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Asthma and allergy in children

An epidemiological study of asthma and allergy in schoolchildren living in Northern Norway and Russia with respect to prevalence trends 1985-1995-2000, geographic differences in prevalence and biomarkers.

By Anders Selnes

Tromsø 2006

Institute of Community Medicine
University of Tromsø, Norway 2006

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Contents

Acknowledgements

Around 1990 I was planning the obligatory 5th year research work at the medical school at The University of Tromsø. It was during a period of much negative focus on the living conditions in Northern Norway with quite a few people leaving their homes and moving southwards. Therefore, when I looked for a health issue for this minor research project, I thought it had to be an issue that might potentially turn out to be positive and optimistic about living in Northern Norway; i.e. an argument to stay. Along with a perhaps naive conviction that the likelihood of contracting asthma and allergy was higher in Oslo than on Senja this subject came to my mind. Thus I came to know a specialist in allergology, chief physician **Roald Bolle**, Department of Paediatrics at The University Hospital of Northern Norway; a man with great and contagious enthusiasm for his field of work that, before I finished medical school, sent me to Japan and London on asthma and allergy conferences. Additionally he promptly gave me access to the data from a study performed by him and chief physician dr.med. **Jan Holt** (Department of Paediatrics, Nordland Central Hospital, Bodø) in 1985 and later also to data from the study performed by the two in 1995 (1;2). As such my interest in epidemiology was evoked, and after finishing medical school I was happy to become a research scholar at The Institute of Community Medicine, founded by The Research Council of Norway, under the leadership of tutor professor **Eiliv Lund**. Although his research scholar had his own ways, professor Lund with apparent limitless patience showed me the epidemiological way; since then he has been a fixture on my top five "admired persons in medicine" list. At The Institute of Community Medicine I also came to know fellow research scholar (now Dr.med.) Tone Smith-Sivertsen with whom I was happy to be a co-worker for a year (3). However, there had been no thesis without the availability of data collected by Dr.med. **Jon Øyvind Odland** in Nikel, Dr.med. **Lars Kåre Dotterud** in Sør-Varanger or without the ISAAC study conducted in 2000 by Dr.scient. **Wenche Nystad** at The Norwegian

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Finally, to my meaning of life **Ola, Halvor, Sivert** and my wife **Lene**; thanks for just being around.

Abbreviations and explanations

AD	Atopic dermatitis
AEDS	Atopic Eczema/Dermatitis Syndrome
AR	Allergic rhinoconjunctivitis
Atopic	IgE sensitized
s-ECP	Serum eosinophil cationic protein
BHR	Bronchial hyperresponsiveness
SPT	Skin prick test
RAST	Radioallergosorbent test
EIB	Exercise-induced bronchial reactivity
B-H-q	Bolle-Holt-questionnaire
ISAAC	International Study of Asthma and Allergies in Childhood
ECRHS	The European Community Respiratory Health Study
GA2LEN	The Global Allergy and Asthma European Network
MMR	measles, mumps and rubella

List of papers

This thesis is based on the following papers (referred to in the text by their Roman numerals):

I. Selnes A, Bolle R, Holt J, Lund E. Cumulative incidence of asthma and allergy in north-Norwegian schoolchildren in 1985 and 1995. Pediatr Allergy Immunol. 2002 Feb;13(1):58-63.

II. Selnes A, Nystad W, Bolle R, Lund E. Diverging prevalence trends of atopic disorders in Norwegian children. Results from three cross-sectional studies. Allergy. 2005 Jul;60(7):894-9.

III. Selnes A, Bolle R, Holt J, Lund E. Atopic diseases in Sami and Norse schoolchildren living in northern Norway. Pediatr Allergy Immunol. 1999 Aug;10(3):216-20.

IV. Selnes A, Odland JO, Bolle R, Holt J, Dotterud LK, Lund E. Asthma and allergy in Russian and Norwegian schoolchildren: results from two questionnaire-based studies in the Kola Peninsula, Russia, and northern Norway. Allergy. 2001 Apr;56(4):344-8.

V. Selnes A, Dotterud LK. No association between serum eosinophil cationic protein and atopic dermatitis or allergic rhinitis in an unselected population of children. J Eur Acad Dermatol Venereol. 2005 Jan;19(1):61-5.

Introduction

During the last few years the term "asthma and allergy" is applied in media and elsewhere to an extent that it has become a bit of a cliché. The traditional 'asthma and allergy' article in the newspapers in springtime concerns hay fever; it is supposed to be a happy story because it reminds us that summer will be here soon. At the same time it is a poorly camouflaged advertisement for the pharmaceutical industry and their possibility to sell antihistamines over the desk and thereby avoiding the obstacles connected to the more profound diagnostic procedures offered by a doctor. Despite the picturesque account of the matter produced by the free press, the by far most breath-taking lyrics about asthma were written by the Norwegian author Agnar Mykle and found in the short story "The shoes" ("Skoene" in Norwegian). It describes how a thirteen-year-old boy wakes up in the middle of the night with a serious asthma attack. He can barely move due to the heavy dyspnoea; the airways are closed by tension and he feels as though a band of iron is strapped around his chest. Over a few lines the reader experiences the utter desperation and anxiety caused by the lack of air, the fear of being strangled which accompanies acute, serious asthma.

A child with allergic asthma bronchiale knows that a new episode with heavy dyspnoe may appear when least expected; at an overnight stay at his grandparents who have got a cat since the last visit, whilst visiting his best friend who has recently got a dog, by sitting next to the girl who is horse riding in her spare time, by being exposed to cigarette smoke in a public area or sitting too close to the fireplace on a school trip. If the child has developed allergy against house-dust-mite (HDM), clinically expressed as allergic chronic bronchitis (asthma) and he sleeps in a bed with dismal HDM clearance, this child will most nights suffer a symptom spectrum ranging from dry cough to heavy dyspnoe. What's more, the troublesome nights are followed by a daytime with sleepiness in school, lack of concentration and obviously being

different to schoolmates because of the inability to follow in lessons as well as physical activity. Parents of an infant with allergic eczema find themselves waking at night and worrying over the crying child with the seriously itchy flexural eruption. Compared to these two categories of patients, the youth with seasonal allergic rhinitis may has moderate complaints by suffering symptoms of a cold and experiencing the asthenia associated to hay fever in the summer holidays.

In medicine, asthma and allergy is a thousand-pieces-puzzle and the ambition of the present thesis is limited to add another piece. It will focus on regional (i.e. northern Norway and its boundaries) schoolchildren characteristics of asthma and allergy in terms of prevalence trends and inter-regional geographical differences. Hopefully, this knowledge is of value for researchers when global prevalence trends are evaluated, additionally when new hypothesis are generated concerning the aetiology of this group of diseases. Lastly the thesis includes an evaluation of a biomarker in asthma and allergy which ought to be of interest for clinicians in this field.

What is asthma and allergy?

The definition of Childhood Asthma is "a disease involving repeated attacks of wheezing and dyspnoea, which either resolve without treatment or can be relieved or ameliorated by treatment" (4). The assumed aetiology of asthma has changed substantially through history. The natural course of the asthma attacks with abrupt onset and relief were in the antiquity believed to represent a state of intrusion by the devil. Hence, asthma was considered (together with epilepsy) a divine disease: "Children are liable to convulsions and asthma which are regarded as divine visitations and the disease itself as sacred" (Hippocrates 460-370 BC). Actually, up to only a few decades ago, medical students learned that the aetiology of asthma was of mental origin and secondary to neurosis. However, similarly to a range of other medical disciplines advances within the field of immunology have dramatically changed the view of asthma and allergy. The discovery of IgE was a milestone and a new era in the diagnosis and research of allergic disease dawned with a consensus meeting in the World Health Organization International Reference Center for Immunoglobulins in Lausanne, Switzerland, in February 1968. From that time on the term IgE was accepted for the serum factor that could spontaneously sensitize skin and mediate a positive immediate-type skin reaction (5;6).

Immunology

During the evolution the human immune system has developed a defence against multicellular parasite infections. The primary immunisation is sparked off by dendrittic cells catching, processing and presenting a parasite antigen integrated with HLA molecules, to T lymphocytes in lymph nodes thus leading to T cell activation (7). The most important cells in the immune response seem to be the CD4+ cells, so called T-helper-cells. These are further sub classified as T-helper-cell type Th0, Th1 and Th2. Important are also the CD8+

lymphocytes that have a regulatory or modifying function and are therefore called 'regulatory T lymphocytes' (8). During early childhood the immune system matures from the immature Th0 type cells with the potential to become differentiated to Th2 cells (type 1 reaction) or Th1 cells (type 4 reaction) in a process named "immune deviation" (9). With the combination of genetic vulnerability for allergy and allergen exposure the balance between Th1 and Th2 will be displaced in direction of increased amount of Th2 cells producing more interleukin-4 and less interferon-γ. In the next step these Th2 lymphocytes stimulate the B lymphocytes to proliferate and differentiate towards plasma cells which produce IgE immunoglobulin. The IgE will bind antigens from the parasites and the IgE-antigen complex is then presented to a variety of immunological cells. These include eosinophilic and to some extent basophilic granulocytes, histamine releasers like mast cells and finally lymphocytes (7). By this cascade an immunologic response to the parasite infection is launched.

In allergen sensitization the immune system processes allergens (i.e. antigen derived from for example house mite dust) similarly to antigens derived from parasites, and the IgE immune response is evoked by each episode of exposure. Depending on the origin of the IgE-allergen complex' presentation, the immune response firstly initiates an acute-, then a delayed- and lastly a chronic inflammation with a symptom picture reflecting the tissue targeted. Furthermore, this illustrates the basic pathology in allergy; an immune reaction developed to take care of a true threat is fired by trivialities. Eosinophilia and elevated serum IgE levels are two central features in the immune response to both parasite infection and allergen exposure. The link between the two principally different situations can be exemplified by the fact that parasitosis is an important differential diagnosis to allergy. Especially, parasitosis must always be considered in cases of extremely high peripheral blood counts of eosinophilic granulocytes and serum IgE levels.

The Siblingeffect, the hygiene hypothesis and the Th1/Th2 paradigm

In 1986 Golding and Peters found a consistent inverse relation between sibshipsize and the prevalence of hay fever and atopic eczema (10). This effect, that is less consistent in the case of asthma, is called "the Siblingeffect" (11;12). The discovery of this association led to formulation of the "hygiene hypothesis": a modern lifestyle with improved hygiene and increased use of antibiotics and vaccines causes a weakened immune deviation from Th1 towards Th2. The proposed imbalance between Th1 and Th2 response resulting in increased allergy was called "the Th1/Th2 paradigm". However, because autoimmune (and Th1 dominated) disorders are increasing as well, the Th1/Th2 paradigm has been questioned. Recent research has instead focused on another type of T lymphocytes called suppressor or regulatory (CD8+) cells. These are supposed to be responsible for immune tolerance, i.e. suppress over-activity in both the Th1 and Th2 systems and avoid an inflammatory response against trivial antigens. Current opinion, still in line with the hygiene hypothesis, is that a reduced bacterial stimulation of the immune system causes a reduced function of the suppressor T cells with a subsequent over-activity in both the Th1 and Th2 systems favouring autoimmunity and allergy (7). Differences in the composition of the gut flora between infants who will and infants who will not develop allergy are demonstrable before the development of any clinical manifestations of atopy (13). It is shown that during colonization of animals with the gut microorganism Bacteroides fragilis, a bacterial polysaccharide directs the cellular and physical maturation of the developing immune system. This host-bacterial symbiosis includes correcting systemic T cell deficiencies and imbalances of the Th1/Th2 - ratio, directing lymphoid organogenesis and by this mediating development of the host immune system (14).

The latest explanation of the immunological process in asthma and allergy is connected to alloimmune responses. It may matter whether the allergen is first presented to the maternal T-cells in the prenatal period of life, because if so, the allergen may be presented by HLA class II from the fetus, evoking a stronger immuneresponse. This process, called prenatal programming or priming, shifts the foetal T cells in a Th2 direction which then result in a Th2 response to an infectious stimulus in infancy. Thus, by prenatal programming, these children have a Th2, and not Th1, response to infections resulting in allergic sensitization. This may explain the inconsistent findings concerning the associations between infectious exposure and asthma and allergy (10).

Several intriguing observations have been made within the field immunology during the last few years (15-19). Firstly, there is evidence that the likelihood of developing allergic sensitization is greatest at lower exposure levels to allergens and that the risk of sensitization actually decreases at higher exposure levels. Secondly, this has led to speculations concerning the relationship between T-regulatory cells and allergen exposures, suggesting that high exposures stimulate the T-regulatory cells and drive the Th2 system in an alternative direction away from an allergic response. Consequently, allergen exposure may, at least in infancy, act as a protective agent towards the allergic phenotypes.

Asthma

According to the U.S. National Institutes of Health Guidelines for Management and Diagnosis of Asthma (20), asthma is defined as;

" A chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular , mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing..... These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper-responsiveness to a variety of stimuli."

Similarly to atopic dermatitis (AD), not all asthma patients are allergen sensitized; in a study from 1999 less than half of all asthma cases were attributable to atopy (21). Moreover, no association is detected between exposure to allergens and development of asthma, but there are also differences in allergens that play a role in allergic asthma; for example are allergens from animals central in this context (19).

Anyway, the airway inflammation plays an important role in the pathophysiology of asthma leading to airway obstruction and hyperresponsiveness (22). The eosinophilic granulocytes dominate the inflammation and these are recruited from the bone marrow to the lower airways by chemokines. Additionally, mast cells, basophilic granulocytes and even smooth muscle cells contribute to the propagation. The morphologic changes in asthma include thickening of the bronchi walls due to mucosal oedema and increased thickness of bronchial smooth muscle, smooth muscle contraction and mucous hypersecretion, all changes leading to narrowing of the bronchi lumen and an increase in airway resistance. An asthma predictive index (API) is developed; The baseline is > 3 episodes of wheezing per year during the first 3

years of life plus either i) AD in child or parental asthma (physician diagnosed) or ii) two of the criteria; elevated blood eosinophils, wheezing apart from colds, physician diagnosed AR (4;12). The level of severity of the disease is assessed in children under the age of two in Stadium 1 to 6, in children above two years in Stadium 1 to 5; increasing stadia indicates increasing severity.

Allergic-/non-allergic asthma (Extrinsic/intrinsic asthma)

Asthma can be divided into two categories, allergic and non-allergic, and the diagnosis of the latter is primary based upon exclusion criteria, i.e. the absence of demonstrable allergy (23;24). Non-allergic asthma is more prevalent in girls than in boys (24;25). Similar to occupational asthma, non-allergic asthma shows an increased number of CD8+ cells in the airway wall (25). A prevalence study of bronchial hyperreactivity as determined by several methods was conducted among Estonian schoolchildren (26). It was concluded that most children with bronchial hyperreactivity in Estonia were not atopics, in contrast to studies in Western Europe. On the other hand, extrinsic asthma may well not be visible on standard SPT and an extended battery of tests is often necessary to detect atopy in the asthmatic patient (17).

Atopic dermatitis (AD)

The nomenclature for allergy is revised repeatedly (27). The terminology concerning this chronic skin disease is somewhat confusing, and a new term allergic eczema/dermatitis syndrome (AEDS) is commonly applied on the condition (28). The characteristics of AD are a chronic or chronically relapsing dermatitis with considerably pruritus with a typical and age dependent distribution throughout the skin surface (29;30). The level of severity of the disease is assessed using the score system given by Rajka and Langeland, i.e. % area of the body affected, severity of pruritus and the course of the eruption (31). The course of the eruption is categorised into three levels; 1) More than three months of remission over a period of one year (mild) 2) Less than three months of remission over a period of one year (moderate) 3) Continuous eruption (severe). The extent to which the phenotype of AD is truly atopic (i.e. due to allergen sensitization) is controversial (32). The association between atopy and AD appears weaker and more complex than previously suggested and up to two thirds of patients have no measurable allergenspecific IgE antibody sensitization (33). However, it is shown that the severity of the disorder is associated with a number of positive skin prick tests responses or with the serum IgE level. A report of the Nomenclature Review Committee of the World Allergy Organisation has suggested the term atopic eczema to denote IgE mediated skin inflammation and the term nonatopic eczema where there is no detectable IgE (28). The allergic inflammation process in AD is biphasic with an acute response dominated by Th2 cells which in turn induce IgE production. Later on the inflammation turns chronic and is then characterized by a Th1 cytokine pattern (32;34).

Allergic rhinoconjunctivitis (AR)

In the upper airway mucosa and the conjunctiva of the eyes, the binding of aeroallergens to mast cell bound IgE, release histamine and other mediators. The result is the immediate, within minutes, symptoms itchy eyes and nose, sneezing, stuffy nose, rhinorhea and lacrimation. These symptoms are due to the histamine affection on sensory nerves, histamine induced secretion of mucus and development of mucosal oedema that is secondary to changed vascular permeability (35). During the course of the next hours inflammatory cells dominated by eosinophils invade the mucosa. The activation and lysis of these eosinophils mediate damage to the mucosal epithelium and a subsequent remodelling process.

Actually, it is of benefit that the nose filters the aeroallergens that evoke allergic rhinitis; otherwise these may be inhaled and trigger allergic asthma. Among the different manifestations of allergic disease, hay fever represents a symptomatology with the highest association to IgE mediated disease. In an International Study of Asthma and Allergies in Childhood (ISAAC), skin prick tests (SPT) were performed and the positive predictive value for atopy among children with symptoms was 70% for reported hay fever (36).

Anaphylaxis. Hypersensivity reactions to food, drugs and insects. (Chronic) urticaria.

Although these subjects are all a part of the allergic spectrum, they are beyond the scope of the present study and will consequently not be further described.

Epidemiology of asthma and allergy in childhood

Numerous epidemiologic studies from all over the world have shown an increase in the asthma and allergy prevalence rates the last decades (37;38). In the first part of the 18th century the British doctor Bostock encountered 28 cases of AR all over England (39). By contrast, in a questionnaire survey of 12-14 year olds throughout England, Wales, Scotland, and the Scottish Islands using the ISAAC protocol (n=27.507), recent AR was reported by 18.2% (40). Based on these accumulating and convincing reports of increasing prevalence trends, atopic diseases are today considered a major worldwide health problem as being the most important causative agent to morbidity in children (41;42). It is stated that only repeated measurements over periods of ≥10 years, in comparable populations with comparable instruments, allow a valid estimate of time trends for atopic diseases (43).

Norwegian studies

Over the 50 year long period from mid forties to mid nineties there has been a substantial increase in childhood asthma in Norway (44). The first epidemiological study on asthma in Norway was published in 1948 and found 0.4% asthma prevalence. However, the author suggested that this estimate was too low (45). Two cross-sectional studies of schoolchildren in Oslo, Norway, conducted 13 years apart (1981/1994), uncovered an increase in asthma prevalence from 3.4% to 9.3%(46). Trends in hospital admissions for childhood asthma, were studied in Oslo, Norway, 1980-95 (47). The study revealed increased first admission rates as well as an increased overall admission rate for acute asthma in children < 4 years of age, suggesting increased prevalence of childhood asthma.

The Oslo Birth Cohort Study

A major Norwegian research project is "The environment and childhood asthma (ECA)" study in Oslo, namely ECA-1 and ECA-2 (48-50). This so-called Oslo Birth Cohort Study was initiated in 1992-1993 by 3754 newborns followed to 2 years of age (ECA-part I). A follow-up study (ECA-part II) of 616 children at the age of ten was orchestrated between 2001 and 2004; the study revealed a lifetime asthma prevalence of 20.2%, ever wheeze 30.3% and current asthma of 11.1% (50).

Studies employing The Bolle-Holt-questionnaire (see methods)

In a questionnaire-based study among 4666 schoolchildren aged 7-13 in Telemark County in 1991 the lifetime prevalence of asthma was 9%, of AR 17.8% and 13.2% had AD (51).
The relation of exposure to airway irritants in infancy to prevalence of bronchial hyper-responsiveness was investigated in 529 schoolchildren living in Aardal and Laerdal from 1989 to 1992 and BHR was found in 14.9% (52). In 1992/93, Dotterud studied the prevalence of AD among schoolchildren in Sør-Varanger Community, northern Norway. The study included a clinical examination of the subjects together with objective measurements (SPT, serum IgE). Definite atopics accounted for 36 %; AD being present in 23 % and mucous membrane atopy in 18 % (53;54).

ISAAC studies (55;56)

The prevalence of respiratory symptoms and asthma among schoolchildren was measured as part of an ISAAC study in three different areas of Norway (57). The lowest lifetime prevalence of asthma was found in Odda (5.4%) and the highest in Oslo (9.4%), but the overall results were not convincing with respect to urban and rural differences in respiratory morbidity.

International changes in prevalence

The rates of reported eczema during early childhood were studied in 3 British national cohorts from 1946, 1958 and 1970; overall scores rose from 5.1% in children born in 1946 to 7.3% in those born in 1958, to 12.2% in the 1970 cohort (58). Several 10-year-follow-up studies of asthma and allergy prevalence in childhood are published, but only a few studies have a third comparable prevalence measurement made after another 5-10 years time period. In Sweden, the prevalence of allergic rhinitis in seven-year-old children increased from 5.4% to 8.1% from 1979 to 1991 (59). The prevalence of skin-test-positive allergic rhinitis in 15 to 41-year-old Danish adults, increased from 12.9% to 22.5% between two cross-sectional surveys 8 years apart (1990/1998) (60). It was concluded that a true increase in respiratory allergy had occurred. In Japan the asthma prevalence among children was approximately 1% during the 1960s, rising to approximately 6% today (61). Annual Health Interview Surveys in the United States showed a 74 % increase in prevalence of self-reported asthma for children 5 to 14 years of age from 4.3 % in 1980 to 7.4 % in 1993-1994 (62).

On the other hand, there are indications that a plateau in prevalence changes may be within sight according to studies published lately. There has been a significant reduction in the prevalence of reported asthma in Melbourne schoolchildren, whereas the prevalence of eczema and allergic rhinitis has continued to increase (63). Three cross sectional surveys studied the changes in asthma and allergy prevalence over a 20 year long period in schoolchildren in Belmont, Australia (64). In contrast to the substantial rise during the period 1982 to 1992, the prevalence of hay fever, eczema, atopy, airway hyperresponsiveness, or current asthma (defined as recent wheeze plus airway hyperresponsiveness) did not change significantly in the last study conducted.

Between countries differences in prevalence

Although the rates have risen all over the world, marked variations in the prevalence of both asthma and allergy were found between the countries in the phase one ISAAC report (65). The ISAAC study revealed a 30 times between country variations in asthma prevalence (37;38). Von Mutius *et al.* studied the prevalence of asthma, AR, atopy and bronchial hyperresponsiveness (BHR) in children nine to eleven-year-old in Western and Eastern Germany (66). They found a higher prevalence of BHR, current asthma and AR in the West German children than in the children in East Germany. It was concluded that sensitisation to aeroallergens was strikingly more frequent in Western Germany than in Eastern Germany. Five years after unification increases in the prevalence of hay fever and atopic sensitization were observed among nine to eleven-year-old children in Leipzig, but not of asthma and bronchial hyperresponsiveness, (67). The prevalence of atopic sensitisation and respiratory symptoms was studied in Estonian schoolchildren (68). The investigators concluded that similar to other post-socialist countries of Europe, the prevalence of atopy, as defined by positive skin-prick tests, asthma and respiratory symptoms, was low in Estonia.

Lastly, asthma morbidity in a closed community can be influenced by local exposures in the ambient atmosphere. Epidemic asthma occurred in New Orleans, Louisiana, in the 1950s and 1960s and subsequently, similar outbreaks of epidemic asthma in Barcelona, Spain. The outbreaks were shown to be caused by the release of soy dust at the harbour and analysis provided evidence that ambient soy dust is very asthmogenic (18;69). Consequently, changing trends in asthma prevalence may partly be explained by minor outbreaks associated to high ambient levels of a specific allergen implying that only a proportion of the large asthma population experience symptoms (17).

In summary, the prevalence of asthma and allergy in children is a function of both time and geographical region. It is not possible to extrapolate the prevalence or trends from other places to say, northern Norway. Furthermore, the north Norwegian region and its boundaries display characteristics that are somewhat unique like a cultural plurality in an artic climate. Therefore, we found good reasons to perform repeated cross-sectional studies of asthma and allergy in north Norwegian schoolchildren.

Risk factors

Complex genetic and environmental interactions appear to play a central role in the development of asthma and allergy and susceptibility varies with both the individual genotype and the environment (70). The term "epigenetic mechanism" is applied in this context due to the dependency in asthma and allergy of the genetic predisposition and environmental interactions, in addition to timing of the allergic exposure. However, we may generally be underestimating the role of environment in gene-environment interaction research due to the higher accuracy of genotyping compared to measurements of environmental exposures (71). The great difference between the two in classification error will necessarily imply highest degree of association with disease for the factor with the least error. When studying risk factors in asthma and allergy, the effect called "avoidance behaviour" is often encountered. This effect often makes it impossible to interpret whether or not a factor in reality is protective, and is difficult to adjust for when designing a study and analysing it (19).

Because atopy arises from a multifactor origin with several risk factors described, identification of the interactions necessitate large, prospective population based studies (72). An overview (and not review!) of hitherto identified factors found associated to asthma and allergies are listed in table 1 a-c, page 30-32. It must be emphasised that there is a principal difference in risk factors associated to

1. allergic sensitization (immunisation to allergens)
2. achieving asthma (triggering a chronic lower airway inflammation)
3. increased morbidity in individuals with the abovementioned conditions

An example of this is the risk factor "air pollution"; there is considerable evidence that asthmatic persons are at increased risk of developing asthma exacerbations with exposure to ozone, nitrogen dioxide, sulphur dioxide and particulate matter. Nevertheless, the impact of air pollution on the prevalence of allergic sensitization or asthma in general, is obscure (73;74).

Atopic March, age and gender differences

Epidemiological studies have demonstrated that asthma, AR and AD are overlapping entities (75) and they serve therefore as risk factors for one another. For example, a Norwegian study showed that concomitant allergic rhinitis in asthmatic children was associated with increased likelihood of asthma-related hospital readmissions and greater total hospital days (76). The term "atopic march" has been applied on a syndrome that may follow the atopic phenotype with allergic sensitization primary manifesting itself as AD, conveying to asthma and ending up with AR (77). Onset of AD is usually in the first weeks and months of life (78) with peak incidence in pre-school age and cessation of symptoms before adolescence is common (75). In a Swedish study, the onset of asthma occurred in 40% before the age of two and 80% of the asthma population had experienced symptoms before the age of seven (79). AR is firstly manifested in school age with the prevalence steadily increasing through to adolescence (80). In this context, by representing the atopic phenotype, AD is very important as the forerunner and predictor of progressive and worsening allergic disease, i.e. asthma (75;81). On the other hand, it is shown that allergic disease is not necessarily all atopic, nor does it always follow a classical "Atopic or allergic March" (82).

The prevalence of asthma is higher in boys than girls during childhood, but the gender difference in prevalence is reversed in adolescence (83). In most studies AR is more prevalent

in boys than girls although the gender difference disappears in adolescence (80). AD is dominating in girls; in The Odense Adolescence Cohort Study on Atopic Disease and Dermatitis the prevalence of AD was 26% in girls and 17% in boys and thus in line with most studies (84).

Genetics. Environment.

There are indications that the interplay between genetics and environment in asthma and allergy may work in both directions and that environmental factors as such can influence the genetic risk factors (15). There is reason to believe that the environmental factors are important on many levels and the topic of environment as a risk factor in asthma and allergy is indeed very complex (18). Concurrences of trends of several potential risk factors are investigated in order to understand the epidemiology of asthma and allergy (19). However, trends in environmental exposures are said generally hard to come by.

A long list of candidate genes of atopy is found to be interesting, but there is reason to believe that the genetic findings may be different according to geographic region and ethnicity (78) and verification in different population samples is demanded. Heredity can be both genetic and environmental. That is, by representing both genetic contributions and social and familiar factors, heredity is a central entity in the aspect of atopy and risk factors. The likelihood of atopy in the child doubles with one atopic parent and triples with both parents being atopic (79). Moreover, studies have detected that the highest inherited risk is conveyed by the mother (53;70) although the risk linkage to the mother includes the perinatal influence that predispose to asthma like preterm and low birth weight. A study from Turkey may illustrate the complexity in this issue; the association between a total of 78 risk factors and different aspects of atopy were analyzed in eight to eleven-year-old school children (n=1144) (85).

Breastfeeding for more than six months (as compared to 0-6 months), maternal smoking during pregnancy and a birth weight under 2500 g were inversely related to atopic sensitization. Maternal atopic disease had significant effects on the risk factors pattern; in children with a maternal atopy history, low birth weight, day care attendance and maternal smoking during the first year of life independently increased the risk of atopic sensitization.

Indoor environment

Numerous studies have looked into the topic asthma and allergy and risk factors. Nowadays the Norwegian Health Services Research Centre is about to terminate a metaanalysis of indoor exposures and risk of asthma and allergy (16). The metaanalysis that focused on indoor allergens, moisture and heating and environmental tobacco smoke (ETS) found consistent increased risk in the case of indoor dampness, moisture and ETS (86).
Exposure to cat or dog allergens seems to be protective in infancy and then turning in to a risk factor later in childhood. That is, early exposure to cats seems to give protection against allergic sensitization in children of non-asthmatic mothers. In children of asthmatic mothers however, it is associated with an increased risk (15). Breast-feeding is now consistently shown to be protective towards allergic sensitization in children (87;88). What's more, breast-feeding may protect from adverse effects of exposure to ETS on children's respiratory health (89).

Outdoor environment. Climate changes.

Many epidemiological studies have described symptom exacerbation in subjects with asthma or chronic obstructive respiratory disease in response to environmental SO_2 (90-92). Because the density of all components simultaneously increase during episodes of heavy pollution it is generally difficult to determine which parts that do most harm, and the risk of confounding is

thus great. Recently, attention is growing for diesel exhausts particles and foremost particles with a diameter less than 10 μm, so called PM10. It is shown that these particles, which due to their small size may reach bronchioles, have allergenic characteristics in terms of evoking an immune response with specific IgE production (17).

Over the same period as the global rise in asthma, there have been considerable increases in atmospheric carbon dioxide concentration and global average surface temperature and it is hypothesized that the anthropogenic climate change is a plausible contributor to the rise in asthma (93). Greater concentrations of carbon dioxide and higher temperatures may increase pollen quantity and induce longer pollen seasons resulting in an allergenic environment. An early life exposure to this altered environment may also provoke the development of other atopic conditions, such as eczema and allergic rhinitis. Hence, evidence is accumulating that there is a link between an increase in emissions of the principal greenhouse gas carbon dioxide, and the rise of asthma (94).

Changed microbial load. Early respiratory infections. Vaccines

With the hygiene hypothesis in mind has a changed microbial load been proposed as an explanation to the increase in allergy prevalence (95). Additionally, some has suggested the explanation to the phenomena is a reduced burden of viral respiratory infections during early life. Nafstad et al. followed a total of 2540 children from birth to the age of 10 years; experiences of respiratory infections were recorded in follow-up surveys at 6 and 12 months (96). At age 10, questions were asked about current symptoms of asthma and allergic rhinitis and about having ever received a doctor diagnosis for these diseases. A sub sample (1740) of the cohort was tested for skin-prick test reactivity. Early respiratory infections did not protect

against the development of asthma, allergic rhinitis, or sensitization to common allergens during the first 10 years of life but increased the risk for asthma symptoms at age 10 in this population. It has been suggested that there is an inverse association between allergic sensitization and markers of exposure to food-borne and orofecal infections (particularly hepatitis A virus, HAV). However, in a population-based study from Spain no significant association between HAV exposure and allergic sensitization is observed after controlling for the confounding effect of age (97). A study from Iceland unveiled that infections during early infancy with respiratory syncytial virus (RSV), influenza- and parainfluenza virus preferentially promoted a TH2-like response in the nose (98). It has been suggested among other things, that a reduction in childhood infections due to routine immunisation could be an explanation of the asthma and allergy epidemic. In a study of 7098 hay fever cases and controls, no association between DTP or MMR vaccines and hay fever was detected, though a slightly increased risk of developing hay fever connected to the BCG vaccination was found (99;100). A cross-sectional study from Switzerland including 1537 schoolchildren aged 13-15 years concluded that exposure by MMR-vaccinations or natural MMR-infections in childhood does not increase the risk of sensitization to common allergens as well as to allergic respiratory diseases. It was stated that MMR-vaccinations or natural MMR-infections are an unlikely factor contributing to the increase in atopic disease in developed countries (101). Besides, it must be emphasized that formerly vaccines contained aluminium hydroxide known to be a potent stimulus to Th2 immune response but the substance has been extracted the last six to eight years (8). Lastly, one review article states that decreased bacterial load or increased allergen exposure do not explain the phenomenon of increased prevalence of allergic diseases starting around 1980 (102). The authors suggest the main risk factors were conveyed by doctors like enforcement of allergen avoidance in infancy, use of antibiotics such as cephalosporins and the switch from aspirin to paracetamol.

