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ALLERGY IN ESTONIAN SCHOOLCHILDREN: TIME TRENDS AND CHARACTERISTICS

TRIINE ANNUS

TARTU UNIVERSITY
PRESS

Department of Pediatrics, University of Tartu, Tartu, Estonia

The dissertation is accepted for the commencement of the degree of Doctor of Medical Sciences on October 19, 2005 by the Council of the Faculty of Medicine, University of Tartu

Opponent: Wenche Nystad, Ph.D., department director, Department of chronic diseases, Division of epidemiology, Norwegian Institute of Public Health, Oslo, Norway

Commencement: December 2, 2005

Publication of this dissertation is granted by the University of Tartu

ISSN 1024–395X
ISBN 9949–11–181–1 (trükis)
ISBN 9949–11–182–X (PDF)

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimus nr. 529

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by their Roman numerals (I–V), and on some unpublished data:

I Riikjärv M-A, Annus T, Bråbäck L, Rahu K, Björksten B. Similar prevalence of respiratory symptoms and atopy in Estonian schoolchildren with changing lifestyle over 4 yrs. Eur Resp J 2000; 16: 86–90.

II Annus T, Björkstén B, Mai X-M, Nilsson L, Riikjärv M-A, Sandin A, Bråbäck, L. Wheezing in relation to atopy and environmental factors in Estonian and Swedish schoolchildren. Clin Exp All 2001; 31: 1846–53.

III Annus T, Montgomery SM, Riikjärv M-A, Björkstén B. Atopic disorders among Estonian schoolchildren in relation to tuberculin reactivity and the age at BCG vaccination. Allergy 2004; 59: 1068–73.

IV Sandin A, Annus T, Björkstén B, Nilsson L, Riikjärv MA, van Hage-Hamsten M, Bråbäck L. Prevalence of self-reported food allergy and IgE antibodies to food allergens in Swedish and Estonian schoolchildren. Eur J Clin Nutr 2005; 59, 399–403.

V Annus T, Riikjärv M-A, Rahu K, Björkstén B. Modest increase in seasonal allergic rhinitis and eczema over 8 years among Estonian schoolchildren. Pediatr Allerg Immunol 2005; 16: 315–20.

DEFINITIONS AND ABBREVIATIONS

According to the recent nomenclature for allergy, proposed by the Nomenclature Review Committee of the World Allergy Organization (Johansson *et al.*, 2004), allergy is "a hypersensitivity reaction initiated by specific immunologic mechanisms" and can be antibody- or cell-mediated. In most patients, the antibodies responsible for an allergic reaction belong to the immunoglobulin E (IgE) isotype and these patients may be said to suffer from IgE-mediated allergy (Johansson *et al.*, 2004). In this thesis the term "allergy" refers to IgE-mediated allergy. Accordingly, the definitions of the terms used in this thesis are as follows:

1 **Hypersensitivity** refers to objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose that is tolerated by normal subjects.

2 **Allergy** is a hypersensitivity reaction initiated by allergen-specific IgE antibodies.

3 **Allergen** is an antigen capable of stimulating IgE antibody formation.

4 **Sensitisation** refers to IgE antibody formation to a specific allergen.

5 **Allergic diseases** refer to clinical manifestations of allergy.

6 **Atopy** is a personal and/or familial tendency to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema.

7 **Asthma** is a heterogeneous chronic inflammatory disorder of the airways involving airflow limitation that is at least partly reversible either spontaneously or upon treatment, and increased airway responsiveness to a variety of stimuli; results in recurrent episodes of symptoms such as wheezing, breathlessness, chest tightness, and cough.

8 **Bronchial hyperresponsiveness** is an exaggerated bronchoconstriction response to both specific (allergens) and non-specific stimuli; an important patophysiological feature of asthma.

9 **Allergic rhinitis** refers to IgE-mediated hypersensitivity symptoms from the nose, eg., itching, sneezing, increased secretion, and blockage. Allergic

rhinitis accompanied by allergic conjunctivitis is termed **allergic rhino-conjunctivitis.**

10 **Atopic eczema** is eczema in which the underlying inflammation is dominated by IgE antibodies.

11 **Food allergy** refers to IgE-mediated hypersensitivity reaction to any food.

Abbreviations used

BCG	Bacillus Calmette-Guérin
BHR	bronchial hyperresponsiveness
CI	confidence interval
ECRHS	the European Community Respiratory Health Survey
FEV_1	forced expiratory volume in one second
Ig	immunoglobulin
ISAAC	the International Study of Asthma and Allergies in Childhood
OR	odds ratio
SD	standard deviation
SPT	skin prick test
Th	T-helper cell

INTRODUCTION

Allergic diseases, such as asthma, allergic rhinitis, and eczema are the most common chronic disorders in children and a common health problem at any age. Allergy has become a major burden in affluent Westernised societies where approximately one third of the general population suffer from various forms of allergic diseases during a life span (Hanson and Telemo, 1997). These conditions may have a profound impact on the subject's physical, emotional, and social wellbeing, and also substantially affect the quality of life of the whole family (Su *et al.*, 1997; Sawyer *et al.*, 2000). Asthma and other allergic diseases account for a large number of lost school- and workdays; they are related to loss of sleep and concomitant fatigue, limitations in physical and social activities, decreased productivity, increased stress, and need to avoid trigger factors (Taylor and Newacheck, 1992; Diette *et al.*, 2000; von Mutius, 2000). Suboptimally treated allergic rhinitis has negative effect on memory, cognitive ability, school performance, and decision-making (Vuurman *et al.*, 1993; Simons, 1996). Subjects with eczema are often very uncomfortable because of the intense pruritus. The appearance and irritability of an infant with eczema may inhibit normal bonding between the child and the parent and affect the parent's care-taking confidence (Lapidus *et al.*, 1993). At school age, eczema can have a tremendous effect on peer relationship. Allergic diseases also cause an immense financial burden to the patient, the family, healthcare services, and society as a whole (Lapidus *et al.*, 1993; Su *et al.*, 1997; Bousquet *et al.*, 2001; Weiss and Sullivan, 2001).

The prevalence of all allergic diseases has increased markedly in affluent Western countries during the last decades of the 20th century (Sly, 1999). Allergic diseases are considerably more common in these countries compared with developing less affluent countries (Cookson, 1987; ISAAC Steering Committee, 1998a; Janson *et al.*, 2001) and such difference exists even among populations with similar genetic background (von Mutius *et al.*, 1992; Nowak *et al.*, 1996). Lower risk of allergy has been observed among populations with a more traditional lifestyle, such as rural dwellers, farmers, and followers of an anthroposophic lifestyle (Alm *et al.*, 1999; Filipiak *et al.*, 2001). These findings indicate a relationship between the risk of allergy and environmental factors, particularly the modern lifestyle in affluent industrialised countries (a "Western lifestyle"). Which aspects of this lifestyle account for the epidemic of allergy, is, however, still largely unknown.

According to the results of previous epidemiological studies, allergic diseases are significantly less common in Estonia than in Western European countries, both among schoolchildren and young adults (Riikjärv *et al.*, 1995; Jõgi *et al.*, 1998). The fall of the socialist system in Estonia has resulted in marked environmental changes and a rapidly altering lifestyle. Thus, the current period of transition provides a unique opportunity to study some aspects of the relationship between a lifestyle and the risk of allergy.

REVIEW OF THE LITERATURE

1. Natural history and phenotypes of allergic diseases

1.1. Natural history

The manifestations of allergy may vary with age, and the symptoms may appear and disappear simultaneously or progress from one to another. Often the natural course of allergy follows a typical sequence known as the "atopic march" (Cantani, 1999). In infancy, the main symptoms of possible allergic nature are eczema, gastrointestinal disorders, and recurrent wheezing, and food allergens are the most common cause of sensitisation (Kjellman and Nilsson, 1998; Kulig *et al.*, 1999; Gustafsson *et al.*, 2000; Høst *et al.*, 2002). All these disorders have a good prognosis and often resolve in a few years, whereas in older children, sensitisation to aeroallergens evolves and asthma, rhinitis, and conjunctivitis become the main symptoms. Risk factors for the development of asthma, allergic rhinitis, and sensitisation to aeroallergens include heredity, early-onset eczema, and early-onset and persistent sensitisation to food allergens (Nickel *et al.*, 1997; Kulig *et al.*, 1998; Gustafsson *et al.*, 2000; Illi *et al.*, 2001b). In the prospective German Multicentre Allergy Study, 69% of the infants who had eczema in the first 3 months of life were sensitised against aeroallergens by 5 years of age and 50% of children with early eczema and family history of allergy had developed allergic airway disease (Bergmann *et al.*, 1998). In a Swedish hospital-based study among children with eczema in the first 3 years of life, only 15% had never experienced symptoms of asthma or rhinoconjunctivitis by the age of 7 years and 43% had current asthma (Gustafsson *et al.*, 2000).

Among children with recurrent wheezing during infancy and early childhood, from 60% to 70% become symptom-free later in childhood (Wennergren *et al.*, 1997; Sherriff *et al.*, 2001; Kotaniemi-Syrjänen *et al.*, 2002). In the prospective Tucson Children's Respiratory Study, 52% of the children had never wheezed by 6 years of age, 20% had had at least one wheezing episode during the first 3 years of life but had no wheezing at 6 years of age, 15% had no wheezing before the age of 3 years but wheezed at 6 years of age, and 14% had wheezing both before 3 years and at 6 years of age (Martinez *et al.*, 1995). Transient early wheezing was related to maternal smoking and poor neonatal lung function, but not to atopy. Late-onset and persistent wheezing were associated with atopy and with normal lung function in infancy. However, in persistent wheezers lung function diminished by 6 years of age.

In longitudinal studies of asthma from childhood to adulthood, reviewed by Sears (1998), the proportion of those who still had asthma as adults ranged between 26% and 86%, depending on the initial selection of the study populations. Even after a prolonged remission, the symptoms may recur later in adulthood (Kelly *et al.*, 1987; Strachan *et al.*, 1996). Most important risk factors for relapsing and persistent asthma are severity of the disease, other allergic diseases, sensitisation, exposure to tobacco smoke, impaired lung function, and bronchial hyperresponsiveness (BHR) (Strachan *et al.*, 1996; Sears, 1998; Grol *et al.*, 1999; Xuan *et al.*, 2002).

Asthma and rhinitis often coexist, suggesting the concept of "one airway, one disease" (Grossman, 1997; Bousquet *et al.*, 2001). Up to 40% of subjects with allergic rhinitis also have asthma, and up to 80% of subjects with asthma experience nasal symptoms (Sibbald and Rink, 1991; Wright *et al.*, 1994; Grossman, 1997; Leynaert *et al.*, 1999). Rhinitis frequently precedes asthma, and both allergic and nonallergic rhinitis are risk factors for the development of asthma (Braman *et al.*, 1987; Linna *et al.*, 1992; Settipane *et al.*, 1994). Even in the absence of asthma, rhinitis is associated with nonspecific BHR (Braman *et al.*, 1987; Walter, 1992; Fireman, 2000).

Conclusion: Allergic symptoms may coexist or appear in sequence. The presence of one symptom is a risk factor for the development and severity of other symptoms.

1.2. Relationship between symptoms of allergy and sensitisation

Asthma, rhinitis, and eczema are typical manifestations of allergic hypersensitivity, mediated by IgE antibodies. However, the relationship between IgE-mediated sensitisation and these disorders is complex and allergy should not be assumed on the basis of symptoms alone. Allergic and nonallergic conditions can present with similar symptoms and in many subjects who suffer from symptoms of asthma, rhinitis, or eczema, the presence of IgE sensitisation cannot be demonstrated by skin prick tests (SPT) or specific serum IgE measurements (however, local IgE production in the shock organ cannot be excluded as suggested by Humbert *et al.*, 1999). On the other hand, the presence of IgE antibodies does not necessarily mean clinically active disease. Thus, among 7–8-year-old Swedish schoolchildren without asthma or any other allergic disease, the prevalence of positive SPT was 12% (Rönmark *et al.*, 1998), and in Italy, about one third of sensitised schoolchildren were without symptoms (Crimi *et al.*, 2001). Therefore, even in a symptomatic subject with verified allergen-specific sensitisation, the identified allergens do not necessarily account for the symptoms and sensitisation may be just a chance finding. Furthermore, in subjects with IgE-mediated allergic diseases, symptoms can also be induced by a variety of nonspecific stimuli, and allergic and nonallergic disease may coexist (Settipane, 2001).

1.2.1. Asthma

Many studies have reported an association between asthma and sensitisation to common allergens, particularly in children (Sears *et al.*, 1989; Peat and Woolcock, 1991; Norrman *et al.*, 1994; Kuehr *et al.*, 1995; Downs *et al.*, 2001; Haby *et al.*, 2001). The risk of asthma increases with increasing number of positive SPTs (Sears *et al.*, 1993; Simpson *et al.*, 2001). Nevertheless, the role of sensitisation in asthma has been under vigorous discussion (Burrows *et al.*, 1989; Pearce *et al.*, 1999).

Burrows *et al.* (1989) found a close relationship between asthma and high levels of serum total IgE even in SPT negative subjects, while allergic rhinitis was associated primarily with positive SPT to common aeroallergens independently of the serum IgE level. The authors challenged the concept that there are basic differences between allergic and nonallergic forms of asthma and suggested that asthma is almost always associated with some type of IgE-related reaction and therefore has an allergic basis. Strong relationship between elevated IgE levels and asthma in school age has also been found in several other studies (Sears *et al.*, 1991; Sporik *et al.*, 1995). In contrast, in Finnish schoolchildren, diagnosis and symptoms of asthma were related to positive SPT, but not to serum total IgE concentration (Remes and Korppi, 1996).

Pearce *et al.* (1999) examined the evidence for the association between sensitisation and asthma in population-based studies with at least 600 subjects. The population-attributable risk for asthma due to atopy based on positive SPT varied from 25% to 63% (a weighted mean 38%) in studies among children, and from 8% to 55% (mean 37%) in adults. The proportion of cases attributable to atopy defined as a raised total serum IgE level varied from 0 to 80% with a weighted mean of 33%. The authors also reviewed standardised comparisons across populations or time periods and found only a weak and inconsistent association between the prevalence of asthma and sensitisation. They concluded that the importance of atopy as a cause of asthma in individuals may have been overemphasised and suggested that the proportion of asthma cases due to atopy is less than one half. More recently, the population-attributable risk for asthma due to atopy (positive SPT) was found to be 35% among 4-year-old children in UK (Arshad *et al.*, 2001).

It has also been disputed whether sensitisation in asthmatic children is the actual cause of the development and persistance of allergic inflammation in the airways or merely a sign of the atopic status of these children (Lau *et al.*, 2000).

1.2.2. Wheezing phenotypes

Wheezing, a nonspecific symptom resulting from lower airway obstruction, is the main clinical expression of asthma. However, childhood wheezing may have different causes and not all wheezing episodes are labelled as asthma, particularly in young children. There is increasing evidence to suggest that wheezing in childhood is a heterogeneous condition, with distinct phenotypic expressions associated with different clinical manifestations, risk factors, and prognosis.

A Norwegian study showed a clear difference between schoolchildren with parental-reported wheezing but without asthma label and wheezing children with diagnosed asthma (Nystad *et al.*, 1999). In children with asthma label, positive SPTs were twice as common as either in children with wheeze but without asthma or in non-wheezers. Lung function and BHR in wheezers without asthma were also more similar to non-wheezers than to asthmatic children. The authors concluded that wheeze with and without asthma label represent, to some extent, different wheezing phenotypes.

In the prospective Tucson Children's Respiratory Study, three phenotypes have been identified in children with asthma: "transient early wheezing" limited to the first three years of life, "non-atopic wheezing" of the toddler and early school years, and "IgE-mediated wheezing/asthma" related to persistent wheezing at any age (Stein *et al.*, 1997; Martinez, 2002). Transient wheezing is associated with decreased lung function, maternal smoking during pregnancy, and exposure to other siblings or children at daycare centres, but not with allergic sensitisation, increased airway lability, or family history of asthma. Wheezing, associated with respiratory syncytial virus infection in the first years of life resolves in most children by 13 years of age; this form is independent of atopy and related to slightly reduced lung function, and BHR. IgE-mediated wheezing/asthma is associated with early sensitisation, significant loss of lung function, and BHR.

Similarly, among asthmatic schoolchildren in Germany, two subgroups of asthma were distinguished (von Mutius *et al.*, 1999). In one group, asthmatic symptoms were induced or triggered by repeated early childhood infections, while the other group was related to positive SPT. Nonallergic phenotype seems to be associated with less severe and less persistent wheeze (Stein *et al.*, 1997; von Mutius *et al.*, 1999; Ponsonby *et al.*, 2002). There is also evidence of differences in airways inflammatory mechanisms between children with different wheezing phenotypes. During asymptomatic periods there is ongoing airways inflammation (eosinophil and mast cell recruitment) in children with atopic asthma, but not in children with virus-related wheeze (Stevenson *et al.*, 1997). Values of nitric oxide concentrations in exhaled air, a marker of asthmatic bronchial inflammation, are markedly higher in atopic than in nonatopic asthmatic children (Barreto *et al.*, 2001).

1.2.3. Rhinitis

IgE-mediated rhinitis accounts for 30% to 70% of patients with chronic perennial rhinitis (Jessen and Malm, 1997). Relationship between self-reported rhinitis and SPT was recently assessed among young Italian adults participating in ECRHS study (Olivieri *et al.*, 2002). The prevalence of positive SPT was 79% in subjects with self-reported allergic rhinitis (89% in subjects with self-reported pollen-related allergic rhinitis and 69% in subjects who related their rhinitis to indoor allergens), 35% in subjects who reported nasal symptoms but not allergic rhinitis, and 16% in subjects reporting neither allergic rhinitis nor nasal symptoms. Among 4-year-old British children with rhinitis, the prevalence of positive SPT was 55%, and 46% of the cases of rhinitis could be attributable to atopy (Arshad *et al.*, 2001).

Patients may have coexisting allergic and nonallergic disease. In a hospital-based survey in the USA 43% of the rhinitis patients had pure allergic rhinitis, 23% pure nonallergic rhinitis, and 34% of the patients were diagnosed with "mixed" rhinitis (a combination of allergic and nonallergic rhinitis) (Settipane, 2001).

1.2.4. Eczema

Similarly to respiratory allergic diseases, eczema is not a single disease, but rather an aggregation of several disorders with certain clinical characteristics in common (Wollenberg and Bieber, 2000; Johansson *et al.*, 2001). Atopic eczema, a genetically determined IgE-mediated delayed-type hypersensitivity reaction of the skin (Novak and Bieber, 2000), is the most prevalent form of eczema. As reviewed by Schmid-Grendelmeier *et al.* (2001), the proportion of IgE-mediated eczema among eczema patients in 11 hospital-based studies ranged from 55% to 90%. In addition, in 3% to 5% of eczema patients without positive SPT or specific serum IgE, sensitisation to inhalant or food allergens can be demonstrated with epicutaneous atopy patch tests (Schmid-Grendelmeier *et al.*, 2001).

The proportion of atopic eczema is smaller in population-based studies. In a UK birth cohort study, in 4-year-old children with eczema verified by a study physician, the prevalence of positive SPT to inhalant and/or food allergens was 43% (Arshad *et al.*, 2001). An independent effect of sensitisation on eczema was observed with three major inhalant (house dust mite, grass pollen, and cat) and two food (egg and peanut) allergens, confirming the atopic nature of eczema at this age. The population-attributable risk for eczema due to atopy was 32%.

Nonallergic eczema is characterised by eczematous skin lesions in typical areas similar to atopic eczema, but is not associated with sensitisation to common inhalant or food allergens (Schmid-Grendelmeier *et al.*, 2001). Characteristically, subjects with nonallergic eczema suffer from an isolated type of eczema, without coexistence or subsequent development of respiratory diseases (Novembre *et al.*, 2001; Wüthrich and Schmid-Grendelmeier, 2002). However, some subjects with this form of eczema develop specific sensitisation in follow-up indicating that nonallergic eczema may be a transition stage in the natural history of atopic eczema (Novembre *et al.*, 2001; Wüthrich and Schmid-Grendelmeier, 2002). It has been suggested that the damaged skin barrier function in eczema may enchance epicutaneous sensitisation to aeroallergens (Schäfer *et al.*, 1999; Saloga and Knop, 2000). In 2-year-old Italian children with eczema, 49/77 (64%) had positive SPT to inhalant or food allergens at 2 years of age ("early atopic" group), 16 (21%) were SPT negative at 2 years of age, but became SPT positive by 11 years of age ("late-onset atopic" group), and 12 (15%) remained SPT negative by 11 years of age ("nonatopic" group) (Novembre *et al.*, 2001). None of the 12 nonatopic children developed asthma by 11 years of age compared with 4 of the 16 children in the late-onset atopic group and 29 of the 49 children with early atopic eczema.

The role of allergens and IgE-mediated reactions in eczema remains controversial (Ring and Thewes, 1999; Schmid-Grendelmeier *et al.*, 2001). An association has been found between the degree of sensitisation and the severity of atopic eczema (Schäfer *et al.*, 1999). However, the markedly elevate IgE-antibody production has been regarded by some authors as a mere epiphenomenon relevant to respiratory symptoms, but not to skin lesions (Sampson, 1989). Compared with allergic respiratory disorders, where the role of IgE is evident, in eczema, the influence of other immunological mechanisms, as well as nonimmunological factors, seems to be more important (Schmid-Grendelmeier *et al.*, 2001).

Conclusion: Allergy-like symptoms represent an aggregation of several different phenotypes, which may or may not be IgE-mediated and may be related to different risk factors.

