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Epidemiology of asthma in primary school children

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

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To my dearest,
those I found
and those I lost

Vladimir: That passed the time.

Estragon: It would have passed in any case.

Vladimir: Yes, but not so rapidly.

(Samuel Beckett, *Waiting for Godot*, 1952)

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ABSTRACT

Childhood asthma has increased worldwide, although recent studies report a prevalence plateau in some western countries. This thesis sought to investigate the prevalence of asthma and the associated risk factor patterns from ages 7-8 to 11-12 with special emphasis on the hereditary component, and further to study prevalence trends at age 7-8 from 1996 to 2006 and the possible determinants of these trends.

The studies involved two cohorts from Kiruna, Luleå and Piteå: one previously identified cohort of 3430 children age 7-8 followed by yearly questionnaires until age 11-12 with 97% yearly participation. Skin-prick tests for allergic sensitisation were performed at ages 7-8 and 11-12 in subsets of 2148 and 2155 children respectively (88% of invited). In 2006 a new cohort of 7-8-year-olds was identified and examined identically. 2585 (96% of invited) and 1700 (90% of invited) participated in the questionnaire and skin-prick tests, respectively. The questionnaire included questions about symptoms of asthma, allergic rhinitis and eczema, and possible risk factors.

In the 1996 cohort, from age 7-8 to 11-12 the prevalence of physician-diagnosed asthma increased (5.7%-7.7%, $P<0.01$) while current wheeze decreased (11.7%-9.4%, $P<0.01$), and 34.7% reported ever wheee at ≥one occasion. Remission was 10% of which half relapsed during the study. Remission was significantly lower among sensitised children. The strongest risk factors for current asthma at ages 7-8 and 11-12 were allergic sensitisation (OR 5) and family history of asthma (OR 3). Several other significant risk factors, e.g. respiratory infections, damp house and low birth weight, had lost importance at age 11-12. At age 7-8, parental asthma was a stronger risk factor (OR 3-4) than parental rhinitis or eczema (OR 1.5-2). Sibling asthma had no independent effect. Biparental asthma had a multiplicative effect (OR 10). Maternal and paternal asthma was equally important, regardless of the child's sex and sensitisation status.

From 1996 to 2006 the prevalence of current wheeze and asthma at age 7-8 did not increase ($P=0.13$, $P=0.18$), while lifetime prevalence of ever wheeze and physician-diagnosed asthma increased ($P<0.01$, $P=0.01$). Symptoms of rhinitis and eczema were unchanged, despite 45% increase ($P<0.01$) in allergic sensitisation. For current asthma the adjusted population attributable fractions of sensitisation and parental asthma increased (35%-41%, 27%-45%). This was however balanced by decreased exposure to infections, maternal smoking and home dampness, resulting in stable asthma prevalence. Stratification by sex revealed that current wheeze increased in boys ($P<0.01$) but tended to decrease in girls ($P=0.37$), seemingly due to symptom persistence in males. Several asthma indices followed this pattern. The boy-to-girl ratio in exposure to all studied risk factors increased, which may explain the sex-specific prevalence trends in wheeze.

Conclusions: The prevalence of current asthma and wheeze did not increase statistically significantly. However, the risk factor pattern has changed considerably since 1996, which will presumably affect the clinical features of childhood wheeze in this region. Sex-specific trends in wheeze can be explained by changes in exposure, and trends in risk factors should be explored parallel to prevalence trends.

Key words: Asthma, wheeze, child, allergic sensitisation, prevalence, remission, risk factor, trend.

SVENSK SAMMANFATTNING

Under den senare hälften av 1900-talet ökade förekomsten av astma hos barn betydligt över hela världen. De senaste 10-15 åren tycks denna ökning ha avstannat i västvärlden, där ökningen först upptäcktes. Ett flertal riskfaktorer för astma har identifierats, men ännu saknas en övergripande förklaring av ökningen. De flesta fall av astma debuterar i barnåren, men fullständig remission och senare återinsjuknanden är vanliga. Syftet med denna avhandling var att studera förekomsten av astma vid 7-8 och 11-12 års ålder (åå) och vilka riskfaktorer som påverkar vid respektive ålder, samt att i detalj studera effekten av astma och allergier i familjen på astma vid 7-8 års ålder. Vidare, att studera trender i astmaförekomst och riskfaktorer hos 7-8-åringar från 1996 till 2006.

Samtliga barn (n=3525) i årskurs 1-2 (7-8 år) i Kiruna, Luleå och Piteå kommuner inbjöds 1996 till en enkätstudie av astmatiska besvär, allergiska sjukdomar och tänkbara riskfaktorer. 3430 barn (97%) deltog, och årliga enkätuppföljningar genomfördes till 11-12 års ålder med 97% årligt deltagande. Pricktester för allergisk sensibilisering genomfördes i Kiruna och Luleå, där 2148 och 2155 barn (88%) deltog 1996 respektive 2000. År 2006 inbjöds alla barn från samma områden i årskurs 1-2 (7-8 år) till enkäter och pricktester, med samma metod som 1996. 2585 barn (96%) deltog i enkäten och 1700 barn (90%) i pricktestet. Genomgående var 48-50% av barnen flickor.

Från 7-8 till 11-12 åå ökade förekomsten av läkardiagnostiserad astma statistiskt säkerställt från 5.7% till 7.7%. Samtidigt minskade förekomsten av pipande/väsande andning (pip/väs) statistiskt säkerställt från 11.7% till 9.4%. Vid 11-12 åå hade vart tredje barn upplevt pip/väs vid minst ett tillfälle. Årligen blev 10% av föregående års astmatiker symtom- och medicinfria (remission), men hälften av dessa fick återfall under studietiden. Remissionen var avsevärt lägre hos barn med allergisk astma. De starkaste oberoende riskfaktorerna för astma vid 7-8 och 11-12 åå var allergisk sensibilisering (5 gånger ökad risk) och astma i familjen (3 gånger ökad risk). Ett flertal viktiga oberoende riskfaktorer vid 7-8 åå, bl a nedre luftvägsinfektioner, fuktskador i hemmet och låg födelsevikt, hade förlorat sin betydelse vid 11-12 åå. Astma hos någon förälder var en starkare riskfaktor (3-4 gånger ökad risk) än hösnuva eller eksem hos någon förälder (1.5-2 gånger ökad risk) för astma hos barnet vid 7-8 åå. Astma hos syskon var ej en oberoende riskfaktor. Astma hos båda föräldrarna hade en multiplikativ effekt, med 10 gångers riskökning. Samtliga dessa riskanalyser korrigerades för effekten av andra viktiga riskfaktorer för astma.

Förekomsten av pip/väs respektive symtomgivande astma under de sista tolv månaderna bland 7-8-åringar förändrades inte 1996-2006, medan livstidsprevalensen av pip/väs någonsin och läkardiagnostiserad astma ökade, resultaten statistiskt säkerställda. Förekomsten av symtom på hösnuva och eksem

förändrades inte, trots att förekomsten av allergisk sensibilisering ökade med hela 45%. Den andel astma som kunde tillskrivas sensibilisering respektive astma hos föräldrarna ökade (35%-41% och 27%-45%). Samtidigt minskade förekomsten och betydelsen av riskfaktorer i omgivningen, ffa nedre luftvägsinfektioner, passiv rökning och fuktskador hemma, vilket sannolikt förklarar varför astman inte hade ökat trots den stora ökningen i sensibilisering. Könsstratifierade analyser visade att förekomsten av pip/väs och andra astmasymtom hade ökat bland pojkar (statistiskt säkerställt), men tenderat att minska bland flickor mellan 1996 och 2006. Samtidigt hade förekomsten av samtliga studerade riskfaktorer ökat bland pojkar relativt sett flickorna, vilket är en möjlig förklaring till de könsspecifika trenderna i astmasymtom.

Således har studierna i avhandlingen visat hur riskfaktormönstret för astma förändras med åldern beroende både på effekter på nyinsjuknande i astma och även på dess persistens. Skillnaderna mellan ärftlighet för astma och för allergiska sjukdomar bör beaktas vid framtida studier av dessa sjukdomar. Vidare har studierna i avhandlingen visat att förekomsten av astmasymtom, hösnuva och eksem ej ökat i Norrbotten under de senaste tio åren. Detta har skett trots en fortsatt stor ökning i förekomst av allergisk sensibilisering. Riskfaktormönstret för astma har förändrats och andelen allergisk astma har ökat, vilket påverkar sjukdomens förlopp och prognos. Könsspecifika trender i förekomst av astma kunde förklaras med olika trender i exponering för riskfaktorer. Metoden att studera trender i sjukdomsförekomst och riskfaktorer parallellt är relativt obeprövad och bidrar till förståelsen av vad som reglerar förekomsten av astma över tid.

SELECTED ABBREVIATIONS

ADRB2	Beta-2-adrenergic receptor
aPAF	Adjusted population attributable fraction
CAP	Solid phase assay for measurement of IgE (Pharmacia, Sweden)
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
EAACI	the European Academy of Allergology and Clinical Immunology
FEV_1	Forced expiratory volume during the first second
FVC	Forced vital capacity
FEV%	FEV_1/FVC ratio
GINA	the Global Initiative for Asthma
GPRA	G-protein coupled receptor for asthma susceptibility
HEP	Histamine equivalent prick test
IgE	Immunoglobulin subclass E
IL9R	Interleukin-9 receptor
IL4RA	Interleukin-4 receptor alpha
ISAAC	the International Study of Asthma and Allergies in Childhood
NO	Nitric oxide
OLIN	Obstructive Lung Disease in Northern Sweden Studies
OR	Odds ratio
RR	Risk ratio
RSV	Respiratory syncytial virus
SPT	Skin prick test

ORIGINAL PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. ***Bjerg-Bäcklund A*, Perzanowski MS, Platts-Mills T, Sandström T, Lundbäck B, Rönmark E.** Asthma during primary school ages – prevalence, remission and the impact of allergic sensitization. *Allergy* 2006; 61: 549–55

II. ***Bjerg A,* Hedman L, Perzanowski MS, Platts-Mills T, Lundbäck B, Rönmark E.** Family History of Asthma and Atopy: In-depth Analyses of the Impact on Asthma and Wheeze in 7- to 8-Year-Old Children. *Pediatrics* 2007; 120: 741-8.

III. ***Bjerg A*, Sandström T, Lundbäck B, Rönmark E.** Sex-specific trends in childhood asthma and wheeze – Prevalence and risk factors in Sweden 1996-2006. *Submitted.*

IV. ***Bjerg A,* Lundbäck B, Platts-Mills T, Perzanowski MS, Rönmark E.** Changes in the risk factor pattern of childhood asthma from 1996 to 2006. *In manuscript.*

INTRODUCTION

"…'Attend to the game, gentlemen! Attend to the game!' So absorbed was his attention that he even forgot to expectorate. The consequence was that his chest gave forth rumbling sounds like those of an organ. His wheezing lungs struck every note of the asthmatic scale, from deep, hollow tones to a shrill, hoarse piping resembling that of a young cock trying to crow."

The French inn-keeper Mr. Follenvie depicted by Guy de Maupassant more than a century ago still holds as a case description of chronic, uncontrolled asthma. Fortunately, whereas the world is experiencing an asthma epidemic, the miserable fate of Mr. Follenvie is today usually prevented by early diagnosis and adequate treatment. The causes of the massive increase in asthma prevalence during the last half-century however remain unclear.

Just like asthma has increased, so has the research focused on asthma and allergic diseases. As the level of knowledge has risen, new research fields have unraveled and evolved. Epidemiological, experimental and genetic studies have all contributed significantly. Still, the central questions – who, when, why and how? – remain to be answered. Modern epidemiology serves the main purpose of surveying and hypothesis generation. By describing disease occurrence, disease manifestation, and what factors predispose for or protect against disease, epidemiology draws the maps and paves the roads for mechanistic investigations.

This work is an epidemiologic study of childhood asthma. It was conducted in Northern Sweden as part of the Obstructive Lung Disease in Northern Sweden (OLIN) studies. Since the start in 1985, the OLIN studies have evolved into one of the largest studies of respiratory disease in the world, including at some time more than 50000 study subjects. In the process of this work, the international perspective has been augmented by collaboration with the Columbia University and the University of Virginia, USA.

Applying modern epidemiology to large cohorts of school children, the aim of this investigation was to measure the occurrence and recent time trends of asthma, wheeze and allergic sensitisation. Moreover, it sought to characterise the spectrum of these disorders and the predictive factors.

BACKGROUND

The prevalence of asthma has increased worldwide.[1-4] To some extent the explanations for this increase are changed diagnostic procedures and increased diagnostic activity,[5-7] but symptoms suggestive of asthma, such as wheeze, have also increased considerably.[8-10] The highest prevalence of asthma and wheeze has been reported from Australia,[11 12] New Zealand,[13] inner-city United States[14] and the United Kingdom,[9 15 16] whereas the lowest rates have been reported from rural areas in Eastern Europe and Africa.[10 17 18] The prevalence in Sweden is similar to that in most countries in Western Europe except the British Isles.[10 19-21] A variety of factors, several of which remain to be clarified, account for this huge geographical variation.

In part, the prevalence of asthma follows a gradient of westernisation,[10] characterised by high economic standard and urbanisation.[18 22] Several attempts have been made to give a comprehensive explanation of the rise in asthma. The house mite hypothesis of the 1980's[23] was largely abandoned for the hygiene hypothesis[24] but recently diet, sedentary lifestyle and obesity have received much attention.[25-28] To date there is no sufficient explanation of the worldwide increase, or of the considerable geographical variation in asthma prevalence.

Interestingly, several recent studies report that the prevalence of asthma is no longer increasing or has even decreased during the last decade.[11 29-31] This plateau also seems to track the gradient of westernisation, and has not been limited to countries with a very high prevalence.[10 32] Very few studies have attempted to explain this development through the study of risk factor trends.[33-35]

The incidence of asthma peaks during childhood.[36-39] Although remission is also high in childhood,[40 41] a large proportion of wheezing children have continuing symptoms into adulthood, or relapse after a remission in adolescence.[39] Early-life wheezers have lower lung function (FEV1, FEV%)[38 42] but lung function does not seem to decline further after school age,[39 41] and not all children with low lung function continue to wheeze.[38] Thus, several of the predictors of childhood wheeze are also risk factors for adult asthma.