Ethnic differences

Cultural and economical differences may explain the geographical differences observed in asthma and allergy prevalence, but ethnicity may also play a part. Several studies have explored the relationship between asthma and allergy and ethnicity in children (103-107). A prevalence study of asthma symptoms among adolescents by ethnicity in the Wellington region, New Zealand, concluded that there are minor differences in asthma prevalence between Maori and nonMaori children (104). A study of Inuit primary schoolchildren living in far Northern Quebec concluded that asthma and atopy were uncommon in this population (103). A study conducted in four rural Australian aboriginal communities concluded that asthma in Aboriginal children was almost non-existent (105). For a study of childhood asthma among Puerto Rican Hispanics, mothers were interviewed ascertaining whether they had asthmatic children younger than 18 year of age and asking about genetic risk factors for asthma (106). Hispanic and African American ethnicity were found to be independent risk factors for asthma. Ethnic differences in the prevalence of asthma were studied in a socio-economically homogenous, middle class, multiethnic population of schoolchildren in Southfield, Michigan, USA (107). The study confirmed the hypothesis that differences in biologic factors between blacks and whites play a role in asthma risk. However, the results are conflicting; by analysing data from the 1988 National Health Interview Survey (USA) and controlling for multiple socioeconomic factors, black children did not have higher rates of asthma, but regardless of race or income, were living in an urban setting associated with increased asthma risk (108). Finally, in a study of atopic diseases among Norwegian Lapps by reviewing medical records, Falk found the frequency of total atopic diseases among individuals < 20 years to be comparable with other studies (109).

Table 1a. Risk factors of asthma and allergy

Risk factor			Increased risk for	Documentation (+/-) References
Genotype	Numerous candidate genes		Allergic sensitization	+ (70;78)
Parental Atopy	One parent		Allergic sensitization X 2 risk	+ (79)
	Both parents		Allergic sensitization X 3 risk	
Gender	Male		Allergic sensitization Asthma in childhood AR	+ (80;83)
	Female		Asthma in adolescence AD in children	+ (53;83;84)
Reduced lung function at birth			Asthma	+ (110)
Early respiratory infections	respiratory syncytial virus (RSV), influenza- and parainfluenza		Asthma Allergic sensitization	+ (96;111) + (98)
Maternal factors	Perinatal exposure to tobacco smoke		Asthma	+ (110;112;113)
	Maternal asthma	Prematurity Low birth weight Restricted intrauterine growth	Asthma	+ (70)
	Maternal atopy	Different profile of risk factors	Allergic sensitization	+ (85)
	Breast feeding		Protective towards allergic sensitization	+(85;87)

Table 1b. Risk factors of asthma and allergy

Risk factor			Increased risk for	Documentation (+/-) References
Western lifestyle	Hygiene Hypothesis: Modification of Th1 and Th2 by T regulatory lymphocytes	Rural/Farm life - Exposure to livestock/ endotoxin	Protective towards allergic sensitization (Dependent on dose, timing, genotype)	+ (20)
		Reduced number of siblings Early birth order	Allergic sensitization	+ (11;12)
		Less day care in early life/ Less viral respiratory infection in early childhood	Allergic sensitization	+/- (20;85)
		Vaccines Use of antibiotics	Allergic sensitization	+/- (99;100;102)
	Physical activity		Protective towards asthma	+ (114)
	Increased BMI		Asthma	+ (115)
	Change in microbial colonisation of the infant's large bowel	Lack of exposure to raw milk, fermented foods. Antibiotic use.	Allergic sensitization	+/- (20)
	Day care	Maternal asthma	Wheeze	+ (116)
		No maternal asthma	Protective towards wheeze	
Diet	Reduced intake of fruits/vegetables	Reduced amount of antioxidants	Allergic sensitization	+ (20;117)
	Reduced intake of fish	Reduced amount of n-3 polyunsaturated fatty acids		

Table 1c. Risk factors of asthma and allergy

Risk factor			Increased risk for	Documentation (+/-) References
Indoor environment	Tobacco smoke	Parental atopy (effect modification)	Asthma	+ (20;118)
	Allergens	House Dust Mite, Cockroach, domestic animals etc.	Allergic sensitization	+ (75)
		Dog/cat exposure in the home in early life	Protective towards allergic sensitization.	Dog + , Cat +/- (119)
	Indoor climate/humidity etc.	Growth of moulds and domestic mites	Allergic sensitization	+ (75)
Outdoor environment	Air pollution		Exacerbation of asthma	+ (90-92)
		Allergens	Asthma epidemics	+ (18;69)
		Diesel exhaust	Allergic sensitization	+/- (120)
		PM10	Allergic sensitization, asthma	+ (17)
Socioeconomic	Poverty		Asthma morbidity and mortality	+ (121)
		Violence exposure		
	Psychological stress		Asthma and Allergic sensitization	+ (122)
	School education (years)	Linear association to SPT* + RAST**	Allergic sensitization	+ (123)
Ethnicity	Black/African American		Asthma morbidity and mortality	+ /- (108)
	Hispanic (Latino)			
		Compared to Caucasian (White)		
	Puerto Rican (Latino)		Asthma and Allergic sensitization	+

*SPT = Skin prick test, **RAST = Radioallergosorbent test

Eosinophilic Cationic Protein (ECP)

Nitric oxide (NO) is produced in the inflammatory process and measurements of exhaled nitric oxide (eNO) serve as a biomarker to the ongoing lower airway inflammation in asthma (22;124). Additionally, plasma-based assays are investigated to track an ongoing allergic inflammation process. Eosinophilic inflammation is one of the hallmarks of allergic asthma (22;125) but eosinophils are also important in AD (34). When activated, these cells release several mediators and among them is eosinophil cationic protein (ECP). The association of this mediator to both asthma, AD and AR has been investigated; serum ECP (s-ECP) is shown to be increased in children with asthma, in children with AR and as well in children with AD (126-129). However, the conclusions regarding ECP measurements and AD are inconclusive; a German study comparing the Severity Scoring of Atopic Dermatitis and s-ECP level, did not find any correlation (130). On the other hand, a study from Japan reported significant elevation of the s-ECP level in patients with severe and moderate, but not mild AD (131). Besides asthma and allergy, several other conditions such as parasitosis and mother's addiction to tobacco, are associated with increased s-ECP (132;133). In the majority of these studies, s-ECP is measured in hospitalised children. Studies of s-ECP and asthma and allergy in unselected populations of children are few. In order to obtain background references when dealing with serum eosinophil cationic protein (s-ECP) measurements in children with allergic diseases, population-based studies are important.

Aims of the doctoral thesis

The overall aim of the doctoral thesis was to estimate the prevalence trends of asthma and allergy in North Norwegian schoolchildren over a 15 year period from 1985 to 2000. Additionally, the thesis aimed at exploring geographical differences in prevalence of asthma and allergy within the study area.

- What are the trends in asthma and allergy prevalence in schoolchildren in northern Norway during the 15 years between 1985 and 2000?

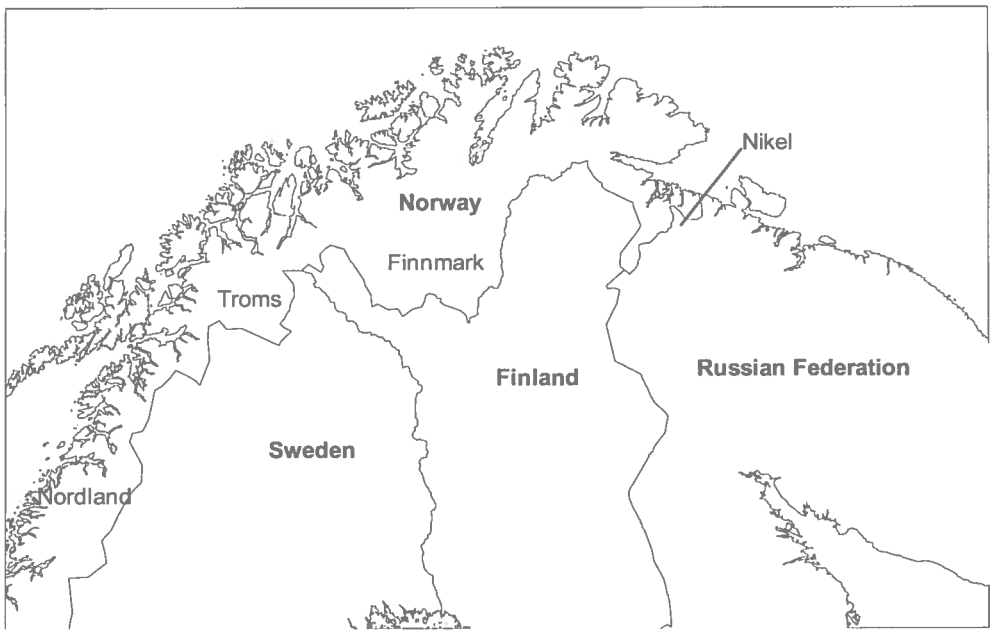
- Are there regional differences, i.e. Norse compared to Sami and Norwegian compared to Russian in prevalence of childhood asthma and allergy?

- By means of detecting allergic diseases, do serum eosinophilic cationic protein measurements of children encountered in community medicine make sense?

Material and methods

Essentially, the thesis is founded on two identical and repeated cross-sectional, written-questionnaire-based studies of asthma and allergies in childhood. The first was launched in 1985 and the second in 1995. Moreover, the thesis consists of data from three other studies of asthma and allergies in childhood; two cross-sectional, written-questionnaire-based studies conducted in 1994 and 2000 plus one clinical follow-up study conducted in 1992-93. Four of these studies were conducted in northern Norway and one in the city of Nikel on the Kola Peninsula, Russia (Figure 1 and table 2). The conclusions in the thesis are thus drawn on bases of data collected from 24.161 children. Details concerning study populations, procedures, sample collection and analyses are given in the papers, so the following is only a short description of the individual studies.

Figure 1. Study area employed in the thesis: The Counties of Nordland, Troms and Finnmark, Norway and City of Nikel, The Russian Federation



The Bolle-Holt-questionnaire (B-H-q)

In 1985, Bolle and Holt formulated a four-paged questionnaire (roughly 70 questions) (1;2) to assess the prevalence of asthma and allergy in schoolchildren (appendix). The questionnaire targeted the subjects' asthma, AR and AD and included the symptomatology associated with these diseases (a symptom based questionnaire). The first edition of the questionnaire aimed solely at lifetime prevalence with questions formulated in terms of "Has the child ever had ..?" However, in 1995 questions were added concerning symptoms and diseases over the last 12 months in order to measure the rates of current disease (point prevalence). The issues familiar atopy, the child's physical environment indoors and outdoors (sources of air pollution, pets, parental smoking etc) and ethnicity (Sami, Norse, and Finnish) were also questioned. To elucidate the conditions questioned, an accompanying letter was composed broadening the description of symptoms and signs.

Labels of disease and definitions employed on the B-H-q data

Asthma:

Two core questions made the bases of the asthma definition in the B-H-q;

1. "Has the child ever had asthma?"
2. "Does the child get a wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors, i.e. animals, grass, infections, changes in weather, food, other?"

When this questionnaire was formulated, the label "asthma" was supposed to be employed in cases of an affirmative answer to either one of the two core questions (and/or). In Paper I the term "Asthma by definition" refers to this definition. However, the ISAAC studies that employ a questionnaire based on symptoms of wheeze the last 12 months were launched after the design of the B-H-q. Consequently, when presenting results from studies employing the

B-H-q it was necessary to make an adjustment of the asthma definition in order to make the two types of studies comparable. The asthma label was therefore restricted to an affirmative answer to the first core question "Has the child ever had asthma?" in papers published after 1999; in Paper II and III the term is "Diagnosed asthma" and in Paper V "Self-reported asthma".

Atopic dermatitis (AD) versus Atopic eczema/dermatitis syndrome (AEDS):

The term "Atopic dermatitis" (AD) was used in the first four papers, but it was changed to AEDS in the last due to recommendations of the new terminology for this group of disorders. According to the B-H-q, AD was recorded in the cases of an itchy eruption lasting for more than four weeks and combined with

1. lesions in face, elbow- or kneeflexures
2. A high degree of itching and lesions elsewhere.

Allergic rhinoconjunctivitis (AR) was defined as episodic symptoms from nose and/or eyes such as rhinorhea associated with nasal stuffiness and sneezing often accompanied by itchy nose/eyes, lacrimation and red eyes.

The ISAAC questionnaire

The ISAAC questionnaire is an 11 paged questionnaire with 117 questions concerning asthma and allergy in children. It is divided in two sections and the last part is answered only by those with symptoms of asthma and allergy. The asthma core question from B-H-q "Does the child get a wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors, i.e. animals, grass, infections, changes in weather, food, other?" was added to this ISAAC questionnaire in order to make the 2000 study comparable with the two former

studies arranged in Troms and Finnmark in 1985 and 1995. The question concerning AR in B-H-q was divided in two separate questions in the ISAAC questionnaire. The same questions used to identify children with AD in the B-H-q were also found in the ISAAC questionnaire. Consequently the B-H-q and the ISAAC questionnaire were comparable with respect to the asthma, AR and AD.

Definitions.

Cumulative incidence, (lifetime) prevalence:

Both "cumulative incidence" and "(lifetime) prevalence" has been employed in the papers when denoting rates of affirmative answers to questions introduced with "Has the child ever had …?". The interpretation of these terms is supposed to be the same.

Point prevalence:

Point prevalence has been employed in the papers when denoting rates of affirmative answers to questions concerning symptoms or disease the last 12 months ("Has the child had … the last 12 months?").

Sami ethnicity:

As opposed to Norse ethnicity, Sami ethnicity was defined as children with two or more grandparents speaking the Sami language.

Studies employed in the thesis

Table 2. Studies employed in the thesis

Study	Study year	Management	Design	Questionnaire	Age	N	Response rate
Northern Norway 85: Nordland, Troms, Finnmark	1985	Bolle and Holt	Cross-sectional written questionnaire	B-H-q	7-13	10.093	90 %
Northern Norway 95: Nordland, Troms, Finnmark	1995	Bolle and Holt	Cross-sectional written questionnaire	B-H-q	7-13	8676	87 %
ISAAC-II: Troms, Finnmark	2000	The Norwegian Institute of Public Health and Bolle	Cross-sectional written questionnaire	ISAAC phase-II	9-11	3853	80 %
The Kolastudy: The city of Nikel, Russia	1994	Dotterud and Odland	Cross-sectional written questionnaire	B-H-q	7-13	1143	89 %
The Sør-Varanger study: Finnmark	1992 + 1993	Dotterud	Clinical (follow-up) study	(B-H-q)	7-13	396	72 %

Northern Norway 85: Nordland/Troms/Finnmark 1985

In 1985, the B-H-q with the accompanying letter was distributed to schoolchildren aged 7 - 13 years attending randomly selected primary schools in northern Norway i.e. Nordland, Troms and Finnmark. At the schools, the local school nurse was in charge of the distribution of the questionnaires to the pupils and she also made sure these were filled in at home by the parents. Before delivery, an additional school authority controlled that all fields were filled in. The questionnaire was handed out to 11.200 schoolchildren and 10.093 responded (90%), gender distribution among the respondents was 51.2 % boys and 48.8 % girls.

Northern Norway 95: Nordland/Troms/Finnmark 1995

'Northern Norway 95' was arranged as 'Northern Norway 85' repeated ten-year-after. Questions of symptoms or diseases the last 12 months (point prevalence) were added to the B-H-q which was distributed to the pupils in the same primary schools as in 'Northern Norway 85'. Overall, the procedure followed was identical to the previous in 1985. In the 1995 study, 9950 schoolchildren were included and 8676 aged 7 – 13 years responded (87.3 %). The gender distribution among the respondents was 49.1 % boys and 50.9 % girls.

ISAAC II: Troms Finnmark 2000

This study was part of International Studies on Asthma and Allergies in Childhood (ISAAC) – fase II Europe study which are multicenter studies on asthma and allergy in children (134). Because of the fase II focus on the identification of new risk factors, the questionnaire was rather extensive. In this study conducted in the counties of Troms and Finnmark all 9-11 years old children in the two counties were included. The study was arranged according to standard ISAAC II procedures (135). The study comprised 3853 children (response rate 80 %) and the proportion of boys and girls was equal.

The Kolastudy: City of Nikel on the Kola Peninsula 1994

This was a cross-sectional written questionnaire-based study conducted in the city of Nikel at the Kola Peninsula, Russia in 1994. The B-H-q was translated to Russian and distributed among schools in Nikel where it was filled in at home by the schoolchildren and their parents. 1598 schoolchildren aged 7-17 years responded (response rate 88.8 %) and of these we excluded 455 because they were 14 years or older, thus leaving 1143 children for the comparative analysis.

The Sør-Varanger study: Finnmark 1992-93, a clinical follow-up study

In 1991 a written questionnaire based study of asthma and allergy employing the B-H-q was conducted among all 575 primary schoolchildren aged 7-13 years in the community of Sør-Varanger (136). One year later a clinical follow-up study was arranged comprising a clinical examination and serum-ECP measurements of 396 schoolchildren.

Statistical analysis

The data has been handled by SAS statistical software (137). Due to the characteristics of the data with an overweight of binominal variables, we have mainly performed cross-tabulations with estimates of relative risk. Statistical significance is by far indicated with 95% confidence interval (95%CI) of relative risk estimates. Concerning the details around the statistical approaches employed, the reader must consult the individual papers.

Ethics

All studies were based on informed consent from the child's parents and approved by the Ethical Committee in northern Norway and by the Regional Health Administration of Murmansk County, Russia.

Data Inspectorate

All five studies in the thesis had different concessionaires and terms. Generally, the Norwegian Data Inspectorate gave approval to file (for a limited time period) the information obtained in the studies. Furthermore, personal information was extracted from the files making any tracing of the participitants later on impossible and thereby also blocking the possibility of follow-up studies.

Results

Paper I

CUMULATIVE INCIDENCE OF ASTHMA AND ALLERGY IN NORTH-NORWEGIAN SCHOOLCHILDREN IN 1985 AND 1995

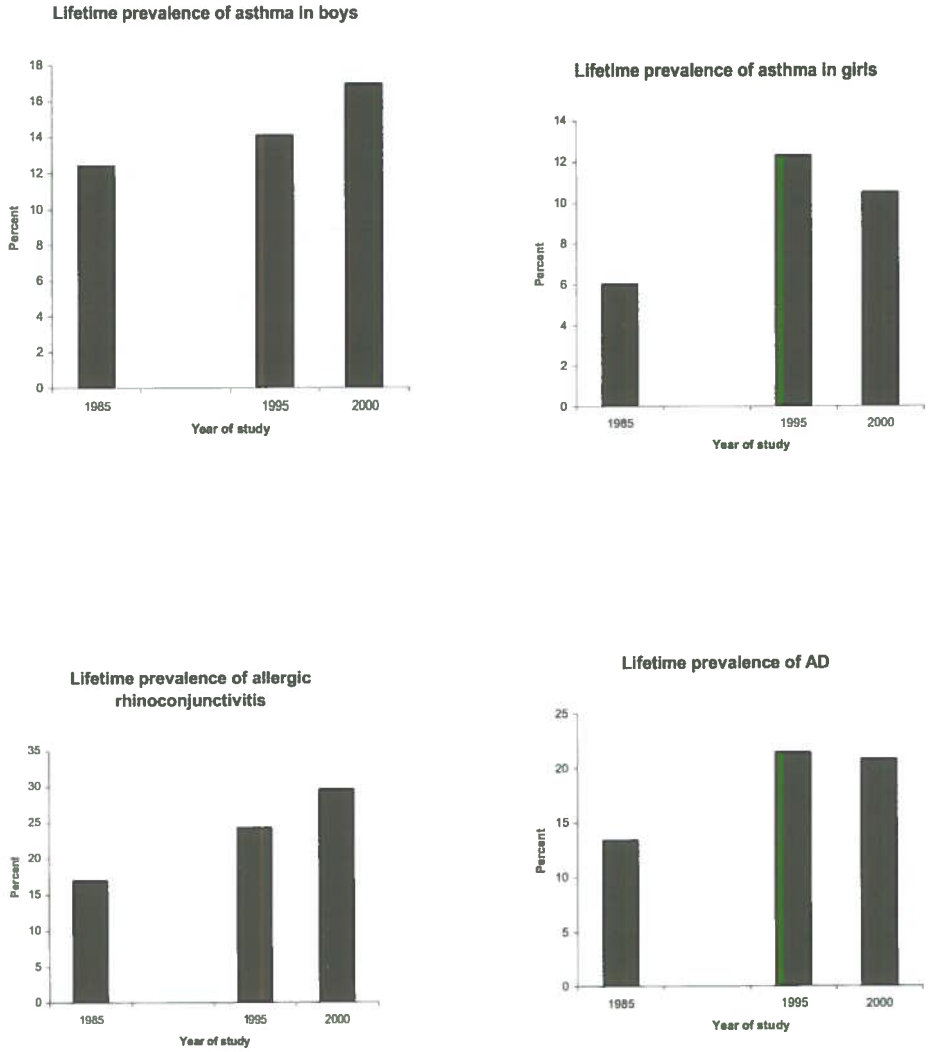
This paper compared 'Northern Norway 85' and 'Northern Norway 95' with respect to prevalence changes. Over the ten years, lifetime prevalence of asthma increased from 5.1% to 8.6%, lifetime prevalence of AR increased from 16.4% to 22.1% and lifetime prevalence of AD increased from 13.2% to 19.7%. In 'Northern Norway 85' the prevalence of AR and AD was higher in children of Sami than Norse ethnicity (respectively 19.4% vs. 16.1% and 16.7% vs. 12.8%, $p<0.05$). Furthermore, there was greater increase in diagnosed asthma, symptoms of asthma, AR and AD from 1985 to 1995 in children of Sami than Norse ethnicity. It was concluded that there had been a marked increase in prevalence of asthma and allergy in schoolchildren in northern Norway from 1985 to 1995.

Paper II

DIVERGING PREVALENCE TRENDS OF ATOPIC DISORDERS IN NORWEGIAN CHILDREN *RESULTS FROM THREE CROSS-SECTIONAL STUDIES*

This paper emerged from the three cross-sectional written questionnaire-based studies 'Northern Norway 85', 'Northern Norway 95' and ISAAC II. Since the analyses only comprised children 9 to 11 years of age only 1794 were included from 'Northern Norway 85' and 1432 from 'Northern Norway 95', ISAAC II counted 3853 schoolchildren. Identical items of asthma and allergy were employed to compare the prevalence in 1985, 1995 and 2000. The lifetime prevalence of asthma was 9.3%, 13.2% and 13.8% in respectively 1985, 1995 and 2000. Analysed by gender the prevalence increased in boys from 1995 to 2000 (14.1% vs. 17.0%) but decreased in girls (12.3% vs. 10.5%). Furthermore, the prevalence in 1985, 1995 and 2000 was as follows; 13.4%, 21.1% and 20.8% in case of AD and 16.5%, 24.7% and 29.6% in case of AR. The paper stated that the prevalence of asthma and allergy in North Norwegian schoolchildren had increased over the first 10 years, but the last five years the trends were diverging; overall prevalence of AD and asthma in girls abated from 1995 to 2000, whereas AR and asthma prevalence in boys were continuously on the increase during the entire 15 years period.

Figure 2. Lifetime prevalence of asthma (boys/girls), AR and AEDS (i.e. AD) in 1985, 1995 and 2000 (Paper II).



Paper III

ATOPIC DISEASES IN SAMI AND NORSE SCHOOLCHILDREN LIVING IN NORTHERN NORWAY

This paper was exclusively based on 'Northern Norway 95'. The collected data that contained 8676 schoolchildren aged 7-13 years, including 491 Sami children, was investigated by means of exploring any association between asthma and allergy and ethnicity (Sami/white Caucasian i.e. Norse). The Sami children scored higher than the white Caucasian (Norse) children in most areas of investigation: the lifetime and point prevalence of asthma (13.6% vs. 8.2% and 6.7% vs. 2.8%) and lifetime and point prevalence of AR (32.6% vs. 21.6% and 10.5% vs. 7.0%) and lifetime prevalence of AD (26.7% vs. 19.2%). We concluded that an association existed between Sami ethnicity and asthma and allergy among schoolchildren in Northern Norway.

Paper IV

ASTHMA AND ALLERGY IN RUSSIAN AND NORWEGIAN SCHOOL-CHILDREN:

results from two questionnaire-based studies in Kola Peninsula, Russia and Northern Norway

In this paper The Kolastudy was compared to 'Northern Norway 95'. Outcome variables were differences in prevalence of asthma, respiratory symptoms, AR and AD in 7 to 13 year old Russian and Norwegian schoolchildren. Lifetime prevalence of asthma was 5.1 % in Russian children and 8.6 % in Norwegian children but the prevalence of all respiratory symptoms was higher in Russian children. The lifetime prevalence of AR and AD was higher in Norwegian than Russian children, 22.1% vs. 16.9 % and 19.7% vs. 7.4%. We concluded that the prevalence of asthma, AR and AD was higher in Norwegian than Russian schoolchildren. On the other hand, we suggested that the high prevalence of respiratory symptoms in the Russian children may reflect a higher prevalence of (undiagnosed) non-allergic asthma.

Paper V

NO ASSOCIATION BETWEEN SERUM EOSINOPHIL CATIONIC PROTEIN AND ATOPIC DERMATITIS OR ALLERGIC RHINITIS IN AN UNSELECTED POPULATION OF CHILDREN

The objectives of the study were to explore the strength of associations between the s-ECP level and AD, AR and asthma in an unselected northern Norwegian schoolchildren population. S-ECP was sampled from 396 schoolchildren aged 7-12 years from Sør-Varanger community, northern Norway, as part of a population-based study of allergy (The Sør-Varanger study). In bivariate analysis, no statistical significant associations were detected between s-ECP and AD, AR or asthma. The highest mean s-ECP level was measured in children with clinical diagnosed asthma. Nevertheless, above the 75-percentile level of s-ECP, only 17.2% of the children had a history of asthma. We concluded that though the s-ECP was

increased in children with asthma, the occurrence of AD or AR was not reflected by an increased in the s-ECP level. More important, the majority of children with high s-ECP values were not asthmatics and we therefore concluded that the associations between s-ECP and allergic diseases are weak in an unselected population of children.

Additional analysis: Sami versus Norse ethnicity in ISAAC II

The question targeting children with two or more grandparents with Sami as their native language was also included in the ISAAC questionnaire. Of the 3853 children from this study, 183 (5%) were recorded with Sami ethnicity. In this study too, there was more asthma and allergy in Sami than Norse children (table 3). Probably due to the low number of Sami children, a statistical significant difference was only observed in case of asthma, but the trend was also present in children with AR and AD. Because a difference in asthma prevalence trends by gender was found in paper II, the same trends for nine to eleven-year-old Sami children is presented in table 4.

Table 3. Lifetime prevalence of asthma and allergy in Sami and Norse children in ISAAC II

	Sami	Norse		
	%		RR Sami/Norse	95% CI
Self-reported asthma (1)	15.4	9.9	1.55	(1.09 – 2.21)
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors? (2)	13.2	10.2	1.30	(0.88 – 1.91)
Asthma question (1) and/or (2)	18.7	13.6	1.37	(1.00 – 1.88)
Self-reported AR	35.0	29.8	1.17	(0.96 – 1.44)
Self-reported AD	24.0	21.9	1.15	(0.88 – 1.50)

Table 4. Lifetime prevalence of asthma, asthma symptoms, AR and AD in 9-11 years old Sami children in 1985, 1995 and 2000, analysed by gender.

		Study		
		Northern Norway 85	Northern Norway 95	ISAAC II
		(n=232)	(n=176)	(n=183)
		%		
Self-reported asthma				
	Boys	10.3	16.5	24.7
	Girls	4.6	5.2	8.6
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?				
	Boys	13.9	19.4	18.2
	Girls	4.8	12.2	9.2
Self-reported AR				
	Boys	24.6	41.8	37.7
	Girls	14.4	31.5	33.0
Self-reported AD				
	Boys	20.5	20.2	23.4
	Girls	13.5	33.3	24.5

General discussion

When critically evaluating the outcome of epidemiological studies, it is custom to do so in terms of chance, bias and confounding; i.e. are the observed differences best explained by random effects, systematic errors or underlying and not recognized factors (138)? The likelihood of the results being solely due to sampling variability is estimated in the statistical analysis which measures the probability of observing the phenomena if it was only a result of chance. Consequently, the role of chance is a mathematical quantity and is by such comprehensible. The systematic errors in an epidemiological study are however impossible to correct for analytically. These errors are only avoided by a properly designed study followed by meticulous conduct. The main classes of bias are the selection bias that concerns the method of identifying the study population, and the information bias that refers to the inaccuracy and incompleteness in sampling and processing which potentially lead to skewed data. The matter of confounding, which involves the possibility that the difference between two groups is due to other effects than the exposure under study, is not further discussed because the papers in the thesis rather than investigating causalities, compared prevalences of asthma and allergy between groups (138).

Sources of bias

Selection bias

When 'Northern Norway 85' was on the drawing board it was, due to an overall impression of increasing prevalence rates, in an era with growing attention to the epidemiology of asthma and allergy. No prevalence studies were so far conducted in children in northern Norway and a written-questionnaire based cross-sectional study among primary schoolchildren was thus the natural method of choice. The design provided a cost-efficient way to obtain an estimate of prevalence of symptoms and disease and simultaneously investigate the frequency and

distribution of known and potential risk factors. Furthermore, the usage of established and well functioning primary school networks implied a very important resource by means of handling the distribution of the questionnaires. A representative sample of schoolchildren from Nordland, Troms and Finnmark was secured by a randomized selection of primary schools and the response rate was generally high (> 80%). However, a selection bias is present in our studies by the fact that families with known asthma and allergy will have the greatest interest in completing the questionnaires which leads to an overestimation of the real prevalence (139). The same mechanisms may have resulted in an overrepresentation of children with asthma and allergy symptoms in The Sør-Varanger study (V); The community of Sør-Varanger comprised 575 primary school children but s-ECP samples were only obtained from 396 (69%). In 'Northern Norway 95', 5.9% of the children where defined as Sami but 4.7% left the question concerning Sami langue among grandparents unanswered (III). Since the proportion of unclassified was almost the size of one of the two study populations in the comparison, the selection bias effect might in this case have substantial implementations on the results.

Response rate

The response rates declined with around 10% during our study period from 1985 to 2000. This trend is a well known phenomenon; there is today an obviously decreasing motivation in the public to participate in epidemiological studies. Possibly people are exhausted due to the repeatedly encountered numbers of questionnaires and polls. Traditionally the margin of error has been judged too wide in epidemiological studies with a response rate below 50%. The contribution of follow-up of non-responders to prevalence and risk estimates was investigated in a Norwegian respiratory health survey (140). After several reminders and telephone follow-up the cumulative response rates increased from 43% to 80%. Anyway, no noteworthy

changes in prevalence and odds ratios were noted when initial responders were compared with all responders. Probably, the multiplicity of personal and practical reasons to not comply with a study represents heterogeneous variables and by this a distortion of risk factors is avoided. How response rates to a postal questionnaire are affected by title and length of the survey instrument was studied in a random sample of one thousand Norwegian women aged 35-49 years targeting breast cancer (141). It was shown that the distribution of risk factors for breast cancer did not vary according to response rate or design of questionnaire.

Migration. Cohort effects

Changes in the patterns of settling over the fifteen year long study period may account for some of the observed prevalence trends in asthma and allergy in north Norwegian schoolchildren. Foremost in this context is migration southwards that hypothetically is associated to social class and education; families from high social classes with high education move southwards in search for employment, leaving behind a higher proportion of families from lower social classes in the study area. It is shown that allergic sensitization (SPT and RAST) to common aeroallergens in adults follows a significant and linear association with school education (123). Additionally can the ethnic differences observed, at least in part, be explained by varying linguistic traditions over time and hence, in reality, an altered definition of Sami from 1985 to 2000.

The term "cohort effect" is used to describe variations in the characteristics of an illness (such as the incidence or the age at onset) over time among individuals who are defined by some shared temporal experience, such as year of birth, and the cross-sectional study design is prone to be confounded by these cohort effects. Changes in birth weight or prematurity over the study period might have been sources of cohort effects, though the probability is low.

Information bias

The framework of the present thesis is the repeated cross-sectional written questionnaire based studies. Above all, it is important to emphasize that the perception of increasing prevalence in such studies should be treated with caution due to the lack of objective data (142). Especially the prevalence of asthma is difficult to follow over time, owing to changes in diagnostic practice, and information bias may explain the trends. Furthermore, our studies were to a high degree based on parents filling-in the written questionnaires. The accuracy of parent reports was investigated in a survey by comparing parents' responses to a self-administered questionnaire with information extracted from paediatricians' records (143). For asthma the percentage with good agreement was 91 % in the last year. The conclusion was that parent reports are generally acceptable for most research purposes. On the other hand, the thesis included a study population with three different languages and some disagreement in interpretation of the questionnaire is to be expected. For example, a cultural difference in the focus on asthma and allergy may have been present; a high public consciousness around this issue could generally be reflected in a greater interest to comply or the responders were more familiar with the subjects of interest. The occurrence of atopic diseases in Sami people was estimated by reviewing medical records in the local health centre of Kautokeino, Norway in the beginning of the nineties (109). The occurrence of AR was remarkably low, 2.3% in males and 1.9% in females. It was speculated that the perception of having a cold in the summertime often represented underdiagnosed AR. The great cultural and socioeconomic differences between Russia and Norway have probably also been reflected in differences in the definition of atopic disease and public awareness of these conditions.

Validity and reliability of the B-H-q.

Information bias is in epidemiology often discussed in terms of validity and reliability of the diagnostically available information. Validity is an estimate of whether the measurements performed in a study in reality measure the target condition. Reliability in a test/retest form is an estimate of whether the same target condition is measured repeatedly.

