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The prevalence and possible risk factors of asthma in a subarctic child population

A study of asthma and allergy among schoolchildren in Nordland county
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Once we accept our limits, we move beyond them.

Albert Einstein

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Contents

Summary

The 'asthma epidemic' has led asthma to become the most frequent chronic disease among children in developed countries. However, the prevalence of asthma and allergic diseases varies greatly around the world, and despite extensive research, there has not been a significant breakthrough in the understanding of the mechanisms and genetics of, and effective preventive strategies for asthma. This thesis is based on the results from the study 'Asthma and allergy among schoolchildren in Nordland county'. Overall aims were to investigate prevalence of asthma, allergic rhinoconjunctivitis (AR) and eczema in schoolchildren, identifying risk factors and possible associative mechanisms for the development of asthma in children and the use of diagnostic tools in relation to asthma and allergic diseases.

The first part of the study consisted of a cross-sectional questionnaire-based survey including 4150 children aged 7-14 years from randomly selected schools in Nordland county. The results in 2008 were compared to the results from similar surveys in 1985 and 1995. In the second part of the study, children reporting asthma ever (cases) in the cross-sectional survey together with matched non-asthmatic controls were invited to participate in a case-control study. The case-control study consisted of the clinical assessment and extensive clinical testing of 801 children, and the results were partly compared to a similar case-control study in 1985.

The results demonstrated an increase in the prevalence of asthma and AR ever in schoolchildren in the period 1985-2008, while the prevalence of eczema ever reached a plateau. The prevalence of the current diseases doubled and trebled between 1995 and 2008. Compared to clinical assessment (gold standard) the survey questionnaire was found to have a high sensitivity (0.96) and specificity (0.87), together with a very good overall agreement. Exploring possible risk factors showed that lower respiratory tract infections (LRTIs), AR and food allergy were most important in 2008, while repeated LRTIs, atopic diseases in the family and urticaria ever had most impact in 1985. During the study period, increased average temperature may have led to a rise in pollen production and thereby the increased prevalence

of AR. Thus, AR might have contributed to the increased asthma prevalence in the study population

In conclusion, the study revealed a considerable increase in the prevalence of asthma and AR in schoolchildren. When validating the questionnaire used against clinical assessment, we found the questionnaire to be a good epidemiological tool. LRTIs seems to be the most important risk factor for developing asthma in this subarctic child population, together with allergic comorbidity, which might have contributed to the increase in asthma prevalence in the period 1985-2008.

Sammendrag

Astmaepidemien de siste årtiene, har ført til at astma er blitt den vanligste kroniske sykdommen blant barn i den vestlige verden. Selv om studier fra ulike steder viser stor variasjon i forekomsten av astma, allergisk øye- og nesekatarr (rhinokonjunktivitt) og eksem, har man på tross av utstrakt forskning ikke funnet årsaken til sykdommene eller entydige forebyggende tiltak. Denne avhandlingen (tesen) er basert på resultater fra studien 'Astma og allergi blant skolebarn Nordland'. Formålet med studien var å undersøke forekomsten av astma, allergisk rhinokonjunktivitt og eksem blant skolebarn, identifisere risikofaktorer og mulige assosiative mekanismer for utviklingen av astma samt evaluere diagnostiske metoder brukt for astma og allergiske sykdommer.

Første del av studien bestod av en tverrsnittstudie som inkluderte 4150 barn, 7-14 år gamle fra tilfeldig utvalgte skoler i Nordland fylke. Resultatene fra 2008 ble sammenlignet med resultatene fra lignende studer fra 1985 og 1995. I den andre delen av studien ble astmatiske barn (cases) fra tversnittstudien invitert sammen med ikke-astmatiske barn (controls) med samme kjønn og alder til en oppfølgende case-control studie. Case-control studien bestod av klinisk vurdering og utstrakt klinisk testing av 801 barn, og resultatene ble delvis sammenlignet med en lignende case-control studie fra 1985.

Resultatene fra studien viser en økning i forekomsten av astma og allergisk rhinokonjunktivitt mellom 1985 og 2008, mens forekomsten av eksem flatet ut i siste del av perioden. Forekomsten av sykdom siste år, doblet og tredoblet seg mellom 1995 og 2008. Sammenlignet med klinisk vurdering (som gullstandard) hadde spørreskjemaet som ble brukt i studien høy validitet (sensitivitet 0.96 og spesifisitet 0.87) og resultatene var samsvarende. Undersøkelsen av mulige risikofaktorer for astma viste at nedre luftveisinfeksjoner, allergisk rhinokonjunktivitt og matvareallergi var viktigst i 2008, mens gjentatte nedre luftveisinfeksjoner, atopisk sykdom i familien og elveblest hadde størst betydning i 1985. I løpet av studieperioden har sannsynligvis en økning i gjennomsnittstemperatur ført til økt pollen produksjon og økt forekomst av allergisk rhinokonjunktivitt. Det kan bety at allergisk rhinokonjunktivitt har bidratt til økningen i astmaforekomst i denne populasjonen.

Som en konklusjon viser studien en kraftig økning av forekomsten av astma og allergisk rhinokonjunktivitt, og at spørreskjemaet fungerer som et godt epidemiologisk verktøy. Nedre luftveisinfeksjon ser ut til å være den viktigste faktoren for utvikling av astma i denne barnepopulasjonen, sammen med allergiske sykdommer. Allergisk rhinokonjunktivitt kan ha bidratt til økningen i forekomst av astma i perioden 1985-2008.

Abbreviations

AD	Atopic dermatitis
AOR	Adjusted odds ratio
AR	Allergic rhinoconjunctivitis
ATS	American Thoracic Society
BHR	Bronchial hyperresponsiveness
BMI	Body Mass Index
CI	Confidence interval
EIB	Exercise-induced bronchoconstriction
ERS	European Respiratory Society
ETS	Environmental tobacco smoke exposure
FEF_{50}	Forced expiratory flow in 50% of FVC
FE_{NO}	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HDM	House dust mite
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IMMULITE®	IMMULITE® 2000
LRTIs	Lower respiratory tract infections
NO	Nitric oxide
OR	Odds ratio
ppb	Parts per billion
SD	Standard deviation
SE	Standard error
sIgE	Allergen-specific IgE
SPT	Skin prick test
UOR	Unadjusted odds ratio

List of Papers

This thesis is based on the three papers listed below. The papers are referred to in the text by their Roman numerals (I-III).

Paper I

> Hansen TE, Evjenth B, Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: Three surveys during the period 1985-2008. Acta Paediatr 2013; 102:47-52.

Paper II

> Hansen TE, Evjenth B, Holt J. Validation of a questionnaire against clinical assessment in the diagnosis of asthma in schoolchildren. J Asthma 2015; 52:262-267.

Paper III

> Hansen TE, Evjenth B, Holt J. Lower respiratory tract infections appear to be the most important risk factor for current asthma in subarctic schoolchildren. Acta Paediatr 2018; DOI: 10.1111/apa.14603.

List of related Papers

1. Evjenth B, Hansen TE, Holt J. Exhaled nitric oxide decreases during exercise in non-asthmatic children. Clin Respir J 2013; 7:121-127.

2. Evjenth B, Hansen TE, Brekke OL, Holt J. Establishing IMMULITE® 2000 cut-off values for serum allergen-specific immunoglobulin and exploring their relationship to exhaled nitric oxide. Acta Paediatr 2014; 103:759-65.

3. Evjenth B, Hansen TE, Holt J. The effect of exercise on exhaled nitric oxide depends on allergic rhinoconjunctivitis in children. J Asthma 2015; 52:795-800.

1. Background

1.1.   The 'asthma epidemic'

Asthma is recognised as a complex condition with differences in severity, natural history, comorbidities, and treatment response (1). In recent decades, the prevalence of asthma and allergic diseases has increased substantially. The upward trend in asthma prevalence has been termed the 'asthma epidemic' (2). This 'asthma epidemic' has led asthma to become the most frequent chronic disease among children in developed countries (3, 4). Even if asthma-related hospitalisations and deaths have declined, the disease globally imposes a considerable burden on patients, healthcare systems and societies (5). Decades of research have not resulted in a significant breakthrough in the understanding of the mechanisms, genetics and possible preventive strategies of asthma (6).

1.2.   Asthma definition

Asthma as a medical term was probably first used by Hippocrates (460-370 BC) (7). Since then the disease has been described in a multitude of ways based on the current knowledge of the time and the most recent understanding of pathogenesis, underlying mechanism and possible causal factors. As an attempt to make international guidelines based on consensus the Global Initiative for Asthma (GINA) was founded in 1993 (8). Over the past 25 years, GINA has published and annually updated the 'global strategy for asthma management and prevention'. This has formed the basis for many national guidelines (9). In 2014, the definition of asthma was revised with the purpose of making it more applicable to clinical practice. In the 2018 updated GINA guidelines the current definition is:

'Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation' (10).

1.3.   Clinical features of asthma

Both symptoms and airflow limitation characteristically vary over time and in intensity. These variations are often triggered by external factors such as viral respiratory infections, allergens or irritant exposure, changes in weather conditions and exercise. Despite the childhood

asthma spectrum being well recognized (11), subgroups are challenging to identify and the number and definitions of asthma types are unknown. Later descriptions refer to asthma as an umbrella term like anaemia or arthritis (1, 12), which may identify syndromes, phenotypes or even multiple diseases rather than a single disease (figure 1). Recognisable clusters of clinical, demographic and/or pathophysiological characteristics with identifiable biomarkers, risk factors, comorbidities and response to therapies are often called 'asthma phenotypes'. However, these subgroups do not necessarily correlate with specific pathological processes or treatment responses (13). In addition, several of the phenotypes overlap (12) making sub-classification complicated.
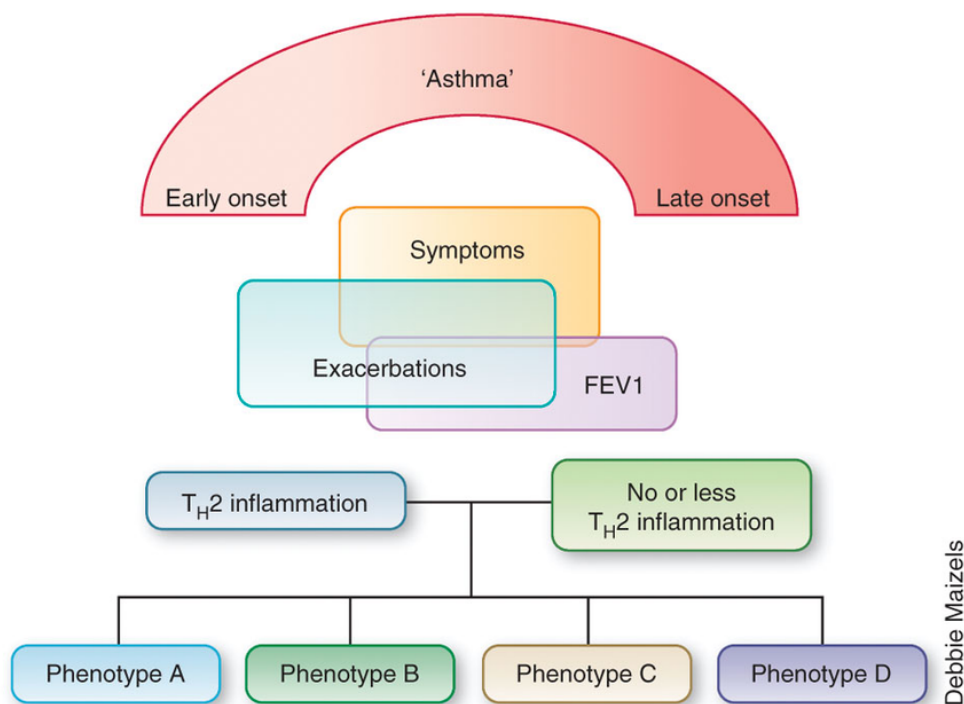
Figure 1. *Schematic presentation of the umbrella term 'asthma'.*

The key clinical features of severity (lung function, symptoms and exacerbations), inflammatory characteristics (particularly TH2 immunity) and their division into associated phenotypes are shown. However, these phenotypes have not yet been fully characterized.

Asthma has different degrees of severity (14). Most children suffering from asthma have mild to moderate symptoms and are able to control the disease by using inhalation medicines (i.e.

short acting β2-agonists and inhaled corticosteroids (ICS)). However, a small fraction, estimated prevalence 4-5% of the children with current asthma (15), experience serious illness with symptoms during the night, frequent periods of exacerbations, numerous absences from school, reduced quality of life and increased risk of hospitalisation. Children suffering from sever asthma often do not respond to standard therapy and are therefore difficult to treat properly. Another feature of asthma is that many patients experience relapse after years without symptoms, which illustrates the importance of long-term follow-up (16).

1.4.   Different epidemiological study designs

Epidemiology is the study of something that afflicts a population. Usually epidemiology is defined as the study of factors that determine the occurrence and distribution of disease in a human population (17). The central goal of epidemiology as a science is to understand the causes of disease variation and use this knowledge to improve the health of populations and individuals. Traditionally epidemiological research has consisted of observational studies where the investigator is not acting upon study participants (18). However, it has become more common to include intervention studies as part of epidemiological (clinical) research.

As many research questions can be answered by different type of study design, the choice of design depends of several considerations, including speed, costs, resources, access to cases and identification of the exposures. Each type of design has advantages and disadvantages, as summarized in table 1. Prospective cohort studies are considered the gold standard of observational studies being the only design suited for suggesting causation (18). In contrast, case-control studies compare exposures between people with a particular disease outcome (cases) and people without that outcome (controls). The longitudinal design makes is possible to measure the incidence and the natural history of disease. One of the most important principle in case-control studies is that the controls should represent the population at risk of the disease (19).

Table 1. Advantages and disadvantages in different designs used in epidemiological studies.

Design	Advantages	Disadvantages
Cross-sectional surveys	Timely Inexpensive Can assess multiple outcomes Can calculate prevalence	Carried out at a singled point in time Do not offer a temporal relationship between risk factors and disease
Cohort studies	Can be performed retrospectively or prospectively Can be used to obtain a incidence and a true measure of risk Can assess multiple outcomes	Time consuming Prospective studies are costly Can only study risk factors included from the beginning Losses to follow-up Not good for rare diseases
Case-control studies	Inexpensive Quick and easy to perform. Can assess multiple exposures or risk factors Good for rare diseases	Can obtain only a relative measure of risk Subjected to selection and recall biases Can assess only one disease outcome
Randomized controlled trials	Evaluation of treatments and interventions (gold standard)	Time consuming Expensive Limited in generalizability

Research has demonstrated a lack of consistency in reporting on quality in observational studies published in high impact medical journals (20). Consequently, the STROBE initiative was set in form of a checklist with the aim to provide helpful recommendations for reporting epidemiological studies to improve the reporting quality (21).

1.5. Asthma screening

The best evidence of changes in disease prevalence comes from repeated studies in the same population at sufficient intervals of time and using the same instrument (2, 22). Screening is defined as 'examination of a group of usually asymptomatic people to detect those with a high probability of having a given disease, typically by means of an inexpensive diagnostic test' (23). Validity is the degree to which an instrument measures what it intends to measure. While no screening test is perfect, valid prevalence estimates require a screening test with a high sensitivity and specificity (24). Sensitivity is the proportion of subjects with 'true' asthma and specificity is the proportion of subjects without asthma classified correctly by the

survey instrument. In the absence of an unambiguous definition of asthma and a diagnostic 'gold standard', clinical assessment is the closest we can get to a true diagnosis (25, 26).

An important challenge with symptoms-based questions is to identify asthma as distinct from other diseases presenting with similar symptoms. The symptom 'wheeze' is a hallmark of early childhood asthma and is used as a proxy marker to determine asthma prevalence in population surveys (27). Still, there are several causes of 'wheeze' other than asthma, for instance lower respiratory tract infections (LRTIs) and poor physical condition. In addition, wheeze is a fluctuating symptom with varying duration, and using wheeze in computing the incidence of childhood asthma might result in over-estimating (28). Furthermore, the lack of an exact translation of the term 'wheeze' in most languages (25) may entail some uncertainty around the interpretation of the results. Thus, parental reported 'wheeze' carries a large risk of misclassification and lacks cross-cultural validity (27, 29).

Efforts have been made to increase the diagnostic accuracy of childhood asthma by adding objective measurements such as lung function tests and tests of bronchial hyper-responsiveness (BHR). These tests provide objective information, which does not change over time, an advantage that can be exploited in repeated studies. On the downside, clinical tests are difficult to perform in large populations and results from several studies demonstrate that these measurements do not necessarily provide additional information (22, 30, 31).

The majority of published data concerning the prevalence of asthma and temporal time trends are based on repeated cross-sectional questionnaire studies, such as the International Study of Asthma and Allergies in Childhood (ISAAC) (32) and The Obstructive Lung Disease in Northern Sweden (OLIN) study (33), together with other studies from Sweden (34), Canada (35), Greece (36) and Italy (37). In addition, knowledge about asthma prevalence has been brought to us by prospective cohort studies using repeated questionnaires like the Tucson Children's Respiratory Study (TCRS) (38), the German Multicentre Allergy Study (MAS) (39), the Environment and Childhood Asthma (ECA) study in Oslo (40), the Barn (Children), Allergy, Milieu Stockholm Epidemiological Study (BAMSE) (41) and the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) (42).