This section addresses the current knowledge of asthma, focusing on the epidemiological aspects. A brief disease characterisation is followed by lessons learned from the epidemiology of asthma: the geographical variation in occurrence and recent time trends, its natural history and the associated predictive factors, with a special emphasis on allergic sensitisation and hereditary asthma.

THE CONCEPT OF ASTHMA

Asthma is an inflammatory disease of the airways with variable airway obstruction, which responds to triggering factors and is partially or completely reversible, either spontaneously or by stimulation with certain drugs. Histopathologically, asthmatic airways are characterised by hyperplastic smooth muscle with impaired relaxation, infiltration with inflammatory cells such as eosinophils and mast cells, and abundant mucus producing goblet cells and sub-mucosal glands. In the acute phase, key features are neural signalling, release of toxic inflammatory mediators, and plasma leakage into the tissue and alveoli. Bronchoconstriction, oedema and mucus all contribute to the clinical presentation with wheezy breathing, breathlessness and cough.[43 44]

In early childhood, however, wheeze is common and not always due to asthma. For symptoms during the first two years of life, the term "wheezy bronchitis" is therefore used. At school age, the spectrum of wheezing disorders is still heterogenous in terms of clinical presentation, prognosis and causal factors. In all, this has led to the idea of characterising asthma more as a syndrome than a distinct disease entity.[45] This heterogeneity will be discussed later.

OCCURRENCE AND TIME TRENDS OF ASTHMA

The reports of an increase in the prevalence of asthma during the second half of the 20th century are numerous.[2 3 9 46-48] Although several of these studies were not properly designed to evaluate prevalence trends (i.e. did not use identical methods on similar populations at different time points), there is at present no doubt that the increase was real.[5 46 48]

However, the magnitude of the increase cannot be measured with certainty, as the prevalence of a medical diagnosis is biased by changes in diagnostic criteria, procedures and activity. Neither do studies of mortality provide an answer. Deaths from asthma increased in several Western countries from 1977 to 1984,[49] but this trend was later broken while the prevalence of an asthma diagnosis was still increasing,[50] likely due to improved diagnostics and medications. Neither do objective methods such as lung function, bronchial hyperresponsiveness and inflammatory activity (exhaled NO, induced sputum) correctly measure trends in asthma, as they all measure distinct features of asthma, but do not define asthma. Repeated cross-sectional surveys of symptoms, in defined similar populations of the same age at different time points using identical methods, is at present the most correct way to study prevalence trends.[10]

In children, asthma is probably a more heterogeneous condition than in adults, which further supports the rationale for studying the prevalence of symptoms rather than diagnosed cases. The presence of wheeze during the last twelve months strongly suggests asthma in children after the age of two years.[51 52]

Several studies have focused on childhood wheeze and have firmly established the prevalence increase worldwide.[53-55]

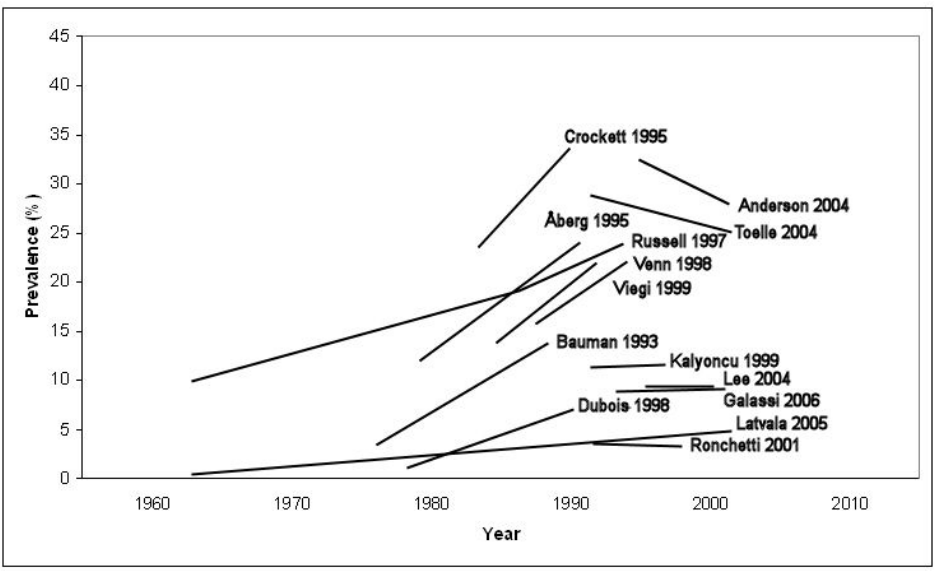

Figure 1. International time trends in the prevalence of wheeze and asthma.

In 2001 the first reports that the prevalence of asthma was no longer increasing in some areas arrived.[56] A number of studies followed, some with data from more than two time points, reporting no increase,[33 34 57-59] or even a decrease.[11 29] During the last ten to fifteen years, the prevalence increase thus seems to have halted in several westernised regions.[10 11 15 32 56] Still, there are slightly diverging prevalence trends within the same geographical region, as observed in the UK.[16 29 60] For children age 13-14, the recent ISAAC phase I-III study reported a slight decrease in the majority of Western European countries, but increases in most of Eastern Europe.[10] The prevalence plateau seems to have occurred where the prevalence increase was first observed, not where the prevalence was highest. Hypothetically, as economic development continues in several underprivileged regions, the prevalence of asthma will continue to increase and subsequently eventually also halt.

RISK FACTORS FOR ASTHMA AND WHEEZE

The considerable geographical variation in the prevalence of and trends in asthma and wheeze has naturally attracted much scientific attention, and studies comparing different geographical regions and studies of regions with high economic growth have contributed significantly.[61-63] The association with a westernised lifestyle suggests that urbanisation and socio-economic status account for the increase in asthma.[18 64] Of the large-scale attempts to explain the prevalence increase and the geographical variations, the most influential one today is the hygiene hypothesis,[24] which suggests that early life infections and exposure to microbes[65-67] decrease the risk of allergic sensitisation through immunomodulatory mechanisms.[68] This is supported by findings of lower prevalence of allergic sensitisation and, to some extent, asthma among children raised in farming conditions,[69-71] who have several older siblings[72] or who keep indoor pets.[73-75] An increase in air pollution[76-78] and lately also high body mass index (BMI) and a sedentary lifestyle[79-81] have also been discussed as the main explanations for the prevalence increase and variation. To date, there is no single explanation for the variations in asthma prevalence. However, the confusion of asthma with allergic sensitisation, rhinitis and eczema in wordings like "allergic/atopic disease" has very likely contributed to the contradictory findings. Having multiple siblings may protect against allergic sensitisation but predispose to wheeze through the exposure to multiple severe respiratory infections. The importance of correct disease characterisation is discussed below.

When studied in more detail, a vast number of risk factors for childhood asthma have been identified,[82] some of which appear consistently across the majority of studies. Allergic sensitisation, a positive family history of asthma, lower respiratory tract infections, male sex, inhaled fumes such as passive tobacco smoke or smoke from gas stoves or indoor wood fire, and low birth weight are all established risk factors for childhood asthma and wheeze.[20 39 83-96] This thesis focused mainly on two of the most important risk factors: allergic sensitisation and a family history of asthma, which are presented in detail below.

Allergic and non-allergic asthma

Throughout the majority of studies of asthma in countries with a westernised lifestyle, allergic sensitisation is the strongest risk factor for asthma in children.[39 86 87 97] In the literature, asthma is commonly regarded as an "allergic disease", although less than half of asthma in children is attributable to allergic sensitisation as demonstrated in a recent review.[98] However, this proportion varies to a great extent globally, is positively related to gross national income,[62] and seems to decrease with age.[99] The latter is in part a cohort effect, as the recent prevalence increase in children will be carried to adulthood. The "allergic (atopic) march" refers to the development of infant eczema, pre-school asthma and subsequent school-age

rhino-conjunctivitis, in subjects with allergic sensitisation.[100] However, far from all sensitised subjects develop asthma, and the time span from sensitisation to subsequent asthma is not well known. Asthma and allergic sensitisation have different risk factors,[20] and asthma and different allergic conditions are inherited in different patterns.[101 102] Thus, asthma and allergic sensitisation have both shared and separate features.

The division of asthma into allergic and non-allergic phenotypes, based on the presence of allergic sensitisation[103] was recognised more than 60 years ago.[104] Allergic asthma is associated with persistence of wheeze,[37 39 105] more frequent attacks of wheeze,[106] and with wheeze requiring hospital admission.[106] Interestingly, higher levels of specific IgE seem to correlate with more frequent episodes of wheeze.[107] Also, subjects with allergic wheeze have more bronchial hyperreactvity and evidence of airways obstruction (FEV%), and are more frequently diagnosed as having asthma.[108]

Moreover, the risk factor patterns for allergic and non-allergic asthma differ, as environmental tobacco smoke, short time of breast feeding and respiratory infections have been related to non-allergic but not to allergic asthma.[37 108-110] Also, risk factors for allergic sensitisation such as parental allergy[111] and urban living[112] will thus indirectly be related to allergic asthma. The histopathologic and chemokine profiles of allergic and non-allergic asthmatic airways show both similarities and differences.[113 114] Allergic asthma is generally associated with higher counts of airway eosinophils and lower counts of neutrophils[115] and thus responds better to inhaled corticosteroids.[116-118] Thus, there is some understanding of the differences between allergic and non-allergic asthma, but the mechanisms are far from fully elucidated.

Inheritance of asthma

A positive family history of asthma is also one of the most important risk factors for asthma. According to a recent review, it increases the risk by 3-5 times.[119] Unlike several other risk factors, it is associated with asthma seemingly at all ages,[7 89 120 121] which may in part be explained by an association with asthma persistence.[122] It is also associated with both allergic and non-allergic asthma.[108 110] Unlike the allergic and non-allergic asthma phenotypes, a family history of asthma does not clearly define a distinct phenotype.

The complex and interesting genetic associations for asthma have only begun to unravel, and epidemiologic studies of asthma inheritance serve to guide future studies in this field. Clearly, asthma is a polygenetic disease and does not follow mendelian inheritance patterns.[123] Rather, it depends on interactions between genes and environment[124-126] as indicated by a high heritability[127] and co-existing strong associations with environmental and lifestyle factors. The importance of these factors is underlined by the prevalence increase, which occurred over too short a time period for genetic changes to have taken place. So far, none of the identified

predisposing genes, such as the IL9R, IL4RA, GPRA and ADRB2 genes, have shown a very strong association with asthma.[124] Important gene-environment interactions have been observed for time of breast feeding,[128 129] environmental tobacco smoke[130 131] and pet allergen exposure.[73 132] Some studies have addressed the possibility of different effects of parental asthma and allergic disease,[89 133] while others refer to "parental atopic disease"[128 134 135] where different conditions are combined.

Parent-of-origin effects, i.e. whether maternal or paternal asthma confers the greater risk, is still under debate.[119] There is some evidence that maternal disease is more important in children before the age of five,[131 133 135] whereafter the importance of paternal disease increases with age.[101 133 136-138] However, there are studies demonstrating similar risks of paternal and maternal disease,[139 140] as well as a greater effect of maternal disease also in teenagers.[89] One plausible mechanism is that exposure to the mother is greater *in utero* and during breast feeding, leading to a stronger association with maternal asthma in infants. Prolonged breast feeding by a mother with asthma is seemingly associated with wheeze, impaired lung function and airway inflammation in the child.[128 141-143]

Even in the absence of parental asthma, asthma in a sibling could theoretically increase the risk in the study child through several mechanisms, and this has some support in epidemiological studies.[89 144 145] Sibling asthma may reflect the children's shared risk environment in the home. Also, the possibility of asthma genes with limited penetrance only giving rise to a symptomatic phenotype in a child's sibling and not in the parents cannot be excluded. Moreover, "silent" asthma genes in the parents can interact with the environment of their children – which is probably an important explanation of the asthma epidemic – and manifest as asthma only in the studied child and its siblings. Finally, increased awareness may lead to detection of asthma in the study child and its siblings, which in the parents was not recognised as asthma but rather as sub-clinical symptoms.

ASTHMA – NOT A SINGLE DISEASE ENTITY

As mentioned previously childhood wheeze and asthma are heterogeneous conditions, and causative factors, age at onset, natural history, severity, eliciting factors, remission probability and responsiveness to medications vary between individuals. In response to the question "What is asthma?", it has even been suggested to "abandon asthma as a disease concept" and replace it with a syndrome concept.[45 146] A broad disease definition, however, enables the researcher to identify more heterogeneous subgroups in order to eliminate some of the "noise" present in the research field. A phenotype refers to certain visible characteristics resulting from gene-environment interactions.[146] Asthma has been phenotyped on the basis of onset age and prognosis,[38 122 147] severity (e.g. the GINA classification),[148] biomarker profile (e.g. eosinophilic/neutrophilic asthma),[149] risk/trigger/prognostic

factors (e.g. allergic sensitisation)[39] and clinical presentation (e.g. cough-variant asthma and exercise-induced asthma). This thesis was not focused on asthma phenotypes, but that subject still has important implications for the general discussion.

LONGITUDINAL STUDIES OF CHILDHOOD ASTHMA

Asthma during the school ages has not been studied to the same extent as infant asthma. There have been several cross-sectional but fewer longitudinal studies of school age children. However, among the available longitudinal studies of childhood asthma through adolescence and into adulthood, a few studies have contributed outstandingly to the present knowledge. Three of these are presented below.

