in Africa and Asia, which was supported by other studies[131]. In contrast, some centers with high prevalence reported no further increase or even a decrease, particularly in the older age group (13-14 years)[130]. The larger phase III ISAAC survey of 2000-2003 confirmed the previous findings of high prevalences of current wheeze in high income countries. It also reported that severe asthma was more prevalent in less affluent regions, e.g., in Latin America, where the prevalence of frequent wheezing or frequently disturbed sleep in Costa Rica was 20.3% among 6-7 year olds[7]. The increasing prevalence in low- and middle-income countries means that the global burden of asthma may increase because the changes affect large populations that may have limited access to medication and qualified personnel[130, 132]. Other studies, more recent or using outcome variables like physician-diagnosed asthma or treatment for asthma in addition to wheezing, support the findings regarding prevalence trends and also indicate that a prevalence plateau may have been reached in the Western world, including in Sweden[12, 133-137].

Incidence and remission

By the end of the 20th century, the number of longitudinal studies on childhood asthma increased. The incidence of asthma in childhood and adolescence has been reported to be around 1 in 100 per year in the Western world[22, 120, 138-140], or expressed as a cumulative incidence from birth in the UK, 18% at age 7 years and 24% at age 16 years[85]. In general, the incidence was found to be highest among young children[120, 141] and higher in childhood and adolescence compared to adulthood[120, 142, 143]. However, high remission rates, from 16% to about 60%, have been reported from childhood to young adulthood[30, 35, 124, 144, 145]. Remission among older adults was less common[146, 147].

In epidemiological studies, a *cohort* often refers to a group of subjects that are followed longitudinally (over time). If the subjects are a sample of the

general population, the cohort is said to be *population-based*, i.e., not hospital- or outpatient-based. One example of a cohort was studied in the National Child Development Study (British 1958 birth cohort), which followed 17,414 children born in March 1958. Data was collected at ages 7, 11, 16 and 23 years, with 7,225 subjects participating on all occasions (43%). This national study was not originally intended for studying asthma or even health research, but for social and educational purposes[24]. Although the study had considerable methodological limitations, including a majority of the children lost to follow-up, it marked an important milestone in asthma epidemiology as one of the first population-based longitudinal studies in a large population sample. Also in the UK, the Avon Longitudinal Study of Parents and Children followed 13,988 children from birth[148]. The participants were recruited based on expected delivery dates, between April 1991 and December 1992. Follow-up included annual questionnaires and annual objective measurements after 7 years of age[112-114]. In the United States, The Tucson Children's Respiratory Study (TCRS) followed about 1,200 children included at birth from 1980, with the aim of studying risk factors, e.g., early respiratory infections, and the prognosis of childhood asthma. The main strengths of that study were very early collection of objective data and a relatively high participation rate. Identification of possible asthma phenotypes, i.e., transient early wheezers - late onset wheezers - persistent wheezers, was also an important result of the TCRS. However, the children in the studied cohort were not a population-based sample but enrolled from a predominantly outpatient population enlisted at a pediatric health maintenance organization[21, 149]. In Australia in 1968, 8,583 7 year old children on the island of Tasmania were included in the Tasmanian Longitudinal Health Study (TAHS)[150] and were then followed into adulthood[151, 152]. The TAHS is one of the oldest and longest running longitudinal studies on childhood asthma development. Recent findings include a description of the impact of allergic rhinitis and eczema on asthma incidence and remission[26, 27, 35]. However, the study subjects in this cohort may not be representative of 7 year old schoolchildren in the early 21st century. In New Zealand, 1,073 children born in 1972 were surveyed from 9 years of age into adulthood in the Dunedin Multidisciplinary Health and Development Study. The studied population represents a population-based unselected birth cohort, which was reassessed repeatedly. Objective methods, such as lung function, bronchial challenge testing, skin prick testing and IgE blood level measurements, strengthened the study design. Only a minor proportion of the study population was lost to follow-up: 1,037 children (91%) participated at three years of age and 954 participated at 26 years[30]. In Norway, the Environment and Childhood Asthma Study (ECA) enrolled 3,754 children at birth in 1992. A representative subsample of 803 children with lung function measurements was found to have a high

prevalence of current asthma at age 10 years. The study retention rate was 77%[153, 154]. In Finland, 96% of children born in the two northernmost provinces in 1966, *n*=12058, were followed into adulthood in a prospective study. This study was not set-up primarily to investigate asthma epidemiology and the number of participants lost to follow-up was substantial[155].

In Sweden, there are several population-based longitudinal studies of asthma and allergic disease in childhood. The BAMSE study has focused on a Swedish population-based birth cohort of 4,089 children from parts of the Stockholm area in 1994 to 1996, with an initial participation rate of 75% of those invited. A broad range of factors related to asthma and allergic disease were studied[156, 157]. The infants of Western Sweden study is a large birth cohort from 2003 focusing on early life risk factor for asthma and allergic disease[158].[159]. Also in northern Sweden, a birth cohort study of more than 1200 children has evaluated risk factors of asthma and allergy, including early life pet keeping[160] .

OLIN

The Obstructive Lung Disease in Northern Sweden (OLIN) studies was founded in 1985 to conduct epidemiological studies about asthma, allergies, allergic sensitization, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and health economics. Among children, food intolerance also is examined. The main aim of the program include identifying preventable risk factors for these conditions. The studies are multidisciplinary and cover traditional and molecular epidemiology, clinical research and genetics. The methods used include longitudinal cohort studies, case-control studies, cross-sectional studies as well as qualitative studies. Collaboration with research groups all over the world, from the United States to Vietnam and New Zealand, are ongoing. Prevalence, trends in prevalence, incidence, remission and risk factors of obstructive lung diseases and allergic sensitization have been studied both among adults and children, the latter since 1996. Out of 250,000 inhabitants, about 50,000 subjects aged 7-93 years have taken part in the collective OLIN studies[161]. OLIN is based and administered in Luleå. The data from these studies in northern Sweden have so far been a part of 17 doctoral theses. Ten thesises were exclusively based on data from OLIN and four of them were based on the two pediatric cohorts[12, 16, 25, 29, 33, 79, 84, 102, 138, 161-164]. A number of PhD-projects are ongoing. The present thesis is based on data from the two pediatric cohorts.

Aims

The objectives of the work described in this thesis were to investigate asthma in school age children by studying environmental factors in relation to new onset, remission and prevalence of asthma and to evaluate how the clinical expression of childhood asthma changes over time.

The specific aims were:

- To compare the severity and clinical expression of asthma among 7-8 year old schoolchildren in 1996 and 2006 (Paper I).
- To study the effect of vehicle traffic on childhood asthma in a small Swedish city (Paper II).
- To quantify remission of asthma during school age and to study the determinants of remission and persistence (Paper III).
- To identify the risk factors for the incidence of asthma and wheeze during adolescence (Paper IV).

Methods

Study area

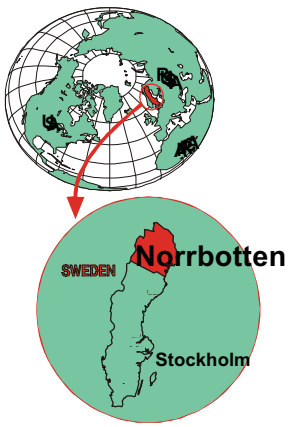

Figure 1. The county of Norrbotten in northern Sweden.

The county of Norrbotten (Fig 1) is located in northern Sweden, bordering Finland in the east and Norway in the west. Despite covering approximately 25% of the land area of Sweden, only 3% of the population lives in Norrbotten. The total population is about 250,000. The southern part of the county lies at the coast of the Gulf of Bothnia and is the most densely populated. The county capital is Luleå, which is located on the coast and had 71,000 inhabitants in 1996 and 72,000 in 2006. A steel mill and a university specializing in technological science are the main employers. A railroad built for iron ore transportation connects Luleå with Kiruna in the northernmost part of Norrbotten. Kiruna, which had 25,500 inhabitants in 1996 and about 23,000 in 2012, is predominantly a mining center, but tourism and space science are also important industries. Piteå is situated on the coast to the southwest of Luleå and had about 41,000 inhabitants in both 1996 and 2006. A paper mill and small enterprises are the main lines of business. Other larger municipalities are Boden, 35 km to the north of Luleå and the main garrison of the Swedish army, Gällivare to the south of Kiruna, which is another important mining site, Kalix on the coast to the east of Luleå and Haparanda at the Finnish border, a commercial center situated close to the

Finnish city of Tornio. The climate is relatively dry and cold: winter lasts from November to March. The main hospital is located outside Luleå with local hospitals in Kalix, Kiruna, Gällivare and Piteå. There is a network of primary healthcare centers located in the cities as well as in some of the larger communities in the countryside.

Study populations

This thesis describes work based on the first and second OLIN pediatric cohorts (OPC I and OPC II, Fig 2).

The first cohort was recruited in 1996 by submitting a questionnaire to the parents of all children attending the first and second grade of primary schools (7-8 years old, median 8 years) in three municipalities of Norrbotten; Luleå, Kiruna and Piteå. The participation rate was 97% and the cohort consisted of 3,430 children. The first survey of OPC I in 1996 was used as baseline for a longitudinal study and OPC I was subsequently followed into early adulthood[165]. In 1997, a study on the validity of the question "physician-diagnosed asthma" was conducted. It identified 248 (7.2%) of the children in the first pediatric cohort as having asthma based on a structured questionnaire and clinical assessment by local pediatricians[16]. These 248 children were then followed by annual questionnaires until 19 years of age. The participation rate in this group was 83%: 205 children remained in the study at 19 years. The second cohort was formed in 2006 by identical methods as used in 1996. The participation rate was 96%. Because the birth rate had decreased, the second cohort contained 2585 children[12, 102, 161].