2. Prevalence of allergic diseases

The majority of the epidemiological evidence relating to allergic diseases is derived from questionnaire surveys of disease history and/or symptoms. Unfortunately, allergic diseases are difficult to define for epidemiological studies and variation in the content of the questionnaires and in the use of diagnostic terms makes it difficult to draw firm conclusions regarding the prevalence of allergic diseases and changes in the prevalence over time. Furthermore, questionnaires insufficiently distinguish between atopic and nonatopic symptoms. Nevertheless, the patterns in the prevalence of allergic diseases are too striking and too consistent to be ignored or explained solely by a methodological imperfection.

2.1. Time trends

Allergic diseases, although known from antiquity, were considered to be rare up to the end of the 19th century (Emanuel, 1988; Meza and Gershwin, 1997; Jones *et al.*, 1998). In less than a hundred years, allergy has reached epidemic proportions (Holgate, 1999). The earliest epidemiological data about the prevalence of allergy come from Switzerland where the prevalence of self-reported current allergic rhinitis was 0.8% in 1926, and subsequently increased to 4.4% in 1958, 9.6% in 1985, and 14.2% in 1993 (Wüthrich *et al.*, 1995). An analysis, based on Finnish military conscripts register, showed a stable and low (0.02–0.08%) prevalence of asthma between 1926 and 1962 (Haahtela *et al.*, 1990). During 1960s a continuous linear rise began, resulting in 20-fold increase in the prevalence (1.79% in 1989). Similarly, significant increase in asthma and allergic rhinitis was observed in Swedish conscipts between 1971 and 1981 (Åberg, 1989). The prevalence of reported early childhood eczema in children in UK, born in 1946, 1958, and 1970, was 5.1%, 7.3%, and 12.2%, respectively (Taylor *et al.*, 1984). These observations have been confirmed by serial studies using the same methods over 10–20 years, which have reported a parallel increase in diagnosis and/or symptoms of asthma, allergic rhinitis, and eczema among children and adolescents in affluent Western countries (Burr *et al.*, 1989; Ninan and Russell, 1992; Peat *et al.*, 1994; Åberg *et al.*, 1995; Lewis *et al.*, 1996). The increase has occured over too short a period to be explained by genetic factors, suggesting an environmental influence.

The increase in allergy has been accompanied by rising awareness and changing diagnostic criteria. Thus, there has been an increase in the readiness to diagnose childhood wheezing as asthma in the English-speaking countries since the 1970s (Hill *et al.*, 1989; Crane *et al.*, 2002). Therefore, several authors have reviewed critically the reports of rise in allergies, and particularly in asthma. Andreson (1989) analysed several British studies and concluded that the existing evidence did not prove an increase in the prevalence of wheezing. The author also insisted that the prevalence of diagnosed asthma was of little use epidemiologically, and that any analysis of trends based on diagnosed asthma should be interpreted with caution.

Magnus and Jaakkola (1997) reviewed reports of repeated cross sectional surveys of asthma and wheezing among children and young adults, published between 1983 and 1996. They identified 16 surveys that used the same methodology in the same geographic area, 12 among children and four among young adults. All reviewed surveys reported an increasing prevalence, 12 in asthma (absolute yearly increase from 0.09% to 0.97% for current and from 0.35% to 2.08% for lifetime asthma) and eight in current wheezing (yearly increase from 0.14% to 1.24%). The increase was generally higher in more recent studies and among children. However, the authors of the review emphasised that the evidence of the increase was mostly based on reported symptoms and/or diagnosed asthma and not on objective measurements. They concluded that the trends could be due to an increased awareness and changes in diagnostic labelling.

Studies based on objective measurements of sensitisation, lung function, and BHR were analysed by Wieringa *et al.* (2001). Their search for the years 1966–2000 resulted only in 16 papers, performed in 13 populations. Only nine papers described measurements of the same markers twice in the whole population. Six of these papers reported a significant increase in at least one measurement, including increase in sensitisation among children in Japan (Nakagomi *et al.*, 1994) and Germany (von Mutius *et al.*, 1998), and among adults in UK (Sibbald *et al.*, 1990). More recently, increase in sensitisation has been observed among adults in Denmark (Linneberg *et al.*, 2000) and Greenland (Krause *et al.*, 2002), and among children in Australia (Downs *et al.*, 2001).

Recently, von Hertzen and Haahtela (2005) reviewed reports on time trends in asthma prevalence, published between 2000 and 2004. Of the 20 identified studies, seven reported an increase in asthma prevalence (five studies in children and two in adults), and 11 revealed a decreasing or stable trend (six studies in children, three in adults, and two in both). In one study (Wang *et al.*, 2004), wheezing increased in the older children and decreased in the younger age group, and in one study (Anderson *et al.*, 2004), the prevalence of asthma increased, whereas wheezing decreased. The authors suggest that in affluent Westernised societies, the increasing trend in asthma in adults may have plateaud or even reversed, while the situation is more ambiguous in children.

Conclusion: Although changes in awareness and diagnostic labelling may account for some of the observed time trends, there has been a distinct increase in the prevalence of allergic disorders in affluent Western countries during the second half of the 20th century, indicating an environmental influence.

2.2. Regional variation

The prevalence of allergic diseases varies widely between countries and also between different populations within countries. In his comparison of asthma prevalence in economically developed and developing countries, Cookson (1987) reviewed 41 studies, published between 1954 and 1983. In children, the prevalence of asthma was around 5% (10% if other wheezing was included) in Western Europe and North America, and less than 1% in economically poorer countries in Asia ans Africa. For adults in Western populations, the prevalence rates were, in general, lower than for children, while the opposite was true in several developing countries. The author concluded that asthma was less common in the developing countries, particularly in children. A position paper on pollen-related allergy in Europe (D'Amato *et al.*, 1998) summarised data from 10 studies of hay fever based both on questionnaire and on measurements of sensitisation, published between 1984 and 1993. The prevalence varied from

3% in Danish farmers to 20% in German conscripts. The Allergic Rhinitis and its Impact on Asthma Workshop report (Bousquet *et al.*, 2001) presented the results of 37 studies of rhinitis from the years 1969–99. The prevalence rates for seasonal allergic rhinitis ranged from less than 1% to 42%, and for perennial rhinitis from 1% to 13%.

The differences between countries have been confirmed by standardised comparative studies. Burr *et al.* (1994) compared diagnosed asthma, asthma symptoms, and BHR to exercise challenge in Wales, New Zealand, South Africa, and Sweden. The prevalence of asthma and BHR were highest in New Zealand (17% and 12%, respectively) and lowest in Sweden (4% and 2%, respectively). Recently, two telephone surveys showed a significant difference in the prevalence of respiratory allergies between Western European countries (Bauchau and Durham, 2004; Dahl *et al.*, 2004).

Comparative studies in populations with similar genetic background are of special interest. Thus, several studies have found marked variation in the prevalence of allergic disorders between geographical areas within countries (Peat *et al.*, 1995; Nystad *et al.*, 1997b; McNally *et al.*, 2000). There were 2- to 6-fold differences in the prevalence of wheezing among children in Hong Kong and in centres of mainland China (Leung and Ho, 1994; Zhao *et al.*, 2000; Wong *et al.*, 2001a). Both in affluent and developing societies, urban living is associated with higher risk for allergic symptoms (Odhiambo *et al.*, 1998; Nilsson *et al.*, 1999), sensitisation (Bråbäck and Kälvesten, 1991; Crimi *et al.*, 1999; Bibi *et al.*, 2002), and BHR (Addo Yobo *et al.*, 1997; Steinman *et al.*, 2003).

The reunification of Germany provided a unique opportunity to compare two genetically similar populations exposured to different lifestyle and environmental conditions over 40 years. Comparative studies conducted shortly after the reunification found markedly higher prevalence of allergic symptoms, sensitisation, and BHR among adults in West Germany, particularly in younger subjects (Nowak *et al.*, 1996; Nicolai *et al.*, 1997). Sensitisation was similar in East and West Germany for those born in 1940s and 1950s, but differed between subjects born in 1960s, suggesting that the prevalence rates were similar before Germany was divided and diverged after the division (Heinrich *et al.*, 1998a). West German children had higher prevalence of allergic rhinitis and sensitisation, and tended also to have higher prevalence of asthma and BHR, while wheezing and other respiratory symptoms, and bronchitis were more common among East German children (von Mutius *et al.*, 1992; von Mutius *et al.*, 1994b; Duhme *et al.*, 1998). The results of the studies were inconsistent for eczema (Schäfer *et al.*, 1996; Duhme *et al.*, 1998). The rapidly occurring Westernisation of the lifestyle in the former East Germany resulted in an increase in the prevalence of allergic symptoms, sensitisation, and BHR, both among adults (Heinrich *et al.*, 1998b; Richter *et al.*, 2000) and among children (von Mutius *et al.*, 1998; Weiland *et al.*, 1999; Frye *et al.*, 2001; Heinrich *et al.*, 2002), while the prevalence of bronchitis and frequent colds in children decreased (von Mutius *et al.*, 1998; Krämer *et al.*, 1999a; Heinrich *et al.*, 2000).

Recently, similar East-West differences were reported in Northern Europe. The prevalence rates of asthma, allergic rhinitis, eczema, and sensitisation were higher in Finland and Norway than in Russia, both in children (Selnes *et al.*, 2001; Dotterud *et al.*, 2004; Klemola *et al.*, 2004) and in adults (Dotterud *et al.*, 2000; Vartiainen *et al.*, 2002), while in children, the prevalence of respiratory symptoms was higher in Russia. However, in one study, the prevalence of IgE-sensitisation was higher in Russian adults than in Norwegian adults (28% *vs* 21%), despite higher prevalence of allergic diseases in Norway (Smith-Sivertsen *et al.*, 2003).

Since the beginning of 1990s, two international surveys have assessed the geographical variation in respiratory and allergic disorders and related factors in a standardised manner, the European Community Respiratory Health Survey (ECRHS) in adults, and the International Study of Asthma and Allergies in Childhood (ISAAC) in children. Both surveys are based on a simple comparison of symptom prevalence in a questionnaire survey of a large number of people in random population sample, followed by more intensive testing of related factors in a subsample (Burney *et al.*, 1994; Asher *et al.*, 1995).

The database of the ECRHS includes information on approximately 140 000 individuals aged 20–44 years from 22 countries (17 European countries, Algeria, India, New Zealand, Australia, and USA). The study found large geographical differences in the prevalence of wheezing (4–32%), current symptomatic asthma (2–12%), allergic rhinitis (10–41%), food allergy/ intolerance (5–19%), specific IgE (16–45%), and BHR to methacholine (3–28%), with high prevalence rates in English speaking countries and low rates in the Mediterranean region and Eastern Europe (Burney *et al.*, 1996; Burney *et al.*, 1997; Chinn *et al.*, 1997; Woods *et al.*, 2001). The fact that the geographical pattern of symptoms is consistent with the distribution of atopy and BHR suggests that the regional variations in the prevalence of allergic disorders are true and most likely due to environmental factors. The study also points to an increasing trend in asthma, as subjects born in 1966 or later had a two-fold higher risk of asthma than the cohort born between 1946 and 1950.

Conclusion: The large variations in the prevalence of allergies between and within countries, particularly between genetically similar populations, support the importance of environmental factors in the development of these diseases.

2.3. The International Study of Asthma and Allergies in Childhood (ISAAC)

The ISAAC was founded to maximise the value of epidemiological research into asthma and allergic diseases by establishing a standardised methodology and facilitating international collaboration (Asher *et al.*, 1995). The programme emerged in 1991, from pre-existing multinational collaborative projects in Auckland, New Zealand and Bochum, Germany, and was designed to allow comparisons of childhood allergic disorders between populations in different countries, across geographical, cultural, and linguistic boundaries.

The ISAAC design comprises three phases. The aims of the ISAAC Phase I (1992–96) were: 1) to describe the prevalence and severity of asthma, rhino-conjunctivitis, and eczema in children living in different regions, and make comparisons within and between countries; 2) to obtain baseline measures for assessment of future trends in the prevalence and severity of these diseases; and 3) to provide a framework for further aetiological research into factors affecting these diseases (Asher *et al.*, 1995). Phase I used simple validated written questionnaires and a video asthma questionnaire designed to measure the prevalence of allergic symptoms and signs in 6–7- and 13–14-year-old children (ISAAC Steering Committee, 1993). Approximately 3000 children in each age group were studied in each centre.

The ISAAC Phase II (1998–2004) aimed to identify determinants of the international differences by studying a limited number of informative populations, using objective measurements (Weiland *et al.*, 2004). The ISAAC Phase III (2000–03) was a repetition of the Phase I after a period of at least 5 years in order to evaluate trends in the prevalence of allergic diseases globally and to obtain information from regions not participating in the Phase I (Ellwood *et al.*, 2005).

The ISAAC Phase I has exceeded expectations in providing for the first time a global picture of the prevalence of childhood asthma, rhinoconjunctivitis, and eczema (ISAAC Steering Committee, 1998b; Warner, 1999). The study was completed in 156 centres from 56 countries and a total of 721 601 children participated. The differences in the prevalence of symptoms between different centres were striking. Thus, the prevalence of current wheeze ranged from 2% to 32%, with economically developed countries tending to have higher rates than less developed countries (ISAAC Steering Committee, 1998c). The highest rates were seen in English-speaking centres in the UK, Ireland, New Zealand, Australia, and Canada, followed by some of the South American centres. The lowest prevalences were observed in several Eastern European countries, Indonesia, Greece, China, Taiwan, Uzbekistan, India, and Ethiopia. A video questionnaire showing asthma symptoms without any language component showed a similar pattern. The prevalence of current rhinoconjunctivitis varied across centres from 1% to 40% (Strachan *et al.*, 1997), and the prevalence of eczema from 1% to 17% (Williams *et al.*, 1999). For these disorders, the centres with the highest prevalences were scattered across the world, while the centres with the lowest prevalences were similar to those for asthma symptoms. Furthermore, widely differing prevalences were found between centres with populations of similar ethnic origins within countries such as China (including Taiwan and Hong Kong), India, Italy, and Ethiopia (ISAAC Steering Committee, 1998b). A comparison of the prevalences of asthma and other allergic disorders in the ISAAC and in the ECRHS found a good agreement in the international patterns observed in the two surveys, adding support to the validity of these studies (Pearce *et al.*, 2000).

The results of the ISAAC Phase I suggest substantial worldwide variations in the prevalence and labelling of allergic symptoms which require further study. The marked differences in populations with similar geographical or ethnic backgrounds suggest that environmental factors are the major determinants of the prevalence of allergic diseases in a community.

Conclusion: The ISAAC has for the first time in a standardised manner shown striking differences in the prevalence of childhood allergies throughout the world and also provides the basis for further studies to investigate factors that potentially contribute to these international patterns.

2.4. Prevalence of allergies in Estonia

Populations with different lifestyle but otherwise similar should be compared to study the influence of lifestyle on a disease. Estonia and Sweden are culturally, geographically, and genetically similar and have similar levels of outdoor allergens (Ekebom *et al.*, 1998). However, in Estonia, the Soviet occupation preserved a more traditional lifestyle resembling the one in Scandinavia 30–40 years ago. Since the regaining of independence, Estonia has experienced profound social and economic changes, although the living conditions in Estonia are still not comparable with those in Scandinavian countries. Therefore studies of temporal changes and comparisons with Sweden may provide useful information about the impact of a Western lifestyle on the development of allergic diseases.

2.4.1. Studies in adults

According to the Estonian Bureau of Medical statistics and a few epidemiological studies, the prevalence of asthma was between 0.2% and 0.9% in Estonia during 1965–90 (Jannus *et al.*, 1972; Jannus *et al.*, 1981; Jannus-Pruljan and Loit, 1994).

In 1994–95, Jõgi *et al.* (1996; 1998) studied 2460 randomly selected subjects aged 20–44 years in Tartu, as a part of the ECRHS. Diagnosed asthma was reported by 2%, allergic rhinitis by 18%, and different respiratory symptoms by 8–41% of the participants (Jõgi *et al.*, 1996). Compared with the results of an identical study in Uppsala in Sweden, symptoms of asthma and allergic rhinitis were less common, but other respiratory symptoms more common in Tartu. A subsample of the subjects was studied using objective measurements. The prevalence of sensitisation was 19% (compared with 32% in Uppsala) based on allergen-specific IgE measurements, and 32% (comparable to Western European countries) based on SPT (Jõgi *et al.*, 1995; Jõgi, 1996; Jõgi *et al.*, 1998). The prevalence of BHR to methacholine was high (19%) and the levels of ECP were low in Tartu (Jõgi *et al.*, 2002; Jõgi *et al.*, 2004). There was an association between BHR and sensitisation in Uppsala, but not in Tartu, indicating that other causes than asthma and atopy could be responsible for the high prevalence of BHR in Estonia. The differences between Tartu and Uppsala were less pronounced in the older age groups, suggesting a cohort effect underlying the increasing prevalence of allergy in Western Europe (Jõgi *et al.*, 1998). Compared with all other ECRHS centres, the residents of Tartu had the lowest prevalence of asthma, and subjects with asthma were the least likely to receive asthma medication in Tartu (Burney *et al.*, 1996).

The FinEsS study, which started in 1995, aimed to compare the prevalence and characteristics of asthma, chronic bronchitis, and respiratory symptoms in Finland, Estonia, and Sweden. Altogether 17 525 subjects age 15–64 years participated in three regions of Estonia, i.e., Tallinn, Narva, and Saaremaa. In Tallinn, the prevalence of doctor-diagnosed asthma (2%) was one third of that in Stockholm and Helsinki, while the prevalence of doctor-diagnosed chronic bronchitis (11%) was three times as high as in Stockholm and Helsinki. Subjects having symptoms common in asthma were more likely to have doctor-diagnosed asthma in Stockholm and Helsinki than in Tallinn (Pallasaho *et al.*, 2002). The prevalence of SPT positivity, studied in a subsample of 516 subjects in Tallinn, was 35% in the whole study group, and as high as 46% in 17–24-year-olds (Raukas-Kivioja *et al.*, 2003). The study points to large differences in diagnostic practices between the three countries and to a considerable underdiagnosis of asthma in Estonia.

2.4.2. Studies in children

As a part of a comparative study in Estonia, Sweden, and Poland, 1519 schoolchildren aged 10–12 years were studied in Tallinn and Tartu in 1992–93. The prevalence of rates of questionnaire-reported disorders were: diagnosed asthma 3%, wheezing 7% (9% in Tallinn and 6% in Tartu), rhinoconjunctivitis 7%, and eczema 14%. Positive SPTs were more common in Tallinn than in Tartu, i.e., 14% and 8%. The prevalence rates of asthma and SPT positivity were similar in Estonia and Poland, and three times as high in Sweden, while the prevalence of wheezing was quite similar in the three countries (Bråbäck *et al.*, 1994; Riikjärv *et al.*, 1995). Methacholine challenge test was positive in 19% and 32% of the children, and exercise challeng test in 6% and 18% in Tallinn and in Tartu, respectively. In contrast to the results of studies in Western Europe, the interrelationship between BHR, diagnosed asthma, and reported wheezing was weak in Estonia, and most children (83%) with BHR were SPT-negative (Vasar *et al.*, 1996).

In 1993–94, children in Tallinn participated in the ISAAC Phase I. The results of the ISAAC in Scandinavia and Eastern Europe reflected the degree of "Westernisation" of the study centres. Thus, the prevalence of symptoms of asthma, allergic rhinitis, and eczema was higher in Sweden and Finland than in Estonia, Latvia, and Poland, which in turn had a higher prevalence than Albania, Romania, Russia, Georgia, and Usbekistan (Björkstén *et al.*, 1998).

In Tartu, two birth cohorts have been followed since 1993–94 (n=251) and 1997–98 (n=110). The cumulative incidence of sensitisation and allergic diseases was similar among Estonian and Scandinavian infants during the first years of life. (Julge *et al.*, 1997; Vasar *et al.*, 2000). After the age of two, the point prevalence of positive SPT dropped in Estonian children, suggesting a down-regulation of skin reactivity (Julge *et al.*, 2001).

So far no serial prevalence studies using the same methods over time have been conducted in Estonia.

Conclusion: In concordance with other East-West comparisons, allergy is significantly less common among children and adults in Estonia than in Scandinavian countries. The country in transition provides an opportunity to study the relationship between a Western lifestyle and the risk of allergy. Due to marked changes in lifestyle, an increase in the prevalence of allergic diseases would be expected in Estonia.

3. Gene-environment interaction in allergic diseases

Allergic diseases are complex and multifactorial. Their development and phenotypic expression depend on an interaction between genetic factors, environmental exposure to allergens, and nonspecific adjuvant factors. The interaction between genotype and environment is complex and variable among distinct populations (Ober, 1998).

3.1. Heredity

Children born from parents with asthma or other allergic diseases present an increased risk of developing similar diseases (Moffatt and Cookson, 1998). The presence of familial aggregation of these diseases may indicate either shared genes or a common household environment and lifestyle. Several genes involved in asthma and allergic diseases have been identified (Duffy, 2001). However, according to twin studies, between 25% and 64% of the susceptibility to asthma is explained by environmental influences (Koppelman *et al.*, 1999).

Maternal heredity is more strongly associated with childhood allergic diseases than paternal heredity (Moffatt and Cookson, 1998). The aetiology of this stronger maternal transmission may be both genetic and environmental, including maternal-fetal interaction, the composition of breast milk, and shared physical environment of mother and child (Moffatt and Cookson, 1998; Björkstén, 1999). This is supported by an association found between the prevalence of asthma in young adults who were adopted as infants and in their adoptive mothers (Smith *et al.*, 1998).

Although heredity is strongly related to the development of allergy, it could not account for the differences in the prevalence of allergic diseases in populations with similar genetic background (von Mutius *et al.*, 1994b; Nowak *et al.*, 1996) or for the increase in these diseases in the span of not one or two generations (Sly, 1999). Furthermore, Christie *et al.* (1998) suggested that much of the recent increase in asthma prevalence is occurring in children without a significant genetic predisposition.

Conclusion: Although heredity is an important risk factor for the development of allergic diseases, it does not account for the current trends in the prevalence of these diseases.

