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ASPECTS OF ECZEMA IN CHILDHOOD

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TO ALL CHILDREN AND TEENAGERS WITH ECZEMA

SUMMARY

Eczema (atopic dermatitis) is a common itchy inflammatory skin disease that often starts in childhood. Having eczema is troublesome and has been shown to reduce quality of life. Eczema is associated with an increased risk for other allergy-related diseases such as asthma and rhinitis. Knowledge concerning the natural course of eczema and its association with asthma and rhinitis in childhood is limited. Even though a majority of children with eczema have mild disease, most studies on quality of life and associations with asthma and rhinitis have been done in selected populations of children with moderate to severe eczema. New knowledge about eczema genetics and skin barrier function has highlighted the need for longitudinal studies to better understand the natural course of eczema as well as its association with eczema, asthma and rhinitis.

The aim of this epidemiological study was to provide a better understanding of childhood eczema in the general population and especially its association with asthma and rhinitis. We used the population-based birth cohort BAMSE, including 4,089 children followed up at age 0, 1, 2, 4, 8 and 12 years with parental questionnaires focusing on symptoms of allergy-related diseases and risk factors.

In paper I we showed that allergy-related diseases affect a majority of children during the first 12 years of life and that eczema, asthma and rhinitis develop dynamically throughout childhood. In addition we found that comorbidity between allergy-related diseases increase with increasing age and that 7.5% of 12-year-old children have two or three of the diseases eczema, asthma and rhinitis.

In paper II we examined eczema severity at 12 years in relation to asthma, rhinitis and *Filaggrin* mutations. We found that the risk of having asthma and rhinitis was associated with eczema severity, with the highest risk among boys with moderate to severe eczema. However, no association between *Filaggrin* mutations and severity of eczema was found. In paper III we showed that eczema and even mild eczema among pre-adolescent girls is associated with impaired self-perceived health.

Finally, in paper IV we examined prognosis and risk factors for eczema, asthma and rhinitis in pre-adolescence among children with infantile eczema. We found that almost half of the children with infantile eczema will have eczema, asthma or rhinitis in pre-adolescence but in three of four children the eczema will have remitted. We also found that eczema in the first but not the second year of life is associated with a good prognosis for eczema but an increased risk of asthma and rhinitis in pre-adolescence.

In conclusion the results of this thesis stress the importance of allergy-related diseases and in particular eczema among children as a public health concern. This thesis also demonstrates a strong association between eczema, asthma and rhinitis in childhood and emphasizes the importance of considering comorbidities between these diseases both in research and in clinical practice.

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2 LIST OF PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their roman numerals.

- I **Ballardini N**, Kull I, Lind T, Hallner E, Almqvist C, Östblom E, Melén E, Pershagen G, Lilja G, Bergström A, Wickman M. *Development and comorbidity of eczema, asthma and rhinitis to age 12 – data from the BAMSE birth cohort*. Allergy. 2012 Apr;67(4):537-44
- II **Ballardini N**, Kull I, Söderhäll C, Lilja G, Wickman M, Wahlgren CF. *Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort*. British Journal of Dermatology. 2013 Mar;168(3):588-94.
- III **Ballardini N**, Östblom E, Wahlgren CF, Kull I. *Mild eczema affects self-perceived health among pre-adolescent girls*. Accepted for publication in Acta Dermato-Venerologica, 2013.
- IV **Ballardini N**, Bergström A, Böhme M, van Hage M, Hallner E, Johansson E, Söderhäll C, Kull I, Wickman M, Wahlgren CF. *Infantile eczema – prognosis and risk of asthma and rhinitis in pre-adolescence*. Accepted for publication in Journal of Allergy and Clinical Immunology, 2013.

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3 LIST OF ABBREVIATIONS

BAMSE	Barn, Allergi, Miljö I Stockholm en Epidemiologisk studie
BESS	BAMSE Eczema Severity Score
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
DNA	Deoxyribonucleic acid
EAACI	European Academy of Allergology and Clinical Immunology
EASI	The eczema area and severity index
FLG	Filaggrin
HRQoL	Health Related Quality of Life
IgE	Immunoglobulin E
ISAAC	International Study of Asthma and Allergies in Childhood
JACI	Journal of Allergy and Clinical Immunology
NESS	The Nottingham Eczema Severity Score
NPV	Negative predictive value
OR	Odds ratio
POEM	The patient oriented eczema measure score
PPV	Positive predictive value
SCORAD	SCORing Atopic Dermatitis
WAO	World Allergy Organization
WHO	World Health Organization

4 PREFACE

I have learned a lot during the work with this dissertation. When I started to write the thesis summary chapter I realized that most of the learning outcomes do not lie in the result of the studies. In my experience, the entire work process that precedes decisions on what to study and analyse and what ultimately to include in each separate paper has given me new and valuable insights.

Research may appear straightforward. You have a hypothesis you want to test. You engage people with the competence needed and together you figure out the best and most efficient way to test your hypothesis. You compose a research plan describing the aim of the study and how it should be carried out, including how data should be collected, analysed and presented in the form of tables and figures. You stick to the plan without any deviations. You discuss the findings and what they mean with your co-authors. You write the paper and then you get it published.

Even though the procedure described above is almost always what we strive for, I am quite sure it seldom happens. I assume that the human mind does not have the capacity to anticipate what questions or obstacles will appear along the way. My guess is that regardless of what efforts are made to ensure that everything has been thought of and planned for in the beginning of a large project, it will not be sufficient. And in the end, when looking back, we will probably ask ourselves, “why didn’t we think of that?”

Looking back on the projects in which I have participated I wonder if the work processes could have been made more straightforward and effective through better planning on my part, and I am sure they could. However, a major lesson for me is that research is a creative and dynamic process where chance, deviations and detours can be essential in order to discover new and unexpected results. Though this is sometimes frustrating, it is also what makes research so intriguing.

Since these insights and experiences have been valuable to me, I choose to share them, hoping that my reflections will illustrate both the fun and the frustration involved in writing a thesis. Hopefully, the framed text in this thesis called reflections can give a somewhat different perspective on what you learn as a PhD student. For an experienced scientist the reflections might seem trivial. So if you are looking for a more traditional reading experience, please just skip the framed sections. Regardless of how you read, I hope you find the reading worthwhile.

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Stockholm 2013

5 INTRODUCTION

Eczema¹ (atopic dermatitis) is an itchy inflammatory skin disease affecting up to 30% of children at some time during childhood.² Having eczema is troublesome and impairs the quality of life for the affected child as well as for the family³ and has been shown to be associated with other allergy-related diseases such as asthma and rhinitis.⁴ Eczema, asthma and rhinitis are all diseases of public health concern, but knowledge regarding natural course and the interrelationship between these diseases is limited. Even though a majority of children with eczema have mild disease most studies on quality of life and the relation between eczema, asthma and rhinitis have been performed in selected populations of children with moderate to severe disease.⁴⁻⁹ Recent developments in our knowledge of eczema genetics and skin barrier function have highlighted the need for longitudinal studies to better understand the natural course of eczema as well as the association with other allergy-related diseases.¹⁰⁻¹²

The BAMSE survey is a population-based birth cohort study initiated 1994 with the aim of studying risk factors for allergy-related diseases.¹³ The papers in this thesis are based on material from the BAMSE study with data from birth up to pre-adolescence. The overall aim of this thesis is to provide a better understanding of eczema in the general population and especially the relation to asthma and rhinitis in childhood.

The first paper describes development and comorbidity of eczema, asthma and rhinitis during the first 12 years of life. In the second paper, including pre-adolescent children, eczema and severity of eczema are studied in relation to sex, filaggrin mutations, asthma, rhinitis and topical treatment. The third paper focuses on the impact of eczema on quality of life and self-perceived health among pre-adolescent boys and girls. In the fourth paper, children with infantile eczema are studied with the aim to examine prognosis and to identify risk factors in infancy for eczema, asthma and rhinitis in pre-adolescence.

The terms allergic diseases and allergy-related diseases are not well defined. In this thesis they are used to refer to eczema (as defined by the WAO nomenclature¹), asthma, rhinitis and rhinoconjunctivitis; thus allergic contact dermatitis among other diseases is not included.

6 BACKGROUND

ALLERGIC DISEASES

Allergic diseases exist worldwide but there are large international differences in prevalence.¹⁴ Over the last decades there has been a marked increase in the prevalence of allergic diseases¹⁵⁻¹⁷ globally and 30-40% of the world population is estimated to be affected.¹⁸ Allergic diseases develop when the immune system reacts to a substance, an allergen, which is normally harmless.¹ Most allergic reactions are caused by allergen-specific IgE-antibodies. Common allergens are proteins in pollens, house dust mites, animal dander and foods.

When an individual who has allergen-specific IgE antibodies (i.e. who is sensitized) is exposed to that specific allergen, allergic symptoms may occur. These symptoms may arise in a number of organs. For instance, the mucous membranes in the nose and eyes can be affected, leading to symptoms of rhinitis and conjunctivitis. If the lungs are affected symptoms of asthma might be triggered; in the skin, eczema or urticarial reactions may arise. Although eczema, asthma and rhinitis may develop as a result of IgE-mediated allergy, these diseases also occur as diseases without any allergic component involved.

Allergic diseases are sometimes called atopic diseases. According to the revised nomenclature for allergy, “atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema”.¹ Thus, an individual with eczema who also has rhinitis caused by IgE-antibodies to pollens has atopic eczema even though the specific IgE-antibodies neither cause nor worsen the eczema.

Comorbidity between allergic diseases has mostly been investigated in cohorts of children who have one specific allergic disease and in high risk birth cohorts selected on the basis of parental allergy. Results have consistently shown that comorbidity is substantial^{4 9 19-22} and some data suggest that allergic comorbidity is associated with more persistent and more severe disease.^{23 24}

In the population-based ISAAC study of 463,801 children aged 13–14 years from 56 countries the prevalence of symptoms of at least two of the three disorders eczema, asthma or allergic rhino-conjunctivitis varied from 0.3% to 18.5% with the highest rates in English-speaking Western countries.¹⁴

Eczema, asthma and rhinitis often debuts in childhood. Data indicate that allergic morbidity in childhood, even though transient, is of importance for allergy related diseases in adulthood.²⁵⁻³¹ The atopic march is a concept developed to describe the progression of allergic diseases from eczema in infancy to asthma and rhinitis later in life.³²

Atopy and allergic diseases run in families and a positive family history is a strong risk factor for developing allergic disease.³³⁻³⁵ In recent years a large number of genetic studies have been conducted to determine the genetic components of these diseases and many genes have been identified.³⁶⁻³⁹ However, the increasing prevalence of allergic diseases cannot be explained by genetic factors alone and the increase – together with the large differences in prevalence between urban and rural regions – points towards environmental factors.

Epidemiological research has therefore focused on identifying possible environmental factors associated with allergic diseases. Even though major efforts have been made, rather little is known about causal factors underlying the increase of allergic diseases over the last decades.

ECZEMA

Nomenclature

The word eczema is of Greek origin (ἐκζεμα); the original meaning is “to boil over” or “thrown out by heat” and it probably refers to the acute oozing, vesicular eczema. The EAACI nomenclature task force proposed a new revised nomenclature for allergy in 2001⁴⁰ but it was not until some years later that agreement was reached within the World Allergy Organization to use the word dermatitis as the general term for what previously had been called eczema.¹

The term “eczema” should be reserved for the condition also called atopic dermatitis, flexural eczema, constitutional neurodermatitis, eczema-asthma syndrome or prurigo Besnier. All other forms of eczema should be called dermatitis, e.g. allergic contact dermatitis and seborrhoeic dermatitis. Furthermore, the WAO nomenclature allows eczema to be sub-divided into atopic and non-atopic eczema based on the presence or absence of IgE-sensitization. Consequently, testing either with IgE-antibody determination or skin test is required for this sub-division.

Atopic eczema refers to eczema in individuals with presence of allergen-specific IgE; non-atopic eczema refers to eczema in individuals who have been tested without allergen-specific IgE being detected. The term eczema without specification refers to eczema of unknown type or can be used as an umbrella-term for both atopic and non-atopic eczema.¹ Even though this nomenclature has gained international recognition the term eczema is still under debate, and the term atopic dermatitis is frequently used in parallel.⁴¹

Definition and diagnostic criteria

Eczema is a pruritic, chronically relapsing inflammatory skin disease with typical morphology and distribution.⁴² Eczema is a clinical diagnosis and there is no definitive diagnostic "gold standard" for diagnosing eczema.⁴³ In general, physicians diagnose the disease through recognition of symptoms and clinical features but without conscious awareness or active use of diagnostic criteria.

However, in research, diagnostic criteria for defining cases are essential and ideally, the same criteria should be used worldwide, to allow comparison between studies.⁴⁴ Also in a clinical setting, when diagnosis is not clear, diagnostic criteria are of great value since there is no specific diagnostic laboratory marker for eczema.

Williams criteria⁴⁵ are commonly used and are the most extensively validated criteria.^{46 47} These criteria, presented in 1994 by Williams and co-workers in the UK working party, was a refinement of the criteria Hanifin and Rajka presented in 1980.⁴⁸ The aim of the UK working party was to develop criteria which were simple to use and suitable for epidemiological studies.

According to Williams the patient must have an *itchy* skin condition (or parental report of scratching or rubbing in a child). Plus 3 or more of the following:

- History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles or around the neck (including cheeks in children under 10).
- A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4).
- A history of a general dry skin in the last year.
- Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4).
- Onset under the age of 2 (not used if child is under 4).