In the study described in Paper I, cross-sectional data on children with physician-diagnosed asthma and wheeze from OPC I in 1996 (n=197 and n=400, respectively) were compared to cross-sectional data from OPC II in 2006 (n=191 and n=335). These data were collected by identical methods in order to compare characteristics of 7-8 year old children with asthma and wheeze ten years apart.

In the study described in Paper II, data from OPC II in Luleå were studied cross-sectionally (n=1357) to analyze asthma and symptoms of asthma in relation to vehicle traffic in the vicinity of the home.

In the study described in Paper III, the 248 children identified as having asthma within OPC I in 1996 were followed into adulthood. Remission and determinants of remission were studied among the 205 children who participated at 19 years of age.

In the study described in Paper IV, all children in OPC I aged 11-12 years (median 12 years) in the year 2000 were followed to an age of 19 years. The populations at risk were defined as the children free from asthma (n=2747)

or wheeze (n=2578), respectively, at the study baseline in 2000. Incidence of asthma and wheeze in adolescence and their determinants were analyzed.

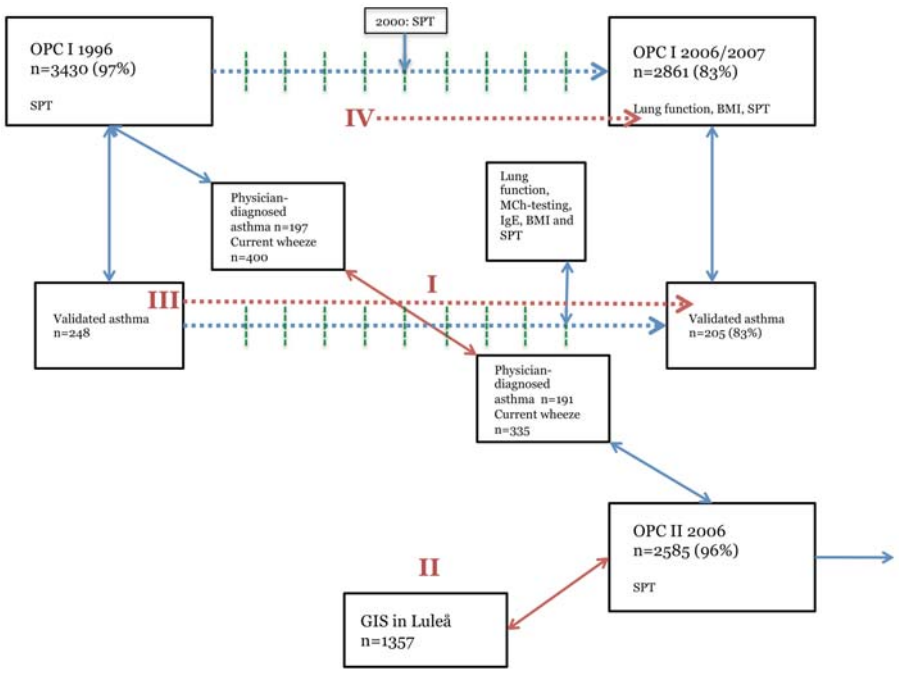

Figure 2: The study design. Red numerals refer to Papers I-IV. Red dotted line: longitudinal study. Red continuous line: cross-sectional study. Blue dotted line: cohort followed by time. Blue continuous line: sub-sample. Green dotted line: yearly reassessments.

The questionnaires

The OLIN questionnaires included ISAAC core questions[18] but were substantially extended. Questions concerning physician-diagnoses of asthma and allergic diseases, symptoms, medication and an extensive screening for possible risk factors, including heredity, indoor and outdoor home environment, were added. The main questions were identical in 1996 and 2006. Answers were collected from February to March in the respective years. The questionnaire used in 1996 is included as an appendix to this thesis. In the validation study of the question "physician-diagnosed asthma" based on the OPC I questionnaire, >99% specificity and 70% sensitivity were achieved[16]. Condensed questionnaires were used for annual resurveys.

Initially, the questionnaire was filled in by the parents, but the children aswered the questions by themselves once they became teenagers. This shift in methodology has been validated. The children tended to report higher prevalences of current wheeze, whereas the parents tended to report higher prevalences of ever having wheeze. However, the agreement regarding symptoms, diagnoses and risk factors was high[162, 166].

Skin prick testing and IgE

All children in Luleå and Kiruna attending the first or second grade of primary school were invited to participate in skin prick testing (SPT) in 1996 (OPC I) and 2006 (OPC II), respectively. The participation rate was 88% in 1996 (2,148 children) and 90% in 2006 (1,700 children). In OPC I, skin prick tests were performed also during follow-up in 2000 and 2006/2007. In 2005, SPT (n=190) and blood samples for total IgE (n=192) were analyzed among the children with asthma in OPC I. Specifically trained personnel within the OLIN study group carried out the tests from February to April in the respective years. The same study supervisor was involved in all surveys. The methods used were identical in both cohorts and followed EAACI guidelines[167]. A mean wheal size $\geq$3mm was considered a positive result. Ten standard airborne allergens with a potency of 10 HEP (histamine equivalent prick test) or 1:20 weight/volume for the molds were tested: *birch pollen, timothy grass pollen, mugwort pollen, horse, cat, dog, Dermatophagoides pteronyssinus, Dermatophagoides farinae, Cladosporium herbarum and Alternaria alternata*. Histamine (10mg/ml) was used as a positive control and glycerol as a negative control (*Soluprick, ALK, Denmark*). Correlation between a positive prick test and a serum level of specific IgE >0.35 was evaluated with very high conformity[102, 163]. Serum IgE was analyzed by CAP (Phadia, Uppsala, Sweden).

Lung function and bronchial challenge testing

In the follow-up of children with asthma at age 7-8 years (Paper III), the *Mijnhardt Vicatest 5* dry volume spirometer was used for lung function measurements in 2005 and a *Spirare*® flow-volume spirometer at the end of the study in 2006/2007. The *Berglund* normal range for lung function was used for reference[168]. In 2005, lung function measurements were performed in 198 children with asthma in accordance with ATS (American Thoracic Society) recommendations, with the exception that nose clips were not used. Bronchial challenge testing was also carried out in 2005 on a random sample of 54 (76% of invited) children with asthma. Methacholine chloride was nebulized in cumulative doses of 35, 176, 529, 1586, 2996 and

5816 μg with an automatic inhalation-synchronized dosimeter jet nebulizer (*Spira Electro 2*, Respiratory Care Centre, Hämeenlinna, Finland)[169].

Geographical information system

The addresses of the children's homes and schools were assigned to coordinates in a geographical information system (GIS, Fig 4). These coordinate locations were combined with geographical data on traffic intensity, i.e., traffic counts of total number of vehicles and number of heavy vehicles (buses, trucks) daily. The local traffic authorities provided traffic counts from Luleå on all major roads as well as on minor roads in the city center (Fig 3). In Piteå and Kiruna, the traffic counts had low spatial resolution, and therefore the analysis was limited to the Luleå area. An exposure model was constructed using separate cut-off levels for traffic counts on any road within 200 m from the coordinated address for heavy vehicles ($\geq$100, $\geq$250, $\geq$500) and total traffic ($\geq$4000, $\geq$8000, including heavy vehicle traffic counts). Children who did not live within 200 m of any road with traffic counts greater than the cut-off values were considered unexposed. The vast majority of traffic counts were collected in 2006 $\pm$ 2 years. The GIS computer program was managed by a GIS-trained research engineer (Lennart Jonsson) in close collaboration with the present author.

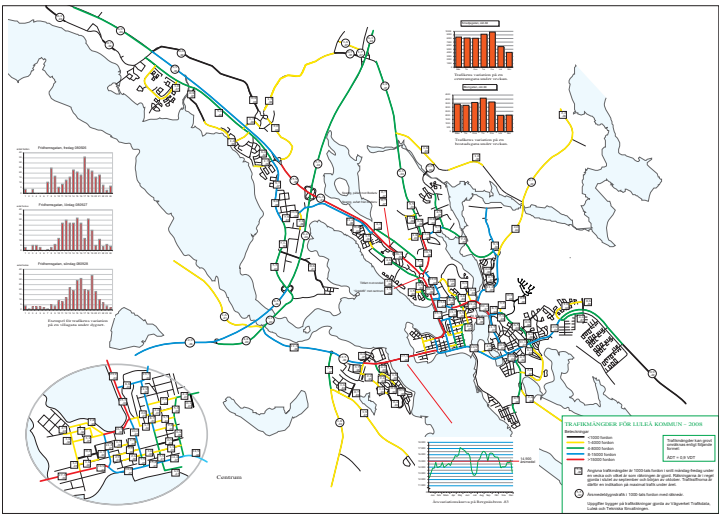

Figure 3: Overview of traffic intensity in central Luleå (published with permission from the local traffic authorities in Luleå). Some major and all minor roads included in the study are not shown.