3.2. Environment

The striking geographical differences in the prevalence of allergic diseases and the short period over which changes in the prevalence have occurred indicate an environmental influence. The importance of environmental factors is further supported by migrant studies. In migrants from developing countries to countries with a Westernised lifestyle, the length of stay increased the risk of sensitisation and allergic symptoms (Leung *et al.*, 1994; Ormerod *et al.*, 1999; Powell *et al.*, 1999). Furthermore, lower risk of allergy has been observed among populations with a more traditional lifestyle, such as rural dwellers, farmers, and followers of an anthroposophic lifestyle (Alm *et al.*, 1999; Filipiak *et al.*, 2001). The modern Western lifestyle, by which people spend more time indoors in well-insulated and warm homes, has resulted in increased indoor humidity and an increased exposure to indoor allergens, new building materials, and air pollutants, which has possibly contributed to the increase in allergies; other potentially important factors incude stress, extensive traveling, and changes in dietary habits and in the microbial environment (Björkstén, 1999). Which aspects of this modern Western lifestyle account for the epidemic of allergy, is, however, still largely unknown.

3.2.1. Allergen exposure

The dose-response relationship between allergen exposure and the development of sensitisation may be different for different allergens (Custovic and Murray, 2002). The effect of allergen exposure on sensitisation is well established for house dust mite (Kuehr *et al.*, 1994; Peat *et al.*, 1996). The relationship is less cosistent for pets and a protective effect of pet ownership on sensitisation and allergic diseases has been reported in several studies (reviewed by Apelberg *et al.*, 2001; Apter, 2003). Exposure to a high level of cat allergen may result in a modified T-helper 2 (Th2) response characterised by the presence of IgG4 antibodies to cat proteins without IgE response, which could be regarded as a form of tolerance (Custovic and Murray, 2002; Hesselmar *et al.*, 2003).

There is good evidence for the association between allergen exposure and disease severity in sensitised individuals (Gelber *et al.*, 1993), and several studies have reported a dose-response relationship between allergen exposure and severity of asthma (Sporik *et al.*, 1993; Chan-Yeung *et al.*, 1995; Platts-Mills *et al.*, 1997). However, the relationship between allergen exposure and development of allergic disease is as yet unresolved (Custovic and Murray, 2002). Thus, in the prospective German Multicentre Allergy Study early indoor allergen exposure was associated with sensitisation, and sensitisation, in turn, with asthma, wheeze, and BHR, whereas no relation was found between allergen exposure and the prevalence of asthma, wheeze, or BHR (Lau *et al.*, 2000). The authors concluded that their data did not support the hypothesis that exposure to environmental allergens causes asthma in childhood, but rather that the induction of specific IgE responses and the development of childhood asthma are determined by independent factors.

The evidence of importance of exposure to allergens is even less consistent for eczema. Some subjects with atopic eczema clearly suffer from exacerbations after contact with or inhalation of aeroallergens (Tupker *et al.*, 1996) or after ingestion of allergy-inducing foods (Eigenmann *et al.*, 1998) and house dust mite avoidance strategies have markedly decreased the severity of symptoms in some studies (Sanda *et al.*, 1992; Tan *et al.*, 1996). However, in one study, domestic house dust mite exposure was inverse related to patch test reactivity in patients with eczema (Gutgesell *et al.*, 1999) and in some double-blind placebo-controlled studies, house dust mite control measures resulted in significant decrease in mite allergen concentration without any change in the severity of eczema among subjects allergic to house dust mite (Gutgesell *et al.*, 2001; Oosting *et al.*, 2002).

3.2.2. Hygiene hypothesis

The rise in the prevalence of allergies is in contrast to the decrease in morbidity related to infectious diseases and to improved hygiene during the 20th century, which has led to the concept of the hygiene hypothesis (Strachan, 1989). The increasing prevalence of allergies in Western countries has been attributed to the lack of induction of immune response due to less exposure to certain infectious agents (Cookson and Moffatt, 1997). Neonates have an immune system skewed towards a Th2 profile, associated with allergen-specific IgE production. It is believed that insufficient exposure to certain infectious agents during early life leads to maintenance of this Th2 profile, instead of the normal maturation towards a Th1 profile, triggered by microbial stimuli (Holt *et al.*, 1997).

3.2.2.1. Number of siblings and daycare attendance

It has been suggested that declining family size may contribute to the increased prevalence of allergic diseases in Western countries (von Mutius *et al.*, 1994a). A review of 53 studies on the effect of the number of siblings on the risk of allergic disorders found an inverse association with the number of siblings in 48 studies, and a positive relation only in three studies (Karmaus and Botezan, 2002). An inverse association with eczema was reported in 9 of the 11 studies [the weighted average odds ratio (OR) 0.66 for having three or more *vs* no siblings]; with asthma and wheezing in 21 of the 31 studies (OR 0.93); with hay fever in all 17 studies (OR 0.56), and with positive SPT or IgE reactivity in 14 of the 16 studies (OR 0.62). Most studies with detailed results by number of siblings indicated a dose-response relation between the number of siblings and allergic disorders. The authors suggest that if the factor causing the sibling effect was identified and applied, at least 30% of allergic diseases could be prevented.

In a series of three studies among schoolchildren in UK, family size was related to asthma symptoms in 1994, while in 1986 there was a nonsignificant, weak association, and no association was observed in 1977, suggesting that the siblings effect was stronger for more recent cohorts (Rona *et al.*, 1999).

The impact of older siblings on allergy has been attributed to an increase in early infections (Strachan, 1989). However, several studies have shown that the protective effect of siblings is independent from early infections (Cullinan *et al.*, 2003; Benn *et al.*, 2004) and there is evidence suggesting that the sibling effect may have its origin in utero (Karmaus *et al.*, 2001).

Wickens *et al.* (1999a) analysed the change in family size in the UK and New Zealand between 1961 and 1991 in relation to asthma and allergic rhinitis. Despite progressive reduction in family size, the expected relative increase in the prevalence of asthma as a result of the smaller family size was only 1% for the UK and 5% for New Zealand, and the increase in the prevalence of allergic rhinitis 4% for the UK. Thus, changes in family size do not appear to explain much of the increase in the prevalence of these diseases.

Children who attend daycare have more infections (Holberg *et al.*, 1991; Krämer *et al.*, 1999b), which could explain the lower prevalence of allergies in the formerly socialist countries where early daycare attendance was more common (von Mutius *et al.*, 1994b). However, according to a review of eight studies (Nystad, 2000), daycare attendance has been associated both with increased and decreased risk of asthma and sensitisation in different populations.

3.2.2.2. Infections

The reports on the relationship between infections and allergy are conflicting. Measles have been associated both with decreased (Shaheen *et al.*, 1996; Bodner *et al.*, 1998) and increased (Paunio *et al.*, 2000) risk of allergic disorders. Similarly, early respiratory infections were related both to protection against asthma and sensitisation (Illi *et al.*, 2001a) and to increased risk of asthma (Ponsonby *et al.*, 1999). Infection caused by respiratory syncytial virus is an important cause of wheezy episodes in early life and is related to decreased lung function and development of asthma (Stein *et al.*, 1999; Sigurs *et al.*, 2000). Both increased (Sigurs *et al.*, 2000) and decreased (Juntti *et al.*, 2003) risk of sensitisation has been related to respiratory syncytial virus.

Seropositivity to orofecal and foodborne infections, such as hepatitis A, *Toxoplasma gondii*, and *Helicobacter pylori*, which may be regarded as a marker of poor hygiene, was related to a lower prevalence of sensitisation and allergic diseases in Italy (Matricardi *et al.*, 1997; Matricardi *et al.*, 2000), but not in the UK (Cullinan *et al.*, 2003).

There are also conflicting data about the association between infections and allergic diseases in children with parental history of allergies. In a recent Norwegian study, airway infections were related to decreased risk of sensitisation in children of atopic parents and to increased risk of asthma in children of nonatopic parents (Njå *et al.*, 2003). In contrast, in the USA, early daycare attendance was associated with decreased risk of asthma in children without maternal history of asthma and with increased risk of wheezing among children with maternal history of asthma (Celedón *et al.*, 2002).

3.2.2.3. Mycobacteria

Exposure to mycobacteria, both natural infection and Bacillus Calmette-Guérin (BCG) vaccination induces a strong Th1-type immune response (Del Prete *et al.*, 1991; Marchant *et al.*, 1999). In animal models, BCG infection protects against subsequent development of IgE antibody formation and allergen induced airway inflammation (Erb *et al.*, 1998; Herz *et al.*, 1998; Tukenmez *et al.*, 1999; Bakir *et al.*, 2000; Su *et al.*, 2001; Major *et al.*, 2002; Tsai *et al.*, 2002), and even against established allergy (Wang and Rook, 1998; Koh *et al.*, 2001; Hopfenspirger and Agrawal, 2002; Yang *et al.*, 2002).

In humans, the relationship between exposure to mycobacteria and atopic diseases is inconsistent. In ecological studies, based on the data from the ISAAC study, the prevalence of asthma symptoms was inversely associated with tuberculosis notification rates (von Mutius *et al.*, 2000; Shirtcliffe *et al.*, 2002), but not with immunisation rates for tuberculosis (Anderson *et al.*, 2001). A history of tuberculosis was related to a lower prevalence of allergic diseases in Finnish women (von Hertzen *et al.*, 1999). Early BCG vaccination protected children against allergen sensitisation in Guinea-Bissau (Aaby *et al.*, 2000), while in Sweden (Alm *et al.*, 1997; Strannegård *et al.*, 1998), a general protective effect was not observed, or was restricted to children with a foreign background. There are also reports suggesting a therapeutic effect of mycobacteria on pre-existing allergic disease (Arkwright and David, 2001; Barlan *et al.*, 2002; Cavallo *et al.*, 2002; Choi and Koh, 2002; Matricardi *et al.*, 2003).

Delayed type hypersensitivity to tuberculin is a marker of Th1-mediated immunity to mycobacteria. Positive tuberculin responses in Japanese schoolchildren were inversely related to allergic diseases, allergen-specific IgE levels, and Th2 cytokine profiles (Shirakawa *et al.*, 1997). This inverse relationship has been interpreted either as the result of an inhibiting effect of different mycobacteria on allergic disorders or as a reflection of an impaired Th1 immunity among atopic individuals (Martinati and Boner, 1997; Strannegård *et al.*, 1998). Nevertheless, several subsequent studies in different populations have failed to demonstrate any association between allergic disorders and tuberculin responsiveness (Omenaas *et al.*, 2000; Yilmaz *et al.*, 2000; Grüber *et al.*, 2001; Wong *et al.*, 2001b; Jentoft *et al.*, 2002; Pahari *et al.*, 2002), and some studies even revealed stronger responses to mycobacteria among allergic children (Strannegård *et al.*, 1998; Ozmen *et al.*, 2002).

3.2.2.4. Intestinal microbiota

Marked differences have been found in the composition of the intestinal microbiota among infants in Estonia and Sweden (Sepp *et al.*, 1997; Sepp *et al.*, 2000). In Estonian children, the counts of aerobic bacteria were more common during the first week of life (Sepp *et al.*, 2000), and lactobacilli more common at 1 month (Sepp *et al.*, 2000), and 1 year (Sepp *et al.*, 1997). The microbiota of the Estonian infants resembled the flora prevailing in infants of Western Europe in the 1960s, suggesting a shift in the microbiota among infants in Western countries (Sepp *et al.*, 1997). There were also differences in the composition of the intestinal microbiota between allergic and nonallergic children both in Estonia and Sweden (Björkstén *et al.*, 1999) and the differences were demonstrable before the development of any clinical manifestations of allergy (Björkstén *et al.*, 2001). These findings suggest that intestinal colonisation in early childhood may contribute to the international variation in allergy. The role of intestinal microbiota in the development of allergy has been confirmed in several studies, as reviewed by Kalliomaki and Isolauri (2003).

3.2.2.5. Antibiotics

The effect of early use of antibiotics on bacterial colonisation of the infant gut may explain the association between allergic diseases and early antibiotic treatment reported in several studies (Farooqi and Hopkin, 1998; Wickens *et al.*, 1999b; Droste *et al.*, 2000), as the reduced gut colonisation by lactic bacilli is associated with antibiotic use (Alm *et al.*, 2002). Another explanation for this association could be that allergic children are more likely to receive antibiotics due to respiratory symptoms.

An ecologic analysis of the relationship between antibiotics sales and the prevalence of symptoms of asthma, rhinoconjunctivitis, and eczema based on data of the ISAAC from 28 countries found an association between per capita antibiotics sales and the prevalence of allergic symptoms, but the associations generally became negative once the analyses had been adjusted for gross national product (Foliaki *et al.*, 2004). There was a statistically significant positive association with wheezing as measured by the asthma video questionnaire; however, even this association was weak and would not account for more than a 1% difference in asthma prevalence between countries. The authors concluded that if there is a causal association of antibiotic use with asthma risk, it does not appear to explain the international differences in asthma prevalence.

3.2.3 Breastfeeding

Although there are some reports that breastfeeding may increase the risk of allergic diseases and sensitisation (Wright *et al.*, 2001a; Wright *et al.*, 2001b; Bergmann *et al.*, 2002; Sears *et al.*, 2002), several recent systematic reviews of the literature indicate a protective effect of breastfeeding against the development of allergy. In a meta-analysis of 18 prospective studies that evaluated the association between exclusive breastfeeding during the first 3 months of life and atopic eczema, the summary OR was 0.68, 95% confidence interval (CI) 0.52–0.88 (Gdalevich *et al.*, 2001a). This effect estimate was higher in children with a family history of atopy (OR = 0.58; CI 0.41–0.92) and negligible in children without a history of atopy in first-degree relatives (OR = 1.43; CI 0.72–2.86). Meta-analyses of 12 prospective studies of asthma (Gdalevich *et al.*, 2001b) and six studies of allergic rhinitis (Mimouni Bloch *et al.*, 2002) in relation to exclusive breastfeeding for at least 3 months resulted in a summary OR of 0.70 (95% CI 0.60–0.81) for asthma in the first 5 years of life and 0.74 (95% CI 0.54–1.01) for allergic rhinitis. In children with a family history of atopy, the ORs were 0.52 (95% CI 0.35–0.79) and 0.87 (95% CI 0.48–1.58) for asthma and allergic rhinitis, respectively.

A review of 56 studies of the impact of early feeding on development of allergic disease was performed by a multidisciplinary group of researches (van Odijk *et al.*, 2003). The review panel agreed that breastfeeding reduces the risk of cow's milk allergy, asthma, and eczema, particularly in children with atopic heredity, and the protective effects seem to persist at least during the first decade of life. Similarly, a group of experts of the Section of Pediatrics of the European Academy of Allergy and Clinical Immunology reviewed critically the existing literature on the subject (Muraro *et al.*, 2004). They concluded that breastfeeding is highly recommended for all infants irrespective of atopic heredity and excusive breastfeeding for at least 4–6 month is effective in the prevention of allergic diseases in high-risk children.

The increase in the prevalence of allergic diseases in Western Europe cannot be related to breastfeeding, however, as a trend towards a higher prevalence and a longer duration of breastfeeding was observed in Western European countries during the last decades of the 20th century (Yngve and Sjöström, 2001). Furthermore, the duration of breastfeeding is longer in Scandinavian countries than in most postsocialist Eastern European countries, and even in these developing countries where the prevalence of breastfeeding is high, breastfeeding is not exclusive due to early introduction of complementary foods (Fleischer Michaelsen *et al.*, 2000).

3.2.4. Environmental tobacco exposure

The effect of parental smoking on respiratory and allergic disorders in offspring was thoroughly reviewed in a series of meta-analyses by Cook and Strachan. Among schoolchildren, the pooled OR was 1.21 (95% CI 1.10–1.34) for asthma (25 studies), and 1.24 (95% CI 1.17–1.31) for wheeze (41 studies) (Cook and Strachan, 1997). While maternal smoking had a greater effect, the effect of only paternal smoking was also significant suggesting a postnatal effect. In longitudinal studies, maternal smoking was associated with an increased incidence of wheezing illness up to age 6 (four studies, pooled OR 1.31, 95% CI 1.22–1.41), but less strongly thereafter (four studies, OR 1.13, 95% CI 1.04–

1.22) (Strachan and Cook, 1998b). The excess incidence of wheezing in smoking households appeared to be largely nonatopic wheezing with a relatively benign prognosis, but among children with established asthma, parental smoking was associated with more severe disease. Maternal smoking (particularly during pregnancy or infancy) was associated with small deficits in spirometric indices in schoolchildren (Cook *et al.*, 1998). There was no clear effect of exposure to environmental tobacco smoke on BHR, while limited evidence suggested greater variation in peak expiratory flow in children of smoking parents (Cook and Strachan, 1998). Among children without asthma or wheezing, there was no association between parental smoking during pregnancy or infancy and SPT positivity (12 studies, pooled OR 0.87, 95% CI 0.62–1.24), concentrations of total serum IgE, allergic rhinitis, or eczema (Strachan and Cook, 1998a).

Mitchell and Stewart (2001) performed an ecological analysis of the relationship between tobacco smoking as reported by the World Health Organisation and the prevalence of symptoms of asthma and other allergic diseases based on data of the ISAAC from 56 countries. Children living in countries with high adult male smoking rates were found to have a lower risk of asthma and rhinitis symptoms, indicating that this well-established individual-level association does not account for the international differences in asthma prevalence, and that other risk factors for asthma must be responsible for the observed international patterns. Consistently, the prevalence of asthma and other allergic disorders was higher in Swedish schoolchildren, although current parental smoking was more common in Estonia and Poland in a previous Estonian-Swedish-Polish study (Bråbäck *et al.*, 1995).

3.2.5. Other lifestyle factors

Other factors related to Western lifestyle that have been suggested to influence the prevalence of allergic diseases include air pollution (Duhme *et al.*, 1998), an increase in overweight/obesity (Chinn and Rona, 2001), decreased physical activity (Rasmussen *et al.*, 2000), use of certain fuels for heating (Duhme *et al.*, 1998), gas cooking (Kerkhof *et al.*, 1999), indoor dampness (Bornehag *et al.*, 2001), changes in diet (with more fatty acids and fewer vegetables) (Black and Sharpe, 1997; Ellwood *et al.*, 2001), and use of paracetamol (Eneli *et al.*, 2005). However, none of the identified factors can more than marginally explain the increase in allergies.

Conclusion: Epidemiological studies have identified several environmental factors related to Western lifestyle, which could influence the prevalence of allergic diseases. However, which lifestyle factors account for the epidemic of allergy is still largely unknown.

AIMS

The main objective of the present investigation was to elucidate the epidemiology of allergic diseases in Estonian schoolchildren. The specific aims were as follows:

1. To compare the following manifestations of allergy in Estonian and Swedish schoolchildren:
   - self-reported symptoms of asthma, rhinitis, and eczema (Paper II);
   - positive SPT to aeroallergens (Paper II);
   - self-reported food hypersensitivity and the presence of IgE antibodies to food allergens in wheezing and non-wheezing children (Paper IV).

2. To assess the impact of the following factors on allergic symptoms in Estonian schoolchildren:
   - sensitisation and BHR (Papers I, II);
   - parental allergy (Thesis);
   - tuberculin reactivity and the age at BCG vaccination (Paper III);
   - home environment and certain lifestyle-related factors (Paper II, Thesis).

3. To assess time trends in the prevalence of allergic disorders in Estonia (Papers I, V).

MATERIALS AND METHODS

This thesis is based on three cross-sectional questionnaire-based prevalence studies (Papers I–III, V) and a case-control study derived from the second prevalence study (Papers II, IV). The design of the studies mainly adhered to the ISAAC Phase I–III protocols (ISAAC Steering Committee, 1993; ISAAC Steering Committee, 1998a; Ellwood *et al.*, 2000; http://isaac.auckland.ac.nz), with some additional study elements. Main characteristics of the four studies are summarised in Table 1.

Table 1. Study characteristics of the ISAAC Phase I–III (Papers I–V)

	Age groups (years)	**Study areas**	**Study period**	**Elements of the study**	**Papers**
Phase I	6–7, 13–14	Tallinn	1993–94	Core questionnaires, video questionnaire *	V
Phase II	10–11	Tallinn, Linköping, Östersund	**Prevalence study**		
			1996–97	Core questionnaires, additional respiratory questionnaire, SPT, data about BCG and Mantoux**	I, II, III, IV
			Case-control study		
			1998–99	Risk factor and food allergy questionnaire, skin examination, lung function tests, IgE food panel	II, IV
Phase III	6–7, 13–14	Tallinn	2001–02	Core questionnaires, video questionnaire *, risk factor questionnaire	V

*: only 13–14-yr-old children; **: only in Tallinn.

In order to examine time trends, the results of the ISAAC Phase II were compared with the results of a similar study, performed among 10–12-year-old children in Tallinn in 1992–93 (Riikjärv *et al.*, 1995). Likewise, the ISAAC Phase III was a repetition of Phase I after a period of 8 years. The time frame of the studies is given in Figure 1.

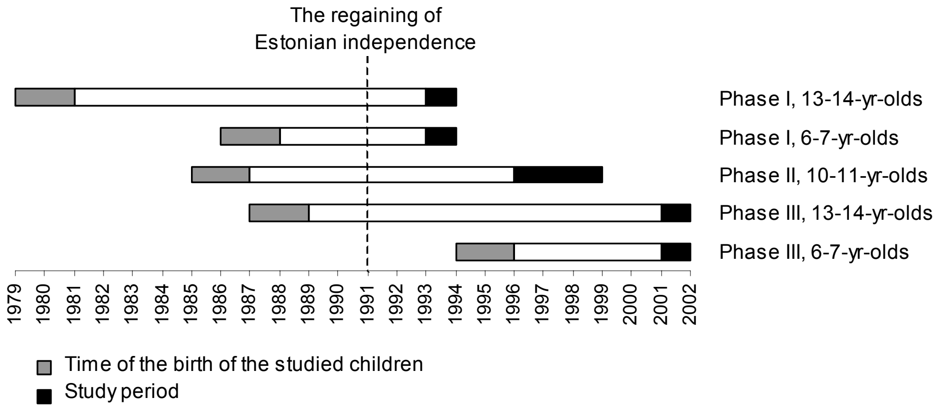


Figure 1. Time frame of the ISAAC Phase I– III (Papers I–V).