1.6   Asthma prevalence and temporal trends

In the northern part of Norway, a questionnaire-based, cross-sectional survey focusing on asthma, allergic rhinoconjunctivitis (AR) and eczema was conducted in 1985 (43) (Appendix 1). The questionnaire was distributed to schoolchildren aged 7 -13 years in randomly selected schools in northern Norway (Nordland, Troms and Finnmark counties) for parental/guardian reply. Altogether, 10 093 (90.1%) children responded. Ten years later a similar questionnaire with additional questions concerning symptoms and diseases during the last 12 months (current diseases) was sent to schoolchildren in the same geographical area (Appendix 2). A total of 8676 (87.3%) responded in Nordland county and the lifetime prevalence of asthma increased from 5.1% to 8.6% over this 10-year period (44). The questionnaire has been used in other surveys in Norway (45-47).

In 1993, the ISAAC study created a cross-sectional questionnaire based trial to maximise the value of epidemiological research in asthma and allergic diseases (32). Compared to the questionnaire created in northern Norway, the ISAAC questionnaire constituted similar questions. The main difference between the ISAAC questionnaire and the questionnaire created in Norway was he question about asthma symptoms. In this question, the ISAAC only asked about wheeze or whistling (Question 1, table 1) (32), while the Norwegian questionnaire (Question 2 in definition of asthma ever) in addition asked about shortness of breath and cough. The ISAAC Phase I results presented in 1998, revealed an up to 20-fold variation in the prevalence of 'current wheeze' between more than 60 centres worldwide (range 1.8-36.7%) (48). The highest prevalences were detected in developed English-speaking countries (e.g. UK, Australia and New Zealand), while the lowest prevalences were found in Eastern Europe and Asia (i.e. India and China). Results from the ISAAC Phase III study (2000-2003) indicated that wide variation in asthma symptom prevalence still existed even if the difference in asthma symptom prevalence between developed and developing countries were reduced (49-51) (figure 2).
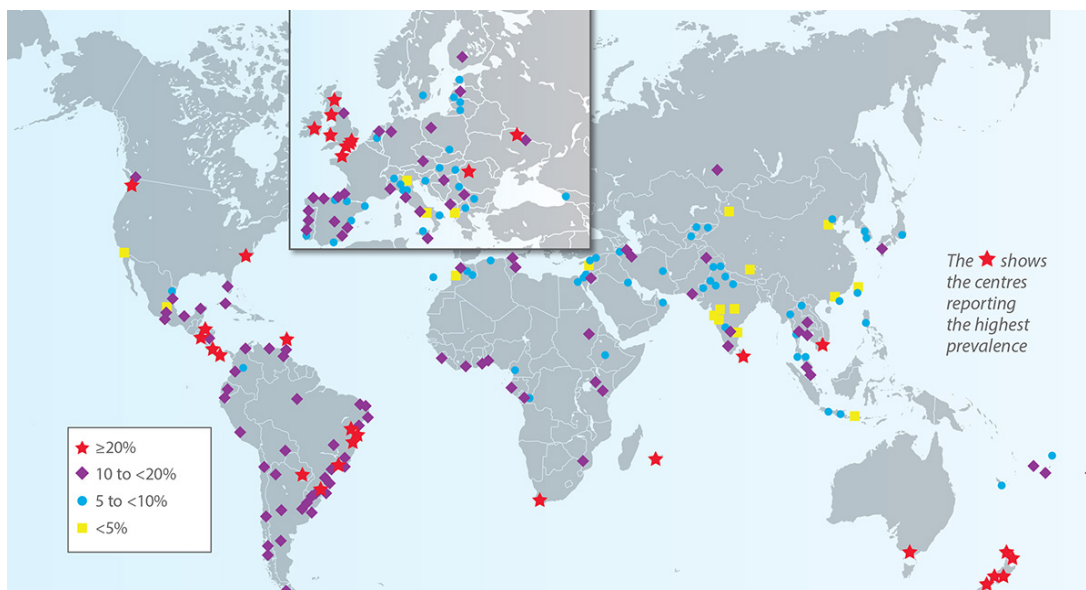
Figure 2. *The worldwide prevalence of current asthma symptoms among 13-14 year olds (ISAAC).*

The prevalence of current wheeze according to the written questionnaire in the 13–14 year age group in ISAAC, phase III. The symbols indicate prevalence values of <5% (yellow square), 5 to <10% (blue circle), 10 to <20% (purple diamond) and >20% (red star).

Other estimates of temporal trends in asthma prevalence are conflicting. Whereas some studies performed in the period from 1995 until present demonstrate an increasing prevalence of asthma and allergic diseases (35, 52, 53), other reports indicate a levelling off or even a decrease in asthma prevalence (54-56). These diverse global trends make repeated regional investigations important to assess time trends. Local surveys provide information about geoclimatic variables and topographical factors that may affect disease prevalence (57, 58).

1.7. The 'atopic march' and asthma comorbidity

Allergy-related or atopic diseases, includes asthma, AR, eczema and food allergy. Atopy is defined as 'a personal or familial propensity to become sensitised and produce immunoglobulin E (IgE) antibodies in response to environmental triggers' (59). The diagnosis of allergic diseases involves both the presence of symptoms and relevant sensitisation. Allergic diseases share several characteristics and are all included within the 'atopic march'.

The 'Atopic March' sometimes called the 'Allergic March' refers to the natural history or typical progression of allergic diseases, which often begins early in life (60). Eczema in the form of atopic dermatitis defines the initial step of the atopic march and is a significant risk factor for the development of asthma and AR, but whether atopic dermatitis is necessary for progression to other atopic diseases, remains to be established (61).

Food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly after exposure to a given food, including both IgE mediated or non-IgE mediated reactivity (62). Food allergy is more prevalent in early childhood. The prevalence of food allergy has increased during recent decades, in the same manner as asthma prevalence (63). In the USA, the prevalence of food allergy overall was found to be 8% in children (0-17 years) (64). The National Health and Nutrition Examination Survey 2005-2006 (USA) showed that study participants with doctor-diagnosed asthma (versus no asthma), particularly those reporting current asthma, exhibited increased risk of allergic sensitisation towards food and increased risk of likely food allergy (65).

The link between AR and asthma is well known and they frequently coexist. In the Norwegian ECA study, current rhinitis was reported in 25.0% of the 10-year-old children and was associated with asthma in 31.7% of the children (66). Investigating the association between asthma and other diseases using healthcare data from children and adolescents (6-17 years of age) in Germany, Jacob and colleagues revealed a strong association between asthma and vasomotor rhinitis and/or AR (OR 4.5-5.9) (67). In asthmatic children, 55-80% are reported to suffer from comorbid rhinitis in other studies (68-70). Asthmatic children suffering from AR have poorer asthma control (69) and experience more severe asthma symptoms, and more asthma exacerbations resulting in more absence from school (71).

Several studies have recorded a substantial degree of comorbidity between asthma, AR and eczema. The BAMSE study in Sweden showed that comorbidity between asthma, eczema and rhinitis increased from 1.8% at 1 year of age to 7.5% at age 12 (70). A prospective cohort study assessing children from 12 ongoing European birth cohort studies (Mechanisms of the Development of Allergy (MeDALL)) pointed out that coexistence of eczema, rhinitis, and asthma in the same child was more common than expected, regardless of IgE sensitisation (72). Other diseases e.g. pneumonia, chronic bronchitis and obesity, have also been found to be associated with asthma (67).

1.8.　Risk factors for childhood asthma

Asthma is a complex disease. It is likely that changes in prevalence are due to multiple factors each contributing a relatively small effect (2, 73, 74). Numerous theories have been launched in order to explain the increased prevalence of asthma and allergic diseases. However, a truly unifying concept is still missing. Much attention has been devoted to the hygiene hypothesis. The epidemiologist D. Strachan proposed the hygiene hypothesis in 1989, which suggested that the rise in prevalence of allergic diseases could be explained by reduced opportunities for cross-infection in young families (75). According to the hygiene hypothesis, a reduction in the diversity and magnitude of 'microbial burden' in early life decreases activation of a common immune control mechanism, namely regulatory T-cells. The reduction in control mechanism leads to a increased propensity for allergy sensitisation (76). Later research has concluded that the original hygiene hypothesis based purely on infection, does not offer a complete explanation of the observed increase in allergic diseases (77).

The wide variation in asthma prevalence between populations and the rapid rise within a relatively short period indicate that environmental factors play a greater role than genetic factors (2). In contrast to this assumption, parental asthma and/or AR often are the strongest risk factors compared with other risk factors in epidemiological studies (58, 78-80). Other individual risk factors are: maternal smoking, gender, AR, allergic sensitisation, birth weight, family stress at birth, overweight, LRTIs, length of breastfeeding, household animals, lifestyle and living conditions (80-83). In addition, some environmental factors at the population level, such as climate changes and outdoor pollution may affect the development of asthma (84-86).

1.8.1.　Non-Environmental risk factors

Allergic sensitization

The prevalence of allergic sensitisation increases during childhood and adolescence, usually starting with sensitisation to food allergens and thereafter sensitisation to inhalant allergens, until the prevalence levels out in early adulthood (52, 87, 88). Some risk factors for allergic sensitisation are known, and heredity seems to be the strongest factor (89). Allergic sensitisation has been reported as one of the strongest determinants of childhood asthma (90).

Birth weight and overweight

Birth weight is a proxy marker for the environment in utero. Low birth weight because of poor intrauterine growth (small for gestational age) and low gestational age at birth seem to be risk factors for later asthma (91-93). The increase in asthma and allergic diseases has occurred in parallel with the obesity epidemic, suggesting a possible association. However, studies in children concerning weight and the risk for developing asthma have not been consistent. It appears to be a U-shaped association between body mass index (BMI) and risk for asthma (94, 95). Some have documented a stronger association between obesity and asthma in those with no allergy history, implying that a distinct obesity phenotype may explain the diversity in study findings (96).

Genetics

Asthma and allergic diseases has a strong heritable component (97), and in epidemiological studies (58, 80), parental asthma is the strongest risk factor. Several genes (>100) with a positive association to asthma or atopic phenotypes have been identified, even though the individual effect of any one of these genes on disease risk is quite small (98, 99). Recently, there has been increased attention on the link between genetics and environmental factors: epigenetics. Epigenetics is the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence (100). Epigenetics may partly explain the heterogeneous appearance of asthma, but further studies are needed to determine its role in its development.

Sex

It is well known that the prevalence of asthma and asthma symptoms differs between males and females. Until teenage, the prevalence of asthma is higher among boys than girls. Studies reporting sex-specific time trends document a change to a female predominance in the sex ratio during puberty and adolescence (28, 56, 101, 102). At which age this shift take place has been debated. A recent study indicated this breaking point to be around 15 years of age (103). One of the reasons why the male disadvantage for asthma disappears during puberty seems to be a higher remission rate among boys than girls (104). Hormonal influences (105) and airway calibre (28) have also been discussed as possible causes for the gender difference.

1.8.2. Environmental risk factors

Breastfeeding

Breastfeeding is an important factor that has been linked to childhood asthma. Although many health benefits of breastfeeding are well documented, studies reporting effects on asthma risk have inconsistent findings. Both the Swedish BAMSE and Danish COPSAC studies have demonstrated a protective effect of breastfeeding on the development of asthma (106, 107), while a randomised trial among nearly 14 000 children receiving an experimental breastfeeding intervention and followed up until age 6.5 years, showed no differences in asthma prevalence or allergic symptoms between the groups (108). Recent studies suggest that the efficacy of the World Health Organization (WHO) breastfeeding guidelines relating to long-term outcomes for allergic disease might be questioned (109).

Climate change and outdoor pollution

Despite efforts to link the 'asthma epidemic' to climate change and increased outdoor pollution, it has been difficult to document a definitive association between air pollution and asthma development. The global patterns of asthma prevalence contradict the hypothesis that air pollution is a major risk factor for the development of asthma, since regions with the highest level of traditional air pollution (e.g. China and Eastern Europe) have considerable lower asthma prevalence than regions with lower air pollution (i.e. Western Europe, Australia, North America) (110). Still it is questioned if traffic-related air pollution has an impact on asthma development alone or in combination with genetics, allergens, tobacco smoke and psychosocial stress (2).

The ISAAC Phase one study has demonstrated a negative association with annual variation of temperature, relative humidity outdoor and childhood asthma symptoms in Western Europe (111). These results suggest that climate might affect the prevalence of asthma (112). A possible explanation for this phenomenon is that the generation and dispersion of air pollutants depend in part on local patterns of temperature, wind, solar radiation and precipitation. Thus, climate changes influence air quality and outdoor air pollution levels, which may influence respiratory health (figure 3) (113).
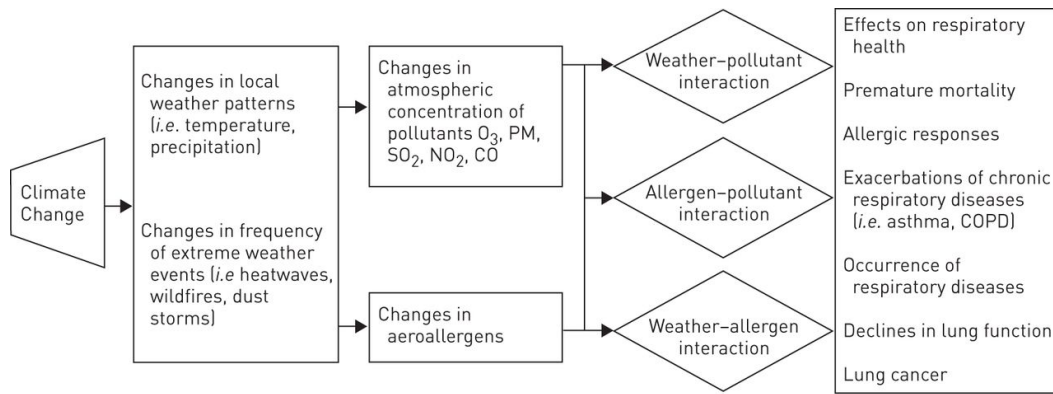
Figure 3. *Climate change: its influence on extreme weather events, air pollution and aeroallergens, and effects on respiratory health.*

PM: particulate matter; COPD: chronic obstructive pulmonary disease.

Early life infections

LRTIs caused by viruses are major triggers for wheeze and asthma exacerbations, especially in infants and young children. Rhinoviruses are the most prevalent viruses detected in all age groups, while Respiratory Syncytial Virus (RSV) is the most common cause of severe bronchiolitis in infants (114, 115). Viral airway infections and atopy may interact in a multiplicative way to promote asthma development in young children. Since early infancy constitutes a particularly vulnerable period of life, a causal relationship has been suggested, but not established, between LRTIs and asthma (116, 117). On the other hand, virus induced wheeze may uncover a predisposition for asthma development followed by impaired lung function (11). The number and severity of early life bronchial obstructive episodes have the greatest impact on risk of pubertal asthma (82).

Environmental tobacco smoke exposure (ETS)

ETS during pregnancy is a known risk factor for the development of asthma and is associated with a lower birth weight, decreased lung function and an increased risk for wheezing (118). Recent reports imply that an association between parental smoking and childhood asthma extends further, beyond maternal smoking during pregnancy and throughout childhood (112, 119). The OLIN studies demonstrated a 50% decrease in the prevalence of maternal smoking from1996 to 2006, diminishing the impact on current asthma to near zero (58). Decreasing ETS will probably positively influence the development of asthma and asthma symptoms.

Exposure to animals

The most commonly studied associations between animal exposure and asthma are exposure to cats and dogs; the most commonly kept household animals in the western world. In a meta-analysis including data from both cross-sectional and cohort studies from 1966 to 2007, Takkouche and colleagues found that exposure to cats exerted a preventive effect on asthma while exposure to dogs increased the risk of asthma (120). In a more recent report from the ISAAC Phase 3 study, it was concluded that exposure to cats in the first year of life was a risk factor for symptoms of asthma, AR and eczema in children aged 6 -7 years (121). One challenge in interpreting the results from these studies is that families with asthma and allergic diseases might refrain from having pets at home or might remove them after disease has been established. This could lead to the erroneous conclusion that pet ownership provides a protective effect (reverse causation) (122).

Another important association is the allegedly protective effect of being exposed to farming environments and farm animals. Two large-scale observational studies of schoolchildren living in predominantly rural areas of Central Europe (PARSIFAL and GABRIELLA) compared children living on farms with a reference group. Both studies came to the same conclusion: Children living on farms were exposed to a wider range of microbes than children in the reference group. The exposure to a wider range of microbes could explain a substantial fraction of the inverse relation between asthma prevalence and growing up on a farm (123).