Our symptom questionnaires are generally biased by problems arising from subjective symptom recognition and recall and they thus needs to be tested in validation studies (144). Since there is no gold standard for defining asthma, clinical assessment represents the most appropriate standard for use in validating instruments for epidemiological studies. It is stated that, when diagnosing asthma by questionnaire in epidemiological surveys, the question "Have you ever had asthma" is remarkably specific, though seriously insensitive (145). In the B-H-q, the combination of two core questions constituted the asthma-label and the questionnaire has been employed in several Norwegian studies after it's introduction in 1985 {85,163,34,320}. The study from Telemark County was followed-up by a clinical study in order to estimate the sensitivity and the specificity of this label (51). It was found that a combination of the two asthma core questions provided high sensitivity and specificity, 0.96 and 0.88 respectively, and additionally a high test-retest reliability Kappa, of 0.91 (146). In 1996 another reliability study of the asthma part of the B-H-q was conducted among 152 (54 cases and 98 controls) respondents from Nordland County of 'Northern Norway 95' (147). Again, a 0.92 reliability (Kappa) coefficient was calculated which implied a high degree of concurrence. The B-H-q was employed to assess atopic diseases in schoolchildren in the community of Sør-Varanger in Northern Norway (136). In a validation study, the overall findings were low sensitivity and high specificity for all atopic manifestations (148). In case of asthma it was found that a combination of the two asthma core questions yielded a

sensitivity and specificity of 0.84 and 0.95 respectively which was considered satisfying. However, the clinical examination that was performed by an experienced dermatologist uncovered a considerably higher frequency of AD than estimated in the questionnaire study (53;148). It was thus concluded that the AD part of the questionnaire was more likely to under- than overestimate the actual prevalence.

In the same validation study, some discrepancy between the B-H-q and the clinical diagnosis was seen for AR with a subsequent overestimation. The sensitivity and specificity was 0.72 and 0.91 respectively (148). The AR core question in the B-H-q was separated in two parts in the ISAAC questionnaire; there was one question for hay fever and one for symptoms. When the two were merged the ISAAC questionnaire and B-H-q were identical in terms of AR. A Swiss study has assessed the ISAAC version of the AR questionnaire (36). Questions of rhinoconjunctivitis were found superior to rhinitis questions alone in encountering allergic disease because of the stronger association to skin prick test and it was recommended to apply the term "hay fever" in addition to questions of symptoms because this complementary information increases sensitivity.

Misclassification

In any study, inaccuracies in the collection of data are inevitable and the potential for misclassification must be considered (138). The most important issue in this regard is whether the inaccuracies in classification of exposure or disease are differential (non-random) or random since the first will arise as a more serious problem. Measurements of degree of misclassification by the responders are obtained by estimates of validity and reliability of the core questions.

Missing responses to core questions, imputations

The management of missing responses to essential questions in our analysis needs to be discussed. In an unpublished pilot study, written questionnaires were reviewed and non-responders to core questions were interviewed by telephone. The overall impression was that the non-responders by far represented healthy subjects without the targeted disease (Professor Eiliv Lund, personal communication). Generally, missing responses to questions of symptoms or disease can be handled in two ways; by exclusion and increasing the prevalence rate or by imputation as a non-affirmative answer and lower the rate. Both ways may imply a risk of differential misclassification. The ISAAC phase-II questionnaire was exhaustive and there was a high rate of missing responses to asthma questions. After a preface symptom-question, the subjects were encouraged to "jump" to questions further below if the answer was in the negative. This encouragement may for some have been misinterpreted to jump over to the next section. Some of the missing responses to solitary questions may also be explained as faltering by the responders as an expression of parental doubt on how to categorise their child's health status. Due to the high frequency of missing, we found it sensible to employ additional asthma questions in the ISAAC questionnaire and perform an imputation, yet that is another potential source of differential misclassification.

Random misclassification: Data processing

The thesis comprises five different studies and in three of the papers these are individually compared. Consequently, substantial effort is put into data processing by converting variables and merging the individual data set. Additionally, taken into account the amount of analysis needed because of the considerable numbers of variables, there is a chance of failure associated to these procedures. Hence, a continuous evaluation and control of the analysis of

data was done by means of repeated (and simple) cross-tabulations and estimates of crude trends, but nevertheless is data processing a source of random misclassification.

In summary, we will argue that the overall influence of selection- and information bias and misclassification in the studies employed in the thesis is kept within acceptable limits. However, only by comparing the results to a range of other and similar studies in a metaanalysis is it possible to further explore the veracity of the data.

Relative Risk (RR) versus Odds Ratio (OR)

We have deliberately chosen to present our data in terms of relative risk (RR) and the corresponding 95 % confidence interval of RR. Primary, we believe that relative risk is statistically a more appropriate estimate in situations with high prevalence (above 5-10%). Secondary, the term relative risk is more comprehensible than odds ratio which, though very often employed, is less intuitive.

Discussion of main results

The intention of performing regional epidemiological research on asthma and allergy is a potential subject of debate. These diseases impose a burden on the child, the family and society (149). Today, this field of research is widely focused on all over the globe, with a multitude of studies from which we can learn more about the traits of these diseases. So why then orchestrate regional studies? What knowledge do these bring us that can not be implemented by projecting the results of other studies on our health region? Primarily due to the high prevalence of asthma and allergy a proportion of children with these diseases are neglected, mainly because they never come in contact with the health service. Regional epidemiological studies focus on and therefore disclose morbidity that otherwise would be left undetected. For clinicians and foremost general practitioners it is important to know that their impression of changing prevalence trends is confirmed by an epidemiological study. For health authorities, epidemiological research forecast the socioeconomic burden asthma and allergy may pose in the future. What is more, regional epidemiological research may reveal geographical differences in prevalence within the region of interest.

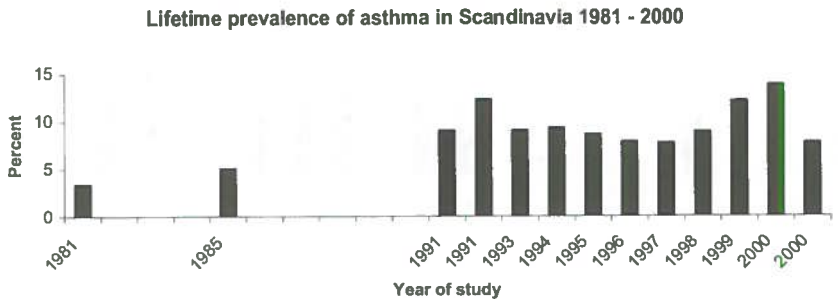
Prevalence trends

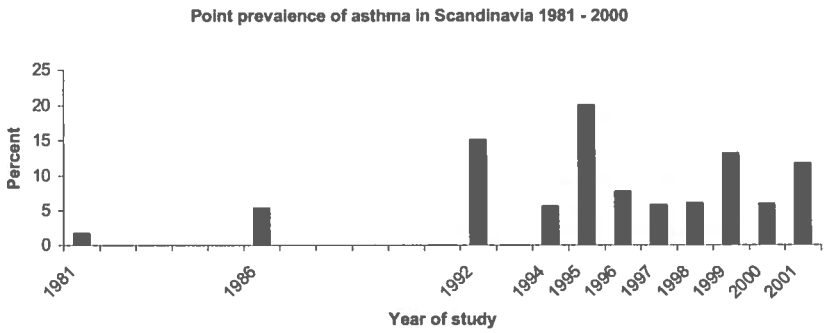
Due to the natural course of asthma and allergy, it is in epidemiology logical to denote the prevalence in an equation being the product of the factors incidence (new cases) and duration (representing persistence and relapse) (18). Since the terms incidence, persistence and relapse sometimes are intermixed, inequalities in estimated frequencies may be avoided by consistently applying the term (lifetime) prevalence.

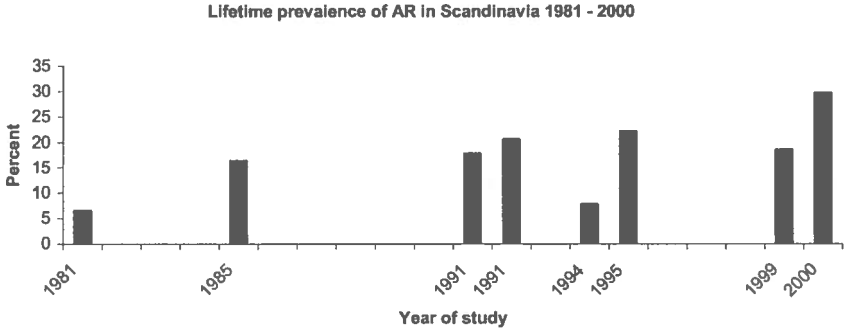
As shown in the introduction, there is considerable evidence that supports the rising prevalence trends in asthma and allergy we found over the period from 1985 to 1995. On the

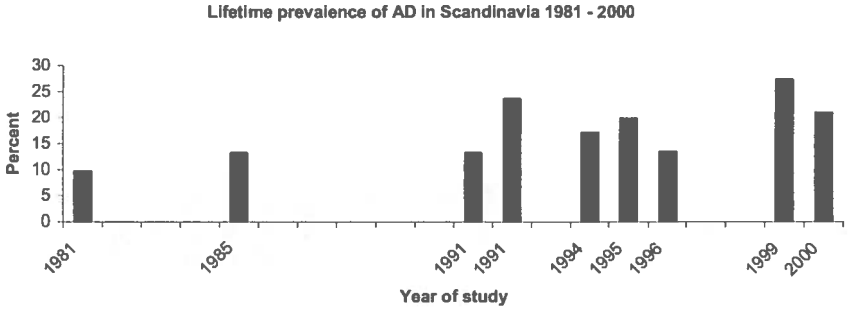
contrary, the levelling of trends unveiled over the next five year period from 1995 to 2000 is somewhat controversial. So far only a limited number of studies are supportive of a "new era" in the epidemiology of asthma and allergy. However, evidence is emerging that in recent years the prevalence of asthma has flattened and even fallen in some countries (150). A recently published study investigated time trends in the prevalence of asthma and allergic sensitisation among school children in Germany between 1992 and 2001 by parental reports of asthma, hay fever, and wheezing and measurements of specific serum IgE antibodies (151). No increase in the prevalence of asthma, allergies, and atopic sensitisation was detected over this time period and it was concluded that the international epidemic of asthma and allergies may have started to level off during the 1990s. The UK arm of ISAAC found in addition to asthma a large reduction in 12 months prevalence of AR and AD but a continuous increase in lifetime prevalence of both asthma, AR and AD (152).

By reviewing the prevalence studies of asthma and allergy conducted among children in Scandinavia from 1981 to 2000, these figures are drawn (37;46;51;57;84;124;136;153-165):









These figures are of course crude trends because the studies compared involve different age groups and different methods of measuring asthma and allergy. Nevertheless, the figures give an impression of the prevalence trends of asthma and allergy in children in Norway, Sweden

and Denmark over the 20 years from 1981 to 2001. Concerning asthma, the lifetime prevalence has been unchanged through the nineties after an increase in the eighties and point prevalence has not increased since mid nineties. In a Finnish article, the literature on time trends in asthma prevalence published between January 2000 and June 2004 was reviewed (166). They found that several studies indicated stable trends in childhood asthma since late 1990s and that the prevalence of lifetime asthma in children peaked between 8-12%. Notwithstanding is the recent published ECA-2 study from Oslo 2001-2004 showing continuous increase in childhood asthma (50).

What may explain the asthma trends?

The time trends in prevalence of asthma were reviewed by Magnus and Jaakkola for the time period 1983 to 1996 and by Wieringa et al. between 1996 and 2000 (142;167). In these reviews, the rising trends in asthma prevalence were questioned and above all found plausible to be a result of increased professional and public awareness and changes in diagnostic labelling. "The abating of asthma prevalence trends observed the last years may be explained by the implementation of asthma prevention and management guidelines with earlier detection and improved treatment" This proposal was put forward by a recently published study aiming at reviewing asthma prevalence in children during the past 15-30 years in The Netherlands (168). The study concluded that in the Netherlands, a steep rise in the prevalence of asthma since the 1980s was followed by a levelling off or a decreasing trend around the turn of the century. The article suggests that these changes in prevalence trends of asthma are likely to be related to improved treatment where especially general practitioners through guidelines have taken up the importance of early and adequate treatment with inhaled corticosteroids. However, in the ECA-2 study of asthma in ten-year-old children in Oslo the

preliminary reports do not support the hypothesis that aggressive antiasthmatic medication (i.e. inhalation steroids) in early childhood may prevent asthma later in childhood (15).

Wheeze versus asthma

In English literature concerning asthma, the term "Wheeze" is commonly applied (19), probably due to its onomatopoeic characteristics. Unfortunately, the word is not matched in all languages and is thus difficult to interpret in epidemiological metaanalysis of asthma prevalence trends. Wheezing and chest tightness are associated with respiratory tract infections and the occurrence of respiratory tract infections may as such influence the prevalence of asthma. In a Norwegian study of children four years of age, the prevalence of wheezing and chest tightness in the last 12 months and four weeks was estimated according to the occurrence of respiratory tract infections during the corresponding time periods (49). The prevalence of wheezing and chest tightness increased with increasing number of different types of respiratory tract infections among all children, both those with and without asthma. It is demonstrated that children with wheeze are more similar to children with no asthma/no wheeze regarding lung function, BHR and SPT reactivity (169). Repeated population surveys of the prevalence of respiratory symptoms were done by parent-completed postal questionnaires in random samples of 1650 (1990) and 2600 (1998) caucasian children aged 1-5 years living in the county of Leicestershire, UK (170). The fact that all preschool wheezing disorders increased (including viral wheeze) made it probable that factors unrelated to atopy are implicated in the changing epidemiology of wheeze in childhood.

Changes in the diagnostic label of asthma?

Although the findings from most repeated surveys is that prevalence of asthma has increased over the past three decades, one study observed that from 1991 to 1998 the increase was confined to milder symptoms (171). Since the early 1990s the incidence of asthma episodes presented to general practitioners, and of hospital admissions, has fallen substantially in the UK and the most likely explanation for the paradoxical increase in prevalence is that the asthma label is applied to an increasingly milder disease (152). Obviously, driven by offensive marketing by the pharmaceutical industry, the doctors' consciousness concerning the issue of asthma and allergy are sharpened. In Norway, mortality from obstructive airways disease has decreased from 1960 through 1987, mostly in children below five years of age, and mortality from bronchial asthma in children below 15 years has remained unchanged. From 1980 through 1988, the national sale of inhaled beta 2-agonists increased two-fold, and of local steroids for inhalation ten-fold (172). Self-reported medical drug use among 15-16 year-old adolescents was studied in Norway in 2001 (163). In the city of Tromsø, 6-7 % had used antiasthmatic medicine and 15-16% had used medicine due to allergy in the last four weeks. A paradox is the significant proportion of children receiving medication but reporting no asthma symptoms, suggesting that some children are being inappropriately treated or overtreated (171). Unfortunately, the studies employed in the thesis did not indicate the severity of asthma, nor could the results be adjusted for antiasthmatic medication, which of course implies limitations to interpretation of these considerations.

Does non-allergic asthma among girls explain the prevalence trends?

We found that the lifetime prevalence of asthma in girls decreased from 1995 to 2000. Evidence is gathering that in addition to a milder expression of asthma, the proportion between atopic and nonatopic asthma has changed (166). A Norwegian study that compared

two samples of school children born 1965-1975 and 1978-1988 found a secular increase in the prevalence of asthma suggesting a separate increase in non-atopic wheezy children (173). Another Norwegian study of respiratory symptoms in adolescents found that girls reported more wheeze and asthma than boys and they seemed to be more susceptible to tobacco smoke and overweight than boys (162). Additionally, girls with asthmatic mothers were more susceptible for the diagnosis of asthma. Serial cross-sectional studies of two different random population samples of children aged 7 to 17 years, living in urban Copenhagen, Denmark, were performed 15 years apart in 1986 and 2001 (157). Asthma was defined on the basis of questionnaire responses and, as opposed to atopic (extrinsic), was regarded nonatopic (intrinsic) if no positive reactions were observed on the SPT. The prevalence of current asthma increased from 5.3% to 11.7% over the study period and primarily due to an increase in intrinsic asthma (4.2-fold increase) compared with extrinsic asthma (1.4-fold) and the changes were more pronounced in girls. It was among other concluded that asthma might be shifting toward female predominance in childhood.

These findings may explain why we in our studies observe a levelling in asthma prevalence in girls but not in boys; girls may have been more prone to a (non-allergic) asthma diagnosis by a possible increased tendency in the eighties to apply this label on milder symptoms of wheeze. Simultaneously, rises in lifestyle risk factors like increased body mass index, inactivity and tobacco smoke may have attributed to more wheezing in girls and thus the increased implementation of the asthma diagnosis. The association between allergic sensitization and AR is known to be high; asthma in boys may be more confined to allergic sensitization compared to girls which explains the similarity in prevalence trends for asthma in boys and AR in our study.

Prevalence trends of AR and AD

By studying the figures made for AR and AD based on the prevalence studies conducted in Scandinavia from 1981 to 2000, conclusions are of course impossible to draw but there is an impression of continuing increase of AR and levelling of AD prevalence. A study from Leipzig conducted after the reunification of Germany found steadily increasing trends for allergic rhinitis but a stable trend for asthma (174). Time trends in prevalence of symptoms of allergic rhinitis in 13-14 year-old schoolchildren were studied in eight areas of Spain between 1993-1994 and 2001-2002 according to the International Study of Asthma and Allergies in Childhood (ISAAC) (175). A divergent time trend of AR prevalence symptoms was observed with a decrease in Barcelona and Bilbao, stabilization in Cartagena, Pamplona, and Valencia, and an increase in Castellon. In Madrid and Valladolid there was an overall increase in nasal allergy. It was concluded that two patterns of time trend of prevalence of symptoms of AR in 13-14 year-old schoolchildren were observed over the time period 1993-1994 to 2001-2002. A Danish study investigated if the increasing trend of AD persisted during the 1990s by comparing the cumulative incidence of AD in 1993 and 1998 (176). In the 1993 study the cumulative incidence of AD at age 7 was 18.9% compared to 19.6% in 1998. It was concluded that the incidence of AD was stable among children in Denmark during the 1990s.

Prevalence trends, general considerations

Naturally, along with the high prevalences reported on asthma and allergy the last decades it is expected that the endemic sooner or later reaches a saturation level, depending though on the genetic composition of the different populations and environmental risk factors (177). We believe that the prevalence trends of asthma and allergy unveiled in north Norwegian schoolchildren over the time period from 1985 to 2000 are by far comparable with the trends observed in many other centres of study. However, and as mentioned above, not supportive

are the latest results from Norway, the ECA-2 study in Oslo, suggesting that the prevalence of asthma is continuously increasing, with over 30 % reporting "wheeze ever" in 2004 (48;50). Among the 616 ten-year-old children examined in the Oslo study, half of their parents had either asthma or AR. It is demonstrated that both maternal and paternal atopy (asthma or hay fever) is a risk factor for childhood wheeze (178). Since the proportion of parental atopy in the ECA-2 study is likely to be above the actual prevalence of asthma and allergy among parents in Oslo, skewed results must at least be suspected. Moreover, it must be remembered that though the lifetime prevalence of asthma in this study was as high as 20.2 %, the corresponding 95 % confidence interval is broad due to a small sample size (17.0 % to 23.4 %). It is hardly straight forward to compare the lifetime prevalence of asthma in the Oslo-birth-cohort-ten-year-follow-up-study with the prevalence found in the cross-sectional population based study from Sør-Varanger in 1991 that represented 96 % of the schoolchildren in the community (136). Lastly, we have not been able to find the gender differences in prevalence trends of asthma (II) described elsewhere and it remains to see whether the prevalence trend of AR continues to rise or will abate.

These comments shall illustrate the complexities and uncertainties in asthma and allergy epidemiology. In northern Norway it is therefore recommendable to conduct another repeated cross-sectional study among schoolchildren for the purpose of elucidating the issue of future trends. Most intriguing in this context is whether the diversities continue, if asthma prevalence in boys and overall AR prevalence will peak or on the contrary, if asthma prevalence in girls and overall AD prevalence again will increase. However, it is not recommended to repeat studies too often because of difficulties in comprehending the results. Hence, a new study of asthma and allergy in north Norwegian schoolchildren employing the B-H-q and launched in (for example) 2010 will probably do.

Geographic differences in prevalence

Traditionally it has been considered of limited value exploring the associations between exposure and disease in a cross-sectional study setting, but this attitude is lately reconsidered (15). The subpopulations Sami versus Norse and Russian versus Norwegian were compared because these variables are (obviously) not susceptible to influence and can thus be treated as independent. Of course, whether the difference in asthma and allergy prevalence explored in these analyses should be considered basically geographical differences or ethnic, socioeconomic or cultural risk factors are a matter of discussion. Worth mentioning is the fact that the latter may represent genetic heritage, social heritage, environment or gene-by-environment interaction (118).

Asthma and allergy in the Sami as opposed to the Norse

Generally, there was a higher prevalence of self-reported asthma and allergy in Sami than Norse children in all three studies where ethnicity was available as an independent variable. The Sami and white Caucasian people immigrated to the northern parts of Scandinavia from different origins and in different historical epochs. Though there today is a Sami Parliament in Norway, elected by people registered as Sami (mainly defined by language), the ethnic minority termed Sami is ill-defined and there is no official statistics available concerning ethnicity in Norway. Indeed, in the north Norwegian population the majority of people have traces of Sami or Finnish inheritance (Jens-Ivar Nergård; Det skjulte Nord-Norge, ad Notam Gyldendal). The distinction between Sami and Norse ethnicity in the thesis is thus merely a socioeconomic or cultural distinction since we must assume that the two groups are more or less identical genetically.

Nevertheless, though generally minor, some differences in living conditions were detected between the two ethnic groups in our study (III). Compared to the Norse children, the Sami children lived in newer houses with more perceived problems with indoor dampness. Smoking in the family was more frequent in the Sami families that also more often kept cats/dogs and (of course) reindeer. It is shown that polyvinyl chloride (PVC) plastics and textile wall materials may influence the development of bronchial obstruction in young children (179). Furthermore, indoor dampness is consistently associated to obstructive airways disease and allergic sensitization in young children (16;86;180). Lastly, exposures to smoking and animal allergens are well known risk factors connected to asthma and allergy (15;16). However, exposure to cats/dogs in infancy has also proven to be protective towards allergic sensitization (119). On the other side, the Norse children had fewer siblings and according to the hygiene hypothesis, a shrinking sibshipsize will promote allergic sensitization. The Norse children lived in bigger houses (square metres) and more often had wall-to-wall carpet in the child's bedroom; the latter thought to be associated to an increased risk of asthma and allergy. We analysed the association between ethnicity and current asthma and simultaneously adjusting for the role of indoor dampness and wall-to-wall carpet but this only implied minor alterations in the relative risks.

From 2003 to 2004 a population based survey concerning the health condition of people of 30 and 36-79 years of age was conducted in selected Norwegian communities and Sami ethnicity was included as a variable (181). In people under the age of 64 (n=14.887) we performed a 2 x 2 cross tabulation with ethnicity (26.1 % Sami) against lifetime prevalence of self-reported asthma. Again, there was a higher prevalence of asthma in people of Sami ethnicity (RR=1.20; 95%CI 1.08 – 1.32). Analysed by gender the difference was confined to females with a prevalence of 14.3 % in Sami and 11.2 % in Norse women ($p<0.001$). In Sami girls,

the prevalence of diagnosed asthma increased from 4 % to 10 % from 1985 to 1995 and symptoms of asthma increased from 4 % to 14 % over the same period (I). Furthermore, in 1985 there was no difference in prevalence of asthma or asthma symptoms between Sami and Norse girls. When estimated in 1995, a 70% increased risk of asthma symptoms was found in Sami girls compared to their Norse sisters (I) but in 2000 the differences again seems to be minor (results, table 4). The prevalence trend of asthma in Sami females resembles the trends described above for asthma prevalence in girls, but with greater effects. Presumably, the high asthma prevalence in Sami females is attributable to the same socioeconomic risk factors that account for the increase in non-allergic asthma. On the other hand, the differences between Sami and Norse children in asthma prevalence in 2000 seemed to be confined to a difference between the boys where the prevalence of self-reported asthma in boys in 2000 was as high as 24.7%. Moreover, the prevalence of AR in Sami boys was around 40 % the last five years of the millennium. Inevitably, these high numbers must point towards the conclusion that allergic sensitization is more frequent in the Sami than Norse, but studies including objective measurements are needed to confirm these findings.

Russian versus Norwegian

The availability of comparable data on asthma and allergy in schoolchildren from Russia and Norway living in the same geographical region but under different regimes made a comparison of these two groups feasible. There were still obvious signs of 70 years of separation with great socioeconomic and cultural differences when the comparative study was conducted only a few years after the fall of the former Iron Curtain. The study unveiled that the prevalence of self-reported asthma and allergy was higher in Norwegian than Russian schoolchildren but the latter had disquieting high prevalence of respiratory symptoms. Generally, our findings were consistent with other studies comparing asthma and allergy

prevalence in former east bloc and western countries and that nourished the theories around the hygiene hypothesis (66;158). Additionally, our study was confirmed by another and similar study by Dotterud et al. that compared The Kolastudy to The Sør-Varanger study (182). It is worth mentioning that the Russian children were living in a heavily polluted area; in 1992 the emissions from the nickel smelters in Nickel and Zapolyarny were about 260 000 tonnes of SO_2 (183). The episodes with highest air pollution in the vicinity were due to meteorological conditions characterised by high atmospheric pressure and low speed ground wind during the winter (184). Because high levels of outdoor pollutants in many studies are shown to be associated to aggravation of asthma symptoms (90-92;185), we suggested that the high prevalence of respiratory symptoms in the Russian study population might imply a high prevalence of (undiagnosed) non-allergic asthma. Moreover, we proposed a non-allergic asthma:allergic asthma ratio to be employed in all prevalence studies of asthma since there was an impression of a higher ratio in Russian than Norwegian children; with information of allergic sensitization status available, such ratio will facilitate comparison of asthma characteristics between populations.

Serum eosinophil cationic protein (s-ECP)

Lastly, the thesis comprises a clinical study (The Sør-Varanger study) that investigated the relevance of s-ECP measurements in an unselected population of children. Due to the eosinophil granulocytes' high content of this highly charged cationic protein, it is well known that eosinophilia, one of the bronchial inflammatory hallmarks of asthma, can be detected by measurements of elevated s-ECP level. The relationship of s-ECP and eosinophil count to disease activity in children with bronchial asthma was investigated in a study from Switzerland (186). It was concluded that although S-ECP and eosinophils are not diagnostic of asthma they are useful inflammation markers especially in the context of clinical studies. In our study, s-ECP was measured in a community based population of schoolchildren identical to the range of patients of this age encountered by a general practitioner whereas most other studies of s-ECP have been done in highly selected populations of children with known asthma and allergy. The study from Sør-Varanger community did not find any convincing associations between s-ECP level and asthma and allergy. A population-based study of schoolchildren in Norway found significantly higher mean s-ECP level in asthmatic than nonasthmatic children (187). Nevertheless, the study did not find any difference in the s-ECP level in atopic and non-atopic asthmatic children. The majority of asthmatic children in our study were treated with antiasthmatic drugs and we believed that this explained the weak association between s-ECP and asthma. A study from Finland showed a corresponding decrease of the s-ECP level in patients treated with inhaled corticosteroids, indicating that decreased bronchial inflammation reflect changes in the s-ECP level (188). Furthermore, most children in Sør-Varanger had mild eczema with flexural dermatitis which also may explain the failing association between s-ECP and AD (53). As a conclusion, we emphasized the importance of our setting with an unselected child population in contrast to most studies of s-ECP undertaken among selected hospitalized children with serious asthma and AD. Therefore

our study indicated that s-ECP measurements have limited value in general practice as a diagnostic tool of childhood asthma and allergy due to the weak associations to mild and moderate cases. Moreover, because only a minority of children with significantly elevated s-ECP had asthma (<20%), our study suggested that s-ECP measurements, in addition to a low sensitivity, are (naturally) highly unspecific in describing the aetiology of the eosinophilia.

General considerations

Taken into account what we today know about the prevalence trends and the risk factors associated to asthma and allergy, these diseases still remain an enigma in default of causation (150;189). Today, several multicenter studies are on the road exploring all thinkable aspects of asthma and allergy; The European Community Respiratory Health Study (ECRHS) (190), The International Study of Asthma and Allergies in Childhood (ISAAC) (37) and GA2LEN--The Global Allergy and Asthma European Network (191). Additionally, quite a few longitudinal studies are ongoing (48;84;192;193). However, due to the enormous amount of information and facts it increasingly difficult to sort out the important topics. In order to gain new insight, it is probably wise to restrict the research somewhat and concentrate on issues less vulnerable to interpretations and subjectivity.

Focus on AR and allergic sensitization

The phenotypes of asthma, AR and AD represent a diversity that may have more dissimilarities than shared characteristics. Therefore, a critical appraisal of the epidemiological research in this field must include a thorough discussion of the variety of diseases under investigation which inevitability lead to interpretation difficulties. An epidemiologic study necessitates often a large questionnaire-based study design including simple, objective procedures in order to perform validation of the questionnaires. Due to a limited public awareness, a limited number of disorders (with a limited number of differential diagnoses) should be surveyed. Evidence is gathering that exhaled nitric oxide is a useful tool in measuring inflammation in asthma which of course facilitates the epidemiological research (124). Nevertheless, the list of differential diagnosis for asthma in children is at least 18 points long including cystic fibrosis, tracheo-/laryngo malaci, infections, gastroeosophagal reflux making the diagnosis of asthma not an easy task (194). Though the border is narrow

between AR and common conditions like infectious rhinitis and polyps (148), AR is a well known symptom picture with a well known term, hay fever, which importantly is not stigmatized. On the contrary, applying a questionnaire to assess AD necessitates multiple questions (site of eruption, degree of itch etc.) in order to separate AD from an eruption of another genesis. A study in the UK investigated the association of atopic sensitization with allergic disease by defining childhood atopic phenotypes with SPT at both 4 and 10 years (82). Positive SPT at both 4 and 10 years was found for 67.7% of children with ever (lifetime) AR, 56.9% of children with ever asthma and 48.8% of the children with ever eczema. Sibship characteristics and risk of self-reported allergic rhinitis and asthma was studied in Denmark (195). The study found a protective effect of increasing sibship size towards allergic rhinitis and asthma with allergic rhinitis but there was no association to asthma without allergic rhinitis. Consequently, it is recommendable to focus on AR in epidemiology when aiming at elucidating the enigma behind increasing allergic sensitization; the condition is highly recognised, it has the highest association to IgE mediated disease and lastly, according to our study (II), may be the only allergic disorder that still increases in prevalence. However, some epidemiologists' advocate today the opposite strategy; namely a comparative disease approach to better understand the aetiology of different illnesses since allergic disease show similar patterns as for example preeclampsia and type 1 diabetes mellitus with among other association to sibshipsize and a higher risk in the firstborn (10).

Do air pollutants (after all) explain the increasing prevalence trends in AR (and atopy)?

A Danish study of sibship characteristics and risk of self-reported AR and asthma, a protective effect towards AR was found in both older and younger siblings but no association was found with age interval between siblings (195). The conclusion supported the hypothesis of an influence of postnatal mechanisms and it was suggested that these may be operating

beyond infancy. We observed a prevalence trend of continuously increasing AR and levelling of AD over the time period from 1995 to 2000. AD and AR are clinically most important in respectively infants and older schoolchildren, and these findings are therefore suggestive of an environmental factor acting in all years of childhood and consequently playing an important part in development of AR (and allergic sensitization). A longitudinal population study in Danish children and adolescents found that new symptoms of asthma or rhinitis were associated with an increased risk for developing sensitization to common aeroallergens in late adolescence (193). The environmental risk factor may well be a continuous PM10 exposure of children (particles with an aerodynamic diameter less than 10 micrometer generated by the combustion of fossil fuels). It is shown that an allergen-PM10 complex elicits allergic sensitization and increased allergen-specific IgE serum levels (196) and deposits of these complexes in the upper airway mucosa are therefore likely to induce AR. A cross-sectional study in France analysed the associations between long-term exposure to background air pollution (NO2, SO2, PM10 and O3) and atopic outcome in 6.672 children aged 9-11 years (185). The children underwent a clinical examination including a skin prick test (SPT) to common allergens, exercise-induced bronchial reactivity (EIB) and skin examination for flexural dermatitis. After adjusting for confounders, EIB, lifetime asthma and lifetime AR were found to be positively related to an increase in the exposure to SO2, PM10 and O3. It was concluded that a moderate increase in long-term exposure to background ambient air pollution was associated with an increased prevalence of respiratory and atopic symptoms in children.

Conclusion

The thesis has focused on asthma, AR and AD in children in a limited geographical region over a limited period of time and has studied the prevalence trends, geographical differences in prevalence and the biomarker s-ECP. These are the main findings in the five papers published:

- The prevalence of asthma and allergy in north Norwegian primary schoolchildren increased substantially between 1985 and 1995.

- By studying the prevalence trends in 9-11 years old children living in Troms and Finnmark over the period from 1985 to 2000, we found that overall prevalence of AR and prevalence of asthma in boys were continuously increasing. The prevalence of AD levelled from 1995 to 2000 and the prevalence of asthma in girls even showed declining trends over the last five years studied.

- In all studies that allowed a distinction between Sami and Norse ethnicity, generally a higher prevalence of asthma and allergy was found among children defined as Sami.

- Russian children on the Kola Peninsula have less asthma and allergy compared to their Norwegian neighbours. However, a high prevalence of respiratory symptoms in these children may represent undiagnosed, non-allergic asthma.

- In an unselected children population (similar to the population of children encountered in general practice) the occurrence of AD or AR was not reflected by

an increased s-ECP level. Despite elevated serum levels in children with asthma, less than 20% of the children with high s-ECP values had asthma. We concluded that the associations between s-ECP and asthma and allergy are weak in an unselected population of children.