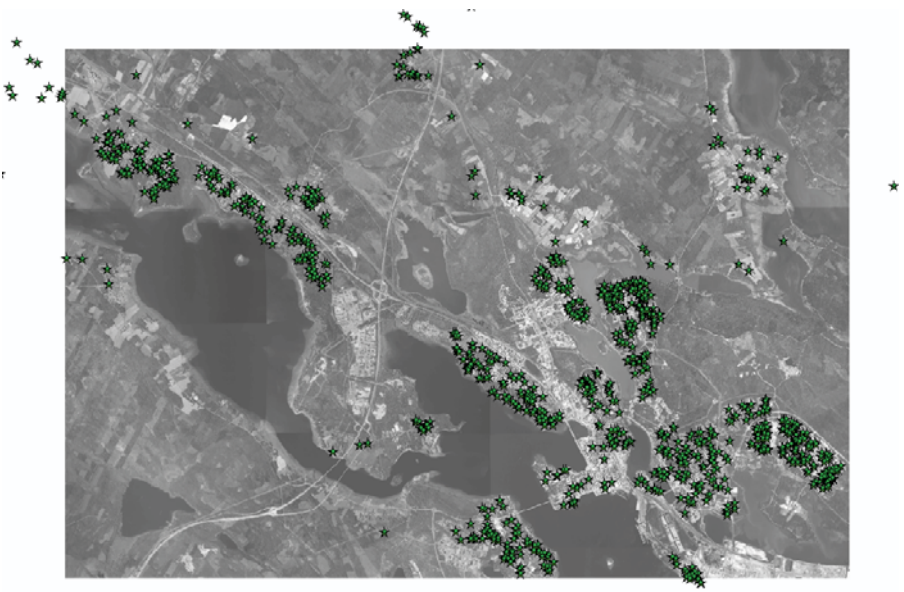

Figure 4: Satellite image of central Luleå with coordinates of home addresses marked in green. (prepared by Lennart Jonsson, Occupational and Environmental Medicine, Umeå University)

Definitions

Commonly used terms in this thesis include the following:

Physician-diagnosed asthma: "Has your child (Have you) been diagnosed by a physician as having asthma?"

Current wheeze: "Has your child had wheezing or whistling in the chest in the last 12 months?"

Cumulative incidence of asthma and wheeze, respectively, were defined as the number of new cases/population at risk. The incident cases had reported having asthma or wheeze, respectively, in any of the annual questionnaire surveys between 13 and 19 years of age. Children who had reported having asthma in any of the questionnaire surveys between 7-8 and 11-12 years of age, or were classified as having asthma in the validation study[16] were excluded from the population at risk for asthma. The population at risk for wheeze excluded those who had reported current wheeze in any of the questionnaire surveys between 7-8 to 11-12 years of age.

Remission of asthma was defined as not having *current wheeze* nor current use of any medication at the endpoint and in the two annual surveys immediately preceding the endpoint, i.e., having been free from symptoms and medication for at least 3 years. Those children not in *remission* were either categorized as *persistent asthma* (asthma symptoms or medication at the endpoint and in at least 8/9 of the preceding years) or *periodic asthma* (neither *remission* nor *persistent asthma).*

Ever wheeze: "Has your child ever had wheezing or whistling in the chest?"

Current asthma medication: Use of any kind of asthma medicine in the last 12 months.

Current asthma: Physician-diagnosed asthma and either *current wheeze* or *current asthma medication.*

Current ICS use: Use of inhaled corticosteroids in the last 12 months. Use of inhaled corticosteroids (ICS) also included use of ICS when administrated with long-acting β-agonists (LABA) in combined inhalers.

Disturbed sleep: "In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?"

Speech-limiting wheeze: "In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?"

Troublesome asthma: Either *speech-limiting wheeze* or *disturbed sleep* ≥1/week in the last 12 months.

Asthma severity score: Based on four ISAAC core questions and one of the OLIN questions about asthma medication, an arbitrary asthma severity score ranging from 0 to 5 points was developed. The items included were *current wheeze*, daily *asthma medication*, ≥1 nights per week with *disturbed sleep*, *>12 episodes of wheezing* and at least one episode of *speech limiting wheeze* during the last 12 months, each yielding one point.

Allergic sensitization: a positive skin prick test (SPT) defined as a reaction with a mean wheal diameter of ≥3mm to at least one allergen.

Physician-diagnosed rhinitis (eczema): "Has the child by a physician been diagnosed as having rhinitis (eczema)?"

Allergic rhinitis: "Has the child during the last 12 months had sneezing, runny nose or nasal obstruction without having had a common cold?"

Eczema: "Has your child during the last 12 months had an itchy rash that was coming and going for at least six months?"

Parental asthma (asthma in the family): Father and/or mother with asthma.

Parental smoking: Father and/or mother smokes.

Ever smoking was defined as a report of daily smoking in any questionnaire survey.

Respiratory infections: Ever having had pertussis, croup, pneumonia or other severe respiratory infection, e.g., respiratory syncytial (RS) virus.

Overweight: body mass index (weight/height^2, BMI) was calculated at the age of 11-12 years. Overweight was defined using the cut-off according to Cole et al.[170].

Ever dampness at home (home dampness): Signs of indoor moisture or molds where the child lived at any time during childhood.

Socio-economic status: Living in a single family house versus in an apartment.

Self-reported traffic exposure: A large busy road or a very frequented bus stop within 200 m of the home.

Rural (urban) living: Having grown up in the city or in the countryside.

Statistical analysis

All statistical analyses reported in this thesis were carried out using the Statistical Package for Social Science Software 16.0-20.0 (SPSS Inc, Chicago, IL, USA). The chi square test (and Fisher's exact test where appropriate) or bivariate logistic regression (as indicated in the papers) was used for bivariate comparisons of categorical variables. When adjusting for possible confounding factors, multivariate logistic regression models were used, as described in Papers I-III. In addition, the multivariate logistic regression models were stratified by sex and sensitization in the work reported in Paper II. In the study described in Paper IV, Cox-regression was used for analyzing cumulative incidence and related factors. When comparing continuous variables between groups, the Student's t-test or ANOVA was used if the variable studied was normally distributed and the Mann-Whitney test or Kruskal-Wallis 1-way ANOVA if not. A 95% confidence interval (CI) was used in all studies, and thus a p-value <0.05 was considered statistically significant.

Results

Clinical expression of asthma over time (Paper I)

In 1996, 5.7% of the children in the first OLIN pediatric cohort reported physician-diagnosed asthma. Ten years later, 7.4% of the children in the same age group (7-8 years) in the second OLIN pediatric cohort reported physician-diagnosed asthma. There was no significant increase in current wheeze[12]. In Paper I, we compared children with physician-diagnosed asthma in 1996 and 2006, respectively, with regard to the prevalence of possible risk factors, such as medication, environmental exposures, sensitization, pertussis infection and signs of asthma morbidity. The main results are presented in Table 1 below.

Table 1: Main findings of Paper I.

	Physician-diagnosed asthma		
Conditions	1996 (n=197)	2006 (n=191)	p
Current wheeze	81.2	69.6	0.008
Troublesome asthma	21.3	11.0	0.006
Number of nights with disturbed sleep during the last 12 months			
Never	50.8	62.3	0.002*
< 1 night per week	38.1	34.6	
≥ 1 night per week	11.2	3.1	
Stayed home from school due to respiratory symptoms/asthma	40.9	31.1	0.047
Current rhinitis	46.7	41.9	0.340
Take full part in physical activities in school	97.9	97.9	1.0
Current ICS	54.8	67.0	0.014
Any positive SPT	49.3	56.6	0.241
Positive SPT to cat	39.9	48.4	0.168
Positive SPT to birch	22.6	25.4	0.600
Currently cat at home	3.1	14.2	<0.001
Ever damp housing	27.9	19.0	0.043
Mother currently smokes	38.7	18.6	<0.001
Pertussis infection	49.2	3.7	<0.001

* ANOVA test for trend

Children with diagnosed asthma had significantly less respiratory symptoms and fewer signs of asthma morbidity in 2006 compared to 1996. Contemporaneously, increased treatment with inhaled corticosteroids (ICS)

and improved indoor environments were reported. There was also a vast reduction in pertussis infections owing to a reinstated immunization program. In a stratified analysis of children using and not using ICS, a substantial reduction of current wheeze was seen among non-users of ICS but not among children on ICS treatment (Paper I, Table 4). Children with physician-diagnosed asthma had a significantly lower asthma severity score in 2006 compared to 1996. Factors related to asthma severity (asthma score$\geq$3) were analyzed in a multivariate logistic regression model. The study year 2006 was inversely associated with an asthma severity score $\geq$3 (Odds ratio, OR 0.44 (0.23-0.87).

Vehicle traffic and childhood asthma (Paper II)

All children in the OPC II who lived in Luleå in 2006 were included in a cross-sectional study, in which home addresses and vehicle traffic counts on all major and many minor roads were added in a GIS model. We found an association between daily vehicle traffic counts and wheezing (adjusted OR ranging from 1.4-1.7) and between daily vehicle traffic counts and asthma (adjusted OR ranging from 1.5-1.8). The results were more pronounced for heavy vehicle traffic (Fig 5). Further, the effect of vehicle exhaust on asthma as well as on wheezing was only observed among non-sensitized subjects (OR ranging from 1.6-2.4 for current wheeze and from 2.3-2.9 for physician-diagnosed asthma). There were no significant associations between traffic flows and allergic rhinitis, sensitization, or sensitization to pollen specifically.

We compared self-reported traffic exposure with our objective exposure classification. Thus, the validity of self-reporting exposure to traffic-related air pollution was evaluated. The sensitivity of the question *"Is there a large busy road or a very frequented bus stop within 200 meters of the home?"* ranged from 50% to 67% depending on which exposure cut-off values were used for comparison. When the cut-off level for daily traffic increased, respondents objectively classified as exposed were more likely to report exposure. The specificity, ranging from 74% to 78%, was highest when the lowest cut-off level for objective exposure was used for comparison.