The British 1958 birth cohort study[37] enrolled 18558 subjects born in 1958 and is at present the longest follow-up of childhood wheeze with repeated assessments. It has contributed importantly to the knowledge of the natural history of asthma: Of children with wheeze before age seven the prevalence of wheeze was 50% (age 7), 18% (age 11), 10% (age 16), 10% (age 23) and 27% (age 33), illustrating that remission in adolescence is often transient.[37] Children with wheeze before the age of seven but with no wheeze at ages 17, 23 or 33, still had an increased risk of reduced lung function at age 33,[150] and of wheezing at age 42.[151] A number of risk factors for childhood wheeze were identified while allergic sensitisation was constantly associated with wheeze also in adolescents and adults. Allergic sensitisation and cigarette smoking were associated with subsequent relapse of childhood wheeze.[37]

The Dunedin Multidisciplinary Health and Development Study[39] followed a birth cohort of 1037 children from age three and onwards. Among the 613 study members remaining in the study at age 26, 27% were currently wheezing, and 73% and 51% had experienced at least one or more than one wheezing episode, respectively. Nearly half of current wheezers at age 26 had a previous remission period and only 17% had no wheeze before age 26, underlining how asthma typically develops before adulthood. Late-onset wheeze, allergic sensitisation and airway hyperresponsiveness at age nine were associated with persistent or relapsing wheeze at age 26. The findings were similar to the small study of high-risk children in Poole, UK.[152] No loss of lung function occurred after school age, consistent with the Melbourne Asthma Study.[41] This latter study also found that loss of lung function was most pronounced in subjects with severe asthma and that children with infrequent episodes of wheeze had milder asthma as adults.

In the Tucson Children's Respiratory Study 1246 children born in 1980-84 were enrolled at birth,[153] thus providing detailed knowledge of very early life events such as respiratory infections and early allergic sensitisation. Its main contribution, however, has been in the field of phenotyping asthma from age at onset and

prognosis. At age six, the study children were divided into never wheezers (no previous wheeze), transient early wheezers (wheeze before age three but not at age six), late-onset wheezers (onset after age three) and persistent wheezers (wheeze both at ages three and six). Transient early wheeze was associated with low maternal age and maternal smoking.[97] Wheeze in adolescence (persistent and late-onset wheeze) was divided into atopic and non-atopic (mainly viral) wheeze on the basis of allergic sensitisation.[97] At age 16, persistent and transient early wheezers both had impaired lung function, although the latter group was symptom-free.[154] Late-onset wheezers, however, had normal lung function.

ALLERGIC SENSITISATION

Allergic sensitisation, or atopy, refers to the development of specific antibodies of the E subclass (IgE) against allergens.[103] The term "allergic sensitisation" is used throughout this thesis, except in papers I and II where "atopy" was used. This nomenclature is only applicable to individuals where specific IgE against allergens is objectively demonstrable, directly by serum analyses or indirectly by skin-prick tests.[103] The correlation between direct and indirect methods in detecting allergic sensitisation is high.[155 156]

The prevalence of allergic sensitisation, like asthma, in children displays a significant global variation. The prevalence of a positive skin test varied from 2% in rural Ghana to 45% in Hong Kong, China.[62] In Sweden the prevalence, depending on the age of the participants, was 20-27%,[20 62 112 156 157] with the higher prevalence in northern study centers. This is quite similar to reports from Iceland, Italy and Germany.[62] The prevalence of allergic sensitisation has increased according to several studies in children[158 159] and adults,[160] while other recent studies report no increase or a decrease.[22 32 33 161] Allergic sensitisation has a strong genetic component,[111 162] although environmental risk factors such as tobacco smoke, have been demonstrated.[163] Prenatal exposure to farming conditions,[164 165] keeping indoor furred pets[75] and having multiple siblings[166 167] have all been associated with decreased risk for allergic sensitisation, although the results are far from unanimous.[168 169] These and similar observations of a protective effect of microbial exposure and infections gave rise to the hygiene hypothesis mentioned previously.

NORTHERN SWEDEN

The study area was three municipalities in the northernmost province of Sweden, Norrbotten. This geographical region is characterised by a cold (average yearly temperature around 0°C), dry climate, which creates indoor environments virtually free of mites and cockroaches. In 1996 the prevalence of allergic sensitisation at age 7-8 was 21%[20] which conforms to previous findings in Sweden,[62 157] and the cumulative incidence over the next four years was 14%.[170] Owing to the absence of mites,[171] furred pets and pollen dominate the sensitisation profiles.[20] This has been used as part of the methodology in a previous thesis from this cohort.[172]

The prevalence of physician-diagnosed asthma at age 7-8 in the first OLIN paediatric cohort (1996) was 6%.[20] The incidence from ages 7-8 to 8-9 was 9/1000/year[173] but slightly lower until age 10-11.[73] The prevalence of wheeze in the last twelve months was 12%,[20] which conforms well to recent findings in 6-7-year olds in central Sweden where the prevalence was 10% in two cohorts studied eight years apart.[10] The major risk factors for asthma at age 7-8 in the first study cohort were allergic sensitisation and a family history of asthma.[20]

The two paediatric study cohorts which this thesis are based on were part of the Obstructive Lung Disease in Northern Sweden (OLIN) studies. These started in 1985 with a study of adult asthma and chronic bronchitis,[174] and has since expanded to enrolling more than 50000 subjects at any time point in both cross-sectional and longitudinal studies of obstructive airway diseases including asthma, chronic obstructive pulmonary disease and obstructive sleep apnoea, allergic sensitisation and its molecular epidemiology, health economics and quality of life. To date the OLIN studies have resulted in seven doctoral theses,[172 175-180] two of which[172 176] were based on the first paediatric cohort also studied in this thesis. At present the OLIN project is involved in international collaboration worldwide, from the United States in the west to New Zealand in the east, and has been included in international doctoral theses.[181-183] OLIN is one of few studies where large population-based samples have been followed for more than 20 years. Other examples are the Bergen-Hordaland studies in Norway[184] and the Po River Delta and Pisa epidemiological studies in Italy.[76 185] Respiratory diseases have also been included as part of a larger study subject area, as in the Copenhagen City Heart Study.[186]

AIMS

The overall aims of this thesis were to study the occurrence and change over time of wheezing conditions, asthma, allergic diseases and allergic sensitisation in primary school children, and to explore the associations with possible determinants of wheeze and asthma.

SPECIFIC AIMS

Disease and risk factors *by age* from age 7-8 to 11-12

To study the development of prevalence of wheeze and asthma

To measure the remission of asthma

To explore the association of asthma and wheeze with possible risk factors and to compare the risk factor patterns between ages 7-8 and 11-12

Disease and risk factors at age 7-8 *by time* from 1996 to 2006

To study time trends in the prevalence of wheezing indices, asthma, rhinitis and eczema, as well as allergic sensitisation

To investigate trends in risk factors parallel to trends in prevalence

To evaluate sex-specific time trends in asthma and wheeze and the associated risk factors

Inheritance of asthma

To assess the impact of different aspects of a family history of asthma and allergic disease on asthma at age 7-8

To evaluate parent-of-origin effects

To explore differences in the impact of heredity by sex and sensitisation status of the child

METHODS

The studies included in this thesis applied epidemiological methods to two large population-based samples of children in Northern Sweden, the OLIN paediatric cohorts I and II.

STUDY AREA AND POPULATIONS

The first two papers in the thesis (I and II) are based on the first OLIN paediatric study, starting in 1996. The following two papers (III-IV) are based on comparisons between the 1996 cohort and the second OLIN paediatric study, which started in 2006. Both paediatric studies were conducted in Kiruna, Luleå and Piteå, three of the largest municipalities of Norrbotten, Sweden. Kiruna, an inland municipality, had 26000 inhabitants in 1996. Luleå and Piteå are coastal municipalities, with 70000 and 40000 inhabitants respectively in 1996.

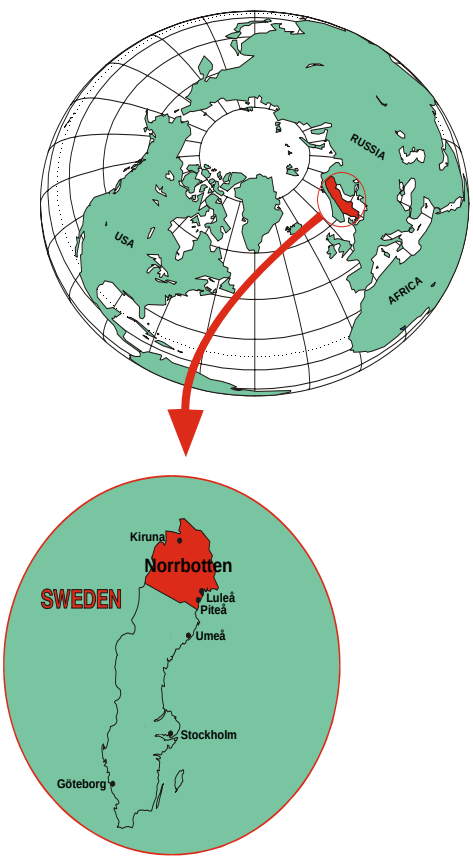

Figure 2. Study area.

First paediatric cohort

The first OLIN paediatric study had the purpose of surveying respiratory symptoms, asthma, and allergic conditions during school age, and further to identify associated risk factors.

In 1996, all school children in first and second grades (n=3525, age 7-8 with few exceptions) in the three municipalities were invited to answer a parental questionnaire, discussed below. The children in Kiruna and Luleå were also invited to skin prick testing.

These school classes were then followed longitudinally so that each year all children in the classes were invited, i.e. they were treated as an open cohort with repeated cross-sectional assessments while also maintaining the original cohort for longitudinal analyses. The children were followed through yearly questionnaires and repeated skin prick testing until the end of upper secondary school. This thesis includes the study years 1996-2000. The participation rate was 97% yearly, as n=3430, n=3453, n=3446, n=3406 and n=3395 children participated each year 1996-2000. Of the 3430 participants in 1996, 3151 (92%) also participated in 2000. Details on participation are given in table 1 and figure 3.

Second paediatric cohort

In 2006, as in 1996, all children in first and second grade (median age 7-8) in the same three municipalities were again invited to a parental questionnaire. Birth rates were lower in the late 1990's, and of the 2704 invited children 96% (n=2585) participated. Skin prick tests, discussed below, were also performed using the same method as in 1996.

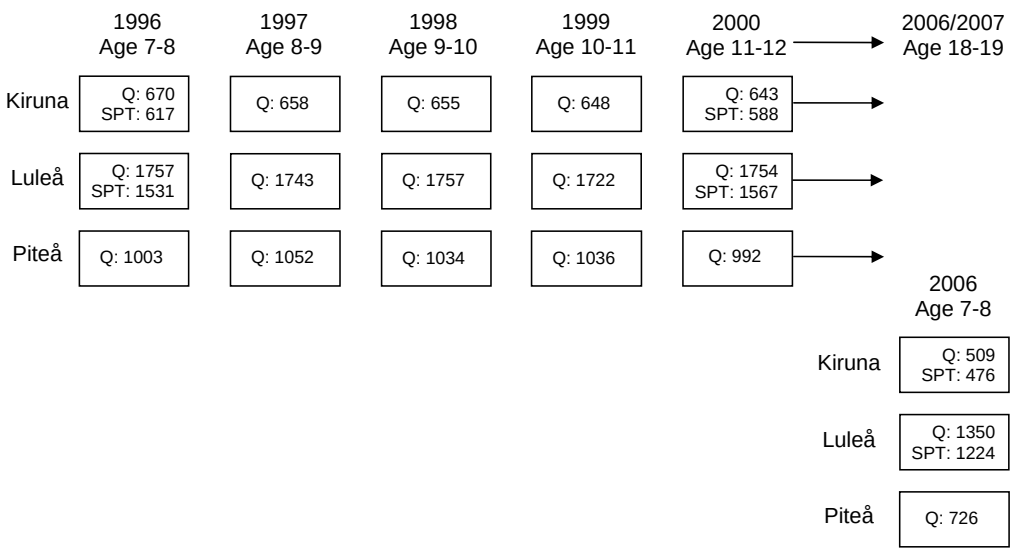

Figure 3. Number of participating children in the two OLIN paediatric cohorts by study centre.
Q: questionnaire, SPT: skin prick test.

QUESTIONNAIRES

The questionnaire was based on the International Study of Asthma and Allergy in Childhood (ISAAC) core questions.[187] The original ISAAC project questionnaire was developed using standardised, comprehensible and translatable questions for the study of asthma and allergies around the world. The eleven-page parental questionnaire used in the OLIN paediatric study had added questions about symptoms of wheeze and allergic conditions, physician's diagnoses of asthma, allergic rhinitis and eczema, medication use and possible determinants of disease, and was distributed by the children's teachers. The questionnaire has been described in detail.[20 176] The same questionnaire was used in 1996 and 2006, with a few questions added or removed (e.g. questions about new medications available in 2006 and additional questions about food allergy). The outcomes and risk factors included in this thesis were identical in 1996 and 2006.

Clinical validation

A clinical validation of the questionnaire was performed in a subset of 215 symptomatic and 104 randomly selected healthy children in 1997. The question of physician-diagnosed asthma had ≥99% specificity and ~70% sensitivity when compared to predefined criteria for a diagnosis of childhood asthma, and comparisons with local paediatricians' assessments gave similar results. The validation has been described in detail by Rönmark *et al.*[20 110 176] and is mentioned here for confirming the validity of the questionnaire results.

Table 1. Participants in the first and second OLIN paediatric studies and the study methods.

		First OLIN paediatric study					Second study
	City	1996	1997	1998	1999	2000	2006
Questionnaire (n)	KLP	3430	3453	3446	3406	3389	2585
% of invited		97%	98%	98%	97%	97%	96%
% girls		49%	49%	49%	49%	49%	48%
Validation	KLP	258					
Skin prick test	KL	2148				2155	1700
% of invited		88%				88%	90%
% girls		50%				48%	50%
Serum	KLP	228				194	

SKIN PRICK TESTS

The children in Kiruna and Luleå were invited to skin prick tests for allergic sensitisation. The tests were performed in the first cohort in 1996 and 2000 with a participation rate of 88% each year (n=2148 and n=2155 in 1996 and 2000 respectively). Similarly, in 2006 the children in the second cohort in Kiruna and Luleå were invited and 90% (n=1700) participated.