1. Study areas

The studies were conducted in Tallinn (Papers I–V), which is the capital of Estonia, and in two towns in Sweden, i.e., Linköping and Östersund (Papers II, IV) (Figure 2). Tallinn (420 470 inhabitants in 1997) is situated in Northern Estonia on the coast of Baltic Sea (latitude 59°), Linköping (132 089 inhabitants in 1997) is a university town in Southern Sweden (latitude 58°), Östersund (59 188 inhabitants in 1997) is an administrative centre in Northern Sweden (latitude 61°) (Fig. 1). The climate is maritime in Tallinn and continental in Östersund. The annual mean temperatures are 4.8° C, 6.1° C, and 2.5° C, and the annual precipitations 609, 517, and 484 mm in Tallinn, Linköping, and Östersund, respectively.

Figure 2. Study centres.

In order to allow comparisons between the centres, the same study protocol was followed and the same equipment used in every study centre. All the field workers were trained to perform the investigations in a standardised manner and checked for consistency during the field work.

2. Study populations

The selection of the study populations met the criteria of the ISAAC Phase I–III (ISAAC Steering Committee, 1993; ISAAC Steering Committee, 1998a; Ellwood *et al.*, 2000).

2.1. ISAAC Phase I and Phase III (Paper V)

All children in those two grades with the highest proportion of 6–7- or 13–14-year-old children from all Estonian language schools and daycare centres in Tallinn were invited to participate in the studies. Participation rates and characteristics of the study population are shown in Table 2. The number of 6–7-year-old participants decreased over the 8 years study period due to the fall in birth rate [crude birth rate 16.2 in 1987 and 9.4 in 1995 (Population 2001, 2002)]. Respondents who were outside of the 5–9 and 12–15 years age range were excluded from the analysis, i.e., no children in the younger and 30 in the older age group in 1993–94 and 5 children in the younger and 29 in the older age group in 2001–02.

Table 2. Participation rates and characteristics of the study population, the ISAAC Phase I and III (Paper V)

	Phase I 1993–94	**Phase III** 2001–02
6–7-year olds		
Invited	3382	2786
Core questionnaires	3070 (91%)	2388 (86%)
Boys	50%	51%
Mean age (years ± SD)	6.46±0.67	6.63±0.62
13–14-year olds		
Invited	3953	3860
Core questionnaires	3506 (89%)	3605 (93%)
Video questionnaire	3454 (87%)	3284 (85%)
Boys	49%	50%
Mean age (years ± SD)	13.59 ± 0.70	13.43 ± 0.73

All the studied children spent their first years of life in the Soviet Union, except for the 6–7-year olds in Phase III who were born well after the restitution of independence (Figure 1).

2.2. ISAAC Phase II, prevalence and case-control study (Papers I–IV)

Clusters of children were randomly selected in each centre for the study, using schools as sampling units. In Tallinn, 20 schools were selected among the Estonian language schools. In Linköping, the survey involved 15 schools and in Östersund, all 25 schools were selected due to the smaller population. All 10–11-year-old children in the targeted schools were invited to participate in the survey.

As the second step in the ISAAC Phase II, all children with a history of wheeze in the past 12 months, as reported in the core questionnaire, and a random sample of nonwheezing children from the original cohorts were invited to a case-control study. Figure 3 shows participation rates in the different parts of Phase II. The lower participation rates for SPT and IgE measurements were due to reluctance by parents or children.

	Tallinn		Linköping		Östersund	
Prevalence study						
Base population	1158		1115		1390	
Core questionnaire	979 (85%)		911 (82%)		1197 (86%)	
SPT	643 (56%)		859 (77%)		992 (71%)	
Case-control study						
Current wheeze	yes	no	yes	no	yes	no
	81	882	72	838	122	1070
Random sample		259		207		244
Additional questionnaire	67 (83%)	227 (88%)	62 (86%)	143 (69%)	109 (89%)	170 (70%)
Skin examination	54 (67%)	188 (73%)	59 (82%)	125 (60%)	109 (89%)	171 (70%)
Spirometry	56 (69%)	188 (73%)	59 (82%)	125 (60%)	109 (89%)	171 (70%)
Bronchial challenge	56 (69%)	184 (71%)	56 (81%)	117 (57%)	77 (63%)	135 (55%)
IgE food panel	38 (47%)	125 (48%)	52 (72%)	110 (53%)	103 (84%)	164 (67%)

Figure 3. Participation rates in different parts of the ISAAC Phase II (Paper I–IV).

3. Questionnaires

The questionnaires were distributed through the schools and were completed by the parents of the 6–7- and 10–11-year-old children. The 13–14-year-old children completed the questionnaires at school.

3.1. Core questionnaires (Papers I–V)

The standardised and validated ISAAC core written questionnaires, inquiring about lifetime and current symptoms and severity of wheezing, rhinitis, and eczema, were used in all the three phases of the study. The questionnaires were translated from the original English version into Estonian and translated back to English in order to check for translation bias. The original questionnaires and the Estonian versions are given in Appendices I and II. Table 3 presents the main definitions used.

Table 3. Definitions of diagnosed asthma and the main symptoms of asthma, rhinitis, and eczema based on the core ISAAC questionnaires.

Term	Affirmative answer to the following question:
Wheeze	Has your child had wheezing or whistling in the chest in the past 12 months?
Exercise-induced wheeze	In the past 12 months, has your child's chest sounded wheezy during or after exercise?
Asthma ever	Has your child ever had asthma?
Current asthma	Has your child ever had asthma? + Has your child had wheezing or whistling in the chest in the past 12 months?
Rhinitis	In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?
Rhinoconjunctivitis	In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?
Seasonal rhinitis	In the past 12 months, did this nose problem occur in any of the following months: April, May, June, July, or August?
Itchy rash	Has your child had an itchy rash, which was coming and going for at least six months, at any time in the past 12 months?
Flexural rash	Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

3.2. Video questionnaire (Paper V)

The ISAAC international video questionnaire (ISAAC Phase I Manual,1993) was shown to the 13–14-yr-old participants after the completion of the core questionnaire. The video presented five scenes with symptoms of asthma in different situations: wheeze at rest, exercise-induced wheeze, sleep-disturbing wheeze, sleep-disturbing cough, and severe wheeze. After each scene, the participants were asked to specify whether they had experienced similar symptoms.

3.3. Supplementary questionnaires (Papers I, II, IV)

Supplementary questionnaires contained questions about additional respiratory symptoms (the ISAAC Phase II Module 2.1, 1998), asthma management, and current treatment (the ISAAC Phase II Module 2.2, 1998), food allergy, and environmental risk factors.

Questionnaire-reported food allergy was defined as a positive response to the question: “Is your child allergic to any food (yes/no)?” (Paper IV). The parents were also asked if and how their child reacted to sixteen different foods, i.e., milk, egg, fish, wheat, mandarin, orange, apple, peach, kiwi, avocado, banana, carrot, tomato, peanut, nut, and almond.

The risk factor questionnaire used in Phase II focused on home environment (Papers I, II), the questionnaire used in Phase III also enquired about parental allergy, breastfeeding, and medication use (Thesis).

4. Skin examination (Papers I, II)

Children were examined for visible flexural eczema according to the ISAAC Phase II Module 3.1 containing a photographic protocol (1998). The presence or absence of signs of eczema was recorded for any of the following areas: 1) around the eyes, 2) around the sides and front of the neck, 3) fronts of elbows, 4) behind the knees, and 5) fronts of ankles. Visible flexural eczema was defined as the presence of signs of eczema at any of these areas.

5. Skin prick tests (Papers I–IV)

Sensitivity to seven prevalent aeroallergens was assessed by SPT with standardised allergen extracts (Soluprick SQ, ALK, Hørsholm, Denmark): *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, cat dander, dog dander, birch pollen, timothy pollen, and *Alternaria tenuis***.** Histamine 10 mg/ml and diluent were used as positive and negative controls. Extracts of the same batch were used in all three towns. The tests were performed on the volar aspect of the left forearm according to the ISAAC Phase II Module 3.2 (1998) using ALK lancets. The results were measured 15 min after the pricks. The test was considered positive if the wheal diameter was ≥ 3 mm, measured as the sum of the orthogonal diameters divided by two. SPT positivity was defined as at least one positive reaction.

All field workers performed series of SPTs with histamine before the onset of the study, until the coefficient of variation was less than 20%. The quality of the test was checked during the field work according to the ISAAC Phase II Module 3.2 (1998). The tests were carried out before the pollen season in all three centres.

6. Lung function tests (Paper II)

Baseline and post-challenge forced expiratory volume in one second (FEV_1) were measured by MasterScope Version 4.3 (Jäger, Würzburg, Germany) adhering to the ISAAC Phase II Module 3.3 (1998). Children were asked to withhold short-acting bronchodilators for 6 h and long-acting bronchodilators for 12 h prior the test. For the baseline FEV_1, the best of two reproducible (within 5%) measurements was chosen.

Bronchial reactivity was assessed by changes in FEV_1 after inhalation of hypertonic 4.5% saline, nebulized via an ultrasonic nebulizer DeVilbiss Ultraneb 2000 (DeVilbiss, Somerset, USA). According to the ISAAC Phase II Module 3.3 (1998), BHR was defined as a decline in FEV_1 of 15% or greater as compared with the baseline during progressively increasing inhalation periods of 0.5, 1, 2, 4, and 8 min. or after the total cumulative inhalation time 15.5 min. To ensure that the output was adequate for each challenge, the output of the nebuliser was measured, by weighing the canister and tubing prior to and on completion of each challenge test. If the baseline FEV_1 was less than 75% of predicted (none in Tallinn, one child in Linköping and four in Östersund), a bronchial reversibility test was performed instead of a challenge. A positive reversibility test was defined as an increase of FEV_1 of 15% or more after two inhalations of 200 μg Salbutamol.

The field workers participated in training sessions arranged by the ISAAC Phase II Steering Committee in Munich and Linköping. The same equipment was used in each town.

7. IgE antibodies (Paper IV)

The sampling and handling of blood samples were done according to the ISAAC Phase II Module 3.4 (1998). Serum samples obtained from the children were stored at $-20^{o}C$ until used**.** IgE antibodies against a panel of six relevant food allergens (fx5; egg white, milk, soya bean, fish, wheat, and peanut) were analysed with the Pharmacia CAP System Specific IgE FEIA (Pharmacia Diagnostics, Uppsala, Sweden) in the ISAAC Phase II reference lab in Stockholm. The IgE antibody levels were expressed in kU_A/l and defined as class 0 (< 0.35), class 1 (0.35 to < 0.7), class 2 (0.7 to < 3.5), class 3 (3.5 to < 17.5), class 4 (17.5 to < 50), class 5 (50 to < 100), and class 6 (100 and larger).

8. Register data (Paper III)

The data about BCG vaccinations and tuberculin testing were obtained retrospectively from the children's medical records at school, which were available for 723 individuals (74% of the children participating in the ISAAC Phase II) from 17 of 20 participating schools.

Of the 723 children with medical records, 717 (99%) had received BCG vaccination. A Soviet *Mycobacterium bovis var* BCG strain (Minmedbioprom, USSR), containing 500 000–1 500 000 live microbes in one dose of 0.05 mg was used for vaccination. At the time of their first BCG vaccination, 89% of the children were less than 1 month (usually 3–4 days) old, 6% were 1 to 11 months, and 5% at least 1 year old. Altogether 282 (39%) children with a negative tuberculin response (no induration, nor hyperaemia) at 7 years of age were vaccinated a second time with the same BCG strain.

The children were periodically tested for tuberculin conversion in policlinics and in school medical offices using intradermal Mantoux test with 2 tuberculin units of purified protein derivate (Minmedbioprom, USSR/Russia) on the volar aspect of the forearm. The results were recorded after 72 hours as the diameter of the induration. The test was considered positive if the diameter of the wheal was $\geq$ 5 mm. As testing had become optional by the end of the 1990s, the frequency and the age of testing varied between the medical offices. Of the 717 BCG vaccinated children, 715 were tested at least once. In our analysis, we used the results of the tuberculin tests performed at the age of 2–3, 6–7, and 10–11 years. If a child was tested at another age, the result of the test was included into the closest of the ranges. Altogether 471 children had been tested at least once at 1–4 years, 599 at 5–8 years, and 343 at 9–12 years of age.

9. Statistical analysis

Data was entered and checked for coding errors and inconsistencies using the Microsoft database management system FoxPro. Statistical analyses were performed using statistical software programs STATA, SAS, and SPSS. To compare the differences in prevalence rates between groups, OR with 95% CI and Chi-squared tests, or Fisher's exact tests if appropriate, were employed. Statistical significance was set at the 5% level. In the Phase I and Phase III studies, the prevalence rates based on questionnaire responses were calculated by dividing the number of affirmative responses to each question by the total number of completed questionnaires (conservative prevalence estimates) adhering to the ISAAC recommendations (ISAAC Steering Committee, 1998c). Missing or inconsistent responses were excluded from bivariate analyses. In Phase II, the prevalence rates were calculated by dividing the number of affirmative responses by the number of those who answered the respective question. Multivariate logistic regression analyses were used to calculate OR with adjustments for different covariables. In the case-control study (Paper II), an univariate variance analysis was used to determine adjusted differences in baseline FEV_1 mean value between the groups and to obtain an estimate of the predicted value for the individuals.

10. Ethical considerations

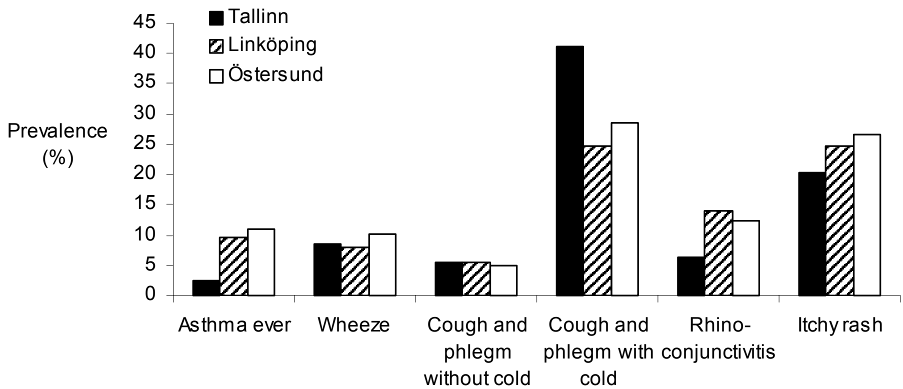
The studies were approved by the Tallinn Medical Research Ethics Committee and the Ethics Committees at Linköping University and Umeå University. The parents of the participating children gave their written informed consent separately for each element of the study.

RESULTS AND DISCUSSION

1. Manifestations of allergy in Estonian and Swedish children

1.2. Respiratory and allergic symptoms (Paper II)

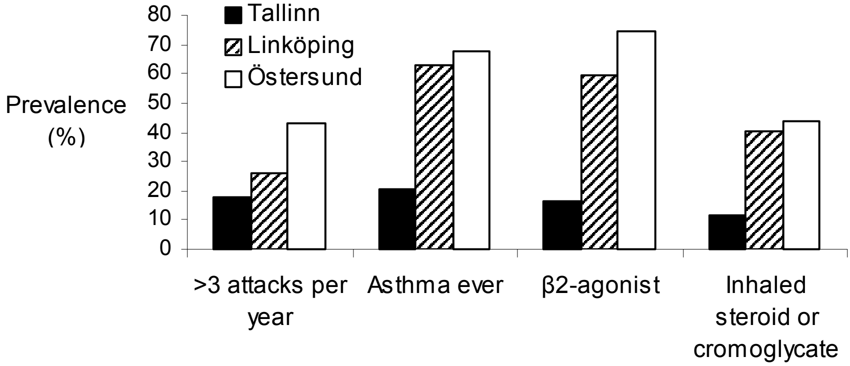
The questionnaire-reported prevalence of symptoms of allergic rhinoconjunctivitis and eczema was higher in Swedish than in Estonian 10–11-year-old children (Figure 4). In addition, the prevalence of objectively verified flexural eczema was 4% in Estonia (both in wheezing and nonwheezing children) compared with 12% (OR 3.6, 95% CI 1.5–8.9) in nonwheezing and 24% (OR 8.4, 95% CI 1.9–37.1) in wheezing children in Sweden. The prevalence of wheezing was similar in the two countries, while diagnosed asthma was four times as common in the two Swedish towns as in Tallinn (Figure 4). On the other hand, cold-related cough and phlegm were reported more frequently in Estonia.



OR (95% CI)		Asthma ever	Wheeze	Cough and phlegm without cold	Cough and phlegm with cold	Rhino-conjunctivitis	Itchy rash
	L *vs* T	4.1 (2.5–6.7)	0.9 (0.7–1.3)	1.0 (0.7–1.5)	0.5 (0.4–0.6)	2.5 (1.8–3.5)	1.3 (1.0–1.6)
	Ö *vs* T	4.7 (3.0–7.6)	1.2 (0.9–1.6)	0.9 (0.6–1.3)	0.6 (0.5–0.7)	2.1(1.5–2.9)	1.4 (1.2–1.7)

Figure 4. Diagnosed asthma and current respiratory and allergic symptoms among 10–11-year-old Estonian and Swedish children, prevalence (%) and OR with 95% CI, Linköping *vs* Tallinn (L *vs* T) and Östersund *vs* Tallinn (Ö *vs* T).

Among wheezing children, frequent wheezing (at least four attacks during the last year), diagnosed asthma, and antiasthmatic medication were more likely in Sweden (Figure 5).



OR (95%CI)		>3 attacks per year	Asthma ever	β2-agonist	Inhaled steroid or cromoglycate
	L *vs* T	1.6 (0.7–3.6)	6.4 (2.9–14.3)	11.4 (4.9–26.4)	5.0 (2.0–12.4)
	Ö *vs* T	3.5 (1.8–7.0)	8.0 (3.9–16.6)	14.7 (6.7–32.5)	5.8 (2.5–13.5)

Figure 5. Frequent wheezing attacks, diagnosed asthma, and asthma medication among 10–11-year-old wheezing children in Estonia and Sweden, prevalence (%) and OR with 95% CI, Linköping *vs* Tallinn (L *vs* T) and Östersund *vs* Tallinn (Ö *vs* T).

These findings are comparable to the results of a previous study of allergic and respiratory disorders in Estonian, Swedish, and Polish schoolchildren, reporting a similar prevalence of wheezing in all three countries, while diagnosed asthma was markedly more common in Sweden, and frequent common colds and prolonged cold-related coughing bouts were more prevalent in Estonia and Poland (Bråbäck *et al.*, 1994; Riikjärv *et al.*, 1995). Several other Estonian-Swedish comparisons have confirmed a lower prevalence of asthma and allergies, and higher rates of nonspecific/infectious respiratory symptoms in Estonian children and adults. Thus, in Estonian infants, respiratory illnesses are more common and allergies less common than Swedish infants (Voor *et al.*, 2005). In Estonian adults, the prevalence of asthma is markedly lower than in Sweden and Finland, while the prevalence of respiratory symptoms and diagnosed chronic bronchitis is significantly higher (Burney *et al.*, 1996; Jõgi *et al.*, 1996; Pallasaho *et al.*, 2002). Similar observations come from East Germany and other Eastern European countries, where bronchitis and non-specific respiratory symptoms were found to be more common and asthma and allergies less common than in Western Europe (von Mutius *et al.*, 1992; von Mutius *et al.*, 1994b; Krämer *et al.*, 1999a; Selnes *et al.*, 2001; Leonardi *et al.*, 2002).

The inconsistency between the prevalence of respiratory symptoms and asthma have led to the presumption that the East-West difference in the prevalence of asthma may be largely attributable to differences in diagnostic practice and thus reflects a higher prevalence of undiagnosed asthma in Eastern Europe (Selnes *et al.*, 2001; Leonardi *et al.*, 2002; Pallasaho *et al.*, 2002). In his recent paper Jõgi (2005) discusses the possibility of over- or underdiagnosis of asthma in Estonia. He concludes that although there is some evidence of underdiagnosis of asthma in Estonia, it does not explain the high prevalence of respiratory symptoms, which may be influenced by the high prevalence of environmental tobacco smoke exposure and frequent respiratory infections due to crowded living conditions. Recently, a screening study was performed among 10–20-year-old Estonian schoolchildren and adolescents in four smaller towns without specialised allergology services (Vasar *et al.*, 2004). After preliminary screening, the children suspected to have asthma or other allergic disease were referred to a paediatric allergologist for the conclusive diagnosis. In this study, the prevalence of asthma was 3.7%, and 35% of these cases were newly diagnosed. Surprisingly, a very similar proportion of underdiagnosed asthma (37%) was found among 12–15-year-old Danish schoolchildren (Siersted *et al.*, 1998). These results show that an underdiagnosis of asthma is not extensive enough to explain the low prevalence of asthma in Estonia, not even in regions without specialised services.

In our study, the prevalence of wheezing was similar in Estonian and Swedish children in spite of the higher prevalence of diagnosed asthma in Sweden. However, regardless of the lower use of asthma medication in Estonia, the prevalence of frequent wheezing attacks was higher in Sweden. This discrepancy suggests that an increased awareness and differences in diagnostic procedures cannot sufficiently explain the lower prevalence of asthma in Estonia. The difference in the aetiology of wheezing in Estonian and Swedish children should also be considered. Furthermore, there seems to be a genuine difference in the prevalence of allergic rhinoconjunctivitis and eczema in Estonia and Sweden, as the assessment of the prevalence of these disorders was based on the description of symptoms, not on the doctor-made diagnosis, and was further confirmed by an objective skin examination for visible eczema. Thus, these findings affirm that the previously found differences in the prevalence of respiratory and allergic disorders between Western industrialised and East European postsocialist countries still exist.