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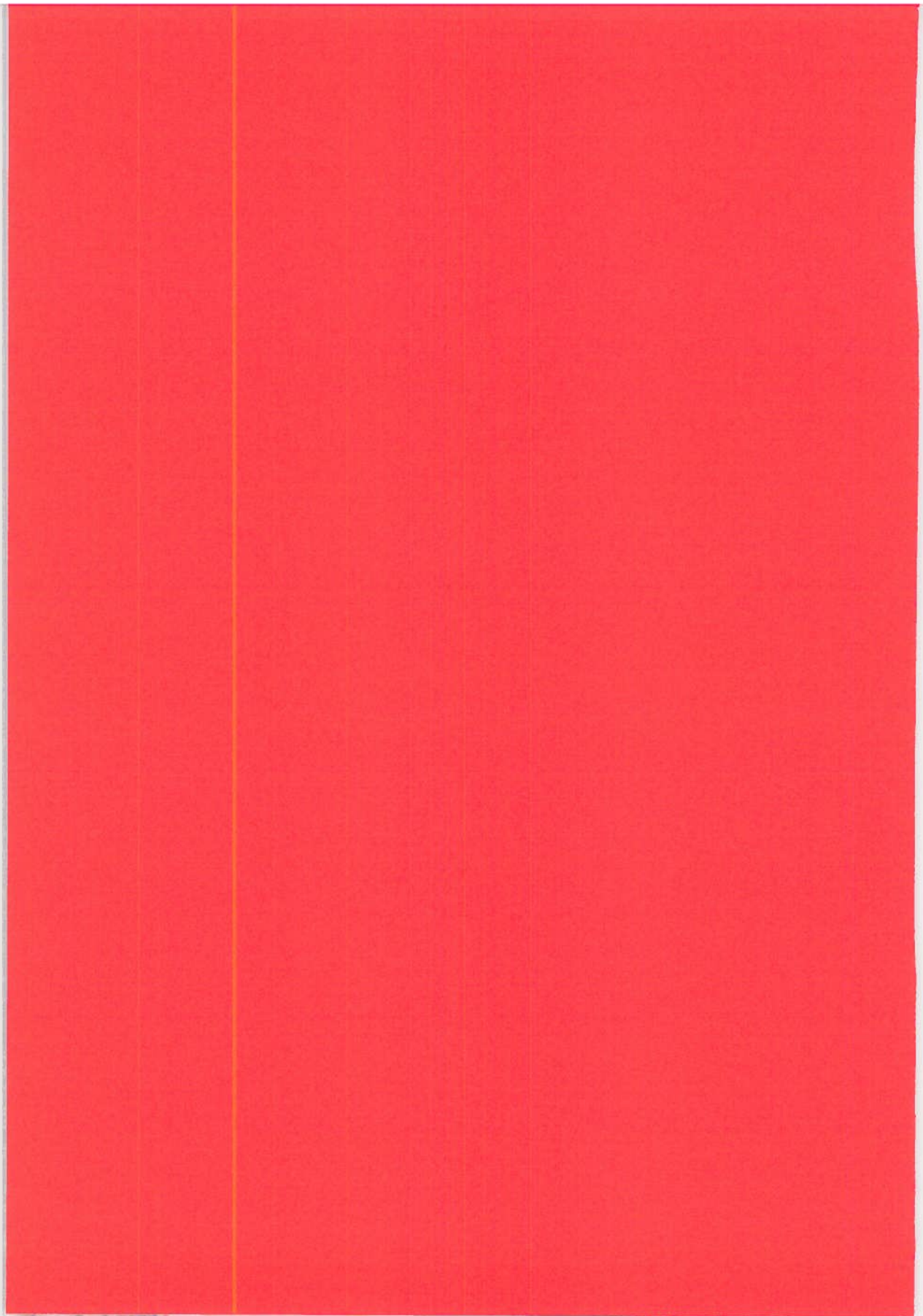
Paper I



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Cumulative incidence of asthma and allergy in north-Norwegian schoolchildren in 1985 and 1995

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The prevalence of asthma and allergy in children is increasing. In order to investigate time trends, follow-up studies conducted several years apart and with identical study designs are essential. We compared two identical, cross-sectional and questionnaire-based studies of asthma and allergy in north-Norwegian schoolchildren (7–13 years of age). The first study was conducted in 1985 (n=10,093) and the second in 1995 (n=8,676). The cumulative incidence was as follows: diagnosed asthma, 8.6% in 1995 vs. 5.1% in 1985, relative risk (RR)=1.71 (95% CI: 1.53–1.90); allergic rhinoconjunctivitis, 22.1% in 1995 vs. 16.4% in 1985, RR=1.39 (95% CI: 1.31–1.47); and atopic dermatitis, 19.7% in 1995 vs. 13.2% in 1985, RR=1.48 (95% CI: 1.39–1.58). The cumulative incidence of allergic rhinoconjunctivitis and atopic dermatitis was higher in children of Sami ethnicity than Norse ethnicity in the 1985 study. Furthermore, although not statistically significant, there was a trend towards a greater increase in the cumulative incidence of diagnosed asthma, symptoms of asthma, allergic rhinoconjunctivitis, and atopic dermatitis from 1985 to 1995 in children of Sami ethnicity than Norse ethnicity. We conclude that there has been a marked increase in the cumulative incidence of asthma and allergy prevalence among schoolchildren in northern Norway from 1985 to 1995.

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Key words: asthma; allergic rhinoconjunctivitis; atopic dermatitis; children; cumulative incidence; time trend; ethnicity; Norway

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Extensive epidemiological research has been carried out on asthma and allergies in children, and considerable geographical variations in the prevalence of these diseases have been observed (1,2). Only repeated measurements after periods of ≥ 10 years, in comparable populations with comparable instruments, allow a valid estimate of time trends for atopic diseases (3).

The cumulative incidence of asthma and allergy in north-Norwegian schoolchildren was studied in a questionnaire-based, cross-sectional study conducted in 1985 (4,5). In 1995, an identical study was carried out. The aim of this article was to compare the two studies by analysing the changes in the cumulative incidence of asthma, allergic rhinoconjunctivitis (AR), and atopic dermatitis (AD) in north-Norwegian schoolchildren over the 10-year period.

Subjects and methods

The questionnaire

In 1985, a written, four-page questionnaire was formulated to assess the frequency of asthma and allergy among schoolchildren in northern Norway (4,5). The questionnaire targeted childhood asthma, AR, and AD, and the symptoms associated with these conditions. A letter accompanying the questionnaire broadened the descriptions of symptoms and signs of the diseases under investigation. The questionnaire included questions concerning ethnicity, e.g. 'Did two or more of the child's grandparents have Sami as their native language?' All questionnaires were written in the Norwegian language.

The 1985 study

In 1985, the questionnaire was distributed with the accompanying letter to schoolchildren (7–

13 years of age) in primary schools in northern Norway. The schools were randomly selected from within the three northernmost counties of Norway, i.e. Nordland, Troms, and Finnmark. The local school nurse was responsible for distributing the questionnaire to the pupils. The questionnaire was filled in at home by the parents. Before delivery, a teacher checked that all fields had been completed. There were 11,200 children included, and 10,093 responded (>90%). The gender distribution among the respondents was 51.2% boys and 48.8% girls.

The 1995 study

The 1995 study was designed as a 10-year follow-up to the study conducted in 1985 (6). Questions concerning symptoms and diseases in the last 12 months were added to the questionnaire described above, which otherwise was unchanged. The questionnaire was distributed with an accompanying letter to the pupils in randomly selected primary schools in the three northernmost counties of Norway. Overall, an identical procedure to that utilized in the 1985 study (and described above) was followed. There were 9,950 schoolchildren included and 8,676 responded (87.3%). The gender distribution among the respondents was 49.1% boys and 50.9% girls.

The children were grouped in the statistical analysis according to age and school class level; the youngest (7–8 years of age) in the first class level and the oldest (12–13 years of age) in the sixth class level. In both studies, the distribution of pupils in the first to the sixth class level ranged from 14.9% to 18.2%.

Ethnicity

Historians believe that ≈1,000–2,000 years bc, the population in Norway was divided into two separate ethnicities. The farmers in the south and west of Norway (white Caucasians), who immigrated from southern Sweden and Denmark, spoke an Indo-European language, which developed into modern Norwegian. In eastern and northern parts of Norway, hunters (influenced from northern Sweden, Finland, and Russia) spoke a language linguistically linked to today's Sami and Finnish language. It is believed that the latter people are the forefathers of the Sami (7). Stereotypically, the Sami has been associated with nomads who keep reindeer. However, the nomads constitute today only a small percentage of the Sami. Although cultural differences still exist, both ethnicities live a modern lifestyle. The most recent generations of Sami speak Norwegian fluently, making misinterpretation of the questionnaire owing to language, unlikely.

Definitions

Sami ethnicity, as opposed to Norse ethnicity, was a label used to distinguish children who had two or more grandparents with Sami as their native language (6).

A diagnosis of asthma was recorded in the cases of affirmative answers to the question, 'Has the child ever had asthma?'. Answering 'yes' to the question, 'Does the child get a wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors', was considered to indicate asthma symptoms. AR was defined as episodic rhinorrhea associated with nasal stuffiness and sneezing in response to known or strongly suspected allergens and often accompanied with itching and lacrimation. AD was recorded in the event of an itchy eruption lasting for >4 weeks combined with lesions on the face, elbowflexures or kneeflexures, or a high degree of itching and lesions elsewhere. As information about symptoms in the previous 12 months (point prevalence) were available solely for the 1995 study, only the differences in cumulative incidence in 1985 and 1995 were analyzed. All responses compared in this report were to questions identical in the two surveys.

Validity of the questionnaire

The questionnaire was used to assess the prevalence of atopic diseases in schoolchildren in both Telemark county and the Sør-Varanger Community, Norway (8–10). Clinical follow-up studies in these regions showed that the sensitivity and the specificity of the questionnaire was high. It was concluded that the questionnaire was a useful epidemiological tool.

The questionnaire studies were conducted after obtaining informed consent from the parents of the children. The studies were approved by the Ethical Committee in north Norway and the Norwegian Data Inspectorate.

Statistical analysis

Cochran-Mantel-Haenszel statistics for 2×2 tables were used together with linear regression, and computed by using the SAS software package (11).

Results

During the 10-year period from 1985 to 1995, there was an increase in the cumulative incidence

Table 1. Cumulative incidence of diagnosed asthma, respiratory symptoms, allergic rhinoconjunctivitis, and atopic dermatitis in schoolchildren in 1985 vs. 1995; relative risk (RR) and corresponding 95% confidence interval (CI) values are shown

	Cumulative incidence (%)				Cumulative incidence in boys (%)				Cumulative incidence in girls (%)			
	Study		1995/1985		Study		1995/1985		Study		1995/1985	
	1985	1995	RR*	95% CI	1985	1995	RR†	95% CI	1985	1995	RR†	95% CI
Diagnosed asthma	5.1	8.6	1.71	(1.53–1.90)	6.6	10.5	1.59	(1.39–1.82)	3.6	6.8	1.93	(1.61–2.31)
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?	6.1	10.6	1.76	(1.59–1.94)	7.6	12.0	1.60	(1.41–1.81)	4.6	9.2	2.03	(1.74–2.37)
Periods with shortness of breath and wheezing and/or episodes with dyspnoe without this being recognized as asthma?	12.7	13.7	1.09	(1.01–1.17)	14.9	15.7	1.05	(0.96–1.16)	10.4	11.8	1.14	(1.01–1.28)
Periods with cough without having a cold?	14.8	20.7	1.40	(1.31–1.49)	16.2	22.5	1.38	(1.27–1.50)	13.3	18.9	1.42	(1.29–1.56)
Episodes with shortness of breath?	9.8	12.4	1.28	1.18–1.39)	12.4	14.4	1.16	(1.04–1.29)	7.1	10.5	1.49	1.30–1.70)
Wheeze or more dyspnoic compared to children of the same age during exercise or in raw, cold air?	5.7	8.6	1.54	(1.39–1.71)	6.5	9.5	1.48	[1.29–1.70)	4.9	7.8	1.62	(1.38–1.90)
Allergic rhinoconjunctivitis	16.4	22.1	1.39	(1.31–1.47)	18.7	25.5	1.38	(1.28–1.49)	13.8	18.9	1.40	(1.27–1.53)
Atopic dermatitis	13.2	19.7	1.48	(1.39–1.58)	12.8	16.6	1.29	(1.17–1.43)	13.6	22.6	1.66	(1.52–1.81)

*RR adjusted by age and gender.
†RR adjusted by age.

of diagnosed asthma, asthma symptoms, respiratory symptoms, AR, and AD in primary schoolchildren in northern Norway (Table 1). The greatest increase was found in diagnosed asthma and asthma symptoms. Moreover, the rise in cumulative incidence of asthma and allergy during the 10-year period was most prominent in girls. In Table 2, the cumulative incidence of diagnosed asthma, AR, and AD is shown according to school class level. The frequency of diagnosed asthma escalated from the first to the sixth class level only in girls in the 1995 study. The frequency of AR increased with increasing class level for both genders in both studies. In contrast to the 1985 study, the frequency of AD decreased with increasing age in the 1995 study.

Ethnicity

In the 1985 study, 7.2% of the children had Sami ethnicity compared to 5.9% in the 1995 study ($p<0.001$). There was a greater, although not

Table 2. Cumulative incidence (%) of diagnosed asthma, allergic rhinoconjunctivitis and atopic dermatitis in schoolchildren in 1985 vs. 1995, according to class level; rate of increase per class level and corresponding 95% confidence interval (CI) and p-values are shown

		Class level								
		1	2	3	4	5	6	Rate of increase	95% CI	p-value
Diagnosed asthma										
Boys	1985	5.0	6.4	7.1	6.8	7.5	6.8	0.3	(–0.1–0.7)	0.12
	1995	10.0	12.5	10.1	9.9	9.9	10.2	–0.2	(–0.8–0.3)	0.46
Girls	1985	2.8	3.0	3.1	4.3	4.0	4.0	0.3	(0.0–0.6)	0.07
	1995	5.1	6.7	5.8	8.4	6.9	8.1	0.5	(0.1–1.0)	0.02
Allergic rhinoconjunctivitis										
Boys	1985	15.8	15.6	18.7	19.9	21.8	19.9	1.1	(0.5–1.8)	<0.001
	1995	23.5	21.1	25.4	26.2	28.1	29.9	1.5	(0.7–2.3)	<0.001
Girls	1985	8.3	11.1	14.4	14.7	17.2	16.1	1.6	(1.0–2.2)	<0.001
	1995	13.9	19.5	19.4	20.3	20.0	21.0	1.1	(0.4–1.8)	<0.01
Atopic dermatitis										
Boys	1985	13.0	13.0	10.9	13.1	14.2	12.3	0.1	(–0.5–0.6)	0.84
	1995	17.1	18.8	17.9	15.6	16.1	13.1	–0.8	(–1.5–0.2)	0.01
Girls	1985	13.6	13.7	13.0	12.4	14.2	14.6	0.2	(–0.4–0.8)	0.49
	1995	23.5	24.5	23.3	23.5	21.7	18.8	–0.9	(–1.6–0.2)	0.02

Table 3. Cumulative incidence of diagnosed asthma, asthma symptoms, allergic rhinoconjunctivitis and atopic dermatitis in Sami and Norse schoolchildren in 1985 and 1995; relative risk (RR) in 1995/1985 and corresponding 95% confidence interval (CI) values are shown

	Cumulative incidence (%)				Cumulative incidence in boys (%)				Cumulative incidence in girls (%)			
			1995/1985				1995/1985				1995/1985	
	1985	1995	RR*	95% CI	1985	1995	RR†	95% CI	1985	1995	RR†	95% CI
Diagnosed asthma												
Sami	6.0	13.6	2.32	(1.62–3.32)	8.0	17.5	2.22	(1.42–3.46)	4.0	9.8	2.51	(1.36–4.64)
Norse	5.1	8.2	1.64	(1.46–1.84)	6.5	9.8	1.51	(1.31–1.75)	3.6	6.6	1.88	(1.55–2.27)
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?												
Sami	7.5	16.1	2.16	(1.56–3.01)	10.6	17.8	1.66	(1.10–2.53)	4.4	14.4	3.35	(1.94–5.81)
Norse	6.0	10.2	1.71	(1.54–1.90)	7.4	11.7	1.59	(1.39–1.82)	4.6	8.7	1.91	(1.62–2.26)
Allergic rhinoconjunctivitis												
Sami	19.4	32.6	1.71	(1.40–2.09)	21.7	37.6	1.74	(1.34–2.26)	17.0	27.8	1.67	(1.22–2.28)
Norse	16.1	21.6	1.38	(1.29–1.47)	18.4	24.9	1.37	(1.26–1.49)	13.7	18.5	1.39	(1.25–1.53)
Atopic dermatitis												
Sami	16.7	26.7	1.57	(1.25–1.96)	18.0	22.6	1.24	(0.89–1.73)	15.8	30.7	1.92	(1.42–2.61)
Norse	12.8	19.2	1.49	(1.39–1.60)	12.2	16.3	1.33	(1.20–1.48)	13.4	22.1	1.64	(1.49–1.80)

*RR adjusted by age and gender.
†RR adjusted by age.

statistically significant, increase in the cumulative incidence of diagnosed asthma, asthma symptoms, AR, and AD in Sami than in Norse children from 1985–95 (Table 3). The greatest difference was found in diagnosed asthma and asthma symptoms, the latter showing an increase of 10% in Sami girls between 1985 and 1995. In the 1985 study, the cumulative incidence of AR and AD was highest in Sami children (Table 4). In the same study, the frequency of asthma symptoms among boys was greater in Sami children.

Discussion

In accordance with recent epidemiological research (2,3), results of our 10-year follow-up study showed an increase in the cumulative incidence of asthma and allergy in north-Norwegian schoolchildren from 1985 to 1995. The greatest increase in cumulative incidence was found in girls with diagnosed asthma and asthma symptoms.

The cumulative incidence of diagnosed asthma increased at a higher rate from the first to the sixth class level in girls in the 1995 study than in the 1985 study. Again, this reflects a rising frequency of girls labeled as asthmatics in the year prior to the 1995 study. In contrast to the 1985 study, the prevalence of AD decreased by nearly 1% per school class level in the 1995 study. The peak incidence of AD occurs in children of preschool age, and cessation of symptoms before adolescence is common (12). We consequently interpret

Table 4. Cumulative incidence of diagnosed asthma, asthma symptoms, allergic rhinoconjunctivitis, and atopic dermatitis in Sami and Norse schoolchildren in 1985 and 1995; relative risk (RR) Sami/Norse and corresponding 95% confidence interval (CI) values are shown

	Cumulative incidence (%)				Cumulative incidence in boys (%)				Cumulative incidence in girls (%)			
			Sami/Norse				Sami/Norse				Sami/Norse	
	Sami	Norse	RR†	95% CI	Sami	Norse	RR†	95% CI	Sami	Norse	RR†	95% CI
Diagnosed asthma												
1985	6.0	5.1	1.21	(0.88–1.65)	8.0	6.5	1.24	(0.85–1.82)	4.0	3.6	1.14	(0.67–1.95)
1995	13.6	8.2	1.69	(1.33–2.15)	17.5	9.8	1.81	(1.34–2.43)	9.8	6.6	1.53	(1.02–2.28)
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?												
1985	7.5	6.0	1.27	(0.96–1.68)	10.6	7.4	1.44	(1.03–2.01)	4.4	4.6	0.99	(0.59–1.65)
1995	16.1	10.2	1.61	(1.29–2.01)	17.8	11.7	1.54	(1.14–2.07)	14.4	8.7	1.70	(1.22–2.37)
Allergic rhinoconjunctivitis												
1985	19.4	16.1	1.22	(1.04–1.44)	21.7	18.4	1.18	(0.95–1.46)	17.0	13.7	1.27	(0.99–1.64)
1995	32.6	21.6	1.52	(1.32–1.76)	37.6	24.9	1.51	(1.25–1.82)	27.8	18.5	1.54	(1.23–1.93)
Atopic dermatitis												
1985	16.7	12.8	1.32	(1.10–1.57)	18.0	12.2	1.48	(1.16–1.89)	15.8	13.4	1.17	(0.91–1.52)
1995	26.7	19.2	1.39	(1.18–1.63)	22.6	16.3	1.39	(1.07–1.79)	30.7	22.1	1.38	(1.13–1.70)

*RR adjusted by age and gender.
†RR adjusted by age.

this finding as an expression of increasing cumulative incidence in the 6 years prior to the study.

The prevalence of skin-test-positive allergic rhinitis in 15–41-year-old Danish adults increased between two cross-sectional surveys, conducted 8 years apart (1990/1998) (13). It was concluded that a genuine increase in respiratory allergy had occured. Two cross-sectional studies of schoolchildren in Oslo, Norway, conducted 13 years apart (1980/1993), revealed an increase in asthma prevalence from 3.4% to 9.3% (14). Trends in hospital admissions for childhood asthma was studied in Oslo, Norway, from 1980 to 1995. The study revealed an increasing first admission rate, as well as an increasing overall admission rate, for acute asthma in children <4 years of age, reflecting an increasing prevalence of childhood asthma (15). Annual Health Interview Surveys in the United States show an increase in the prevalence of self-reported asthma for children 5–14 years of age, from 4.3% in 1980 to 7.4% in 1993–94, an increase of 74% (16). In 1992/93, Dotterud et al. studied the prevalence of AD among schoolchildren in Sør-Varanger Community, northern Norway, a study area which was also included in our two cross-sectional studies. The study incorporated a clinical examination of the subjects together with objective measurements (skin-prick test, serum immunoglobulin E [IgE]). Definite atopics accounted for 36% of the study participants, i.e. AD was present in 23% and mucous membrane atopy in 18% (9,10).

The cumulative incidence of AR and AD was higher in Sami children than in Norse children in 1985. This was also the case concerning asthma symptoms in boys. Furthermore, there was a trend towards a greater increase of asthma and allergy in children of Sami than Norse ethnicity during the 10-year study period. In the study conducted in 1995, marked differences in the frequency of asthma and allergy were found between children of Sami and Norse ethnicity (6). These findings indicate that attention should be paid to the development of asthma and allergy in children of Sami ethnicity. Above all, we speculate that these children are more vulnerable when confronting a modern, western lifestyle.

Because the questionnaires in the two studies were identical, a valid estimate of the time trend is allowed (3). However, owing to the lack of objective data, the increasing cumulative incidences in our repeated cross-sectional study, should be interpreted with caution (17). In the previous few decades, asthma and allergy have been increasingly focused upon, both by medical science and by the public. Consequently, the higher awareness of these diseases in general may partly explain the increasing frequencies in studies based on self-reported questionnaires. Nevertheless, awareness by the public and the medical profession cannot alone explain an increase of the magnitude found in our study. We therefore conclude that, in line with the findings of epidemiological research in the western world, the frequency of asthma and allergy in north-Norwegian schoolchildren is rising.

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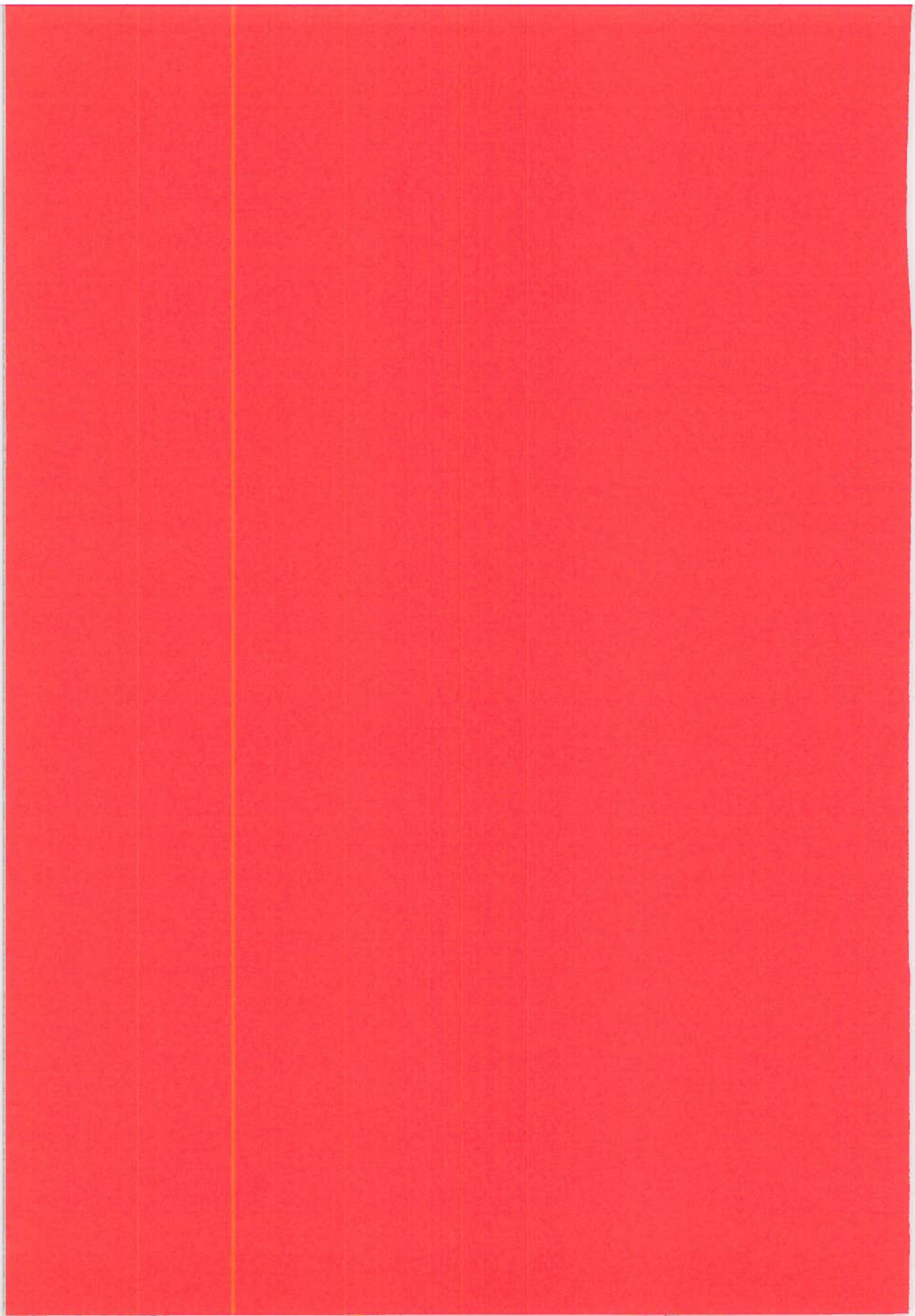
Paper II



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Original article

Diverging prevalence trends of atopic disorders in Norwegian children. Results from three cross-sectional studies

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Background: During the last decades there has been extensive epidemiological research to explore the increasing prevalence of asthma and allergy in childhood. The worldwide variations in prevalence of these diseases necessitate regional rapports. Furthermore, time-trend analyses with comparable methods are important in order to monitor the rapidly changing prevalence of these diseases.
Methods: Three cross-sectional questionnaire-based studies of asthma and allergy in schoolchildren were conducted in the counties of Troms and Finnmark, in northern Norway in 1985, 1995 and 2000. The two former studies included children from randomly selected primary schools (n = 1794/1985, n = 1432/1995). The latter study was a part of ISAAC-II Europe study (n = 3853). Identical items of asthma and allergy were employed. The analyses comprised only children 9–11 years of age.
Results: The prevalence of asthma was 9.3, 13.2 and 13.8% in 1985, 1995 and 2000, respectively. However, great gender differences were detected; the prevalence of asthma increased in males from 1995 to 2000, from 14.1 to 17.0%, RR = 1.2 (95% CI 1.0–1.5), but decreased in females 1995 to 2000, from 12.3 to 10.5%, RR = 0.9 (95% CI 0.7–1.1). Furthermore, in children with asthma, a changing trend was found in the external factors that perceived symptoms, from typical allergens towards other, unspecific agents. The prevalence of self-reported atopic eczema/dermatitis syndrome (AEDS) was 13.4, 21.1 and 20.8% in 1985, 1995 and 2000, respectively. The prevalence of self-reported allergic rhinoconjunctivitis was in 16.5, 24.7 and 29.6% 1985, 1995 and 2000, respectively, RR (2000/1995) = 1.2 (95% CI 1.1–1.3).
Conclusion: The prevalence of asthma in girls has reached a plateau and even decreased from 1995 to 2000 which is in contrast to the asthma prevalence in boys that tends to continuously increase. The prevalence of AEDS which increased substantially between 1985 and 1995 did not change from 1995 to 2000. However, the prevalence of allergic rhinoconjunctivitis increased steadily from 1985, 1995 to 2000.

Key words: allergic rhinoconjunctivitis, asthma; atopic eczema/dermatitis syndrome; schoolchildren; time trends.

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Epidemiological research on asthma and allergy in children has during the last decades focused on an increasing prevalence observed worldwide (1). Sooner or later this increase may reach a plateau, and only through repeated comparable studies, time trends in childhood asthma and allergy prevalence can be followed. There has been a significant reduction in the prevalence of reported asthma in Melbourne schoolchildren, whereas the prevalence of eczema and allergic rhinitis has continued to increase (2). Although several 10-year follow-up studies concerning this issue are published, only a few studies have a third comparable prevalence measurement made after another 5–10 years time period. Prevalence of asthma and allergy was studied in schoolchildren in Belmont, Australia: three cross-sectional surveys over 20 years were conducted. The prevalence of hay fever, eczema, atopy, airway hyperresponsiveness or current asthma (defined as recent wheeze plus airway hyperresponsiveness) did not change significantly. These trends were in contrast with the substantial rise in the prevalence of most of these indicators during the period 1982–1992 (3).

We present a time trend study of asthma and allergy prevalence in primary schoolchildren in northern Norway. The present study is based on three separate cross-sectional written questionnaire-based studies orchestrated in 1985, 1995 and 2000. The objectives of this study were to assess whether or not the prevalence of these diseases was continuously increasing during the study period.

Material and methods

Study area

Troms and Finnmark are localized in the subartic area of Norway north of the polar circle. The population counts 223 000 inhabitants and the counties covers an area of 75 000 km^2. Around 57% of the population live in regional centres whereas 43% live in sparsely populated districts along the coastline. Although some live in a dry inland climate, the majority of people live in a costal humid climate.

Studies

The questionnaire employed in the 1985 and 1995 studies. In 1985, a written, four-paged questionnaire was formulated by Bolle and Holt to assess the frequency of asthma and allergy among schoolchildren in northern Norway (4–6). The questionnaire targeted the subjects' childhood asthma, allergic rhinoconjunctivitis (AR) and atopic eczema/dermatitis syndrome (AEDS) and the symptoms associated with these conditions. In the questionnaire, two core questions concerning asthma were employed; 'Has the child ever had asthma?' and 'Does the child experience wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?' A clinical validation estimated the test–retest reliability (κ) to be 0.91 when these two questions were combined (and/or) as a definition of asthma (7). A letter accompanying the questionnaire broadened the descriptions of symptoms and signs of the diseases under investigation.

The 1985 study. In 1985, this questionnaire was distributed with the accompanying letter to schoolchildren aged 7–13 attending primary schools (n = 11 200). The schools were randomly selected within the three northernmost counties of Norway, i.e. Nordland, Troms and Finnmark. The local school nurse was in charge of the distribution of the questionnaire to the pupils. The questionnaire was filled in at home by the parents. Before delivery, a teacher controlled that all fields were filled in.

The 1995 study. The 1995 study was designed as a 10-year follow-up to the study conducted in 1985. Questions concerning symptoms and diseases the last 12 months were added to the questionnaire described above, which otherwise was identical. Similarly to the 1985 study, the questionnaire was distributed with the accompanying letter to the pupils in randomly selected primary schools in the three northernmost counties of Norway (n = 9950). Overall, an identical procedure to the one utilized in the 1985 study (and described above) was followed.

The 2000 (ISAAC) study. The 2000 study was part of an ISAAC-II Europe study. All 9–11 years old children in the counties of Troms and Finnmark were invited to participate. The study was arranged according to standard ISAAC procedures (8–12).

Comparability between the 1985, 1995 and 2000 study. In order to ensure comparability between the three studies, these steps were taken: (i) from the 1985 and 1995 studies, only children in third to fourth level (9–11 years) from Troms and Finnmark were included (ii) in the 2000 study, identical core questions from the Bolle/Holt questionnaire were added to the ISAAC questionnaire.

Variables compared between the 1985, 1995 and 2000 studies

The study is based on parental reports of asthma, allergic rhinoconjunctivitis (AR) and AEDS. Two core questions concerning asthma (mentioned above) were employed; 'Has the child ever had asthma?' and 'Does the child experience wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?'. The first question is referred to as 'self-reported asthma', and the latter is referred to as 'asthma symptoms'. Affirmative answers to the questions 'Has the child ever had hay fever?' or 'Does the child experience periods with complaints from nose and or eyes like a runny nose, nose stuffiness, sneezing, itchy nose/eyes swelling around eyes, red eyes?' were recorded as AR. AEDS was recorded in the cases of an itchy eruption lasting for more than 4 weeks combined with (i) lesions in face, elbow- or kneeflexures or (ii) high degree of itching and lesions elsewhere. In the cases of missing answers to core questions, the answer was assumed to be non-affirmative (no disease/symptoms).