As indicated by Williams's criteria it is possible to diagnose eczema in a child without skin symptoms at examination. However, the relapsing course of the disease complicates epidemiological studies and there are no accepted standards for how incident cases or remission should be defined.⁴⁴ Many studies define remission of eczema as a disease-free state lasting at least 12 consecutive months; however, definitions of remission vary.^{49 50}

Prevalence

Eczema is very common among children in western industrialized countries and there has been a marked increase during the last decades.^{15 17 51 52} According to Phase One of the ISAAC study, started in 1991, the 12-month period prevalence of eczema in children aged six or seven years ranged from less than 2% in Iran to around 20% in England, Australia and the Scandinavian countries.⁵³ Phase Three, carried out 5-10 years later, showed an increase in prevalence of eczema in children aged 6-7 years in most countries. This was also true for children 13-14 years old in developing countries. However, in countries where the prevalence rates of eczema had been high from the start of the study, no increase was seen in the older age group.¹⁶

Causes

Eczema is a complex disease: both genetic and environmental factors are important in the pathogenesis. A strong genetic predisposition has been confirmed in twin studies showing a concordance of 0.72 for monozygotic and 0.23 for dizygotic twins.⁵⁴

The genetics of eczema is complex and a large number of genes of importance for both adaptive and innate immunity as well as for skin barrier function have been identified to be associated with eczema.²⁻⁵⁵ The strongest associations found are for genes encoding Filaggrin (FLG) and mutations in these genes lead to impaired skin barrier function and confer a genetic predisposition for dry skin and eczema, as well as predisposing persons with eczema for asthma.⁵⁶⁻⁶⁰ *FLG* mutations have also been associated with eczema severity: the disease seems to be more severe in patients who are *FLG* mutation carriers.⁶¹⁻⁶⁴

Data indicate that *FLG* mutations differ between populations.⁶⁵⁻⁶⁶ This might contribute to the nationwide variance in prevalence of eczema. However, it cannot explain the difference between rural and urban regions.⁶⁷⁻⁶⁸ Affluence and the western life-style are associated with high prevalence of eczema and studies in immigrants have shown that individuals who move from countries with low prevalence take on the higher risk of eczema in their adoptive country.⁶⁹ These findings, together with the increased prevalence rates of eczema during the last decades, point towards environmental factors.

In 1989, David P Strachan found that hay fever and infantile eczema were associated with family size and the individual's position in the household, with higher risk for children who had few siblings.⁷⁰ Based on his findings he suggested that allergic diseases might be prevented by infection in early childhood and that declining family size, improvements in household amenities, and higher standards of personal cleanliness had reduced the opportunity for cross-infection leading, in turn, to increased prevalence of atopic diseases. His findings were confirmed by others and his hypothesis spread rapidly under the name "the hygiene hypothesis". Since then many studies have been conducted to evaluate the impact of early infections and microbial exposures early in life on development of allergic diseases.⁷¹

In 2005 and 2011 Flohr et al reviewed studies that examined environmental exposures in relation to eczema and that might confirm the "hygiene hypothesis".⁷²⁻⁷³ No particular childhood infection or single environmental pathogen was found that could explain Strachan's findings. However, studies from developing nations showed that helminth infections during pregnancy might protect against the development of eczema in childhood.⁷⁴

The reviews from 2005 and 2011 also found protective effects of consumption of unpasteurized milk, endotoxin exposure, day care during infancy and being brought up with a dog during early life. Broad-spectrum antibiotics used both during pregnancy and infancy increased the risk of eczema significantly. Flohr et al argued that this finding, in combination with studies showing protective effects of probiotics,⁷⁵ makes early priming of the immune system via the gut mucosa a possible key factor for development of eczema.⁷³

A recent overview of reviews of randomized clinical trials for prevention of eczema in infants and children found some evidence that prebiotics as well as exclusive breastfeeding for at least 6 months might reduce eczema incidence in high-risk children. Apart from this, no effect was seen for the other interventions tested, including maternal antigen avoidance, omega oil supplementation, probiotics and different types of hypoallergenic formulas.⁷⁶ Environmental triggers of eczema include IgE-mediated allergy, with foods and house dust mites as major allergens.^{77 78} In addition, airborne allergens such as pollens and dander from furred pets may also cause deterioration of eczema.^{79 80} Non-allergic triggers of eczema include sweating, infections, climate factors, skin irritants and emotional stress.^{42 80 81}

Clinical Features

Most eczema cases debut in infancy and at this age the eczema is usually located to cheeks, head, trunk and extensor surfaces of the extremities.⁸² Based on the distribution, eczema is divided into three age-related stages starting with the above mentioned infantile phase (0-2 years). In the childhood phase (3-11 years) eczema involving flexures (folds of elbows, behind knees, fronts of ankles, wrists and neck) predominates. The adolescent/young adult phase (≥ 12 years) resembles the childhood phase with the addition of involvement of the face and upper trunk.⁸² Characteristic of eczema at all ages are dry skin and dermal itch.

Treatment

The first-line treatment for eczema for patients of all ages is topical glucocorticoids together with emollient creams.⁸³ Topical glucocorticoids have an anti-inflammatory effect, reduce itch and inflammation and should be used for treatment of flares but can also be used as maintenance therapy two or three times weekly.^{84 85}

Emollients are recommended for regular use; they reduce dryness and itching of the skin and have been shown to reduce eczema flares.^{83 86} Emollient as an adjunctive therapy to topical glucocorticoids has also been shown to reduce the need of topical glucocorticoids among children with eczema to moderate eczema.⁸⁷ Other treatments available for eczema include topical calcineurin inhibitors, phototherapy and systemic immunosuppressive treatments.^{83 88}

Disease severity measurement

Many different scales are employed to measure the severity of eczema and severity results can differ depending on the method used.⁸⁹ However, population-based studies consistently show that a majority of children have mild disease (45-84%) and only a minority have severe disease (0-13%).⁸⁹⁻⁹⁶ Scales for evaluation of eczema severity have mainly been developed for use in clinical trials, to evaluate interventions and treatments.⁹⁷ A review by Schmitt and co-workers published in 2007 declared that there are too many published outcome measures for eczema. Moreover, apart from SCORAD,⁹⁸ EASI,⁹⁹ and POEM¹⁰⁰ the scales had not been tested properly or did not perform adequately when tested.^{97 101}

The diversity of scales is a problem since it hampers scientific communication and makes it difficult to compare the efficacy of various therapeutic interventions.^{101 102} Some scales include only physician-oriented “objective” outcome measures, while others take patient-oriented outcome measures into account, such as patients’ or parents’ reports of itch and sleep disturbance.

Most scales aim to assess the current disease severity by evaluating ongoing skin symptoms and by asking questions about subjective symptoms the previous week.^{100 101 103-105} These scales provide an estimate of the current disease severity and work well for evaluation of interventions. However, since eczema is seasonally variable^{79 106} and is intermittent by nature these scales fail to provide information of severity or disease burden over time. In contrast, the Nottingham Eczema Severity Score (NESS),⁹¹ based on the Rajka and Langeland grading,¹⁰⁷ is a scale developed for population-based research. NESS assesses eczema severity during the last 12 months, even though disease extent is estimated based on a single evaluation. NESS has been validated in the age group 1-5 years, but has subsequently been used in a study population with a mean age of 11.7 years.^{108 109}

Comorbidity

Children with eczema have an increased risk of asthma and rhinitis.^{4 110 111} Most studies addressing comorbidity have been performed in selected cohorts of eczema patients from specialized clinics or hospital settings. The association between eczema and asthma is well documented, as are the increased risk of asthma later in life among children with eczema.^{9 19 112-115}

In a systematic review including 13 prospective cohort studies, of which 4 followed birth cohorts and 9 followed eczema cohorts, van der Hulst and co-workers evaluated the risk that children who had eczema before age 4 would develop asthma after age 6.¹¹⁶ The pooled odds ratio for the risk of asthma after eczema, compared with children without eczema was found to be 2.14 (95% CI, 1.67-2.75) in birth cohort studies. In eczema cohort studies the prevalence of asthma at the age of 6 years was 35.8% (95% CI, 32.2% to 39.9%) for inpatients and 29.5% (95% CI, 28.2% to 32.7%) for outpatients, indicating that severity of eczema is associated with the risk of developing asthma.

Prognosis

In a Swedish cohort of children from a hospital-based outpatient clinic, 60% of children with eczema were free of disease in early adolescence.¹¹⁷ However, up to 50% may have recurrences in adulthood.¹¹⁸ In addition to concomitant asthma and rhinitis, early-onset disease, severe early disease and a family history of eczema may predict a more persistent course of eczema.¹¹¹ Furthermore, sensitization to foods or inhalant allergens has been found to predict a worse prognosis for eczema with more persistent disease during childhood.¹⁹

There are some studies indicating that *FLG* null mutations are associated with more persistent disease.^{119 120} For children with eczema and their parents, the eczema prognosis is of interest, as is the risk of future development of asthma or rhinitis. The associations between eczema, asthma and rhinitis are evident and many studies support the concept of the atopic march. However, whether the association between eczema in infancy and asthma and rhinitis later in life is causal, or not, has been under debate.^{10 19 113 121 122}

Quality of life

It is well known that eczema may affect the health related quality of life (HRQoL) of children with eczema as well as that of their families. Living with a chronic disease such as eczema may affect several dimensions of life. Sleep disturbance due to itching is common and it is estimated that up to 60% of children with eczema have disturbed sleep, with numbers increasing to 83% during exacerbations.¹²³ Treatment is demanding, often including time-consuming daily topical applications. In many cases eczema is a disease that shows, sometimes affecting the patient's social life and interaction with others.¹²⁴

To measure the impact of eczema on health-related quality of life both disease-specific and generic instruments have been used. Disease-specific questionnaires investigate the areas of HRQoL considered to be most relevant for one particular disease or condition. These questionnaires often have high response rates, since directly disease-related questions are meaningful to the sufferers.¹²⁵ One such questionnaire is the Children's Dermatology Life Quality Index (CDLQI), a well validated instrument that has been widely used to evaluate the impact of eczema and other skin diseases on HRQoL.^{126 127} Studies using CDLQI have shown that severity of eczema correlates with HRQoL and have revealed greater impairment among children with severe eczema.^{5 128 129}

Generic instruments have the advantage of being applicable in both healthy and chronically ill subjects across a wide range of populations.^{130 131} By using generic instruments it has been shown that generalized childhood eczema is associated with impairment of quality of life of the same magnitude or even worse than other childhood diseases, such as epilepsy, asthma and diabetes.³
¹³² A study carried out in an outpatient paediatric dermatology setting, reported that the quality of life among the families of children with mild eczema was impaired to the same degree as that of families of children with diabetes.¹³³

Thus, mild eczema may also have a profound impact on HRQoL. However, since most children with eczema are treated by general practitioners and only more severe cases by specialists, findings from these settings cannot be generalized to children with eczema in general.

Self-perceived health is often used in health studies that examine the physical and mental health of children and teenagers, such as the WHO collaborative cross-national study.¹³⁴ By asking a simple question such as “*How are you feeling?*” an overall assessment of health, both mental and physical, is obtained. Self-perceived health has been shown to correlate well with objective measures of physical health status and also with psychological health; for example, adolescents suffering from depression report lower self-perceived health than others.¹³⁵⁻¹³⁷ When assessing the impact of eczema on HRQoL using a generic instrument or self-perceived health it is important to take comorbidity into account so that the results are not confounded by concomitant asthma or rhinitis.

EPIDEMIOLOGY

Epidemiology can simply be described as “the study of the occurrence of illness”.¹³⁸ There are two main measures of disease occurrence: prevalence and incidence. Prevalence describes the proportion of people in a population who have a disease at a specific time and reflects both disease duration and incidence. Incidence, on the other hand, describes the number of people in a population that go from being healthy to having a disease over a specified period of time. Thus, calculating incidence require longitudinal studies, such as cohort studies, while prevalence can be measured at one time point as is done in cross-sectional studies.

Prevalence is commonly used in areas of public health since it measures the disease burden in a population. However, in studies of preventive measures or in research on causation, incidence measures are more appropriate. For diseases with insidious onset and diseases with a fluctuant course it may be difficult to define onset.⁴⁴ It is therefore sometimes necessary to describe these conditions in terms of prevalence rather than incidence. For allergic diseases, measures of “period prevalence” are commonly used.¹³⁹ A 12-month period prevalence refers to the proportion within a population that had a disease at any time during a period of 12 months. Another type of period prevalence is lifetime prevalence, which refers to the proportion who had the disease at any time in life. Various errors that may occur in epidemiological research are elaborated on in the Discussion section of this thesis.

7 AIMS

The overall aim was to provide a better understanding of childhood eczema in the general population and especially the relation to asthma and rhinitis.

The specific objectives were:

To study development of eczema, asthma and rhinitis in relation to sex and parental allergy throughout childhood, in a population-based cohort.

To investigate eczema severity in relation to sex, *FLG* mutations, topical treatment, asthma and rhinitis among pre-adolescents.

To assess the impact of eczema for quality of life among pre-adolescent children in a population-based cohort, taking both eczema severity and comorbidity into account.

To examine prognosis of eczema and risk factors for eczema, asthma and rhinitis in pre-adolescence among children with infantile eczema.

8 MATERIAL AND METHODS

STUDY SUBJECTS

The BAMSE project

All papers in this thesis are based on material from the BAMSE cohort. The BAMSE project is a longitudinal population-based cohort in which children have been prospectively followed during childhood and early adolescence. The abbreviation “BAMSE” is a Swedish acronym that stands for “Barn, Allergi, Miljö i Stockholm en Epidemiologisk studie”. The English translation reads “Children, Allergy, Milieu, Stockholm, Epidemiological Study”. The main aim of the BAMSE study was to establish risk factors for development of allergy-related diseases in childhood. The original plan was to follow the children up to the age of four years, but most of the cohort have now been followed well into their teens.

Recruitment

Parents of all children born between 1994 and 1996 living in predefined areas of the central and north-western parts of Stockholm were asked to participate. The areas were chosen to represent both urban and suburban environments with a representative mix of housing and socio-economy. A community population register made it possible to reach the parents of infants born in the areas during the study period.¹³ Figure 1 shows a flow chart of the study with included and excluded children. Of the 7,221 children born in the recruitment area during the study period, 477 could not be reached and 1,256 were actively excluded, leaving 5,488 eligible subjects (Figure 1).

The BAMSE cohort

The study base of the BAMSE cohort comprised 4,089 infants, corresponding to 75% of the eligible subjects. Detailed data on residential characteristics, environmental factors and parental allergy were obtained from a baseline parental questionnaire when the infant was two months old. Non-responders and actively excluded families were contacted in 1996 with a short questionnaire on key exposures and parental allergy.¹³ Response rates were 58% and 83%, respectively.

In this group of non-responders and actively excluded families, smoking was significantly more common. However, other background factors including parental allergy did not differ when included families were compared with non-responders and excluded families.