1.2. Sensitisation to aeroallergens (Paper II)

The results of SPTs with aeroallergens among 10–11-year-old children were in concordance with the questionnaire-reported symptoms of allergy; i.e., compared with Tallinn, the prevalence of positive SPT to at least one allergen was higher both in Linköping (OR 1.5, 95% CI 1.1–1.9) and in Östersund (OR 2.1, 95% CI 1.6–2.8) (Figure 6). Furthermore, positive SPTs were less common in Estonia than in several other European and Asian centres of the ISAAC Phase II (Figure 6), indicating that sensitisation is still relatively low in Estonia.

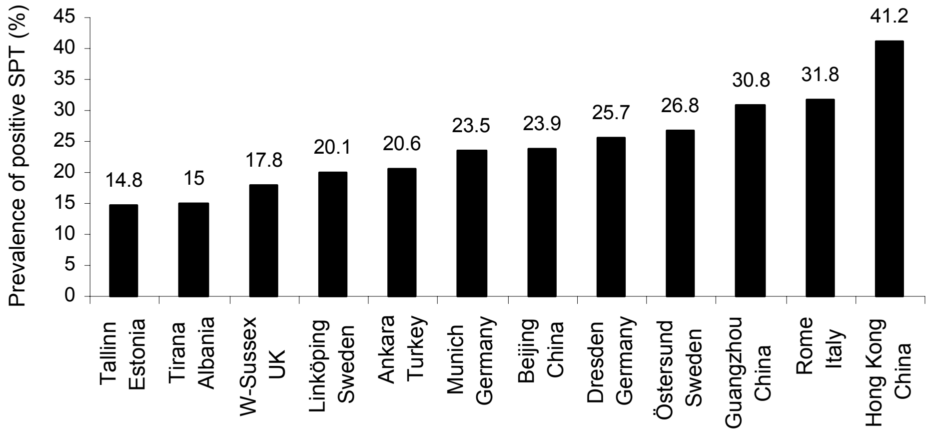
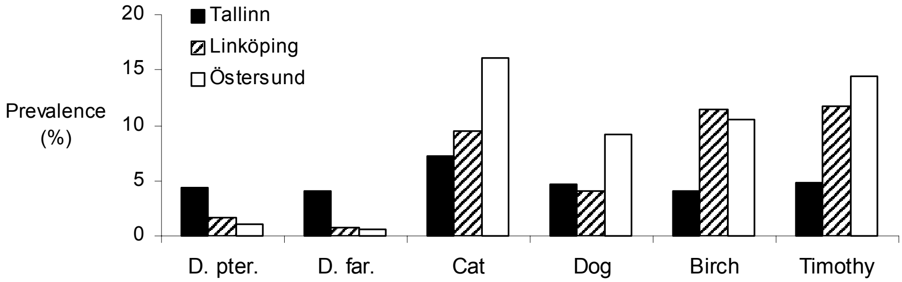


Figure 6. Prevalence of positive SPT to at least one aeroallergen among 10–11-year-old children in Estonia and Sweden and in the ISAAC Phase II centres in Albania (Priftanji *et al.*, 2001), UK (Priftanji *et al.*, 2001), Turkey (Kuyucu *et al.*, 2004), Germany (Weiland *et al.*, 1999), China (Wong *et al.*, 2002), and Italy (Di Domenicantonio *et al.*, 2003).

The use of a standard battery of aeroallergens for SPTs in our study may have caused some underestimation of the prevalence of sensitisation, both in Sweden and in Estonia. According to more recent reports, mites other than *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* contribute to sensitisation in Sweden (Warner *et al.*, 1998; Warner *et al.*, 1999). Furthermore, our choice of allergens did not include four of the five allergens, which were the most common cause of sensitisation in a recent study among adults in Tallinn, i.e., cockroach, mugwort, *Lepidoglyphus destructor,* and *Acarus siro* (Raukas-Kivioja *et al.*, 2003). However, the tested sample in that study comprised only 28% of the initial study population, and therefore may poorly represent the general population. A recent study assessed SPT positivity among Estonian schoolchildren in Tartu using an extended panel of allergens (Julge, 2005). In that study, the prevalence of sensitisation to these four allergens (1.4% to cockroach, 2.3% to mugwort, and 1.9% to *Lepidoglyphus destructor* and *Acarus siro*) was low compared with the allergens in the standard battery (Julge, 2005). Low prevalence of sensitisation to mugwort (2.6%) has also been reported among schoolchildren in Tallinn (Riikjärv *et al.*, 1995). Therefore, it is not likely that an extended panel of allergens would have markedly increased the prevalence of sensitisation in Estonian children.

A deeper analysis revealed allergen-specific differences in the pattern of positive SPTs in Estonia and Sweden (Figure 7). In Tallinn, sensitivity to pollens was less common than in both Swedish towns and sensitivity to animals less common than in Östersund. In contrast, positive SPTs to dust mites were more common in Tallinn. Domestic allergen levels have been found to be moderately higher for animals and remarkably higher for dust mites in Tartu (Estonia) than in Linköping (Böttcher *et al.*, 2003), while airborne pollen concentrations are similar in Estonia and in Sweden (Ekebom *et al.*, 1998). Thus, when exposed to similar allergen levels, fewer children become sensitised in Estonia than in Sweden.



		D. pter.	D. far.	Cat	Dog	Birch	Timothy
OR	L *vs* T	0.4 (0.2–0.7)	0.2 (0.1–0.5)	1.3 (0.9–2.0)	0.8 (0.5–1.4)	3.1 (2.1–4.6)	2.6 (1.7–4.0)
(95% CI)	Ö *vs* T	0.2 (0.1–0.5)	0.1 (0.1–0.4)	2.5 (1.8–3.5)	2.0 (1.9–4.1)	2.8 (1.8–4.4)	3.3 (2.2–5.0)

Figure 7. Positive SPTs to aeroallergens among 10–11-year-old children in Estonia and Sweden, prevalence (%) and OR with 95% CI, Linköping *vs* Tallinn (L *vs* T) and Östersund *vs* Tallinn (Ö *vs* T). D. pter.: *Dermatophagoides pteronyssinus*; D. far.: *Dermatophagoides farinae*.

1.3. Food hypersensitivity (Paper IV)

The prevalence of self-reported food allergy to any food was similar among 10–11-year-old children in Estonia and Sweden and about twice as likely in wheezing children as in nonwheezing children, both in Estonia and Sweden (Figure 8). However, only 3% of the Estonian wheezing children reported reactions to more than three food allergens compared with 16% among wheezers in Sweden. Furthermore, different foods were reported as the main triggers of symptoms in Estonia and Sweden (Figure 8). Swedish children more frequently reported allergy to nut, peanut, apple, peach, kiwi, and carrot, which are known to cross-react with birch pollen (Sicherer, 2001; Vieths *et al.*, 2002). Thus, these reactions were likely IgE-mediated. In Estonia, however, symptoms were most frequently associated with orange, mandarin, or tomato, which are not considered as common allergens.

Similar results have been reported in a study among patients (mainly adults) with a history of food hypersensitivity in Sweden, Denmark, Estonia, Lithuania, and Russia (Eriksson *et al.*, 2004). Birch pollen related foods, such as nuts, apple, kiwi, and peach were most often reported to cause symptoms in the Scandinavian countries and the reactions correlated strongly with SPT to birch pollen. Furthermore, in these countries, oral allergy syndrome, a typical feature of pollen-related food allergy, was the most frequent expression of food hypersensitivity. In the Eastern European countries, however, citrus fruits, chocolate, and honey were the most common causes of hypersensitivity, and urticaria or itching was the leading complaint. These results, together with our findings, suggest that self-reported reactions to foods are frequently IgE-mediated in Scandinavia, while in Eastern Europe perceived food hypersensitivity is mostly related to nonallergic reactions. The interpretation of these observations is related both to a different perception of food allergy in the two countries and a higher prevalence of pollen allergy in Scandinavia. A possible role of different dietary habits should also be considered, as consumption of fruits and vegetables is low in Baltic countries (Pomerleau *et al.*, 2001). In addition, dietary habits and food handling may affect the gut microbiota. The intestinal microbiota in Estonian children comprise more lactobacilli than in Swedish children (Sepp *et al.*, 1997), which may possibly affect the development of tolerance to foods (Björkstén *et al.*, 1999).

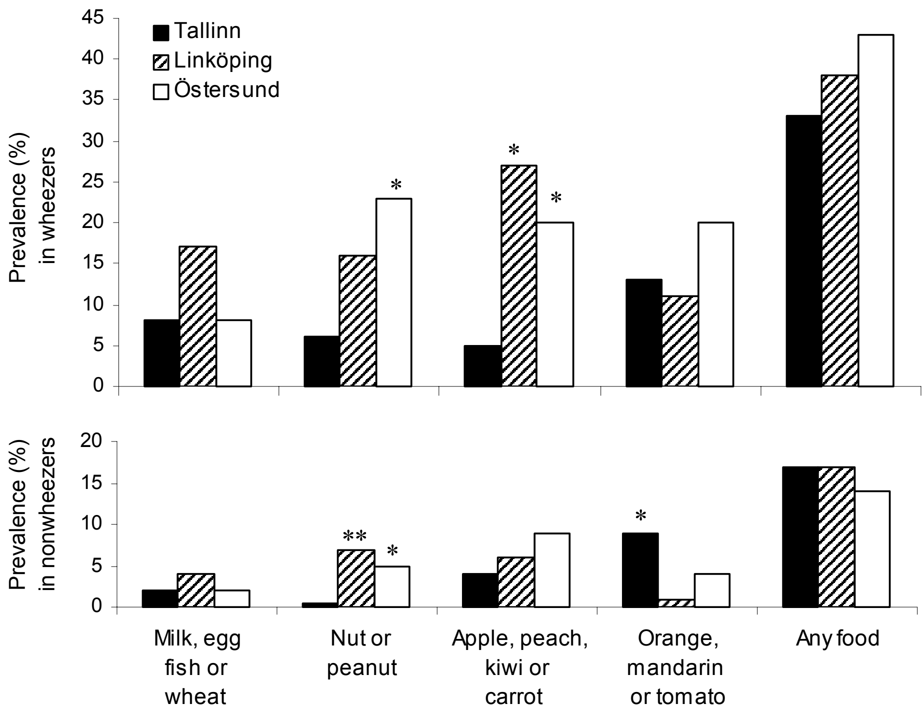


Figure 8. Prevalence of self-reported food allergy among wheezing and nonwheezing 10–11-year-old children in Estonia and Sweden. *: $p < 0.01$, **: $p < 0.001$.

The prevalence of circulating IgE antibodies to food allergens was similar in wheezing and nonwheezing Estonian children and similar to the prevalence in nonwheezing Swedish children, but significantly higher in Swedish wheezing children (Table 4).

Table 4. Prevalence rates, OR and 95% CI of positive IgE to food allergens among wheezing and nonwheezing 10–11-year-old Estonian and Swedish children

	Positive IgE to food allergens			
	Wheezers		Nonwheezers	
	Prevalence	OR (95% CI)	Prevalence	OR (95% CI)
Tallinn	3/38 (8%)	1	10/125 (8%)	1
Linköping	20/52 (39%)	7.3 (2.0–26.9)	12/110 (11%)	1.4 (0.6–3.4)
Östersund	25/103 (24%)	3.7 (1.1–13.2)	12/164 (7%)	0.9 (0.4–2.2)

Furthermore, in Estonian children, the antibody levels were generally low, i.e., among the 12 children with positive IgE panel, only one child had level 3 and none had level 4 or higher. Among the 69 Swedish children with positive IgE panel, 13 had level 3 and 12 had level 4 or higher. In addition, low levels of IgE antibodies were associated with reported food allergy in Sweden, but not in Estonia, i.e., among children with IgE class 1–2, food allergy was reported among 16/44 children in Sweden and among 2/12 children in Estonia. Two prospective studies have shown that low levels of circulating IgE antibodies to food and aeroallergens are common in Estonian children, and are not related to SPT positivity and clinical symptoms, indicating a downregulation of allergic manifestations in Estonia (Julge *et al.*, 2001; Voor *et al.*, 2005).

Our study suggests that IgE-mediated food reactions are less common in Estonia than in Sweden, and low levels of IgE antibodies are not associated with allergic manifestations in Estonia. In addition, the perception of food allergy and thereby the meaning of self-reported food allergy appears to be different in the two countries.

2. Relationship between allergic symptoms, sensitisation, and BHR

2.1. Symptoms and SPT positivity (Paper I)

Estonian children with positive SPT had significantly higher prevalence of diagnosed asthma (6% *vs* 2%), wheezing (15% *vs* 7%), exercise wheezing (11% *vs* 5%), rhinitis without cold (33% *vs* 16%), rhinoconjunctivitis (16% *vs* 5%), and flexural rash (26% *v*s 15%), while there was no such association with night cough and itchy rash without specified location (ORs shown in Figure 9, a). When both sexes were analysed separately, wheezing was related to positive SPT in girls (OR 3.5, 95% CI 1.4–9.1), but not in boys (OR 1.6, 95% CI 0.6–3.9), although sensitisation was twice as common in boys (20% *vs* 10%, OR 2.2, 95% CI 1.4–3.4). Despite the relationships between symptoms and SPT positivity, only minority of the symptomatic children were sensitised, i.e., about one third of the children with diagnosed asthma or rhinoconjunctivitis, and about one quarter of the children with wheezing, rhinitis, or flexural rash (Figure 9, b). Positive SPT was most common in children with combination of rhinoconjunctivitis and flexural rash, i.e, 52.9% (OR 7.2, 95% CI 2.7–19.5). The low correlation between symptoms and SPT results indicate that allergy-like symptoms in Estonian schoolchildren are mostly of nonallergic origin.

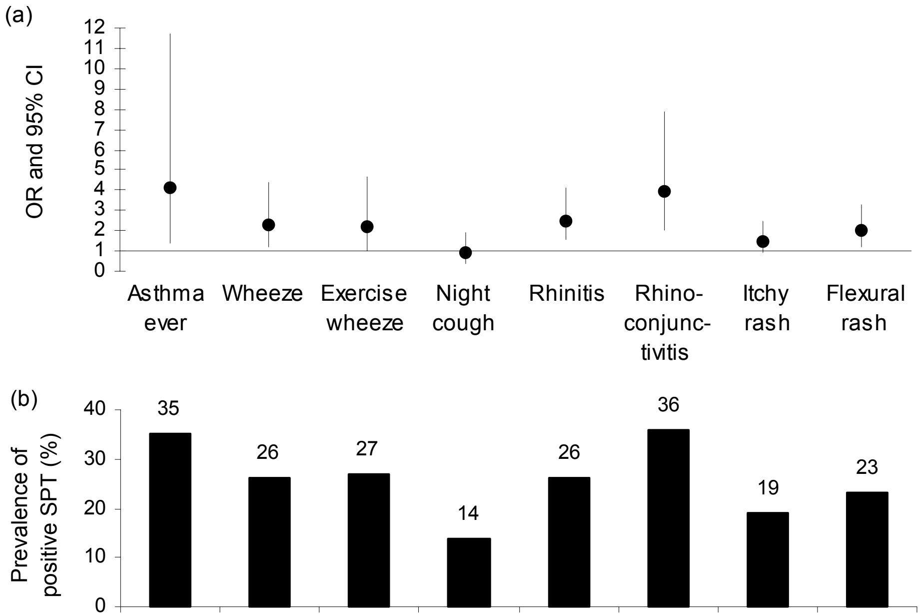


Figure 9. Positive SPT in relation to diagnosed asthma and current respiratory and allergic symptoms among 10–11-year-old Estonian children. (a) OR and 95% CI, SPT-positive *vs* SPT-negative children. (b) Prevalence (%) of positive SPT in symptomatic children.

Shortly after the reunification of Germany, the prevalence of eczema was found to be higher among children in East Germany than in West Germany, in contrast to the data about other allergic diseases and sensitisation (Schäfer *et al.*, 1996). Still, the prevalence of positive SPT was 50% among children with eczema in West Germany, compared with 37% in East Germany, indicating that the excess of eczema in East Germany was related to nonallergic type (Schäfer *et al.*, 2000). These findings, together with our results, suggest that factors other than sensitisation could be responsible for allergy-like symptoms in less affluent countries. However, when comparing the prevalences of sensitisation and symptoms over different areas worldwide, no distinct pattern can be shown. In some regions, such as China and some African coutries, asthma is uncommon despite markedly high prevalence of sensitisation (Leung and Ho, 1994; Sunyer *et al.*, 2000; Zhao *et al.*, 2000; Wong *et al.*, 2001a). Furthermore, in Ethiopia, positive SPT was a risk factor for asthma in urban area and a protective factor in rural area (Yemaneberhan *et al.*, 1997). There was no significant difference in SPT results among schoolchildren in Australia and Nigeria, while in Australia, wheezing was twice as common and asthma five times as common as in Nigeria (Faniran *et al.*, 1999). In a Lima shanty town with a high prevalence of asthma-like symptoms among schoolchildren, neither symptoms nor BHR to exercise correlated with SPT, and the prevalence of positive SPT was 29% in children with current asthma compared with 24% in the whole population (Penny *et al.*, 2001). In the ECRHS, the overall attributable fraction of asthma symptoms caused by atopy (specific IgE) was 30%, ranging from 4% in Tartu, Estonia to 61% in Barcelona (Sunyer *et al.*, 2004). These discrepancies between symptoms and sensitisation might partly reflect differences in awareness of allergies, but they also suggest that the factors related to the development and persistence of sensitisation and allergy-like disorders would be different.

2.2. Wheezing in relation to atopy and BHR in Estonia and Sweden (Paper II)

Wheezing was strongly associated with rhinoconjunctivitis, positive SPT, and BHR to hypertonic saline among 10–11-year-old children both in Estonia and in Sweden (Table 5). However, the proportion of children with rhinoconjunctivitis, positive SPT, or a positive bronchial challenge was much lower in Estonia than in Sweden, both in wheezing and nonwheezing children. Furthermore, the baseline FEV_1 mean value was lower in Sweden than in Estonia both in wheezing and nonwheezing children and lower in wheezers than in nonwheezers in Sweden but not in Estonia. The mean difference between Tallinn and Linköping (after adjustment for sex, height, weight, and age) was 0.2 L (95% CI 0.09–0.4) in wheezers and 0.2 L (95% CI 0.1–0.3) in nonwheezers. The mean difference between Tallinn and Östersund was 0.3 L (95% CI 0.2–0.4) in wheezers and 0.3 L (95% CI 0.2–0.4) in non-wheezers. Six children in Sweden (five with current wheezing) and none in Estonia had a baseline FEV_1 of less than 75% of the predicted value.

Table 5. Current rhinoconjunctivitis, positive SPT, and lung function among wheezing (W) and […] year-old Estonian and Swedish children

	Tallinn			Linköping		
	W %	NW %	OR (95% CI)	W %	NW %	OR (95% CI)
Rhinoconjunctivitis	16	2	12.0 (3.8–38.0)	49	11	8.0 (4.2–15.2)
≥1 positive SPT	26	9	3.4 (1.5–7.5)	49	16	5.1 (2.7–9.6)
Positive bronchial challenge	13	3	5.1 (1.6–16.8)	48	15	5.1 (2.5–10.6)
Positive bronchial challenge or reversibility test	14	4	3.8 (1.3–10.5)	50	16	5.2 (2.6–10.6)

Numerous studies have demonstrated a close relationship between SPT reactivity, BHR, and the frequency of wheezing symptoms (Clifford *et al.*, 1989; Pattemore and Holgate, 1993; Burrows *et al.*, 1995). Consistently, a positive bronchial challenge in children with current wheezing was closely related to SPT positivity in our study. In Sweden, the proportion of children with BHR was 52% in current wheezers with positive SPT, and only 26% in current wheezers with negative SPT (OR 3.1, 95% CI 1.5–6.5). Corresponding proportions among wheezing children in Estonia were 30% and 6%, respectively (OR 6.4, 95% CI 0.9–46.1).

Wheezing in childhood may represent different phenotypes, which differ in relation to atopy and other characteristics (von Mutius *et al.*, 1999; Martinez, 2002). In our study, although wheezing symptoms were equally common in Estonia and Sweden (Figure 4), the wheezing children differed remarkably. Estonian wheezers were characterised by higher baseline lung function, and lower prevalence of BHR and atopy. Furthermore, they had less severe symptoms and were also less likely to be labelled as asthmatics and to receive asthma medication (Figure 5). Our findings are in concordance with the results of a Norwegian study, which indicated that diagnosed asthma and wheezing without asthma label represent different wheezing phenotypes (Nystad *et al.*, 1999).

An increased awareness of asthma and allergies could explain the high proportion of wheezing children with diagnosed asthma and current treatment in Sweden. However, the high rate of BHR and frequent wheezing in Sweden despite antiasthmatic medication would rather suggest a difference in the severity of wheezing between Swedish and Estonian children. A major part of the wheezers in Sweden used β_2-agonists (Figure 5). Concerns have been raised that long-term treatment with β_2-agonists could contribute to increased BHR and worsening of asthmatic symptoms (Beasley *et al.*, 1999).