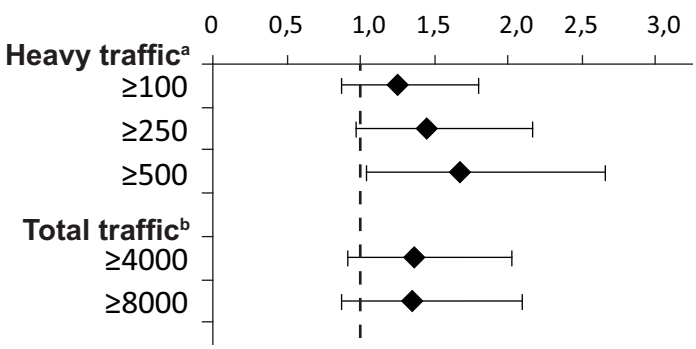

Figure 5: Risk of current wheeze by exposure to vehicle traffic, expressed as odds ratios (OR) with 95% confidence interval (CI). [a]= number of heavy vehicles daily within 200 m of the home address. [b]= total number of vehicles daily within 200 m of the home address.

Remitted, persistent or periodic asthma in adolescence? (Paper III)

A cohort of children with asthma in OPC I were identified in 1996/1997. These children (*n*=248) were followed prospectively until the age of 19 years, when 205 still participated (Fig 6).

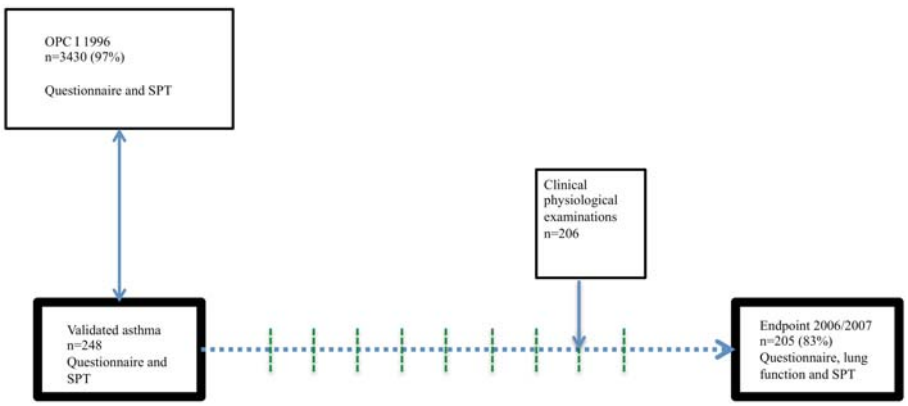

Figure 6: The study design of paper III.

At the age of 19 years, 43 children (21%) were in remission, 78 children (38%) had periodic asthma and 84 children (41%) had persistent asthma.

Male sex (OR 2.66, 95%CI 1.00-7.03) increased the probability of asthma remission, whereas a positive SPT to furred animals (OR 0.14, CI 0.04-0.55) and higher asthma severity (OR 0.19, CI 0.07-0.54) were inversely related to asthma remission. Sensitization to furred animals was a stronger predictor than sensitization to pollen. Sensitization to pollen was not a significant prognostic factor when adjusted for animal sensitization in a multivariate model. There were no significant associations between persistent or remittent asthma and environmental factors. Children with persistent asthma had significantly lower FEV_1, FEV_1/VC, PD_{20} to methacholine and significantly higher reversibility in FEV_1 and total IgE levels at clinical examinations performed in 2005 and 2006/2007.

Predicting incident asthma (Paper IV)

The cumulative incidence of asthma from age 12 to 19 years was 7.6% (*n*=197) and the cumulative incidence of wheeze was 22.0% (*n*=567), both significantly higher among girls. In the multivariate Cox regression model, having asthma in the family was associated with increased incidence of physician-diagnosed asthma (Hazard ratio, HR 1.68, CI 1.20-2.35). The number of siblings was inversely related to the incidence of asthma (HR 0.84, CI 0.72-0.97). A positive skin prick test to furred animals was associated with an increased incidence of physician-diagnosed asthma (HR 2.19, CI 1.38-3.50), whereas sensitization to pollen was not.

Having a parental history of asthma was borderline significantly associated with the incidence of wheeze (HR 1.17, CI 0.94-1.45). The number of siblings was inversely related to the incidence of wheeze (HR 0.89, CI 0.83-0.97), whereas ever having smoked and damp housing were significant risk factors for the incidence of wheeze (HR 1.95, CI 1.60-2.38 and HR 1.29, CI 1.07-1.56, respectively). The effects of female sex and smoking were only apparent for non-sensitized subjects.

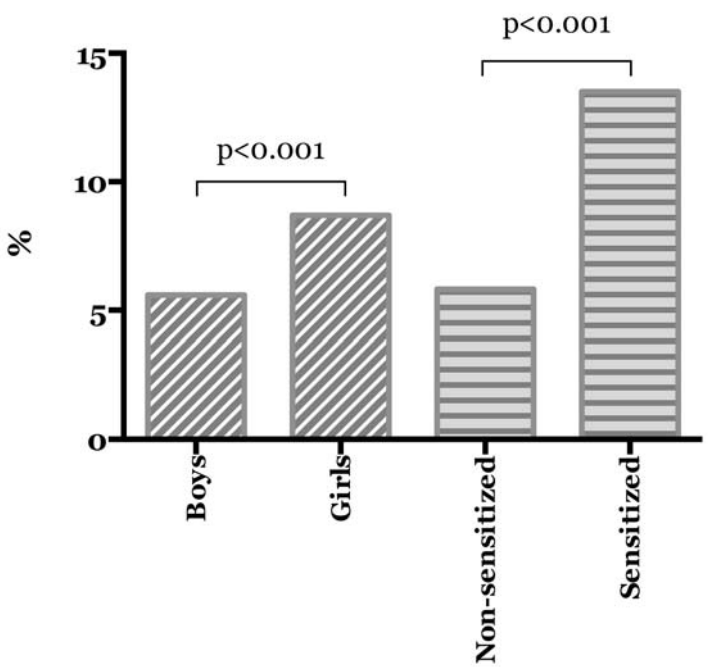

Figure 7: Cumulative incidence of physician-diagnosed asthma from age 12-19 years by sex and sensitization, respectively.

Discussion

Discussion of methodology

Epidemiological concepts

Validity or *accuracy* are the extent to which a scientific study is unaffected by systematic errors (systematic bias), i.e., that we measure what was intended. The *reliability* or *precision* describes the degree of (absence of) non-systematical errors, i.e., that we obtain the same or a very similar result every time a measurement is repeated. Validity may be divided into internal and external validity. Internal validity describes the trustworthiness of an association found in the study, whereas external validity describes whether the results are applicable to other settings and populations. The reliability increases with increasing study population. Systematical errors, on the other hand, are not dependent on the study sample but on the correct (non-coincidental) classification of the possible determinants and outcomes studied. Systematical errors might be caused by, e.g., use of a non-calibrated instrument for measuring an exposure or a study question that is not associated with the studied disease, but another condition. Achieving high validity necessitates obtaining high reliability. However, the reverse does not hold; high reliability might be achieved with low validity, i.e., if the wrong result is obtained in a very repeatable way[171, 172].

There are different types of systematical errors, or *bias*. *Selection bias* may occur if one group is more prone to accept the invitation to participate or stay in the proposed study[171, 172]. Examples of *information bias* are *reporting bias,* which is the under- or over-reporting of disease or exposure by certain groups and *recall bias,* which is a time-dependent systematical error, e.g., children who have had mild asthma in the past may forget this fact at the time of the study[85]. Another form of systematical error may arise because different questionnaires are used on different occasions in the study or the questionnaire is completed by different people. Also, confounding factors are sometimes considered as a source of bias.

All papers included in this thesis benefit from a high participation rate as result of close collaboration with the schools and the mandatory primary school system in Sweden. This is one of the advantages of using school children at the study baseline instead of birth cohorts, for which it is harder to achieve high participation rates. Participation close to 100% as well as high retention rates, ensured us that this was a representative population-based study where no group of children, e.g., those with low socioeconomic

status, is excluded, minimizing selection bias. In Papers III and IV, children were followed prospectively and annually, which limits the impact of recall bias.

All papers in this thesis share a common limitation because the results are mostly based on questionnaire-based reports. We have tried to reduce this potential systematical bias, i.e., reporting bias, by an objective classification where feasible, most notably in the GIS traffic exposure model. We have also used objective measurements to validate our questionnaire-based classification of asthma and allergic sensitization, i.e., lung function, bronchial hyperreactivity testing, skin prick tests and IgE assays[102, 163]. However, most reassuringly, the questionnaire has been validated, both locally and internationally[16, 18]. By using almost identical questionnaires throughout the studies and validating the shift from parental to teenager respondents[162], we have also tried to limit possible sources of bias. Thus, these studies have a high level of validity. Further, the reliability is strengthened by, in general, relatively large study samples.

We believe that our study populations are representative of children in communities in other parts of Sweden and probably also of children with similar socio-economical circumstances around the world, as others have reported similar findings regarding trends in prevalence[134, 135, 173] and risk factors[73, 80, 82, 99]. Thus, the external validity of our results must be regarded as high.