Handling of missing values. Missing values to the question 'Has the child ever had asthma?' was found in 2.2% in 1985, 1.0% in 1995 and 8.2% in 2000. Missing values to the question 'Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?' was found in 4.8% in 1985, 3.7% in 1995 and 18.1% in 2000. By means of reducing the high percentage of missing answers to the asthma core questions in the 2000 study, this step was taken; in these cases we projected the answers to an additional question concerning asthma only present in the ISAAC questionnaire: 'Has the child ever had one of the following diseases: asthma, hay fever, adverse reactions to food, other kind of allergic reactions?'. If asthma was confirmed or denied in this question, the same value was applied to the asthma core questions. The missing in the 2000 study was thereby reduced to 0.5 % (n = 20).

Analyses

The comparison between the three studies was made by measurements of relative risk (RR) 1995/1985 and 2000/1995. These RR estimates were (alternatively to P-value) accompanied by a 95% confidence interval (95%CI) of the RRs and handled by Cochran–Mantel–Haenszel statistics based on table scores. Linear regression and trend analysis was only preferred in situations of probable linearity. The statistics were taken care of by SAS software package (13). All studies were based on informed consent from the child's parents. The studies were approved by the Ethical Committee in North-Norway and the Norwegian Data Inspectorate.

Results

The main results are presented in Tables I–3.

Asthma

Overall, the prevalence of self-reported asthma increased from 1985 to 2000. On the contrary, the prevalence of self-reported asthma symptoms increased from 1985 to 1995 but decreased between 1995 and 2000. When the two questions were combined (self-reported asthma and/or asthma symptoms), the prevalence of asthma increased from 1985 to 2000. However, great gender differences were detected concerning asthma; in males, asthma prevalence increased more between 1995 and 2000 than it did between 1985 and 1995. In contrast, in females the prevalence of self-reported asthma was unchanged from 1995 to 2000.

Table 1. The prevalence of asthma, allergic rhinoconjunctivitis (AR) and atopic eczema/dermatitis syndrome (AEDS) in the studies from 1985, 1995 and 2000. Differences in prevalence between 1995/1985 and 2000/1995 are quantified with relative risk (RR) and corresponding 95% confidence interval (95% CI)

	Prevalence (%)						
	Study			1995/1985		2000/1995	
	1985 (n = 1794)	1995 (n = 1432)	2000 (n = 3853)	RR	95% CI	RR	95% CI
Response rate (%)	>90	87	80				
Gender distribution (male/female ratio)	1.0	1.0	1.0				
Asthma							
Self-reported asthma (1)	6.7	8.8	10.2	1.31	1.03–1.67	1.16	0.95–1.40
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors? (2)	7.2	10.5	10.3	1.46	1.17–1.83	0.98	0.82–1.17
Asthma question (1) and/or (2)	9.3	13.2	13.8	1.42	1.17–1.73	1.04	0.89–1.22
Self-reported allergic rhinoconjunctivitis	16.5	24.7	29.6	1.49	1.30–1.72	1.20	1.08–1.33
Self-reported atopic eczema/dermatitis syndrome	13.4	21.1	20.8	1.57	1.35–1.83	0.99	0.88–1.11

Table 2. The prevalence of asthma, allergic rhinoconjunctivitis (AR) and atopic eczema/dermatitis syndrome (AEDS) in the studies from 1985, 1995 and 2000. Differences in prevalence between 1995/1985 and 2000/1995 are quantified with relative risk (RR) and corresponding 95% confidence interval (95% CI) (males)

	Prevalence (%)						
	Study			1995/1985		2000/1995	
Males	1985 (n = 1794)	1995 (n = 1432)	2000 (n = 3853)	RR	95% CI	RR	95% CI
Asthma							
Self-reported asthma (1)	8.9	10.0	12.7	1.13	0.83–1.53	1.27	0.99–1.63
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors? (2)	10.1	10.6	12.5	1.05	0.78–1.40	1.18	0.93–1.51
Asthma question (1) and/or (2)	12.4	14.1	17.0	1.13	0.88–1.46	1.20	0.98–1.48
Self-reported allergic rhinoconjunctivitis	18.5	27.2	32.2	1.47	1.23–1.76	1.18	1.03–1.36
Self-reported atopic eczema/dermatitis syndrome	12.7	18.2	18.2	1.44	1.14–1.81	1.00	0.83–1.20

Table 3. The prevalence of asthma, allergic rhinoconjunctivitis (AR) and atopic eczema/dermatitis syndrome (AEDS) in the studies from 1985, 1995 and 2000. Differences in prevalence between 1995/1985 and 2000/1995 are quantified with relative risk (RR) and corresponding 95% confidence interval (95% CI) (females)

	Prevalence (%)						
	Study			1995/1985		2000/1995	
Females	1985 (n = 1794)	1995 (n = 1432)	2000 (n = 3853)	RR	95% CI	RR	95% CI
Asthma							
Self-reported asthma (1)	4.4	7.6	7.6	1.71	1.15–2.55	1.00	0.74–1.35
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors? (2)	4.2	10.5	8.1	2.49	1.71–3.65	0.77	0.59–1.00
Asthma question (1) and/or (2)	6.0	12.3	10.5	2.04	1.47–2.82	0.86	0.68–1.08
Self-reported allergic rhinoconjunctivitis	14.5	22.1	27.0	1.53	1.24–1.89	1.22	1.04–1.42
Self-reported atopic eczema/dermatitis syndrome	14.2	23.9	23.5	1.68	1.37–2.07	0.98	0.84–1.14

The prevalence decreased from 1995 to 2000 when asthma was defined by the combination of both core questions.

In children with asthma, we investigated with trend analysis which external factor(s) that made the children perceive symptoms (Table 4); there was a decreasing tendency of reporting grass pollen as a trigger of asthma attacks from 1985 to 2000 and an opposite, increasing trend for reporting other (and unspecific) factors. Again gender differences were apparent; in females these trends were more predominant with additionally animal dander decreasingly notified as a causative factor to perceive asthma symptoms.

Table 4. External factors which made the asthmatic children ($n = 674$) perceive asthma symptoms (see text). Time trend is given in per cent change in frequency by year Δ (%), statistical significance tested by probability (*P*-value)

	All					Males					Females				
	Study			Time trend		Study			Time trend		Study			Time trend	
	1985 ($n = 128$)	1995 ($n = 151$)	2000 ($n = 395$)	Δ (%)	*P*-value	1985 ($n = 91$)	1995 ($n = 75$)	2000 ($n = 241$)	Δ (%)	*P*-value	1985 ($n = 37$)	1995 ($n = 76$)	2000 ($n = 154$)	Δ (%)	*P*-value
Animal dander	50.0	50.1	43.5	−0.47	0.16	45.1	45.3	45.6	0.03	0.92	62.2	56.6	40.3	−1.61	<0.01
Grass pollen	49.2	38.4	33.9	−1.02	<0.01	48.4	41.3	36.5	−0.79	<0.05	51.4	35.5	29.9	−1.41	<0.05
Infections	23.4	26.5	27.3	0.26	0.39	25.3	21.3	26.6	0.10	0.77	18.9	31.6	28.6	0.05	0.32
Weather	28.1	26.5	29.9	0.14	0.66	28.6	22.7	30.7	0.02	0.65	27.0	30.3	28.6	0.01	0.90
Food	7.0	15.2	12.4	0.33	0.14	4.4	14.7	13.3	0.58	<0.05	13.5	15.8	11.0	−0.23	0.57
Other factors	14.1	23.2	30.4	1.10	<0.01	13.2	21.3	29.5	1.10	<0.01	16.2	25.0	31.8	1.07	<0.05

Allergic rhinoconjunctivitis and atopic eczema/dermatitis syndrome

The prevalence of self-reported AR increased steadily in the studies from 1985, 1995 and 2000. Unlike asthma, the increase in self-reported AR showed no gender differences. The prevalence of self-reported AEDS increased substantially from 1985 to 1995, but no further prevalence changes were observed from 1995 to 2000. Again, no gender differences were apparent concerning prevalence changes in self-reported AEDS.

Discussion

According to this study of 9–11 years old schoolchildren from northern Norway, somewhat new and surprising trends have occurred in the context of prevalence of atopic disorders. In spite that the asthma prevalence in boys tends to continuously increase over the 15 years studied from 1985 to 2000, the prevalence of asthma in girls has reached a plateau and has even decreased from 1995 to 2000. Moreover, the prevalence of AEDS which increased substantially between 1985 and 1995 did not change from 1995 to 2000. However, the prevalence of allergic rhinoconjunctivitis increased continuously among schoolchildren in northern Norway in these cross-sectional studies from 1985, 1995 to 2000.

The increasing prevalence of asthma and AEDS is considered a major worldwide health problem (14, 15). Several epidemiological studies on the prevalence of asthma and allergy in childhood are orchestrated in our region from the beginning of the 1980s to date (7, 12, 16–25). According to the Norwegian lifetime prevalence studies, both AEDS and AR continued to increase during the period 1981–1995 (4, 7, 16). On the contrary, a review of these studies showed that the prevalence of asthma culminated in the beginning of the 1990s after an increase in the 1980s. Furthermore, recent published studies have shown a stabilization of the prevalence rates of allergic diseases among primary school children other than allergic rhinitis (26, 27). The prevalence of asthma and AEDS has even showed declining trends in children from the first half of the nineties (28–30). The rate of hospitalizations for asthma is on the decline or low and stable in children aged 3 years or older in a study from 1984 to 2000 in Rogaland, Norway (31). No increase in hospital admission due to asthma was detected in schoolchildren in Oslo during 1980–1995 (32).

Nevertheless, despite the interesting and encouraging changes to AEDS and asthma prevalence, we did find that the prevalence of AR, which above of all is associated with IgE-mediated allergy, is continuously increasing. Obviously, these differences in prevalence changes between asthma, AR and AEDS in our study are not easy to explain. Atopy and atopic disorders arise from a multifactor origin with an interaction between environment and genetics (33). It is hypothesized that the increased prevalence of asthma and allergy is connected to the wealth increase and a higher prevalence is found in rich families (34). The differences in prevalence rate in 1985, 1995 and 2000 we observe in our study may reflect the changes in standard of living in Norway the last decades; similarly to other industrialized countries, the socioeconomic conditions in Norway improved greatly in the 1960s and 1970s, but reached a plateau in the 1980s. Consequently, as AEDS and asthma occur earlier in life, it is expected that the prevalence of AEDS and asthma will first culminate, and later this will also be the case with AR. On the contrary, the differences between asthma, AEDS and AR in prevalence changes over time may also reflect a better understanding in public in avoidance of offending allergens; Whereas (typical) allergens connected to asthma and AEDS are in part possible to avoid (animal dander/food), the allergens typically causing AR (pollen) are however impossible to avoid. The causative factor when the children perceive asthma symptoms have over the 15 years studied transitioned from traditional allergens to other and unspecific external factors, which may reflect that asthmatics today are a more heterogenic group than 'yesterdays' asthmatics. This observation that especially girls with asthma to a lesser extent experience symptoms due to allergens in 2000 than in 1985, may point towards a changing expression of asthma. However, the great difference between girls and boys observed

in asthma trends from 1995 to 2000 does not favour an environmental or public opinion (avoidance) explanation to the changes. Yet, physical activity can possibly lay behind the expression 'other factors' when asthma symptoms are perceived. We do know that children are increasingly inactive and that asthmatic symptoms are associated with physical activity in children with increased body mass index (35–37).

Although the Bolle/Holt-asthma-questionnaire has been validated and the combination of the two core questions provides a high sensitivity and specificity (0.96 and 0.88, respectively) (7), systematic bias concerning the asthma label must be expected in a cross-sectional, written questionnaire-based design that is employed in these studies. We have no information neither if the children suffer a mild, moderate or severe asthma, nor do we know about the use of antiasthmatic medication. Furthermore, in a cross-sectional setting, it is impossible to do judgement about causality. This is especially true in case of the finding of the trend changes in asthma symptoms due to allergens and 'other factors'. We do not know if these changes are due to increasing knowledge about allergy and allergens in families with allergies (and hence avoidance) or if the population of asthmatic children over the 15 years studied has transitioned in direction of a greater percentage of children with mild, 'intrinsic' asthma.

The prevalence of asthma is difficult to follow over time owing to changes in diagnostic practice and information bias may explain the trends (38). There is a methodological difference between the two former and the latest (ISAAC) study that is a potential source of bias. The ISAAC questionnaire was more profound with multiple questions and the core questions employed in this study did not have the same central position like in the two former studies. This may be an explanation to the differences in missing answers to core questions. Additionally, the response rate has been declining during our study period. An interpretation may be decreasing motivation in the public to participate in such epidemiological studies. A lack of motivation may also be partly responsible to the high rate of missing data to the asthma questions in the 2000 (ISAAC) study. However, some of the missing data can be explained by uncertainties by the responders, an expression of doubt whether the child is asthmatic or not. Lastly, the trend of falling response rate from 1985 to 2000 must inevitable decrease the reliability of the latter studies.

The high rate of missing responses to the asthma core questions in the 2000 (ISAAC) study could potentially be handled by three ways; by excluding the missing data from analysis, by employing an interpretation that the missing data represents no disease and hence can be treated as such, and lastly, by applying the additional asthma-question available in the ISAAC questionnaire and subsequently reduce the number of missing. In our opinion, excluding all subjects with missing responses to the asthma core question would result in serious misinterpretation of the asthma prevalence in the 2000 (ISAAC) study and lead to a false high prevalence. Epidemiological studies on prevalence of disease in persons who do not complete questionnaires have shown that this mode of response implies no disease (Professor Eiliv Lund, personal communication). In cases of missing answers to core questions we therefore could had chosen to interpret these values as nonaffirmative in order to avoid false over reporting. However, we choose the third and applied the additional asthma-question available in the ISAAC questionnaire and thereby reduced the high rate of missing without obvious misinterpretation of the data and the results.

We conclude that the prevalence of childhood asthma shows diverging trends in northern Norway; although it tends to increase in boys, the prevalence has ceased in girls from 1995 to 2000. Furthermore, our study indicates that after a substantial increase in the prevalence of AEDS from 1985 to 1995, no further increase has occurred from 1995 to 2000. However, the prevalence of allergic rhinoconjunctivitis has been continuously increasing over the 15 years studied.

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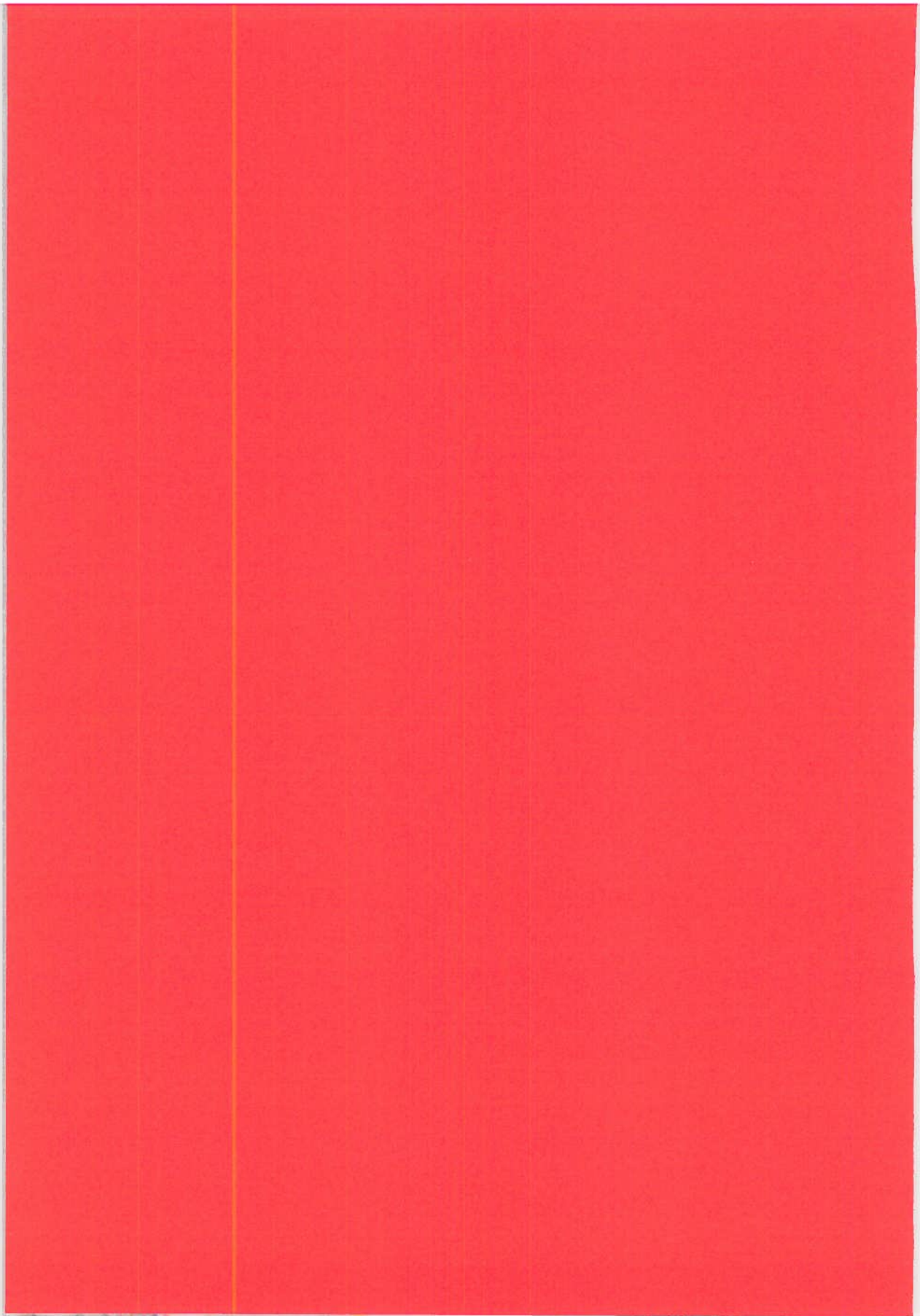
Paper III



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Atopic diseases in Sami and Norse schoolchildren living in northern Norway

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Among children in the western world, atopic diseases are a major cause of morbidity. However, several prevalence studies have indicated that the frequency of these diseases displays both geographic and ethnic variations. In 1995, we conducted a questionnaire-based, cross-sectional survey in northern Norway. Atopic diseases among 8676 schoolchildren, aged 7–13 years, including 491 children with Sami ethnicity, were studied. The role of ethnicity (Sami/white Caucasian) was determined by comparing the reported atopic disease rate in each of the respective groups. In the areas under investigation (the cumulative incidence, the point prevalence of asthma and allergic rhinoconjunctivitis and the cumulative incidence of atopic dermatitis), the Sami children scored higher than the white Caucasian Norwegian children. The relative risks (RR) in Sami children were: current asthma RR 2.01 [95% confidence interval (CI) 1.48–2.73]; current allergic rhinoconjunctivitis RR 1.51 (95% CI 1.14–1.99); lifetime atopic dermatitis RR 1.39 (95% CI 1.18–1.63). We thus conclude that there is an association between Sami ethnicity and asthma and allergy among schoolchildren in northern Norway.

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Key words: atopic diseases; schoolchildren; prevalence; Norway; ethnicity

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Owing to the high prevalence of atopic diseases (bronchial asthma, allergic rhinoconjunctivitis and atopic dermatitis) in children, several epidemiological studies have been performed to obtain a better understanding of their complexity (1–3). Ascertaining demographic information such as geographic and ethnic distribution is essential. Interactions between atopic traits and genetic and environmental risk factors can thus be elicited.

This work presents a cross-sectional, questionnaire-based study of children of Sami and Norse (white Caucasian) ethnicity in northern Norway. Study parameters were the atopic diseases: asthma, allergic rhinoconjunctivitis and atopic dermatitis. The study objective was to compare the prevalence of atopic diseases among children of different ethnicity living within the same geographic boundaries.

aterials and methods

In 1995, a questionnaire dealing with atopic diseases in childhood was distributed to schoolchildren aged 7–13 in the counties of Nordland, Troms and Finnmark in northern Norway. The primary schools included were randomly chosen within each county. The local school nurse distributed the questionnaires and an accompanying letter, with a description (symptoms and signs) of the diseases under investigation, to the schoolchildren and their parents. The questionnaire targeted the symptoms of bronchial asthma, allergic rhinoconjunctivitis and atopic dermatitis. Questions about urticaria and adverse reactions to food were also included. Furthermore, information about atopic disease in close relatives, residence, housing, indoor/outdoor environment and ethnicity was collected. The present study was a 10 year follow-up of a study conducted in northern Norway in 1985 and the questionnaires used in both surveys were almost identical.

Of the 9950 schoolchildren selected, 8682 subjects (87.3%) returned a completed questionnaire. Six questionnaires lacked information about gender or age and these were deleted from the study. The questionnaire was answered

by the child's mother in 78.5% of cases and by the father in 12.3%, by both mother and father in 5.0%, by the child in 2.9% and by others in 1.3%.

Definitions

There were 491 children (5.9%) with two or more grandparents who had Sami as their native language, and who were defined as being of Sami ethnicity. In 404 children (4.7%) this question was left unanswered. In accordance with previous Norwegian studies where a similar questionnaire was employed (4,5), asthma was recorded if there was an affirmative answer to either one or both of the questions 'Has the child ever had asthma?'/'Does the child get a wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?'. Atopic dermatitis was recorded in the cases of an itchy eruption lasting for more than four weeks combined with (i) lesions in face, elbow- or kneeflexures or (ii) high degree of itching and lesions elsewhere. The term 'atopy' in this article refers to children recorded with one or more of the diseases asthma, allergic rhinoconjunctivitis or atopic dermatitis.

Validity of the asthma questionnaire

The same questionnaire was previously used to assess atopic diseases among schoolchildren in Telemark county, Norway (4). A clinical follow–up study showed that the sensitivity and the specificity of the asthma questionnaire was high. It was concluded that the questionnaire was a useful epidemiological tool.

Reliability of the asthma questionnaire

In 1996, a reliability study was conducted among 152 of the respondents from Nordland county. The study comprised 54 cases in a restricted geographic area, with episodes of asthma the last 12 months in the 1995 survey. The 98 controls were chosen as follows. For each case, two controls were randomly selected. These were the two pupils in the same grade and of the same gender as the case, appearing closest before and after in the alphabetical order of the grade. All were paid a home visit, at which time samples were taken to investigate the indoor climate. Additionally, an asthma questionnaire identical to that used in the 1995 survey was filled in during the home visit. To estimate the reliability of our asthma questionnaire, the results from the follow-up survey were compared with those from the 1995 study by calculating the Kappa coefficient (6). Among the children recorded with asthma in the 1995 study, parents reported no asthma in the child in 6.5% of cases in the 1996 study. Among the controls, 2.2% reported a history of asthma a year later. The reliability test yielded a Kappa coefficient of 0.92.

The present survey was based on informed consent from the parents. Approval was obtained from The Norwegian Data Inspectorate and The Ethical Committee in North-Norway. All statistics were computed by SAS software package (7).

Results

Both the cumulative incidence of asthma according to our definition and the prevalence in the last 12 months were higher in Sami than in Norse children (Table 1). The differences were found both for the single question of asthma and for asthma symptoms. By adding children with symptoms to children with an affirmative answer to the question of asthma, the frequency of children with asthma according to our definition increased markedly in both study populations. However, the frequency of children with lifetime or current asthma defined by symptoms only did not differ between the Sami and Norse (data not shown).

The cumulative incidence of allergic rhinoconjunctivitis, atopic dermatitis and atopy was higher in Sami children. This was also the case when looking at the prevalence of symptoms in the last 12 months of allergic rhinoconjunctivitis and atopy (Table 2).

Table 3 presents the associations between the living conditions and ethnicity. The greatest ethnic difference in atopic disease was found for the question 'Has the child had asthma in the last 12 months?'. Consequently, the associations between living conditions and an affirmative answer to this question are included in Table 3. Only indoor dampness during winter and a wall-to-wall carpet in the child's bedroom were associated to both ethnicity and current asthma. When the association between ethnicity and current asthma was adjusted by these two risk factors, the relative risk (RR) Sami/Norse decreased to 2.12 [95% confidence interval (CI) 1.48–3.05].

Discussion

In this cross-sectional, questionnaire-based study among Sami and Norse schoolchildren in Northern Norway we found higher frequencies of parent-reported atopic diseases in children of Sami than of Norse ethnicity. The difference was

Table 1. Atopic diseases in Sami and Norse schoolchildren living in northern Norway. Cumulative incidence and symptoms in the last 12 months of asthma among Sami and Norse children with relative risk (RR) Sami/Norse adjusted by age and gender with 95% confidence interval (95% CI) of RR

	Sami %	Norse %	Sami/Norse RR	95% CI
as the child ever had asthma?	13.6	8.2	1.69	(1.33–2.15)
Does the child get a wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?	16.1	10.2	1.61	(1.29–2.01)
Asthma by definition cumulative incidence	19.1	12.3	1.57	(1.29–1.92)
as the child had asthma in the last 12 months?	6.7	2.8	2.40	(1.70–3.41)
Does the child get a wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?				
ccurrence in the last 12 months	5.5	3.6	1.57	(1.07–2.30)
Asthma by definition				
symptoms in the last 12 months	9.0	4.6	2.01	(1.48–2.73)

greatest concerning asthma in the last 12 months with a more than twofold increased risk among the children of Sami origin.

There are obvious limitations to a questionnaire-based survey in diagnosing bronchial asthma and allergy. Ideally, the diagnosis of these diseases should be made in a clinical examination by an experienced doctor. A detailed clinical history and lung-function test, skin-prick test, blood specimen sampling for serum immunoglobulin E (IgE) and radio-allergo-sorbent test (RAST) should all be investigated. When diagnosing asthma by questionnaire in epidemiological surveys, it is shown that the question 'Have you ever had asthma' is remarkably specific, although markedly insensitive (1). In order to increase the sensitivity of our asthma questionnaire, we consequently added questions concerning symptoms. The accuracy of parent reports was investigated in a survey by comparing parents' responses to a self-administered questionnaire with information extracted from pediatricians' records (8). For asthma in the last year the percentage with good agreement was 91%. It was concluded that parent reports are generally acceptable for most research purposes. The reliability test of our asthma question in the reliability study showed a high degree of agreement. We would therefore argue that misinterpretation of the asthma question by the respondents was insignificant. The description of hay fever in the questionnaire and the accompanying letter was unambiguous and a consequent high degree of sensitivity and specificity can thus be expected. Although with some minor alterations, the same questionnaire was employed to assess atopic dermatitis among schoolchildren in the community of Sør-Varanger in northern Norway (5). In a follow-up study, the clinical examination by an experienced dermatologist uncovered a considerably higher frequency of atopic dermatitis than that estimated in the questionnaire study (9). Consequently, the frequency of atopic dermatitis detected in our survey is most likely an underestimate.

The ethnic minority termed Sami is ill-defined. In Norway there is a Sami Parliament elected by people registered as Sami, mainly defined by language. The Sami and white Caucasians immigrated to the northern parts of Scandinavia from different origins and in different historical periods. Until today, the Sami have traditionally been divided in two categories: those living permanently by the seaside, and the

Table 2. Atopic diseases in Sami and Norse schoolchildren living in northern Norway. Cumulative incidence and symptoms for the last 12 months of allergic rhinoconjunctivitis/atopic dermatitis/atopy among Sami and Norse children with relative risk (RR) Sami/Norse adjusted by age and gender with 95% confidence interval (95% CI) of RR

	Sami %	Norse %	Sami/Norse RR	95% CI
Allergic rhinoconjunctivitis cumulative incidence	32.6	21.6	1.52	(1.32–1.76)
Allergic rhinoconjunctivitis symptoms in last 12 months	10.5	7.0	1.51	(1.14–1.99)
Atopic dermatitis cumulative incidence	26.7	19.2	1.39	(1.18–1.63)
Atopic dermatitis symptoms in last 12 months	6.7	5.1	1.29	(0.91–1.83)
Atopy cumulative incidence	49.4	38.8	1.28	(1.15–1.42)
Atopy symptoms in last 12 months	17.1	13.2	1.30	(1.06–1.61)

Table 3. Associations between living conditions and ethnicity/current asthma

	Sami n 491	Norse n 7781	p-value*	Response to as the child had asthma in the last 12 months? p-value**
Number of siblings (mean ± SD)	2.0 ± 1.4	1.8 ± 1.2	0.001	0.86
Building year of house (19–) (mean ± SD years)	75 ± 15	73 ± 18	0.006	0.42
Area of house (square meters) (mean ± SD)	127 ± 65	139 ± 71	0.001	0.87
Indoor dampness during winter (%)	6.7	3.0	0.001	0.001
eating the household with firewood (%)	78.4	73.9	0.027	0.25
eating the household with oil heater (%)	15.9	12.3	0.021	0.89
ow many do usually sleep in the child s bedroom? (mean ± SD)	1.3 ± 0.6	1.2 ± 0.5	0.001	0.56
Is there a wall-to-wall carpet in the child s bedroom? (%)	10.0	25.9	0.001	0.001
Does someone in the family smoke? (%)	56.6	51.6	0.035	0.70
Does the family keep animals? (%)	54.6	51.6	0.20	0.001
Does the family keep cats/dogs? (%)	46.2	41.9	0.059	0.001
Does the family keep reindeer? (%)	7.7	0	0.001	0.99

* or continuos variables p-value from anova, for categorized variables p-value from chi-square. **Associations analyzed by logistic regression.

nomads who keep reindeer. These stereotypes are today minorities as the majority of the Sami are integrated in the modern Norwegian society. However, there are today no official statistics available concerning ethnicity in Norway. Our multi-ethnic study population comprised a socio-economic comparable population that encouraged an investigation of ethnic differences in the prevalence of asthma and allergy.

In a study of atopic diseases among Norwegian Lapps by reviewing medical records, Falk found the frequency of total atopic diseases among individuals under 20 years to be comparable with other studies (10). We are not aware of other studies comparing the prevalence of asthma and allergy in Sami and white Caucasians. Several studies have explored the relationship of ethnicity with prevalence of asthma and atopy in children (11–15). A study of Inuit primary schoolchildren living in far-northern Quebec concluded that asthma and atopy were uncommon in this population (11). A prevalence study of asthma symptoms among adolescents by ethnicity in the Wellington region, New ealand, concluded that there are, at most, minor differences in asthma prevalence between Maori and non-Maori children (12). A study conducted in four rural Australian Aboriginal communities concluded that asthma in Aboriginal children was almost non-existent (13). For a study of childhood asthma among Puerto Rican Hispanics, 9 276 mothers were interviewed to ascertain whether they had asthmatic children younger than 18 years of age and asking about genetic risk factors for asthma (14). Hispanic and African–American ethnicity were found to be independent risk factors for asthma in 7 776 children. Ethnic differences in the prevalence of asthma were studied in a socio-economically homogenous, middle-class, multi-ethnic population of schoolchildren in Southfield, Michigan, USA (15). The study confirmed the hypothesis that differences in biological factors between black and white people play a role in asthma risk.

Adjusting the associations between ethnicity and current asthma by differences in living conditions only implied minor alterations in the relative risks. Hence, the present study does not explain the ethnic differences uncovered in asthma and allergy prevalence. A clinical case–control study controlling environmental risk factors is thus necessary to draw further conclusions concerning associations between ethnicity and atopic diseases in northern Norway.

Ac no led ments

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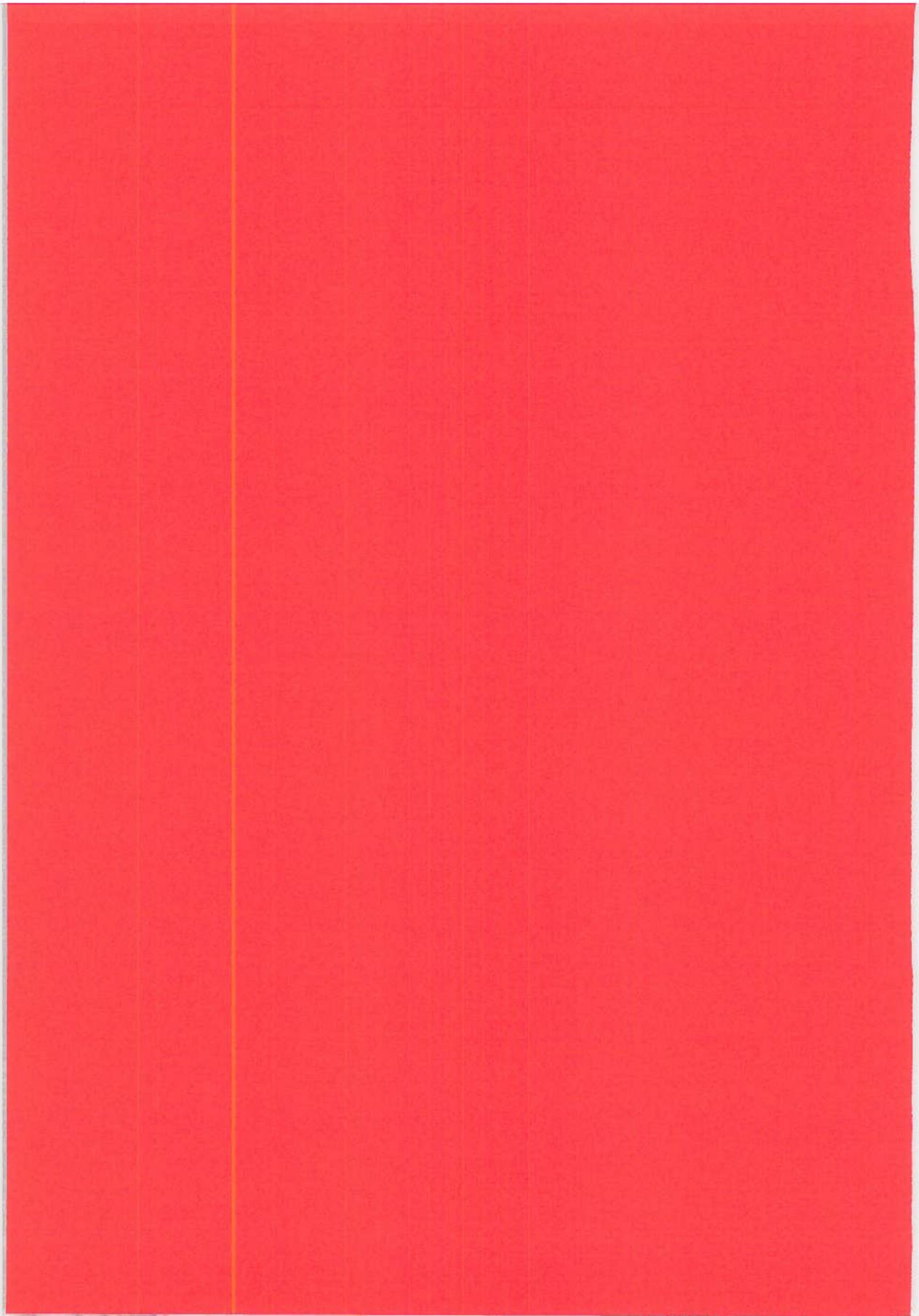
Paper IV



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Asthma and allergy in Russian and Norwegian schoolchildren: results from two questionnaire-based studies in the Kola Peninsula, Russia, and northern Norway

Previous studies have shown that the prevalence of asthma and allergy in children is lower in Eastern than Western Europe.