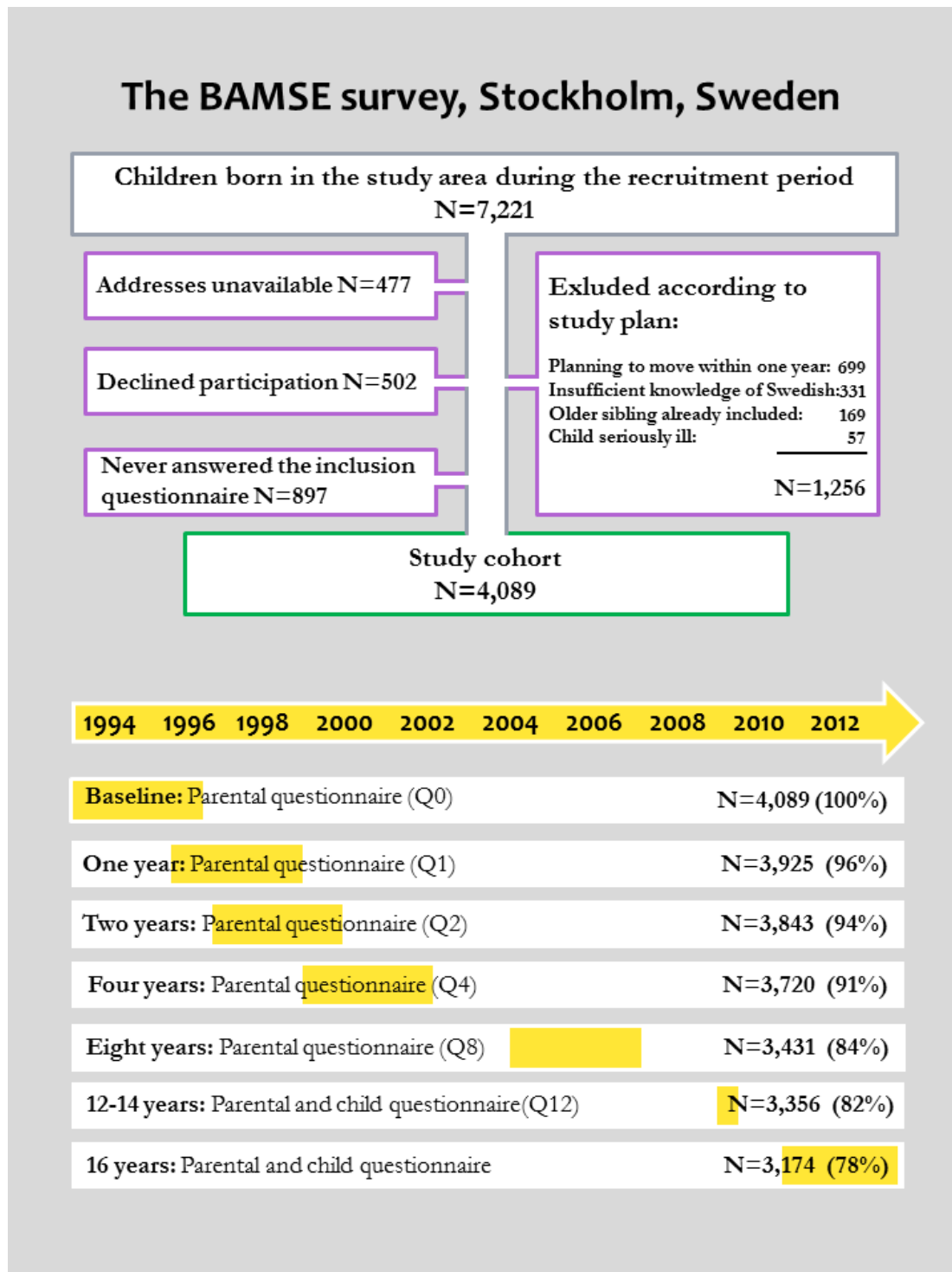


Figure 1. Description of the BAMSE birth cohort. Yellow fields in the lower section represent periods of data collection.

Follow-ups

When the 4,089 children in the cohort reached the ages of one, two, four and eight years, the parents received questionnaires focusing on symptoms of eczema, asthma and rhinitis, life style factors and key exposures. The response rates were 96%, 94%, 91% and 84% respectively. For the 12-year follow-up, all questionnaires were sent out on one occasion in springtime 2008. The children were then between eleven and fourteen years old (mean age 12.9 years).

At the 12-year follow-up, both the parent and the child were asked to participate. Parents and children completed one questionnaire each, intended to collect information about symptoms related to eczema, asthma, rhinitis, life style factors and key exposures. The response rate among parents was 82% at the 12-year follow-up. The children, of whom 2,801 (69%) completed the questionnaire, also answered questions for evaluation of self-perceived general health. Children with skin symptoms during the last week were in addition asked to answer a disease-specific questionnaire for evaluation of quality of life.

As part of a nested case-control study¹⁴⁰ during 1995 to 1996, 137 children from the BAMSE cohort with infantile eczema provided blood at two years for analyses of allergen-specific IgE against foods and airborne allergens.

STUDY POPULATIONS STUDY I-IV

The study populations for paper I-IV are derived from the BAMSE cohort, but differ somewhat between the studies as described below. Data collection for the 16-year follow-up was ongoing when the studies in this thesis were performed. Thus only data up until the 12-year follow-up have been used. Figure 2 illustrates the origin of the follow-up data used for the studies in this thesis.

Reflection – study population

In studies like the the ones I have been involved in, there is always a trade-off between wanting to have a large study population and having to handle missing data. In my experience a lot of work can be saved if you are thorough when thinking through and discussing what study population to use. This is best done early in the process with all co-authors involved.

For study I we included 2,916 children (71% of the original cohort) who had participated at the follow-ups at age 1, 2, 4, 8 and 12 and had provided complete data on i) parental allergy at baseline and ii) eczema, asthma and rhinitis symptoms at every follow-up (Figure 2).

Study II included 3,301 children (81% of the original cohort) from the 12-year follow-up with complete data on parentally reported eczema, asthma, and rhinitis symptoms. DNA collected at 4 or 8 years was available for 1,854 individuals (Figure 2).

For study III the study population consisted of 2,756 children (67% of the original cohort) who had completed the 12-year child questionnaire with parentally reported data about eczema symptoms during the last year (Figure 2).

Study IV included 3,208 children (78% of the original cohort) who had participated at the 1-, 2- and 12-year follow-up with complete data on parentally reported eczema symptoms from all three follow-ups (Figure 2).

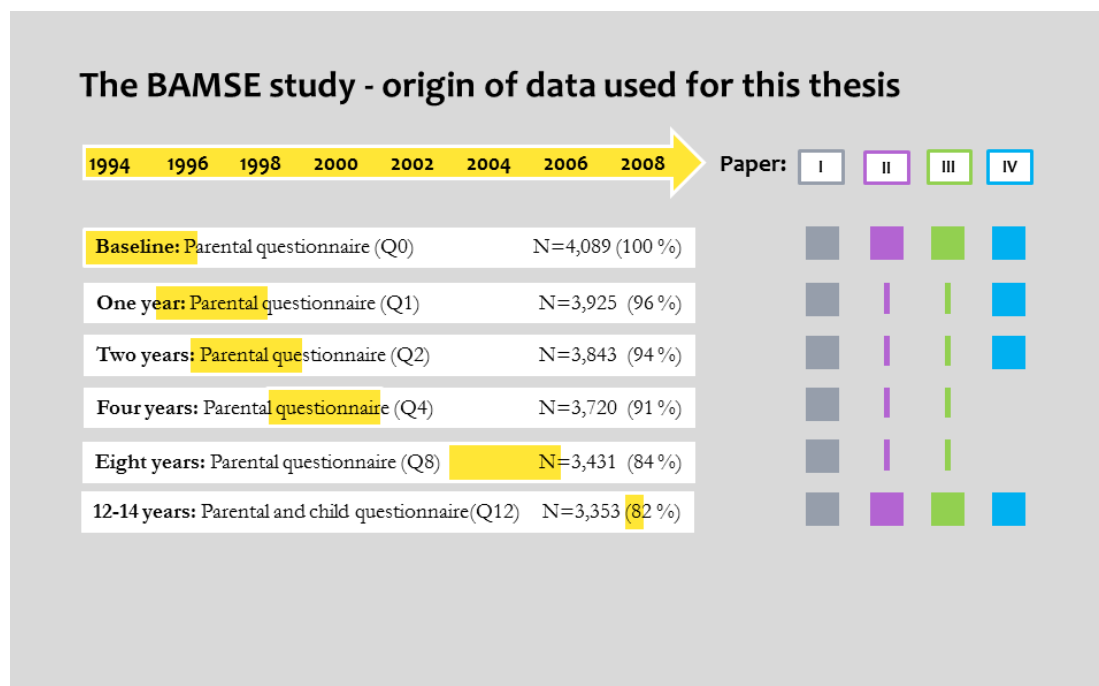


Figure 2. Origin of data used for paper I, II, III and IV. Narrow symbols signify that relatively little data have been used from these follow ups.

DEFINITIONS OF BACKGROUND VARIABLES (I- IV)

Background variables used in study I-IV are defined in table I. In study I and III tobacco smoke exposure (defined as maternal smoking) was used for comparison of the study population and the original cohort. In study IV tobacco smoke exposure was assessed as a risk factor for eczema, asthma and rhinitis in pre-adolescence among children with infantile eczema. In this study, based on previous publications, we used a variable that also included paternal smoking at the time of inclusion.¹⁴¹

Table I Definitions of background variables used in study I-IV

Variables	Definition (based on data collected at Q0, Q1)*	Paper
Parental allergy	Mother and/or father with doctor's diagnosis of asthma and asthma medication and/or doctor diagnosed hay fever in combination with allergy to furred pets and/or pollen and/or doctor's diagnosis of eczema at the time of enrolment. (Q0)	I, II, III, IV
Low socio-economic status	Both parents are blue collar workers according to the Nordic standard occupational classification and Swedish socio-economic classification. ¹⁴² (Q0)	I, II, IV
Young mother	Maternal age \leq 25 years at birth of the child. (Q0)	I
Exclusive breastfeeding \geq 4 months	Exclusive breastfeeding during the first four months of life without exposure to formula (cow's milk or hydrolysate) or solid foods. ¹⁴³ (Q1)	I, II, IV
Tobacco exposure	Mother smoked at least one cigarette per day during pregnancy or at the time of enrolment. (Q1)	I, II
Tobacco smoking	Mother smoked at least one cigarette per day during pregnancy and/or any of the parents smoked at least one cigarette per day at the time of enrolment. (Q0, Q1)	IV

*See Figure 2, page 22

DEFINITIONS OF HEALTH OUTCOMES (I- IV)

Health outcome variables for study I-IV are defined in table II. In study I, variables reflecting a 12-month period prevalence were used. Owing to the way the questionnaires had been constructed it was not possible to calculate a 12-month period prevalence for allergic rhinitis. Instead, we used a rhinitis definition which we derived from the ISAAC study which made it possible to evaluate a 12-month period prevalence (Table II). In study II, III and IV a variable for allergic rhinitis was used (Table II and Table IV).

Table II. Definitions of health outcomes used in study I-IV

Variables	Definition (based on data collected at Q1, Q2, Q4, Q8, Q12)*	Paper
Eczema at one year	Dry skin, itchy rashes for two weeks or more and specific location of rash (face or outer aspect of arms/legs or flexures of knees/elbow or wrists/front of ankles) and/or doctor's diagnosis of eczema after three months and up to one year of age. (Q1)	I, IV
Eczema at two years	Dry skin, itchy rashes for two weeks or more and specific location of rash (face or outer aspect of arms/legs or flexures of knees/elbow or wrists/front of ankles) and/or doctor's diagnosis of eczema after one year and up to two years of age. (Q2)	I, IV
Eczema at four years	Dry skin, itchy rashes for two weeks or more and specific location of rash (face or outer aspect of arms/legs or flexures of knees/elbow or wrists/front of ankles) and/or doctor's diagnosis of eczema after two year and up to four years of age. (Q4)	I
Eczema at eight years	Dry skin, itchy rashes for two weeks or more and specific location of rash (face or flexures of arms/legs or wrists/front of ankles or neck) and/or doctor's diagnosis of eczema from the age of seven years. (Q8)	I
Eczema at the 12-year follow-up	Dry skin and itchy rash and specific location of rash (flexures of arms/legs or wrists/front of ankles or neck) in the last 12 months and/or doctor's diagnosis of eczema from the age of 10 years. (Q12)	I, II, III, IV
Asthma at one year	At least three episodes of wheeze between three months and 1 year of age in combination with inhaled steroids and/or signs of hyper-reactivity without concurrent upper respiratory infection. (Q1)	I, IV
Asthma at two years	At least three episodes of wheeze between 1 year and 2 years of age, in combination with inhaled steroids and/or signs of hyper-reactivity without concurrent upper respiratory infection. (Q2)	I, IV
Asthma at four, eight and 12 years	At least four episodes of wheeze in the last 12 months or at least 1 episode of wheeze in the last 12 months in combination with occasional or regular use of prescribed inhaled steroids. (Q4, Q8, Q12)	I, II, III, IV
Rhinitis at one and two years	ISAAC-rhinitis; prolonged rhinitis symptoms two months or more in the past 12 months. (Q1, Q2)	I
Rhinitis at four, eight and 12 years	ISAAC-rhinitis; prolonged rhinitis without common cold in the past 12 months. (Q4, Q8, Q12)	I
Rhinitis at the 12 year follow-up	Symptoms from eyes/nose (suspected or evident) after exposure to furred pets and/or pollen and/or doctor's diagnosis of allergic rhinitis from the age of 10 years. (Q12)	II, III, IV

*See Figure 2, page 22

EVALUATION OF ECZEMA SEVERITY (II, III)

The questionnaire used for the BAMSE 12-year follow-up was more comprehensive concerning eczema than at earlier follow-ups. Questions modified from the Rajka and Langeland index¹⁰⁷ for evaluation of eczema severity had been included. In study II a BAMSE Eczema Severity Score (BESS), scale 3-14, was constructed based on the responses to three questions: number of months with eczema during the last year, disturbed sleep, and number of affected body sites (multiple choice alternatives: face, scalp, ears, arms and/or legs, armpits, knees and/or elbows, wrist and/or ankles, hands, feet, throat and/or neck, buttocks, chest and/or abdomen and/or back and/or shoulders, groin and/or genitals).