2. Aims of the thesis

The overall aim of 'Asthma and allergy among schoolchildren in Nordland county' was to investigate:

- The occurrence and time trends of atopic diseases in a subarctic child population
- Factors that may influence the degree of severity and course of bronchial asthma
- Underlying risk factors and possible associative and causal mechanisms for the development of asthma among schoolchildren
- Fractional exhaled nitric oxide (FE_{NO}) levels in relation to asthma, AR, serum specific IgE (sIgE) and exercise and establish cut-off levels for sIgE to diagnose AR.

The specific aims in this thesis were:

1. To explore whether or not the prevalence of asthma, AR and eczema in schoolchildren in Nordland county continued to increase over a 23 year period (paper I).

2. To validate the questionnaire used in paper I and make an assessment of its reliability and practical usefulness (paper II).

3. To explore associative and possible risk factors for asthmatic disease in this child population and compare the results with data from 1985: can transformation of risk factors explain altered prevalence of asthma and/or local conditions that may have affected disease prevalence (paper III)?

3. Methods

3.1.　　Study area

The Northern part of Norway consists of three counties: Nordland, Troms and Finnmark, with a subarctic population of 485 000 inhabitants. Nordland county, which covers an area of 38 000 km2 has a population of 243 000 (124). Its unique geography features a long coastline (25% of Norway's total coastline), half of it located north of the Arctic Circle. Thus, most of Nordland's inhabitants live in sparsely populated areas and experience a coastal climate.

3.2.　　Overall study design

This thesis is based on data from a cross-sectional survey and a case-control study from 'Asthma and allergy among schoolchildren in Nordland county', together with data from previously published cross-sectional surveys in 1985 and 1995 (paper I) and from a previously unpublished case-control study performed in 1985 (paper III). The overall study design in 'Asthma and allergy among schoolchildren in Nordland County' and in the 1985, study follows a similar pattern (figure 4):

1. A cross-sectional survey.

   A questionnaire for determining the prevalence of asthma, AR and eczema was distributed to randomly selected schoolchildren. All surveys compared used identical questions for defining disease.

2. A case-control study

   Study subjects who reported ever having asthma (cases) together with matched non-asthmatic controls were invited to a case-control study including a new questionnaire, a structured interview and clinical examination and testing. Based on the clinical assessment (interview and clinical examination) children were categorised as asthmatic or non-asthmatic and asthma severity was classified.

3. Study subjects fulfilling the definition criteria for current asthma (cases) and non-asthmatics controls were then compared.
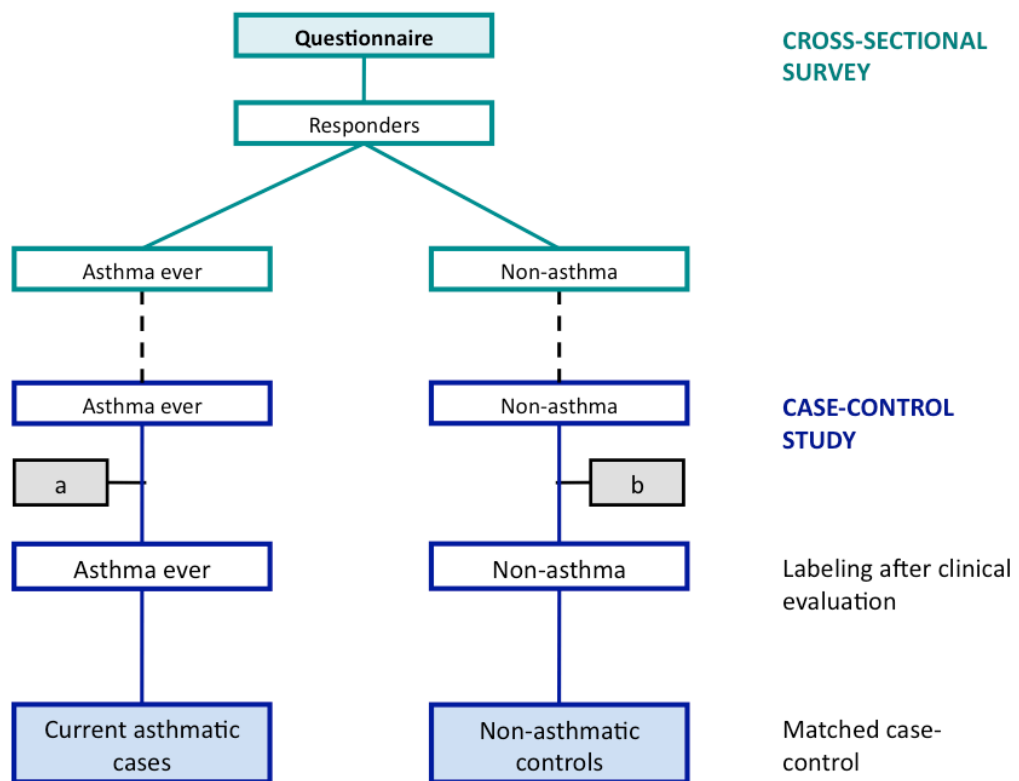
Figure 4. *A schematic flow chart for study subjects in 'Asthma and Allergy among schoolchildren in Nordland County.*

[a]*Subjects categorised as non-asthmatic after clinical assessment.*

[b]*Subjects misclassified as non-asthmatics, new cases of asthma.*

The matched case-control design was chosen over the preferred prospective cohort (longitudinal) design due to limited resources for conducting the study, the timeline and since we aimed to validate the questionnaire used in the cross-sectional survey, evaluate different diagnostic tools and assess associations between asthma and different exposures. The main reason for choosing a matched design was to ensure that the cases and control were similar with respect to the possible confounding factors age and gender. Age and gender are both strongly associated with the outcomes asthma, AR and eczema together with several of the exposure variables. Matching for these variables, we believe, ensured better statistical efficacy in the study. For further discussion of study design, see section 5.4.2.

3.3.   Ethical considerations

Children as study subjects are vulnerable since they cannot give their own, independent consent to participating. Hence, when conducting research in children one must be very careful in the consideration of ethical aspects. In the cross-sectional survey, the parents/guardians signed a written consent for their children's participation. In addition, they gave a written response to the question: Do the parents allow us to contact you with information on a follow-up survey if your child is selected to participate? Only individuals who answered yes to this question were invited to the case-control study. At enrolment, a renewal of the consent was obtained from all the participating children and their parents/guardians. The participants were informed that they could withdraw from the study at any time.

Written information about risks and benefits for the study participants was sent together with the invitation to the case-control study. When the children met for their assessment and examinations, the risks and benefits for the participants were repeated verbally to the child. Since participating was voluntary, the children could withdraw from any part of the study if desired. The main risks for participating in the case-control study were sharing sensitive information with the researchers and experiencing discomfort from some of the tests (e.g. blood sampling). The benefits of participating in the study were a thorough clinical assessment of their asthma, AR and eczema status, extensive examinations using different diagnostic tests and gaining information about the diseases and evaluation of treatments as adding or discontinuing medication. All participants examined with blood sampling received a letter containing the test results with comments, after analysis.

At enrollment, each participant received a unique record id number to secure anonymity and making any tracing of the participants impossible for unauthorized people. In order of combining record id numbers to names at follow up, a key only known to the two main researchers in the study was used. The anonymous data was stored in a separate computer with login and password. Later, the data files were sent for secure storage at Nordland Hospital Trust.

The Regional Committee for Medical and Health Research Ethics, Northern Norway and the Norwegian Data Inspectorate approved both the study in 1985 and to 'Asthma and allergy

among schoolchildren in Nordland County'. In 'Asthma and allergy among schoolchildren in Nordland County', Health Research Ethics were conducted in accordance with the ethical standards of the 2000 Helsinki Declaration. All written documents and questionnaires from the study was shredded and an end report of the study has been sent to the Norwegian Data Inspectorate.

3.4. The 1985-study

Two paediatricians Jan Holt and Roald Bolle developed a questionnaire concerning asthma, AR and eczema and used it for the first time in 1985 (Appendix 1). The questionnaire was distributed to randomly selected schoolchildren in Northern Norway aged 7-13 years. In 1995, the survey was repeated (43, 44) (paper I) (Appendix 2). From the survey in 1985 approximately one third of the children reporting asthma ever (those with birthdays between the first to tenth of every month) together with non-asthmatic controls matched for age, gender and school affiliation, were invited to participate in the case-control study during 1986-1987. The children lived in different geographical areas in Nordland, representing both coast and inland.

Participating children with parents/guardians completed a structured interview including questions concerning socio-economic conditions, LRTIs, passive smoke exposure, and detailed questions about asthma symptoms and treatment. In addition, the participants underwent a clinical examination and clinical testing including spirometry and sIgE. SPTs were performed in cases only. A modified Kjell Aas scale, a system proposed by Norwegian paediatric allergologist (45) was employed for the evaluation of severity. A paediatrician, Jan Holt, conducted all interviews, examinations and tests at the local healthcare station or in the children's homes. Data from this case-control study are previously unpublished (paper III).

3.5. Asthma and allergy among schoolchildren in Nordland county

To identify symptomatic and non-symptomatic children suffering from atopic diseases, schoolchildren aged 7-14 years from 65 randomly selected schools of the 244 schools in Nordland county were invited to participate in a cross–sectional questionnaire-based survey. Parents and children received a questionnaire with identical questions for defining disease (asthma, AR and eczema) as in the 1985 and 1995 surveys (Appendix 3). The questionnaire

was distributed between February and May 2008. All participants received one reminder. The study closed four weeks after the reminder was distributed (paper I).

To validate the questionnaire and to verify diagnosis and risk factors for atopic diseases, we performed a case-control study. Pupils who reported asthma ever (cases) in the questionnaire and who lived within two hours by car from the study locations along with two matched non-asthmatic controls were invited to participate. The cases were matched to non-asthmatic controls on an individual basis for gender and age, choosing the non-asthmatic child closest in age. Preferably, cases and controls went to the same school; however, when this premise was violated due to the small number of pupils at the school, the control was chosen from the same geographic area.

The children, together with their parents or guardian, completed a questionnaire and a structured interview. A clinical examination, spirometry, exercise treadmill testing, skin prick tests (SPTs) and measurements of FE_{NO}, sIgE and total IgE were obtained. Based on the clinical assessment (interview and clinical examination) as the golden standard, children were finally categorised as asthmatic or non-asthmatic (paper II).

The asthmatic children were categorised as current asthmatics or not, and asthma severity was classified according to the GINA guidelines (14). The assessments of children fulfilling the definition criteria for current asthma and non-asthmatics age- and gender-matched controls were compared (paper III).

The participants were examined at least two weeks after any suspected respiratory tract infection during the school term from March 2009 to June 2010. The examination took place at Nordland Hospital Trust, Bodø, and three other locations in Nordland county (Fauske, Mo i Rana and Sortland). Bjørg Evjenth MD, Phd and the author conducted all the interviews and procedures. The same medical instruments were used to secure standardised measurement conditions.

3.6.   Definitions

3.6.1. The cross-sectional survey (paper I)

'Asthma ever' was considered if the parent answered 'yes' to the question: Has the pupil ever had asthma? and/or to the question: Does the pupil experience wheeze, periods of coughing or acute shortness of breath (asthma) due to external factors?

′Allergic rhinoconjunctivitis (AR) ever′ was based on a positive answer to the question: Has the pupil ever had hay fever (runny or blocked nose, sneezing, itching of the nose and/or eyes, or swollen or red eyes)?

′Eczema ever′ was recorded if the pupils reported an itchy rash lasting at least four weeks combined with lesions on the face, elbows or knee flexures, or a high degree of itching and lesions elsewhere.

′Current disease′ was considered among those answering yes to the main questions about asthma, AR or eczema and reporting symptoms the last 12 months.

3.6.2. The case-control studies (paper II and III)

Based on the structured interviews and clinical findings, the final diagnoses in the surveys were confirmed by a doctor.

Asthma: At least two of the following three criteria fulfilled at any time in life: 1) recurrent dyspnoea, chest tightness and/or wheeze; 2) a doctor's diagnosis of asthma; 3) Use of asthma medication including β-2 agonist, sodium chromoglycate, ICS, leukotriene antagonists and/or aminophylline.

Current asthma: asthma as defined above, plus symptoms and/or medication within the last year.

Allergic rhinoconjunctivitis (AR): a history of watery rhinorrhea, blocked nose, sneezing, nasal itching accompanied by itchy watery eyes in the absence of airway infection.

Eczema: an itchy rash lasting at least 4 weeks combined with lesions on the face, elbows or knee flexures, or a high degree of itching and lesions elsewhere.

Food allergy: a history of related food allergy symptoms as evaluated by a doctor.

Current disease: symptoms as defined above within the last year.

Atopic disease in the family: a positive response to the question: 'Does anyone in the family (parents and/or siblings) suffer from asthma, AR, eczema or urticaria'.

Allergic sensitisation: a positive SPT (wheal diameter ≥3 mm larger than the negative control) and/or a positive sIgE (>0.35 kU/L) to > 1/14 of the allergens tested for.

3.7. Questionnaires, structured interview and clinical examination

3.7.1. Questionnaire used in the cross-sectional survey

A questionnaire was earlier used in 1985 (43) (Appendix 1) and 1995 (125) (Appendix 2) to assess atopic disease among schoolchildren in northern Norway. The questions covered gender, age, family history of atopy, socio-economic conditions, passive smoke exposure and household animals. In 2008, we used the same questionnaire (Appendix 3), and added some questions about physical activity, diagnosis of asthma and asthma medication. The additional questions did not change the definition of diseases.

3.7.2. Questionnaire and structured interview in the case-control study

The children together with their parents/guardians completed a detailed questionnaire and a structured interview relating to asthma, AR, eczema, food allergy, urticaria, anaphylaxis, the use of medications, exposure to allergens, exposure to tobacco smoke, infections and other diseases during the first three years of life, diet and physical activity. Additional questions regarding demographic and socio-economic factors were answered and recorded.

3.7.3. Clinical examination

A clinical examination was performed including height and weight measurements and assessment of the skin, the upper airways, lungs and heart. ICS and short acting β-2 agonists were withheld for 12 hours prior to testing; inhaled long acting β-2 agonist for the last 48 hours; leukotriene modifiers for the last 24 hours; and histamine in the last 5 days. No children were using oral steroids.

3.8. Clinical tests

3.8.1. Allergic sensitisation

Serum total IgE and sIgE: Blood samples were obtained using standard venepuncture using Vacutainer® tubes (Becton Dickinson, Plymouth, UK). Serum was collected and stored at -80°C until assayed. Total IgE and sIgE levels were analysed employing the IMMULITE® 2000 (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA) using 3gAllergy® kits. The detection range for sIgE was ≥0.10-100 kU/L. The following were tested: sIgE to timothy, birch and mugwort pollens; dog dander, cat and rabbit epithelial dander; house dust mite *Dermatophagoides pteronyssinus*; moulds *Alternaria tenius* and *Cladosporium herbarium*

and German cockroach. Seroatopy was defined by a sIgE $\geq$0.35 kU/L to at least one of the listed allergens. Blood samples were requested for all children.

Skin prick tests: SPTs were performed for the above listed allergens and egg white, milk, peanut and codfish with Soluprick® allergens (ALK Abello, Denmark). Histamine was used as positive control and saline as negative control. SPT was considered positive in the presence of a wheal diameter $\geq$3 mm larger than the negative control (126). During the initial study period, SPT was requested for all children. Thereafter, SPT was requested for children with asthma and/or allergy symptoms.

3.8.2. Fractional exhaled nitric oxide (FENO)

FE_{NO} was measured online by the single breath method with a chemiluminescence analyser, EcoMedics Exhalyzer® CLD 88sp with Denox 88 (Eco Medics AG, Duernten, Switzerland), (detection range 0.1-5000 ppb, accuracy $\pm$ 2%). The procedure was performed in accordance with published guidelines (127). The participants inhaled nitric oxide (NO) free air (< 5 parts per billion, ppb) to near total lung capacity to avoid contamination from ambient NO. The expiratory pressure was 5-20 mmHg to close the soft palate. Mean exhaled flow rate was 50 mL/s $\pm$ 10% during the NO plateau. The manoeuvre was repeated until two exhalations agreed to within 5% coefficient of variation (CV) or three exhalations agreed to within 10% CV. The NO concentration, FE_{NO}, was defined as the mean of these values expressed in ppb. The analyser was calibrated daily using a standard NO calibration gas (Air Liquide Deutschland GmbH, Krefeld, Germany) and was corrected for ambient temperature and humidity. FE_{NO} was measured at baseline, prior to spirometry, and immediately after exercise (1 min) and 30 min later.

3.8.3. Lung function and exercise test

Spirometry

Spirometry was performed in accordance with international guidelines (128) with an ambulant electronic spirometer, Spiro USB with Spida 5 software (Micro Medical, Rochester, UK). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow at 50% of FVC (FEF_{50}) were reported using the reference values of Zapletal (129) and the global lung function 2012 equation (130).