Methodology

Testing was performed identically on all occasions using a lancet on the forearm, following European Academy of Allergology and Clinical Immunology (EAACI) recommendations.[188] Ten standard allergens were used: birch, timothy, mugwort, cat, dog, horse, *Dermatophagoides pteronyssinus, D. farinae, Cladosporium herbarum* and *Alternaria alternata*, with histamine 10 mg/ml as positive control and glycerol as negative control (Soluprick, ALK, Hørsholm, Denmark). The potency of the allergens was 10 HEP (histamine equivalent prick test) except the two moulds, which were 1:20 weight/volume. A mean wheal diameter of ≥3 mm measured after 15 minutes was considered positive, and allergic sensitisation was defined as at least one positive test. Three specifically trained study nurses performed the testing in 1996 (LG, KKB, ER) and in 2000 (KKB, AJ, ER). In 2006 the testing was carried out by two specifically trained study nurses (SS, ER) and the present author. The same study supervisor attended the testing on all three occasions.

Serum validation

A validation of the skin prick tests was performed in 1997 in a stratified sample of 228 children from the first cohort. This has been described in detail previously.[171 172 189] Likewise, in 2006 serum was drawn from a sample of 50 children from the second cohort (unpublished data). On both occasions, the sensitisation profiles assessed by CAP showed an excellent correlation between a wheal size of ≥3 mm and specific IgE >0.35 I.U./ml.

DEFINITIONS

The variables of importance to this thesis are described below, using the translated question where appropriate. All study variables except allergic sensitisation were based on the questionnaire reports. Synonymous definitions appearing in individual papers are also given.

Outcomes

Ever wheeze – "Has the child ever had wheezing or whistling in the chest?".[187]

Current wheeze – Wheezing symptoms during the last twelve months prior to the study (named "*wheeze in the last 12 months*" in papers I and II).[20]

Infrequent/frequent wheeze – Three or fewer/four or more episodes of wheeze during the last twelve months.

Wheeze before age 7-8 – Report of ever wheeze but not current wheeze at age 7-8 years.

Ever asthma – "Has the child ever had asthma?".[187]

Physician-diagnosed asthma – "Has the child been diagnosed by a physician as having asthma?".[20]

Asthma medications – "During the last twelve months, how often has the child taken medicines for asthma?".[20]

Current asthma – *Physician diagnosed asthma* and either *current wheeze* or use of *asthma medications*, or both.[20]

Remission from asthma – *Current asthma* in the previous year and no report of wheezing or use of asthma medications in the present questionnaire.

Rhinitis symptoms – "Has the child suffered from sneezing, runny nose or nose blocking without having a cold in the last twelve months?".[187]

Eczema symptoms – An itching rash persisting for at least six months, and "Has the child had this rash at any time in the last twelve months?".[187]

Physician-diagnosed rhinitis (eczema) – "Has the child been diagnosed by a physician as having rhinitis? (eczema)".[20]

Allergic sensitisation – At least one positive skin prick test (≥3 mm). (named "*atopy*" in paper II).[20]

Risk factors

Family history of asthma (atopy) – Past or present asthma (allergic rhinitis and/or eczema) in the child's parent(s) or sibling(s).[20]

Parental asthma (atopy) – Past or present asthma (allergic rhinitis and/or eczema) in the child's mother or father.

Early city living – Living in a city during the child's first year in life.

Damp home – Past or present indoor moisture damage or moulds.[20]

Road within 200 m – Past or present large road or bus stop within 200 meters from the child's home.

Maternal smoking – Mother currently smoking.[20]

Cat (dog) at home – Past or present having kept a cat (dog) in the child's home.[20]

Respiratory infections – A history of pertussis, croup, pneumonia or severe respiratory infections (e.g. respiratory syncytial (RS) virus).[173]

EPIDEMIOLOGICAL METHODS

The papers I-IV were all based on cross-sectional data. However, paper I also included data on four-year cumulative incidence and remission of asthma in the 1996 year cohort. Prevalence was measured in all children participating in the questionnaire, and missing answers to questions about symptoms and/or conditions were considered negative. However, there were few missing answers to the most important prevalence questions, e.g. 0.9% for ever wheeze, 0.7% for current wheeze, 2.2% for ever asthma and 2.9% for physician-diagnosed asthma in 1996. In assessing exposures or risk factors, missing answers to the question at issue were excluded from the analysis. Prevalence and risk factors at age 7-8 have been reported from the 1996 cohort previously.[20 110 176] However, paper I compared these prevalence and risk data from age 7-8 with data from 11-12 years of age; paper II studied in detail the heredity relationships of asthma, and papers III-IV compared prevalence and risk data at age 7-8 in the 1996 cohort with the 2006 cohort.

STATISTICAL PROCEDURES

For all original papers included in this thesis, the author managed the database and conducted all analyses.

Prevalence, incidence and risk assessment

In prevalence comparisons and univariate risk analyses, the two-sided χ^2 Test was used (with continuity correction if expected cell count was 5-10 and using Fisher's Exact Test if expected cell count was ≤5). $P<0.05$ was considered statistically significant, and $P<0.10$ was considered borderline significant. In univariate risk analyses, risk ratios (RR) or odds ratios (OR) were calculated, including their 95% confidence intervals (CI).

Multivariate analyses by binary logistic regression models were used to calculate odds ratios with 95% confidence intervals. Hence, all multivariate analyses were limited to questionnaires with complete data for all questions included in the model, and to the skin prick tested children where allergic sensitisation was included in the model. In paper II the multivariate model did not include allergic sensitisation and thus data from the entire 1996 cohort was analysed. Four-year cumulative incidence of physician-diagnosed asthma and of allergic sensitisation was calculated in paper I. The population at risk was defined as participating children free of the condition in 1996, participating in the questionnaire and the skin prick test also in 2000. All prevalence, incidence and risk analyses were performed using the Statistical Package for Social Science (SPSS) software version 11.5.0 (SPSS Inc, Chicago, IL, USA).

Population attributable fraction

In paper IV, adjusted population attributable fractions were calculated. The population attributable fraction (PAF) estimates the proportion of disease in the population attributable to each exposure, using the formula $PAF = (p[r-1])/(p[r-1]+1)*100$ where p is the exposed proportion in the population, and r is the relative risk of disease in the population. Adjusted population attributable fractions (aPAF) were calculated from the multivariate risk factor model presented in paper IV, thus adjusting for covariance between risk factors. The method described by Eide *et al*[190] was applied, using the *aflogit* procedure in STATA 9.1 (STATA Corp, Texas, USA).

Special remarks

In paper I, prevalence was measured each year 1996-2000, i.e. the study was treated as an open cohort. Risk factors significantly associated with asthma 1996 or 2000 in univariate risk analysis were included in a binary logistic regression model. In paper II, risk factors significantly associated with asthma in the multivariate analysis from paper I were included as covariates in a multivariate model for studying family history of asthma. However, allergic sensitisation was not included since it limited the study cohort size and did not significantly affect the relationship between parental disease and asthma in the child. Several interaction terms were also tested in the binary logistic regression analyses.

In paper III, prevalence was compared between the 1996 and 2006 cohorts and between boys and girls separately. Sex-specific trends in prevalence of disease and prevalence of risk factors were tested. The boy-to-girl ratio in exposure to each risk factor was tested. Multivariate relationships were calculated, and interaction term risk factor * sex was tested in both cohorts. In paper IV, prevalence, univariate and multivariate relationships were calculated in the 1996 and 2006 cohorts, and similarly in papers I and II. The adjusted population attributable fraction (aPAF) above was also calculated.

RESULTS

These studies mainly focused on prevalent wheeze and asthma and risk factors for these conditions. Prevalence and risk factors *by age* were studied repeatedly in the open cohort starting in 1996. Further, prevalence and risk factors *by time* were studied by comparing the two cohorts of 7-8 years old children. Finally, the importance of a family history of asthma was studied in detail in the first cohort.

PREVALENCE *BY AGE* (PAPER I)

The 1996 cohort was followed by yearly questionnaires as an open cohort, i.e. all children in the respective school classes were invited each year. The prevalence of physician-diagnosed asthma increased significantly from 5.7% at age 7-8 to 7.7% at age 11-12 ($P<0.01$) (table 2). The prevalence of ever asthma increased similarly, from 6.4% to 9.3%, $P<0.01$. Both conditions were statistically significantly more prevalent in boys than in girls each year. Current wheeze on the contrary decreased significantly from 11.7% at age 7-8 to 9.4% at age 11-12, $P<0.01$. The proportion of current wheezers diagnosed with asthma by a physician concurrently increased from 44% to 60%.

Life-time prevalence

The life-time prevalence (children reporting a condition in the present or in any previous questionnaire) increased more by age than did the point prevalence (table 2). At age 11-12 34.7% of the children had reported ever wheeze at some time point, and 9.6% had reported physician-diagnosed asthma.

Remission

From ages 7-8 to 11-12 approximately 10% of children reporting current asthma the previous year reported no wheeze or medication use the next year. However, half of these children had subsequent relapse, yielding a 5% yearly persistent remission. The cumulative four-year remission was 25.5% with no difference between boys and girls ($P=0.96$) or between children with and without a family history of asthma ($P=0.61$). It was, however, significantly related to allergic sensitisation: The four-year cumulative remission was 44.9% among non-sensitised and 17.5% among sensitised children, $P<0.01$.

Table 2. Prevalence (%), life-time prevalence and asthma remission from age 7-8 to 11-12.

	Age (years)					
	7-8	8-9	9-10	10-11	11-12	7-8 *v* 11-12
	n=3430	n=3453	n=3446	n=3406	n=3395	P-value
Prevalence						
Ever wheeze	21.3	22.0	22.5	21.8	19.8	0.383
Ever asthma	6.4	7.7	8.9	9.4	9.3	<0.001
Physician-diagn asthma	5.7	6.5	7.1	7.7	7.7	<0.001
Current wheeze	11.7	10.7	10.2	9.7	9.4	0.001
Life-time prevalence						
Ever wheeze	21.0	27.1	30.8	33.0	34.7	<0.001
Physician-diagn asthma	5.7	7.0	8.0	8.7	9.6	<0.001
Remission	-	10.2	10.3	7.5	11.8	-
Lasting remission	-	4.0	6.2	5.2	-	-

RISK FACTORS *BY AGE* (PAPER I)

Multivariate relationships at ages 7-8 and 11-12 (table 3) were calculated using risk factors statistically significant in univariate analysis. For current asthma, allergic sensitisation was the strongest factor at both assessments, OR 4.9 (3.3-7.2) and 5.6 (3.9-8.2) with no difference between sexes. A family history of asthma was the second strongest risk factor, OR 3.0 (2.1-4.5) at age 7-8 and 2.8 (2.0-3.9) at age 11-12, and tended to differ between boys (OR 2.2 [1.3-3.7]) and girls (OR 5.0 [2.7-9.4]) at age 7-8. Male sex, low birth weight, respiratory infections and living in a damp house were all significant risk factors for current asthma at age 7-8.

When the children were four years older, however, several risk factors had lost statistical significance and only allergic sensitisation, a family history of asthma and ever having had a cat in the home (OR 0.5 [0.3-0.9]) were significantly associated with current asthma. Interestingly, consuming seven or more citrus fruits per week in the winter season was significantly inversely related to current asthma at age 11-12 (not tested at age 7-8), OR 0.6 (0.4-0.97). Current wheeze and physician-diagnosed asthma (paper I, table 3) were also studied and showed risk factor patterns similar to those of current asthma, but generally with lower odds ratios and wider 95% confidence intervals, indicating lower specificity.

Table 3. Risk factors for current asthma at ages 7-8 and 11-12 by multivariate analysis.

		Age 7-8		Age 11-12	
Risk factor		OR	95% CI	OR	95% CI
Male sex		**1.58**	**1.07-2.33**	1.18	0.83-1.69
Family history of asthma		**3.04**	**2.07-4.47**	**2.78**	**1.96-3.94**
Breast-fed ≤3 months		1.26	0.81-1.97	1.12	0.73-1.72
Birth weight <2500g		**2.57**	**1.22-5.40**	0.91	0.37-2.28
Respiratory infections		**2.14**	**1.40-3.27**	2.20	0.90-5.37
Maternal smoking		1.50	0.99-2.26	1.41	0.95-2.08
Cat ever at home		0.71	0.43-1.17	**0.54**	**0.34-0.86**
Living in damp house		**2.18**	**1.45-3.28**	0.86	0.36-2.05
Allergic sensitisation		**4.88**	**3.31-7.20**	**5.63**	**3.88-8.18**
Citrus fruits/week	≤2	-	-	1.00	-
	3-6			0.89	0.60-1.31
	≥7			**0.58**	**0.35-0.97**

PREVALENCE *BY TIME* (PAPERS III AND IV)

The study from 1996 was repeated in 2006 using identical methods to assess time trends in asthma and wheeze (table 4). There were no statistically significant increases in the prevalence of current wheeze (11.7% to 13.0%, P=0.13), infrequent current wheeze (6.2% to 6.8%, P=0.38) (paper III table 2) and sleep-disturbing wheeze (5.1% to 5.9%, P=0.18). Current use of asthma medications, however, increased significantly (7.1% to 8.7%, P=0.02), as did physician-diagnosed asthma (5.7% to 7.4%, P=0.01). Lifetime prevalence of several asthma indices increased, e.g. ever wheeze (21.3 to 24.1%, P<0.01).

Similarly, the prevalence of current symptoms of allergic rhinitis and eczema did not increase statistically significantly, despite increases in the prevalence of diagnoses of these conditions. This occurred parallel to a considerable increase by 45% in the prevalence of allergic sensitisation, from 20.6% to 29.9%, P<0.01. This increase in prevalence of allergic sensitisation was evenly distributed (P=0.82) between wheezing (from 40% to 54%, P<0.01) and non-wheezing (18% to 26%, P<0.01) children.