After having collected the data we discovered that the questions in BAMSE were very similar to the questions used for the Nottingham Eczema Severity Score (NESS).⁹¹ We therefore used NESS as a template for BESS. Children were divided into three groups on the basis of their score: mild (BESS 3-7), moderate (BESS 8-10) and severe eczema (BESS 11-14).

Reflection – BESS versus modified NESS

When planning for study II, I tried to figure out how to evaluate eczema disease severity based on the questionnaire data from the 12-year follow-up. I searched the literature to find out how others had done and came across NESS. The scientists who constructed NESS had, like us, asked questions based on the Rajka and Langeland index. I was very disappointed when I realized that we could not compute NESS with the data we had. I did an evaluation based on the questions we had and decided to use our data in such a way that our evaluation would be as close as possible to NESS. When I did the calculations I was excited to find that the proportions of mild, moderate and severe cases of eczema in our material were similar to the proportions in the validation study of NESS. I came up with the idea of calling our modified NESS-scale “BESS”. My co-supervisor Magnus Wickman immediately came up with a number of possible sentences that would generate the acronym “Porgy”. After a while we got back to work and decided to call our scale BESS instead of modified NESS. As argued in the background section of this thesis, there is really no need for yet another scale for evaluation of eczema severity. Thus, our approach might be considered inappropriate. However, I think we all felt satisfied with a scale of our own and furthermore BESS sounds much better than modified NESS. I am sure that BESS will be useful for future papers from the BAMSE project, but vanity is probably one of the reasons why it is so difficult to achieve consensus, even in the world of research.

GENOTYPING FOR FILAGGRIN MUTATIONS (II)

DNA from blood samples collected at the 4- or 8-year follow-up was available for 1,854 of 3,301 children in study II. Genotyping was performed for the *FLG* mutations that are most common in Scandinavia (R501X, R2447X and 2282del4).⁵⁹ Children with any of these mutations were classified as mutation carriers.

ASSESSMENT OF SELF-PERCEIVED HEALTH (III)

In the 12-year follow-up, three questions for evaluation of self-perceived health were included in the child questionnaire (Table III).

Table III. Questions concerning self-perceived general health^{144 145}

Question	Response alternatives
How are you feeling?	Excellent / very good / good / fairly good / not good
How healthy do you consider yourself to be?	Completely healthy / fairly healthy / not very healthy
How happy are you with your life right now?	I am very happy / I am fairly happy / I am not very happy / I am not happy at all

ASSESSMENT OF DISEASE-SPECIFIC QUALITY OF LIFE (III)

At the 12-year follow-up children with itchy rash in the preceding seven days were asked to answer the “Children’s Dermatology Life Quality Index (CDLQI)” questionnaire in order to collect information on the impact of disease on health-related HRQoL. The CDLQI includes ten questions, each scoring 0-3, giving a maximum of 30; the higher the score, the more negative effect on the HRQoL.

DEFINITIONS OF RISK FACTORS IN STUDY IV

Among children with infantile eczema, the following exposures were evaluated as risk factors for the outcomes eczema, asthma and rhinitis at twelve years: sex, parental allergy, tobacco exposure, asthma before two years of age, rhinitis before two years of age, sleep disturbance due to itch, persistent eczema and widespread eczema in the first two years of life. For definitions see Table I and Table IV.

Table IV. Definitions of risk factors in paper IV

Risk factors	Definition (based on data collected at Q1, Q2)*
Asthma before 2 years of age	At least three episodes of wheeze between three months and 1 year of age, and/or between 1 year and 2 years of age, in combination with inhaled steroids and/or signs of hyper-reactivity without concurrent upper respiratory infection. (Q1, Q2)
Rhinitis before 2 years of age	Symptoms from eyes/nose (suspected or evident) after exposure to furred pets and/or pollen and/or doctor's diagnosis of allergic rhinitis sometime between 3 months and 1 year of age, and/or between 1 year and 2 years of years of age. (Q1, Q2)
Sleep disturbance due to itch	Reported sleep disturbance due to itch, before 2 years of age. (Q1, Q2)
Persistent infantile eczema	Having fulfilled the eczema definition in both the first and second years of life. (Q1, Q2)
Widespread infantile eczema	Defined as more than 5 body sites affected by eczema before 1 year of age and/or between 1 and 2 years of age. Sites (multiple choice alternatives): face, scalp, ears, arms and/or legs, armpits, knees and/or elbows, wrist and/or ankles, hands, feet, throat and/or neck, buttocks, chest and/or abdomen and/or back and/or shoulders, groin and/or genitals. (Q1, Q2)
Atopic infantile eczema	Defined as positive fx5® (allergen-specific IgE \geq 0.35kU _A /L) and /or positive Phadiatop® (allergen-specific IgE \geq 0.35kU _A /L). Sera collected at 2 years of age were analysed for IgE antibodies to a mix of common inhalant allergens with Phadiatop® (cat, dog, horse, birch, timothy, mugwort, <i>Dermatophagoides pteronyssinus</i> and <i>Cladosporium herbarum</i>) and to a mix of common food allergens with fx5 (milk, egg, cod, soy, peanut and wheat) by using the ImmunoCAP System (Thermo Fisher Scientific, Uppsala, Sweden).

*See Figure 2, page 22

ETHICAL APPROVAL

The studies included in this thesis are part of the BAMSE project, which has been approved by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden. Reference numbers; 93:189, 98:175, 02:420 and 2007/1634-31. Informed consent was obtained from all participants.

STATISTICAL METHODS

All statistical analyses were performed with STATA Statistical Software (release 11.1; StataCorp, College Station, Texas, USA).

Confidence intervals (I, II, III, IV)

For evaluation of differences concerning background factors and prevalence of disease between the original cohort and children in the study populations, proportions with 95% confidence intervals (95% CI) were calculated. Intervals that did not overlap were considered significantly different.

Chi²-tests (I, II, III, IV)

For comparison between groups for dichotomous variables χ^2 -tests were used.

Wilcoxon Rank Sum test (I, II, III)

For evaluation of differences between groups for categorical outcomes Wilcoxon Rank Sum test was used.

Spearman correlation test (III)

To test the correlation between eczema severity and disease-specific health-related quality of life (CDLQI), and to test the correlation between CDQLI and self-perceived health, we used Spearman correlation test.

Logistic regression (III, IV)

Logistic regression was used in study III (for evaluation of the association between eczema, asthma, rhinitis and self-perceived health) and study IV (for evaluation of the association between infantile eczema and the outcomes at age twelve). In both studies univariate analysis was done to identify factors associated with the outcomes. Potential confounders were tested using backwards selection. Covariates that changed the β -coefficient more than 10% for any of the tested variables were considered confounders. In study III, concurrent asthma, rhinitis and eczema were kept *a priori* for all analyses. Sex and parental allergy were kept *a priori* for all analyses in study IV. Covariates that were significantly associated with any of the outcomes in the unadjusted model were kept in the final model. Effect modification by sex and parental allergy was also tested in both study III and IV. Sex was found to be an effect modifier for the association between eczema and self-perceived health and accordingly the analysis in study III was stratified by sex.

Generalized estimated equations (I)

Generalized estimated equations¹⁴⁶ with an unstructured correlation matrix were used to assess the impact of parental allergy and sex on development of any allergy-related disease over time in paper I and also for eczema in the thesis summary chapter. The model incorporated an interaction between time and exposure to evaluate the effect of exposure over time. The models were adjusted for exclusive breastfeeding ≥ 4 months, maternal smoking, low socio-economic status and young mother (≤ 26 years).

Absolute risk (IV)

Absolute risks in study IV were calculated as the number of children having both the outcome and the risk factor, divided by the total number of children with the risk factor. For 95% confidence intervals the binomial test of statistical significance was used.

Reflection – what is the value of a high odds ratio?

Measuring illness is a fundamental feature of epidemiology. By comparing disease occurrence in groups of people that are exposed to a factor with occurrence in groups not exposed, knowledge has been gained about the causes of various diseases. When comparing disease occurrence, both absolute and relative measures can be used. Most people, including researchers, are insensitive to variations of risk among small probabilities.¹⁴⁷ To exemplify, a healthy young smoker who is informed that the absolute risk of developing cancer within 10 years is 0.001% for people who continue to smoke compared to 0.00001% for people who stop smoking, will probably consider both risks as quite low. However, if confronted with the relative risk instead, being informed that the risk of getting cancer is 100 times higher if she continues to smoke compared to if she quits, she will probably think differently. The odds ratio is another way of expressing the relative risk and for small risks the odds ratio equals the risk ratio,¹³⁸ thus the odds ratio for smoking on the risk of developing cancer in the above example is 100. However, the same absolute effect will result in a high relative risk if the disease is rare and a lower relative risk if it is a prevalent disease.¹⁴⁸ In my experience, this is not intuitively understood. Thus, when it comes to allergy-related diseases, which are all common, the use of relative risk measures can make risks appear deceptively small even when the absolute risk difference conferred by the factor being studied is high.

9 RESULTS

DEVELOPMENT OF ALLERGY-RELATED DISEASES TO AGE 12 (I)

Up to pre-adolescence 58% of the 2,916 children with complete data on eczema, asthma and rhinitis who were included in study I had had eczema, asthma and/or rhinitis (Figure 3a). Included children did not differ from the original cohort (N=4,089) in terms of risk factors for development of allergy-related diseases (Table V).

Table V. Distribution of risk factors for allergy-related diseases in the study population of paper I compared to the original cohort

Variable*	Original cohort			Study population		
	N=4,089 (100%)			n=2,916 (71.3%)		
<i>Data collected at enrolment</i>	n	%	95% CI	n	%	95% CI
Sex						
Male	2065/4089	50.5	49.0–52.0	1488/2916	51.0	49.2–52.8
Parental allergy†						
either or both	1746/4045	43.2	41.6–44.7	1291/2916	44.3	42.5–46.1
Maternal age						
< 25 years	319/4088	7.8	7.0–8.6	196/2915	6.7	5.8–7.6
Socioeconomic status						
blue collar workers	695/4018	17.3	16.1–18.5	431/2882	15.0	13.7–16.3
Maternal tobacco smoking‡						
Yes	563/4086	13.8	12.7–14.8	346/2916	11.9	10.7–13.0
<i>Data collected at 1 year</i>	n=3,925 (96%)			n=2,916 (71.3%)		
	n	%	95% CI	n	%	95% CI
Exclusive breastfeeding ≥4 months						
No	803/3919	20.5	19.2–21.8	543/2912	18.7	17.2–20.1

*Internal missing 0–1.7%

†Doctor's diagnosis of asthma and/or hay fever in combination with allergy to furred pets and/or pollen and/or doctor's diagnosis of eczema at enrolment

‡Mother smoked at least one cigarette per day during pregnancy and/or at the time of enrolment

Furthermore, we found no differences when comparing prevalence rates of eczema, asthma and rhinitis of children in the study population with children in the study base (Table VI). Twenty-two percent (629 of 2,916) of all children had had one disease at only one follow-up, while 36% (1,066 of 2,916) either had one disease at more than one follow-up, or two or more of eczema, asthma and rhinitis during the study period.

Among children with parental allergy, 66% (858 of 1,291) had an allergy-related disease before 12 years of age, compared to 52% (837 of 1,625) of children with no parental allergy, $p < 0.001$. Boys had a lifetime prevalence of any allergy related disease of 60% (892 of 1,488) up to 12 years and the corresponding proportion for girls was 56% (803 of 1,428), $p = 0.042$. This difference was mainly explained by higher prevalence rates of asthma and rhinitis among boys.

Table VI. Twelve-month prevalence rates of allergy-related diseases in the study population of paper I compared to the study base

Variable	Original cohort (4,089)			Study population (2,916)		
	N	%	95% CI	n	%	95% CI
1 year						
Eczema	594/3923	15.1	14.0–16.3	440/2916	15.1	13.8–16.4
Asthma	151/3924	3.9	3.2–4.5	101/2916	3.5	2.8–4.1
Rhinitis	145/3920	3.7	3.1–4.3	103/2916	3.5	3.1–4.3
2 years						
Eczema	730/3839	19.0	17.8–20.3	542/2916	18.6	17.2–20.0
Asthma	219/3835	5.7	5.0–6.4	157/2916	5.4	4.6–6.2
Rhinitis	154/3840	4.0	3.4–4.6	112/2916	3.8	3.1–4.5
4 years						
Eczema	729/3721	19.6	18.3–20.9	546/2916	18.7	17.3–20.1
Asthma	260/3704	7.0	6.2–7.8	182/2916	6.2	5.4–7.1
Rhinitis	413/3685	11.2	10.2–12.2	314/2916	10.8	9.6–11.9
8 years						
Eczema	428/3397	12.6	11.5–13.7	355/2916	12.2	11.0–13.4
Asthma	215/3397	6.3	5.5–7.1	177/2916	6.1	5.2–6.9
Rhinitis	462/3409	13.6	12.4–14.7	380/2916	13.0	11.8–14.3
12 years						
Eczema	399/3353	11.9	10.8–13.0	339/2916	11.6	10.5–12.8
Asthma	221/3339	6.6	5.8–7.5	189/2916	6.5	5.6–7.4
Rhinitis	693/3337	20.8	19.4–22.1	601/2916	20.6	19.1–22.1

Disease turnover and persistence

Disease turnover was substantial, with a large number of new and remitting cases throughout the study period (Figure 3b). The average proportion of new cases of the diseases studied over all observational time points was 53%. The corresponding proportion for total remission, defined as not having the disease again at any subsequent follow-up, was 44%.

Figure 3b also shows the proportions of children who had had i) eczema, ii) asthma and iii) rhinitis at one, two or three or more follow-up occasions up to 12 years of age. The pattern of onset and remission for eczema, asthma and rhinitis was similar among children with and without parental allergy, as well as among boys and girls. Children with parental allergy had more persistent eczema, asthma and rhinitis than children without parental allergy, all $p < 0.001$. Boys and girls did not differ in terms of disease persistence.