Standardised exercise test

An exercise challenge test was performed by running for 6-8 min on a motor-driven treadmill (Woodway PPS Med, Woodway GmbH, Weil am Rhein, Germany) following the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines (131). The mean target heart rate during the last 4 min was 95% of maximum heart rate (calculated as 220 minus age in years), though a minimum heart rate of 180 beats per minute, (85-88%) was accepted. In accordance with the study protocol, the exercise-induced bronchoconstriction (EIB) test was considered positive with a decrease in $FEV_1 \geq 10\%$ of baseline FEV_1 measured at 3, 6, 10, 15 and 20 min after the exercise. Exclusion criteria were strenuous exercise within 4 hours of testing and pre-exercise FEV_1 lower than 75% of predicted value.

3.9. Annual pollen count and temperature measurements

Pollen grains are tiny particles, which are released into the air and spread by the wind in order to pollinate plants of the same species. The pollen types of greatest significance for pollen allergy in Norway come from the tree species alder, hazel and birch and from all grass species, particularly timothy-grass and orchard grass. Other producers of pollen include wormwood, Salix (goat willow, osage orange and willow) and mugwort. Annual pollen counts are performed in twelve different meters placed in different locations in Norway (132). One of the meters is placed in the middle of our study area (Bodø). The meter counts the pollen (pollen grains/cbm air) from Alnus (alder), Coryllus (hazel), Salix, Betula (birch), Poaceae (grass) and Artemisa (mugwort) (133).

The Norwegian Meteorological Institute (MET) produces forecast weather, monitors the climate and conducts research (134). MET publish global and national annual-mean surface air temperatures collected from monitoring stations throughout the world and in Norway. Annual-mean surface air temperatures are compared to the expected temperature or norm. The norm is defined as the 1961-1990 (30 years) mean. The annual-mean surface air temperature deviation from the norm is estimated and used to describe time trends.

3.10 Statistical analyses

Normally distributed values were presented as means and standard deviations (SD) or 95% confidence intervals (CIs). Categorical data were presented as percentages (percentage). All tests were two-sided using a significance level of 0.05. The distribution of FeNO values was

right skewed, and hence analyses were executed with natural log (ln) transformed data. The results were presented as back-transformed values and expressed as geometric means

Paper I: The main outcome was differences in prevalence between the periods 1985-95 and 1995-2008. The analyses were performed using chi-square statistics, and the differences in secular prevalence were quantified with odds ratios (OR). For values measured three times, chi-square tests for trend (linear-by-linear associations) were calculated.

Paper II: The validity of the questionnaire was determined by agreement between questionnaire responses and clinical assessments. Agreement was measured as sensitivity and specificity. Corrected estimates for the prevalence of asthma ever and current asthma were calculated as the sum of the positive predictive values (PPV) for both positive and negative questionnaire replies to asthma, weighted by their relative frequencies. Agreement between EIB and clinical assessment was assessed using post-test odds and the probability for a positive EIB tests. The test-retest reliability of the questionnaire was assessed using Cohen's kappa. Corrected inter-group comparisons were analysed with Pearson's chi-square test for categorical data and independent t- test for continuous data.

Paper III: To assess possible differences comparing demographical data between groups we used Pearson`s chi square-test for categorical data and independent t-test for continuous data. Since the survey design in paper III was a matched case-control design, the other analysis used had to take the matching between cases and controls into account and adjust for paired data. When comparing the matched case-control groups, McNemar's chi square-test was used for categorical (binary) variables (e.g. LRTI shown in table 2) and paired-sample t-test for continuous variables, both methods comparing cases and controls without adjusting for any confounders. The use of McNemar`s chi-squared test is valid provided that the total number of discordant pairs is at least 10.

Table 2. McNemar's test applied for the variable lower respiratory tract infections (LRTIs).

Non - asthmatic		Current asthmatic		
		LRTIs yes	LRTIs no	**Total**
Non - asthmatic	LRTIs yes	5	9	**14**
	LRTIs no	59	80	**139**
	Total	**64**	**89**	**153**

The results from paired chi-square test based on the discordant pairs in table X can be used to calculate chi-square to establish the p-value by the formula: $\chi^2 = (r-s)^2/r+s$, d.f = 1. The odds ratio = ratio of discordant pairs. For LRTIs (table 2) OR = 59/9 = 6.56.

To compare cases and controls in an adjusted model, we needed to use a regression model. A standard logistic regression model would assume that all observations were independent. However, with paired data the observations within each pair were interdependent. This assumption had to be adjusted in the model by using conditional logistic regression. Conditional logistic regression is a variant of logistic regression in which cases are only compared to the controls in the same pair (19). This method is implemented in most statistical packages but not in SPSS. However, one can still perform conditional logistic regression in SPSS using stratified Cox proportional hazards model to estimate odds ratios. Cox requires a specified observation time for each individual, which was achieved by creating a constant time link i.e. had equal value for each individual in the data set. A stratified Cox model where the status variable was current asthma (yes/no), the observation time variable had equal value (time = 1) for each individual and a strata variable indicating each pair (pair number) gave identical regression coefficients, and thus also OR, as with conditional logistic regression.

Building the model, we first assessed whether or not an independent variable was a potential confounder, which could be difficult to determinate. We considered the biological relations between the variables and compared the regression coefficient before and after adjusting for possible confounders. If the regression coefficient changed by more than 10%, we most likely had a confounding variable. Two variables in 2008 were considered as confounders, namely AR and hospitalization. Thus, they were included in the final model. Likewise, atopy in the family was considered as a confounder in 1985, and was therefore included in the model.

Of potential risk factors, the most relevant relationships were assessed in unadjusted analysis and factors with an unadjusted p-value < 0.25 were included in the model. Variables considered as mediators or colliders were not included in the model. Deciding whether or not the variables were mediators or colliders, was done by consideration in addition to statistical analysis. Working with the multivariable model, we identified 'regular use of asthma medication during the first three years of life' as a collider interrupting the model since it is strongly correlated to current asthma (reverse causality). The same situation applied to the

variable 'asthma symptoms during the first three years of life'. Variables in the multivariable model were excluded in a stepwise fashion to increase the strength of the model regardless of significance. The final model included statistically significant covariates as well as confounders whether or not formally statistically significant at the 5% level.

All analyses were made using Graph Pad Prism version 5 (Graphical Software, San Diego, CA, USA) and Statistical Package for Social Science (SPSS) software version 19.0 and version 22.0 (IBM Corporation, Armonk, New York, USA).

4. Results
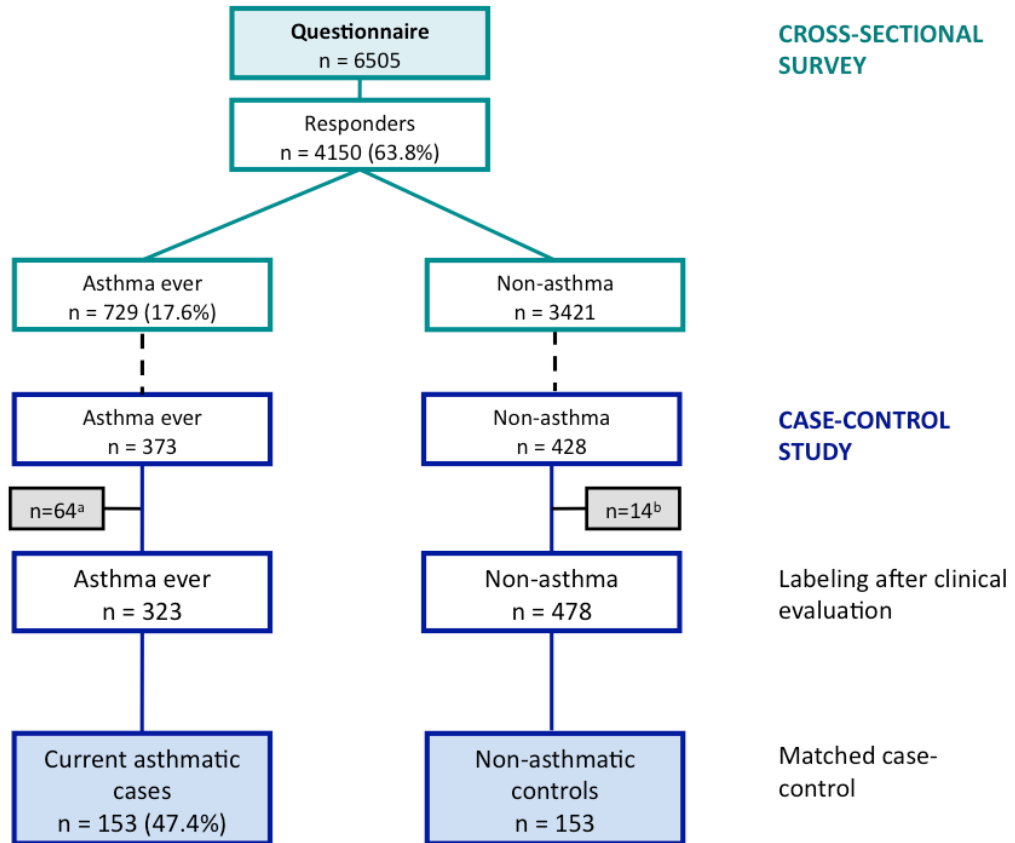
Figure 5. *A flow chart for study subjects in 'Asthma and Allergy among schoolchildren in Nordland County.*

[a]*Subjects categorized as non-asthmatic after clinical assessment.*
[b]*Subjects misclassified as non-asthmatics, new cases of asthma.*

4.1.   Prevalence of asthma, AR and eczema 1985-2008

Of the 6505 pupils invited to participate, 4150 (63.8%) answered the questionnaire (figure 5) and were enrolled in the study (49.1% boys). Demographic data from the three questionnaire based surveys performed in 1985, 1995 and 2008 are presented in table 3.

Table 3. Demographic data of the study groups from the questionnaire based surveys in 1985, 1995 and 2008 in Nordland County.

| | **Surveys** | | | | | | |
	1985	**%**	**1995**	**%**	**2008**	**%**	**p for trend**
Number of children invited to participate	5134	100	5121	100	6505	100	
Responders	4870	94.9	4456	87.0	4150	63.8	
Boys (n)	2505	51.4	2248	50.4	2036	49.1	0.025
Girls (n)	2365	48.6	2208	49.6	2114	50.9	0.025
Mean age (years)	10.3		10.8		10.8		
Atopic diseases among family members	2387	49.0	2813	63.1	2878	69.9	< 0.001
Parental history of asthma	363	7.7	519	11.6	690	16.8	< 0.001
Parental history of allergy	699	14.8	980	22.0	1294	31.4	< 0.001

The data are presented in exact numbers and in percentages (%). N varies due to missing data.

Adapted from Hansen et al. Acta Paediatr 2012; 102:47-52.
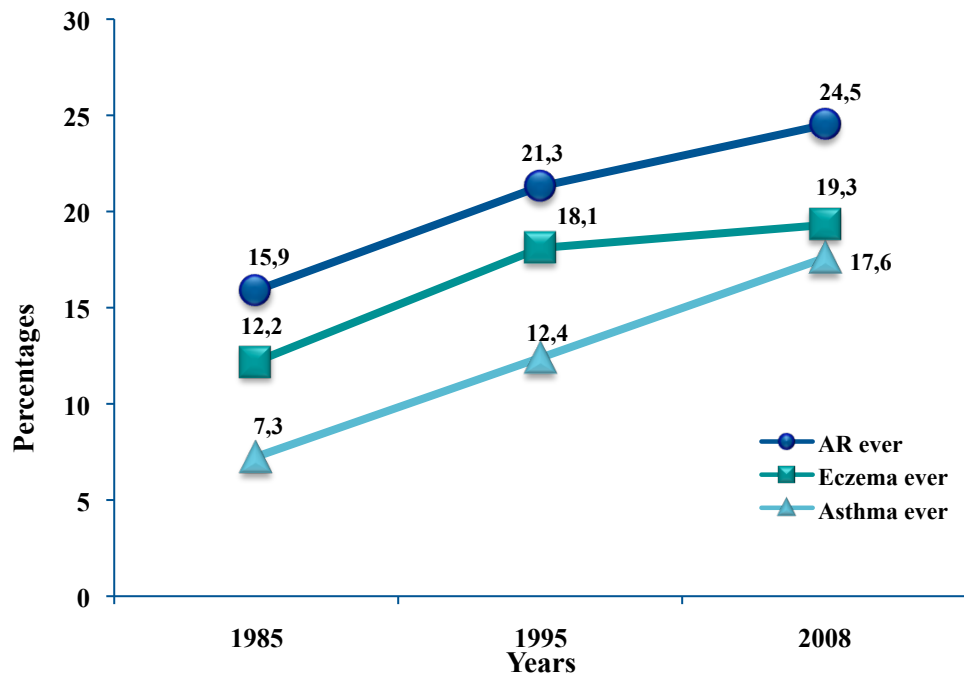
Figure 6. *The prevalence (%) of asthma ever, AR ever and eczema ever in schoolchildren from the three questionnaire-based surveys in Nordland, 1985–2008.*

The main findings were an increasing prevalence of asthma ever (p for trend <0.001) and AR ever (p for trend <0.001), while the prevalence of eczema ever, after an increase between 1985 and 1995, remained unchanged in the last period (figure 6).

The results demonstrated a gender difference (figure 7). The prevalence of asthma ever and AR ever were significantly higher among boys compared to girls in all three surveys, while the prevalence of eczema ever was approximately similar between girls and boys in 1985 and higher among girls in 1995 and 2008.
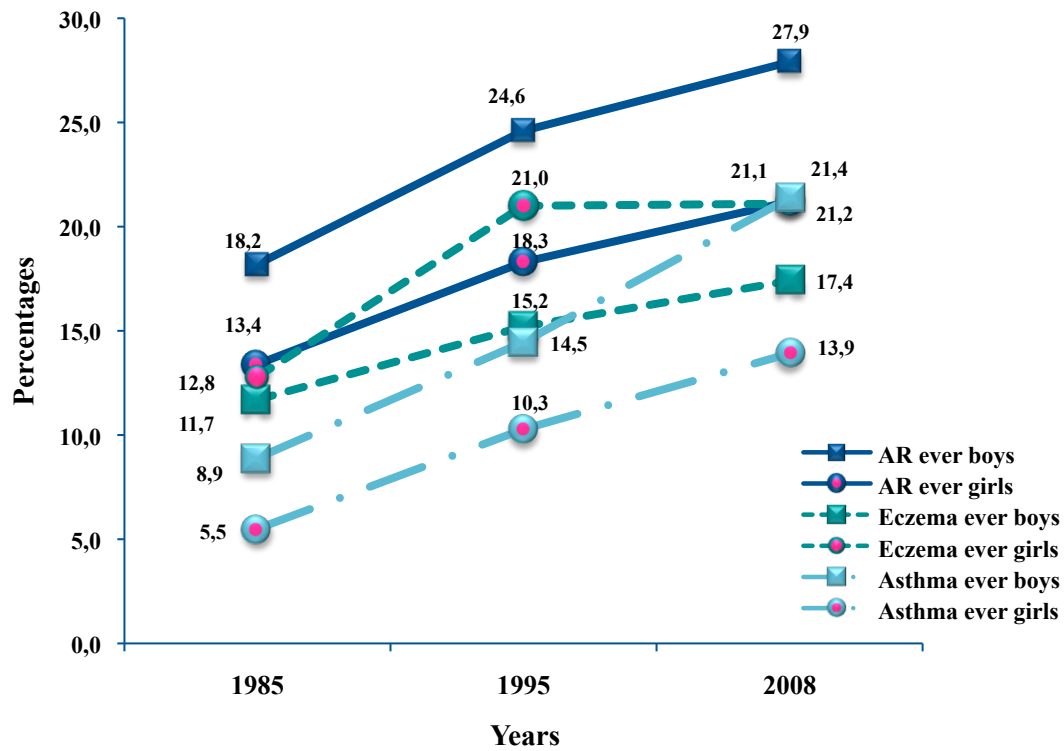
Figure 7. *The prevalence (%) of asthma ever, AR ever and eczema ever from the three questionnaire-based surveys in Nordland, 1985–2008, divided by gender.*

The prevalence of current disease doubled and trebled between 1995 and 2008 for all three diseases and the same gender pattern as for disease ever, was discovered (table 4).

Table 4. The prevalence of current asthma, allergic rhinoconjunctivitis and eczema in children aged 7-14 years from the 1995 and 2008 questionnaire-based surveys in Nordland County.

| | Prevalence (%) | | | |
| | Surveys | | 2008/1995 | |
	1995	2008	OR	95 % CI
All				
Current asthma	4.8	9.9	2.21	1.86-2.62
Current rhinoconjunctivitis	6.7	21.5	3.83	3.33-4.40
Current eczema	6.4	13.5	2.27	1.96-2.64
Boys				
Current asthma	5.6	12.0	2.29	1.83-2.87
Current rhinoconjunctivitis	7.5	24.4	3.80	2.15-4.58
Current eczema	6.2	12.3	2.11	1.70-2.62
Girls				
Current asthma	3.9	8.0	2.13	1.63-2.78
Current rhinoconjunctivitis	5.8	18.7	3.70	3.01-4.56
Current eczema	6.6	14.6	2.43	1.97-2.99

The difference in prevalence between 2008/1995 is quantified with odds ratio (OR). Corresponding 95 % confidence intervals (95% CI) are presented.