Study designs

Epidemiological studies on large numbers of people in the general population or in groups affected or exposed to a certain disease or suspected risk factor have their own inherent limitations. Naturally, the use of appropriate methods is crucial in epidemiology to obtain unbiased results. However, different methods have different strengths and while some may be considered more suitable than others, no method is without limitations or better than the others in all circumstances. Relations of exposure and different factors with disease outcomes are in reality often very complex, and taking a lot of possible confounding factors into account makes large study samples and complex statistical methods necessary. Nevertheless, classical epidemiological study designs hold as the best approach for describing and analyzing associations among large groups of population-representative people and could generate specific hypotheses for testing in mechanistic studies later on, where randomized controlled trials, if possible, may excel.

Prevalence is measured in cross-sectional studies and describes the percentage affected in a defined population at a specific time, whereas *incidence* describes the frequency of new onset cases with time[171, 172]. Incidence may be obtained by studying a number of subjects initially free from disease, the population at risk, prospectively or calculated retrospectively from a cross-sectional study, although the latter may be prone to recall bias[85], i.e., poor memory of mild episodes of asthma or because the responding person was too young at the asthmatic episode. Not only the definition of the outcome but also the definition of the population at risk affects the incidence estimate[142]. Incidence may be categorized as cumulative, i.e., all cases over a specific time period, or as an incidence rate, i.e., number of cases per person and year under study. Asthma is considered as a more or less chronic disease, and therefore incidence rate can be estimated by dividing the cumulative incidence by the number of study years. *Remission* describes the reverse case, i.e., the numbers of recovering from disease with time, starting with a number of subjects affected by the disease under study. The results are dependent on the definition of the outcome, on the definition of the study population and the frequency of follow-up; the longer time between follow-up examinations or questionnaires, the more susceptibility are the results to recall bias[25]. In conclusion, although following large numbers of children over time to collect data on incidence and remission is costly and inherently time-consuming, a longitudinal approach is less susceptible to bias by design. If the potential risk factors are not stable over time, a longitudinal study facilitates causal inference.

In this thesis, each paper describes a specific epidemiological study design. In Paper I, two cross-sectional studies were compared to evaluate the clinical expression of asthma ten years apart, i.e., 7-8 year old children in 1996 and other 7-8 year old children in 2006. As the concept of asthma may change by time[134, 135, 173], this method gives us information that is unobtainable with other designs. We also used an identical methodology in both surveys, which is crucial to ensure a trustworthy result.

Paper II describes a cross-sectional study evaluating the effect of vehicle traffic exposure on childhood asthma and wheeze. The associations between traffic counts on roads and asthma or wheeze were adjusted for possible confounding factors. For example, children living in apartments could have a lower (or higher) socioeconomic level than children living in singe family houses[53], and because apartments may more often be situated close to major roads, we risk obseving an association between roads and asthma that are confounded by socioeconomic status. By adjusting for socioeconomic level, this potential confounding variable was taken into account in the analysis. It

is difficult to rule out all confounding factors, especially in a cross-sectional study. Also, the cross-sectional study is often considered less suitable for causal inference compared to a longitudinal design, due to the inability to establish that a certain exposure or risk factor was present before the disease was, i.e., the design is prone to reverse causation. Reverse causation may be more or less probable in different situations, and a cross-sectional study could be an important part in the puzzle of causal inference if well designed and thoroughly discussed. We wanted to study the possible effect of traffic exhaust in a small city rather than definitely stating the causal mechanism and because longitudinal data has only been gathered for a short time in the second OPC, we found that the study design used was suitable for an initial study on traffic exhaust and childhood asthma in this part of the world.

Increased reporting of air pollution exposure by parents to children with symptoms of asthma has been suspected[174, 175]. Therefore, objective assessment of traffic exposure is warranted. However, factors other than vehicle exhaust may be responsible for the observed association between traffic flows and asthma. In the cold climate of northern Scandinavia, use of studded tires in wintertime is prescribed by law and biomass fuels are often used in indoor open stoves. Studded tires may increase particle exposure in this area in wintertime[176] but it seems unlikely that the use of biomass fuels would be related to residential proximity to intense traffic. In the analysis of the risks from vehicle traffic, we could not separate different components in the complex mixture of air pollution[57-60]. This was however not a study of the mechanisms by which air pollution affects health. More complex models than vehicle counts have been developed for measuring exposure, e.g., land use regression. The use of such methods would be an interesting comparison in future studies. Further, as the background urban concentration of NO_2 (often used as an indicator of vehicle exhaust levels) was low[177], we conclude that our method was unlikely to underestimate the risk attributable to vehicle traffic.

In Papers III and IV, longitudinal study designs were applied to follow the first OPC during childhood and adolescence. Study of the onset and remission of disease longitudinally requires characterization of the "population at risk", i.e., the study population at the study start must not have asthma if studying asthma onset and must have asthma if studying remission. In paper III, 248 children were followed from 7-8 years and ten years onwards. This study sample was considerably smaller than in Paper IV, because in the general population fewer children have asthma than are healthy. However, the group of children in study III were formed as a result of a validation study including pediatric examination, which ensured that only children with current asthma were included in the study population. As

discussed in Paper III, it is important to correctly classify diseases like asthma to obtain the best possible results, both when defining the asthma cohort at the study start and the outcome. Further, our findings illustrate the difficulties of correct classification of remission in the complex natural history of asthma. The cumulative remission frequency was almost two fold higher when using only endpoint data compared to the main remission definition that symptoms and medication must have been absent for at least three years (37% versus 21%). Using the latter definition also revealed a group of periodic asthma, partly different from both remission and persistent asthma. The large variation in size of both incidence[22, 24, 27, 83, 85, 123, 142] and remission[30, 35, 124, 144, 145] reported in the previous literature is probably due to differences in both the study design, definition of the population at risk and definition of the outcomes.

Discussion of major findings

We have found that asthma symptoms and the severity of asthma in primary school children with physician-diagnosed asthma decreased from 1996 to 2006. Possible explanations for this include increased use of corticosteroid medication, improved housing conditions, decreased pertussis infection rate and increased diagnosis rates and awareness. The most important risk factors for incident asthma in adolescence were found to be a family history of asthma, sensitization to furred animals and being female. Damp housing and smoking increased the risk of chest wheeze. Girls, sensitized to furred animals and children with a less mild asthma were also more likely to have asthma persisting during adolescence. Vehicle traffic was associated with increased asthma symptoms also in a small European city with low overall traffic intensity and low background air pollution levels.

Asthma among primary school children in 1996 and 2006.

In Paper I, we found a significant increase in physician-diagnosed asthma but not the symptoms of asthma, particularly more severe symptoms. These findings are in line with those of other studies conducted in high-prevalence countries[132, 134, 135, 173] and may be attributed to changes in treatment, environment or diagnostic practices. In children who did not use inhaled corticosteroids (ICS), a dramatic decrease in symptoms of asthma was observed. This may be an effect of the increased ICS medication, i.e., also children with very few or mild symptoms may have been prescribed inhaled corticosteroids in 2006 but not in 1996. Nevertheless, such a large decrease (Paper I, Table 4) is unlikely to be caused by increased medication alone and probably reflects an increased diagnosis rate of children with milder or more atypical symptoms. In addition, risk factors for asthma symptoms, such as smoking[80] and damp housing[74], decreased markedly between 1996 and 2006, contributing to more favorable conditions for an inhibition of asthma symptoms and asthma development in the population. However, the logistic regression model presented in Paper I showed that the study year 2006 was also associated with lower asthma severity when adjusting for environmental factors, which indicates that environmental factors like smoking and damp housing are not the only explanation for the change in clinical expression of asthma between 1996 and 2006. An expected finding was the virtual elimination of pertussis infections due to the reintroduction of general immunization, which applied to the second OLIN cohort but not the first. This finding is supported by pertussis surveillance data from the Swedish National Institute for Communicable Diseases, SMI[178]. As severe respiratory infections like pertussis have been reported as risk factors for asthmatic

disease[20, 161] this might also explain the decrease in symptoms. However, pertussis immunization cannot explain why the diagnose of asthma has become more common as there is no evidence for an increase in asthma because of vaccination[103-106]. Our study design enabled an in-depth analysis of asthma in children and possible determinants by using different outcome variables, i.e., physician-diagnosed asthma, current wheeze and current asthma, in addition to studying the impact of environmental, behavioral and hereditary factors.

Exposure to vehicle traffic

In Paper II, we reported an association between vehicle traffic and both asthma diagnosis and asthma symptoms. This association was strongest and most consistent for symptoms of asthma, i.e., current wheeze. The less consistent association regarding physician-diagnosed asthma was probably due to insufficient statistical power for this analysis, as asthma is less prevalent than symptoms of asthma. However, current wheezing has been suggested as the best substitute for asthma in epidemiological studies[17], which strengthens our findings regarding physician-diagnosed asthma. When stratified by sensitization status, the findings only applied to non-sensitized children among those with asthma or current wheeze. Allergic sensitization has been shown to be the strongest risk factor for childhood asthma[22, 23], and thus, if a relation with vehicle traffic exists, it may not be obvious among sensitized children as they are at a high risk regardless of air pollution exposure. On the other hand, as exposure to other environmental factors, such as dampness in the home and environmental tobacco smoking has been related to non-allergic asthma[16], these results could be interpreted as a demarcation between allergic and non-allergic asthma. The literature is however not univocal; another European study reported the opposite; i.e., an effect was observed only among sensitized children[48].