Reflection – trying to give the whole picture

In study I we made every effort to find a way to illustrate development of allergy-related diseases in childhood. I had a vision of a graph which would explain it all. The problem was that I didn't know what it would look like. I made one graph after another and they were all too complicated and impossible to understand. Others had created nice illustrations showing the development and course of one disease over time^{19 149 150} but I could not find anything similar to what I wanted to do. I finally asked myself how many possible phenotypes there could be in study I. It was easily calculated: three diseases and five follow-ups results in 32,768 possible "phenotypes". For comparison, one disease and four follow-ups gives 16 possible "phenotypes". At that point I gave up the idea of a single graph that would explain it all. However, I believe that Figure 3a together with Figure 3b will give you a fairly good notion of the dynamics of eczema, asthma and rhinitis in childhood even if they fail to provide any information whatsoever of the interrelationship between the diseases.

Prevalence rates, disease turnover and persistence for eczema, asthma and rhinitis 0-12 years (n=2,916)

Figure 3a

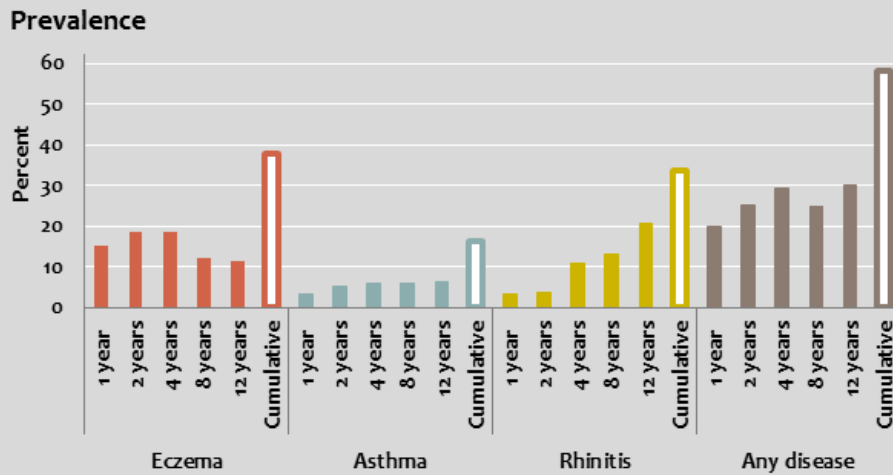


Figure 3b

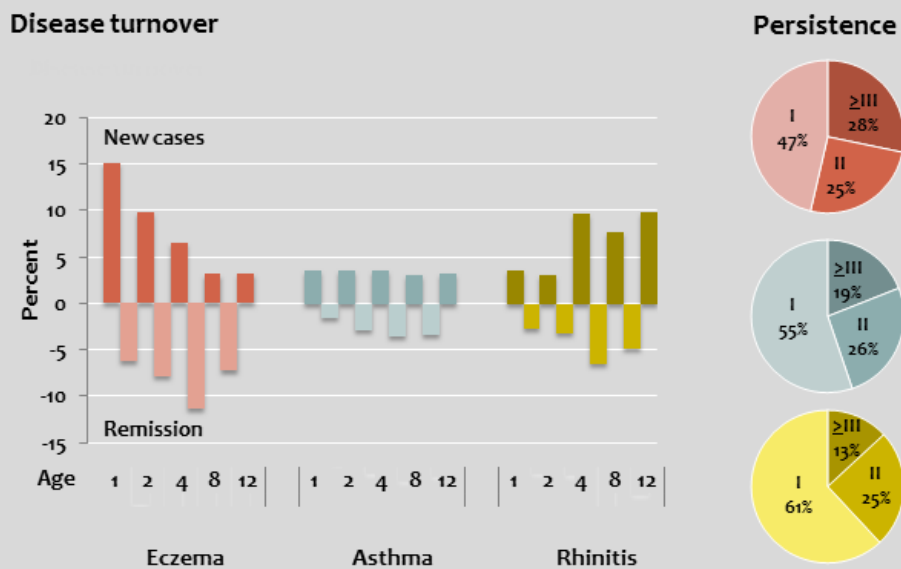


Figure 3a. Twelve-month prevalence rates of eczema, asthma, rhinitis and any of these diseases at age 1, 2, 4, 8, and 12 years. Empty bars show the percentage of children who had been affected at some follow-up before 12 years, n=2,916.

Figure 3b. Disease turnover indicates the percentage in the population (n=2,916) of new and remitting cases at each observation. New cases were defined as onset of disease which had not been present at any previous observation and remission was defined as not having a disease that had been present at the previous observation. Persistence indicates the proportion of children who had a disease at one, two or three or more observation timepoints among the children who had ever had the same disease.

Development of eczema to age 12

As shown in figure 3a 1,100 (38%) of the 2,916 children had eczema at some time during the study period. Among these, more than a quarter had eczema at three or more follow-up occasions. Thus, in the whole study population of 2,916 children, 11% had eczema at three or more follow-up occasions.

ADDITIONAL RESULTS - DEVELOPMENT OF ECZEMA TO AGE 12

Only 45 of the 1,100 children with eczema had eczema at all five follow-ups. Figure 4 provides detailed information on the course of eczema among the 1,100 children in the study population of paper I who had eczema at any time up to 12 years of age. Note that 66% (725/1,100) had onset of eczema before the age of two years.

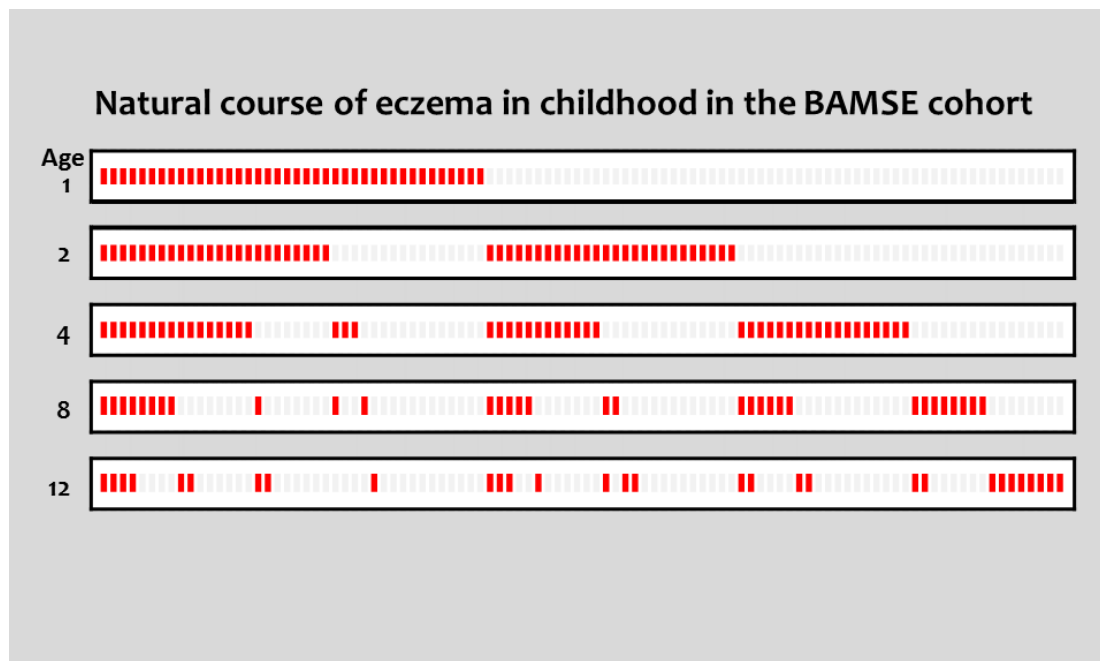


Figure 4. Course of eczema up to age 12 years in the BAMSE birth cohort $n=2,916$. Each row contains 100 rectangles, representing the 1,100 children in study I who had eczema at any of the one, two, four, eight and 12-year follow-ups. The course of each 1/100 subsample can be traced vertically. Each red rectangle represents subjects with eczema in the respective time period.

Generalized estimated equations were used to evaluate the impact of parental allergy on development of eczema up to 12 years. After adjustment for known confounders the overall OR was 1.76 (95% CI, 1.43-2.16). As shown in Figure 5 the impact of parental allergy on the risk of having eczema was similar the first 12 years of life.

Male sex was associated with an increased risk (adjusted OR 1.25, 95% CI 1.02-1.54) of eczema at age one but with a significantly reduced risk (adjusted OR 0.62, 95% CI 0.49-0.78) of eczema at 12 years (Figure 5).

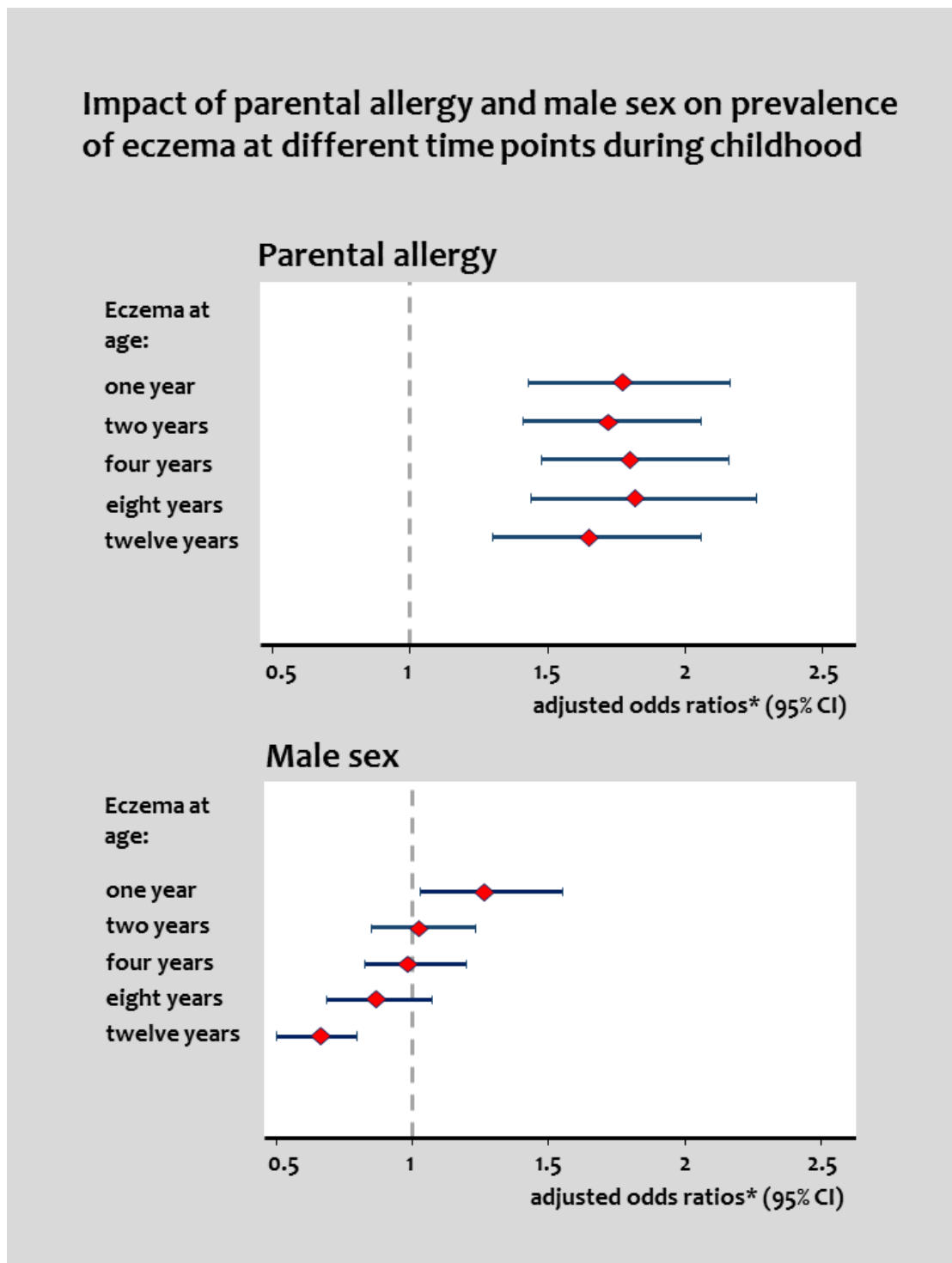


Figure 5. Parental allergy and sex in relation to eczema up to 12 years in the population-based BAMSE birth cohort, n=2,916.

* Odds ratios and 95% confidence intervals were calculated by using generalized estimated equations, adjusted for: exclusive breastfeeding <4 months, maternal smoking, low socio-economic status and young mother (< 26 years).

ECZEMA SEVERITY (II)

At twelve years, disease severity was evaluated based on questionnaire data including information on clinical course, disease intensity and extent of disease the previous year. Of the 394 children with eczema in paper II, 79% had mild disease, 17% moderate and only 4% had severe eczema (Figure 6). There was no significant difference in eczema severity between boys and girls. However, boys had a somewhat higher mean BESS (5.9; 95% CI 5.5-6.3) compared with girls (5.5; 95% CI 5.2-5.7).