Adapted from Hansen et al. Acta Paediatr 2012; 102:47-52.

The proportion of children reporting at least one disease (asthma, AR or eczema) increased from 26.2% in 1985 to 43.3% in 2008 (p for trend <0.001). The proportion of children with all three diseases and the proportion of children with both asthma and eczema increased during the study period, while the proportion of children reporting the combination of asthma and AR or AR and eczema after an increase in the first period stayed unchanged in the last period. An increasing proportion of the responders reported atopic disease in the family (p for trend < 0.001) (table 3).

4.2.   Validation of the survey questionnaire

Of the 1144 pupils invited, 801 children accepted to participate in the case-control study. This represents a participation rate of 70%. In the case-control study, 373 children reported

'asthma ever' (figure 5). After the clinical assessment, 64 of the designated 373 asthmatic children did not meet the asthma definition criteria (i.e. false positives). Of the 428 apparent non-asthmatic children, 14 met the asthma definition criteria after the clinical assessment (i.e. false negatives). After reclassification, the group of asthmatic included 323 children (63.2% boys) and the non-asthmatic group included 478 children (figure 5). Asthmatic children had higher mean body mass index (BMI) and suffered more frequently from eczema, AR and food allergy than non-asthmatic children (table 5), otherwise the two groups were similar regarding demographic features.

Table 5. Demographic data of asthmatic and non-asthmatic children in the case-control study from "Asthma and allergic diseases among schoolchildren in Nordland"

	Asthmatic n = 323	Non-asthmatic n = 478	P - value
Boys (%)	204 (63.2)	286 (59.8)	0.343
Mean age (years)	12.4	12.6	0.185
Mean Body mass index (BMI)	20.3	19.6	0.014
Mean birth weight (grams)	3467	3537	0.150
Mean gestation age (weeks)	39.3	39.5	0.222
Mean fathers' years in school	13.2	13.5	0.103
Mean mothers' years in school	14.0	14.1	0.529
Passive smoke exposition (%)	116 (35.9)	143 (29.9)	0.075
Comorbidity			
Eczema (%)	157 (48.6)	153 (32.0)	< 0.001
Allergic rhinoconjunctivitis (%)	156 (48.3)	127 (26.6)	< 0.001
Food allergy (%)	49 (15.2)	32 (6.7)	0.001
Urticaria (%)	56 (17.3)	93 (19.5)	0.441

The data are presented in exact numbers and in percentages (%).

Adapted from Hansen et al. J Asthma 2014; 52:3, 262-267

Compared to clinical assessment, the survey questionnaire had a sensitivity of 0.96 and a specificity of 0.87. The overall agreement (kappa) was 0.80 (standard error (SE) 0.02). Assuming that the clinical assessment represents a true diagnosis of asthma ('gold standard'), the estimated prevalence of asthma ever in the 2008 survey was adjusted from 17.6% to 16.9% (SE 0.006, 95% CI: 15.8-18.0). Similarly, the prevalence of current asthma was

adjusted from 9.9% to 10.8% (SE 0.005, 95%CI: 9.8-11.8). The most sensitive and specific questions identifying asthmatic children by the questionnaire were questions asking about diagnosis ('Has the child ever had asthma?') rather than those covering asthma symptoms such as wheeze, shortness of breath and/or cough (data not presented).

Asthmatic children were often sensitised to allergens, had higher FE_{NO} values and had more often a positive EIB test than non-asthmatics. However, spirometric values were not significantly different between the groups (table 6). A positive exercise test yielded a sensitivity of 0.12 and a specificity of 0.92 relative to the clinical assessment. The post-test odds and the post-test probability were 0.33 and 0.25, respectively.

Table 6. The test results for asthmatic and non-asthmatic children in the case-control study from 'Asthma and allergic diseases among schoolchildren in Nordland'.

	Asthmatic n = 323	Non-asthmatic n = 478	p - value
Positive skin prick test (%)	162/216 (75.0)	118/169 (69.8)	0.258
Positive IgE, Inhalation	162/162	118/118	
Positive IgE, Food	28/162	11/118	
One or more positive sIgE (%)	179/257 (69.6)	234/385 (60.8)	0.022
Positive specific IgE, Inhalation	172/179	213/234	
Positive specific IgE, Food	82/179	81/234	
Allergic sensitisation (%)	218 (67.5)	259 (54.2)	0.000
Mean baseline FeNO (95%CI)	14.74	10.75	0.000
Mean baseline lung function			
FEV1 (95% CI)	2.59 (2.51-2.67)	2.63 (2.56-2.69)	0.492
FVC (95% CI)	3.00 (2.90-3.09)	3.06 (2.98-3.14)	0.273
FEV1% (95% CI)	86.1 (85.4-86.8)	85.8 (85.3-86.4)	0.547
FEF50 (95%CI)	3.13 (3.01-3.24)	3.15 (3.06-3.24)	0.695
predFEV1 (95%CI)	2.73 (2.65-2.80)	2.67 (2.61-2.73)	0.295
predFVC (95%CI)	3.24 (3.15-3.33)	3.16 (3.09-3.23)	0.244
pred FEF50 (95%CI)	3.85 (3.76-3.94)	3.80 (3.72-3.88)	0.486
Positive exercise test (% of total)	57/315 (18.1)	26/466 (5.6)	0.000

The numbers are presented as exact numbers and percentages or means

Misclassified children who were transferred from the asthma group to the non-asthma group (false positive) after the clinical assessment, 21/64 (32.8%) answered affirmatively to

Question 1 in the original questionnaire and 52/64 (83.9%) answered affirmatively to Question 2. The interview revealed that 39.1% of the 64 children had experienced respiratory symptoms, but not asthma during the first three years of life. In 22/25 (88.0%) of these children the episodes of symptoms were associated with fever, colds or other airway infections. In the group of misclassified children that changed groups from non-asthmatic to asthmatic (n=14) after the clinical assessment (false negative), eight children represented new asthma cases.

4.3.   Risk factors for the development of asthma

Demographic data from the study populations in 1985 (n = 207) and 2008 (n = 801) displayed a male dominance of 65.7 % and 61.2 %, respectively. Mean ages were 11.4 years in 1985 and 12.5 years in 2008. Atopic diseases in the family was significantly different between cases and controls in both studies, otherwise the subgroups were similar in terms of demographic data and clinical characteristics. Comparing demographic and clinical data between sexes revealed a significant difference in the prevalence of AR in 2008 (boys 38.4% and girls 30.5%; p = 0.024), while there were no differences between the sexes in 1985.

4.3.1. The 1985 study

Of the 105 cases, 62 fulfilled the criteria for current asthma. Comparing these to their respective controls revealed associations between some variables and the outcome current asthma. The final model revealed significant differences between cases and their matched controls in adjusted OR (95% CI) (P-value): Repeated LRTIs AOR 52.11 (95% CI 4.62-587.97) (p = 0.000), atopy in the family AOR 13.20 (95% CI 1.60-108.63) (p = 0.016), urticaria ever in the child AOR 11.27 (95% CI 1.01-125.33) (p = 0.049), and duration of breastfeeding AOR 1.35 (95% CI 1.02-1.80) (p= 0.039).

4.3.2. The 2008 study

Of the 323 cases, 153 fulfilled the criteria for current asthma (figure 5). Comparing them to their controls revealed associations between a number of variables and the outcome current asthma. The final model included a total of seven variables: duration of breastfeeding, mean number of hours watching television and/or data during weekdays, AR, food allergy, LRTIs during the first three years of life, hospitalisation caused by LRTIs and allergic sensitisation. The explained variance for current asthma by all seven variables was 61% with the most

important risk factors; food allergy AOR 7.06 (95% CI 1.61-31.07) (p = 0.010), LRTIs during the first 3 years of life AOR 5.80 (95% CI 1.96-17.21) (p = 0.002), and hospitalisation caused by LRTIs OR 4.60 (95% CI 1.01-20.96) (p = 0.049). The only factor associated with a reduced risk for current asthma was length of breastfeeding OR 0.93 (95% CI 0.87-0.99) (p = 0.025).

Analysing the present data by gender displayed some differences from the data for all children. For boys food allergy AOR 18.32 (95% CI 1.54-217.74), LRTIs during the first 3 years of life AOR 8.87 (95% CI 2.07-37.96) and AR AOR 4.12 (95% CI 1.10-15.4) were significantly different between cases and controls. For girls LRTIs during the first 3 years of life AOR 7.70 (95% 1.18-50.36), duration of breastfeeding AOR 0.89 (95% 0.79-0.99) and time spent in front of television or data AOR 1.65 (95% CI 1.11-2.45) were significantly different between the cases and controls.

4.3.3. Changes in the climate and pollen count

During the period 1985-2008, the average temperature raised 0.5°C in northern Norway compared to the norm (figure 8). In the same period, the global average temperature increased by 0.2°C compared to the norm (figure 9).
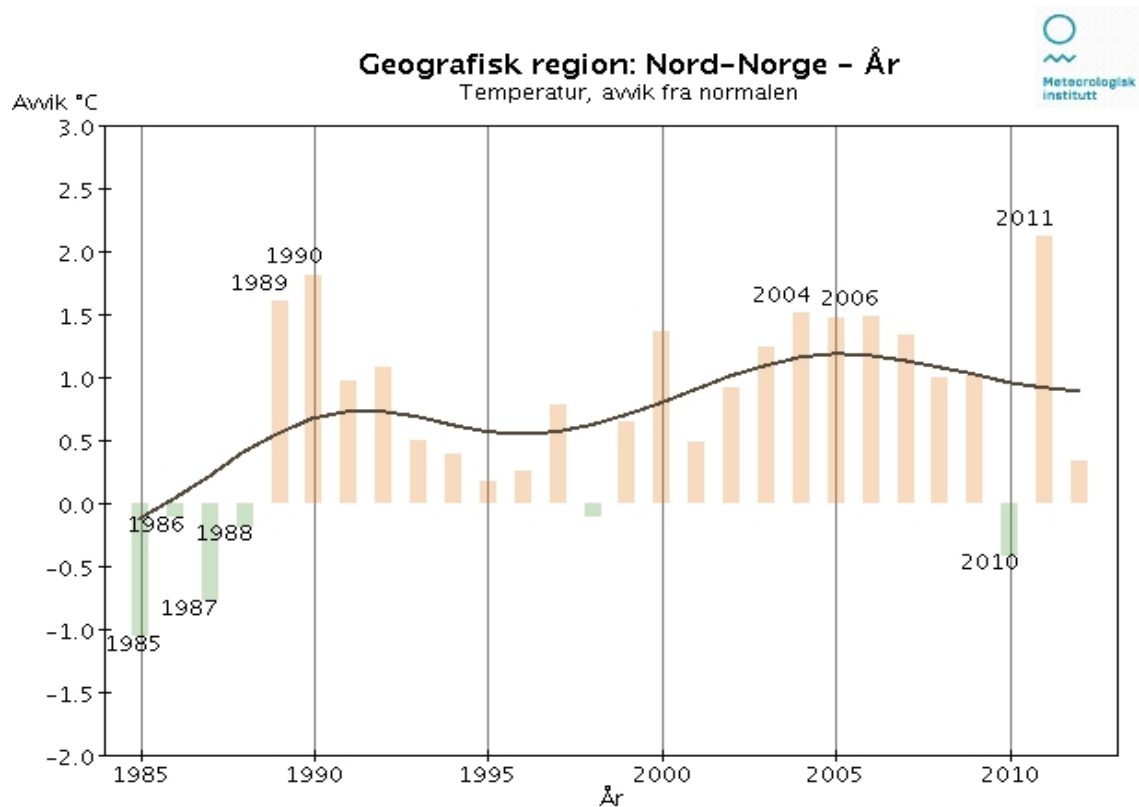
Figure 8. *Deviation in annual-mean temperature from the expected (norm) temperatures in northern Norway in the period 1985-2011.*

The bars show the annual-mean deviation from the norm, while the line shows the time trend.

Source reference: The Norwegian Meteorological Institute
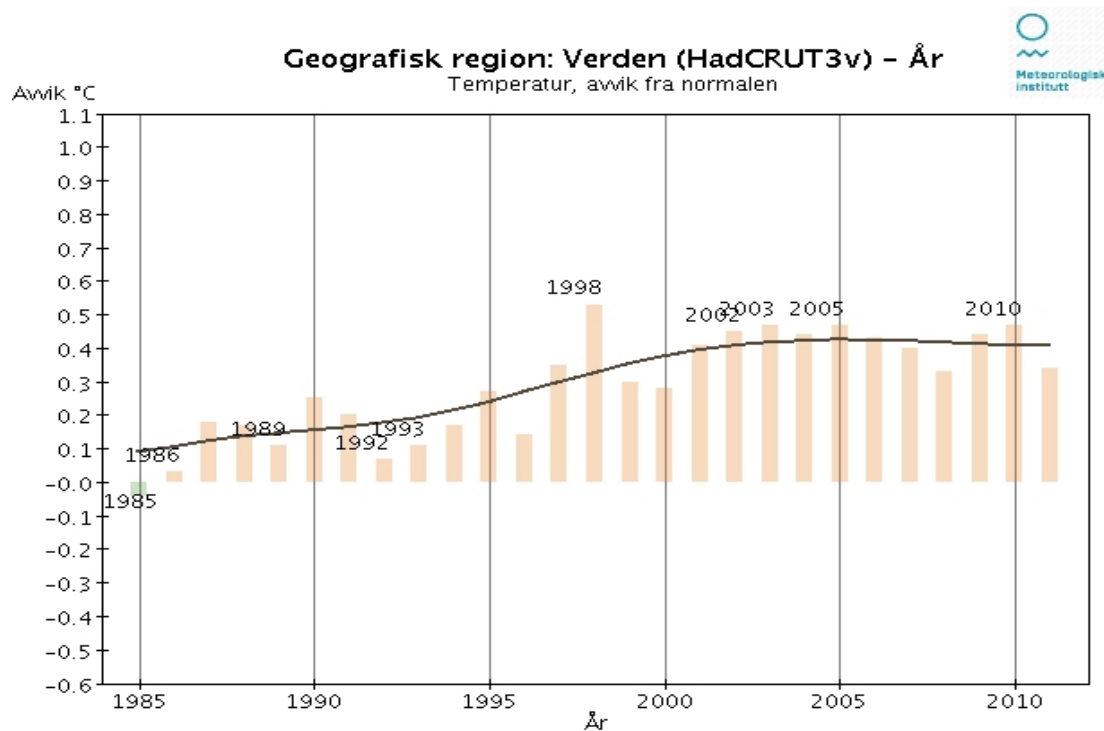
Figure 9. *Deviation i annual-mean temperature from the expected (norm) temperatures global in the period 1985-2011.*

The bars show the annual-mean deviation from the norm, while the line shows the time trend.

Source reference: The Norwegian Meteorological Institute

The total pollen count measured in Nordland (Bodø) during the period 1985-2011, displayed an increasing temporal trend (figure 10). In particular, 2008 when the cross-sectional survey was conducted was a top year regarding total pollen production.
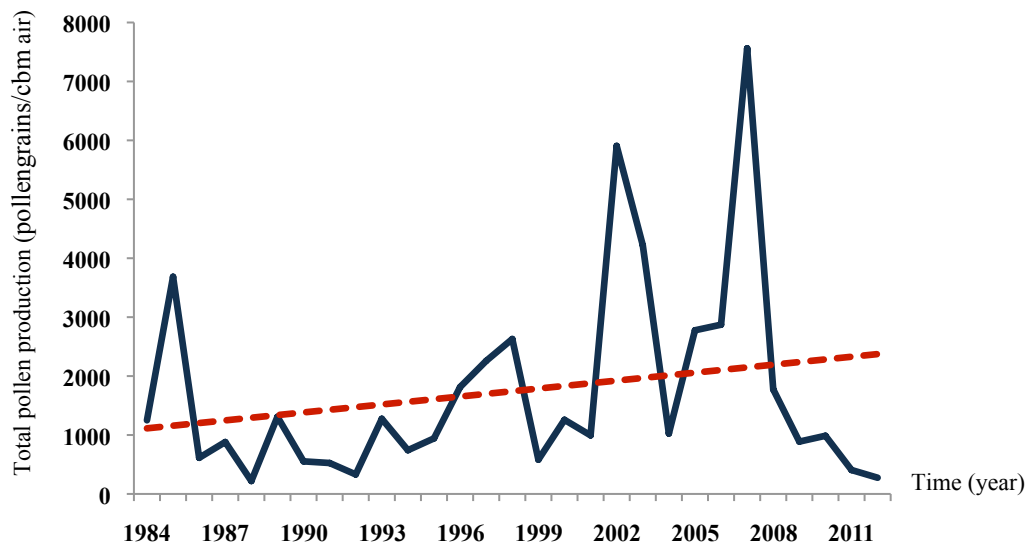
Figure 10. *Total pollen production (pollen grains/cbm air) in Nordland county during the period 1984-2011 (133).* *The total pollen production includes pollen from Salix, Betula (birch) and Poaceae (grass). The dotted line marks the temporal trend.*

Source: NAAF (The Norwegian Asthma and Allergy Association)

5. Discussion

5.1. Prevalence of asthma, AR and eczema 1985-2008

We demonstrated an increasing prevalence of asthma ever and AR ever, while the prevalence of eczema ever, after an increase between 1985 and 1995, stayed unchanged in the last period. The prevalence rates found in 2008 are similar to those reported from the ECA study in Oslo (52), but somewhat higher compared to results in the OLIN study in northern Sweden (103, 135). In contrast to prevalence studies in comparable populations (34, 49, 52, 136), we found a substantial increase in the proportion of children reporting current diseases in the last period.