Of children with wheeze only before age 7-8, a larger proportion had a physician-diagnosed asthma in 2006 (25%) than in 1996 (14%), P<0.01. Moreover, current wheeze and/or use of asthma medications decreased significantly among children with physician-diagnosed asthma, or with ever asthma, from 1996 to 2006 (paper III, figure 2).

Table 4. Prevalence (%) of asthma, symptoms and allergic sensitisation in 7-8 year-old children in 1996 and 2006.

	1996	2006	% change	P-value
Current wheeze	11.7	13.0	+11.1	0.128
Sleep-disturbing wheeze	5.1	5.9	+15.3	0.184
Current asthma	5.3	6.1	+15.1	0.184
Physician-diagnosed asthma	5.7	7.4	**+28.6**	**0.010**
Current asthma medications	7.1	8.7	**+23.9**	**0.016**
Current rhinitis symptoms	14.0	15.2	+8.9	0.177
Current eczema symptoms	27.2	25.8	-5.2	0.215
Rhinitis diagnosis	6.5	7.8	**+20.2**	**0.049**
Eczema diagnosis	13.4	15.2	**+13.4**	**0.048**
Allergic sensitisation	20.6	29.9	**+45.1**	**<0.001**

Sex-specific prevalence trends

When the prevalence trends were stratified by sex, it was found that current wheeze, infrequent wheeze, sleep-disturbing wheeze, use of asthma medications and physician-diagnosed asthma all increased statistically significantly in boys, while none of these indices suggestive of asthma increased significantly in girls (figure 4 and also paper III table 3). Hence, the statistically significant prevalence increases as well as non-significant tendencies of increase in prevalence of current conditions observed from 1996 to 2006, were confined to boys.

However, lifetime prevalence of several asthma indices increased in both sexes (paper III table 3). Wheeze only before age 7-8 was unchanged in boys ($P=0.69$) but increased in girls ($P<0.01$). Interaction term sex * study year was statistically significant for current wheeze ($P=0.02$) and borderline significant for wheeze before age 7-8 ($P=0.06$). Nevertheless, a 45% increase in the prevalence of allergic sensitisation occurred both in boys and in girls, respectively (figure 4).

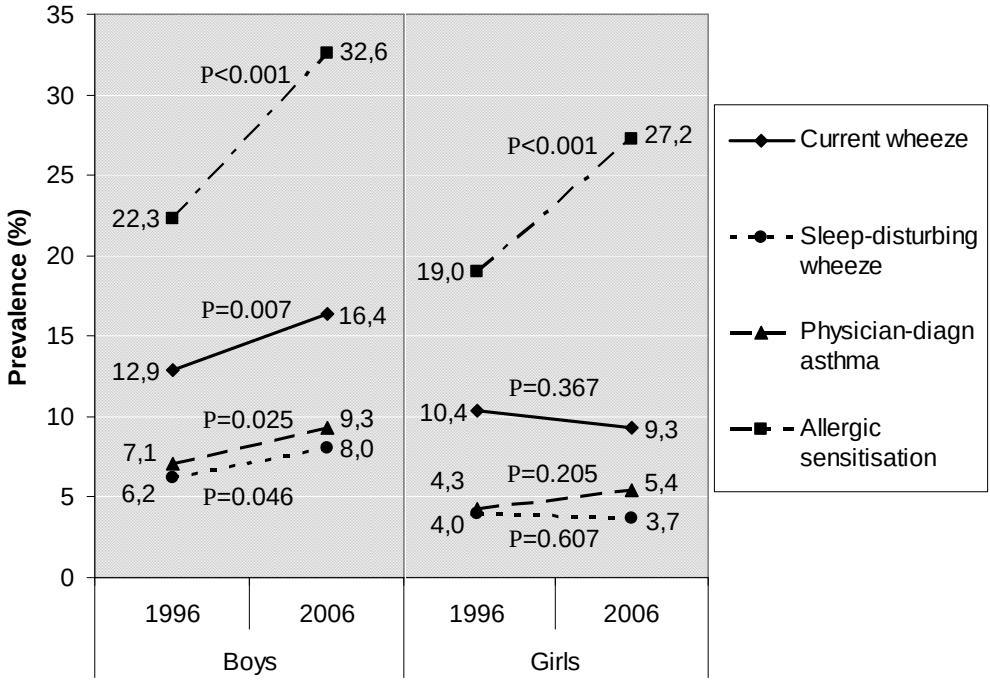

Figure 4. Prevalence in 7-8-year-old boys and girls in 1996 and 2006 respectively.

RISK FACTORS *BY TIME* (PAPERS III AND IV)

Trends in risk factors from 1996 to 2006 were measured as prevalence of the risk factor and as strength of association (odds ratio) (paper IV). The strongest risk factors for current asthma in 1996 and 2006 were allergic sensitisation (OR 4.3 and OR 3.7) and parental asthma (OR 3.1 and 4.7). For current wheeze, the strongest factors were respiratory infections (OR 3.3 and 4.6) and allergic sensitisation (OR 3.4 and 3.6). Ever cat at home was significantly negatively associated with current wheeze both years, and with current asthma in 1996.

Using these measures, the adjusted population attributable fraction, aPAF, was calculated, estimating the population-level impact of each risk factor. For current asthma (figure 5), from 1996 to 2006 the most important risk factors were allergic sensitisation (aPAF 35% to 41%), parental asthma (aPAF 27% to 45%) and respiratory infections (aPAF 36% to 32%). In 1996 male sex, early city living, damp home and maternal smoking all had aPAF:s 14-20%. In 2006, however, the importance of early city living, damp home and maternal smoking had all decreased to near zero, and this was due to a combination of decreased prevalence and strength of association. The significant negative association of having a cat in the

home in 1996 also had disappeared by 2006. In all, the model explained more than 85% of current asthma in 1996 and 2006.

For current wheeze (Paper IV, figure 2), the most important risk factor was respiratory infections, aPAF 51% and 41% in 1996 and 2006, respectively. The importance of allergic sensitisation increased from 24% to 34%, while that of parental asthma was level at 14% to 15%. Male sex was not significantly associated with current wheeze in 1996, while in 2006 it explained 25% of current wheeze, suggesting sex-specific prevalence trends in current wheeze. The entire risk factor model explained approximately 78% of current wheeze in 1996 and 2006.

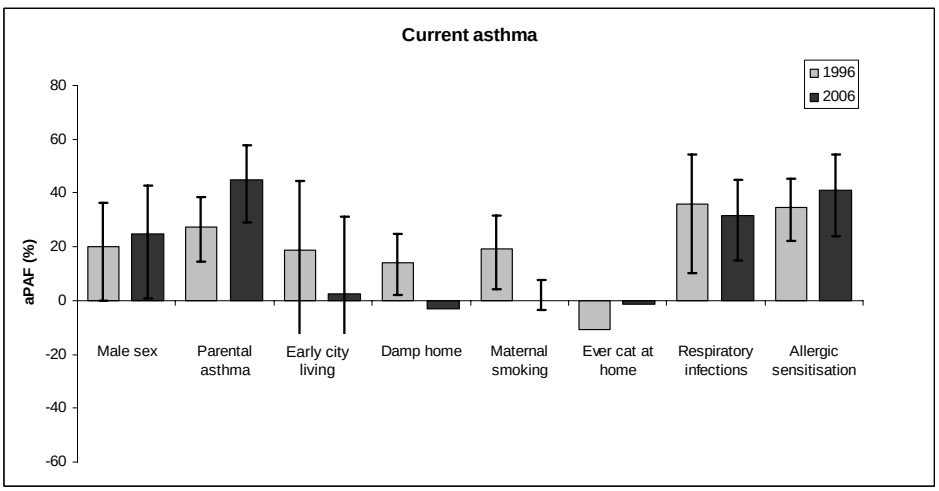

Figure 5. Adjusted population attributable fractions (%) of current asthma in 7-8-year-old Children in 1996 and 2006 respectively.

Risk factors in boys and girls

As prevalence trends in current wheeze 1996-2006 were significantly different between boys and girls, multivariate risk analyses stratified by sex were performed (paper III). Only factors significantly associated with current wheeze in univariate analysis were included. In 1996, the majority of risk factors were more prevalent in girls (table 4). In 2006, however, the boy-to-girl ratio in exposure to all studied risk factors had increased by 2-19%. This was seen for parental asthma (+15%) and respiratory infections (+19%), both strong risk factors, as well as for weaker risk factors like maternal smoking (+19%) and damp home (+13%). A significant risk interaction by sex was observed in 2006 for ever cat at home, which was a significant negative factor in girls but not in boys, interaction term P=0.02.

Table 5. Risk factors for current wheeze in 1996 and 2006 by multivariate analysis, stratified by sex. Boy-to-girl (B:G) prevalence ratio and relative change in this ratio for each risk factor.

	1996			2006			
	OR (95% CI)		Prev.	OR (95% CI)		Prev.	B:G ratio change
	Boys (B)	Girls (G)	B:G	Boys (B)	Girls (G)	B:G	
Parental asthma	**2.0 (1.3-3.1)**	**2.5 (1.6-3.9)**	0.97	**2.2 (1.4-3.4)**	**2.1 (1.1-3.6)**	1.11	+ 15%
Birth w. <2500 g	1.9 (0.8-4.4)	**2.5 (1.1-5.7)**	0.83	0.5 (0.1-2.1)	1.3 (0.3-4.7)	0.92	+ 12%
Respir. infections	**2.7 (1.7-4.3)**	**4.2 (2.4-7.2)**	1.00	**4.6 (3.0-7.1)**	**3.4 (2.2-6.9)**	1.19	+ 19%
Maternal smoking	1.5 (0.98-2.3)	1.3 (0.9-2.1)	0.90	0.9 (0.5-1.6)	1.8 (0.9-3.8)	1.07	+ 19%
Damp home	**1.7 (1.1-2.7)**	**2.0 (1.2-3.1)**	0.89	1.2 (0.7-2.1)	2.0 (0.97-4.3)	1.00	+ 13%
Ever cat at home	0.7 (0.4-1.2)	0.6 (0.4-1.1)	0.87	*1.0 (0.6-1.7)	**0.2 (0.1-0.6)**	0.95	+ 8%
Allergic sens.	**2.9 (1.9-4.5)**	**3.6 (2.3-5.7)**	1.17	**2.9 (1.9-4.4)**	**4.3 (2.4-7.5)**	1.20	+ 2%

* Significant interaction by sex, P=0.016

HEREDITARY ASTHMA AND ALLERGIC DISEASE (PAPER II)

The 1996 cohort was used for an in-detail study of the epidemiological aspects of asthma inheritance (paper II).

Prevalence in the children and their families

As previously stated, the prevalence of current asthma in the 1996 cohort was 5.3%. In children with at least one parent with allergic disease (allergic rhinitis or eczema), the prevalence of current asthma was 7.2%. If both parents had allergic

diseases, the prevalence was 14.0%, similar to the prevalence if at least one parent had asthma, 12.7%. If both parents had asthma, the prevalence of current asthma in the children was 35.7%. The prevalence of asthma among the parents was 9%, while the prevalence of allergic disease was 34.5% in the mothers and 26.5% in the fathers.

Adjusted risks of hereditary disease

Using a multivariate model based on the statistically significant risk factors for current asthma in 1996, independent relationships with hereditary asthma were calculated (table 6). For current asthma at age 7-8, a family history of asthma was a stronger risk factor, OR 3.3 (2.4-4.5), than a family history of allergic disease, OR 1.9 (1.3-2.8). Maternal and paternal asthma yielded OR 3-4, respectively. The significant association with sibling asthma disappeared if children of asthmatic parents were omitted, and sibling asthma had no additional effect if at least one parent had asthma. Having two parents with asthma was a strong determinant, OR 10.0 (4.4-22.9). Allergic disease in both parents on the other hand only yielded OR 2.7 (1.8-3.9).

Table 6. A family history of asthma and of allergic disease as risk factors for current asthma by multivariate analysis. Mother (M), father (F) and sibling (S).

	Positive family history of	
	Asthma*	Allergic disease**
	OR (95% CI)	OR (95% CI)
M or F or S	3.3 (2.4-4.5)	1.9 (1.3-2.8)
M	2.8 (1.9-4.1)	1.5 (1.1-2.1)
F	3.7 (2.6-5.4)	2.0 (1.5-2.8)
S	1.9 (1.3-2.8)	1.2 (0.9-1.7)
F + S	3.5 (1.7-7.4)	1.5 (1.0-2.2)
M + S	2.9 (1.5-5.4)	1.6 (1.1-2.2)
M + F	10.0 (4.4-22.9)	2.7 (1.8-3.9)
M + F + S	9.2 (2.7-31.3)	2.3 (1.4-3.7)

* Corrected for *damp house, birth weight <2500 g, male sex* and *respiratory infections*.
** Also corrected for *parental asthma*.

DISCUSSION

The discussion in this thesis is divided into two parts: first, a discussion of the methodology used and second, a discussion of the main findings.

DISCUSSION OF METHODOLOGY

A thorough digression on the methods used in a study is absolutely necessary to understand the strengths as well as the limitations of its findings. This section is divided according to the distinct study features, which in turn cover the subjects of internal and external validity, reliability, random error and bias.

Cross-sectional and longitudinal designs

Longitudinal studies have several advantages over cross-sectional studies in risk factor assessments, as exposure can be recorded prior to disease occurrence. The first OLIN paediatric study combined the longitudinal (closed cohort) and cross-sectional (open cohort) design, while the second paediatric study was cross-sectional. When the cross-sectional design was used, exposure and outcome variables were chosen to introduce a longitudinal element: Several exposures such as birth weight, time of breast feeding and parental asthma are unchanged over time, while several outcome variables were chosen to reflect present conditions, such as "current" asthma or wheeze. Moreover, most of the risk factors tested have been reproduced in several previous studies, both cross-sectional, longitudinal and experimental. In the study of time trends, repeated cross-sectional studies of similar populations using identical methods is currently the preferred method.