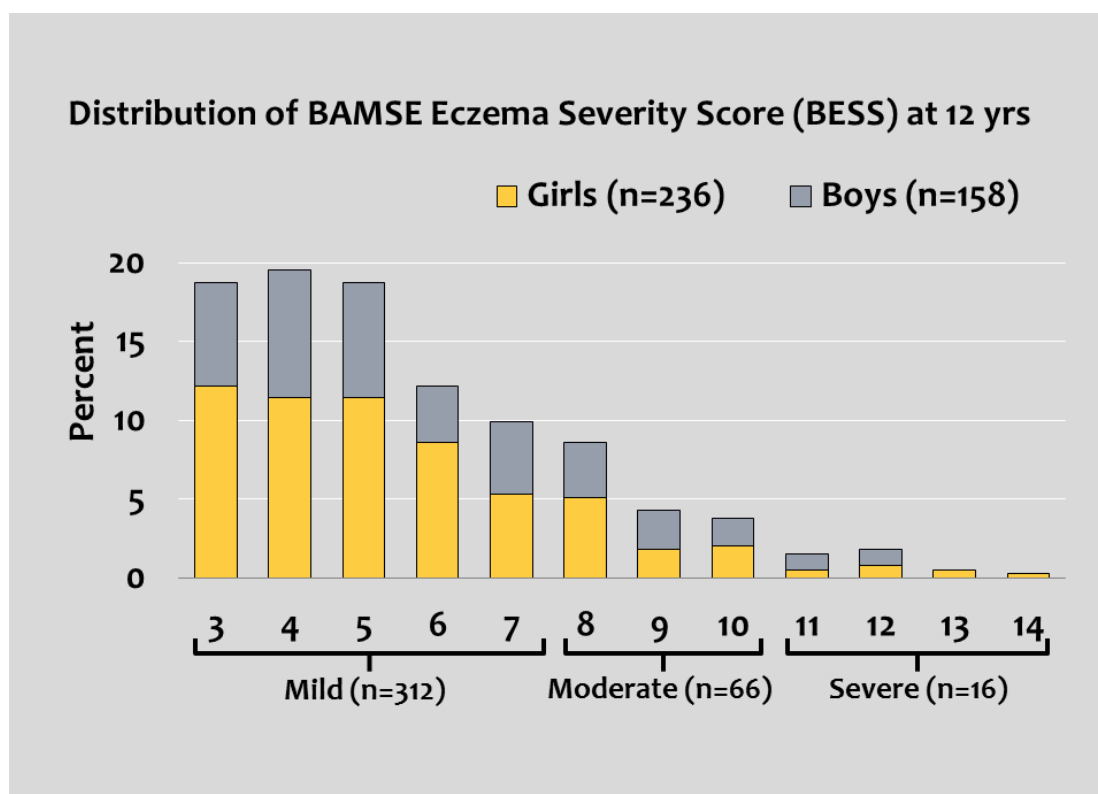


Figure 6. Severity of eczema evaluated as BAMSE Eczema Severity Score (BESS) among pre-adolescent girls and boys in the BAMSE birth cohort.

FLG MUTATIONS (II)

FLG mutations were found in 7.3% (136 of 1,854) of genotyped children included in study II, all heterozygotes with two children being compound heterozygotes (Table VII). At the 12-year follow-up 13% (32 of 246) of the children with eczema and 6.5% (104 of 1,608) of children without eczema had at least one *FLG* mutation ($p < 0.001$).

FLG mutations in relation to eczema severity (II)

FLG mutations were present in 26 of 198 pre-adolescent children with mild eczema and in 6 of 48 children with moderate to severe eczema (13.1% *vs* 12.5%, $p=0.907$). One child with mild eczema and one child with moderate to severe eczema were compound heterozygotes (Table VII).

Table VII. Type of *FLG* mutation in relation to eczema status among 1,854 genotyped children in the population-based BAMSE birth cohort

<i>FLG</i> mutation*	No eczema	Mild eczema	Moderate-to-severe eczema	Total
	n=1,608 n (%)	n= 198 n (%)	n=48 n (%)	n=1,854 n (%)
R501X	28 (1.7)	11 (5.6)	2 (4.2)	41 (2.2)
2282del4	62 (3.9)	11 (5.6)	5 (10.4)	78 (4.2)
R2447X	14 (0.9)	5 (2.5)	0	19 (1.0)
Total	104 (6.5)	26 (13.1)	6 (12.5)	136 (7.3)

* Two children were compound heterozygotes; a girl with mild eczema (2282del4 and R2447X) and a boy with moderate to severe eczema (R501X and 2282del4). No child was homozygote for any *FLG* mutation.

Reflection - how to please reviewers

For paper I we had decided to do a descriptive study without a hypothesis but with the aim of describing development of allergy-related diseases in childhood, and we did. However, the reviewers wanted us to go beyond descriptive analysis; they wanted longitudinal analyses as well as evaluation of different phenotypes and predictors for subsequent disease development. We agreed that this could be interesting, but that it would be a totally different study. In order to please the reviewers we analysed the impact of sex and parental allergy on the risk of developing any allergy-related disease at different ages. This was doable without having to rewrite the whole paper. But as pointed out to us after the paper had been published, it is not very logical to evaluate the impact of sex on any disease, since we know the impact is not the same for eczema, asthma or rhinitis. I guess that at the end of the review process, things slip through that normally would not pass, because everyone is tired of the manuscript and just wants it to move on. In the summary of my thesis these results have not been included. Instead, I chose to present the corresponding calculations for eczema as shown in Figure 5.

COMORBIDITY OF ALLERGY RELATED DISEASES (I)

The overlaps between eczema, asthma and rhinitis at the different follow-ups are illustrated in Figure 7. Comorbidity became more prevalent with age. At least two allergy-related diseases were found in 1.8% of children at one year of age. At two, four, eight, and 12 years the corresponding proportions were 2.3%, 5.9%, 5.5%, and 7.5%. Among children who had an allergy-related disease, allergic comorbidity was more prevalent among those whose parents had allergy. Differences in comorbidity between boys and girls were minor.

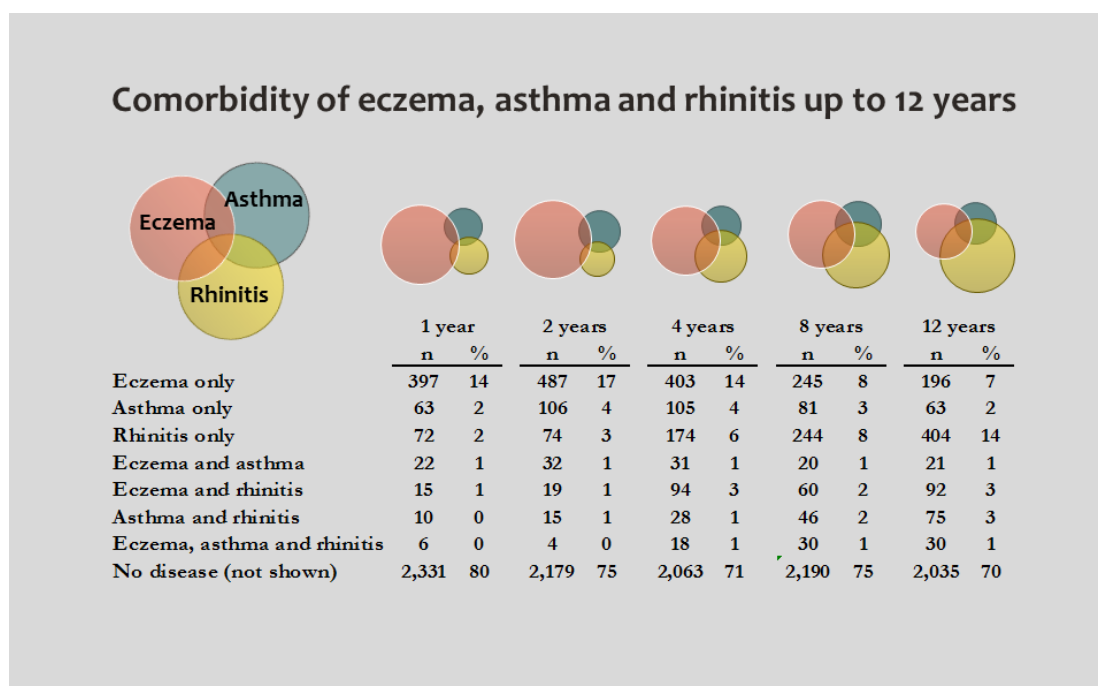


Figure 7. Comorbidity of eczema, asthma and rhinitis up to 12 years of age in the population-based BAMSE birth cohort, n=2,916. Venn diagrams are proportional.

Comorbidity among children with eczema (I, II)

Asthma and/or rhinitis were present among 9.8% of children with eczema at one year of age. At two, four, eight, and 12 years the corresponding proportions were 10.1%, 26.2%, 31.0%, and 42.2% (Figure 7). In paper II we evaluated comorbidity in relation to sex and eczema severity in pre-adolescence. We found that among children with moderate to severe eczema, rhinitis was significantly more prevalent (45.1% *vs* 32.7%, $p=0.036$) and asthma tended to be more prevalent (22.0% *vs* 13.8%, $p=0.069$) than among children with mild eczema. Also, the combination of asthma and rhinitis was significantly more prevalent in the group with moderate to severe eczema (18.3% *vs* 9.0%, $p=0.016$) than in the group with mild eczema.

Figure 8 shows the proportions with asthma and/or rhinitis among boys and girls with no, mild and moderate to severe eczema at the 12-year follow-up. Both asthma and rhinitis were more prevalent among boys compared to girls, irrespective of eczema status. Of boys with moderate to severe eczema, 59.0% had asthma, rhinitis or both diseases (Figure 8).

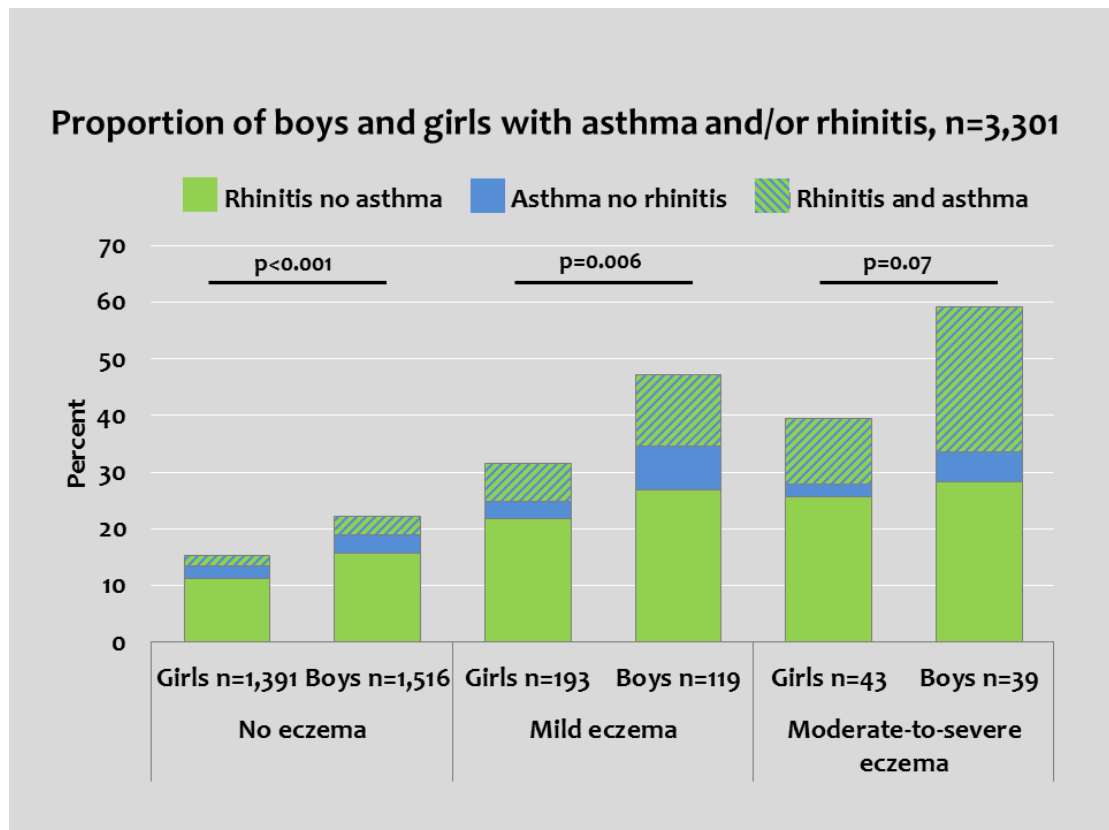


Figure 8. Proportion of girls and boys with asthma and/or rhinitis among pre-adolescent children with no, mild and moderate-to-severe eczema in the BAMSE birth cohort.

Infantile eczema, comorbidity and prognosis (IV)

In study IV we found that presence of asthma in infancy among children with infantile eczema was associated with asthma in pre-adolescence (adjusted OR 5.83; 95% CI 3.46-9.81). Rhinitis before age two among children with infantile eczema was associated with eczema (adjusted OR 1.73; 95% CI 1.10-2.71), asthma (adjusted OR 3.15; 95% CI 1.87-5.29) and rhinitis (adjusted OR 2.01; 95% CI 1.30-3.10) in pre-adolescence. Adjustment was made for sex and parental allergy.

INFANTILE ECZEMA – PROGNOSIS (IV)

Almost half of the 810 children with infantile eczema in study IV had eczema, asthma or rhinitis at the 12-year follow-up (Figure 9).

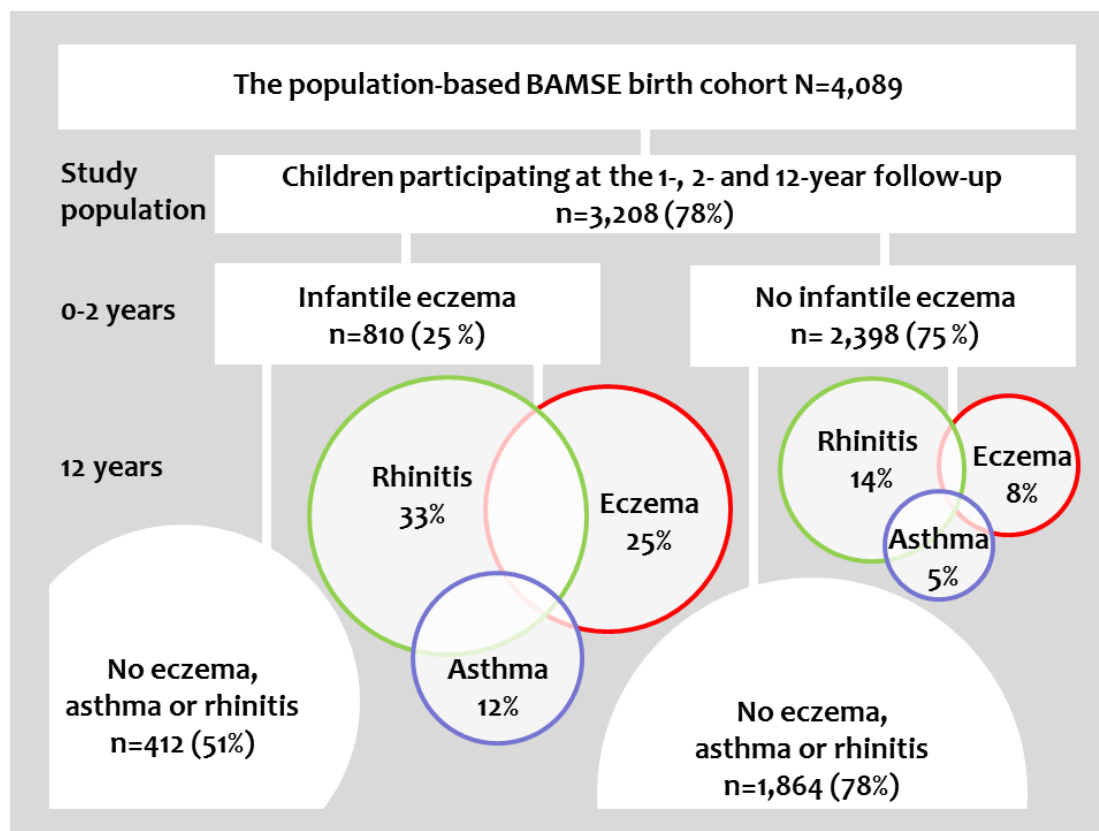


Figure 9. Allergy-related disease in pre-adolescence in relation to infantile eczema. Subjects of the BAMSE birth cohort included in the study population in paper IV and outcome of allergy-related disease at twelve years for children with and without infantile eczema. Venn diagrams are proportional. Since some children have more than one disease, the numbers add up to more than 100%.