Assessing time trends in asthma prevalence, a continuing increase has been revealed in some countries even though the prevalence of asthma has declined in other countries (2). The main challenges studying asthma prevalence are the absence of a standardised definition of asthma and the lack of a gold-standard diagnostic test (25). These challenges make comparison between different studies difficult and may influence the interpretation of the results.

Asthma, AR and eczema are common and closely related (52, 70). Even if the interrelationships are not well understood, studies have suggested a shared causal mechanism (72). The proportion of children suffering from asthma, AR and eczema increased and the proportion of children with none of these diseases decreased significantly in the study population from 1985 to 2008. The combination of asthma and eczema increased during the entire period while the combinations of asthma/AR and AR/eczema increased in the period 1985-95 and then levelled off in 2008. This pattern is in line with the findings in a report from the ISAAC III study (137). The extensive overlap between these atopic diseases is important to acknowledge since the risk of asthma and other allergic diseases might increase with an increasing number of allergic manifestations in infancy (138). A recent study from the MeDALL showed that at the population level, childhood asthma, rhinitis and eczema are more accurately classified together as an allergic comorbidity cluster, rather than three independent diseases (139). Taken together, these findings imply that diagnosing and treating comorbid rhinitis and eczema is important as it has consequences for treatment and prevention strategies and for reducing the burden of asthma in children.

5.2. Validation of the questionnaire from the cross-sectional survey

Validation of epidemiological tools is important in order to achieve knowledge about their usefulness. When validating the questionnaire from the cross-sectional surveys against clinical assessment, we found very good agreement between the questionnaire-based diagnosis of asthma and the clinical assessment by a doctor. For a questionnaire to be a useful research tool, the responses must be repeatable (minimum measurement error). The test-retest reliability of asthma definition by questionnaire can be judged substantial (140), especially considering the time interval between the cross-sectional survey and the case-control study. Thus, the questionnaire is a useful epidemiological tool.

The diagnosis of asthma is problematic as episodic symptoms and exacerbations are essential components of the disease. This makes the use of clinical testing as a diagnostic and epidemiological tool challenging. In agreement with other studies (24, 31,141), the intensive examinations performed in the case-control study yielded little additional information compared to clinical assessment. The EIB test increased the post-test probability only to a minor degree, whilst spirometric values and SPT results did not differ between asthmatic and non-asthmatics. However, baseline FeNO was significantly higher in asthmatic than in non-asthmatic children, which is in line with findings from the ECA study in Oslo (142). The difference in baseline FeNO is probably due to the higher proportion of asthmatic children suffering from comorbid AR, as showed in an earlier publication from the study 'Asthma and allergy among schoolchildren in Nordland' (143).

Investigating the misclassifications and over-diagnoses in the case-control study, we found that most of them were due to parents response to Question 2 in the 2008 survey. Question 2 covered several symptoms including the cardinal symptom of asthma, wheeze, as opposed to the corresponding question in ISAAC covering only wheeze (32). This represents a difference in the definition of asthma ever making directly comparison between the results from the present study and the ISAAC studies (49) difficult. Thus, a crucial consideration is which approach is more appropriate for assessment of the prevalence of asthma. A Danish study from 2012 found that doctor-diagnosed 'wheeze' is not a prerequisite for the diagnosis of asthma either and proposed focus on symptom burden in clinical practice to reduce the risk of misclassification of asthma in young children (144). Other symptoms as persistent cough, has been shown to be as closely related to asthma as wheeze (16). On the other hand, several

symptoms included in one question could lead to misinterpretations and insecurity towards differential diagnosis of asthma. The clinical assessment revealed that parents responding positive to Question 2 in the 2008 survey misinterpreted their child's symptoms associated with respiratory infections in early life as asthma. This finding is in line with results from an international study among preschool children (145). In our opinion, the false positive children in the study may represent 'transient infantile wheeze' (11).

Questions covering diagnosis rather than symptoms in the 2008 survey provided a better prediction of asthma prevalence, even though diagnosis itself does not constitute an 'objective' record. Even if diagnostic customs change over time, questions relating to diagnosis may be more useful than symptom-based questions in some instances. Hence, in future studies regarding the prevalence of asthma, we must critically consider the need for revising Question 2 or excluding it from the questionnaire.

In the 2008 case-control study, no cases suffered from moderate or severe asthma. Similarly, the ISAAC studies have revealed that the overall increase in asthma prevalence reflects milder disease (50). This may represent a real change in diagnostic habits in the period of 1985-2008. In addition, physicians seems more prone to include children with milder symptoms who previously would not have had an asthma diagnosis (2). One likely cause for the observed change is the introduction of ICS treatment, which took place in the early 1980s (146). There is no doubt that the introduction of inhaled steroid therapy revolutionised the management of patients with chronic asthma, including the milder cases that previously did not have a real treatment offer.

5.3.　　Possible risk factors for current asthma

One or repeated LRTIs during the first three years of life, reported by the parents, was the strongest association for current asthma in both 1985 and 2008, together with severe LRTIs in the 2008 study. Others studies showing that early severe LRTIs are associated with up to a four-fold risk of subsequent wheeze during early school years (147) supported these results. In a Norwegian study, the risk of development of asthma and lung function alterations after bronchiolitis in early life was found to be influenced by gender and type of virus involved (148). Recent research from the COPSAC study revealed that otherwise healthy children experienced a median of 10 episodes of respiratory tract infections (one episode per child for

LRTIs) during the first 3 years of life (149). Findings in this Danish study suggest that host factors are the major determinants of infection susceptibility in early childhood (149). To some extent our findings contradict the assumption of the hygiene hypothesis stating that more infections early in life prevent the development of atopic diseases due to the diversity of the 'microbial burden' (76). Whether the infection susceptibility in early childhood has changed during recent decades leading to an increase in the incidence of respiratory tract infections, is unknown.

AR and food allergy were risk factors for current asthma in the 2008 study. Both diseases frequently coexist with asthma (70, 150). Food allergy and atopic dermatitis commonly coexist at the beginning of the 'atopic march'. Questions have been asked as to whether the observed association between asthma and food allergy is related to co-manifestation or if it is a consequence of food allergy itself (60). Although gender difference in asthma prevalence is well documented, gender-dependent risk factors for asthma have not been fully elucidated (151). Stratification by sex in the 2008 study displayed sex-dependent risk factors: comorbidity of AR and food allergies was significantly different between cases and controls in boys. Although these associations were strong, this could be the result of a higher prevalence of AR in boys in the original study groups and twice as many matched pair of boys than girls. Our findings are in line with results from the ECA study (152) and support the hypothesis that asthma and combinations of allergic comorbidities may represent a gender-related phenotype.

The greatest distinctions between the results in 1985 and 2008 were the association of breastfeeding to current asthma and the significance of atopy in the family. In the case of breastfeeding, we believe this may be an example of inverse causation: debut of asthma symptoms prolong the duration of breast-feeding because of the general belief in its protective effect. Such inverse causation could be misinterpreted, drawing the conclusion that longer breast-feeding leads to asthma, when in fact it is the reverse (107). Breast-feeding presumably has a protective effect against viral respiratory infections (153). Since LRTIs show a strong association towards current asthma, the association with breastfeeding in the 2008 study might be brought about by its protective effect against LRTIs (154).

In the 1985 study, current asthma was associated with family atopy. Unlike other studies (58, 80), we were unable to find an association between current and parental asthma, AR and/or

eczema in the 2008 survey. In the period 1985-2008, there was a substantial increase (up to 70 %) in the prevalence of atopic diseases in the family. This high prevalence regardless of asthma status in the child, may partly explain the difference.

Compared to the global annual-mean temperature, the annual-mean temperature in northern Norway has increased more than twice during the study period. Although the underlying causes of the rising trend of allergic disease are not clear, links have been made to various climatic factors as temperature, and their impact on the production and distribution of pollen and mould (155). Others have shown that warmer temperatures positively correlate with physician-diagnosed allergic rhinitis (156). Temperature is an important variable for spring and early summer pollination of allergenic trees and grasses (155). The yearly pollen count in the study area had an upward trend, with exceptionally high counts during the years of 2008-2010, compared to previous years. These raised counts suggest that the increased annual-mean temperature in northern Norway may have led to a rise in pollen production and furthermore increased the prevalence of AR. AR was identified as a risk factor for current asthma in 2008. Hence, AR might have contributed to the increased asthma prevalence in the in the period 1985-2008. In addition, other local environmental factors might have contributed to the increased asthma prevalence. During winter, children living in a cold and coastal subarctic climate are expected to spend more time indoors compared to children living in a warmer climate. Others have proposed this as having a negative effect on the development of asthma and eczema symptoms (111).

5.4.   Methodological considerations

When evaluating the outcome in epidemiological research, it is custom to consider random and systematic error that may affect the internal validity of the study. Random error reflects a problem of precision in assessing a relationship between exposure and disease and can be reduced by increasing the sample size (157). Systematic error (bias) is a systematic deviation of a study's result from a true value and can be divided in selection and information bias and confounding (21). Selection bias concerns the process of identifying study subjects, while information bias occurs when any information used in a study either is measured or recorded inaccurately (158). Possible biases in epidemiological studies of asthma have many sources, including but not restricted to: sampling method and timeframe, response rates, recall bias, awareness of asthma, diagnostic habits, the nature of the questions asked and definition

criteria of asthma. In addition, observer bias and seasonal bias may influence results (159,160). Confounding occur when a variable is related with the exposure and also influences the disease outcome which may lead to incorrect conclusions about the effect of the exposure of interest on the outcome (161). In the following sections, the most important strengths and limitations of 'Asthma and allergy among schoolchildren in Nordland County' are discussed in relation to study design, bias and confounding.

5.4.1. The cross-sectional survey (paper I)

The original study cohorts in 1985, 1995 and 2008 were large and consisted of unselected children in Nordland county randomly selected, making the study group a representative fraction of the general child population. We used identical study design and the same questions defining disease in three repeated cross-sectional surveys during three decades in the same population, forming a basis for valid time trends for self-reported asthma, AR and eczema. The best evidence of changes in prevalence comes from repeated studies using the same questionnaires or investigations in the same population at sufficient time intervals (2). The cross-sectional study design was chosen due to its time- and cost-efficient way to assess the prevalence and because it is as close a proxy as it is possible to attain for the preferred method of longitudinal data.

Selection bias is best avoided by achieving a high response rate. Even though a high participation rate is preferable, most empirical work suggests that lower participation rates are not likely to have a substantial influence on the measures of interest (162). Different factors affect participation in epidemiological studies: methods of recruitment, family and medical history, disease status, questionnaire structure and method and number of contact (20). The response rate in the three surveys decreased during time and the rate in the 2008 survey was lower than desirable. Due to ethical considerations, in 2008 we were not allowed to give personal reminders to the participants in contrast to the earlier studies. We believe this partly explains the lower response rate in 2008. In addition, decreasing participation rates have become more common in recent decades. This is most likely due to the increasing number of studies and research projects offered to the public. Thus, refusals to participate have increased (163).

The lower response rate in 2008 may represent a selection bias if there were differences in characteristics between those who did respond and those who declined participation. Such a

difference may have affected the estimates of prevalence (21). Unfortunately, it was not possible to perform any analysis of the non-responders in the 2008 survey to investigate if they differed from the study subjects. Analyses of non-responders have been performed in other studies with contrasting results. Some have demonstrated differences in socio-economic conditions affecting outcome (164), while others have concluded that differences in sociodemographic background between responders and non-responders did not influence prevalence estimate noteworthy (165, 166). In a large postal survey performed in Sweden (167) non-responders did not differ significantly in the prevalence of airway diseases or symptoms compared with responders. Either way, study subjects willing to participate in unselected cohort studies are generally more likely to have a history or risk of asthma or related diseases (16). In addition, parents suffering from atopy are thought to be more aware of symptoms and diseases in their children (168).Considering the increase in prevalence of atopic diseases in the family from 1985-2008, an overrepresentation of children with a positive family history of atopic diseases in the present study were likely. This overrepresentation might entail a selection bias affecting the prevalence estimates and making the result difficult to generalise to other populations.

Repeated cross-sectional written questionnaires based surveys lack objective data. Thus, perception of increased prevalence should be treated with caution due to changes in awareness and diagnostic habits. Asthma and allergic diseases have been given considerable public health and media attention especially in Western societies in the same period as the 'asthma epidemic' has arisen. The impact of increased general awareness has been proposed to explain some of the increasing trend in the prevalence of asthma (2, 57). The increased general awareness together with changed diagnostic habits represents information bias and may have influenced the time trends in our study population.

When calculating the estimated time trends of asthma, AR and eczema, we did not evaluate or adjust potentially confounding factors. In order of making the analysis more reliable, we could have included potentially confounding factors as gender and family atopy, in the time trend analysis.

5.4.2. The case-control study (paper II and III)

A major advantage of the case-control study was the substantial clinical characterisation of the participating children together with detailed questionnaires and structured interviews. Two

paediatric doctors conducted all the interviews, clinical examination and clinical testing using the same medical instruments to secure standardised measurement conditions. The procedures were performed in accordance with validated published guidelines (127, 128, 131). Hence, the clinical assessment can be regarded as consistently reported and reliable, which strengthens the statistical power and the internal validity of the results.

Confirmative parental reports on asthma (question 1 and/or 2) defined the status of asthma ever for the entire cross-sectional survey (paper I). The two paediatric doctors determined the asthma status in the case-control study during the clinical assessment (paper II). After the asthma status and the severity of disease were determined, clinical testing was conducted. It was executed in this way for two reasons: a) we did not want to let the test results influence the decision about asthma status and, b) we wanted to investigate if clinical tests added extra information to clinical assessment. However, there are two obvious limitations with this approach. The first is the lack of probability weighting to correctly estimate how many true asthma cases and true controls one would have in the total population from the cross-sectional survey and how many of them were test positive and test negative. Without probability weighting, one needed to be sure that the original randomisation process for choosing test positives and test negatives really fulfilled the criteria for random sampling. If not, it may violate independence between disease status and exposure status in the case-control study and influence the sensitivity and specificity measures. We believe that the randomisation process was good enough to prevent a massive influence on the validation measurements, even if lower response rate than preferred likely entailed a selection bias (as discussed in section 5.4.1). This assumption is strengthened by the results from another Norwegian study, which demonstrated similar sensitivity (0.96) and specificity (0.88) when they validated the current questionnaire (45).

A second limitation to the approach used is that the reviewers were not blinded to the previous parental reported asthma status in the child. Bias can occur if reviewers are aware of the study hypothesis and subconsciously or consciously gather data selectively (21). Ideally, the reviewers should have been blinded to avoid misclassifications based on prejudice or beliefs. Unfortunately, this was not possible within the organization of the study due to limited resources. This is one of the unfortunate disadvantages when performing extensive research outside university premises in small research environments. However, the reviewers

had no knowledge about the specific answers to the individual questions in the cross-sectional survey. Therefore, we believe that this has only influenced the results in a minor degree.

Misclassification of outcomes caused by inter-observer variation is a risk in classical epidemiologic studies based on information from questionnaires. Misclassification is a type of information bias and may be defined as the assignment of a wrong value for a given piece of information (158). This is especially important when analysing diseases, such as asthma, in which the clinical presentation is essential to the diagnosis (16). The present study combined the best qualities in combining questionnaires and testing, namely, by first performing a questionnaire survey and subsequently conducting more intensive examinations on a large subsample of children. This led to a reduced risk of further misclassification in the case-control survey. However, it is important to remember that sensitivity and specificity of 'diagnostic tools' must be interpreted in the light of the definition of asthma that was used and the population that was studied (9). Since both symptomatic and non-symptomatic study subjects were examined, it was possible to estimate the extent of misclassification in the questionnaire survey. We used current asthma (symptoms and/or use of medication the last 12 months) as the definition of cases when comparing asthmatic and non-asthmatic children (paper III), since questions about current disease are more reliable than questions about symptoms ever due to less recall bias.