Longitudinal studies may also have major limitations, the most important being attrition, the "study effect" and the "cohort effect". Study attrition not only lowers the statistical power but more importantly introduces bias, as subjects may choose to participate based on the distribution of diseases and exposures. The powerful statistical methods and stringent definitions of statistical significance used presently are of very limited value if the study population is not representative. The very high participation in the first OLIN paediatric study, however, effectively counteracted this. The "effect of being enrolled in a study" (or "Hawthorne effect") correctly denotes that study subjects may change behaviour (i.e. health behaviour and tendency to seek medical attention) relative to the general population due to their participation in a study. As a result of the yearly questionnaires in the first OLIN paediatric study, a slight upward bias of the prevalence could thus be expected. However, 1995, one year before the first OLIN paediatric study started, was announced the "Swedish year of asthma" by public health authorities. Hence the knowledge in the general population had increased

prior to the study start. Moreover, Sears *et al* could not empirically demonstrate that repeated assessments in a study of asthma biased the prevalence rates [191].

The "cohort effect" denotes the possibility that the cohort subjects are not representative of a general population before entering the study, i.e. they may belong to a generation with special lifestyle features or exposures and may thus give a false picture of exposure and disease in "any population at any given time". This inevitably applies to all cohort studies and the fact that much of the present knowledge on the time course of asthma emanates from a few well-designed birth cohort studies underlines the importance of repeated studies in different regions and times. The generalisability can, however, be increased by using standardised measurements, well-characterised study cohorts and statistical methods to adjust for known exposures (e.g. stratification and multivariate analyses), thus turning unknown confounders into known co-variates.

Strict inclusion criteria also affect the representativity of a study sample. One example is the well-designed Swedish BAMSE study[192] in which of 7221 infants born during the recruitment period 1733 were excluded prior to the study and 1399 declined participation, leaving 4089 subjects (56.6%) in the cohort at study start, even before attrition took place.

Schoolchildren *vs* birth cohorts

The ideal study of asthma would follow a very large cohort, using all kinds of measures, from before birth and until the death of each study subject. During the last twenty years, a number of well-designed birth cohort studies have extended the knowledge of childhood asthma. However, the longer the study time, the more error is introduced. Thus, sometimes a cohort followed from birth is not ideal for the study of adult or adolescent asthma. Also, besides cohort attrition, there are the previously mentioned "effect of being in a study" and the risk of the initial identification and study methods being out-of-date. Measurements based on the best knowledge 20 or 30 years ago may not be of the same interest today.

Owing to the mandatory primary school attendance in Sweden, the first and second OLIN paediatric study cohorts were truly population-based. Further, the excellent participation rate vouch for the inclusion of virtually the entire population of 7-8 years old children in the study. The representativity should be considered very high for Northern Sweden.

Questionnaire studies

The major strength of questionnaire surveys is their low cost and rapid data acquisition, facilitating detailed studies of large populations. They, however, lack the detail and objective measurements that experimental, molecular and genetic studies have. For the study of asthma, there is at present no gold standard objective

test. Pulmonary function tests, bronchial hyperreactivity challenges, exhaled nitric oxide and induced sputum are all important complements and all measure distinct features of asthma but yet do not define asthma. Criticism has also been raised against the reproducibility of some common objective measures of childhood asthma.[193] Hence, not only is a questionnaire survey able to obtain large quantities of data; it may still also be the key method in epidemiological studies of asthma and wheeze.[194] The clinical validation of self-reported asthma in the first OLIN paediatric cohort firmly supported the ability of the questionnaire to correctly identify asthma. For risk factors, report bias is a serious concern. Under-reporting of parental smoking can be assumed, as can over-reporting of possible risk factors among symptomatic children.

The measurement of several outcomes related to asthma and wheeze made for better precision and greater reliability in that a trend across several outcomes is less affected by chance and bias. Risk calculations depend mainly on the specificity of the outcome variable and accordingly most risk analyses focused on highly specific variables such as physician-diagnosed asthma and current asthma. Prevalence and incidence, however, rely on both the sensitivity and specificity of the variable. Thus, a broader spectrum of outcomes was studied, also in order to better address the central question "What is asthma?".

Skin prick tests

As shown, the definition of atopy has changed over time and hence the term allergic sensitisation was used. Allergic sensitisation was measured by *in vivo* skin prick tests and validated by *in vitro* specific IgE in subsets in 1996 and 2006 with high correlation. Specific IgE can be quantified and thus has less inter-observer variance, and so has become widely used in epidemiological studies due to better standardisation and lowered costs. However, in repeated studies such as the longitudinal first OLIN paediatric study, and when comparing different cross-sectional studies such as the 1996 vs 2006 comparison in this thesis, using the same methodology is essential. Thus, the same skin prick test protocol, carried out by a small group of specifically trained personnel, was applied on all occasions.

The prevalence of sensitisation found in 1996 was slightly lower than expected from previous studies in Northern Sweden,[92 112 195] which were however performed in older children. The huge difference in prevalence of sensitisation between 1996 and 2006 could be explained by underestimation in the first cohort. However, at age 11-12 the children in the first cohort had reached the same sensitisation prevalence as the 2006 cohort had reached at age 7-8, supporting the validity of the 1996 results.

Statistical notes

Large study populations enable detailed analyses. Statistically underpowered studies are prone to type-II errors (failing to reject the null hypothesis). This in turn increases the risk of drawing false conclusions, as some uncommon exposures fail to reach statistical significance, while more common exposures do. On the other hand, very large study populations such as have been obtained in some recent multi-centre studies,[196] run the risk of measuring statistically significant but clinically irrelevant associations.

Risk, expressed as risk ratio or odds ratio, is widely used and is influenced by the prevalence of the disease and of the risk factor. Also, it is used to extrapolate the risk among the exposed vs the non-exposed to the individual level. Still, it does not measure the risk of disease in the population which, however, can be estimated by the adjusted population attributable fraction used in paper IV. Attributable fractions, despite the terminology, must not be confused with true causal fractions of disease, especially not in multi-factorial diseases with partly unknown causation such as asthma. This said, the adjusted population attributable fraction could still be a useful estimate, especially when assessing time trends and as long as true causal fraction is not inferred.

Heredity

The first OLIN paediatric study was originally designed to screen for a variety of risk factors and to create a basis for a longitudinal study. It was not specifically designed to study the inheritance of asthma and allergic diseases, i.e. unlike the children's responses, parental disease was not clinically validated and no genetic analyses were made. Nonetheless, as discussed in paper II, the prevalence of parental asthma was similar to findings in adults in this region, and the strength of association found in the study conformed to pooled data from 17 separate studies in a review.[119] Moreover, this was not a study of single asthma susceptibility genes but, rather, set out to answer the common question "What is the risk of my child developing my disease?". Finally, questionnaires were more often completed by the mother.[197] This could lead to underreporting of paternal symptoms or to reporting only more severe paternal symptoms. This may have decreased the sensitivity and increased the specificity of the question of paternal asthma as compared to maternal asthma.

DISCUSSION OF MAIN RESULTS

In this section the main results are put into context and discussed in relation to previous findings. The first part is focused on the findings from age 7-8 to 11-12 in the first OLIN paediatric cohort and changes in prevalence and risk factor patterns as well as the remission rate are discussed. The middle part is focused on the inheritance of asthma, and addresses several topics of scientific debate. The final part discusses trends from 1996 to 2006 in wheezing prevalence and the characteristics of wheeze and asthma. Moreover, such trends in risk factors are discussed, as are the implications for future epidemiologic study of asthma.

Prevalence and risk factors *by age* from age 7-8 to 11-12

Prevalence of asthma in children is determined by the high incidence,[36-39 173] but also dynamic course, with significant remission and relapse rates.[39] At age 7-8 the prevalence of physician-diagnosed asthma and current wheeze (paper I) conformed to other European findings, as discussed previously by Rönmark *et al.*[20 110 173 176] At age 11-12 the prevalence of current wheeze was slightly lower than observed during the ISAAC phase I in Swedish 13-14-year-olds and quite similar to the prevalence observed in Mediterranean Europe.[10]

Wheeze and asthma

From ages 7-8 to 11-12 the prevalence of current wheeze decreased while physician-diagnosed asthma increased, and the ratio thus decreased from 2.1 to 1.2. The proportion of current wheezers with an asthma diagnosis increased from 44% to 60%. A previous Swedish study presented prospective (ages 7-9 to 12-13, 1992-1996) data from Kiruna, where the prevalence of current wheeze, asthma and several indices of asthma increased.[198] However, the cohort was rather small in comparison (201 subjects) and was studied by interviews. Moreover, the prevalence of sensitisation at age 7-9 was higher both in general (27%) and in the children with asthma (75%), which may have have contributed to a very high incidence and persistence of wheeze observed. A stable prevalence of wheeze during school age has previously been demonstrated in Sweden.[19] Interestingly, the point prevalence of ever wheeze tended to decrease with age (paper I), also in the incidence cohort, i.e. in participants both at ages 7-8 and 11-12. The relevance of measuring lifetime prevalence, which increased by 65% for ever wheeze from age 7-8 to 11-12, and performing close follow-ups is clear: symptoms, mild symptoms in particular, are easily forgotten. This has also been shown by Strachan *et al.*[37]

The study effect may have contributed to the increase in asthma diagnoses, which was steepest in the first years of the study.[173] Nevertheless, the diverging developments in prevalence of physician-diagnosed asthma and current wheeze reflect both the persistent nature of a medical diagnosis and the fact that some of

the diversity of childhood wheeze disappears with age.[38 39] The answer to the central question "what is asthma?" becomes increasingly clearer with age. The study of school age asthma thus encompasses the transition from childhood wheeze to adolescent asthma.

Remission

The four-year remission was high among children with current asthma at age 7-8. Still, the long-term prognosis is difficult to predict as relapses are common in adulthood.[37 39 151 199 200] Airway inflammation and bronchial hyperresponsiveness seem to persist despite even in the absence of symptoms,[201] although this result was not compared with never-asthmatics. Half of the previous year's remittent cases relapsed (paper II), which illustrates the short-term variance. However, the short follow-up period precluded any meaningful calculations of cumulative relapse rates.

Remission was strongly related to the sensitisation status of the child, but not to sex or the presence of parental asthma. Parental asthma has been linked to asthma persistence,[122 202] although the evidence is limited. Remittent subjects with parental asthma may relapse at higher age, not covered by this study. In adolescence and adulthood the prevalence of asthma is higher in females.[203 204] This is seemingly explained by higher incidence rather than persistence of asthma in girls, since remission rates were equal between the sexes. The observed relationship (paper II) of asthma persistence with allergic sensitisation is well known. Allergic asthma is more prevalent in higher age, i.e. teenage, adolescence and young adults,[38 39] seemingly due to the associations of sensitisation both with incidence and with persistence of asthma. Interestingly, it has not been studied whether later sensitisation, after asthma remission occurred, predisposes for relapse of asthma.

Risk factors for current asthma and wheeze

The strongest risk factors for current asthma at age 7-8 were allergic sensitisation, a family history of asthma, low birth weight and respiratory infections. This is mainly a corroborative finding.[140 205-207] The majority of studies in westernised countries identify allergy in some form, heredity and severe lower respiratory infections as risk factors for childhood wheeze and/or asthma. At age 11-12 the strong association with parental asthma reflects mostly incidence[73] whereas the association with allergic sensitisation reflects both incidence and persistence as discussed below. With increasing age, both early life factors such as short time of breast feeding and low birth weight, as well as environmental exposures such as maternal tobacco smoke and damp housing conditions, lost importance. The high incidence of mainly transient symptoms in children is thus explained by high susceptibility to a multitude of risk factors.

There were differences in the risk factor patterns of current wheeze and current asthma. Wider confidence intervals indicated lower specificity for current wheeze, and the strongest determinants of current asthma were considerably less associated with current wheeze. Respiratory infections were more strongly associated with wheeze than asthma, in keeping with the finding that transient wheezing symptoms are related to respiratory infections in children.[39 65 108] However, this seems to be the case also during the pre-teenages (paper I). The differences between wheeze and asthma highlight the importance of accurate phenotyping of symptoms. Through the study of multiple outcomes both high sensitivity and specificity can be gained, while maintaining the distinction between unspecific symptoms and asthma.

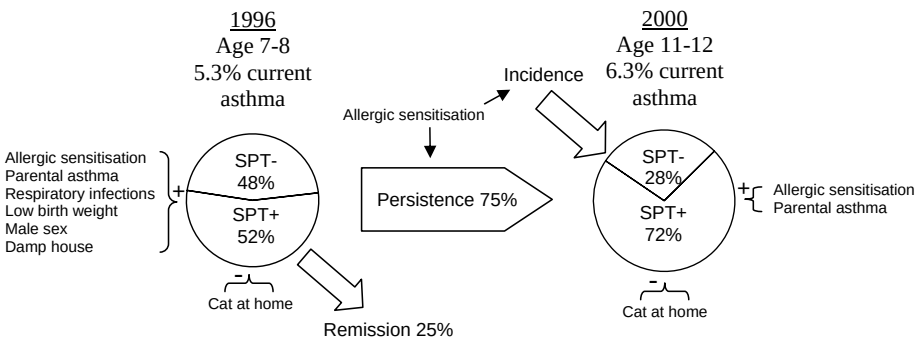

Figure 6. Schematic overview of the prevalence development of current asthma from age 7-8 to age 11-12 in the first OLIN paediatric study including the proportions with allergic (SPT+) and non-allergic (SPT-) asthma, and the associated determinants of current asthma.