M We have compared the prevalence of asthma, respiratory symptoms, allergic rhinoconjunctivitis, and atopic dermatitis in schoolchildren aged 7–13 years in a questionnaire-based study conducted in the city of Nikel on the Kola Peninsula, Russia, in 1994 (*n* 1143) and another conducted in northern Norway in 1995 (*n* 8676).

R The prevalence of diagnosed asthma was 5.1% in Russian children and 8.6% in Norwegian children; RR 0.58 (95% CI: 0.44–0.76). The prevalence of all respiratory symptoms was higher in Russian children. The prevalence of allergic rhinoconjunctivitis was 16.9% in Russian children and 22.1% in Norwegian children: RR 0.74 (95% CI: 0.65–0.85). The prevalence of atopic dermatitis was 7.4% in Russian children and 19.7% in Norwegian children; RR 0.38 (95% CI: 0.31–0.46).

C We conclude that the prevalence of diagnosed asthma, allergic rhinoconjunctivitis, and atopic dermatitis was higher in Norwegian than Russian schoolchildren. The higher prevalence of respiratory symptoms in Russian children probably reflects a higher prevalence of undiagnosed, nonallergic asthma.

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ey words allergic rhinoconjunctivitis; allergy; asthma; atopic dermatitis; Norway; prevalence; respiratory symptoms; Russia; schoolchildren.

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Epidemiologic studies have shown a higher prevalence of asthma in Western than Eastern Europe (1–3). In the phase I report from the International Study of Asthma and Allergies in Childhood (ISAAC), marked variations in the prevalence of both asthma and allergy were found between the countries (4, 5). The authors suggest that the major differences are likely to be due to environmental factors. von Mutius et al. studied the prevalence of asthma, allergic rhinoconjunctivitis (AR), atopy, and bronchial hyperresponsiveness (BHR) in children 9–11 years old in West and East Germany (1). They found a higher prevalence of BHR, current asthma, and AR in the West German children than in the children in East Germany. They concluded that sensitization to aeroallergens was strikingly more frequent in West Germany than in East Germany. The prevalence of atopic sensitization and respiratory symptoms was studied in Estonian schoolchildren (2). The investigators concluded that, as in other former socialist countries of Europe, the prevalence of atopy as defined by positive skin prick tests, asthma, and respiratory symptoms, was low in Estonia.

A questionnaire-based prevalence study of asthma and allergy in schoolchildren was conducted in the city of Nikel, Russia, in 1994, and in northern Norway in 1995. Here, we compare the prevalence of asthma, respiratory symptoms, AR, and atopic dermatitis (AD) in the Russian and Norwegian schoolchildren.

aterial and methods

The questionnaire

In 1985, Bolle and Holt formulated a four-page questionnaire to assess the prevalence of asthma and allergy in schoolchildren aged 7–13 years in northern Norway (6, 7). This questionnaire has been employed in many Norwegian studies of atopic diseases in children (8–10). It focuses on asthma, AR, AD, urticaria, and food intolerance and symptoms related to these diseases (symptom-based questionnaire). It also focuses on atopic diseases in parents/siblings, and indoor/outdoor environments. The questionnaire includes an accompanying letter with a broader description of symptoms and signs of the diseases in question.

Norwegian study

In 1995, this questionnaire was distributed to primary schoolchildren in northern Norway (11). The primary schools were randomly selected within the three northernmost counties of Norway, i.e.,

Nordland, Troms, and Finnmark. The local school nurse provided the schoolchildren with questionnaires, which were filled in at home. In agreement with the respondents, the school nurse ensured that all fields were filled in before the questionnaires were returned to the Institute of Community Medicine, University of Tromsø, Norway. In the Norwegian survey, 9950 schoolchildren aged 7–13 years were included, and 8676 subjects (87.3%) returned a completed questionnaire. The Norwegian questionnaire was answered by the child's mother in 78.5% of cases and by the father in 12.3%, by both mother and father in 5.0%, by the child in 2.9%, and by others in 1.3%.

Russian study

In 1994, a similar study was conducted among all primary schoolchildren aged 7–17 years, in the city of Nikel on the Kola Peninsula, Russia. The questionnaire described above was translated into Russian by a person well acquainted with both written Norwegian and written Russian. In order to evaluate the translation, an independent translator, with medical experience, back-translated the Russian version into Norwegian. The questionnaires were filled in at home by the schoolchildren and their parents. Before delivery, the schoolteacher went through the questionnaire with the respondents to ensure that all fields were completed. There were 1800 subjects in the Russian study, and 1598 (88.8%) returned a completed questionnaire. Among these, 455 were at least 14 years old and were therefore excluded, leaving 1143 children for comparative analysis. The Russian questionnaire was answered by the child's mother in 82.0% of cases, by the father in 6.8%, by the child in 8.0%, and by others in 3.1%.

In both countries, the ratio of boys to girls was 1.0. In the statistical analysis, the children were distributed in six age groups according to school class. Because the children in the first class level (7–8 years) were on vacation by the time of the Russian study, these children represented only 5.0% of the Russian study population. The other five Russian age groups represented 16–22% each. In the Norwegian study population, the six age groups represented 15–18% each. The mean age of the Russian children (10 years) was higher than the Norwegian (9½ years) (P 0.001). The studies were based on informed consent by the parents, and the Norwegian Data Inspectorate gave the approval to file the questionnaires. The surveys were also approved by the ethics committee of northern Norway and the Regional Health Administration of Murmansk County. All statistics, including Cochran-Mantel-Haenszel statistics for 2 2 tables and linear regression, were computed by the SAS software package (12).

Definitions

An affirmative answer to the question, "Has the child ever had asthma?", will be referred to as diagnosed asthma. With the question, "Does the child suffer from wheeze, periods with cough, or attacks of shortness of breath (asthma) caused by external factors?", the questionnaire encouraged respondents to indicate what causes were responsible among the following six: animals, grass, infections, changes in weather, food, and other (external factors). AR was defined as episodic rhinorrhea associated with nasal stuffiness and sneezing in response to known or strongly suspected allergens and often accompanied by itching and lacrimation. AD was recorded in the cases of itchy eruption lasting for more than 4 weeks combined with either lesions in the face, elbow, or knee flexures, or a high degree of itching and lesions elsewhere.

Validity of the questionnaire

The questionnaire was used to assess atopic diseases among schoolchildren in Telemark County and Sør-Varanger Community, Norway (9, 13–15). Clinical follow-up studies showed that the sensitivity and the specificity of the questionnaire were high. It was concluded that the questionnaire was a useful epidemiologic tool.

Results

The prevalence of diagnosed asthma was highest in the Norwegian study population, and the relative risk was of the same magnitude for boys and girls (Table 1). On the other hand, the highest prevalence of all respiratory symptoms was found in the Russian study population. The difference between the study populations was

Table 1. Prevalence of diagnosed asthma, respiratory symptoms, allergic rhinoconjunctivitis, and atopic dermatitis in Russian and Norwegian schoolchildren; relative risk (RR) and corresponding 95% confidence interval (CI)

	Prevalence (%)				Prevalence in boys (%)				Prevalence in girls (%)			
	Country		Russia/Norway		Country		Russia/Norway		Country		Russia/Norway	
	Russia	Norway	RR[1]	95% CI	Russia	Norway	RR[2]	95% CI	Russia	Norway	RR[2]	95% CI
Diagnosed asthma												
	5.1	8 6	0.58	(0.44–0.76)	6.0	10.5	0.57	(0.40–0.81)	4.2	6.8	0.60	(0.39–0.91)
Wheeze, periods with cough or attacks with shortness of breath (asthma) caused by external factors?												
	16.3	10.6	1.52	(1.30–1.79)	15.4	12.0	1.26	(1.00–1.59)	17.3	9.2	1.86	(1.48–2.32)
Periods with shortness of breath and wheezing and/or episodes with dyspnea without this being recognized as asthma?												
	35.3	13.7	2.58	(2.32–2.87)	36.9	15.7	2.33	(2.02–2.70)	33.7	11.8	2.91	(2.49–3.40)
Periods with cough without having cold?												
	42.7	20.7	2.08	(1.90–2.28)	42.2	22.5	1.89	(1.67–2.15)	43.1	18.9	2.30	(2.03–2.62)
Episodes with shortness of breath?												
	24.5	12.4	1.95	(1.71–2.21)	26.8	14.4	1.85	(1.56–2.19)	22.1	10.5	2.08	(1.72–2.52)
Wheeze or more dyspneic compared to children of same age during exercise or in raw, cold air?												
	12.7	8.6	1.42	(1.18–1.70)	13.0	9 5	1.34	(1.04–1.72)	12.5	7.8	1.52	(1.17–1.97)
Allergic rhinoconjunctivitis												
	16.9	22.1	0.74	(0 65–0.85)	15.9	25 5	0 62	(0.51–0.75)	17.8	18.9	0.91	(0.75–1.10)
Atopic dermatitis												
	7.4	19.7	0.38	(0.31–0.46)	7.1	16.6	0.43	(0.32–0.57)	7.6	22.6	0.34	(0.26–0.44)

[1] RR adjusted by age and sex.
[2] RR adjusted by age.

Table 2. Prevalence (%) of diagnosed asthma, allergic rhinoconjunctivitis, and atopic dermatitis in Russian and Norwegian schoolchildren according to age, including rate of increase per class level and corresponding 95% confidence interval (CI) and value

		Age (years)								
		7–8	8–9	9–10	10–11	11–12	12–13	Rate of change	95% CI	value
Diagnosed asthma										
Boys	Russia	4.3	5.0	6.3	5.3	9.0	5.2	0.4	(1.1–1.8)	0.61
	Norway	10.0	12.5	10.1	9.9	9.9	10.2	0.2	(0.8–0.3)	0.46
Girls	Russia	3.9	2.0	1.0	5.7	5.8	7.3	1.3	(0.1–2.5)	0.03
	Norway	5.1	6.7	5.8	8.4	6.9	8.1	0.5	(0.1–1.0)	0.02
Allergic rhinoconjunctivitis										
Boys	Russia	23.8	13.8	14.6	17.3	22.8	9.8	0.4	(2.6–1.8)	0.73
	Norway	23.5	21.1	25.4	26.2	28.1	29.9	1.5	(0.7–2.3)	0.001
Girls	Russia	12.0	12.9	12.4	16.2	27.4	23.2	3.3	(1.1–5.6)	0.01
	Norway	13.9	19.5	19.4	20.3	20.0	21.0	1.1	(0.4–1.8)	0.01
Atopic dermatitis										
Boys	Russia	13.0	8.3	7.9	8.8	4.9	2.5	1.5	(3.0–0)	0.05
	Norway	17.1	18.8	17.9	15.6	16.1	13.1	0.8	(1.5 to 0.2)	0.01
Girls	Russia	11.1	7.8	7.6	6.5	2.1	13.8	0.2	(1.3–1.7)	0.80
	Norway	23.5	24.5	23.3	23.5	21.7	18.8	0.9	(1.6 to 0.2)	0.02

greatest in children with symptoms of asthma without the children being recognized as asthmatics. Furthermore, the greatest difference in prevalence of respiratory symptoms was found between Russian and Norwegian girls. The prevalence of AR was highest in Norwegian children although the difference between the study populations was restricted to boys. Moreover, the prevalence of AD was highest in Norwegian children, both boys and girls. In Table 2, the prevalence of diagnosed asthma, AR, and AD in the two study populations is shown by age and presented by sex. The prevalence of diagnosed asthma increased with age in both Russian and Norwegian girls. With the exception of Russian boys, the prevalence of AR increased with age, and the increase was greatest in Russian girls. The prevalence of AD decreased with age in Russian boys, and in both girls and boys of the Norwegian study population. Symptoms caused by exposure to animals and grass were more frequently reported in Norwegian than Russian children with external provoked asthma (Table 3). On the contrary, more Russian than Norwegian children experienced asthma caused by changes in the weather. Among the children with asthma symptoms caused by external factors, 52% of the Russian and 76% of the Norwegian had either AR or AD (P 0.001). Furthermore, among these same children, 32% of the Russian and 58% of the Norwegian had a mother or father with either asthma, AR, or AD (P 0.001).

Discussion

The present comparative prevalence study of asthma, respiratory symptoms, and allergy in Russian and Norwegian schoolchildren revealed higher prevalences of diagnosed asthma, AR, and AD in the Norwegian study population. However, generally, the prevalence of asthma symptoms caused by external factors and respiratory symptoms was higher in the Russian study population.

The method of translation of the Norwegian written questionnaire into Russian was not standardized according to the guidelines adopted for ISAAC (4). However, the translation involved two independent translators both familiar with the terminology of the questionnaire. Some language disagreement is inevitable, particularly in questions concerning wheeze. The public awareness of asthma may well differ in Russia and Norway. In addition, cultural differences in the threshold of reporting symptoms and the opinion of the stigma of disease may have been a source of bias. The studies we compared did not include a clinical examination, respiratory function measurements, skin prick tests, and blood specimen sampling for serum IgE and the radioallergosorbent test (RAST). Consequently, no objective measurements were available with which to label children with BHR or IgE-mediated allergy.

The prevalence of asthma is higher in boys than girls during childhood, but the sex differences in prevalence are reversed in adolescence (16, 17). In our study, this trend seemed to exist for diagnosed asthma in both Russia and Norway. The prevalence of AR is known to increase throughout the school years, as observed in our study, with the exception of Russian boys (18). The peak incidence of AD is in the pre-school age, and cessation of symptoms before adolescence is common (19). The observed decrease in AD prevalence with age in Russian boys and Norwegian children may represent an actual increase in prevalence in the youngest children. However, another explanation is simply that

Table 3 External factors associated with affirmative answer to question, Does child suffer wheeze, periods with cough, or attacks of shortness of breath (asthma) caused by external factors? , relative risk (RR), and corresponding 95% confidence interval (CI)

	Prevalence (%)				Prevalence in boys (%)				Prevalence in girls (%)			
	Country		Russia/Norway		Country		Russia/Norway		Country		Russia/Norway	
	Russia	Norway	RR[1]	95% CI	Russia	Norway	RR[2]	95% CI	Russia	Norway	RR[2]	95% CI
Animals	11.0	51.5	0.21	(0.15–0.29)	12.3	50.9	0.24	(0.16–0.38)	9.8	52.3	0.18	(0.11–0.29)
Grass	7.7	39.1	0.20	(0.13–0.30)	11.0	41.5	0.26	(0.16–0.45)	4.9	36.1	0.13	(0.06–0.25)
Infections	31.0	29.0	1.07	(0.82–1.38)	31.5	25.8	1.36	(0.92–2.01)	30.5	33.1	0.98	(0.69–1.41)
Changes in weather	37.4	27.6	1.37	(1.08–1.75)	39.7	28.8	1.38	(0.99–1.93)	35.4	26.0	1.36	(0.96–1.93)
ood	12.9	14.0	0.92	(0.60–1.43)	17.8	13.1	1.33	(0.76–2.33)	8.5	15.2	0.60	(0.29–1.24)
ther factors	29.0	28.6	1.02	(0.78–1.33)	28.8	25.2	1.10	(0.74–1.64)	29.3	32.8	0.89	(0.62–1.29)

[1] RR adjusted by age and sex.
[2] RR adjusted by age.

the AD symptoms were left out in many cases of older children who had recovered from a modest eruption many years prior to the study.

Asthma symptoms due to aeroallergens from animals and grass were more often reported in the Norwegian children. On the contrary, changes in weather provoked symptoms in a higher proportion of Russian children. In 1992, the emissions from the nickel smelters in Nikel and the neighboring city of apolyarny were about 260 000 t of SO_2 (20). The episodes with highest air pollution in the vicinity are due to meteorologic conditions characterized by high atmospheric pressure and slow ground wind during the winter (21). Among the subjects with asthma symptoms caused by external factors, the prevalence of atopic diseases in both children and parents was highest in Norway. Among the Russian children, asthma symptoms caused by external factors predominated in girls. Asthma can be divided into two forms, allergic and nonallergic, and the diagnosis of the latter is primary based upon exclusion criteria, i.e., the absence of demonstrable allergy (22, 23). Nonallergic asthma is more prevalent in girls than in boys (23, 24). Like occupational asthma, nonallergic asthma is characterized by an increased number of CD8 cells in the airway wall (24). Many epidemiologic studies have described symptom exacerbation in subjects with asthma or chronic obstructive respiratory disease in response to environmental SO_2 (25–27). A prevalence study of BHR, as determined by several methods, was conducted among Estonian schoolchildren (28). It was concluded that most children with BHR in Estonia were not atopic, in contrast to studies in Western Europe. In summary, the high prevalence of asthma symptoms caused by external factors in the Russian study population is likely to reflect a high prevalence of nonallergic asthma. Necessarily, estimating asthma prevalence in epidemiology depends on whether nonallergic asthma is labeled asthma. Consequently, we suggest that a nonallergic/allergic asthma prevalence ratio be employed when asthma prevalence in Western and Eastern Europe is compared.

Ac no led ments

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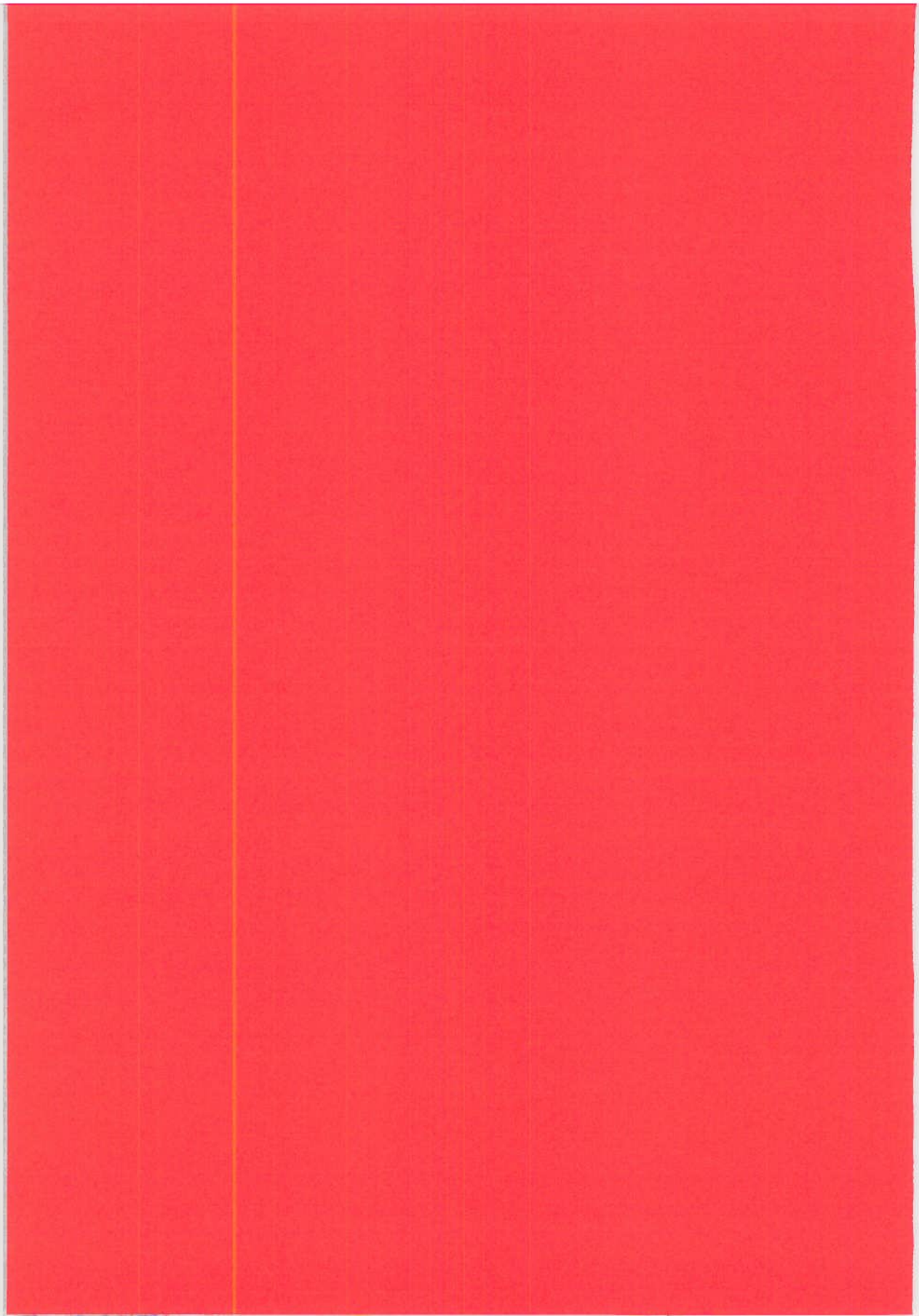
Paper V



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ORIGINAL ARTICLE

No association between serum eosinophil cationic protein and atopic dermatitis or allergic rhinitis in an unselected population of children

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ABSTRACT

Background In order to obtain background references when dealing with serum eosinophil cationic protein (s-ECP) measurements in children with allergic diseases, population-based studies are important. The objectives of our study were to explore the strength of associations between the s-ECP level and atopic dermatitis (AD), allergic rhinitis (AR) and asthma in an unselected northern Norwegian schoolchildren population.

Methods s-ECP was sampled from 396 schoolchildren aged 7–12 years from Sør-Varanger community, northern Norway as a part of a population-based study of allergy. In advance, anamnestic information concerning a history of AD, AR and asthma were obtained. The children underwent a clinical investigation, including skin prick tests and peak expiratory flow measurements, where the presence of AD, AR and asthma were evaluated. The associations of these diseases to the s-ECP values were examined in bivariate statistical analysis.

Results No statistical significant associations were detected in bivariate analysis between s-ECP and AD, AR or asthma: the mean s-ECP in children without self-reported AD/AR/asthma was 4.6 μg/L [95% confidence interval (CI) 4.0–5.2]. The mean s-ECP in children with self-reported AD or AR or asthma was 5.2 μg/L (95% CI 4.1–6.2), 4.6 μg/L (95% CI 3.5–5.7) and 6.4 μg/L (95% CI 4.4–8.3), respectively. The highest mean s-ECP level was measured in children with clinically diagnosed asthma; 7.1 μg/L (95% CI 4.0–10.3). Above the 75-percentile level of s-ECP, only 17.2% of the children had a history of asthma.

Conclusions In this unselected children population, the occurrence of AD or AR was not reflected by an increase in the s-ECP level. The s-ECP was increased in children with asthma, but was not statistically significant. Furthermore, the majority of children with high s-ECP values were not asthmatics. We conclude that the associations between s-ECP and allergic diseases are weak in an unselected population of children.

Key words: allergic rhinitis, asthma, atopic dermatitis, eosinophil cationic protein, Norway, population-based, schoolchildren

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Introduction

Atopic diseases are chronic or chronically relapsing skin and respiratory disorders, and eosinophilic inflammation is one of the hallmarks of these diseases. When activated, these cells release several mediators and among them is eosinophil cationic protein (ECP). The correlations of this mediator to atopic dermatitis (AD), allergic rhinoconjunctivitis (AR) and asthma are widely studied. Serum ECP (s-ECP) is shown to be increased in children with asthma, AR and AD.[1–3] However, in the vast majority of studies, s-ECP is measured in hospitalized children, and studies of s-ECP and asthma and allergy in unselected populations of children are few.

We present a population-based study of s-ECP and atopic diseases in schoolchildren from a community in north Norway. The aim of the study was to investigate the strength of association between mean s-ECP level and AD, AR and asthma in an unselected population of children.

Methods

From February 1992 to March 1993, a clinical follow-up study was conducted in Sør-Varanger community, northern Norway. The community comprised 575 primary school children aged 7–12 years. All children had a year in advance been enrolled in a questionnaire-based study of asthma and allergy ($n = 551$).[4] In the study presented in this paper ($n = 424$), a clinical examination of this schoolchildren population was performed, including blood sampling and skin prick test (SPT). In advance, the physician filled in a one-paged questionnaire concerning a history of asthma, AR and AD, age of onset and symptoms during the last year, and information about indoor environment and family history of allergic disease was obtained.[5,6] All information given in the questionnaires was discussed and reviewed with each child and their escort (by a dermatologist: LKD). An affirmative answer to the questions 'Have you had eczema/asthma/hay fever?' will be referred to as self-reported disease.

The diagnosis of asthma, AR and AD was made upon the results of the clinical examination and SPT. The clinical examination of the children was taken care of by an experienced dermatologist (LKD). Asthma was diagnosed if the child had had three or more recurring attacks of bronchial obstruction causing wheezing, coughing, or heavy breathing due to external factors such as animal dander, pollen, house dust or food. A pathological peak expiratory flow (PEF) was used as a parameter for a diagnosis of asthma in children reporting earlier bronchial obstruction or suspected symptoms during the clinical examination. AR is here defined as episodic rhinorrhoea associated with nasal stuffiness and sneezing in response to known or strongly suspected allergen(s) and often accompanied by lacrimation and red and itchy eyes.[6] The diagnosis of AD was made according to Hanifin and Rajka.[7] The disease severity was assessed using the score system given by Rajka and Langeland, i.e. percentage area of the body affected, severity of pruritus and the course of the eruption.[8] The course of the eruption was categorized into three levels: (i) more than 3 months of remission over a period of 1 year (mild); (ii) less than 3 months of remission over a period of 1 year (moderate); and (iii) continuous eruption (severe).

The SPT were undertaken with following allergens (Allergologisk Laboratorium A/S, Hørsholm, Denmark): house dust mite (*Dermatophagoides pteronyssinus*), animal dander (cat, dog), mugwort pollen, birch pollen, grass (Timothy) pollen, mould (*Cladosporium herbarum*), and the following food allergens: fish (cod), hen's egg, cow's milk and white flour. As a positive reference, a histamine dihydrochloride solution was used.[6] The negative control was an allergen diluent with 0.9% NaCl and 0.5% phenol. The skin was punched through a droplet of extract with a Prick Lancette 1 mm needle (Ewo care AB) on the volar side of the forearm and the reactions were recorded after 15 min. The histamine-induced weal was recorded as half the sum of the largest, plus the perpendicular diameter. The weal reactions elicited by the allergen preparation were recorded as 3+ when the weals were of the same order of size as that of the histamine reference. A 2+ reaction was half of, and a 4+ twice the histamine reaction. A reaction was considered positive if it was 2+ or greater.[9]

The blood samples for s-ECP and s-IgE measurements were collected as follows. Through a venous puncture, blood was sampled in Vacutainer® tubes and inverted five times before stored at room temperature for 30 min.[10,11] Afterwards, the tubes were centrifuged to separate the serum, which was stored at −20 °C until analysed. The values of s-ECP and s-IgE were determined using the Pharmacia CAP-system, FEIA (Pharmacia AB, Uppsala, Sweden). Concerning s-ECP, the limit of detection was 1.0 μg/L, which thus was the lowest level recorded. According to the manufacturer's recommendations, an upper limit of 180 μg/L for normal s-IgE was chosen.

Because the s-ECP distribution was skewed left and hence not normally distributed (fig. 1), all statistics were by non-parametric bivariate analysis of variance, i.e. Wilcoxon scores, and handled by the SAS software package.[12] The study was approved by the Ethical Committee of Tromsø University.

Results

The s-ECP level was measured in 396 children (47% girls) and the mean level was 4.9 μg/L (SD 5.3, 95% confidence interval 4.4–5.5). The s-ECP level was not associated neither to gender nor to age. Moreover, we did not find any statistical significant association between neither s-ECP level and SPT, nor s-ECP and s-IgE (data not shown).

There was no statistically significant association between s-ECP and asthma. However, the mean s-ECP level was elevated in asthmatics compared with non-asthmatics (Table 1) with the highest mean level detected in children with diagnosed asthma at the clinical consultation. Among the asthmatics, the mean

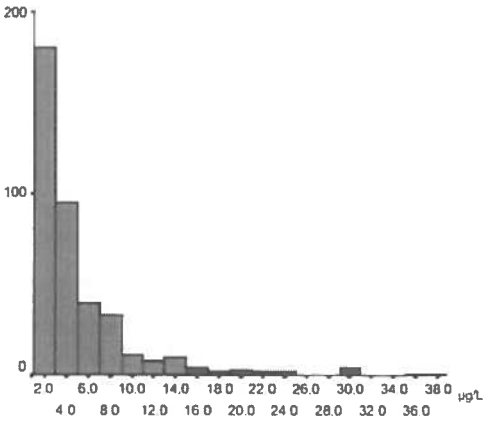

fig. 1 Histogram of s-ECP distribution.

Table 1 Mean serum eosinophil cationic protein with 95% confidence interval in children with asthma, allergic rhinoconjunctivitis (AR) and atopic dermatitis (AD)

	n	Mean (μg/L)	95% confidence interval
Self-reported asthma	49	6.4	4.4–8.3
Clinically diagnosed asthma	27	7.1	4.0–10.3
Self-reported AR	71	4.6	3.5–5.7
Clinically diagnosed AR	20	3.8	2.0–5.7
Self-reported AD	142	5.2	4.1–6.2
Clinically diagnosed AD	96	4.5	3.5–5.6
Children without self-reported asthma/AR/AD	201	4.6	4.0–5.2

s-ECP level did not differ between children with a positive and negative SPT. Above the 75-percentile (s-ECP 6.0 μg/L), only 17.2% of the children had a history of asthma.

The mean s-ECP level was neither elevated in children with self-reported AD/AR nor in children with AD/AR diagnosed at the clinical examination (Tables 2 and 3). Concerning children with AD, no associations were detected; neither between s-ECP and the severity score, nor between s-ECP and the three level course of the eruption categorization.

Discussion

In this unselected population-based study of 396 children aged 7–12 years, the occurrence of AD or AR was not reflected by an increased s-ECP level. The level of s-ECP was increased in children with asthma, but was not statistically significant. Furthermore, the majority of children with high s-ECP levels were not asthmatics.

The relationship between s-ECP measurements and the plasma coagulation process was investigated by Swedish researchers.[11] They concluded that the raised ECP levels in serum are unrelated to the coagulation process, but are due to the continuous secretion *ex vivo* of ECP from active eosinophils. The s-ECP values in this study were measured after 30 min coagulation time at room temperature before spinning. This protocol was according to the recommended standards at the time of the study.[10] The mean s-ECP level in our study is lower than in other studies where 60 min coagulation time has been used.[13] Anyway, this is compensated for by a large study population ($n = 396$ children), and we will argue that our study is descriptive of the associations that exist between s-ECP and mild AD, AR and asthma in children.

The theory that asthma is associated with an elevation of the s-ECP level is widely accepted. A population-based study of schoolchildren in Norway found significantly higher mean s-ECP level in asthmatic than non-asthmatic children.[13] However, the study did not find any difference in the s-ECP level in atopic and non-atopic asthmatic children. A study from Finland showed a corresponding decrease of the s-ECP level in patients treated with inhaled corticosteroids, indicating that decreased bronchial inflammation reflects changes in the s-ECP level.[14] The design of this clinical study focused on AD.

Table 2 Mean serum eosinophil cationic protein values in children with atopic dermatitis (AD) and non-AD, with SD and *P*-value

	n	Mean (μg/L)	SD	*P*-value
Children with a history of AD	142	5.2	6.3	NS
Children without a history of AD	254	4.8	4.7	
Children with a history of AD and without a history of asthma/AR	90	5.7	7.2	NS
Children with no history of asthma/AR/AD	201	4.6	4.2	
Children with AD at the time of investigation	96	4.5	5.1	NS
Children without AD at the time of investigation	300	5.1	5.4	
Children with AD at the time of investigation and without a history of asthma/AR	59	4.7	5.8	NS
Children with no history of asthma/AR/AD	201	4.6	4.2	

NS, not significant; AR, allergic rhinoconjunctivitis.

Table 3 Mean serum eosinophil cationic protein values in children with allergic rhinoconjunctivitis (AR) and non-AR, with SD and *P*-value

	n	Mean (μg/L)	SD	*P*-value
Children with a history of AR	71	4.6	4.6	NS
Children without a history of AR	322	5.0	5.5	
Children with a history of AR and without a history of asthma/AD	28	4.0	2.9	NS
Children with no history of asthma/AR/AD	201	4.6	4.2	
Children with AR at the time of investigation	20	3.8	3.9	NS
Children without AR at the time of investigation	376	5.0	5.4	
Children with AR at the time of investigation and without a history of asthma/AD	7	2.2	0.8	NS
Children with no history of asthma/AR/AD	203	4.6	4.2	

AD, atopic dermatitis.