The surprisingly low prevalence of BHR in Estonian children was unexpected. In a previous study among 10–11-year-old children in Tallinn, BHR to methacholine was observed in 38% of the wheezers and 16% of the nonwheezers, and a positive exercise test in 18% and 5%, respectively (Vasar *et al.*, 1996). However, a poor agreement between BHR and positive SPT was found in that study. In our study, the prevalence of BHR to hypertonic saline among SPT positive wheezers was five times as high as among SPT negative ones (although the difference was not statistically significant due to a small number of subjects). The mechanisms underlying bronchial responsiveness probably differ in allergic and nonallergic individuals and different stimuli act through different bronchoconstricting mechanisms (Siersted *et al.*, 1996; Grootendorst and Klaus, 2004). Direct airway challenges with agonists such as methacholine or histamine are highly sensitive, but not specific to asthma, whereas indirect challenges with exercise, hypertonic aerosols, or adenosine may reflect more directly the ongoing airway inflammation and are therefore more specific, but less sensitive to identify active asthma (Riedler *et al.*, 1998;

Joos *et al.*, 2003). Hyperresponsiveness to adenosine is likely to be a marker of allergic inflammation in the airways (Lúdvíksdóttir *et al.*, 2000). If this was also true for BHR to hypertonic saline, it would at least partly explain the low number of positive challenges among wheezing children in Estonia.

Due to the striking difference in the prevalence of BHR in Estonian and Swedish children, a difference in the performance of the test in Estonia and Sweden could be suspected. However, the mean output from the nebulizer was slightly higher in Estonia than in Sweden, i.e., 1.85 ml/min (standard deviation, SD 0.48) in Tallinn, 1.41 ml/min (SD 0.86) in Linköping, and 1.45 ml/min (SD 0.86) in Östersund. Furthermore, the percentage of children, not completing the challenge test due to subjective complaints or lack of motivation was smaller in Estonia than in Sweden, i.e. 0%, 2% and 13% for wheezers and 2%, 7% and 16% for nonwheezers in Tallinn, Linköping, and Östersund, respectively. Thus, poor technique would not explain the lower prevalence of BHR in Estonia. Moreover, a higher baseline FEV_1 in Estonian children would be in agreement with the lower prevalence of sensitisation and BHR in this population.

In another comparison between ISAAC Phase II centres, a 7-fold difference in the prevalence of both asthma and BHR and a 3-fold difference in the prevalence of wheezing were found between the schoolchildren in UK and Albania, while the prevalence of positive SPT was similar (Priftanji *et al.*, 2001). In Costa Rica, an ISAAC Phase II centre with one of the highest asthma prevalences in the world, current wheezing was reported in 50% of the children (Celedon *et al.*, 2002). The prevalence of BHR to hypertonic saline was 78% and 36% and the prevalence of positive SPT 91% and 61% among children with and without asthma, respectively. However, in a multivariate analysis, high level of total IgE, but not positive SPT, was related to asthma. In contrast, in Chinese ISAAC Phase II centres in Hong Kong, Beijing, and Guangzhou, the prevalence of current wheeze was only 6%, 4%, and 3%, while the prevalence of positive SPT was 41%, 24%, and 31%, respectively. Wheezing was associated with sensitisation to individual allergens, but not with atopy, defined as at least one positive SPT result (Wong *et al.*, 2002).

A recent comparison of ISAAC Phase II centres in 17 countries shows large international differences in the prevalence and characteristics of wheezing (Weinmayr *et al.*, 2004). The prevalence of current wheezing ranges from 3% (China) to 22% (New Zealand). Among wheezing children, diagnosed asthma ranges from 20% to > 80% and positive SPT from 4% to 70%. The prevalence of atopic wheeze (wheeze plus positive SPT) varies from < 1% to 14% and the prevalence of nonatopic wheeze from 3% to 10%. Altogether 33% of the variation in prevalence of wheeze between centres can be explained by atopy. These results of other ISAAC Phase II centres, together with our ones, indicate that there are not only geographical differences in the prevalences of allergic diseases, but allergy-like symptoms in regions with different lifestyles also represent different phenotypes of these diseases.

3. Factors related to allergic diseases

3.1. Parental allergy

The relationship between questionnaire-reported allergic diseases in 6–7-year-old children and their parents was assessed in the ISAAC Phase III (data only presented here). A parental history of an allergic disease was a risk factor for allergic disorders in the offspring, in particular for the same condition (Figure 10). Adjustment for significant environmental risk factors (discussed in section 3.5) did not significantly influence the results (data not shown).

The greatest risk was associated with maternal asthma, which had the most pronounced influence on asthma in girls (OR 9.9, 95% CI 4.1–23.8). There was also a strong association between asthma in fathers and daughters (OR 7.2, 95% CI 2.5–20.5), in mothers and sons (OR 5.8, 95% CI 2.7–12.5), and in fathers and sons (OR 4.5, 95% CI 1.9–10.9). Studies, which have used the ISAAC questionnaire to assess the relationship between asthma among schoolchildren and their parents in countries with higher prevalence of asthma, reported ORs between 2.6 and 3.0 for atopic or nonspecified asthma/wheeze and between 3.9 and 4.1 for nonatopic asthma/wheeze (Rönmark *et al.*, 1999; Celedon *et al.*, 2001; Soto-Quiros *et al.*, 2002; Kurukulaaratchy *et al.*, 2004). In a study in UK, the association between parental history of an allergic disease and asthma in offspring was weaker than what had been reported in similar studies in the past (Christie *et al.*, 1998). The authors suggest that much of the increase in asthma prevalence is occurring in children without a significant genetic predisposition, i.e., in children who would have been at low risk of developing asthma one or two generations earlier. It has been suggested that the environmental factors that are related to the current increase in asthma exert their influences in subjects with certain genetic background, which differs from the genetic factors associated with more "endemic " forms of asthma and other allergic diseases (Patino and Martinez, 2001). The strong relationship between parents' and offspring's asthma in our study may indicate that the proportion of new "epidemic" forms of asthma that are related to novel environmental factors and specific genetic background is still smaller in Estonia than in countries with higher prevalence of asthma.

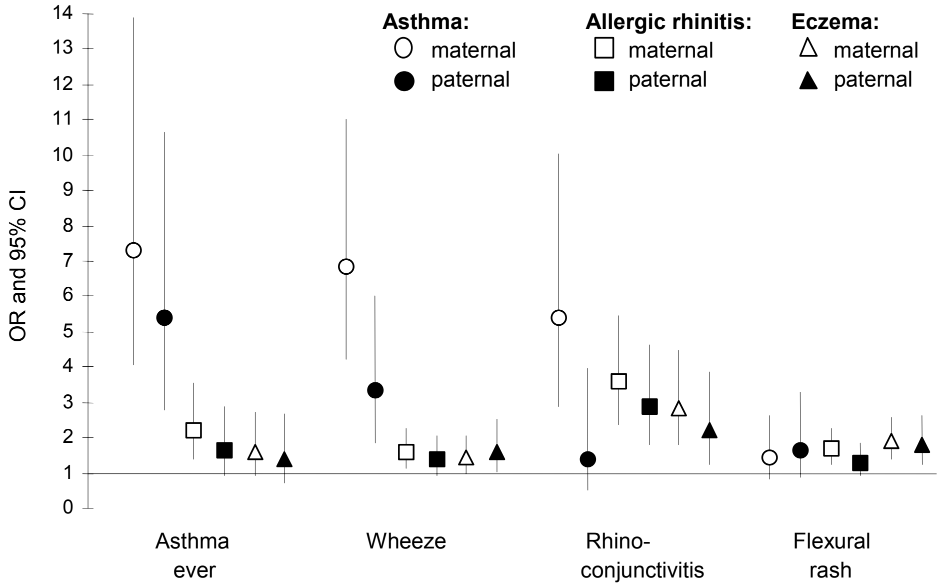


Figure 10. Sex-adjusted OR and 95% CI of diagnosed asthma and current allergic symptoms among 6–7-year-old Estonian children in relation to parental asthma, allergic rhinitis, and eczema.

3.2. Age at BGC vaccination (Paper III)

Although the prevalence of allergic symptoms at 10–11 years of age tended to be lower in children who were vaccinated during the first month of life (mostly at the age of 3–4 days) compared with children immunised later, the difference was not statistically significant (Figure 11).

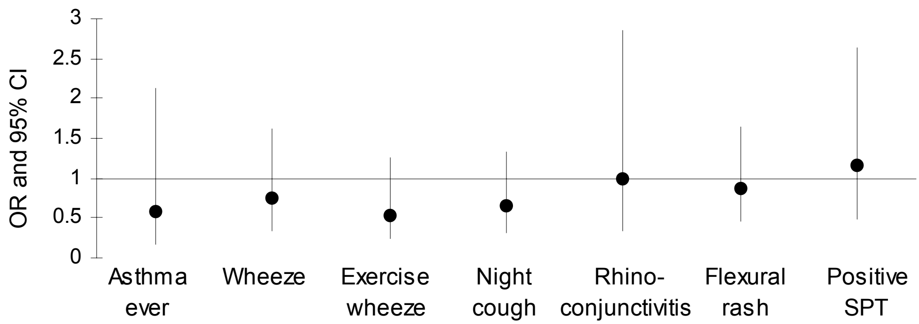


Figure 11. Diagnosed asthma, current respiratory and allergic symptoms, and positive SPT in Estonian children at 10–11 years of age in relation to the age at BGC vaccination (≤ 1 month *vs* > 1 month).

Stimulation of Th1-type immunity during the first months of life has been suggested to enhance protection against allergy later in life (Holt *et al.*, 1997; Martinez and Holt, 1999). In Guinea-Bissau, BCG vaccination was associated with decreased risk of positive SPT and the protective effect of BCG was greater if the vaccination was received at an early age, especially during the first week of life (Aaby *et al.*, 2000). However, the majority of the children were younger than 6 years at the time of SPT assessment in that study. In a German study, the influence of BCG vaccination on allergic diseases decreased over time (Grüber *et al.*, 2001). In our study, the children were 10–11 years old when their allergic status was assessed. By this age, any effect of early vaccination could have been overshadowed by more recent exposure with natural myco-bacteria in a region of relatively high incidence of tuberculosis [incidence rate 51/100,000 in 1997 (Statistical Yearbook of Estonia, 1998)]. Similarly, no relationship between early BCG vaccination and sensitisation or allergic diseases was found among schoolchildren in Greenland (Krause *et al.*, 2003) and among adults in Denmark (Bager *et al.*, 2003).

In several studies, the protective effect of BCG vaccination has been restricted to certain subgroups. In a Swedish study, a lower prevalence of allergy was observed only in BCG-vaccinated children with a foreign back-ground (Strannegård *et al.*, 1998). In a Brazilian study, BCG reduced the risk of asthma only among children with allergic rhinitis (da Cunha *et al.*, 2004), and in an Australian study, only among children with a family history of allergic diseases (Marks *et al.*, 2003). Thus, the effect of BCG on the development of allergic diseases may be different for populations with different degree of allergy risk and different lifestyle. This suggestion is supported by the compa-rison of neonates from Eastern and Western Germany, showing differences in T cell reactivity already at birth, i.e., decreased interferon-γ and tumor necrosis factor-α and increased interleukin-4 production by neonates in Western Germany (Lehmann *et al.*, 2002). Divergent reports on the effect of BCG vaccination on the development of allergy between studies may also possibly be explained by differences in used BCG strains and doses.

3.3. Tuberculin reactivity (Paper III)

The proportion of positive tuberculin responses (induration ≥5 mm) increased from 18% at 2–3 years to 45% at 10–11 years of age ($p < 0.001$) and large responses (≥10 mm) increased from 6% to 22%, respectively ($p < 0.001$). A positive tuberculin response was inversely related to current exercise induced wheezing, night cough, and flexural dermatitis, but only for tuberculin tests performed at 10–11 years of age, i.e., at the same time as symptoms were assessed (Figure 12). Of the 343 children who were tuberculin tested at 10–11 years of age, 101 (29%) had been revaccinated with BCG at 7–8 years. The prevalence of positive tuberculin responses was similar in children who were and were not revaccinated (50% vs 42%, p = 0.16). When the children who were and were not revaccinated with BCG at 7–8 years, were analysed separately, the association between allergic symptoms and tuberculin response at 10–11 years was similar and in the same direction in both groups, although in the revaccinated children, it did not reach statistical significance (data not shown). This was probably due to the smaller sample size in that group. There was, however, no relationship between allergy at 10–11 years and tuberculin reactivity at 2–3 and 6–7 years (Figure 12), indicating that if there is any causal relationship between allergy and exposure to mycobacteria, the effect is likely not long-lasting. In addition, we found no relationship between tuberculin responses at any age and the prevalence of positive SPT.

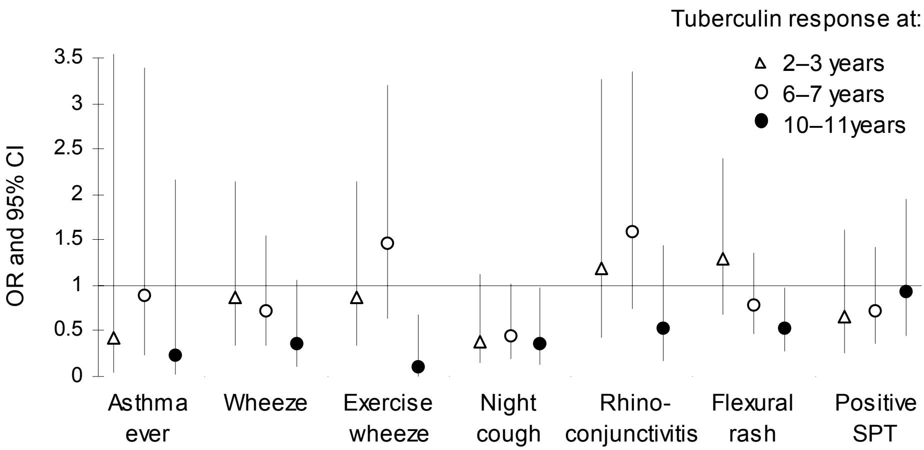


Figure 12. Diagnosed asthma, current respiratory and allergic symptoms, and positive SPT in Estonian children at 10–11 years of age in relation to tuberculin response (≥ 5 *vs* < 5 mm) at 2–3, 6–7, and 10–11 years of age.

We used retrospective data about tuberculin tests, which were performed and read by several different persons. This could lead to some misclassification of the tuberculin responses. This misclassification would be random in respect of atopic disorders, however. Although the data about tuberculin responsiveness was not available at every age period for all subjects, it would unlikely bias the results substantially, because the prevalence of allergic diseases and allergen sensitisation was similar among children with and without the data (data not shown).

While positive tuberculin responses in Japanese schoolchildren correlated inversely with allergic diseases, specific IgE levels, and Th2 cytokine profiles (Shirakawa *et al.*, 1997), several more recent studies have failed to demonstrate any association between allergic disorders and tuberculin responsiveness

(Omenaas *et al.*, 2000; Yilmaz *et al.*, 2000; Wong *et al.*, 2001b; Jentoft *et al.*, 2002; Pahari *et al.*, 2002). In a recent international study among children who were BCG-vaccinated at birth, a positive tuberculin response at 9–12 months of age was inversely related to allergic disorders at 2 years of age in Turkey and Thailand, but not in Argentina (Townley *et al.*, 2004). Possible explanations for the inconsistency between studies include differences in study design (especially the time of the testing), tuberculin preparations, doses, assessment of the test results, concurrent environmental factors, and immune responsiveness of different populations.

Besides a possible protective effect of mycobacterial infection against allergy, an inverse relationship between tuberculin responsiveness and allergic disorders could also be explained by altered immune responsiveness in the atopic individuals (Strannegård *et al.*, 1998), as allergic diseases have been associated with deviation towards Th2-type immune response and decreased capacity to produce Th1 cytokines (Prescott *et al.*, 1999). However, there is now increasing evidence questioning this possibility. The prevalence of both IgE-mediated and autoimmune diseases have increased in parallel during the last decades, and the disorders are significantly associated and share common risk factors (Kero *et al.*, 2001; Simpson *et al.*, 2002; Sheikh *et al.*, 2003). Furthermore, concomitant Th1 and Th2 cytokine production to allergens was recently demonstrated in atopic children (Smart and Kemp, 2002).

In our study, in the subgroup of BCG revaccinated children, SPT positivity tended to be associated with a positive tuberculin response (24% *vs* 11 %, OR 2.5, 95% CI 0.7–10.5). Furthermore, among SPT-positive children, a positive tuberculin response was more common after the BCG revaccination than would be predicted by their first test. There was a significant association of the interaction of BCG revaccination and SPT positivity with a positive tuberculin response, OR 4.0 (95% CI 1.1–14.4). Increased delayed type hypersensitivity to mycobacteria among allergic children has also been reported in some other studies (Strannegård *et al.*, 1998; Ozmen *et al.*, 2002). Recently, among Turkish children who where vaccinated with BCG only once, no difference was found in tuberculin wheal size between atopic asthmatic children and healthy children (Kale *et al.*, 2004). However, among children vaccinated with BCG twice, the responses to tuberculin were significantly stronger in atopic asthmatic than in healthy children. These results, together with our findings, indicate that the tuberculin response after BCG revaccination is stronger in sensitised than in nonsensitised children. Furthermore, in a recent study, Estonian children who were SPT positive to common allergens, showed stronger delayed type hypersensitivity responses to diphtheria and tetanus antigens than SPT negative children (Julge *et al.*, 2002). The observations are not easily accommodated within the Th1/Th2 concept as the cause of allergic disease, but could rather indicate differences in immune regulation between allergic and nonallergic children.

3.4. Wheezing in relation to home environment in Estonia and Sweden (Paper II)

Parents' replies to the risk factor questionnaire in the case control study illustrate some of the major differences in the living conditions between Estonia and Sweden (Table 6). Compared with 10–11-year-old Swedish children, children in Tallinn more frequently lived in damp and crowded blockhouse apartments with less than four rooms. Despite these differences, there was no strong relationship between wheezing status and current home environment, neither in Estonia, nor in Sweden. The only exception was the inverse relation between domestic crowding (number of persons per room) and wheezing in Sweden where crowding was much less common than in Tallinn.

In a previous Estonian-Swedish-Polish study, sensitisation was more strongly related to overcrowding than to family size (Bråbäck *et al.*, 1995). If the relationship between allergy and presence of older siblings was due to exposure to microbes, domestic crowding would further enhance it. As there is clearly bigger difference in domestic crowding than in the number of siblings between Eastern and Western European countries this could also partly explain the East-West gradient in the prevalence of allergic diseases.

The finding, based on cross-sectional data, should be interpreted with caution, because it is difficult to conclude whether the exposure to a risk factor preceded the development of wheezing or not. A protective effect of domestic crowding (and older siblings) probably acts predominantly during a rather short period early in life (Ball *et al.*, 2000). In our study, one third of the children with wheeze and a quarter of the children without wheeze had lived less than five years in the current dwelling (similar in the three study areas) and the reported data on home conditions referred to the current situation.

3.5. Lifestyle-related factors

We assessed the influence of several environmental and lifestyle-related factors reported by the parents of the 6–7-year-old children in the ISAAC Phase III (data only presented here). In a univariate analysis, allergic disorders were related to use of antibiotics and paracetamol, parental smoking, and frequent truck traffic through the street where the child lived, while there was an inverse association with breastfeeding for more than 3 months and current exposure to cats (Table 7).

Table 6. Home environment in wheezing (W) and nonwheezing (NW) 10–11-year-old children in Estonia and Sweden

	Tallinn			Linköping + Östersund			Sweden vs Estonia, among nonwheezers
	W %	NW %	OR (95% CI)	W %	NW %	OR (95% CI)	OR (95% CI)
Older siblings (≥ 1)	45	54	0.7 (0.4–1.2)	62	66	0.8 (0.6–1.2)	1.7 (1.2–2.3)*
Younger siblings (≥ 1)	52	46	1.3 (0.7–2.3)	49	53	0.8 (0.6–1.2)	1.4 (1.0–1.9)
One-family house	31	28	1.2 (0.6–2.1)	75	69	1.4 (0.9–2.1)	5.6 (3.9–8.1)**
> 3 rooms	33	34	1.0 (0.5–1.7)	89	92	0.8 (0.4–1.6)	19.5 (12.7–30.0)**
≥ 1 person per room	82	85	0.8 (0.4–1.6)	32	46	0.6 (0.3–0.9)*	0.15 (0.1–0.2)**
Condensation on the windows	46	36	1.5 (0.9–2.6)	26	21	1.3 (0.8–2.0)	0.5 (0.3–0.5)**
Damp damage in the home	43	46	0.9 (0.5–1–5)	32	33	1.0 (0.6–1.4)	0.6 (0.4–0.8)*
Mother smoked during pregnancy	3	5	0.7 (0.1–3.1)	24	20	1.3 (0.8–2.0)	5.3 (2.8–10.0)**
Mother current smoker	29	38	0.7 (0.4–1.2)	23	20	1.2 (0.8–1.9)	0.4 (0.3–0.6)**

*: $p < 0.05$; **: $p < 0.01$

Table 7. Factors related to the prevalence of allergic disorders among 6–7-year-old Estonian children

		Crude OR (95% CI)				
		Current asthma	**Wheeze**	**Rhino-conjunctivitis**	**Seasonal rhinitis**	**Flexural rash**
Antibiotics during the 1st year of life	36	3.1 (1.7–5.4)***	1.7 (1.3–2.3)***	1.4 (1.0–2.1)	1.8 (1.3–2.4)***	1.6 (1.3–2.0)***
Paracetamol during the 1st year of life	66	1.9 (1.0–3.7)*	1.3 (1.0–1.8)	1.3 (0.9–2.0)	1.4 (1.0–2.0)*	1.5 (1.1–1.9)**
Paracetamol in the past 12 months	84	5.1 (1.2–20.9)*	2.0 (1.3–3.3)**	1.3 (0.7–2.3)	1.3 (0.8–2.1)	1.2 (0.8–1.6)
Cat at home in the past 12 months	24	0.9 (0.5–1.7)	1.1 (0.8–1.5)	0.8 (0.5–1.3)	0.7 (0.4–1.0)*	0.9 (0.7–1.2)
Frequent truck traffic	42	0.9 (0.5–1.5)	1.3 (1.0–1.7)	1.3 (0.9–1.9)	1.5 (1.1–2.1)**	1.3 (1.0–1.6)*
Mother smoked during child's 1st year of life	11	1.8 (0.9–3.6)	1.5 (1.0–2.2)*	1.0 (0.6–1.9)	1.4 (0.9–2.2)	1.4 (1.0–1.9)
Mother current smoker	24	1.9 (1.1–3.2)*	1.9 (1.5–2.6)***	0.8 (0.5–1.3)	1.2 (0.9–1.7)	1.4 (1.0–1.8)*
Farther current smoker	43	0.8 (0.5–1.4)	1.3 (1.0–1.7)	0.9 (0.6–1.3)	1.1 (0.8–1.5)	1.5 (1.2–1.9)**
Breastfeeding > 3 months	56	0.5 (0.3–0.8)**	0.8 (0.6–1.1)	0.6 (0.4–0.9)**	0.9 (0.6–1.2)	0.9 (0.7–1.1)

*: p < 0.05; **: p < 0.01; ***: p < 0.001.