The association between traffic and current wheeze was strongest for heavy vehicle traffic, which is in line with previous studies of areas with very intense traffic[48]. The importance of our findings is not that an association was found, but the magnitude of the association and where it was found. The study area was the city of Luleå with about 70,000 inhabitants and on an international scale, comparably low levels of traffic and background concentrations of air pollutants (the yearly average urban background level of NO_2 was 9.7 $\mu g/m^3$ in 2007). Thus, the increased relative risk comparable to that found in large metropolitan areas[42, 46, 64, 65] suggests that the risk in these metropolitan areas may have been underestimated. Consideration of the effect of vehicle exhaust exposure on children's health may be of

importance for for city planning also in smaller cities. The associations between vehicle traffic and respiratory symptoms or asthma remained after adjusting for heredity, environmental tobacco smoke, damp housing, gender and socioeconomic status. For current wheeze, a dose-response relationship with increasing traffic exposure was indicated, as shown by others[179]. However, the exposure groups were not exclusive, e.g., the group of children exposed to more than 250 heavy vehicles daily also included children exposed to more than 500 heavy vehicles daily. Paper II aimed to explore whether an association between traffic and childhood respiratory health also existed in smaller cities in the Western world. Although further work is needed to verify the results, we were able to demonstrate an association also in this city of about 70,000 inhabitants, which to the best of our knowledge is a novel finding.

Determinants of incidence and remission

Well-designed longitudinal studies of incidence as well as remission and relapse from asthma are useful for describing risk factor patterns of asthma. Previously, studies of the OPC I have identified allergic sensitization as the strongest risk factor for incident asthma in the time period from 7-8 years until teenage. A family history of asthma was the second strongest risk factor in the same period. Damp housing, maternal smoking, respiratory infections, short time of breast-feeding and low birth weight were also risk factors for asthma in OLIN[16, 29, 138], as in other studies[3, 99, 100]. In Paper IV, we identified damp housing and smoking as risk factors for symptoms of asthma in addition to verifying sensitization, especially to furred animals, and heredity of asthma as predictors of incidence. For asthma to persist, we demonstrated the importance of sensitization (especially to furred animals), female sex and more severe asthma (Paper III).

To date, primary prevention seems to be the only public health strategy for asthma as no cure has been found. There is no convincing evidence that inhaled corticosteroids, despite having revolutionized the treatment of asthma symptoms, cause manifest remission[180]. Therefore, a better understanding of what risk factors are involved and how to prevent them, if at all possible, is needed. The number of population-based studies on the risk factors for incident asthma in adolescence has so far been limited[22, 24-27, 83, 123]. Further, in earlier studies, the incidence may have been underestimated because remission is common[30, 146]. Relapse from remission into clinical disease is also common[29, 30, 85] and difficult to detect if the time intervals between surveys and resurveys[25] are too long. Thus, remission may be overestimated. Population-based studies that have evaluated remission

and factors related to remission of asthma prospectively among children are also scarce[29, 30, 35, 144] and, as mentioned above, susceptible to misclassification due to the risk of relapse. We found a cumulative remission frequency of 37% from age 7-8 years to age 19 years when using endpoint data alone. When using a remission definition that specified that symptoms and medication must have been absent for at least three years, we found a remission frequency of 21%. Despite showing the variation in results of using different definitions, both these proportions are in the same range as seen in other studies[30, 35, 124, 144, 145]. The cumulative incidence of asthma from age 12 to 19 years was 7.6% in our study area, which agrees with other studies from Western countries reporting an incidence of asthma of about 1%/year in childhood and adolescence[22, 120, 138-140].

The past asthma prevalence increase in some parts of the world, as well as the leveling or decrease in others, are still not well understood. So far, the main explanatory theory has been "the hygiene hypothesis", a concept interlinked with a "westernized life-style". This theory suggests that early in life or in utero, microbial exposure or viral infections due to overcrowding, bad hygiene, large number of siblings and day-care attendance protect from developing allergic sensitization, atopic asthma and allergies by suppressing TH2 (T-helper cell 2)-immunity[181-184]. The theory has been developed to consider also later or specific ages and that, e.g., the diversity of microbial exposure[185, 186], growing up and living on a farm[187-189], exposure to animals[190, 191] and immunomodulation by intestinal microbes like lactobacilli[192], may play a role in asthma development. However, it seems unlikely that the hygiene hypthesis is the sole explanation for the asthma epidemic. Firstly, not only atopic asthma has increased[193], and farming environments protect also from non-atopic asthma[187, 194]. Secondly, the prevalence of asthma has leveled or even decreased in some parts of the Western world where there is no evidence of growing family size or unhygienic conditions[10, 195]. Unexpectedly, in Latin America high prevalences of current asthma symptoms have consistently been reported, also from less developed parts, comparable or higher than in Spain or Portugal[196, 197]. Daycare attendance and farm animal exposure have been shown to be protective in Latin America as in Europe[198], but it seems unlikely that Latin Americans have less animal exposure, a more hygienic environment, smaller family sizes and fewer infections in early life than Europeans as expected from the theory. In Paper IV, we found that a higher number of siblings was inversely related to the incidence of asthma and wheeze, in line with the hygiene hypothesis[181]. However this inverse relation was found among adolescents and the association of both house dampness and number of siblings with incidence was observed only among non-sensitized subjects in the stratified analysis (Paper IV, Table 2), which contrasts with the original theory. Thus, asthma

development is complex and the risk factor pattern probably varies across the globe. Synergism between risk factors may be necessary to develop asthma in some cases[199]. The hygiene hypothesis could still be a valid explanation provided the complexity of asthma development is taken into account.

Asthma is often referred to as an "atopic disease". This is only partly true as a substantial proportion of asthma cases do not present atopic sensitization in the Western world and even more so in less affluent countries. The global differences in prevalence of sensitization cannot explain the variation in the prevalence of wheeze[200]. However, a study of New York neighborhoods suggests that variations in the distribution of allergens may indeed be one of the explanatory factors[9] and our findings presented in Papers III and IV clearly show an increased risk of developing asthma and decreased risk of remission among sensitized children. We also describe the importance of the sensitization pattern, i.e., that sensitization to furred animals is more important than to pollen, both regarding the incidence and remission of asthma.

The relationship between exposure to allergens and specific sensitization is not yet fully understood, nor is the relation between exposure to allergens and asthma[160, 164, 190, 201-204]. While potent allergens may indeed worsen asthma in susceptible children[205] and increased levels of total IgE positively correlate with more severe asthma[206], some studies have indicated a protective effect on asthma development of allergen exposure, e.g., to cats[164, 190, 202, 207], or having grown up on a farm[208, 209]. In Paper I, we found that more children with asthma kept a cat at home in 2006 compared to 1996. However, although sensitization to cats increased among asthmatic children as well as in the whole cohort[102] in the same time period, allergic rhinitis and symptoms of asthma did not (Paper I, Table 2). This finding is interesting, but unfortunately we did not have sufficient statistical power for analyses of morbidity among sensitized children that kept a pet at home. Nevertheless, among children with both asthma and sensitization, not all cases are attributable to sensitization, i.e., the attributable fraction among sensitized asthmatic is not 100%. Allergic asthma is one thing in epidemiological studies and another if only considering children whose asthma becomes worse by exposure to specific allergens as "allergic asthmatics". There is no clear evidence supporting the removal of dearly loved pets if the child does not have allergic symptoms[204] and removal of pets does not inhibit sensitization as the children are also substantially exposed at school[210]. However, high awareness is necessary as symptoms of asthma may be hard to recognize if the child is exposed almost all the time. Allergic asthma to,

e.g., cats may be very troublesome and make removal of pets absolutely necessary.

As expected, in our study area heredity for asthma increased the risk of children developing asthma in adolescence[22, 25 33]. Further, our data suggest that asthmatic children with heredity for asthma have the same chance of asthma remission in adolescence as others. However, the results of other studies are not univocal[31, 35, 36]. Asthma severity was inversely related to remission, in line with other studies[28, 146, 211]. The boy-to-girl prevalence ratio changes during adolescence from asthma being more common in boys to being more common among girls and women[24, 120-122]. We observe that both an increased incidence among girls in adolescence and a higher remission rate among boys in the same time period contribute. This finding is supported by the previous literature, regarding an increased incidence[24, 25, 123] as well as a lower remission[30, 124, 125] of asthma in adolescent girls.

We found that personal smoking, but not environmental tobacco smoke (ETS), was related to the incidence of wheeze during adolescence, in line with others studies[83, 212]. A possible explanation is that ETS affects adolescents less than children because the fomer spend less time with their parents. Further, we observed an association between the incidence of current wheeze and house dampness. Sensitization to mites, that thrive in damp conditions, and mite allergy are well established risk factors for asthma[30] and have been suggested as one, but not the only explanation for the association between dampness and asthma or wheeze. This is illustrated by our finding of an association between damp buildings and asthma symptoms also in an area where there are no mites because of the climate. Other mechanisms have not yet been identified, but microbial compounds from molds and bacteria have been suggested as possible factors[213, 214]. Chemical emissions from degrading building materials and of microbial origin, including volatile organic compounds (VOC) have also been suggested as a factor in a causal pathway[215, 216]. Thus, regarding preventable risk factors, interventions of smoking are warranted and there is evidence for avoiding dampness in buildings, especially among children[74].

Conclusions

- Children aged 7-8 years with physician-diagnosed asthma had less respiratory symptoms in 2006 compared to 1996. Concurrently, ICS treatment increased and the indoor environment was improved. An increased diagnostic intensity resulted in a greater proportion being diagnosed as having asthma.

- There was an association between vehicle traffic and wheeze among 7-8 year old children in the city of Luleå in northern Sweden, despite the overall traffic intensity being low. The risk of respiratory illness due to exposure to traffic exhaust may be underestimated globally.