Therefore, two important issues concerning asthma were left out: (i) a detailed examination of current use of inhaled corticosteroids was not recorded, and (ii) instead of spirometry and measurements of bronchial responsiveness, peak expiratory flow measurements were performed. The majority of asthmatic children in our study were treated with antiasthmatic drugs, including inhaled corticosteroids, but unfortunately, this could not be adjusted for in the statistical analysis as this confounder was not recorded. Because of these uncertainties concerning the asthma label and treatment, our results concerning associations between s-ECP and asthma must be handled with care.

Some studies have shown that AR and AD can lead to an increase in the s-ECP level.[1,3,15] In contrast, a German study comparing the Severity Scoring of Atopic Dermatitis and s-ECP level, did not find any correlation.[16] Nevertheless, a recent study from Japan reported significant elevation of the s-ECP level in patients with severe and moderate, but not mild AD.[17] In our study most children had mild symptoms with flexural dermatitis. That is, two-thirds of the children had mild AD, one-third moderate, and only three children had severe symptoms of AD.[5] The lack of association between AD and s-ECP may partly be explained by this fact.

Despite asthma and allergy, several other conditions such as parasitosis and mother's addiction to tobacco, are associated with increased s-ECP.[18] In our study population, only 17.2% of the children with s-ECP level above the 75-percentile, had a history of asthma. In order to investigate further the relevance of s-ECP measurements in children, population-based studies which include all known parameters, i.e. asthma and allergy, parasitosis, etc., is recommended. The aim of controlling all determinants of s-ECP is required to explore further the place of s-ECP measurements in childhood asthma and allergy.

It is important to remember that this study was done in an unselected children population. Most studies on s-ECP in children are undertaken in a hospital setting where it is likely to assume that the children tested have more severe asthma or allergic disease. However, in order to explore the rationale of s-ECP testing in community medicine, trials on unselected populations are essential. Our study indicates that s-ECP measurements have limited value as a screening procedure in asthma and allergy in children. Furthermore, as the associations between s-ECP and asthma are at best weak in cases of mild disease and non-existent in mild AD and AR, s-ECP measurements may be of little interest in most clinical settings concerning asthma and allergy in children in primary care.

Acknowledgements

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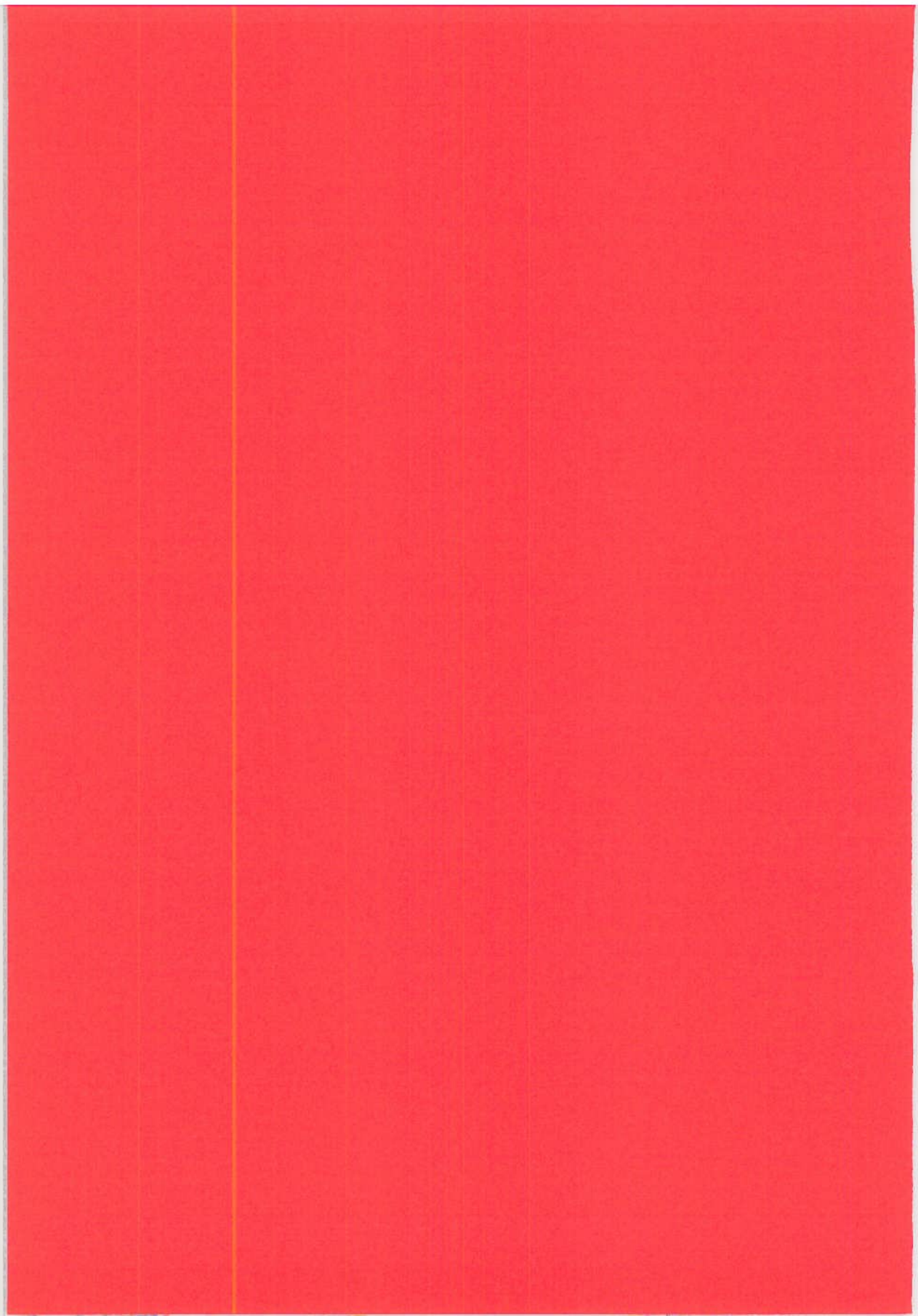
Appendix A

The Bolle-Holt –questionnaire (B-H-q); 1985- and 1995 version



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

	Ja	Nei
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).....	☐	☐

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)..... ☐

	Ja	Nei
Boligen ligger i: Sterkt trafikert område.....	☐	☐
Middels trafikert område.....	☐	☐
Lite trafikert 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

	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 ..:....	☐	☐

Ja Nei

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

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

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..... ☐ ☐

Ja

Hvis ☒, 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. bronkitt eller lungebetennelse..... Ja ☐ Nei ☐

"HØYSNUE"

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 ☐

Nei

Hvis ☒, vennligst fortsett til neste avsnitt HUDSYKDOMMER

Ja

Hvis ☒, kryss av: Nesetetthet ☐ Renning fra nesen ☐ Kløe i nesen ☐

Kløe i øynene ☐ Hovne øyne ☐ Nysing ☐

Hevelse rundt øynene ☐ Rødhet i øynene ☐ Andre ☐

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

Ja

Hvis ☒, Dyrekontakt ☐ Gress ☐ Trær ☐

Matvarer ☐ Andre ☐

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

Ja

Hvis ☒, 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

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

Ja

Hvis ☒, hvilke.....

HUDSYKDOMMER

Ja Nei

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

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

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

Ja
Hvis ☒, 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 minutter/timer og forsvinner etter timer eller dager)..... Ja ☐ Nei ☐

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

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

Ja Nei

HAR ELEVEN REAGERT PÅ MATVARER..... ☐ ☐

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

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

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

Ja Nei

Har eleven noen gang hatt andre allergiske reaksjoner..... ☐ ☐

Ja
Hvis ☒, 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..... .....
Foreldre/foresattes underskrift

Barneavdelingen
Regionsykehuset i Tromsø

Barneavdelingen
Nordland Sentralsykehus

Universitetet i Tromsø

Kjære foreldre/foresatte

Vi henvender oss til dere for å å få svar på et viktig spørsmål:
Øker astma og allergiske sykdommer blandt barn i Nord-Norge?

I 1985, nøyaktig for 10 år siden, ble det gjort samme undersøkelse.
Over 11.000 barn i tilfeldig utvalgte skolekretser i Nordland, Troms og Finnmark fikk tilsvarende spørreskjema som dere nå har fått. Det vil si over 1/4 av alle skolebarn fra og med første til og med sjette klasse i Nord-Norge. Bare noen få prosent unnlot å svare.

I vår første undersøkelse fant vi at omtrent 7-8 % av skolebarna hadde astma 16 % høysnue og 12 % eksem. Noe høyere forekomst var ikke påvist i Norge. Og det er faktisk tegn som tyder på at disse sykdommene er mest utbredt i nord.

Derfor er det særlig viktig å gjøre en slik undersøkelse i Nord-Norge.Det er viktig å finne ut om disse sykdommene øker. I neste omgang vil resultatene av undersøkelsen kunne føre til mer ressurser for å bekjempe sykdommene.

Vedlagt finner dere et spørreskjema og en konvolutt merket: TIL HELSESØSTER.
Vi håper dere vil fylle ut spørreskjemaet så fullstendig som mulig, legge det i konvolutten og returnere det senest over helgen til klasseforstander, som så leverer konvolutten uåpnet til helsesøster.

Alle opplysninger på spørreskjemaet vil bli behandlet under full taushetsplikt. Datatilsynet og regional etisk komité har gitt tillatelse til å kunne gjennomføre undersøkelsen.

Undersøkelsen er godkjent av skolemyndighetene i Nordland, Troms og Finnmark.

I a forhånd vil vi rette en hjertlig takk til alle som er med på å få undersøkelsen vel i havn!

For evt. å lette utfyllingen av spørreskjemaet har vi nedenfor beskrevet nærmere noen av sykdommene det spørres om.

Høysnue: er allergiske plager fra nese og/eller øyne. Plagene skyldes ikke bare allergi mot høy og gress, men kan være forårsaket av kontakt med dyr, husstøv, matvarer og annet.
Eksem: kommer ofte i de første leveår, er fra småbarnsalderen oftest lokalisert til albuebøyer, knehaser, håndledd og ankelledd og er ledsaget av kløe. Utslettet varer oftest i flere måneder/år. (Kontakteksem, som skyldes f.eks. nikkel, krom, vaskemidler etc., skal ikke tas med i dette spørreskjemaet, heller ikke andre hudsykdommer som psoriasis m.v.).
Elveblest: er et kløende utslett som kommer og går raskt og som gjerne flytter seg fra sted til sted.

Igjen takk for hjelpen
vennlig hilsen

Roald Bolle
overlege/allergolog, RITØ

Jan Holt
avd.overlege, NSS

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 helsemyndigheter er opptatt av å finne et mål for og årsakene til økningen for å kunne forebygge. Dette spørreskjemaet er et ledd i denne satsingen, 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 medvirker.

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

---

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 ☐

TRYKK: TROMS TRYKK AS, TROMSØ

LUNGESYKDOMMER

VIKTIG! Hvis JA - kryss av her hvis slike plager har meldt seg siste 12 måneder

	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)	☐	☐	☐

<u>Hvis NEI, vennligst fortsett til neste avsnitt HUDSYKDOMMER</u>

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

VIKTIG! Hvis JA - kryss av her hvis slike plager har meldt seg siste 12 måneder ☐

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 ☐ Albuebøyer ☐

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

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) Ja ☐ Nei ☐

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	☐	☐

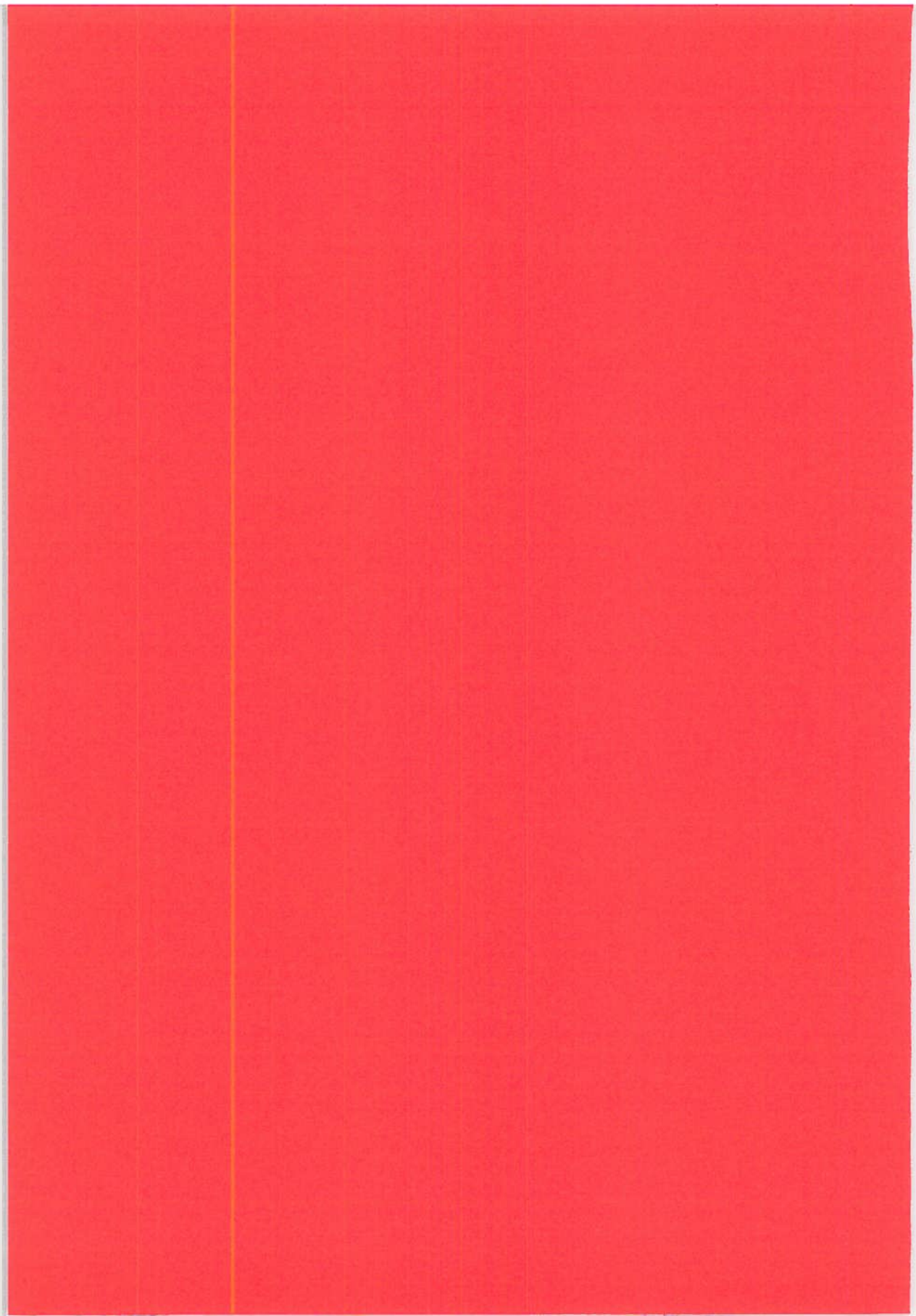
Eventuelle kommentarer eller tilføyelser:

.....

.....

Appendix B

Pages from the ISAAC questionnaire employed in Paper II



Vi bryr oss - sammen tar vi ansvar

RiTø
Regionsykehuset i Tromso
Et sykehus i utvikling

FOLKEHELSA
Statens Institutt for Folkehelse

Luftveislidelser og allergi blant barn

Kjære foreldre/foresatte

Regionsykehuset og Universitetet i Tromsø gjennomfører i samarbeid med Statens institutt for folkehelse en undersøkelse om luftveisproblemer og allergi blant skolebarn. Undersøkelsen er en del av et stort europeisk prosjekt hvor mange land gjennomfører den samme studien. For Norge deltar skolebarn fra Troms og Finmark. Hensikten er å finne årsakene til luftveisproblemer og allergi hos barn.

Vi håper at alle slutter opp om denne undersøkelsen, fordi høy svarprosent og nøyaktig utfylte skjema er nødvendig for at undersøkelsen skal lykkes.

Spørreskjemaet som dere skal besvare blir brukt i alle land som deltar i undersøkelsen. Noen spørsmål kan virke ganske like, og vi beklager at enkelte ord og uttrykk går igjen på denne måten. Det er imidlertid viktig å få klarhet i hvordan ulike spørsmål gir oss opplysninger om luftveislidelser og allergi. Dere får svare så nøyaktig som mulig på alle spørsmålene.

Alle opplysninger vil bli behandlet med taushetsplikt i samsvar med Datatilsynets retningslinjer. Det vil ikke bli offentliggjort opplysninger som kan føres tilbake til det enkelte barn.

Barnets fødselsnummer blir registret slik at vi kan undersøke hvordan forhold omkring svangerskap og barnets fødsel kan påvirke utviklingen av luftveislidelser og allergi. De opplysningene som blir brukt er kun de som vanligvis blir registrert på sykehusets fødeavdeling. Av disse kan nevnes lengde, fødselsvekt og hodeomkrets.

Når du har svart på spørreskjemaet, legger du det i den vedlagte konvolutten som limes igjen. Konvolutten leveres klassestyrer på skolen innen en uke.

Skjemaet skal leses av en maskin. Det er derfor viktig at du legger vekt på følgende ved utfylling: Bruk blå eller sort kulepenn. Sett tydelige kryss og skriv med store bokstaver (blokkbokstaver).

Alle som deltar i undersøkelsen er med i et lotteri på en reise til en verdi av 10 000 kroner.

På forhånd takk for hjelpen!

Vennlig hilsen

Roald Bolle
Regionssykehuset i Tromsø

Wenche Nystad
Statens institutt for folkehelse

0003337

I dette spørreskjemaet vil **"barnet"** bety det barnet som deltar i undersøkelsen og som bragte spørreskjemaet hjem fra skolen. Vennligst svar på spørsmålene ved å krysse av i passende boks eller skriv i rubrikken som er ment for dette.

1. **Er barnet gutt eller pike?**
   ☐ Gutt ☐ Pike

2. **Hvor høy er barnet?** ☐☐☐ *cm*

3. **Hvor mye veier barnet?** ☐☐ *kg*

4. **Når er barnet født?** *(Skriv hele fodselsnummeret)*
   ☐☐ ☐☐ ☐☐ ☐☐☐☐☐
   Dag Mnd År

5. **Er barnet født i Norge?**
   ☐ Ja ☐ Nei
   Hvis nei, i hvilket land? ☐

6. **I hvilket år er barnets mor født?** ☐☐☐☐

7. **Er hun født i Norge?**
   ☐ Ja ☐ Nei
   Hvis nei, hvilket land er hun født i? ☐

8. **I hvilket år er barnets far født?** ☐☐☐☐

9. **Er han født i Norge?**
   ☐ Ja ☐ Nei
   Hvis nei, hvilket land er han født i? ☐

10. **I hvor mange år har barnets foreldre gått på skole eller tatt annen utdanning?**

	Mor	Far
Grunnskole og videregående skoler	☐☐ *år*	☐☐ *år*
Universitet/høyskole	☐☐ *år*	☐☐ *år*
Antall år totalt:	☐☐ *år*	☐☐ *år*

Pusteproblemer

11. **Har barnet noen gang hatt tung pust, tetthet eller piping i brystet ?**
    ☐ Ja ☐ Nei
    HVIS DU HAR SVART "NEI ", VENNLIGST HOPP TIL SPØRSMÅL 16.

12. **Har barnet hatt tung pust, tetthet eller piping i brystet i de siste 12 månedene?**
    ☐ Ja ☐ Nei
    HVIS DU HAR SVART "NEI", VENNLIGST HOPP TIL SPØRSMÅL 16.

13. **Hvor mange anfall med tung pust/tetthet har barnet hatt i de siste 12 månedene?**
    ☐ Ingen ☐ 4 til 12
    ☐ 1 til 3 ☐ Mer enn 12

14. **I de siste 12 månedene; hvor ofte, i gjennomsnitt, har barnets søvn blitt forstyrret på grunn av tung pust/tetthet?**
    ☐ Har aldri våknet på grunn av tung pust/tetthet
    ☐ Mindre enn en natt per uke
    ☐ En eller flere netter per uke

15. **I de siste 12 månedene; har tung pust/tetthet noen gang vært så alvorlig at barnet har hatt problemer med å snakke slik at hun/han bare kunne si ett eller to ord av gangen mellom hvert pust?**
    ☐ Ja ☐ Nei

16. **Har barnet noen gang hatt astma?**
    ☐ Ja ☐ Nei

17. **I de siste 12 måneder; har barnet hørtes tungpusten eller tett ut under eller etter fysisk aktivitet?**
    ☐ Ja ☐ Nei

18. **I de siste 12 måneder; har barnet hatt tørr hoste om natten uten å være forkjølet eller ha andre luftvelsinfeksjoner?**
    ☐ Ja ☐ Nei

Nese- og øyeplager

19. **Har barnet noen gang hatt problemer med nysing, rennende eller tett nese, når han/hun IKKE HADDE forkjølelse eller influensa?**
    ☐ Ja ☐ Nei
    HVIS DU HAR SVART "NEI", VENNLIGST HOPP TIL SPØRSMÅL 24

20. I de siste 12 måneder; har barnet hatt problemer med nysing, rennende eller tett nese når han/hun IKKE HADDE forkjølelse eller influensa?
(1) ☐ Ja (2) ☐ Nei

HVIS DU HAR SVART "NEI", VENNLIGST HOPP TIL SPØRSMÅL 24

21. I de siste 12 måneder; har neseproblemet vært ledsaget av kløende, rennende øyne?
(1) ☐ Ja (2) ☐ Nei

22. I hvilke(n) av de siste 12 måneder har barnet hatt neseproblemene?
23-33
(Vennligst kryss av hvilke som passer)
(1) ☐ Januar ☐ Mai ☐ September
☐ Februar ☐ Juni ☐ Oktober
☐ Mars ☐ Juli ☐ November
☐ April ☐ August (12) ☐ Desember

(34) 23. I de siste 12 måneder: hvor mye har dette neseproblemet virket inn på barnets daglige aktiviteter?
(1) ☐ Ikke i det hele tatt
(2) ☐ Litt
(3) ☐ Moderat
(4) ☐ Mye

(35) 24. Har barnet noen gang hatt høysnue?
(1) ☐ Ja (2) ☐ Nei

(36) 25. Her barnet hatt perioder med plager fra nese og eller øyne som f. eks. renning fra nesen, nesetetthet, nysing, nysing, kløe I nese/øyne, hovne øyne, "røde øyne"?
(1) ☐ Ja (2) ☐ Nei

Hudplager

26. Har barnet noen gang hatt kløende utslett som har kommet og gått i minst seks måneder?
(1) ☐ Ja (2) ☐ Nei

HVIS DU HAR SVART "NEI", VENNLIGST HOPP TIL SPØRSMÅL 32

27. Har barnet hatt dette kløende utslettet noen gang de siste 12 måneder?
(1) ☐ Ja (2) ☐ Nei

HVIS DU HAR SVART "NEI", VENNLIGST HOPP TIL SPØRSMÅL 31

28. Har dette kløende utslettet noen gang sittet på noen av de følgende stedene: i albuene, bak knærne, foran på anklene, under baken, eller rundt halsen, ørene eller øynene?
(1) ☐ Ja (2) ☐ Nei

29. I hvilken alder oppsto dette utslettet første gang?
(1) ☐ Under 2 år
(2) ☐ 2 - 4 år
(3) ☐ 5 år eller mer

30. Har dette utslettet blitt helt borte noen gang i de siste 12 månedene ?
☐ Ja ☐ Nei

31. I de siste 12 månedene, hvor ofte i gjennomsnitt, har barnet vært våken om natten på grunn av dette kløende utslettet?
(1) ☐ Aldri i de siste 12 måneder
(2) ☐ Mindre enn en natt per uke
(3) ☐ En eller flere netter per uke

32. Har barnet noen gang hatt eksem?
(1) ☐ Ja (2) ☐ Nei

33. Har barnet hatt utslett som har vart mer enn 4 uker?
(1) ☐ Ja (2) ☐ Nei
b) (1) ☐ Hvis ja, kryss av i denne boksen hvis slike plager har meldt seg de siste 12 måneder

c) 34. Hvis ja, på spørsmål 33, var det med:
(1) ☒ Mye kløe
(2) ☐ Lite kløe
(3) ☐ Ikke kløe

b) Kryss av for hvor utslettet var lokalisert:
(1) ☒ Ansikt (4) ☐ Rygg
(2) ☐ Mage (5) ☒ Knehaser
(3) ☒ Albuebøyer (6) ☐ Andre steder

c) Hvor gammel var barnet da utslettet begynte? ☐☐ *år*

Hoste

35. I de siste 12 månedene: har barnet vanligvis virket tett i brystet eller hostet opp slim ved forkjølelse?
(1) ☐ Ja (2) ☐ Nei

36. I de siste 12 månedene: har barnet vanligvis virket tett i brystet eller hostet opp slim når han /hun ikke var forkjølet?
(1) ☐ Ja (2) ☐ Nei

HVIS DU HAR SVART "NEI" PÅ BEGGE SPØRSMÅLENE, VENNLIGST HOPP OVER SPØRSMÅL 37 OG 38

37. **Er barnet tett i brystet eller hoster opp slim de fleste dager (4 eller flere dager i uken), så lenge som 3 måneder i året?**
☐ Ja ☐ Nei
HVIS DU HAR SVART "NEI", VENNLIGST HOPP OVER SPØRSMÅL 38

38. **I hvor mange år har dette skjedd?**
☐☐ *År*

Spebarnstiden

39. **Hvor mye veide barnet ved fødsel?**
☐ Mindre enn 1500 g
☐ 1500 – 1999 g
☐ 2000 – 2499 g
☐ 2500 – 3499 g
☐ Mer enn 3500 g
☐ Vet ikke

40. **Var barnet født innenfor 3 uker av antatt termin?**
☐ Ja
☐ Nei, mer enn 3 uker tidligere
☐ Nei, mer enn 3 uker senere
☐ Vet ikke

41. **Er barnet tvilling?**
☐ Ja ☐ Nei

42. **Ble barnet ammet?**
☐ Ja ☐ Nei

Hvis ja, hvor lenge?
☐ Mindre enn 6 måneder
☐ 6-12 måneder
☐ Mer enn et år

Hvis ja, hvor lenge ble barnet ammet uten å få morsmelktillegg, annen mat eller juice i kosten?
☐ Mindre enn 2 måneder
☐ 2 - 4 måneder
☐ 5 - 6 måneder
☐ Mer enn 6 måneder

43. **Har barnet eldre brødre eller søstre?**
☐ Ja ☐ Nei
Hvis ja, hvor mange eldre brødre? ☐☐
hvor mange eldre søstre? ☐☐

44. **Har barnet yngre brødre eller søstre?**
☐ Ja ☐ Nei
Hvis ja, hvor mange yngre brødre? ☐☐
Hvor mange yngre søstre? ☐☐

45. **Har barnet noen gang gått hos dagmamma eller i spebarnstue?**
☐ Ja ☐ Nei
Hvis ja, fra hvilken alder? ☐☐ *år* ☐☐ *mnd*
Antall dager per uke: ☐

46. **Har barnet noen gang gått i barnehage?**
☐ Ja ☐ Nei
Hvis ja, fra hvilken alder? ☐☐ *år* ☐☐ *mnd*
Antall dager per uke: ☐

Sykdom og vaksinasjon

47. **Har barnets mor noen gang hatt en eller flere av de følgende sykdommene?**
(merk av i de boksene som er aktuelle)
☐ Astma
☐ Høysnue
☐ Eksem

48. **Har barnets far noen gang hatt en eller flere av de følgende sykdommene?**
(merk av i de boksene som er aktuelle)
☐ Astma
☐ Høysnue
☐ Eksem

49. **Har barnet blitt vaksinert mot en eller flere av de følgende sykdommene?**
(merk av i de boksene som er aktuelle)
☐ Kikhoste (Pertussis) (alene eller i kombinasjon med difteri og stivkrampe)
☐ Meslinger (alene eller i kombinasjon med kusma og røde hunder)
☐ Tuberkulose/BCG

50. **Har barnet noen gang hatt en eller flere av de følgende sykdommene?**
(merk av i de boksene som er aktuelle)
☐ Meslinger
☐ Kikhoste
☐ Tuberkulose
☐ Innvollsorm (eks bendelorm)

51. Har barnet hatt noen av følgende sykdommer i løpet av de siste 12 måneder og i tilfelle hvor mange ganger?

	Nei	Ja	Antall
Forkjølelse	☐	☐	☐☐
Halsbetennelse	☐	☐	☐☐
Bronkitt	☐	☐	☐☐
Lungebetennelse	☐	☐	☐☐
Ørebetennelse	☐	☐	☐☐

⊥

52. Har barnet noen gang:

	Ja	Nei	Hvor gammelt var barnet
Fjernet mandlene	☐	☐	☐☐ år
Fjernet den falske mandelen	☐	☐	☐☐ år
Stukket hull på trommehinnen	☐	☐	☐☐ år
Lagt inn dren i trommehinnen	☐	☐	☐☐ år

53. Har barnet noen gang hatt følgende sykdommer? Hvis ja, har sykdommen blitt bekreftet av lege og har barnet hatt symptomer de siste 12 måneder? *(Kryss av)*

	Har hatt sykdom (1) Ja	Nei	Bekreftet av lege (2) Ja	Nei	Symptomer siste 12 mnd (3) Ja	Nei
a 1-3 Astma	(1) ☐	(2) ☐	(1) ☐	(2) ☐	(1) ☐	(2) ☐
b 1-3 Høysnue	(1) ☐	(2) ☐	(1) ☐	(2) ☐	(1) ☐	(2) ☐
c 1-3 Reaksjon på mat (matvareallergi)	(1) ☐	(2) ☐	(1) ☐	(2) ☐	(1) ☐	(2) ☐
d 1-3 Annen allergi	(1) ☐	(2) ☐	(1) ☐	(2) ☐	(1) ☐	(2) ☐

54. Hvis barnet har hatt astma, når hadde barnet astma første gang og når ble barnet eventuelt kvitt astmaen?

a) Første gang Alder: ☐☐ år b) Kvitt astmaen ☐☐ år

⊥

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

a) (1) ☐ Ja (2) ☐ Nei

a=2) (1) ☐ Hvis ja, kryss av i denne boksen hvis slike plager har meldt seg de siste 12 måneder

Hvis ja, kryss av for hvilke faktorer:

a) 3 ☐ Dyr a) 6 ☐ værforandringer
a) 4 ☐ Gress a) 7 ☐ Matvarer
a) 5 ☐ Infeksjoner a) 8 ☐ Andre

Ditt hjem

I denne delen spør vi spørsmål om barnets hjem. For hvert spørsmål, vennligst gi svar for det hjemmet der barnet bor for tiden, og for det hjemmet hvor barnet bodde det første leveåret (hvis du har flyttet, vennligst velg det hjemmet hvor barnet tilbrakte mesteparten av tiden første leveår). Vennligst vær sikker på at du merker av i begge kolonner!