Potential risk factors tested but found to be nonsignificant included maternal education, presence of younger and older siblings, daycare attendance in early life and ever, combination of older siblings and/or daycare attendance, fuels used for cooking (gas, wood/coal, and electricity), fuels used for heating (gas, wood/coal, electricity, and central heating), exposure to cats and dogs during the first year of life, and current exposure to dogs (data not shown). As there was no relationship between allergic disorders and exposure to cats in infancy, it is possible that the observed borderline association between current exposure and seasonal rhinits is due to current avoidance of pets.

When children with a maternal history of allergic diseases were analysed separately, the associations were similar to the whole study group, although for some factors the associations did not reach statistical significance because of the smaller sample size (data not shown). Thus, in children with maternal allergy, breastfeeding for more than 3 months was inversely related to current asthma (OR 0.4, 95% CI 0.2–0.9) and rhinoconjunctivitis (OR 0.6, 95% CI 0.4–0.9).

In order to obtain the independent effect of risk factors, logistic regression models were created using significant factors. As maternal smoking in infancy was closely related to current smoking and use of paracetamol in infancy to current use, these factors were analysed together. In a multivariate analysis, the influence of truck traffic and use of paracetamol became less pronounced (Table 8). It is possible that in this population paracetamol is not an independent risk factor but a confounder related to the use of antibiotics.

In a recent prospective study, the use of antibiotics during the first year of life was related to sensitisation in Estonian, but not in Swedish children, while there was no association between sensitisation and the use of antibiotics during the second year of life in either country (Voor *et al.*, 2005). Although the use of antibiotics may be a marker of infections, in that study, there was no correlation between the number of episodes of infections and allergy in either country. However, the use of antibiotics was more common in Estonia where majority of the children received broad-spectrum antibiotics compared with penicillin in Sweden, which may explain the different association between allergy and antibiotic use in Estonia and Sweden.

The results were generally similar in girls and boys, except for breastfeeding, which had a significant protective effect only on boys, and maternal smoking, which was a risk factor mainly for girls. Several studies have found that the relationship between smoking (both passive and active) and asthma is stronger in girls and women than in males suggesting that females are more susceptible to tobacco smoke (Larsson, 1995; Chen *et al.*, 1999; Toren and Hermansson, 1999; Li *et al.*, 2000; Chen *et al.*, 2002). Similarly, in FinEsS study among Estonian adults, women were more troubled by environmental smoke exposure than men (Larsson *et al.*, 2003), and the prevalence of diagnosed chronic bronchitis was higher among women than among men, although smoking was twice as common in men (Meren *et al.*, 2001).

Table 8. Multivariate analysis of the factors related to the prevalence of allergic disorders among 6–7-year-old Estonian children, adjusted mutually to the other factors in the table, to parental allergy, and (if appropriate) to sex

	Adjusted OR (95% CI)				
	Current asthma	**Wheeze**	**Rhino-conjunctivitis**	**Seasonal rhinitis**	**Flexural rash**
Antibiotics during the 1st year of life	2.8 (1.6–5.1)**	1.7 (1.3–2.3)***	1.3 (0.9–1.9)	1.6 (1.1–2.2)**	1.4 (1.1–1.8)**
Paracetamol	1.8 (0.4–7.5)	1.7 (0.9–3.2)	1.2 (0.5–2.6)	1.4 (0.7–2.8)	1.8 (1.0–3.1)*
Frequent truck traffic	0.8 (0.4–1.4)	1.2 (0.9–1.6)	1.3 (0.8–4.2)	1.5 (1.1–2.1)*	1.3 (1.0–1.6)
Maternal smoking					
Girls	6.1 (2.0–18.6)**	2.8 (1.8–4.4)***	0.9 (0.4–1.9)	1.7 (1.0–3.0)*	1.3 (0.9–2.0)
Boys	1.2 (0.6 –2.5)	1.7 (1.1–2.5)*	0.6 (0.3–1.2)	1.0 (0.6–1.7)	1.4 (0.9–2.0)
Breastfeeding > 3 months					
Girls	0.7 (0.5–2.1)	0.9 (0.6–1.4)	0.5 (0.3–1.1)	1.1 (0.6–1.8)	1.1 (0.8–1.6)
Boys	0.4 (0.2–0.9)*	1.0 (0.6–1.4)	0.6 (0.3–1.0)*	0.7 (0.5–1.1)	0.7 (0.5–1.0)

*: p < 0.05; **: p < 0.01; ***: p < 0.001.

The most remarkable finding of our study is the lack of association between allergic disorders and several risk/protective factors previously identified in Western countries. One possible reason for this discrepancy is the cross-sectional design of our study, which does not provide information about the sequence of events. As we do not have data about preventive measures taken by affected subjects, this could influence the relationship between symptoms and environmental factors. Recall bias may also result in different reporting of events by parents of children with and without symptoms. However, several other explanations are also possible. As discussed previously, there may be different risk factors for the development of sensitisation and symptoms, since allergy-like symptoms in Estonian children are less related to sensitisation and BHR than in Western countries. If a factor affects the prevalence of symptoms mainly by enhancing sensitisation or BHR, it may influence the prevalence of asthma in regions were allergic asthma is common, but not in Estonia. Furthermore, it is possible that a factor related to symptoms is just a marker of certain lifestyle in one population, but not necessarily in another one. The use of coal or wood for heating had a protective effect against allergic rhinitis, sensitisation, and BHR in Germany (von Mutius *et al.*, 1996), but not in Estonia. It is likely, that heating with coal or wood is related to a very different lifestyle in Southern Bavaria and Estonia.

Another explanation for regional differences in the influence of environmental factors is the impact of other factors and interaction between factors. Older siblings are generally associated with lower prevalence of allergy in Western countries (Karmaus *et al.*, 2001). In countries with more traditional lifestyle, however, where the microbial load in the environment is sufficient to provide protection, contact with siblings may not provide additional effect.

4. Time trends in the prevalence of allergic disorders

We assessed the time trends in the occurrence of allergic disorders in two comparisons: 1) the ISAAC Phase II (1996–97) *vs* a similar study among 10–12-year-old children in Tallinn (1992–93) (Riikjärv *et al.*, 1995); and 2) the ISAAC Phase III (2001–02) *vs* Phase I (1993–94).

4.1. 1996–97 *vs* 1992–93 (Paper I)

Despite a changing lifestyle over these 4 years, there was no increase in the prevalence of diagnosed asthma or symptoms of asthma and rhinoconjunctivitis in 10–11-year-old Estonian children (Table 9). An increase was observed in rash, however, there was a considerable difference in the question regarding rash between the two studies. Similarly, there was no change in the prevalence of positive SPT to at least one of the aeroallergens (14.3% in both studies) or to any individual allergen, except for increasing sensitivity to dog (Table 9).

Table 9. Prevalence (%), OR, and 95% CI of diagnosed asthma, current allergic symptoms, and positive SPT in 10–11-year-old Estonian children, 1996–97 *vs* 1992–93

	1992–93 %	**1996–97** %	OR (95% CI)
Asthma ever	3.2	2.5	0.8 (0.4–1.3)
Wheeze	9.4	8.3	0.9 (0.6–1.2)
Exercise-induced wheeze	5.7	5.6	1.0 (0.7–1.5)
Rhinoconjunctivitis	7.4	6.1	0.8 (0.6–1.2)
Itchy rash	14.9	20.0	1.6 (1.2–2.1)
Positive SPT			
Any allergen	14.3	14.3	1.0 (0.8–1.4)
Derm. pteronyssinus	6.1	4.4	0.7 (0.4–1.2)
Cat	6.1	7.2	1.2 (0.8–1.9)
Dog	2.0	4.7	2.4 (1.2–4.7)
Birch	2.5	4.8	1.6 (0.9–3.1)
Timothy	4.8	4.1	1.0 (0.6–1.7)
Alternaria	0.2	0.6	3.7 (0.4–33.2)

Thus, there is a difference between our results and the findings from Leipzig, East Germany where a rapid rise occurred in the prevalence of allergies and sensitisation over a 4-year period shortly after the reunification of Germany (von Mutius *et al.*, 1998). This difference may be due to the fact that the reunification of Germany rapidly resulted in pronounced environmental changes, while in Estonia, during the first years of independence, the transition was slower due to severe economic constraints. Furthermore, the children, studied in 1996–97, had spent their first 4–5 years of life under Soviet conditions, and were exposed to a changing lifestyle only during the following 6 years.

4.2. 2001–02 *vs* 1993–94 (Paper V)

Over this 8-year period there was a modest increase in the prevalence of symptoms of eczema both among 6–7-year-old children (OR 1.4, 95% CI 1.2–1.7 for itchy rash and OR 1.2, 95% CI 1.0–1.4 for flexural rash) and among 13–14-year-old children (OR 1.5, 95% CI 1.3–1.7 and OR 1.3, 95% CI 1.1–1.5, respectively) (Figure 13).

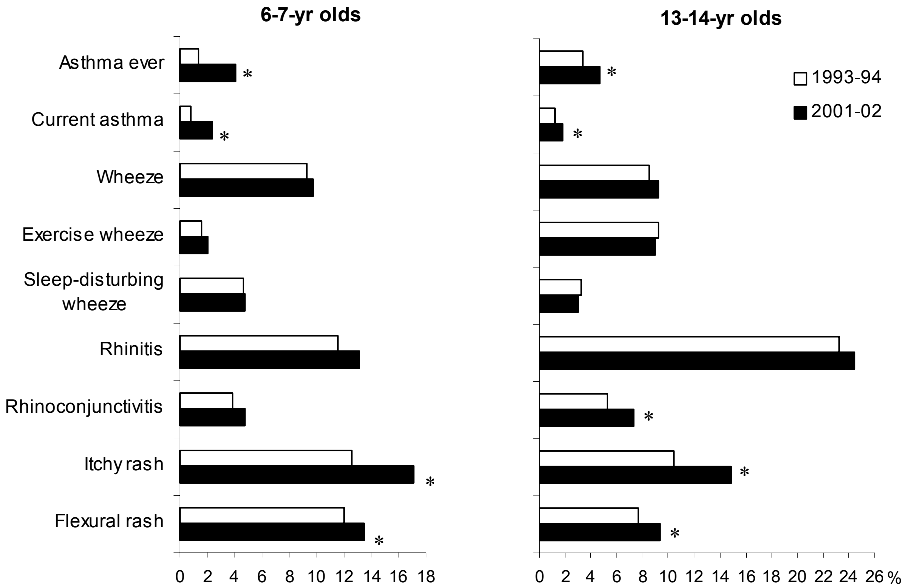


Figure 13. Prevalence (%) of asthma and current respiratory and allergic symptoms among 6–7- and 13–14-year-old Estonian children in 1993–94 and 2001–02. *: significant difference compared with 1993–94.

While the prevalence of rhinitis was unchanged, the prevalence of rhino-conjunctivitis increased in the older age group (OR 1.4, 95% CI 1.2–1.7). Furthermore, there was an increase in the prevalence of rhinitis during pollen season in both age groups, whereas the prevalence of rhinitis in winter months decreased (Figure 14).

A difference in the seasonal variation of rhinitis has been observed in East-West comparisons. A study, conducted shortly after the reunification of Germany, found a strong peak in symptoms of rhinitis in May and June among children in Munich, West Germany, while the seasonal fluctuation of the symptoms was modest in Leipzig, East Germany (von Mutius *et al.*, 1992). Similarly, the ISAAC phase I found the peak prevalence of rhinitis in spring and summer months in Sweden and Finland, and in winter months in East European countries (Björkstén *et al.*, 1998). The change in the seasonal variation of rhinitis in our study indicates a true increase in the prevalence of allergic rhinitis, while nonallergic rhinitis seems to decrease.

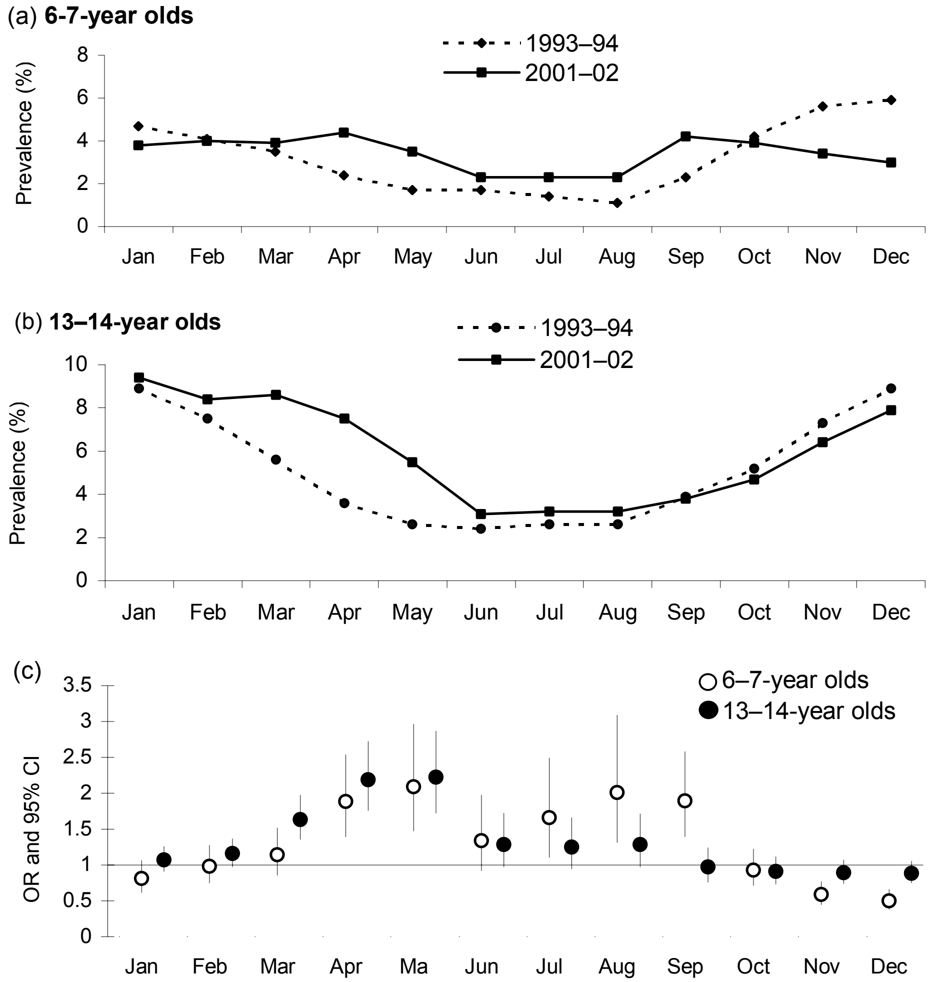


Figure 14. Seasonal variation of current rhinitis: prevalence (%) among 6–7-year-old (a) and 13–14-year-old (b) Estonian children; sex-adjusted OR and 95% CI, 2001–02 *vs* 1993–94 (c).

The prevalence and severity of most of the questionnaire-reported asthma symptoms were similar in the two studies (Figure 14), although there was an increase in the prevalence of some of the asthma symptoms derived from the video questionnaire, reaching statistical significance for exercise-induced wheeze and sleep-disturbing cough in boys and for severe wheeze in girls (Table 10).

Table 10. Prevalence (%), OR, and 95% CI of current asthma symptoms from the video questionnaire among 13–14-year-old Estonian children, 2001–02 *vs* 1993–94

	Boys			Girls		
	1993–94 %	2001–02 %	OR (95%CI)	1993–94 %	2001–02 %	OR (95%CI)
Wheeze at rest	1.5	2.0	1.3 (0.8–2.2)	2.6	2.4	0.9 (0.6–1.4)
Exercise-induced wheeze	3.3	6.8	2.2 (1.6–3.0)	7.5	6.6	0.9 (0.7–1.2)
Sleep-disturbing wheeze	0.8	1.2	1.5 (0.7–3.1)	1.5	1.7	1.1 (0.6–1.8)
Sleep-disturbing cough	3.2	5.0	1.6 (1.1–2.6)	8.9	9.1	1.0 (0.8–1.3)
Severe wheeze	0.6	0.7	1.2 (0.5–2.9)	1.3	2.2	1.7 (1.0–3.0)

Our results are similar to those reported in the early time trend studies in the former East Germany where an increasing prevalence of hay fever but not of asthma was observed 5–6 years after the reunification of Germany (von Mutius *et al.*, 1998; Weiland *et al.*, 1999). However, studies of longer duration showed a parallel increase in asthma and the other allergic symptoms among East German children (Heinrich *et al.*, 2002). It has been hypothesised that environmental factors may influence the risk of asthma and allergic rhinitis at different ages (von Mutius *et al.*, 1998) and that a rising trend in the prevalence of asthma may take longer time (Matricardi, 2001). Remarkable economic changes took place in Estonia between 1992 and 2001, e.g. average monthly gross wages increased from 35 to 353 EUR and per capita gross domestic product in current prices from 609 to 4520 EUR (Statistical Yearbook of Estonia, 1994; Statistical Yearbook of Estonia, 2003), while early neonatal death per 1000 live births decreased from 10.3 to 2.5 (Population 2001, 2002). However, the living conditions are still not comparable with those in Western Europe (Table 6). The markedly slower transition to a Western lifestyle may explain the less pronounced increase in allergic diseases and the lack of change in the prevalence of wheezing in Estonian children compared to East German children.

An alternative expanation to the absence of an increase in wheezing may arise from a possible change in the proportions of different phenotypes of asthma. The increase in summer rhinitis and decrease in winter rhinitis in our study, and similarly, an increase in allergic symptoms and decrease in bronchitis and respiratory symptoms in East Germany (von Mutius *et al.*, 1998; Heinrich *et al.*, 2000; Heinrich *et al.*, 2002) suggest that an increase in allergy may be accompanied by a decrease in respiratory infections. If nonallergic wheezing decreases, while allergic wheezing increases, the overall prevalence of wheezing may remain unchanged.

In contrast to reported wheezing, the prevalence of diagnosed asthma increased markedly in both among 6–7-year-old children (OR 3.4, 95% CI 2.4–4.9 for asthma ever and OR 3.2, 95% CI 2.0–5.4 for current asthma) and among 13–14-year-old children (OR 1.6, 95% CI 1.2–2.0 and OR 1.6, 95% CI 1.1–2.4, respectively) (Figure 14). The increase was more pronounced among 6–7-yr-old boys, i.e., from 1.4 to 5.1% (OR 4.2, 95% 2.5–7.2). Our finding is probably due to an increased awareness and to changes in diagnostic procedures, rather than a genuine increase in prevalence. This is also suggested by the significantly increased proportion of diagnosed asthma among children with current wheeze, i.e., from 8.6% to 24.7% in the younger and from 14.1% to 19.6% in the older age group. Virus-related wheezing episodes in young children are increasingly labelled as asthma, which may explain the more pronounced inconsistency between the time trends of reported wheezing and diagnosed asthma in the younger age group. An increased awareness leads to improved asthma management and thus to a better controlled disease (Goldman *et al.*, 2000; Kumana *et al.*, 2001), which also may partly explain the absence of parallel increase in asthma-like symptoms and diagnosed asthma. A smaller increase in asthma symptoms than in diagnosed asthma has been reported in several studies in children (Burr *et al.*, 1989; Burney *et al.*, 1990; Anderson *et al.*, 1994; Nystad *et al.*, 1997a). Barraclough *et al.* (2002) found an increase in asthma with a concurrent decrease in BHR among adults in UK and suggested that the current changes in asthma epidemiology may result from increased awareness of symptoms, and from an increased willingness of doctors to make the diagnosis and prescribe treatment. Recent continuing increase in asthma among schoolchildren in Australia was mainly associated with nonallergic asthma (Downs *et al.*, 2001) and in the UK Upton *et al.* (2000) suggested that increased awareness was related to the rising trend in nonallergic, but not in allergic asthma in adults.

The results of the time trend studies in other ISAAC Phase III centres are quite conflicting. Similarly to our findings, an increase in rhinitis and eczema, but not in asthma was found in Hong Kong (Lee *et al.*, 2004) (only data from the younger age group were presented). In Münster, Germany, a slight increase was reported in all allergic diseases among both age groups (Maziak *et al.*, 2003). In Spain, the prevalence of allergic symptoms increased in the younger age group, while in the older age group, there was an increase only in the prevalence of diagnosed asthma (Garcia-Marcos *et al.*, 2004). Furthermore, in UK (older age group) the prevalence of all allergic symptoms decreased and the prevalence of diagnosed asthma, hay fever, and eczema increased (Anderson *et al.*, 2004). Garcia-Marcos *et al.* (2004) suggest that over time, asthma became less a stigmatising disease in Spain, and the word “asthma” became more readily accepted by doctors and parents. This is another possible explanation for the increasing prevalence of self-reported diagnosed asthma also in Estonia. The findings of the ISAAC Phase III studies underline the importance of exploring prevalences of symptoms rather than diagnoses in epidemiological surveys and studies of time trends.