Children with infantile eczema had a threefold risk of eczema in pre-adolescence (adjusted OR 3.97; 95% CI, 3.18-4.95, adjusted for sex and parental allergy) compared with children without eczema before two years of age (Figure 10). Children with infantile eczema also had an increased risk of asthma, adjusted OR 2.22; 95% CI 1.65-2.98 (adjusted for sex, parental allergy and asthma before two years) and rhinitis, adjusted OR 2.69; 95% CI, 2.22-3.26 (adjusted for sex, parental allergy and rhinitis before two years).

To ensure that the increased risk of asthma and rhinitis in pre-adolescence among children with infantile eczema was not explained by children who had eczema in pre-adolescence with concomitant asthma and rhinitis, we restricted the analyses, including only the 606 children with infantile eczema who did not have eczema in pre-adolescence. When this was done, the adjusted ORs decreased to 2.06; 95% CI 1.89-2.96 for asthma and 2.36; 95% CI 1.89-2.96 for rhinitis.

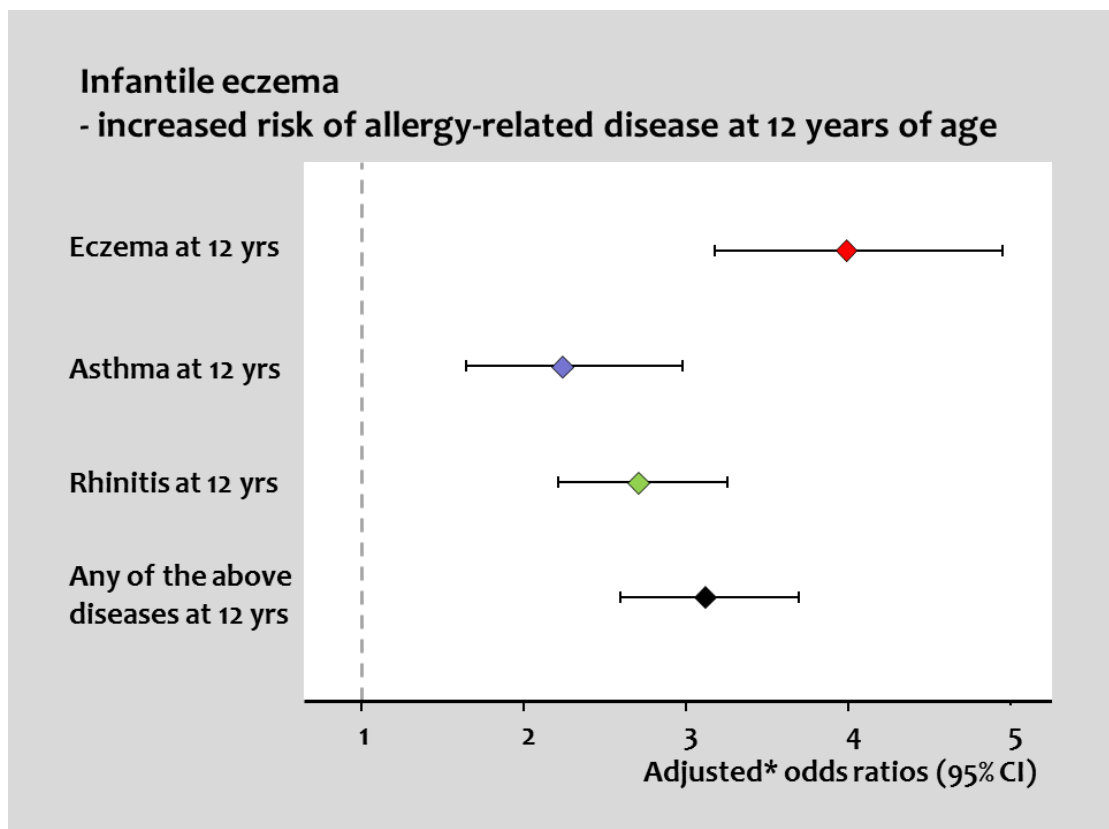


Figure 10. Increased risk of eczema, asthma, rhinitis and any of the diseases in pre-adolescence for children with infantile eczema (n=810), in the population-based BAMSE birth cohort (n=3,208). All odds ratios (OR) were adjusted for sex and parental allergy. In addition, the OR for asthma was adjusted for asthma before two years, the OR for rhinitis for rhinitis before two years and the OR for any disease for asthma and rhinitis before two years of age.

INFANTILE ECZEMA – RISK FACTORS (IV)

Table VIII shows adjusted ORs for significant risk factors for eczema, asthma and rhinitis in pre-adolescence among children with infantile eczema.

Table VIII. Risk factors for allergy-related disease in pre-adolescence for children with infantile eczema (n=810) in the BAMSE birth cohort

Risk factors* (%) before 2 years of age among children with infantile eczema	Eczema at age 12 205/810 Adjusted [†] OR (95% CI)	Asthma at age 12 93/804 Adjusted [†] OR (95% CI)	Rhinitis at age 12 263/808 Adjusted [†] OR (95% CI)
Sex (boys vs. girls) (50.9)	0.77 (0.56-1.06)	1.62 (1.03-2.53)	1.33 (0.99-1.80)
Parental allergy [°] (54.3)	1.45 (1.05-2.01)	1.96 (1.23-3.13)	1.88 (1.39-2.56)
Tobacco exposure [▲] (25.6)	1.42 (1.00-2.03)	1.68 (1.05- 2.69)	1.03 (0.73-1.45)
Asthma before 2 years of age (10.8)	1.17 (0.70-1.94)	5.83 (3.46-9.81)	1.48 (0.93-2.36)
Rhinitis before 2 years of age (12.5)	1.73 (1.10-2.71)	3.15 (1.87-5.29)	2.01 (1.30-3.10)
Sleep disturbance due to itch (28.8)	1.98 (1.41-2.78)	1.84 (1.17- 2.89)	1.65 (1.19-2.28)
Widespread infantile eczema (13.1)	1.60 (1.02-2.50)	1.23 (0.67-2.25)	2.46 (1.61-3.75)
Persistent infantile eczema (35.6)	1.94 (1.40-2.69)	2.05 (1.32-3.20)	2.10 (1.54-2.86)
Atopic infantile eczema [□] (44.5)	3.10 (1.47-6.54)	3.19 (1.20-8.50)	4.32 (2.04-9.12)

* Internal missing ranged between 0% and 2%.

† Adjusted for sex and parental allergy.

° Doctor's diagnosis of asthma and/or hay fever in combination with allergy to furred pets and/or pollen and/or doctor's diagnosis of eczema at enrolment.

▲ Mother smoked at least one cigarette per day during pregnancy and/or any of the parents smoked at least one cigarette per day at the time of enrolment.

□ Defined as allergen-specific IgE \geq 0.35 kU_A/L against foods and/or airborne allergens at age 2 years based on data from 137 cases.

Reflection - how to present data

When we discussed how to present the results in paper IV, I argued for the use of simple measures that could be easily understood to describe factors of importance for future disease among infants with eczema. We considered the use of sensitivity, specificity, PPV (positive predictive value) and NPV (negative predictive value), for risk factors or combinations of risk factors in infancy for the outcomes eczema, asthma and rhinitis in pre-adolescence. To me this felt intuitively wrong because I associate these measures with evaluation of diagnostic tests. However, it is perfectly correct and these measures are also frequently used in studies similar to study IV.^{151 152} In the end we agreed on the use of OR and absolute risk. Meanwhile, I realized that absolute risk, which is actually nothing other than the simplest risk measure, is calculated in exactly the same way and corresponds to PPV.

INFANTILE ECZEMA – ABSOLUTE RISKS (IV)

We also combined different risk factors in infancy and calculated absolute risks for eczema, asthma and rhinitis at age twelve. Absolute risks for several phenotypes of infantile eczema, as well as for children with no allergy-related disease before age two, are presented in Table IX. As expected, children without infantile eczema, asthma or rhinitis before age two had the lowest risks for all three diseases at age twelve. As shown in Table IX persistent infantile eczema was a significant risk factor for both eczema, asthma and rhinitis in pre-adolescence. The reference was children with infantile eczema only in their first or second year of life. We evaluated these two groups separately and found that children with eczema in their first year of life, but not in their second year, had half the risk of eczema at age twelve (Table IX) compared with children with eczema in their second, but not in their first year of life. Despite the marked difference in risk of eczema these two groups had similar risks for asthma and rhinitis at age twelve (Table IX).

Reflection – word count

Paper IV contained many sub-group analyses, and was therefore a lengthy article of 3,622 words, two figures and 7 tables when we submitted it to JACI. The word limit for original articles in JACI is a generous 3,500 words. However, I could not find a way to cut 122 words out of the manuscript and still retain the messages and the data we had agreed to present. Therefore, we decided to submit the article as it was. The paper was not accepted as a full length article but the Editor gave us a chance to resubmit the paper as a Letter to the Editor. This format has a word limit of 1000 words and allows a maximum of two figures and tables. At first I thought it impossible: if I had not been able to cut the paper by 122 words how could I possibly shorten it 2,622 words? On the other hand, if this was the Editor's suggestion, it was probably doable, so I decided to give it a try. The referees' comments helped me and I was surprised by how easily the manuscript was shortened. Making radical changes is sometimes easier than making minor ones.

Table IX. Absolute risks for eczema, asthma and rhinitis in pre-adolescence for various combinations of risk factors up to two years (n=3,208)

Risk factors up to 2 years of age (number of children the calculations are based on)	Absolute risk* for eczema at 12 years % (95% CI)	Absolute risk* for asthma at 12 years % (95% CI)	Absolute risk* for rhinitis at 12 years % (95% CI)	None of the diseases at 12 years % (95% CI)
Among all children (n=3208)				
No eczema, asthma or rhinitis before two years (2086)	7.2 (6.1-8.4)	4.4 (3.6-5.4)	13.3 (11.9-14.9)	78.9 (77.1-80.7)
Among all children with infantile eczema (IE) (n=810)				
IE (810)	25.3 (22.3-28.4)	11.6 (9.4-14.0)	32.5 (29.3-35.9)	50.7 (47.2-54.2)
IE in the first but not the second year of life (203)	12.3 (8.1-17.6)	10.9 (7.0-16.0)	27.2 (21.1-33.9)	63.9 (56.8-70.5)
IE in the second but not the first year of life (319)	26.3 (21.6-31.5)	6.94 (4.4-10.3)	25.7 (21.0-30.9)	56.0 (50.3-61.5)
Persistent IE (288)	33.3 (27.9-39.1)	17.2 (13.0-22.1)	43.9 (38.1-49.9)	35.8 (30.2-41.6)
Persistent IE causing sleep disturbance (131)	36.6 (28.4-45.5)	21.5 (14.8-29.6)	53.8 (44.9-62.6)	24.4 (17.3-32.7)
IE only, no asthma, no rhinitis (642)	24.1 (20.9-27.6)	8.0 (6.0-10.4)	30.3 (26.7-34.0)	53.4 (49.5-57.4)
IE and asthma (87)	27.6 (18.5-38.2)	36.8 (26.7-47.8)	42.5 (32.0-53.6)	42.5 (32.0-53.6)
IE and rhinitis (100)	36.0 (26.6-46.2)	27.0 (18.6-36.8)	49.5 (39.3-59.7)	31.0 (22.1-41.0)
IE and comorbidity† (152)	30.3 (23.1-38.2)	27.6 (20.7-35.5)	43.7 (35.7-52.0)	38.2 (30.4-46.4)
IE and asthma and rhinitis (35)	40.0 (23.9-57.9)	48.6 (31.4-66.0)	57.1 (39.4-73.7)	28.6 (14.6-46.3)
Among children with IE and complete data on sensitization at 2 years of age (n=137)				
IE without sensitization° (non-atopic IE) (76)	22.4 (13.6-33.4)	10.5 (4.7-19.7)	28.9 (19.1-40.5)	53.9 (42.1-65.5)
IE with sensitization° (atopic IE) (61)	45.9 (33.1-59.1)	27.9 (17.1-40.8)	65.0 (51.6-76.9)	23.0 (13.2-35.5)
Among children with IE and comorbidity† and complete data on sensitization at 2 years of age (n=26)				
IE with comorbidity†, no sensitization° (9)	33.3 (7.5-70.1)	33.3 (7.5-70.1)	33.3 (7.5-70.1)	22.2 (2.8-60.0)
IE with comorbidity† and sensitization° (17)	64.7 (38.3-85.8)	52.9 (27.8-77.0)	75.0 (47.6-92.7)	17.6 (3.8-43.4)
IE with comorbidity† and sensitization both to foods and airborne allergens (8)	75.0 (34.9-96.8)	75.0 (34.9-96.8)	100 (59.0-100)□	0 (0-36.9)□

*Absolute risk was calculated as the number of children having both the outcome and the risk factor, divided by the total number of children with the risk factor. For 95% confidence intervals, the binomial test of statistical significance was used.