56. Deler eller delte barnet soverom med andre mennesker? (voksne eller barn)

	For tiden	I barnets første leveår
Ja	☐	☐
Nei	☐	☐

57. Hvilke av de følgende kjæledyr har du eller hadde du i barnets hjem?

	For tiden	I barnets første leveår
Hund	☐	☐
Katt	☐	☐
Annet kjæledyr med pels	☐	☐
Fugl	☐	☐
Annet	☐	☐

⊥

58. Har eller hadde barnet kontakt med noen av de følgende dyrene utenfor hjemmet, minst en gang i uken?

	For tiden	I barnets første leveår
Hund	☐	☐
Katt	☐	☐
Husdyr (gård)	☐	☐
Andre dyr	☐	☐

59. Røyker eller røykte mor til barnet?

	For tiden	I barnets første leveår	Under graviditeten
Ja	☐	☐	☐
Nei	☐	☐	☐

60. Er det noen som for tiden røyker inne i barnets hjem?

☐ Ja ☐ Nei

Hvis ja, hvor mange sigaretter totalt røykes det per dag i ditt barns hjem?
(f.eks: mor røyker 4+ far røyker 5 + andre personer røyker 3 = 12 sigaretter)

☐ Mindre enn 10 sigaretter
☐ 10 - 20 sigaretter
☐ Mer enn 20 sigaretter ⊥

61. **Hva slags brensel benytter eller benyttet du for å lage mat?** For tiden pluss barnets første leveår!
(merk av i de boksene som er aktuelle)

	For tiden	I barnets første leveår
Elektrisitet	☐	☐
Gass	☐	☐
Kull/vedfyring	☐	☐
Annet	☐	☐

62. **Hvordan er eller var barnets hjem varmet opp?** For tiden pluss barnets første leveår
(Merk av de *boksene som er aktuelle)*

	For tiden	I barnets første leveår
En peis, ovn eller fyrkjele inne i huset	☐	☐
Mer enn en peis, ovn eller fyrkjele inne i huset	☐	☐
En peis, ovn eller fyrkjele utenfor huset	☐	☐
Er ikke oppvarmet	☐	☐

63. **Hvilken type brensel bruker du eller brukte du til oppvarming?** *(merk av i de boksene som er aktuelle)*

	For tiden	I barnets første leveår
Gass	☐	☐
Olje	☐	☐
Parafin	☐	☐
Elektrisitet	☐	☐
Kull eller koks	☐	☐
Ved	☐	☐
Annet	☐	☐

64. **Har eller hadde barnets hjem ventilasjonsanlegg?**

	For tiden	I barnets første leveår
Ja	☐	☐
Nei	☐	☐

65. **Har eller hadde barnets hjem fuktige flekker på vegger eller tak?**

	For tiden	I barnets første leveår
Ja	☐	☐
Nei	☐	☐

66. **Har eller har det vært vannlekkasje i barnets hjem?**

	For tiden	I barnets første leveår
Ja	☐	☐
Nei	☐	☐

67. **Har eller hadde barnets hjem synlig mugg eller sopp på vegger eller tak?**

	For tiden	I barnets første leveår
Ja	☐	☐
Nei	☐	☐

68. **Er det vanlig med fukt på vinduene om vinteren?**
☐ Ja ☐ Nei

69. **Hva slags gulvbelegg er eller var det i barnets soverom?**

	For tiden	I barnets første leveår
Vegg til vegg teppe	☐	☐
Løse tepper/ryer	☐	☐
Bart gulv/parkett	☐	☐
Tregulv/furu	☐	☐
Vinyl (PVC plast)	☐	☐
Linoleum	☐	☐

70. **Hva slags vinduer er eller var det i barnets soverom?**

	For tiden	I barnets første leveår
Enkelt vinduer	☐	☐
Dobbelt vinduer	☐	☐
Thermovinduer	☐	☐
Ingen vinduer	☐	☐

71. **Hva slags pute bruker eller brukte barnet?**
(merk av i de boksene som er aktuelle)

	For tiden	I barnets første leveår
Skumgummi	☐	☐
Syntetiske fibre	☐	☐
Fjær/dun	☐	☐
Annet	☐	☐
Bruker ikke pute	☐	☐

72. **Hva slags sengetøy bruker eller brukte barnet?** *(merk av i de boksene som er aktuelle)*

	For tiden	I barnets første leveår
Syntetiske dyne	☐	☐
Dundyne	☐	☐
Tepper	☐	☐
Annet materiale	☐	☐

73. Har du gjort noen forandringer i hjemmet på grunn av barnetss astma eller allergi-problemer? *(merk av i de boksene som er aktuelle)*

	Ja	Nei	Hvis ja, hvor gammelt var barnet?
Fjernet kjæledyr	☐	☐	☐☐ år
Sluttet eller redusert røyking	☐	☐	☐☐ år
Skiftet puter	☐	☐	☐☐ år
Skiftet sengetøy	☐	☐	☐☐ år
Skiftet gulvbelegg	☐	☐	☐☐ år
Andre forandringer	☐	☐	☐☐ år

Beskriv: ☐

74. Utenfor skoletid, hvor ofte driver barnet så mye fysisk aktivitet, at han/hun blir andpusten eller svett? *(kryss av)*

- ☐ Hver dag
- ☐ 4-6 ganger i uken
- ☐ 2-3 ganger i uken
- ☐ En gang i uken
- ☐ En gang i måneden
- ☐ Mindre enn en gang i måneden

75. Er barnet medlem i et idrettslag?

☐ Ja ☐ Nei

76. Hvordan vil du beskrive omgivelsene til barnets hjem?

	For tiden	I barnets første leveår
Landlig, åpent landskap med jorder i nærheten	☐	☐
Landlig, åpent landskap i nærheten av kysten	☐	☐
I sentrum/tettsted i innlandet	☐	☐
I sentrum/tettsted ved kysten	☐	☐

77. Hva er navnet på gaten barnet bor i?

☐

78. Hva er postnummeret der barnet bor?

☐☐☐☐

Kosthold

79. Hva fikk barnet å drikke første leveuke? *(Sett ett eller flere kryss)*

- ☐ Brystmelk
- ☐ Vann
- ☐ Sukkervann
- ☐ Morsmelkerstatning
- ☐ Vet ikke/husker ikke
- ☐ Annet, hva? _____

80. Hvor ofte, i gjennomsnitt, spiser eller drikker barnet det følgende, for tiden?

	Aldri	Mindre enn 1 gang i uken	1 - 2g i uken	3 - 6g i uken	Daglig/ oftere
Kjott	☐	☐	☐	☐	☐
Fisk	☐	☐	☐	☐	☐
Frisk frukt	☐	☐	☐	☐	☐
Rå, grønne grønnsaker	☐	☐	☐	☐	☐
Kokte, grønne grønnsaker	☐	☐	☐	☐	☐
Andre rå grønnsaker	☐	☐	☐	☐	☐
Hamburger	☐	☐	☐	☐	☐
Frukt juice	☐	☐	☐	☐	☐
Mineralvann/ brus	☐	☐	☐	☐	☐

81. Hva fikk barnet å drikke det første leveåret? *(Sett ett eller flere kryss for hver måned)*

Melketype: ⊥	0-1 mnd	1-3 mnd	3-6 mnd	6- 12 mnd
Barnet fikk bare brystmelk i følgene måneder	☐	☐	☐	☐
Morsmelkerstatning (NAN eller andre) ble gitt I følgende måneder	☐	☐	☐	☐
Barnet fikk en hjemmelaget blanding av kumelk	☐	☐	☐	☐
Barnet fikk helmelk, lettmelk eller skummet melk	☐	☐	☐	☐
Barnet fikk kulturmelk, yoghurt, annen surmelk	☐	☐	☐	☐
Annen melk, hva? _____	☐	☐	☐	☐

⊥

82. Hva drikker barnet for tiden vanligvis av følgende? *(Sett ett kryss per linje)*

	Aldri/sjelden	1-3 ganger i måneden	1-3 ganger per uke	4-6 ganger per uke	Minst en gang daglig
Vann	☐	☐	☐	☐	☐
Te (urt-, nype-, vanlig te)	☐	☐	☐	☐	☐
Saft , alle typer	☐	☐	☐	☐	☐
Cola, brus, alle typer	☐	☐	☐	☐	☐
Juice (appelsin, eple etc)	☐	☐	☐	☐	☐
Melk, hel, lett, skummet	☐	☐	☐	☐	☐
Kefir, kulturmelk, yoghurt	☐	☐	☐	☐	☐
Cultura, Biola	☐	☐	☐	☐	☐

83. Hvor ofte i gjennomsnitt tar eller tok barnet tran eller fiskeoljekapsler?

	For tiden	I barnets første leveår
Aldri	☐	☐
Sjeldnere enn 1 gang i uken	☐	☐
1 gang i uken	☐	☐
2 ganger i uken	☐	☐
3 ganger i uken	☐	☐
4 ganger i uken eller oftere	☐	☐

84. Får eller fikk barnet daglig kosttilskudd (C vitamin, Sanasol, Biovit, Tran)?

⊥	For tiden	I barnets første leveår
Ingen tilskudd	☐	☐
C vitamin	☐	☐
Sanasol	☐	☐
Biovit	☐	☐
Tran	☐	☐
Annet (vennlist spesifiser):	☐	☐

85. Hva spiser barnet vanligvis for tiden av følgende? *(Sett ett kryss per linje)*

	Sjelden/ aldri	1-3 ganger i måneden	1-3 ganger per uke	4-6 ganger per uke	Minst en gang daglig
Loff, fint brød (inkludert fine rundstykker, pitabrød, lyst knekkebrød)	☐	☐	☐	☐	☐
Mellomgrovt eller grovt brød, f.eks kneipp, hjemmebakt , mørkt knekkebrød ⊥	☐	☐	☐	☐	☐
Cornflakes, puffet ris, honnikorn	☐	☐	☐	☐	☐
Kornblanding, havregrøt	☐	☐	☐	☐	☐
Grønnsaker med sterk grønn farge (brokkoli, Spinat, erter etc)	☐	☐	☐	☐	☐
Kinakål, salat, blandet salat	☐	☐	☐	☐	☐
Gulrot, kålrot	☐	☐	☐	☐	☐
Poteter	☐	☐	☐	☐	☐
Blomkål, hodekål, rosenkål, annen kål	☐	☐	☐	☐	☐
Grønnsakblandinger	☐	☐	☐	☐	☐
Løk, hvitløk	☐	☐	☐	☐	☐
Eple, banan, annen frukt	☐	☐	☐	☐	☐

Fortsettelse fra forrige side, spørsmål 85 ⊥	Sjelden/ aldri	1-3 ganger i måneden	1-3 ganger per uke	4-6 ganger per uke	Minst en gang daglig
Appelsin, grapefrukt	☐	☐	☐	☐	☐
Pølser, hamburgere, kjøttkaker etc, (kjøttretter med spedd kjøtt)	☐	☐	☐	☐	☐
Biff, koteletter, steik etc (kjøttretter uten utspedning)	☐	☐	☐	☐	☐
Retter med reinsdyr-kjøtt, elg, rype	☐	☐	☐	☐	☐
Lungemos, lever, blodmat	☐	☐	☐	☐	☐
Kylling, høne	☐	☐	☐	☐	☐
Fiskekaker, fiskeboller og liknende	☐	☐	☐	☐	☐
Torsk, sei, hyse, uer, steinbitt	☐	☐	☐	☐	☐
Sild, ørret, laks, makrell, kveite	☐	☐	☐	☐	☐
Retter med erter/bønner/linser	☐	☐	☐	☐	☐
Vegetarretter eller retter med mest grønnsaker	☐	☐	☐	☐	☐
Kaker, wienerbrød el.l. søte kjeks	☐	☐	☐	☐	☐
Boller, søt gjærbakst	☐	☐	☐	☐	☐
Sjokolade, alle typer	☐	☐	☐	☐	☐
Smågodt	☐	☐	☐	☐	☐
Tørket frukt (rosiner, fiken osv)	☐	☐	☐	☐	☐
Egg, mås-egg	☐	☐	☐	☐	☐

⊥

86. Hva slags fett får barnet for tiden i seg?

	Smør	Hard margarin	Myk margarin	Oljer	Bruker ikke
På brødet	☐	☐	☐	☐	☐
I matlagningen	☐	☐	☐	☐	☐

87. Hvem har svart på dette spørreskjemaet?

(1) ☐ Far
(2) ☐ Mor
(3) ☐ Annen person

88. Når ble spørreskjemaet besvart?

☐☐ ☐☐ ☐☐
Dag *Måned* *År*

89. Har to eller flere av besteforeldrene hatt finsk som morsmål?

(1) ☐ Ja (2) ☐ Nei

90. Har to eller flere av besteforeldrene hatt samisk som morsmål?

(1) ☐ Ja (2) ☐ Nei

⊥

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.

Prosjektet har også en del II som inkluderer allergitesting. Hvis barnet blir trukket ut til å være med i del II, kan vi få lov til å kontakte dere?

☐ Ja ☐ Nei

Neste del av spørreskjemaet Del II, skal kun besvares av dere som har barn med pusteproblemer (tung pust, tetthet, åndenød), astma, nese-,øyeplager eller eksem

⊥

Tusen takk for hjelpen

Del II besvares kun av dere som har barn med pusteproblemer (tung pust, tetthet, åndenød), astma, nese-, øyeplager eller eksem

Tung pust, tetthet og åndenød

91. I de siste 12 månedene: har barnet vært tungpusten eller tett under eller etter fysisk aktivitet?
☐ Ja ☐ Nei

92. I de siste 12 månedene: har barnet vært tungpusten eller tett når han eller hun ikke nylig har vært fysisk aktiv?
☐ Ja ☐ Nei

93. I de siste 12 månedene: har barnet hatt tung pust, tetthet eller piping i brystet når han/hun var forkjølet eller hadde influensa?
☐ Ja ☐ Nei

94. I de siste 12 månedene: har barnet hatt tung pust, tetthet eller piping i brystet når han/hun ikke var forkjølet eller hadde influensa?
☐ Ja ☐ Nei

95. Har barnet ditt noen gang våknet opp med åndenød?
☐ Ja ☐ Nei

96. Har barnet ditt noen gang våknet opp med tetthet i brystet?
☐ Ja ☐ Nei

97. I de siste 12 månedene: hva har gjort barnets tungpustenhet/tetthet verre?

☐ Vær	☐ Ullklær
☐ Pollen	☐ Forkjølelse eller influensa
☐ Følelser	☐ Sigarettrøyk
☐ Avgasser/røyk	☐ Mat eller drikke
☐ Støv	☐ Såpe, sprayer, vaskemidler
☐ Kjæledyr	☐ Kulde

☐ Andre ting (vennligst skriv nedenfor)

Behandling av astma

98. I de siste 12 månedene: har barnet brukt medisin, spray, inhalator, piller, eller andre medikamenter for tung pust, tetthet eller astma?
☐ Ja ☐ Nei

HVIS "JA", VENNLIGST NAVNGI MEDISINEN(E):

Medisiner foreskrevet av lege:
(Med fast medisin menes at medisinen brukes hver dag i minimum 2 måneder av året)

Navngi hvilke medisiner barnet bruker fast	Navngi hvilke medisiner barnet bruker ved anfall

"Alternativ medisin":

Navngi hvilke medisiner barnet bruker fast	Navngi hvilke medisiner barnet bruker ved anfall

99. I de siste 12 månedene: har barnet ditt brukt medisin, spray, inhalator, tabletter eller andre medikamenter før, under eller etter fysisk aktivitet?
☐ Ja ☐ Nei

HVIS "JA", VENNLIGST NAVNGI MEDISINEN(E):

Medisiner foreskrevet av lege:
(Med fast medisin menes at medisinen brukes hver dag i minimum 2 måneder av året)

Navngi hvilke medisiner barnet bruker fast	Navngi hvilke medisiner barnet bruker ved anfall

"Alternativ medisin":

Navngi hvilke medisiner barnet bruker fast	Navngi hvilke medisiner barnet bruker ved anfall

100. Har du en skriftlig plan som viser hvordan du skal ta deg av barnets astma?
☐ Ja ☐ Nei

101. Har barnet en PEF-måler hjemme?
☐ Ja ☐ Nei

102. I de siste 12 månedene: hvor mange besøk har barnet hatt hos følgende helsepersonell for tung pust, tetthet eller astma?

a) For episoder av tung pust/tetthet?

	Ingen	1-3	4-12	Mer enn 12
Helsearbeider	☐	☐	☐	☐
Sykepleier	☐	☐	☐	☐
Lege	☐	☐	☐	☐
Legevakt/ sykehus	☐	☐	☐	☐

b) For vanlig kontroll for astma?

	Ingen	1-3	4-12	Mer enn 12
Helsearbeider	☐	☐	☐	☐
Sykepleier	☐	☐	☐	☐
Primærlege	☐	☐	☐	☐
Legespesialist	☐	☐	☐	☐
Legevakt/ sykehus	☐	☐	☐	☐

103. I de siste 12 månedene: hvor mange ganger har barnet vært innlagt på sykehus på grunn av tung pust, tetthet eller astma?

☐ Ingen
☐ 1 gang
☐ 2 ganger
☐ Mer enn 2 ganger

104. I de siste 12 månedene: har barnet vært hos noen av de følgende for tung pust, tetthet eller astma:

☐ Akupunktør
☐ Kiropraktor
☐ Homøpat
☐ Fysioterapeut
☐ Psykiater/Psykolog
☐ Sosialarbeider
☐ Andre (vennligst spesifiser):

105. Har barnet noen gang hatt en allergi-injeksjon for å forebygge eller behandle astma?

☐ Ja ☐ Nei

106. I de siste 12 månedene: hvor mange skoledager (eller deler av skoledager) har barnet gått glipp av på grunn av tung pust, tetthet eller astma?

☐ Ingen
☐ 1 - 5 ganger
☐ 6 - 10 ganger
☐ Mer enn 10 ganger

Behandling neseplager

107. I de siste 12 månedene: har barnet brukt medisiner, tabletter, nesespray eller andre medikamenter for høysnue eller neseproblemer?

☐ Ja ☐ Nei

HVIS "JA", VENNLIGST NAVNGI MEDISINEN(E):

Medisiner foreskrevet av lege:
(Med fast medisin menes at medisinen brukes hver dag i minimum 2 måneder av året)

Navngi hvilke medisiner barnet **bruker fast**	Navngi hvilke medisiner barnet bruker **ved anfall**

"Alternativ medisin":

Navngi hvilke medisiner barnet **bruker fast**	Navngi hvilke medisiner barnet bruker **ved anfall**

108. I de siste 12 månedene: hvor mange besøk har barnet hatt hos følgende helsepersonell for høysnue eller neseproblemer?

	Ingen	1-3	4-12	Mer enn 12
Farmasøyt/apoteker	☐	☐	☐	☐
Helsearbeider	☐	☐	☐	☐
Sykepleier	☐	☐	☐	☐
Primærlege	☐	☐	☐	☐
Legespesialist	☐	☐	☐	☐
Legevakt/ sykehus	☐	☐	☐	☐
Annet (vennligst spesifiser):	☐	☐	☐	☐

109. Har barnet noen gang fått allergiinjeksjon for å forebygge eller behandle høysnue eller neseproblemer?

☐ Ja ☐ Nei, hvis nei gå til spm. 111

110. I de siste 12 månedene: har barnet fått allergiinjeksjon for å forebygge eller behandle høysnue eller neseproblemer?

☐ Ja ☐ Nei

111. I de siste 12 månedene: har barnet vært hos kiropraktor, akupunktør, homøopat eller annen alternativ helsearbeider for høysnue eller neseproblemer?

☐ Ja ☐ Nei

112. I de siste 12 månedene: hvor mange skoledager (eller deler av skoledager) har barnet gått glipp av på grunn av høysnue eller neseproblemer?

☐ Ingen
☐ 1 – 5 ganger
☐ 6 – 10 ganger
☐ Mer enn 10 ganger

Behandling av eksem

113. I de siste 12 månedene: har barnet brukt medisiner, salver, kremer, tabletter eller andre medikamenter for kløende hudutslett eller eksem?

☐ Ja ☐ Nei

HVIS "JA", VENNLIGST NAVNGI MEDISINEN(E):

Medisiner foreskrevet av lege:
(Med fast medisin menes at medisinen brukes hver dag i minimum 2 måneder av året)

Navngi hvilke medisiner barnet bruker fast	Navngi hvilke medisiner barnet bruker ved oppblussing

"Alternativ medisin":

Navngi hvilke medisiner barnet bruker fast	Navngi hvilke medisiner barnet bruker ved anfall

114. I de siste 12 månedene: hvor mange ganger har barnet vært hos følgende helsepersonell for kløende hudutslett eller eksem?

	Ingen	1-3	4-12	Mer enn 12
Farmasøyt/Apoteker	☐	☐	☐	☐
Helsearbeider	☐	☐	☐	☐
Sykepleier	☐	☐	☐	☐
Primærlege	☐	☐	☐	☐
Legespesialist	☐	☐	☐	☐
Legevakt/ intensivavdeling	☐	☐	☐	☐
Annet (vennligst spesifiser:)	☐	☐	☐	☐

115. I de siste 12 månedene: har barnet vært innlagt på sykehus på grunn av kløende hudutslett eller eksem?

☐ Ja ☐ Nei

116. Har du en skriftlig plan som viser hvordan du skal ta deg av barnets eksem?

☐ Ja ☐ Nei

117. I de siste 12 månedene: hvor mange skoledager (eller deler av skoledager) har barnet gått glipp av på grunn av kløende hudutslett eller eksem?

☐ Ingen
☐ 1 – 5 ganger
☐ 6 - 10 ganger
☐ Mer enn 10 ganger

Takk for hjelpen!

Når du har svart på spørreskjemaet, legger du det i den vedlagte konvolutten som limes igjen. Konvolutten leveres klassestyrer på skolen så raskt som mulig!

ISM SKRIFTSERIE - FØR UTGITT:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskættede i Sør-Varanger kommune.
Av Anders Forsdahl, 1976. (nytt opplag 1990)

2. Sunnhetstilstanden, hygieniske og sosiale forhold i Sør-Varanger kommune 1869-1975 belyst ved medisinal-beretningene.
Av Anders Forsdahl, 1977.

3. Hjerte-karundersøkelsen i Finnmark - et eksempel på en populasjonsundersøkelse rettet mot cardiovasculære sykdommer. Beskrivelse og analyse av etterundersøkelsesgruppen.
Av Jan-Ivar Kvamme og Trond Haider, 1979.

4. D. The Tromsø Heart Study: Population studies of coronary risk factors with special emphasis on high density lipoprotein and the family occurrence of myocardial infarction.
Av Olav Helge Førde og Dag Steinar Thelle, 1979.

5. D. Reformer i distriktshelsetjenesten III: Hypertensjon i distriktshelsetjenesten.
Av Jan-Ivar Kvamme, 1980.

6. Til professor Knut Westlund på hans 60-års dag, 1983.

7.* Blodtrykksovervåkning og blodtrykksmåling.
Av Jan-Ivar Kvamme, Bernt Nesje og Anders Forsdahl, 1983.

8.* Merkesteiner i norsk medisin reist av allmennpraktikere - og enkelte utdrag av medisinalberetninger av kulturhistorisk verdi.
Av Anders Forsdahl, 1984.

9. "Balsfjordsystemet." EDB-basert journal, arkiv og statistikksystem for primærhelsetjenesten.
Av Toralf Hasvold, 1984.

10. D. Tvunget psykisk helsevern i Norge. Rettsikkerheten ved slikt helsevern med særlig vurdering av kontrollkommisjonsordningen.
Av Georg Høyer, 1986.

11. D. The use of self-administered questionnaires about food habits. Relationships with risk factors for coronary heart disease and associations between coffee drinking and mortality and cancer incidence.
Av Bjarne Koster Jacobsen, 1988.

12.* Helse og ulikhet. Vi trenger et handlingsprogram for Finnmark.
Av Anders Forsdahl, Atle Svendal, Aslak Syse og Dag Thelle, 1989.

13. D. Health education and self-care in dentistry - surveys and interventions.
Av Anne Johanne Søgaard, 1989.

14. Helsekontroller i praksis. Erfaringer fra prosjektet helsekontroller i Troms 1983-1985.
Av Harald Siem og Arild Johansen, 1989.

15. Til Anders Forsdahls 60-års dag, 1990.

16. D. Diagnosis of cancer in general practice. A study of delay problems and warning signals of cancer, with implications for public cancer information and for cancer diagnostic strategies in general practice.
Av Knut Holtedahl, 1991.

17. D. The Tromsø Survey. The family intervention study. Feasibility of using a family approach to intervention on coronary heart disease. The effect of lifestyle intervention of coronary risk factors.
Av Synnøve Fønnebø Knutsen, 1991.

18. Helhetsforståelse og kommunikasjon. Filosofi for klinikere.
Av Åge Wifstad, 1991.

19. D. Factors affecting self-evaluated general health status - and the use of professional health care services.
Av Knut Fylkesnes, 1991.

20. D. Serum gamma-glutamyltransferase: Population determinants and diagnostic characteristics in relation to intervention on risk drinkers.
Av Odd Nilssen, 1992.

21. D. The Healthy Faith. Pregnancy outcome, risk of disease, cancer morbidity and mortality in Norwegian Seventh-Day-Adventists.
Av Vinjar Fønnebø, 1992.

22. D. Aspects of breast and cervical cancer screening.
Av Inger Torhild Gram, 1992.

23. D. Population studies on dyspepsia and peptic ulcer disease: Occurrence, aetiology, and diagnosis. From The Tromsø Heart Study and The Sørreisa Gastrointestinal Disorder Studie.
Av Roar Johnsen, 1992.

24. D. Diagnosis of pneumonia in adults in general practice.
Av Hasse Melbye, 1992.

25. D. Relationship between hemodynamics and blood lipids in population surveys, and effects of n-3 fatty acids.
Av Kaare Bønaa, 1992.

26. D. Risk factors for, and 13-year mortality from cardiovascular disease by socioeconomic status. A study of 44690 men and 17540 women, ages 40-49. **Av Hanne Thürmer, 1993.**

27. Utdrag av medisinalberetninger fra Sulitjelma 1891-1990. **Av Anders Forsdahl, 1993.**

28. Helse, livsstil og levekår i Finnmark. Resultater fra Hjerte-karundersøkelsen i 1987-88. Finnmark III. **Av Knut Westlund og Anne Johanne Søgaard, 1993.**

29. D. Patterns and predictors of drug use. A pharmacoepidemiologic study, linking the analgesic drug prescriptions to a population health survey in Tromsø, Norway. **Av Anne Elise Eggen, 1994.**

30. D. ECG in health and disease. ECG findings in relation to CHD risk factors, constitutional variables and 16-year mortality in 2990 asymptomatic Oslo men aged 40-49 years in 1972. **Av Per G. Lund-Larsen, 1994.**

31. D. Arrhythmia, electrocardiographic signs, and physical activity in relation to coronary heart risk factors and disease. The Tromsø Study. **Av Maja-Lisa Løchen, 1995.**

32. D. The Military service: mental distress and changes in health behaviours among Norwegian army conscript. **Av Edvin Schei, 1995.**

33. D. The Harstad injury prevention study: Hospital-based injury recording and community-based intervention. **Av Børge Ytterstad, 1995.**

34.* D. Vilkår for begrepsdannelse og praksis i psykiatri. En filosofisk undersøkelse. **Av Åge Wifstad, 1996.** (utgitt Tano Aschehoug forlag 1997)

35. Dialog og refleksjon. Festskrift til professor Tom Andersen på hans 60-års dag, 1996.

36. D. Factors affecting doctors´ decision making. **Av Ivar Sønbø Kristiansen, 1996.**

37. D. The Sørreisa gastrointestinal disorder study. Dyspepsia, peptic ulcer and endoscopic findings in a population. **Av Bjørn Bernersen, 1996.**

38. D. Headache and neck or shoulder pain. An analysis of musculoskeletal problems in three comprehensive population studies in Northern Norway. **Av Toralf Hasvold, 1996.**

39. Senfølger av kjernefysiske prøvespreninger på øygruppen Novaya Semlya i perioden 1955 til 1962. Rapport etter programmet "Liv". Arkangelsk 1994.
Av A.V. Tkatchev, L.K. Dobrodeeva, A.I. Isaev, T.S. Podjakova, 1996.

40. Helse og livskvalitet på 78 grader nord. Rapport fra en befolkningsstudie på Svalbard høsten 1988. **Av Helge Schirmer, Georg Høyer, Odd Nilssen, Tormod Brenn og Siri Steine, 1997.**

41.* D. Physical activity and risk of cancer. A population based cohort study including prostate, testicular, colorectal, lung and breast cancer.
Av Inger Thune, 1997.

42. The Norwegian - Russian Health Study 1994/95. A cross-sectional study of pollution and health in the border area.
Av Tone Smith-Sivertsen, Valeri Tchachtchine, Eiliv Lund, Tor Norseth, Vladimir Bykov, 1997.

43. D. Use of alternative medicine by Norwegian cancer patients
Av Terje Risberg, 1998.

44 D. Incidence of and risk factors for myocardial infarction, stroke, and diabetes mellitus in a general population. The Finnmark Study 1974-1989.
Av Inger Njølstad, 1998.

45. D. General practitioner hospitals: Use and usefulness. A study from Finnmark County in North Norway.
Av Ivar Aaraas, 1998.

45B Sykestuer i Finnmark. En studie av bruk og nytteverdi.
Av Ivar Aaraas, 1998.

46. D. No går det på helsa laus. Helse, sykdom og risiko for sykdom i to nord-norske kystsamfunn.
Av Jorid Andersen, 1998.

47. D. The Tromsø Study: Risk factors for non-vertebral fractures in a middle-aged population.
Av Ragnar Martin Joakimsen, 1999.

48. D. The potential for reducing inappropriate hospital admissions: A study of health benefits and costs in a department of internal medicine.
Av Bjørn Odvar Eriksen, 1999.

49. D. Echocardiographic screening in a general population. Normal distribution of echocardiographic measurements and their relation to cardiovascular risk factors and disease. The Tromsø Study.
Av **Henrik Schirmer, 2000.**

50. D. Environmental and occupational exposure, life-style factors and pregnancy outcome in artic and subartic populations of Norway and Russia.
Av Jon Øyvind Odland, 2000.

50B Окружающая и профессиональная экспозиция, факторы стиля жизни и исход беременности у населения арктической и субарктической частей Норвегии и России
Юн Ойвин Удлан 2000

51. D. A population based study on coronary heart disease in families. The Finnmark Study 1974-1989.
Av Tormod Brenn, 2000.

52 D. Ultrasound assessed carotid atherosclerosis in a general population. The Tromsø Study.
Av Oddmund Joakimsen, 2000.

53. D. Risk factors for carotid intima-media thickness in a general population. The Tromsø Study 1979-1994.
Av Eva Stensland-Bugge, 2000.

54. D. The South Asian cataract management study.
Av Torkel Snellingen, 2000.

55. D. Air pollution and health in the Norwegian-Russian border area.
Av Tone Smith-Sivertsen, 2000.

56. D. Interpretation of forearm bone mineral density. The Tromsø Study.
Av Gro K. Rosvold Berntsen, 2000.

57. D. Individual fatty acids and cardiovascular risk factors.
Av Sameline Grimsgaard, 2001.

58. Finnmarkundersøkelsene
Av Anders Forsdahl, Fylkesnes K, Hermansen R, Lund E, Lupton B, Selmer R, Straume E, 2001.

59. D. Dietary data in the Norwegian women and cancer study. Validation and analyses of health related aspects.
Av Anette Hjartåker, 2001.

60. D. The stenotic carotid artery plaque. Prevalence, risk factors and relations to clinical disease. The Tromsø Study.
Av Ellisiv B. Mathiesen, 2001.

61. D. Studies in perinatal care from a sparsely populated area.
Av Jan Holt, 2001.

62. D. Fragile bones in patients with stroke? Bone mineral density in acute stroke patients and changes during one year of follow up.
Av Lone Jørgensen, 2001.

63. D. Psychiatric morbidity and mortality in northern Norway in the era of deinstitutionalisation. A psyhiatric case register study.
Av Vidje Hansen, 2001.

64. D. Ill health in two contrasting countries.
Av Tom Andersen, 1978/2002.

65. D. Longitudinal analyses of cardiovascular risk factors.
Av Tom Wilsgaard, 2002.

66. Helseundersøkelsen i Arkangelsk 2000.
Av Odd Nilssen, Alexei Kalinin, Tormod Brenn, Maria Averina et al.,2003.

67. D. Bio-psycho-social aspects of severe multiple trauma.
Av Audny G. W. Anke, 2003.

68. D. Persistent organic pollutants in human plasma from inhabitants of the artic.
Av Torkjel Manning Sandanger, 2003.

69. D. Aspects of women's health in relation to use of hormonal contraceptives and pattern of child bearing.
Av Merethe Kunmle, 2003.

70. Pasienterfaringer i primærlegetjenesten før og etter fastlegereformen.
Av Olaug Lian, 2003.

71. D. Vitamin D security in northern Norway in relation to marine food traditions.
Av Magritt Brustad, 2004.

72. D. Intervensjonsstudien i Finnmark. Evaluering av lokalsamfunns basert hjerte- og kar forebygging i kystkommunene Båtsfjord og Nordkapp.
Av Beate Lupton, 2004.

73. D. Environmental factors, metabolic profile, hormones and breast and endiometrial cancer risk.
Av Anne-Sofie Furberg, 2004.

74. D. Det skapende mellomrommet i møtet mellom pasient og lege.
Av Eli Berg, 2004.

75. Kreftregisteret i Arkhangelsk oblast i nordvest Russland. Med en sammenligning av kreftforekomst i Arkhangelsk oblast og Norge 1993 - 2001.
Av Vaktskjold Arild, Lebedintseva Jelena, Korotov Dmitrij, Tkatsjov Anatolij, Podjakova Tatjana, Lund Eiliv, 2004

76. D. Characteristics and prognosis of long-term stroke survivors. The Tromsø Study.
Av Torgeir Engstad, 2004

77. D. Withdrawal and exclusion. A study of the spoken word as means of understanding schizophrenic patients.
Av Geir Fagerjord Lorem, 2005.

78. "Søkelys på safunnsmedisinene." Evaluering av kommunal samfunnsmedisinsk legetjeneste, offentlig legearbeid og de forebyggende oppgaver i Fastlegeordningen.
Av Betty Pettersen og Roar Johnsen, 2005.

79. Prosjekt egenmelding Kristiansand kommune. Evaluering av kontrollert intervensjonsforsøk i stor skala, med utvidet rett til egenmelding i kombinasjon med økt og formalisert samhandling mellom arbeidstaker og arbeidsplassen ved sykefravær.
Av Nils Fleten og Roar Johnsen, 2005.

80. D. Abdominal aortic aneurysms:Diagnosis and epidemiology. The Tromsø study.
Av Kulbir Singh, 2005.

81. D. A population based study on cardiovascular diseases in Northwest Russia.The Arkhangelsk study 2000.
Av Maria Averina, 2005.

82. D. Exposure to exogenous hormones in women: risk factors for breast cancer and molecular signature.
Av Vanessa Dumeaux, 2005.

83. D. Repeated ultrasound measurements of carotid artery plaques in a general population. The Tromsø Study 1994-2001.
Av Stein Harald Johnsen, 2005.

84. D. Risk Factors For Fractures In Tromsø. The Tromsø Study.
Av Luai Awad Ahmed, 2005.

85. D. The quality and use of two health registries in Russia. The Arkhangelsk Cancer Registry and the Kola Birth Registry
Качество и использование двух медицинских регистров в России. Архангельск регистр рака и Кольский регистр родов
Av Arild Vaktskjold, 2005.

86. D. Haemoglobin, anaemia and haematological malignancies.
Av Tove Skjelbakken, 2006

87. D. The sick-listed - an under-recognised resource in handling sickness absence.
Av Nils Fleten, 2006.

88. D. Longitudinal changes in forearm bone mineral density in women and men from 25 to 84 years. The Tromsø Study.
Av Nina Emaus, 2006.

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De som er merket med * har vi dessverre ikke flere eksemplar av.