A major challenge in retrospective studies is recall bias, a second type of information bias. Recall bias occurs when study subjects report inaccurate information. In case-control studies, cases are more likely to recall previous risk factors than controls. Recall bias affecting only one of the study groups may produce a spurious association between the exposure and the outcome resulting in higher prevalence and positively biased odds ratio estimates. Inconsistency concerning information on children's chronic health conditions (asthma) based on medical record data and parents-reports has been reported (169, 170). On the other hand, self-reported symptom history seems to represent the necessary basis for defining asthma in epidemiological studies (31, 57). Reliability in the present study could have been checked by resubmitting the questionnaire used in the cross-sectional survey to a subgroup of participants. Unfortunately, we did not preform such test of reliability. However, during the structured interview in the case-control study some of the questions were repeated as part of the assessment of asthma, AR and eczema status. In addition, the proportion of children reporting use of asthma medication ever and last year in the cross-sectional survey was

similar to the prevalence of asthma ever and current asthma, which strengthen the results.

Another limitation inherent in asthma questionnaires is that questions covering diagnosis and clinical assessment may not be truly independent of each other. As a diagnosis is not merely an objective record, it could include an intervention that may affect parental perception. This problem with 'circularity' can make it difficult to evaluate whether parents are just recalling previous outcomes when answering questions concerning diagnoses. Thus, caution is needed when making definitive statements.

Case-control studies include the ability to control for multiple confounders and the ability to assess multiple exposures of interest. Confounding in any direction is important to the degree that it results in erroneous conclusions about the effect of the exposure on the outcome (161). We performed a matched case-control study to minimize for potential confounders in the exposure-outcome relationship and to increase the statistical efficiency (171). One problem with the matched analysis is the loss of all the information from the concordant pairs. Thus, unless the matching factors are strongly associated with both outcome and exposure, the gained efficiency may not be worth the extra analytic complexity (19). Studying asthma, we considered the matching to be worth the effort since sex and age are strongly associated with asthma and several of the exposures variables. It is essential to note that since matching was used in the design, the analysis had to take this into account.

Even if confounding bye age and gender were addressed through the matching, we had to consider confounding from the other measured variables. The variables atopy in the family in 1985 and AR and hospitalization in 2008 were considered as confounders. Thus, we needed to minimize the confounding by including the variables in their respective models. Even if confounding was addressed through the study design and analysis, still confounding by chance or unmeasured factors may have remained. The likelihood of strong baseline confounding occurring by chance decreases as he study size increases (161). The size of original study cohorts were large as was the subsample examined in the case-control in 2008. We believe this minimalized unmeasured confounding and confounding by chance.

In a case-control design, both exposures and outcome are assessed at the same time. Consequently it is unknown if the development of the asthma truly preceded the exposure (e.g. LRTIs). This is a disadvantage with case-control studies (18), and for this reason the

present findings might not be generalizable to other children populations. Measuring post-test odds and post-test probability has its limitations. Both post-test odds and probability are depending on the pre-test odds or prevalence of the disease in question. As different populations have different pre-test odds and prevalence of asthma, they will experience different post-test probability even if similar clinical tests were used. This makes comparison of results between different populations and generalization challenging. Finally, the case-control studies from 1985 and 2008 were not identical in respect of screening of variables and clinical testing, and this was a limitation. Thus, caution was necessary in drawing conclusions and in generalizing, but nonetheless we believe that the data and analysis were useful to the discussion concerning associative and risk factors for the development of current asthma.

6. Conclusions

In Nordland county, repeated cross-sectional surveys between 1985 and 2008 revealed an increase in the prevalence of asthma and AR ever among schoolchildren (7-14 years), while the prevalence of eczema ever reached a plateau. The prevalence of current diseases doubled and trebled between 1995 and 2008.

Validation of the survey questionnaire used in several studies, found it to be a valid proxy for clinical assessment in terms of identifying cases of asthma in schoolchildren. Within the limitations of our case-control study design, questions covering disease predicted asthmatic children better (with higher sensitivity) than those covering symptoms. Detailed clinical testing adds little additional information and seems unnecessary in terms of establishing disease prevalence for asthma. The questionnaire used seemed to be a good research tool for cross-sectional surveys. However, with future research one might consider removing questions related to symptoms to reduce the questionnaire burden.

One or repeated lower respiratory tract infections during the first three years of life was identified to be the most important risk factor for current asthma in this subarctic child population when adjusting for other variables. Whether or not lower respiratory tract infections have contributed to the increased asthma prevalence in this population over these 23 years is still unresolved. During the period, 1985-2008 increased average temperature may have led to a rise in pollen production and thereby he increased prevalence of AR. Since allergic comorbidity was identified as a risk factor for current asthma in 2008, AR might have contributed to the increased asthma prevalence in the study population. In 1985, atopic diseases in the family had a major impact on current asthma, but not in 2008. The contrast in these findings might be explained by the substantial increase in the prevalence, regarding of the asthma status in the child, of atopic diseases among the family members between 1985 and 2008.

7. Future perspectives

The results of the papers included in the present thesis raises two main questions. First: Is the prevalence of asthma and AR still rising in the study area? Diverse global trends in the prevalence of asthma and allergic diseases make regional repeated investigations important to assess time trends. Thus, from an epidemiological point of view the need for a follow-up survey in our study area after an appropriate interval is evident. A new survey will serve at least two purposes: 1) answer if the prevalence in asthma and allergic diseases is still increasing or if it has reached a plateau and 2) provide information about local conditions that may affect disease prevalence. The preferred design for a follow up study would be a cross-sectional survey, using the same questionnaire as previously except for a possible modification of questions related to asthma symptoms. To ensure a high participation rate the questionnaire should be designed using an online survey software and web tools (e.g. Questback) making it more accessible for the study participants and their parents. An investigation of non-responders as well as responders would give valuable insight to whether or not the results from the survey could be fully generalized.

Second: Which risk factors are the most important ones when it comes to preventing asthma development in children? Because of the considerable burden of asthma, it is important to identify individual risk factors associated with childhood asthma for developing preventative strategies (172). As LRTIs and AR are major risk factors for the asthma development in children (173, 174), it is of the utmost importance for future research to focus on preventing strategies for LRTIs and AR. Persistent asthma might result from interactions between immune responses to allergens and respirator tract viruses, mainly RSV and Rhinovirus. Could therapeutic approaches that activate innate immune responses prevent acute viral LRIs and be used to prevent asthma (173)? In addition, studies has shown prednisolone treatment to be beneficial in subgroups of young children with high viral loads at presentation of first wheeze episode (175), which would be an interesting subject for further investigations. A recent German study revealed allergy immunotherapy (AIT) as a possible effective tool preventing the progression of AR to asthma in a real-life setting (176). Could AIT induce long term remission of asthma (177)? The preferred study design for answering these questions would be a prospective birth cohort, including all pregnant women from Nordland

county during a defined period (e.g. one year). A longitudinal design is needed to establish causal inferences to better understand underlying mechanisms for asthma, to identify different asthma phenotypes and subgroups and developing preventive strategies.

In a recent comprehensive international study, children with asthma were found to have epigenetic (acquired) DNA changes in certain cells of the immune system (178). The findings in this study promise epigenetic regulation as a new treatment strategy for improved diagnosis and treatment for individuals. With different phenotypes and stronger focus on different individual subtypes, it is important in the future to include shared decision-making for people with asthma, including children. Research in this field so far cannot provide meaningful overall conclusions (179). Thus, despite the extensive research conducted, the need for new research in this field is indisputable.

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Papers I-III

Paper I

Paper II

Paper III

Appendix

Appendix I

BARNEAVDELINGEN, REGIONSYKEHUSET I TROMSØ
BARNEAVDELINGEN, NORDLAND SENTRALSYKEHUS, BODØ

TIL FORELDRE/FORESATTE

Mange barn har astma, høysnue, eksem eller elveblest. Ved siden av allergi kan andre forhold som arv, røyking, infeksjoner, boligforhold og klima spille en rolle for forekomsten av disse sykdommene. Vi ønsker å undersøke hvor utbredt "allergiske sykdommer" er blant nord-norske skolebarn og hva som er de viktigste årsakene til disse sykdommene.

Derfor håper vi dere vil hjelpe oss med å fylle ut dette spørreskjemaet. Les først gjennom den vedlagte veiledningen og fyll ut skjemaet så nøye som mulig De fleste spørsmålene kan besvares med et kryss ☒.

Alle opplysninger vil bli behandlet med taushetsplikt, og det vil ikke bli offentliggjort opplysninger som kan føres tilbake til en bestemt elev. Det er frivillig om man vil svare, men vi håper alle slutter opp om denne undersøkelsen for da blir resultatene mest pålitelige. På forhånd takk for hjelpen

Hilsen

Roald Bolle
Allergolog

Jan Holt
Overlege

Elevens navn.......................Skole...................Klasse.............

Postnr.......Poststed...............Telef........Fødselsnr |__|__|__|__|__|__|__|__|__|__|__|

Hvor bodde barnet det første leveåret (poststed).....................

	Ja	Nei
Har to eller flere av besteforeldrene hatt finsk som morsmål..........	☐	☐
Har to eller flere av besteforeldrene hatt samisk som morsmål..........	☐	☐

Spørreskjemaet er utfylt av: Eleven selv ☐   Mor ☐   Far ☐   Andre ☐

FAMILIE

BOLIG

DYR

Har noen i familien (foreldre, søsken) hatt astma, "høysnue", eksem, elveblest eller andre sykdommer som dere tror kan skyldes allergi (se beskrivelse av sykdommene i følgeskrivet).......... Ja ☐ Nei ☐

Hvis ☒, kryss av

	Mor	Far	Søstre	Brødre
Astma......				
"Høysnue"..				
Eksem......				
Elveblest..				
Andre allergiske sykdommer..				

Hvor mange søsken har eleven......................... ☐

Hvor mange i familien bor nå sammen.................. ☐

I hvilket år ble boligen bygget..................... ☐

Boligens størrelse (ca boligareal i kvadratmeter)...... ☐

Boligen ligger i: Sterkt trafikkert område............................ Ja ☐ Nei ☐

　　　　　　　　　 Middels trafikkert område............................ ☐ ☐

　　　　　　　　　 Lite trafikkert område............................ ☐ ☐

　　　　　　　　　 Område med mye industriell luftforurensning.......... ☐ ☐

　　　　　　　　　 Område med middels mye industriell luftforurensning.. ☐ ☐

　　　　　　　　　 Område med lite industriell luftforurensning......... ☐ ☐

Blir det fukt eller rim på innsiden av noen av veggene
i boligen om vinteren.. ☐ ☐

Bruker familien vanligvis ekstra luftfukter................. ☐ ☐

Oppvarming av boligen.......... Elektrisk ☐　　Vedfyring ☐

　　　　　　　　　　　　　　　　　 Olje ☐　　　Annen ☐

Hvilket sengetøy bruker eleven....... Dun ☐　　Syntetisk ☐

　　　　　　　　　　　　　　　　 Annet ☐

Hvor mange sover i elevens soverom vanligvis.......... ☐

Hvor stort er elevens soverom (kvadratmeter)......... ☐　　Ja Nei

Er det teppegulv på elevens soverom..................... ☐ ☐

Luftes vanligvis elevens soverom om dagen............. ☐ ☐

Røyker noen i familien daglig........................ ☐ ☐

Hvis ☒ Ja, hvem.................... Far ☐　　　Mor ☐
　　　　　　 Søsken ☐　　Eleven ☐　　Andre ☐

　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　Ja Nei

Har familien selv dyr............................ ☐ ☐

Hvis ☒ Ja, hvilke　 Hund ☐　　Katt ☐　　　Hest ☐
　　　　　　　　　　 Ku ☐　　　Geit ☐　　　Reinsdyr ☐
　　　　　　　　　　 Sau ☐　　　Kanin ☐　　Fugl(er) ☐
　　　　　　　　　 Marsvin ☐　　Hamster ☐　　Andre ☐　　　Ja Nei

Hvis ☒ Nei: Har eleven omtrent daglig kontakt med dyr................... ☐ ☐

LUNGESYKDOMMER

　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　Jr Nei

Har eleven hatt astma.................................... ☐ ☐

Har eleven hatt perioder med tetthet og piping i brystet og/eller
anfall med tung pust uten at dette har vært oppfattet som astma ..::.... ☐ ☐

Har eleven hatt perioder med hoste uten å være forkjølt............... Ja ☐ Nei ☐

Har eleven hatt anfall med tung pust......................... Ja ☐ Nei ☐

Får eleven piping i brystet eller blir han/hun mer tungpusten
enn jevnaldrende ved anstrengelser eller i rå, kald luft............ ☐ ☐

Får eleven piping i brystet, perioder med hoste eller anfall
med tung pust (astma) på grunn av ytre faktorer.................... ☐ ☐

    Hvis ☒ Ja, kryss av   Dyr ☐   Gress ☐ Infeksjoner ☐

        Værforandringer ☐   Matvarer ☐   Andre ☐

Har eleven noen gang vært behandlet av lege eller innlagt i sykehus
for annen sykdom enn ovenfor nevt i bronchier eller lunger, f. eks. Ja Nei
bronkitt eller lungebetennelse.................................. ☐ ☐

"HØYSNUE"

Har eleven hatt "HØYSNUE" (Perioder med plager fra nese og/eller
øynene som f. eks. renning fra nesen, nesetetthet, nysing, kløe   Ja Nei
i nese/øyne, hovne øyne, "røde" øyne)........................... ☐ ☐

   Hvis ☒ Nei, vennligst fortsett til neste avsnitt HUDSYKDOMMER

   Hvis ☒ Ja, kryss av: Nese-   Renning   Kløe
                tetthet ☐ fra nesen ☐ i nesen ☐

             Kløe i øynene ☐ Hovne øyne ☐ Nysing ☐

             Hevelse rundt   Rødhet i
                øynene ☐   øynene ☐   Andre ☐

Vet dere om forhold som utløser høysnueplagene................... Ja ☐ Nei ☐

   Hvis ☒ Ja,   Dyrekontakt ☐   Gress ☐   Trær ☐

             Matvarer ☐   Andre ☐

Er det noen årstid hvor høysnueplagene er verst................... Ja ☐ Nei ☐

   Hvis ☒ Ja, kryss av   Sommer ☐   Høst ☐
                     Vinter ☐   Vår ☐

Alder da høysnueplagene begynte......................... ☐ år

Dersom eleven tidligere har hatt høysnue, men nå er kvitt
disse plagene: Hvor gammel var eleven da plagene forsvant ☐ år

                                         Ja Nei
Bruker eleven medisiner for sine høysnueplager..................... ☐ ☐

   Hvis ☒ Ja, hvilke.....................................

HUDSYKDOMMER

	Ja	Nei

HAR ELEVEN HATT UTSLETT SOM HAR VART MER ENN 4 UKER.................. ☐ ☐

Hvis ☒ Ja, med... Mye kløe ☐   Lite kløe ☐   Ikke kløe ☐

Hvis ☒ Ja, hvor var utslettet
lokalisert, kryss av   Ansikt ☐   Mage ☐
                         Albubøyer ☐   Rygg ☐
                         Knehaser ☐ Andre steder ☐

Hvis ☒ Ja, hvor gammel var han/hun da utslettet begynte   ☐ år

Dersom eleven tidligere har hatt utslett som ovenfor
nevnt, men nå er kvitt disse plagene: Hvor gammel var
han/hun da utslettet forsvant................. ☐ år

HAR ELEVEN HATT ELVEBLEST (kløe og hevelse - vabler- i
huden. Utslettet flytter seg fra sted til sted i løpet av   Ja Nei
minutter/timer og forsvinner etter timer eller dager)......... ☐ ☐

Hvis ☒ Ja, hvor mange slike perioder
har eleven hatt............. 1-2 ☐   3-5 ☐
                             6-10 ☐   Mer enn 10 ☐

Hvis ☒ Ja, hvor gammel var han/hun da plagene begynte.... ☐ år

HAR ELEVEN REAGERT PÅ MATVARER............................   Ja Nei
                                                                    ☐ ☐

Hvis ☒ Ja,.....................Bare en gang ☐ Flere ganger ☐

Hvis ☒ Ja, hvordan reagerte han/hun..................................

Hvis ☒ Ja, hva reagerte han/hun på.................................

                                                                    Ja Nei
Har eleven noen gang hatt andre allergiske reaksjoner............... ☐ ☐
   Hvis ☒ Ja, hvilke...

                                                                    Ja Nei
Har eleven noen gang vært allergitestet............................. ☐ ☐
Har eleven noen gang vært "vaksinert" (hyposensibilisert) mot allergi.. ☐ ☐
Tillater foreldre/foresatte at vi tar kontakt med familien
dersom vi mener det er nødvendig.................................. ☐ ☐

VENNLIGST SE OVER SKJEMAET-HAR DERE SVART PÅ ALLE SPØRSMÅL

TAKK FOR HJELPEN !

Eventuelle kommentarer eller tilføyelser

Sted, dato.................