Inheritance of asthma

This inquiry sought to give a detailed characterisation of the heritable component of asthma, and addressed several questions that are subject to considerable disagreement in the available literature. By way of introduction, the clinical question "what is the risk in the child of a parent with asthma?" received a direct answer. The prevalence of asthma increased from 5% to 13% in children with one parent with asthma (three to four times, adjusted risk), and to 36% (ten times, adjusted risk) in those with biparental asthma. Similar results have been reported by Åberg *et al.*[208] The association with current wheeze in the child was weaker, verifying that asthma is more specific than childhood wheeze, not only in terms of symptom diversity but in aetiology as well.

Modern asthma epidemiology, also when not specifically targeting heritability, usually includes some measure of inheritance as a covariate.[131 209-211] Inheritance patterns would be expected to show less variance in different studies than, say, environmental exposures. Nevertheless, the multitude of studies seems to have

contributed more to the divergence of findings than to creating a consensus, partly owing to methodological differences and even methodological insufficiency. Although as many as 33 studies were reviewed by Burke *et al*[119] they failed to present satisfactory answers to several of the central issues listed below. However, when parental asthma is defined explicitly, the relationship with asthma in the child is rather homogenous regardless of the prevalence, as demonstrated also in adults in Northern Europe.[181 182 212]

Parental asthma *versus* parental allergic disease

Despite the differences between asthma and allergic diseases discussed previously, a family history of these conditions is commonly combined into "a family history of allergic disease/atopy", and the differences are thus neglected. This rather non-specific approach has been used e.g. in the otherwise well-designed and influential European Community Respiratory Health Survey and in the Dunedin study.[128 196 213] At age 7-8 (paper II) there were important differences between the effect of a family history of asthma and a family history of allergic disease (rhinitis or eczema). *Pro primo*, the risk increase was greater for parental asthma than for parental allergic diseases, regardless of the affected family member. *Pro secundo*, if asthma was present in at least one parent, the presence of allergic disease in either parent contributed very little to increasing the risk in the child (paper II, figure 1). *Pro tertio*, whereas parental asthma showed a statistically multiplicative effect when present in both parents, biparental allergy conferred less than additive risk. Taken together, these findings strongly suggest that these two risk factors should be analysed separately.

The literature is inconsistent on the importance of parental allergic disease. Several studies[128 134 135 196 213] did not separate parental asthma from allergic diseases, which obscures the relationship as these conditions often coexist. Four out of 14 studies found no association between asthma in the child and "parental allergic disease other than asthma", while seven studies did.[119] The sensitivity of "parental allergic disease" depends on the criteria used. There was no difference if only parental rhinitis was used (paper II). However, parental disease was not clinically validated which may have decreased the observed odds ratio as some parents with allergic symptoms may not be sensitised. In a European multi-center study, 75% of adults (aged 20-44) with rhinitis were sensitised,[214] very similar to a recent Danish study.[215] Parental rhinitis thus seems to be a reasonable marker for parental sensitisation although its negative predictive value is low.[214]

Parent-of-origin effects

In the first OLIN paediatric study, which applied stratification, different multivariate models and testing for interaction by parental sex, no parent-of-origin effect could be demonstrated. This was seen at age 7-8, and this age likely

encompasses the aforementioned transition from maternal to paternal asthma being more important, which seems to occur after the age of five.[124] The possible mechanisms of parent-of-origin effects are discussed in paper II. No consistent parent-of-origin effects in school-age children could be demonstrated in the recent review,[119] and the majority of studies reporting such effects did not test for interaction by parental sex, but concluded that the effect of only one of the parents was statistically significant. First, this stratification does not prove a statistically significant difference by parental sex[216] and second, it reduces the statistical power so that an association with the other parent may be missed. Finally, a publication bias – where positive findings of parent-of-origin effects are more often reported – may very well exist.

The effect of sibling asthma

At first glance, there was a significant association between sibling asthma and asthma in the child at age 7-8. However, when sibling asthma was analysed in the absence of parental asthma, this association disappeared (paper II). Moreover, sibling asthma did not add any effect to parental asthma, contrary to the multiplicative effect of asthma in both parents. This unambiguously suggests that sibling asthma was just a marker of parental disease. Some previous studies have demonstrated a significant effect of sibling asthma also when corrected for parental asthma[89 144 145] and, as was stated in the background, in theory there are several underlying mechanisms. In contrast to paper II, none of these studies applied stratification or used different multivariate models, and until significant associations have been demonstrated using this stringent methodology, the validity of such observations remains uncertain.

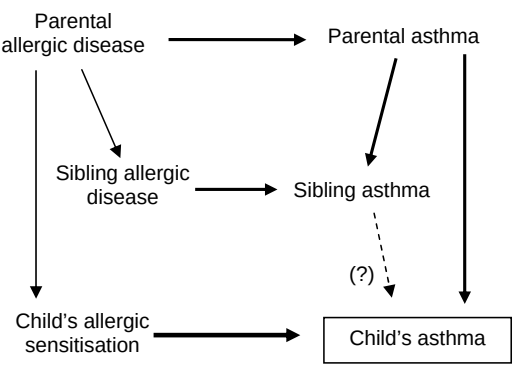

Figure 7. Inheritance patterns of asthma and allergic diseases (rhinitis and eczema).

Sex and sensitisation status of the child, and parental asthma

Interestingly, there were no signs of interaction of parental asthma with the child's sex or sensitisation status. Thus, testing for allergic sensitisation is of equal value in children with and without parental asthma. The positive predictive value of a family history of asthma is too low (11%-37%) to be of clinical use[119] and this was also the case when skin prick testing was added, as the prevalence of asthma was only 29%

in sensitised children with parental asthma (paper II). This relationship may change as the prevalence of asthma and sentitisation, as well as the proportion of allergic asthma increase with age. It seems that the two independently most important risk factors for asthma – allergic sensitisation and parental asthma – identify a group at very high risk but not the majority of asthma cases at age 7-8. Interactions of other risk factors with parental asthma should thus be explored further.

Prevalence and risk factors *by time* from 1996 to 2006

Trends in symptom prevalence 1996 to 2006

The two study populations were identical with respect to age and geographic area (paper III) and participation was excellent, vouching for good comparability. The prevalence of current wheeze, the primary outcome also in the ISAAC phase I-III study,[10 187] did not increase statistically significantly. This supports the findings from the ISAAC I-III center in central Sweden (Linköping), where the prevalence of current wheeze was unchanged.

In the OLIN paediatric study, this stable prevalence was seen also for frequent and infrequent wheeze, sleep-disturbing wheeze, and for symptoms of allergic rhinitis and eczema. Nevertheless, there were increases in physician-diagnoses of asthma, rhinitis and eczema, and in use of asthma medications. This was probably attributable to increased awareness and diagnostic activity, and presumably (for asthma) also to the increase in lifetime symptoms. Trends in physician-diagnoses do not necessarily reflect trends in symptom prevalence.[6 7 217 218] However, by only measuring twelve-month symptom prevalence as in the ISAAC I-III, previous symptoms and possible changed awareness are missed.

Stratification by sex revealed interesting trend differences. Current indices of asthma had consistently increased in boys while in girls there were non-significant decreases. Averaged across all children this resulted in the observation of a stable prevalence. Thus, the boy-to-girl prevalence ratio increased contrary to findings from several recent studies,[53 58 219] but in keeping with other studies.[30 57] Unfortunately, the Swedish ISAAC center did not stratify by sex. This precludes not only the detection of any sex-specific trends but probably also, in combination with the rather low participation (64%) and assessment of only one outcome variable, the detection of most small to moderate prevalence changes.

Increases limited to mild symptoms have been linked to use of medications.[29 60] In boys, however, both infrequent wheeze and the more severe sleep-disturbing wheeze as well as use of asthma medications increased, and thus severity changes cannot be concluded. In girls, there was a clear increase in wheeze before age 7-8. It seems that persistence of early childhood wheeze was higher in boys in the second study, which is more plausible than a prevalence peak in girls before age 7-

8, followed by a marked increase in wheeze in boys. This is an interesting finding; especially in the light of risk factor patterns discussed below but cannot be explored further without prospective data from infancy.

Certain features of the results support the validity. First, both the increase in boys and the level prevalence in girls were consistent across the majority of current asthma indices. Increased awareness would likely primarily affect the prevalence of mild and infrequent symptoms. Second, the difference between sexes is supportive, as it is unlikely that increased awareness of current symptoms was limited to boys.

Diverging trends in symptoms and sensitisation

The differences between trends in objectively measured allergic sensitisation and questionnaire-based symptoms were striking and are unlikely to be solely a result of methodological differences (paper III). This again emphasises that childhood wheeze and allergic sensitisation are different conditions. The large increase in sensitisation could not be related to increases in risk factors in this region.[20 170] It is, however, possible that smaller family size, owing to lower birth rates, in the latter cohort contributed to some extent.

Far from all childhood asthma is attributable to allergic sensitisation, and this proportion varies considerably.[98] The proportions of sensitised/non-sensitised asthmatics correlated well with the corresponding proportions among non-asthmatics in a recent review.[220] Accordingly, in Northern Sweden sensitisation increased considerably both among wheezing and non-wheezing children (paper III). However, the stable prevalence of rhinitis and eczema symptoms requires future follow-ups in the 2006 cohort, to study whether symptoms will occur in the sensitised symptom-free children, as seen for wheeze previously (paper II).

Characterisation of wheeze and asthma in the two studies

The increase in allergic asthma from 1996 to 2006 was seemingly not related to increased severity. The presence of allergic sensitisation may, however, have important implications for the future course of symptoms, as dilated upon in the introduction of this thesis. Most importantly persistence, but also lung function has been related to allergic asthma.[39 108] Hence, the natural course of wheeze in the second cohort may not follow that observed in the first cohort.

At age 7-8, the question about physician-diagnosed asthma probably reflects lifetime prevalence. Physician-diagnosed asthma increased more than ever wheeze (paper III). Among physician-diagnosed cases the prevalence of current symptoms and/or medications decreased, while wheeze only before age 7-8 nearly doubled. Seemingly, physicians in the latter cohort more often diagnosed wheeze, especially early transient wheeze, as asthma. Parallel to this there was an increase in wheeze only before age 7-8. The ratios of current and ever wheeze, respectively, to

physician-diagnosed asthma decreased more in girls than in boys (paper III). This could indicate under-diagnosis of asthma in girls during the 1990's, as demonstrated previously,[221 222] and a decrease of this phenomenon during the last ten years.

International studies of risk factor trends

Of the three available studies of trends in asthma and risk factors,[33-35] the Italian SIDRIA study[34] is best suited for comparison with the OLIN paediatric studies. SIDRIA invited more than 25000 children aged 6-7 years (1994/5 and 2002) to an expanded ISAAC questionnaire with high participation. There was no increase in current wheeze and lifetime prevalence of asthma. Parental education improved parallel to increased (3.6%) prevalence of parental asthma and decreased (6.2%) maternal smoking. Although these risk factor changes were not as dramatic as those observed in Northern Sweden (paper IV), the direction of change was similar and correspondingly resulted in a stable prevalence of wheeze. Unfortunately, several of the important risk factors in Northern Sweden, including allergic sensitisation, were not included in the SIDRIA study, which complicates further comparison of the two studies.

In contrast, the prevalence of several asthma indices increased in the ten million inhabitant city of Istanbul, Turkey, despite no major prevalence increase in the studied risk factors for wheeze.[35] The authors suggested that population growth and associated increases in affluence and air pollution accounted for these changes. However, none of these demographic characteristics were seen in Northern Sweden. A Swiss study by Braun-Fahrländer *et al*[33] showed no increase in the prevalence of asthma, rhinitis or allergic sensitisation from 1992 to 2000, despite increases in students' smoking, parental education level and maternal rhinitis. Since odds ratios were not displayed, the importance of these changes is hard to compare to Northern Sweden. Further, as concluded by the authors the participation was low and the study was conducted in teenagers.

Trends in risk factors 1996 to 2006

When measured in all children, the major trend in risk factors for current asthma was decreased exposure to environmental factors, parallel to an increased impact of allergic sensitisation and parental asthma. The prevalence of maternal smoking and severe respiratory infections each decreased by 50%, owing mostly to intense campaigns against smoking and to vaccination against *Bordetella pertussis*, which was re-introduced into the Swedish national vaccination programme between the two cohorts. The prevalence of pertussis infections accordingly decreased from 48.0% to 2.6%. The relationship between vaccination and allergic diseases has been debated,[223 224] but for asthma there seems to be a protective effect[225] in line with our

findings. Vaccinations may in theory impact on allergic sensitisation, while still counteracting asthma through protection of the airway epithelium against pertussis.

The importance of early city living and damp home decreased mainly due to decreases in strength of association (paper IV, table 1). This was seen also for maternal smoking in addition to the prevalence decrease. Early city living was not significantly associated with current asthma either year but was included to demonstrate the trend. In 1996 eight of the eleven risk factors were significantly associated with current asthma, compared to five in 2006.

Allergic sensitisation and parental asthma increased in prevalence, and for parental asthma the association tended to increase as well. The increased effect of parental asthma is interesting. Its prevalence increase is not surprising, given the general prevalence increase during the last decades. However, the prevalence of asthma susceptibility genes is unlikely to have increased, as genetic changes on the population level do not occur that rapidly. Rather, the association with asthma in the child would diminish, as an increasing proportion of the parents' asthma is caused by environmental exposures. In keeping with this, one previous study[33] demonstrated that the association with childhood asthma was unaffected by the prevalence of parental asthma.

If one assumes that the genetic composition of the parents and children in both cohorts, considered as four different populations, were very similar or identical, environmental exposure can principally explain the abovementioned finding in one of two ways. First, environmental risk factors not corrected for in the multivariate analysis may be associated with parental asthma, and may thus confound the heritable component. If so, these exposures in families with hereditary asthma were more pronounced in the second cohort. Second, there may be exposures uncorrected for which interact with parental asthma, i.e. which cause asthma only in genetically predisposed individuals. An increased association with parental asthma would be seen if these exposures increased from 1996 to 2006.