- One in five children with asthma remitted from the age of 7 to 19 years. Absence of allergic sensitization, in particular to furred animals, mild asthma and male sex predict asthma remission.

- Sensitization to furred animals, female sex and asthma heredity were related to the incidence of asthma. The number of siblings were inversely related to both asthma and wheeze. Smoking prevention and improvement in the indoor environment could help to reduce the incidence of wheezing among teenagers.

Perspectives

Prevention is better than intervention, and intervention is better than having to find a cure. In this thesis, we describe risk factors for prevalent and incident asthma as well as remission of asthma in childhood and adolescence, a time in life where both asthma onset and remission are common. Whereas genetics do not offer such opportunities, the identification of environmental factors may help to reveal targets for prevention. We identified an increased risk of asthma or symptoms of asthma due to smoking, damp housing and traffic-related air pollution. Reductions in exposure to tobacco smoke, damp housing and vehicle traffic where children grow up are surely justifiable, not only from the perspective of respiratory health but also for future cardiovascular health, cancer prevention and reduction of traffic injuries. The effects of exposure to pets at home on childhood respiratory health are less clear, and earlier advice to asthmatic or sensitized children may have to be revised in the future. However, proper treatment of allergic conditions and removal of pets if the child experiences symptoms are still warranted.

In northern Sweden and other Western countries, the leveling prevalence increase and reduced asthma severity suggested in this work, as well as in other studies, are hopeful. Directing future research to the detailed study of allergic sensitization and its relation to asthma and allergic conditions by examining symptoms, animal exposure and impact of medication and desensitization could provide interesting results. Further, more attention should be paid to the possible asthma epidemic in developing countries.

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ENKÄT OM LUFTVÄGS-, NÄS- OCH HUDBESVÄR HOS BARN I ÅRSKURS 1 OCH 2 I LULEÅ OCH KIRUNA KOMMUN

Skola	Klass

Barnets namn	

Barnets personnummer	10 siffror

Barnets hemadress	
Barnets hempostnr	
Barnets hemtelefonnr	

	År	Månad	Dag
Dagens datum			

Namn på den förälder/vårdnadshavare som besvarat enkäten
.....
tel nr hem .....
tel nr arb .....

Information om pricktest

Pricktest är en enkel och snabb metod för allergidiagnostik. Testen går till så att ett antal droppar som innehåller allergen t ex björk, katt, osv placeras på underarmens insida. Sedan prickas det yttersta hudlagret genom dropparna. Dropparna torkas sedan bort och resultatet avläses efter 15 minuter. Den som är allergisk brukar reagera med ett litet nässelutslag och kortvarig klåda på platsen för prickningen. Jämfört med vaccinationer och blodprovstagning brukar en pricktest inte uppfattas som smärtsam. Självklart avbryts testningen om barnet skulle uppleva den som obehaglig.

- ❑ Ja, jag ger mitt godkännande till att mitt barn pricktestas
- ❑ Nej, jag vill inte att mitt barn pricktestas

Huvudfrågor - pipande och väsande andning

Sätt kryss i ja, nej eller lämplig ruta.

		JA	NEJ
1.	Har barnet **någonsin** haft väsande eller pipande andningsljud i bröstet? Om du svarat "nej" var god gå direkt till fråga 6.		

		JA	NEJ
2.	Har barnet haft väsande eller pipande andningsljud i bröstet någon gång **under de senaste 12 månaderna?** Om du svarat "nej" var god gå direkt till fråga 6.		

		Ingen	1 - 3 ggr	4 - 12 ggr	Mer än 12 ggr
3.	Hur många episoder med väsande andning har barnet haft **under senaste 12 månaderna?**				

		Aldrig vaknat med besvär	Mindre än 1 natt/ vecka	1 eller flera nätter/ vecka
4.	**Under de senaste 12 månaderna**, hur ofta har i genomsnitt barnets sömn störts av väsande andning?			

		JA	NEJ
5.	**Under de senaste 12 månaderna,** har barnets väsande andning någon gång varit så svår att det endast kunnat säga ett - två ord mellan andetagen?		

		JA	NEJ
6.	Har barnet **någonsin** haft astma?		
7.	**Under de senaste 12 månaderna,** har barnet haft väsande i bröstet under eller efter ansträngning?		
8.	**Under de senaste 12 månaderna,** har barnet haft nattlig torrhosta utan att ha varit förkylt eller att ha haft en infektion i bröstet?		

Tilläggsfrågor - pipande och väsande andning

		JA	NEJ
9.	Har barnet under de senaste 12 månaderna haft pipande eller väsande andning utan samtidig förkylning?		
10.	Har barnet under de senaste 12 mån haft hostattacker vid ansträngning utan samtidig förkylning?		
11.	Tycker Du att barnet har lika bra ork (kondition) som sina jämnåriga kamrater?		
12.	Deltar barnet i skolans gymnastik och idrott i full omfattning? Om "nej" varför inte?.....		
13.	Har barnet varit hemma från skolan vid något tillfälle pga andningsbesvär eller astma? Om "ja", hur många dagar totalt under de senaste 12 mån? ..... dagar		
14.	Har barnet av läkare fått diagnosen astma?		
15.	Går barnet på regelbundna läkarkontroller för astma?		

		Aldrig	Ibland	Ofta/ period-vis	Varje dag
16.	Hur ofta har barnet behövt ta medicin pga astma under de senaste 12 månaderna?				

		JA	NEJ
17.	Om barnet behövt ta medicin, har barnet använt något av följande?		
	Ventoline, Bricanyl, Inspiryl eller andra luftvägsvidgande		
	Becotide, Pulmicort eller andra kortisonpreparat		
	Lomudal eller annat		

		Har inga besvär/ inte alls	Något, litet	Måttligt	Ganska mycket
18.	Under de senaste 12 mån, hur mycket påverkade barnets andningsbesvär/astma barnets dagliga aktiviteter?				
19.	Tycker du att barnets andningsbesvär/astma förvärras när barnet är i skolan?				
	Om du tycker barnets andningsbesvär/astma försämrats, vad i skolmiljön tror du orsakar försämringen?				

Huvudfrågor vid näsbesvär

		JA	NEJ
20.	Har barnet **någonsin** varit besvärat av nysningar, rinnsnuva eller nästäppa **utan att** ha varit förkyld? Om du svarat "nej", var god gå direkt till fråga 25		

		JA	NEJ
21.	Har barnet **under de senaste 12 månaderna** varit besvärat av nysningar, rinnsnuva eller nästäppa **utan att** ha varit förkylt? Om du svarat "nej", var god gå direkt till fråga 25		

		JA	NEJ
22.	Har **under de senaste 12 månaderna** dessa näsbesvär förekommit samtidigt med kliande, rinnande ögon?		

23.	I vilken/vilka månader hade barnet dessa näsbesvär? Sätt X i lämpliga rutor												
	Januari		Februari		Mars		April		Maj		Juni		
	Juli		Augusti		September		Oktober		November		December		

		Inte alls	Något litet	Måttligt	Ganska mycket
24.	**Under de senaste 12 månaderna**, hur mycket påverkade näsbesvären barnets dagliga aktiviteter?				

		JA	NEJ
25.	Har barnet **någonsin** haft "hösnuva"?		

Tilläggsfrågor vid näsbesvär

Karaktäristiskt för allergiska näs- och ögonbesvär är **rinnsnuva, nästäppa, klåda i näsan, upprepade nysningar, röda och kliande ögon.** Vanligaste orsaken till besvär är djur och pollen.

		JA	NEJ
26.	Har barnet haft ögon- näsbesvär av ovan nämnda typ? Om "nej" gå till fråga 34.		

27.	När får barnet besvär? Kryssa det alternativ som passar bäst.	
	När som helst under året	
	Främst under pollensäsongen (vår/sommar)	
	Endast under pollensäsongen (vår/sommar)	

		JA	NEJ
28.	Har barnet varit hemma från skolan vid något tillfälle för dessa näs- eller ögonbesvär?		
	Om"ja", hur många dagar totalt under de senaste 12 månaderna? ..... dagar		

		JA	NEJ
29.	Har barnet av läkare fått diagnosen hösnuva eller allergiska näs-/ögonbesvär?		
30.	Går barnet på regelbundna läkarkontroller för hösnuva eller allergiska näs-/ögonbesvär?		

		Aldrig	Ibland	Ofta/ periodvis	Varje dag
31.	Hur ofta har barnet behövt ta medicin pga allergiska näs- eller ögonbesvär under de senaste 12 mån?				

32.	Om barnet behövt ta medicin, vilket eller vilka preparat har han/hon använt?..... ....

		Inte alls	Något,lite	Måttligt	Ganska mycket
33.	Tycker du att barnets näs-/ögonbesvär förvärras när han/hon är i skolan?				
	Om du tycker att barnets besvär förvärrats, vad i skolmiljön tror du orsakar försämringen				

Huvudfrågor vid hudbesvär

		JA	NEJ
34.	Har barnet **någonsin** haft ett kliande utslag som kommit och gått under minst 6 månader? Om du har svarat "nej" var god gå direkt till fråga 40.		

		JA	NEJ
35.	Har barnet haft detta kliande utslag någon gång **under de senaste 12 månaderna**? Om du har svarat "nej" var god gå direkt till fråga 40.		

		JA	NEJ
36.	Har detta kliande utslag **vid något tillfälle** förekommit på något av följande ställen: armvecken, knävecken, fotleder, på lårens baksidor eller på halsen, kring öronen eller ögonen?		

		Under 2 år	2-4 år	5 år - äldre
37.	Vid vilken ålder fick barnet detta kliande utslag för första gången?			