Appendix II

BARNEAVDELINGEN, REGIONSYKEHUSET I TROMSØ
UNIVERSITETET I TROMSØ
BARNEAVDELINGEN, NORDLAND SENTRALSYKEHUS, BODØ

TIL FORELDRE/FORESATTE

Astma- og allergi er et økende problem. Stortinget har nylig vedtatt at det må satses for å stoppe denne økningen. Våre helsemyndig-heter er opptatt av å finne et mål for og årsakene til økningen for å kunne forebygge. Dette spørreskjemaet er et ledd i denne satsing-en, og vi ber om deres hjelp til å fylle det ut. det er en gjentakelse av den undersøkelse som ble gjort for 10 år siden hos skolebarn i nøyaktig de samme skolekretsene - over 11.000 barn i Nord-Norge deltar.

De fleste spørsmålene kan besvares med et kryss. ⊠

Alle opplysninger vil bli behandlet med taushetsplikt, og det vil ikke bli offentliggjort opplysninger som kan føres tilbake til en bestemt elev. Det er frivillig om man vil svare, men vi håper at alle slutter opp om denne undersøkelsen. Høy svarprosent og nøye utfylling av skjemaet er nødvendig for at undersøkelsen skal kunne lykkes. Norsk Forskningsråd og Universitetet i Tromsø medvir-ker.

På forhånd takk for hjelpen! Med vennlig hilsen,   Roald Bolle   Jan Holt
                                                                    allergolog/overlege

Elevens navn: .... Gutt ☐ Pike ☐ Skole ....Klasse..............

Postnr......................Poststed ....Telefon.............................Fødselsnr. ....

Hvor bodde barnet det første leveåret (poststed)...

Hvor lenge har barnet bodd i nåværende område..

Spørreskjemaet er utfylt av: Eleven selv ☐   Mor ☐   Far ☐   Andre ☐

FAMILIE

Har noen i familien (foreldre, søsken) hatt astma, "høysnue", eksem, elveblest eller andre sykdommer som dere tror kan skyldes allergi (se beskrivelse av sykdommene i følgeskrivet)	Ja ☐	Nei ☐

Hvist JA, kryss av

	Mor	Far	Søstre	Brødre
Astma				
"Høysnue"				
Eksem				
Elveblest				
Andre allergiske sykdommer				

Hvor mange søsken har eleven ☐

LUNGESYKDOMMER

	Ja	Nei	
● Har eleven hatt astma	☐	☐	☐
Har eleven hatt perioder med tetthet og piping i brystet og/eller anfall med tung pust uten at dette har vært oppfattet som astma	☐	☐	☐
Har eleven hatt perioder med hoste uten å være forkjølet	☐	☐	☐
Har eleven hatt anfall med tung pust	☐	☐	☐
Får eleven piping i brystet eller blir han/hun mer tungpustet enn jevnaldrende ved anstrengelser eller i rå, kald luft	☐	☐	☐
● Får eleven piping i brystet, perioder med hoste eller anfall med tung pust (astma) på grunn av ytre faktorer	☐	☐	☐

Hvis JA, kryss av: .... Dyr ☐ .... Gress ☐ .... Infeksjoner ☐

Værforandringer ☐ .... Matvarer ☐ .... Andre ☐

	Ja	Nei
Har eleven noen gang vært behandlet av lege eller innlagt i sykehus for annen sykdom enn overfor nevnt i bronchier eller lunger, f. eks. bronkitt eller lungebetennelse	☐	☐

HØYSNUE

	Ja	Nei	
● Har eleven hatt "HØYSNUE" (Perioder med plager fra nese og/eller øynene som f. eks. renning fra nesen, nesetetthet, nysing, kløe i nese/øyne, hovne øyne, "røde" øyne)	☐	☐	☐

Hvis NEI, vennligst fortsett til neste avsnitt HUDSYKDOMMER

Hvis JA, kryss av: .... Nesetetthet ☐ .... Renningfra nesen ☐ .... Kløe i nese ☐

Kløe i øynene ☐ .... Hovne øyne ☐ .... Nysing ☐

Hevelse rundt øynene ☐ .... Rødhet i øynene ☐ .... Andre ☐

	Ja	Nei
Vet dere om forhold som utløser høysnueplagene	☐	☐

Hvis JA, kryss av: .... Dyrekontakt ☐ .... Gress ☐ .... Trær ☐

Matvarer ☐ .... Andre ☐

	Ja	Nei
Er det noen årstid hvor høysnueplagene er verst..	☐	☐

Hvis JA, kryss av :........................... Sommer ☐ .... Høst ☐

Vinter ☐ .... Vår ☐

Alder da høysnueplagene begynte.. ☐ år

Dersom eleven tidligere har hatt høysnue, men nå er kvitt
disse plagene: Hvor gammel var eleven da plagene forsvant .... ☐ år

	Ja	Nei
Bruker eleven medisiner for sine høysnue plager	☐	☐

Hvis JA, hvilke...

HUDSYKDOMMER

	Ja	Nei.	
● HAR ELEVEN HATT UTSLETT SOM HAR VART MER ENN 4 UKER	☐	☐	☐

Hvis JA, med: .... Mye kløe ☐ .... Lite kløe ☐ .... Ikke kløe ☐

Hvis JA, hvor var utslettet
lokalisert, kryss av: .... Ansikt ☐ .... Mage ☐ .... Albubøyer ☐

Rygg ☐ .... Knehaser ☐ .... Andre steder ☐

Hvis JA, hvor gammel var han/hun da utslettet begynte... ☐ år

Dersom eleven tidligere har hatt utslett som overfor
nevnt, men nå er kvitt disse plagene: Hvor gammel var
han/hun da utslettet forsvant .... ☐ år

	Ja	Nei
HAR ELEVEN HATT ELVEBLEST (kløe og hevelse - vabler- i huden Utslettet flytter seg fra sted til sted i løpet av minutter/timer og forsvinner etter timer eller dager)...	☐	☐

Hvis JA, hvor mange slike
perioder har eleven hatt: .... 1 - 2 ☐ .... 3 - 5 ☐

6 - 10 ☐ .... Mer enn 10 ☐

Hvis JA, hvor gammel var han/hun da plagene begynte.. ☐ år

	Ja	Nei
HAR ELEVEN REAGERT PÅ MATVARER	☐	☐

Hvis JA: .... Bare en gang ☐ .... Flere ganger ☐

Hvis JA, hvordan reagerte han/hun..

Hvis JA, hva reagerte han/hun på ....

	Ja	Nei
Har eleven noen gang hatt andre allergiske reaksjoner..	☐	☐
Hvis JA, hvilke...	Ja	Nei
Har eleven noen gang vært allergitestet	☐	☐
Har eleven noen gang vært "vaksinert" (hyposensibilisert) mot allergi...........................	☐	☐

BOLIG

Hvor mange i familien bor nå sammen .... ☐

I vilket år ble boligen bygget .... ☐

Boligens størrelse (ca boligareal i kvadratmeter) .... ☐

		Ja	Nei
Boligen ligger i:	Sterkt trafikkert område	☐	☐
	Lite trafikkert område	☐	☐
	Område med mye industriell luftforurensning	☐	☐
	Område med middels mye industriell luftforurensning	☐	☐
	Område med lite industriell luftforurensning	☐	☐

Blir det fukt eller rim på innsiden av noen av veggene
i boligen om vinteren .... ☐ .... ☐

Bruker familien vanligvis ekstra luftfukter .... ☐ .... ☐

Oppvarming av boligen: .... Elektrisk ☐ .... Vedfyring ☐

Olje ☐ .... Annen ☐

Hvilket sengetøy bruker eleven: .... Dun ☐ .... Syntetisk ☐ .... Annet ☐

Hvor mange sover i elevens soverom vanligvis .... ☐

Hvor stort er elevens soverom (kvadratmeter) .... ☐

	Ja	Nei
Er det teppegulv på elevens soverom	☐	☐
Luftes vanligvis elevens soverom om dagen	☐	☐
Røyker noen i familien daglig	☐	☐

Hvis JA, hvem: .... Far ☐ .... Mor ☐

Søsken ☐ .... Eleven ☐ .... Andre ☐

	Ja	Nei
Har familien selv dyr	☐	☐

Hvis JA, hvilke : .... Hund ☐ .... Katt ☐ .... Hest ☐

Ku ☐ .... Geit ☐ .... Reinsdyr ☐

Sau ☐ .... Kanin ☐ .... Fugl (er) ☐

Marsvin ☐ .... Hamster ☐ .... Andre ☐

	Ja	Nei
Hvis NEI: Har eleven omtrent daglig kontakt med dyr	☐	☐

VIKTIG! Vennligst se over skjemaet om alle spørsmålene er besvart.
Hvis spørsmålene merket med ● ikke er besvart, tillater vi oss å ta kontakt med familien, fordi disse svarene er særlig viktig for å kunne si noe om økningen gjennom 10 år.
Hvist foreldre/foresatte **ikke** ønsker at vi skal ta kontakt, kryss av .... ☐

Universitetet i Tromsø har et særlig ansvar for forskning i nordområdene.
Derfor tillater vi oss å be om svar også på følgende spørsmål med tanke på allergi og arv:

	Ja	Nei
Har to eller flere av besteforeldrene hatt finsk som morsmål	☐	☐
Har to eller flere av besteforeldrene hatt samisk som morsmål	☐	☐

Eventuelle kommentarer eller tilføyelser:

Appendix III

UNIVERSITETET I TROMSØ

NORDLANDSSYKEHUSET
NORDLÁNDA SKIHPPIJVIESSO

Skjema nr. [　　　　]

INNLEDNING

Dette er spørreskjemaet som vi ber dere fylle ut hvis dere vil delta i forskningsprosjektet. Spørreskjemaet inneholder 49 spørsmål. Undersøkelsen baserer seg på frivillig deltakelse, men for det beste resultatet, er det viktig at så mange som mulig deltar.

Vi ønsker å delta i forskningsprosjektet: Ja [　]

Sted/dato	**Underskrift foreldre/foresatte**

PERSONOPPLYSNINGER

Gutt [　] Jente [　]   Fødselsdato [　　　　　　]

Skole:…………………………………………………………….   Klasse [　　　　]

Hvor bodde eleven det første leveåret(poststed)?………………………………………………………

Hvor lenge har eleven bodd i nåværende område (antall år)? [　　]

Spørreskjemaet er fylt ut av:

Eleven selv		Mor		Far		Andre	

FAMILIE

1. Har noen i familien til eleven (foreldre, søsken) hatt astma, "høysnue",
   eksem, elveblest eller andre sykdommer som dere tror kan skyldes allergi?   Ja [　] Nei [　]

2. **Hvis JA:** kryss av:

	Mor	Far	Søstere	Brødre
Astma				
Høysnue				
Elveblest				
Eksem				
Andre allergiske sykdommer				

3. Hvor mange søsken har eleven? [　　]

LUNGESYKDOMMER

4. Har eleven hatt astma?   Ja ☐ Nei ☐

5. **Hvis JA:** har eleven hatt slike plager siste 12 måneder?   Ja ☐ Nei ☐

6. Har eleven brukt astmamedisiner?   Ja ☐ Nei ☐

7. **Hvis JA:** har eleven brukt slike medisiner siste 12 måneder?   Ja ☐ Nei ☐

8. Har lege diagnostisert astma hos eleven?   Ja ☐ Nei ☐

9. Har eleven hatt perioder med tetthet og piping i brystet,
og/eller anfall med tung pust uten at dette har vært
oppfattet som astma?   Ja ☐ Nei ☐

10. Har eleven hatt perioder med hoste uten å være forkjølet?   Ja ☐ Nei ☐

11. Har eleven hatt anfall med tung pust?   Ja ☐ Nei ☐

12. Får eleven piping i brystet eller blir han/hun mer tungpustet
enn jevnaldrende ved anstrengelser eller i rå, kald luft?   Ja ☐ Nei ☐

13. Får eleven piping i brystet, perioder med hoste eller anfall
med tung pust (astma) på grunn av ytre faktorer?   Ja ☐ Nei ☐

14. **Hvis JA:** kryss av:

Dyr		Gress		Matvarer	
Værforandringer		Infeksjoner		Andre	

15. Har eleven noen gang vært behandlet av lege eller innlagt i
i sykehus for annen sykdom enn nevnt ovenfor i bronkier
eller lunger, f. eks bronkitt eller lungebetennelse?   Ja ☐ Nei ☐

HØYSNUE

16. Har eleven hatt "høysnue"(Perioder med plager fra nese og/eller
øynene som f. eks renning fra nesen, nesetetthet, nysing,
kløe i nese/øyne, hovne øyne, "røde øyne")?   Ja ☐ Nei ☐

17. **Hvis JA:** har eleven hatt slike plager siste 12 måneder?   Ja ☐ Nei ☐

Hvis NEI: fortsett til spørsmål nr. 27.

18. **Hvis JA:** kryss av:

Nesetetthet		Renning fra nesen		Kløe i nesen	
Kløe i øynene		Hovne øyne		Nysing	
Hevelse rundt øynene		Rødhet i øynene		Andre	

19. Vet dere om forhold som utløser høysnueplagene?   Ja ☐ Nei ☐
20. **Hvis JA:** kryss av:

Dyrekontakt		Gress		Trær	
Matvarer		Andre			

21. Er det noen årstid hvor høysnueplagene er verst?   Ja ☐ Nei ☐
22. **Hvis JA:** kryss av:

Sommer		Høst	
Vinter		Vår	

23. Hva var elevens alder (år) da høysnueplagene begynte?   ☐
24. Dersom eleven tidligere har hatt høysnue, men nå er kvitt
    disse plagene: Hvor gammel var eleven da plagene forsvant?   ☐

25. Bruker eleven medisiner for sine høysnue plager?   Ja ☐ Nei ☐
26. **Hvis JA:** hvilke medisner bruker han/hun?
    ....

HUDSYKDOMMER

27. Har eleven hatt utslett som har vart i mer enn 4 uker?   Ja ☐ Nei ☐

Hvis NEI: fortsett til spørsmål nr. 32.

28. **Hvis JA:** har eleven hatt slikt utslett siste 12 måneder?   Ja ☐ Nei ☐

29. **Hvis JA:** med:

Mye kløe		Lite kløe		Ingen kløe	

30. **Hvis JA:** hvor var utslettet lokalisert?

Ansikt		Mage		Albuebøyer	
Rygg		Knehaser		Andre steder	

31. **Hvis JA:** hvor gammel var eleven da utslettet begynte   ☐
32. Dersom eleven tidligere har hatt utslett som ovenfor nevnt,
    men nå er kvitt plagene: Hvor gammel var han/hun da utslettet
    forsvant?   ☐
33. Har eleven hatt elveblest (kløe og hevelse i huden – utslettet
    flytter seg fra sted til sted ila minutter/timer og forsvinner
    etter timer eller dager)?   Ja ☐ Nei ☐

Hvis NEI: fortsett til spørsmål nr. 36.

34. **Hvis JA:** hvor mange slike perioder har eleven hatt?

Mindre enn 5		Flere enn 5	

35. **Hvis JA:** hvor gammel var han/hun da plagene begynte?   ☐

36. Har eleven reagert på matvarer? Ja ☐ Nei ☐

Hvis NEI: fortsett til spørsmål nr. 40.

37. Hvis JA:

Bare en gang		Flere ganger	

38. Hvis JA: hvordan reagerte han/hun?

Kløe i halsen		Tungpust	
Utslett/elveblest		Allergisjokk	

39. Hvis JA: hva reagerte han/hun på?

……

BOLIG

40. Hvor mange i familien bor nå sammen? ☐
41. I hvilket år ble boligen bygget? ☐
42. Hvor stor er boligen (ca boligareal i kvadratmeter)? ☐

43. Ligger boligen i et tettbebygget område med gater? Ja ☐ Nei ☐
44. Ligger skolen så langt unna hjemstedet at eleven må ha skyss til skolen? Ja ☐ Nei ☐
45. Røyker noen i familien daglig? Ja ☐ Nei ☐
46. Røyker noen i familien innendørs? Ja ☐ Nei ☐
47. Har familien selv dyr? Ja ☐ Nei ☐
48. Hvis JA: hvilke:

Hund		Katt		Hest	
Ku		Geit		Reinsdyr	
Sau		Kanin		Fugl (er)	
Marsvin		Hamster		Andre	

49. Hvis NEI: har eleven omtrent daglig kontakt med dyr? Ja ☐ Nei ☐

Vi ber dere om å se over at alle spørsmål som dere ønsker å besvare, er besvart. Spesielt viktig er det at spørsmålene uthevet med gult er besvart. Vi sender ut spørreskjemaet på nytt etter ca 3 uker for de som ikke da har svart. De som svarte ved første henvendelse, kan se bort fra andre gangs utsendelse.
Noen elever som har astma, og en kontroll for hver slik elev, vil senere bli invitert til en nærmere undersøkelse med testing. De dette gjelder, vil få nærmere informasjon om den planlagte oppfølgningsundersøkelsen, og det er frivillig om man vil delta.

Tillater foreldre/foresatte at vi tar kontakt med informasjon om oppfølgings-undersøkelsen dersom deres barn blir valgt ut til dette? Ja ☐ Nei ☐

TUSEN TAKK FOR HJELPEN!