The first phase of the present study was performed 2 years after the restitution of independence, while the second took place 10 years after the beginning of the changes towards Western living conditions. Thus, the younger participants in the second phase of the study were born well after the beginning of the political and economical changes, whereas the older children spent their first 3–4 years of life in the Soviet Union (Figure 1). It is suggested that the environmental risk factors associated with asthma and allergies are particularly important during the first years of life (Björkstén, 1994; Holt, 1995). Therefore, we hypothesised that the increase in the prevalence of allergic diseases would be more pronounced in the younger than in the older children. However, the increase in allergic symptoms was similar in both age groups. Increasing prevalence in allergic disorders among adults in the former East Germany (Heinrich *et al.*, 1998b; Richter *et al.*, 2000) and among migrants to more affluent countries (Leung *et al.*, 1994; Tedeschi *et al.*, 2003; Ventura *et al.*, 2004), and decreasing prevalence among subjects who moved to rural areas (Kauffmann *et al.*, 2002) suggest that the influence of environment on the development of allergy is not restricted to infancy. Our study supports the observation that factors, related to a Western lifestyle and affecting the prevalence of allergic symptoms, may be operative throughout childhood.

CONCLUSIONS

1. Both the prevalence of symptoms of rhinitis and eczema, and the prevalence of sensitisation are still lower in Estonian than in Swedish children.
2. IgE-mediated food reactions are less common in Estonia than in Sweden, and low levels of IgE antibodies to food allergens are not associated with allergic manifestations in Estonia.
3. Only a minority of the Estonian children with symptoms of asthma, rhinitis, or eczema have positive SPT to common aeroallergens, suggesting that the symptoms are mostly of nonallergic origin.
4. The prevalence of wheezing is similar in Estonian and Swedish children. However, in Estonia, wheezing is less severe and diagnosed asthma, BHR, and sensitisation are less common among wheezing children, suggesting different aetiology of wheezing.
5. Parental allergy is a strong risk factor for allergic disorders in Estonian schoolchildren, in particular for the same condition.
6. The age at BCG vaccination has no impact on the allergy at school age in Estonian children. Positive tuberculin response is inversely related to allergic symptoms, but not to sensitisation.
7. Allergic symptoms in Estonian schoolchildren are related to use of antibiotics in infancy, use of paracetamol, exposure to truck traffic, and maternal smoking, and inversely related to breastfeeding. However, there is no relationship between allergies and several known environmental risk/protective factors, indicating that the relationship between allergy and environment differs in different populations.
8. There has been a moderate increase in the prevalence of seasonal allergic rhinitis and eczema among Estonian schoolchildren during recent years in relation to a changing lifestyle.
9. The prevalence of wheezing has not changed, while the prevalence of diagnosed asthma has increased markedly in the whole study population and particularly among children with current wheeze, probably due to an increased awareness and modified diagnostic criteria.
10. The increase in allergic diseases is similar in children born before and after the collapse of the socialist system, suggesting that the influence of potential risk factors related to a changing lifestyle is not restricted to the first years of life, but may be operative throughout childhood.

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APPENDIX I

The original ISAAC core questionnaires

Core questionnaire for asthma

1. Has your child ever had wheezing or whistling in the chest at any time in the past? Yes/No
IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 6

2. Has your child had wheezing or whistling in the chest in the past 12 months? Yes/No
IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 6

3. How many attacks of wheezing has your child had in the past 12 months? None/1 to 3/4 to 12/more than 12

4. In the past 12 months, how often, on average, has your child's sleep been disturbed due to wheezing? Never woken with wheezing/Less than one night per week/One or more nights per week

5. In the past 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breath? Yes/No

6. Has your child ever had asthma? Yes/No

7. In the past 12 months, has your child's chest sounded wheezy during or after exercise? Yes/No

8. In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection? Yes/No

Core questionnaire for rhinitis

1. Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu? Yes/No
IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 6

2. In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu? Yes/No
IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 6

3. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes? Yes/No

4. In which of the past 12 months did this nose problem occur? January/February/ March/April/ May /June /July/August/September/October/November/December

5. In the past 12 months, how much did this nose problem interfere with your child's daily activities? Not at all/A little/A moderate amount/A lot

6. Has your child ever had hay fever? Yes/No

Core questionnaire for eczema

1. Has your child ever had an itchy rash which was coming and going for at least six months? Yes/No
IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 7

2. Has your child had this itchy rash at any time in the past 12 months? Yes/No
IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 7

3. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes? Yes/No

4. At what age did this itchy rash first occur? Under 2 years/Age 2–4 years/Age 5 or more

5. Has this rash cleared completely at any time during the past 12 months? Yes/No

6. In the past 12 months,, how often, on average, has your child been kept awake at night by this itchy rash? Never in the past 12 months/Less than one night per week/One or more nights per week

7. Has your child ever had eczema? Yes/No

APPENDIX II

The Estonian version of the ISAAC core questionnaires

Core questionnaire for asthma

1. Kas Teie lapsel on kunagi olnud vilinaid ja kiuneid hingamisel? Jah/Ei

KUI VASTASITE SELLELE KÜSIMUSELE "EI", SIIS JÄTKAKE VASTAMIST SELLE LEHEKÜLJE KÜSIMUSEST NR. 6.

2. Kas Teie lapsel on olnud vilinaid ja kiuneid hingamisel viimase 12 kuu jooksul? Jah/Ei
KUI VASTASITE SELLELE KÜSIMUSELE "EI", SIIS JÄTKAKE VASTAMIST SELLE LEHEKÜLJE KÜSIMUSEST NR. 6.

3. Mitu korda on Teie lapsel viimase 12 kuu jooksul olnud hingeldushoogusid vilinatega ja/või raskendatud väljahingamisega? Mitte ühtegi/1- 3/4 –12/Üle 12

4. Kui tihti viimase 12 kuu jooksul on Teie lapse und häirinud raskendatud vilistav hingamine? Mitte kunagi/Harvem kui 1 ööl nädalas/1 või enamal ööl nädalas

5. Kas viimase 12 kuu jooksul on Teie lapse hingamine olnud nii raske, et kahe hingetõmbe vahel sai ta öelda vaid 1 – 2 sõna? Jah/Ei

6. On Teie lapsel kunagi diagnoositud astmat? Jah/Ei

7. Kas viimase 12 kuu jooksul on Teie lapsel olnud vilistavat hingamist füüsilise koormuse ajal või selle järel? Jah/Ei

8. Kas viimase 12 kuu jooksul on Teie lapsel olnud öösiti kuiva köha ilma, et tal oleks olnud külmetus- või viirushaigust? Jah/Ei

Core questionnaire for rhinitis

1. Kas Teie lapsel on kunagi olnud aevastamishoogusid või vesist nohu või tugevat ninahingamise takistust, ilma, et tal oleks olnud külmetus- või viirushaigust? Jah/Ei
KUI VASTASITE SELLELE KÜSIMUSELE "EI", SIIS JÄTKAKE VASTAMIST SELLE LEHEKÜLJE KÜSIMUSEST NR. 6.

2. Kas viimase 12 kuu jooksul on Teie lapsel olnud aevastamishoogusid või vesist nohu või tugevat ninahingamise takistust, ilma, et tal oleks olnud külmetus- või viirushaigust? Jah/Ei

KUI VASTASITE SELLELE KÜSIMUSELE “EI”, SIIS JÄTKAKE VASTAMIST SELLE LEHEKÜLJE KÜSIMUSEST NR. 6.

3. Kas viimase 12 kuu jooksul on eelpool kirjeldatud nähtudele kaasnenud ka sügelevad ja punetavad silmad? Jah/Ei

4. Millisel viimastest 12 kuust oli Teie lapsel selline probleem ninaga? Jaan/Veebr./Märts/ Aprill/Mai/Juuni/Juuli/Aug./Sept./Okt./Nov./Dets.

5. Kas viimase 12 kuu jooksul on selline nohu seganud Teie lapse päevaseid toimetusi? Ei/Vähe/Mõõdukalt/Palju

6. Kas Teie lapsel on kunagi olnud heinanohu? Jah/Ei

Core questionnaire for eczema

1. Kas Teie lapsel on kunagi olnud sügelevat löövet nahal, mis esineb vahelduvalt vähemalt 6 kuu jooksul? Jah/Ei
KUI VASTASITE SELLELE KÜSIMUSELE “EI”, SIIS JÄTKAKE VASTAMIST SELLE LEHEKÜLJE KÜSIMUSEST NR. 7.

2. Kas Teie lapsel on olnud seda sügelevat löövet nahal viimase 12 kuu jooksul? Jah/Ei
KUI VASTASITE SELLELE KÜSIMUSELE “EI”, SIIS JÄTKAKE VASTAMIST SELLE LEHEKÜLJE KÜSIMUSEST NR. 7.

3. Kas see lööve on Teie lapsel kunagi olnud: küünarliigese eespinnal, põlveõndlas, hüppeliigese kohal, tuharatel, kaelal või kõrvade ja silmade ümbruses? Jah/Ei

4. Mis vanuses esines selline sügelev lööve Teie lapsel esmakordselt? Alla 2 aasta vanuses /2–4 aasta vanuses/Üle 5 aasta vanuses

5. Kas see lööve on Teie lapsel kadunud täielikult mingil ajavahemikul viimase 12 kuu jooksul? Jah/Ei

6. Kui tihti viimase 12 kuu jooksul on Teie laps pidanud olema öösel üleval selle sügeleva lööbe tõttu? Mitte kunagi/Harvem kui 1 ööl nädalas/1 või rohkem ööd nädalas

7. Kas Teie lapsel on kunagi olnud ekseemi? Jah/Ei

SUMMARY IN ESTONIAN

Allergiahaigused Eesti kooliõpilastel: levimuse dünaamika ja tunnusjooned

Taust

Laste allergiahaiguste sagenemine arenenud tööstusriikides ja tagasihoidlik levimus vähemarenenud majandusega riikides viitab allergia kujunemise seostele keskkonnaga, eeskätt moodsa ("lääneliku") elustiiliga. Seniste epidemioloogiliste uuringutega on selgunud rida keskkonnategureid, mis suurendavad allergiahaiguste riski lapseeas, kuid ükski neist ei selgita ammendavalt suuri erinevusi arenenud ja arenguriikide vahel. Sotsialistliku süsteemi kokkuvarisemisele järgnenud üleminekuperiood on toonud Eestis kaasa märkimisväärseid muutusi elukeskkonnas ja -stiilis, võimaldades uurida allergia ja elustiili vahelise seose mõningaid aspekte.

Uurimuse eesmärgid

1. Võrrelda allergiahaiguste ja sensibiliseerumise levimust Eesti ja Rootsi kooliõpilastel.
2. Selgitada mõningate tegurite seost allergiahaiguste levimusega.
3. Hinnata allergiahaiguste levimuse dünaamikat Eesti kooliõpilastel.

Uuritavad ja meetodid

Rahvusvahelise laste astma- ja allergiauuringu (ISAAC) raames viidi koolilaste seas läbi kolm rahvastikupõhist levimusuuringut:

1. 1993.–94. a. vastasid Tallinna 6–7-aastaste laste (n = 3070) vanemad ja 13–14-aastased lapsed (n = 3506) standardsele küsimustikule astma, riniidi ja ekseemi sümptomite esinemise kohta, 13–14-aastased lapsed vastasid ka astma sümptomeid esitaval videol põhinevale küsimustikule.
2. Süvendatud uuringus 1996.–97. a. vastasid 10–11-aastaste laste vanemad Tallinnas (n = 979), Linköpingis (n = 911) ja Östersundis (n = 1197) laiendatud küsimustikule, naha torketestidega hinnati laste sensibiliseerumist aeroallergeenide suhtes ning (ainult Tallinnas) koguti andmeid BCG vaktsinatsioonide ja tuberkuliintestide tulemuste kohta. Järgnevasse juhtkontrolluuringusse võeti küsimustiku alusel kõik lapsed, kellel oli viimase 12 kuu jooksul esinenud hingamisel vilinaid, ja juhuvalik selle kaebuseta lastest.

Uuritavate vanemad vastasid küsimustele lapse elukeskkonna ja toiduallergia kohta. Lastel hinnati bronhide hüperreaktiivsust 4,5% soolalahusele ja määrati IgE antikehad toiduallergeenide vastu.

3. 2001.–02. a. viidi Tallinnas läbi 1993.–94. a. uuringuga identne uuring 6–7-aastaste (n = 2388) ja 13–14-aastaste (n = 3605) laste seas.

Uurimuse peamised tulemused ja järeldused

Eesti koolilastel on nii riniidi- ja ekseeminähud kui ka allergiline sensibiliseerumine endiselt olulisel vähem levinud kui Rootsi koolilaste seas. Samuti esineb Eesti lastel harvemini IgE-vahendatud toiduallergiat ja madalas kontsentratsioonis IgE antikehad ei ole Eesti lastel seotud allergiasümptomite esinemisega.

Kuigi astmale iseloomuliku viliseva hingamise levimus on Eesti ja Rootsi laste seas ühesugune, on Eesti lastel sümptomid kergemad ja harvemini seotud sensibiliseerumise ning bronhide hüperreaktiivsusega, osutades, et viliseva hingamise etioloogia Eestis ja Rootsis on erinev. Vaid veerandil kuni kolmandikul Eesti lastest, kellel esineb astma, riniid- või ekseemi sümptomeid, on naha torketestid aeroallergeenidega positiivsed, viidates nende sümptomite mitteallergilisele olemusele.

Vanus BCG vaktsineerimise ajal ei ole Eesti lastel seotud allergiahaiguste esinemisega koolieas. Positiivse tuberkuliinprooviga lastel on väiksem küll allergia sümptomite, mitte aga sensibiliseerumise risk.

Allergiahaiguste sümptomite esinemine on Eesti koolilastel seotud antibiootikumide kasutamisega imikueas, paratsetamooli kasutamisega, tiheda veoautode liiklusega kodutänaval ja ema suitsetamisega, samas kui toitmine rinnapiimaga vähendab allergiariski. Samas paljud teadaolevad allergiahaiguste riski- või kaitsetegurid ei mõjuta oluliselt allergianähtude esinemist Eesti lastel, viidates sellele, et seos allergia ja keskkonnategurite vahel on erinevatel rahvastikurühmadel erinev.

Sessoonse allergilise riniidi ja ekseemi sümptomid on Eesti koolilastel mõnevõrra sagenenud, mida võiks seostada muutuva elustiiliga. Kuigi ka astma diagnoosimine on sagenenud, ei ole muutunud astma sümptomite levimus, mis viitab pigem muutustele astma diagnostikas kui haiguse sagenemisele. Allergianähud on sagenud nii Eesti taasiseseisvumise eel kui järel sündinud lastel, osutades sellele, et lääneliku elustiiliga seotud riskitegurite mõju ei piirdu esimeste eluaastatega, vaid toimib ka hilisemas lapseeas.

ACKNOWLEDGEMENTS

The accomplishment of this thesis would have been impossible without the contribution and help of many people, and it is my pleasure and privilege to express my sincere gratitude and indebtedness to all of them. I particularly would like to give my deepest gratitude to the following persons:

First of all, Prof.em. Bengt Björkstén, my primary supervisor, for his continuous support and encouragement, for his patient guidance in connection with scientific writing, and for generously sharing his priceless knowledge of epidemiology with me during all these years.

Mall-Anne Riikjärv, my co-supervisor, the National Coordinator of the ISAAC in Estonia, for leading the Estonian ISAAC, for introducing me to the research work and to the ISAAC and having faith in me, and for her balanced and constructive criticism.

My co-supervisor, Prof.em. Tiina Talvik, for accepting me as a Ph.D. student at the Department of Pediatrics of the University of Tartu and for her encouragement to complete the thesis.

Prof. Alan Altraja for critical reading of the thesis and for valuable comments.

Lennart Bråbäck for his support and generous help.

Kaja Rahu for her contribution to the computerisation and analysis of the data and for fruitful discussions concerning statistics and epidemiology.

Maie Thetloff for valuable help with the statistical analysis.

My co-authors, Anna Sandin, Xiao-Mei Mai, Lennart Nilsson, Marianne van Hage-Hamsten, and Scott M Montgomery, for their excellent contribution.

All the members of the Estonian ISAAC team, particularly Kairit Joost, Reet Taba, Katri Kallas, Zhanna Bogdanova, Kristjan Pomm, Sigrit Eilart, Helgi Erilane, Tatiana Sosinovitch, Doris Laur, Gerli Seppik, Teele Gornoi, and Raja Rekkaro, for their contribution to the collection and entering of the data.

All the members of the Swedish ISAAC teams for conducting the studies in Sweden and for the laboratory support.

The nurses, doctors, and teachers of the participating schools for their tolerance and assistance during the phase of data collection.

All the children and their parents for their willingness to participate in the study and for their patience with regard to the inconveniences involved.

My head of department Esti Põldmaa and all my kind colleagues at Tallinn Children's Hospital, particularly Malle Orn, Marja Pärlist, and Urve Putnik for the friendly atmosphere and their support and understanding during the years of completing this study.

My "academic sisters" Tiia Voor and Kaja Julge for fruitful friendship, stimulating discussions, and constant invaluable help and support.

And finally, my beloved mother, Heesi Annus, for her care and endurance and for creating a carefree environment for my studies.

The research programme has been supported by grants from Glaxo-Welcome, Stevenage, UK, the Swedish Institute, the Asthma and Allergy Association in Sweden, the Swedish Heart and Lung Association, and the Swedish Foundation for Allergy and Caring Sciences.

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CURRICULUM VITAE

Triine Annus

Citizenship: Estonia
Born: March 14, 1966 in Tallinn, Estonia
Address: Ravi 27, 10138 Tallinn, Estonia
Phone: +372 6207 347
Fax: +372 6207 324
E-mail: triine.annus@mail.ee

Education

1973–1984	Tallinn Secondary School No 44
1984–1990	University of Tartu, Faculty of Medicine
1990–1991	Tallinn I Children's Hospital, internship
1999–2004	Department of Pediatrics, University of Tartu, postgraduate student

Special courses

1998	EAACI Summer Course "Environment and Allergy", Budapest, Hungary
1999	EAACI Summer Course "Assessment of Exposure and Inflammation in Allergic Disease", Stockholm, Sweden
2000	Nordic Summer School "Methods of Infectious Disease Epidemiology", Skjoldenæsholm, Denmark
2000	EAACI Summer Course "Environment, Sports and Allergy", Rome/Villasimius, Italy
2001	Salzburg-Philadelphia Seminar "Pediatric Pulmonology/Asthma", Salzburg, Austria
2001	Research Training Course "Allergy in a global health perspective", Karolinska Institutet, Stockholm, Sweden
2001	Post-graduate Course "Epidemiology", the Nordic School of Public Health, Göteborg, Sweden
2004	ICAS/University of Ulm 15th International Summer School of Epidemiology Course "Clinical Epidemiology", Ulm, Germany
2005	ERS/ATS joint School Course "Methods in clinical research", Prague, Czech Republic

Professional employment

1991–95 Tallinn Kivimäe Hospital, paediatric pulmonologist
1995– Tallinn Children's Hospital Central Policlinic, paediatric allergist

Scientific work

Main research field: epidemiology of allergic diseases in childhood
22 scientific publications, 9 presentations at international scientific conferences
Membership: the European Respiratory Society, the European Academy of Allergy and Clinical Immunology, the Estonian Medical Association, the Estonian Pediatric Association, the Section of Allergology of the Estonian Pediatric Association, the Estonian Respiratory Society, the Estonian Society of Immunology and Allergology

CURRICULUM VITAE

Triine Annus

Kodakondsus: Eesti
Sündinud: 14. märtsil 1966 Tallinnas Eestis
Aadress: Akadeemia 4–58 12612 Tallinn Eesti
Telefon: +372 6207 347
Fax: +372 6207 324
E-mail: triine.annus@mail.ee

Haridus

1973–1984	Tallinna 44. Keskkool
1984–1990	Tartu Ülikooli arstiteaduskond
1990–1991	Tallinna I Lastehaigla, internatuur
1999–2004	Tartu Ülikooli Lastekliinik, doktorant

Erialane täiendõpe

1998	EAACI suvekursus "Keskkond ja allergia", Budapest, Ungari
1999	EAACI suvekursus "Ekspositsiooni ja põletiku mõõtmine allergiahaiguste korral", Stockholm, Rootsi
2000	Põhjamaade Suvekool "Nakkushaiguste epidemioloogia meetodid", Skjoldenæsholm, Taani
2000	EAACI suvekursus "Keskkond, sport ja allergia", Rome/ Villasimius, Itaalia
2001	Salzburg-Philadelphia seminar "Laste pulmonoloogia/asthma", Salzburg, Austria
2001	Karolinska Instituudi uuringukursus "Allergia globaalse tervise perspektiivis", Stockholm, Rootsi
2001	Kursus "Epidemioloogia", Põhjamaade Rahvatervise Kool, Göteborg, Rootsi
2004	ICAS/Ulmi Ülikooli 15. rahvusvahelise epidemioloogia suvekooli kursus "Kliiniline epidemioloogia", Ulm, Saksamaa
2005	ERS/ATS kool-kursus "Kliinilise uuringu meetodid", Praha, Tšehhi Vabariik

Erialane teenistuskäik

1991–1995	Tallinna Kivimäe Haigla, laste kopsuarst
1995–	SA Tallinna Lastehaigla Kesklinna Lastepolikliinik, lastearst-allergoloog

Teadustegevus

Peamine uurimisvaldkond: laste allergiahaiguste epidemioloogia
22 teaduspublikatsiooni, 9 ettekannet rahvusvahelistel konverentsidel
Kuulumine erialaorganisatsioonidesse: Euroopa Respiratoorne Ühing, Euroopa Allergia ja Kliinilise Immunoloogia Akadeemia, Eesti Arstide Liit, Eesti Lastearstide Selts, Eesti Lastearstide Seltsi allergoloogia sektsioon, Eesti Kopsuarstide Selts, Eesti Immunoloogide ja Allergoloogide Selts