		JA	NEJ
38.	Har detta utslag helt försvunnit vid något tillfälle **under de senaste 12 månaderna**?		

		Aldrig	Ej så ofta som 1 natt/v	1 el flera nätter/ vecka
39.	**Under de senaste 12 månaderna**, hur ofta, i genomsnitt, har detta kliande utslag hållit barnet vaket nattetid?			

		JA	NEJ
40.	Har barnet **någonsin** haft eksem?		

Tilläggsfrågor vid hudbesvär

Man brukar tala om **böjveckseksem**, eftersom eksemet främst brukar vara lokaliserat till armbågsveck, knäveck samt framtill på fotlederna. Kliande handeksem liksom eksemfläckar baktill på låren och skinkorna brukar också vara varianter på böjveckseksem. Eksemet brukar vara torrt och kliande och många blir förbättrade eller kanske helt besvärsfria under sommarhalvåret.

		JA	NEJ
41.	Har barnet haft hudbesvär av ovan nämnda typ? Om "nej" gå till fråga 49.		

		Aldrig	Ibland	Ofta
42.	Brukar barnet ha eksem på händerna?			

		JA	NEJ
43.	Har barnet varit hemma från skolan vid något tillfälle pga sitt eksem? Om "ja" hur många dagar totalt under de senaste 12 mån ..... dagar.		

		JA	NEJ
44.	Har barnet av läkare fått diagnosen eksem?		

		JA	NEJ
45.	Går barnet på regelbundna läkarkontroller för sitt eksem?		

		Aldrig	Ibland	Ofta
46.	Hur ofta använder barnet kortisonsalva för eksemet?			

		Inte alls	Något litet	Måttligt	Ganska mycket
47.	Tycker du att barnets eksembesvär förvärras när han/hon är i skolan?				
	Om du tycker att besvären förvärrats, vad i skolmiljön tror du orsakar försämringen?				

Tilläggsfrågor om allergi eller annan överkänslighet

		JA	NEJ
48.	Har barnet någonsin haft symptom på nickelallergi, dvs klåda/ utslag av smycken, t ex halskedjor, öronringar, metallknappar eller spännen?		

		JA	NEJ
49.	Har barnet hål i öronen?		

		JA	NEJ
50.	Finns det något som barnet är allergisk mot, eller tidigare har varit allergisk mot? Om du svarat nej, gå till fråga 54.		

51.	Vad är ditt barn allergiskt mot eller får besvär av? Kryssa i lämpliga rutor.								
	Pälsdjur			Pollen (frömjöl)			Födoämnen		
	Mögel			Damm			Tobaksrök		
	Starka dofter			Kyla			Annat		

52.	Vad har ditt barn tidigare varit allergiskt mot eller fått besvär av? Kryssa i lämpliga rutor.								
	Pälsdjur			Pollen (frömjöl)			Födoämnen		
	Mögel			Damm			Tobaksrök		
	Starka dofter			Kyla			Annat		

		JA	NEJ
53.	Har barnet någonsin genomgått allergitestning?		
	Om "ja", vilket år och vad blev resultatet?		

Barnets bakgrundsdata

54.	Vad var barnets födelsevikt? ..... gram

55.	Till vilken ålder fick barnet bröstmjölk?.....mån

56.	Vid vilken ålder fick barnet för första gången tillägg/ersättning? .....mån

57.	Hur många syskon har barnet?

58.	Vilket barn i ordningen är barnet?

59.	Förekommer allergiska besvär hos övriga familjemedlemmar? Sätt kryss i aktuell ruta, även om besvären försvunnit.	Far	Mor	Syskon
	astma			
	allergiska näs/ögonbesvär			
	eksem			
	ofta luftvägskatarr			

60.	Vistades barnet på daghem före skolåldern? Kryssa för lämpligt alternativ.	
	Aldrig	
	Började första gången före ett års ålder	
	Började första gången mellan 1 och 2 års ålder	
	Började första gången efter 2 års ålder	

61.	Vistades barnet på familjedaghem/dagmamma före skolåldern? Kryssa för lämpligt alternativ.	
	Aldrig	
	Började första gången före ett års ålder	
	Började första gången mellan 1 och 2 års ålder	
	Började första gången efter 2 års ålder	

62.	Har barnet haft	JA	NEJ
	kikhosta		
	krupp		
	lunginflammation		
	svårare luftvägssjukdom, t ex RS-virus		
	övrig svårare infektionssjukdom		

		JA	NEJ
63.	Brukar barnet vara förkylt mer än 6 ggr/år?		

		JA	NEJ
64.	Brukar barnet hosta mer än 2 veckor i samband med förkylning?		

Barnets bostad och miljö

65. Hur och var har barnet bott under uppväxttiden? Har barnet bott i stadsområde (tätort med stadsbebyggelse) eller ute på landet? Har barnet bott i villa/radhus? Sätt kryss i lämplig ruta. Ange också hur länge barnet bott på varje ställe. Börja med bostaden där barnet föddes. Avsluta med barnets nuvarande bostad.

Bostadsort	Bostad för barnet för hur länge	Typ av område		Typ av bostad	
		Stad	Landsbygd	Villa/radhus	Lägenhet

66. Kompletterande frågor kring barnets nuvarande eller tidigare bostad samt miljö. Har nedanstående förekommit? Sätt kryss i tillämpliga rutor i tabellen.

	Nuvarande bostad	Tidigare bostad	Aldrig
Tecken på fukt- eller mögelskada			
Förekomst av onormal eller instängd lukt			
Förekomst av imma/fukt på insidan av fönstren			
Heltäckningsmatta i rum där barnet sover			
Braskamin/vedeldning			
Större trafikerad väg eller mycket använd busshållplats inom 200 m från hemmet			
Bilverkstad, större garage eller bensinstation inom 200 m från hemmet			
Stall eller ladugård inom 200 m från hemmet			
Området utsatt för utsläpp eller damm från SSAB			
Området utsatt för utsläpp eller damm från gruva			

Barnets nuvarande bostad

67.			På vilket våningsplan?	Ungefärligt byggnadsår	Antal rum inkl kök	Ungefärlig bostadsyta
	Villa/radhus					
	Lägenhet					

68.	Hur många vuxna bor i hemmet?

69.	Hur många barn bor i hemmet?

70.	Har nuvarande bostad förändrats under de senaste 15 åren? Kryssa för lämpliga rutor.	JA	NEJ
	Tilläggsisolering		
	Fönster/dörrtätning		
	Annan större ombyggnad		

		Självdrag	Fläktstyrd	Värmeväxlare
71.	Typ av ventilation. Kryssa för lämpligt alternativ. (OBS gäller ej köksfläkten)			

		JA	NEJ
72.	Stänger ni eller sänker ventilationen när ingen är hemma?		

		JA	NEJ
73.	Blir det imma/fukt eller is på **insidan** av barnets sovrumsfönster vintertid?		
	Om "ja", hur högt går kondensen på fönstret? högst 5 cm		
	5-10 cm		
	mer än 10 cm		

74.	Vilken **städmetod** används **huvudsakligen** i hemmet? Kryssa **ett** alternativ	
	vanlig dammsugare	
	centraldammsugare	
	vattendammsugare	
	våttorkning	

Djur och fritid

75.	Har Ni nu eller har Ni tidigare haft husdjur någon gång under barnets uppväxt? Kryssa i tillämpliga rutor i tabellen	Nu	Tidigare under barnets uppväxt	Aldrig
	Katt			
	Hund			
	Kanin/marsvin/hamster			
	Annat pälsbärande djur			
	Burfågel			
	Annat husdjur			

		JA	NEJ
76.	Finns pälsdjur eller burfåglar i barnets hemmiljö?		
	Om "nej" beror detta på känd allergi/överkänslighet i familjen?		

		JA	NEJ
77.	Fanns pälsdjur i hemmet under någon period under barnets första två levnadsår?		

		Nu	Tidigare under barnets uppväxt	Aldrig
78.	Har eller har familjen haft jordbruk?			
	Har eller har familjen haft kor?			
	Har eller har familjen haft hästar/stall?			
	Har eller har familjen haft renar?			

		Nu	Tidigare under barnets uppväxt	Aldrig
79.	Rider barnet?			
	Rider annan familjemedlem?			

		JA	NEJ
80.	Idrottar barnet regelbundet inomhus?		
	Idrottar barnet regelbundet utomhus?		
	Idrottar barnet regelbundet i ishall?		

		Aldrig	Sällan	Ibland	Ofta
81.	Brukar barnet åka skoter?				

Rökning

Aktuella rökvanor i familjen. Kryssa i tillämpliga rutor i tabellen.

		Röker inte	Röker 0-4 cig/dag	Röker 5-14 cig/dag	Röker 15-24 cig/dag	Röker 25 cig/dag eller mer
82.	Far					
	Mor					
	Annan familjemedlem					

		Nej, aldrig	Ja, högst 1 ggr/vecka	Ja, mer än 1 dag/vecka
83.	Brukar någon röka inomhus eller under köksfläkten i hemmet?			

		JA	NEJ
84.	Förekommer rökning i annan miljö där barnet brukar vistas?		

	Förekom rökning hemma under barnets första levnadsår?	JA	NEJ
85.	Far rökte		
	Mor rökte		
	Annan familjemedlem rökte		

	Förekom rökning hemma under barnets andra levnadsår?	JA	NEJ
86.	Far rökte		
	Mor rökte		
	Annan familjemedlem rökte		

		JA	NEJ
87.	Rökte modern under graviditeten?		