In the 1996 cohort, a number of environmental risk factors significantly associated with non-allergic asthma did not reach statistical significance for allergic asthma, which was only associated with a family history of asthma.[110] Thus, one may speculate that the increased importance of inheritance and allergic sensitisation in the second cohort attenuated the effects of previously important environmental exposures through risk factor interactions. It is also likely that asthma and wheeze would have increased considerably, had not the vaccinations against pertussis and decrease in maternal smoking occurred. Thus, the total risk factor burden in the two cohorts was rather similar, theoretically providing an explanation for the level prevalence of wheeze and current asthma.

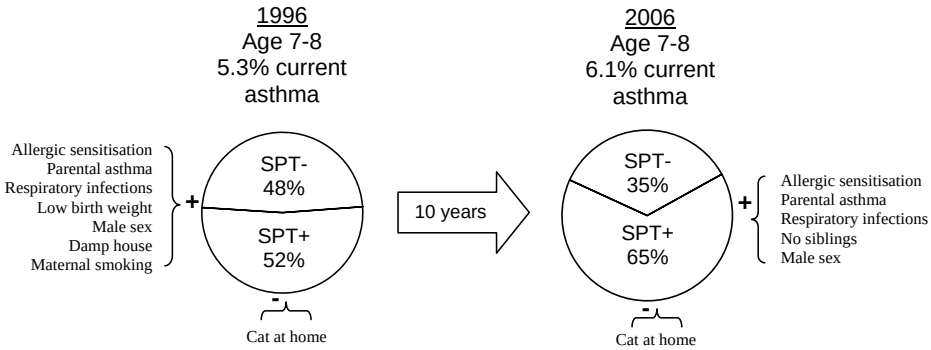

Figure 8. Changes in current asthma at age 7-8 from 1996 to 2006: The proportions of skin prick test (SPT) positive and negative current asthmatics and the determinants of asthma.

Sex-specific trends in risk factors

The prevalence trends of two asthma symptom indices were statistically significantly different between boys and girls: current wheeze increased in boys but not in girls, and the inverse was seen for wheeze before age 7-8. In 1996, the exposure prevalence tended to be higher in girls, however not statistically significantly. Quantitative measures of e.g. maternal smoking (pack-years) or damp housing conditions (years of living in a damp home) were not included, which introduces some variance into the results. In 2006, the boy-to-girl prevalence ratio of exposure to every measured risk factor had increased, including important factors such as respiratory infections and parental asthma which increased relatively by 19% and 15%, respectively. There is no reasonable explanation for this development, which seemingly occurred by chance.

Interestingly, the prevalence of obesity (BMI >30), a risk factor for asthma,[81] increased from 1.5% to 5.0% in Swedish conscripts from 1980 to the 2000's[226] and the highest prevalence, 8%, was seen in Norrbotten. However, in a recent report the prevalence of overweight or obesity at ages 9-10 was very similar between boys and girls in Umeå in Northern Sweden,[227] and thus we cannot conclude whether high BMI contributed to the observed sex-differences in asthma prevalence.

With the previous reservations, our findings provide a rather plausible explanation for the increased symptom prevalence in boys only, if boys and girls are pictured as different populations. First, male sex is an independent risk factor for wheeze.[228 229] In the first cohort, the risk effect of male sex was balanced to some degree by lower exposure. In the second cohort, it was heightened by increased exposure. In fact the opposite, a prevalence increase without an increase in exposure to the relevant risk factors, would have been surprising: However, risk factor patterns are very complex and the role of interactions is probably underestimated.

PERSPECTIVES

It seems that the asthma epidemic has stalled, insofar that the prevalence in children in westernised regions is no longer increasing. The explanations are yet unknown, as are the causes of the previous prevalence increase, which is still in progress in several nonaffluent regions. Cross-sectional, and lately also prospective cohort studies, have increased the knowledge, but still much controversy remains as to why these trends occurred.

To some extent, the divergence of findings emerges from different definitions of outcome. Not only are wheeze, asthma and sometimes allergic sensitisation confused in the discussion, but differences within each outcome definition may explain contradictory findings. Transient, persistent or relapsing wheeze, allergic or non-allergic asthma, infection-induced wheeze and cough-variant asthma all reflect the diverse disease spectrum, and may give different answers to what asthma is. Through more exact definitions and the study of multiple outcomes, some of the confusion can probably be overcome. Hopefully, asthma phenotypes will be linked to different etiologies, enabling future intervention strategies with influence on the prognosis of disease. This in turn requires large population-based samples followed longitudinally.

One important role of future epidemiological research lies in making large, representative samples from the general population available for experimental research. When applied to such study samples, clinical and mechanistic research, and studies of genetics and proteomics, will render very valid and reliable data.

Several risk factors have initially been identified through cross-sectional and case-control studies, and these relationships have then been tested in prospective studies. Trends in disease and to some extent, trends in risk factors have been followed. However, this approach is highly speculative for a disease with complex risk interactions such as asthma and stands little chance of predicting future disease trends. As demonstrated, the prevalence of the most important risk factor may increase substantially without an increase in the associated disease.

The parallel study of trends in disease and risk factors pilots future inquiry into what factors influence disease trends. This type of studies may ultimately bridge the gap between studies of disease and studies of risk factors for disease seen today. Against the background of a continuously changing environment, risk interactions for multifactorial diseases such as asthma, actually mean that causation and patterns of occasion are not static but dynamic. This requires for future epidemiology to survey trends in disease characteristics and in causation as they occur and not after they have occurred.

CONCLUSIONS

Based on the findings in this thesis, the following conclusions can be drawn:

From age 7-8 to 11-12 there was a reduction in the prevalence of non-specific respiratory symptoms parallel to an increased prevalence of asthma diagnoses, reflecting the transition from childhood wheeze to pre-teenage asthma. Remission from asthma, especially the non-allergic phenotype, was high but half of the remittent cases relapsed during the four-year period.

Asthma at age 7-8 was associated with a large number of risk factors, the importance of which decreased until the pre-teenages. The increasing impact of allergic sensitisation was attributable both to the associated incidence and to the persistence of asthma, and resulted in an attenuation of the effect of risk factors for non-allergic asthma.

The heritable component of asthma is important at seemingly all ages. Parental asthma was more important than parental allergic diseases, and these should be treated separately when assessing asthma risk. There were no parent-of-origin effects, and no independent effect of sibling asthma could be detected.

The previous continuous rise in the prevalence of wheeze and asthma has halted in Northern Sweden during the last ten years, as seen in several westernised countries. This occurred despite a considerable increase in allergic sensitisation, which was balanced by decreased exposure to environmental risk factors for asthma. This divergence of trends underlines the differences between asthma and allergy.

There was an upward trend in asthma symptoms in boys and tendencies of a decrease in girls. The observed increase in boy-to-girl ratio of exposure to a number of environmental risk factors for asthma provides a reasonable explanation.

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APPENDIX

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	

Dagens datum	År	Månad	Dag

Namn på den förälder/värdnadshavare 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	Mättligt	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 klåande, 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, kläda 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 fotledema. 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		

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

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?	JA	NEJ
	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?		

ENKÄT OM LUFTVÄGS-, NÄS- OCH HUDBESVÄR HOS BARN I ÅRSKURS 1 OCH 2 I LULEÅ, KIRUNA OCH PITEÅ KOMMUNER, 2006

Skola	Klass

Barnets namn

Pojke	
Flicka	

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. Testet går till så att ett antal droppar med allergen placeras på underarmens insida. Sedan prickas det yttersta hudlagret genom dropparna. Dropparna torkas 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.

Frågor numrerade med **fet** siffra besvaras av alla.

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.	Tycker Du att barnet har lika bra ork (kondition) som sina jämnåriga kamrater?		
11.	Deltar barnet i skolans gymnastik och idrott **i full omfattning**?		
12.	Har barnet **under de senaste 12 månaderna** varit hemma från skolan vid något tillfälle pga andningsbesvär eller astma?		
13.	Har barnet av läkare fått diagnosen astma?		
14.	Går barnet på regelbundna kontroller för astma?		

		Aldrig	Ibland	Ofta/ periodvis	Varje dag
15.	Hur ofta har barnet behövt ta medicin pga astma **under de senaste 12 månaderna**?				

16.	Om barnet behövt ta medicin, har barnet använt något av följande?	JA	NEJ
	Ventoline, Bricanyl, Inspiryl eller andra luftvägsvidgande		
	Becotide, Pulmicort, Flutide eller andra kortisonpreperat		
	Oxix eller Serevent (långtidsverkande luftvägsvidgande)		
	Symbicort eller Seretide (kombinationspreperat)		
	Lomudal, Singulair eller annat		

		Har inga besvär/ inte alls	Något, litet	Måttligt	Ganska mycket
17.	**Under de senaste 12 månaderna**, hur mycket påverkade barnets andningsbesvär/astma barnets dagliga aktiviteter?				
18.	Tycker du att barnets andningsbesvär/astma förvärras när barnet är i skolan?				

Huvudfrågor vid näsbesvär

		JA	NEJ
19.	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
20.	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
21.	Har **under de senaste 12 månaderna** dessa näsbesvär förekommit samtidigt med kliande, rinnande ögon?		

22. 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
23.	**Under de senaste 12 månaderna**, hur mycket på verkade näsbesvären barnets dagliga aktiviteter?				

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

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

		JA	NEJ
26.	Har barnet av läkare fått diagnosen hösnuva eller allergiska näs-/ögonbesvär?		

Huvudfrågor vid hudbesvär

		JA	NEJ
27.	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 34.		

		JA	NEJ
28.	Har barnet haft detta kliande utslag någon gång **under de senaste 12 månaderna**? Om du har svarat "nej" var god gå direkt till fråga 34.		

		JA	NEJ
29.	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
30.	Vid vilken ålder fick barnet detta kliande utslag för första gången?			

		JA	NEJ
31.	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
32.	**Under de senaste 12 månaderna**, hur ofta, i genomsnitt, har detta kliande utslag hållit barnet vaket nattetid?			

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

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

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

		JA	NEJ
36.	Har barnet någonsin haft symtom på nickelallergi, dvs klåda/utslag av smycken, tex halssmycken, öronringar, metallknappar eller spännen?		
37.	Har barnet hål i öronen?		

Frågor om matallergi

		JA	NEJ
38.	Är barnet allergisk mot något i maten? **Om "ja"** besvara fråga 39.		

39.	Reagerar barnet på något av följande? Kryssa lämpliga alternativ. (Flera alternativ på varje rad möjliga)

	Vet ej	Inga besvär	Klåda i munnen	Andnings-besvär	Kräkningar, diarré eller ont i magen	Kliande utslag
Mjölk						
Ägg						
Fisk						
Skaldjur						
Vetemjöl						
Soja						
Äpplen						
Persikor						
Kiwi						
Avokado						
Banan						
Apelsin						
Råa morötter						
Potatis						
Jordnötter						
Nötter						
Mandel						
Annat, vad?						
.....						
.....						

Barnets bakgrundsdata

40.	Vad var barnets födelsevikt? .....gram

41.	Till vilken ålder fick barnet bröstmjölk? .....månader

42.	Vid vilken ålder fick barnet för första gången tillägg/ersättning/välling? .....månader

43.	Hur många syskon har barnet?

44.	Vilket barn i ordningen är barnet?

45.	Vad är barnets nuvarande längd? ..... cm
46.	Vad är barnets nuvarande vikt? ..... kg

47.	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			

48.	Vistades barnet på daghem/förskola 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	

49.	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	

50.	Har barnet haft	JA	NEJ
	Kikhosta		
	Krupp		
	Lunginflammation		
	svårare luftvägssjukdom, t ex RS-virus		
	övrig svårare infektionssjukdom		

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

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

Barnets bostad och miljö

53. Var och i vilken typ av bostad bodde barnet under det första levnadsåret?
Ange bostadsort samt sätt kryss i lämplig ruta för typ av område (stad/tätort eller ute på landet) och typ av bostad. (Om flera bostäder, ange den som barnet bott längst i under det första levnadsåret)

	Typ av område		Typ av bostad	
Bostadsort	Stad	Landsbygd	Villa/radhus	Lägenhet

54. 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 imma/fukt på insidan av fönstren			
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			

55.	**Nuvarande bostaden är:**		Ungefärligt Byggnadsår	Antal rum inkl kök	Ungefärlig bostadsyta
	Villa/radhus				
	Lägenhet				

56.	Hur många vuxna bor i hemmet?
57.	Hur många barn bor i hemmet?

Djur, fritid och kost

58.	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
59.	Fanns pälsdjur under någon period under barnets första två levnadsår?		
60.	Har Du/Ni valt att **inte** ha pälsdjur (tex katt eller hund) på grund av allergi i familjen?		
61.	Har Du/Ni valt att **inte** ha pälsdjur (tex katt eller hund) på grund av rädsla för att barnet ska bli allergiskt?		

62.		Nu	Tidigare under barnets uppväxt	Aldrig
	Har eller har familjen haft jordbruk?			

		JA	NEJ
63.	Rider barnet?		
	Rider annan familjemedlem?		

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

65.	**Hur ofta** äter barnet någon slags frukt?	
	Varje dag, minst två	
	Varje dag, ungefär en	
	Nästan varje dag	
	1-3 gånger per vecka	
	Mindre än en gång per vecka	

66.	**Hur ofta** äter barnet fisk?	
	Minst 3 gånger per vecka	
	Ungefär 2 gånger gånger per vecka	
	Ungefär 1 gång per vecka	
	Ungefär 1-3 gånger per vecka	
	Mindre än 1 gång per månad	
	Aldrig	

67.	**Hur ofta** äter barnet snabbmat (t.ex mat från Mac Donalds, Frasses, Max eller andra grill- och korvkiosker)?	
	Ungefär 1 gång per dag	
	Ungefär varannan dag	
	Ungefär 2 gånger per vecka	
	Ungefär 1 gång per vecka	
	Enstaka gånger per månad	
	Aldrig eller nästan aldrig	

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
68.	Far					
	Mor					
	Annan familjemedlem					

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

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

		JA	NEJ
71.	Rökte modern under graviditeten?		

Tack för Din medverkan!