†Comorbidity is defined as any or both of the diseases asthma and rhinitis before age 2.

°Sensitization is defined as allergen-specific IgE \geq 0.35 kU_A/L to food and/or airborne allergens.

□One-sided confidence interval.

QUALITY OF LIFE IN PRE-ADOLESCENCE (III)

A majority of the 2,756 pre-adolescent children included in study III reported good self-perceived health. Seventy-nine percent responded “*Excellent*” or “*Very good*” to the question “*How are you feeling?*” and 72% reported that they were completely healthy, while 66% responded “*I am very happy*” to the question “*How happy are you with your life right now?*” Of the 350 children with eczema in study III, 120 children had ongoing symptoms when they answered the 12-year questionnaire.

In total, 274 children had mild eczema and 76 had moderate-to-severe disease. The proportion of children with moderate-to-severe eczema was 40.8% in the group with ongoing eczema at the time of the 12-year questionnaire and 11.7% among children without ongoing skin symptoms. Among children with moderate-to-severe eczema, 88% had had a doctor's diagnosis of eczema at some time up to twelve years of age, compared with 57% of the children with mild eczema ($p=0.001$). The impact of eczema, asthma and rhinitis on self-perceived health was calculated by using multiple logistic regression with adjustment for parental allergy, low socio-economic status, having a young mother and comorbidity. Sex was found to be an effect modifier and therefore the analysis was stratified by sex.

Self-perceived health among girls (III)

Girls with eczema had impaired self-perceived health, as evaluated by all three questions, compared with girls with no allergy-related disease (Table X). We restricted the analyses to include only girls with mild eczema and found that they reported significantly impaired self-perceived health for all three questions: adjusted OR 1.73 (95% CI 1.14-2.64) for the question "*How are you feeling?*", adjusted OR 1.90 (95% CI 1.27-2.86) for the question "*How healthy do you consider yourself to be?*", and 1.63 (95% CI 1.11-2.40) for the question "*How happy are you with your life right now?*". Finally, we evaluated the impact of asthma and rhinitis for self-perceived health among girls and found these diseases to be associated with significantly impaired self-perceived health for the question "*How healthy do you consider yourself to be?*", but not for the other questions (Table X).

Reflection – impact factors

The impact of impact factors in the world of medical research is incredibly large. Even though impact factor is a journal metric and should not be used to assess individual researchers, this is not how it works. Anyone who strives for a research career should acquire a thoughtful approach when it comes to impact factors. I have learned that a short article in a high ranked journal is more "valuable" than a long article in a lower ranked journal, as long as the article deals with original data. I have also learned that a "Letter to the Editor" does not count as a citable format and will therefore not be counted as "citable" when the journal's impact factor is being calculated, but if cited anyway, it can contribute to the impact factor of the journal. Thus, publishing articles with original data as a "Letter to the Editor" is a tactic a journal might use to raise its impact factor.

Self-perceived health among boys (III)

In contrast to girls, eczema among boys was not associated with impaired self-perceived health (Table X). However, as for girls, boys with asthma and rhinitis reported significantly impaired self-perceived health for the question “How healthy do you consider yourself to be?” (Table X).

Table X. Adjusted* odds ratios (OR) for impaired self-perceived health among pre-adolescent girls (upper section) and boys (lower section) in relation to eczema, asthma and rhinitis in the population-based BAMSE birth cohort N=2,756

Question asked	How are you feeling?	How healthy do you consider yourself to be?	How happy are you with your life right now?
Response alternatives	Not good/fairly good /good vs. Excellent/very good	Not very healthy/fairly healthy vs. Completely healthy	I am not happy at all / I am not very happy / I am fairly happy vs. I am very happy
	adjusted OR* (95% CI)	adjusted OR* (95% CI)	adjusted OR* (95% CI)
GIRLS (n=1,375)			
No eczema, asthma or rhinitis (n=972)	1	1	1
Eczema (n=210)	1.72 (1.16-2.55)	1.89 (1.29-2.76)	1.69 (1.18-2.42)
Subgroup with ongoing eczema (n=80)	2.32 (1.26-4.27)	2.44 (1.34-4.43)	3.20 (1.72-5.95)
Mild eczema (n=171)	1.73 (1.14-2.64)	1.90 (1.27-2.86)	1.63 (1.11-2.40)
Moderate to severe eczema (n=39)	1.79 (0.70-4.58)	1.84 (0.74-4.56)	2.14 (0.88-5.19)
Asthma (n=68)	1.18 (0.48-2.86)	2.79 (1.30-6.00)	0.57 (0.24-1.35)
Rhinitis (n=228)	1.05 (0.68-1.61)	1.78 (1.22-2.59)	1.20 (0.84-1.73)
Eczema, asthma and rhinitis (n=16)	1.85 (0.63-5.44)	3.72 (1.35-10.2)	1.74 (0.64-4.73)
	adjusted OR* (95% CI)	adjusted OR* (95% CI)	adjusted OR* (95% CI)
BOYS (n=1,381)			
No eczema, asthma or rhinitis (n=951)	1	1	1
Eczema (n=140)	0.78 (0.40-1.52)	0.70 (0.38-1.29)	0.73 (0.41-1.27)
Subgroup with ongoing eczema (n=40)	0.94 (0.26-3.41)	0.88 (0.28-2.76)	0.62 (0.19-1.98)
Mild eczema (n=103)	0.68 (0.31-1.50)	0.51 (0.24-1.10)	0.66 (0.34-1.26)
Moderate to severe eczema (n=37)	1.26 (0.39-4.10)	1.53 (0.55-4.25)	0.94 (0.32-2.70)
Asthma (n=116)	1.17 (0.57-2.42)	1.97 (1.06-3.64)	0.83 (0.43-1.62)
Rhinitis (n=300)	1.42 (0.98-2.07)	2.31 (1.67-3.19)	1.00 (0.71-1.40)
Eczema, asthma and rhinitis (n=23)	7.84 (3.32-18.5)	6.37 (2.66-15.3)	1.60 (0.68-3.75)

*Adjusted for parental allergy, low socio-economic status, having a young mother and comorbidity (eczema, asthma and rhinitis at the 12-year follow-up).

Statistically significant differences are written in bold.

Disease-specific HRQoL (III)

The mean total score of CDLQI for all children with eczema was 3.98 (95% CI 3.37-4.58). Children with moderate-to-severe eczema reported a total score of 5.12 (95% CI 4.21-6.04), compared with 3.18 (95% CI 2.42-3.95) for children with mild eczema. Ninety-five percent of the 120 children with ongoing eczema reported that they were troubled by itching and scratching. Other questions with high scores among both boys and girls were the questions about i) being embarrassed or upset because of skin symptoms, ii) trouble with treatment and iii) disturbed sleep. There was a significant correlation ($r=0.493$) between CDLQI scores and eczema severity as well as between CDLQI scores and health impact as assessed in the three questions on self-perceived health, all $p < 0.05$.

10 DISCUSSION

STRENGTHS AND LIMITATIONS

The major strength of this thesis is the population-based study design and that data were collected prospectively. The comparatively large number of participants and limited loss to follow-up enables subgroup analysis and allows for stratified analysis in many cases. Furthermore, assessment of exposures, eczema, asthma and rhinitis, on five occasions during the first 12 years of life, reduces the risk of recall bias. A weakness of the study is that information on outcomes was obtained from questionnaires only.

METHODOLOGICAL CONSIDERATIONS

Both random and systematic errors are likely to occur in observational studies and might possibly affect the precision, internal validity and generalizability of the results. It is important to consider these possible errors throughout the whole research process, from deciding what study design to choose and how many subjects to include, later on when one performs the analysis and finally when one interprets the results.

Random error

The relatively large study populations and the fact that the diseases studied in this thesis are all common have contributed to minimizing random errors. Confidence intervals were computed in all papers to demonstrate the precision of estimates. In general, the confidence intervals are rather narrow, indicating good precision. However, for some subgroup analyses in paper IV estimating absolute risk, the statistical uncertainty is large.

Systematic error – selection bias

Selection bias in this thesis might have occurred at three stages. First, when the BAMSE cohort was recruited, second when children were lost to follow-up, and third when the study populations were selected. At recruitment 75% of the eligible children were included. A survey of the non-responders/excluded group showed that parental smoking was more prevalent in non-participating families, but otherwise no significant differences concerning parental allergy and other known risk factors for allergy-related diseases were found.¹³

To evaluate possible selection bias due to loss to follow-up and selection of study populations the study populations were compared to the original cohort for: i) background factors that have been shown to be associated with the outcomes (papers I (*see Table V*), III, IV), and ii) allergy-related diseases (papers I (*see Table VI*), IV). No significant differences were found. Taken together, this indicates that the study populations used in this thesis are less exposed to parental smoking but seem otherwise to be comparable to the source population. Thus, selection bias is probably of minor importance, but might have led to a small underestimation of allergy-related disease since parental smoking has been shown to be a risk factor for allergy-related diseases.^{141 153}

Reflection – which families came to all follow-ups?

When doing the analysis for paper I, I was very surprised to find that 58% of children had had an allergy-related disease before adolescence. I first figured that I had made some mistake in my syntax for the calculations, but that was not the case. My second thought was that it must be a result of selection bias. In study I, we had selected only the children who had participated at all five follow-ups. When looking at the high numbers I felt convinced that by doing so we had selected the families with children who had allergy-related diseases, who probably had an extra motivation to participate. However, as shown in table VI we found no significant differences and rather a tendency of higher rates of allergy-related diseases among children who had not participated at all follow-ups. The same phenomenon has been described in the ALPSAC and PIAMA studies.¹⁵⁴ Thus, the presence of allergy-related disease does not appear to bias the decision to participate at each follow-up in a positive direction.

Systematic error – information bias

Information bias due to recall bias has been minimized by the prospective study design with collection of background information before development of disease and with assessment of exposures, eczema, asthma and rhinitis, on five occasions during the first 12 years of life. Misclassification of disease is bound to have occurred for all diseases in all studies presented in this thesis. How diseases are defined is critical in order to minimize misclassification. A strict definition will exclude milder cases while an inclusive definition risks classifying healthy children as having disease.

The gold standard for assigning a diagnosis of eczema, asthma and rhinitis is that the patient has been evaluated and diagnosed by a physician. In this thesis, however, all diseases are classified based on parentally reported symptoms and parentally reported doctor's diagnosis. If reported doctor's diagnosis of disease had been used as the sole measure of disease, prevalence rates (especially for eczema and rhinitis) would probably have been underestimated since treatment is available over the counter and mild cases do not always prompt contact with the health care system. Moreover, these diseases are fluctuant by nature and even physicians often base their diagnosis on parentally reported symptoms.

The eczema definition used in BAMSE has been validated in children up to 2 years and was found to have high sensitivity (92%) and specificity (100%) in relation to clinical diagnosis by a dermatologist,¹⁵⁵ indicating that misclassification of eczema in young children is limited. The eczema variable used in this thesis has not been evaluated in older children but data from the 16-year follow-up that include both a validated eczema severity score (POEM)¹⁰⁰ and clinical evaluation of children with eczema by a nurse specialized in paediatric dermatology will provide an estimate of the reliability of the eczema definition in older children.

Misclassification – possible consequences

The definition used for rhinitis at age 1 and 2 years in study I was prolonged rhinitis > 2 months. Since the questionnaires did not include any question on the association with common cold, the prevalence rates of rhinitis at age 1 and 2 have probably been overestimated. In contrast, the asthma definition used in all papers for all ages is rather strict and milder cases have probably not been included, which could explain the rather low prevalence rates presented in paper I. Another consequence might be that turnover of asthma was overestimated while persistence of asthma was underestimated in study I.

Individuals who are in contact with the health care system for one disease are more likely to be diagnosed with, or medicated for, another disease, especially when it comes to known comorbidities. This phenomenon, called “biased follow-up”, could possibly have affected the results in study II since a larger proportion of children with moderate-to-severe eczema had a doctor's diagnosis of eczema compared to children with mild eczema.

However, children were classified with asthma and rhinitis mainly based on reported symptoms and in addition a majority of children both with mild and moderate-to-severe eczema had a doctor's diagnosis of eczema. Thus, taking all this together, I do not expect misclassification to have influenced the results of study II. Apart from the types of misclassification mentioned above, misclassification of disease is most likely non-differential and might have diluted the associations found both in study III and study IV.

Systematic error – confounding

Confounding was in part dealt with in this thesis by the BAMSE study design itself. By including the study subjects at birth and arranging for follow-ups at specific time-points, age as a confounder was controlled for. In addition, collection of detailed information on background factors and allergy-related diseases enabled adjustment for several potential confounders. In study I and in the thesis summary, we used generalized estimated equations when assessing the impact of parental allergy and sex on development of any allergy-related disease and eczema, thus controlling for confounding. In study III and IV multivariate regression models were used, making it possible to adjust for several confounders. As in all non-randomized studies, influence of unknown or unmeasured factors (residual confounders) cannot be excluded.

Generalizability

In all papers included in this thesis the population-based design has been emphasised as a strength and a major concern is therefore whether the results are valid even in other populations. Given the limited selection bias described above, the relatively good precision, and how the source population was selected, it is plausible to assume that the results can be generalized to paediatric populations in other high-income and urban-industrial settings with comparable rates of allergy-related diseases and background factors.

MAIN FINDINGS

Prevalence rates (I)

One of the most striking findings in this thesis was the high prevalence rates of allergy-related diseases. As many as 38% had had eczema and in total 58% in the population-based birth cohort had had an allergy-related disease before adolescence.

A valid concern is whether these figures are overestimated. As argued in the previous section, these findings can probably not be explained by methodological errors. The fact that the prevalence rates of eczema and rhinitis at each follow-up are comparable to, and those of asthma somewhat lower than, the rates reported by others^{17 23 33 49 52 150 156 157} speaks against an overestimation. The overall prevalence rates for allergy-related diseases found in our study are comparable to those in the Isle of Wight birth cohort study, where children were evaluated yearly up to the age of 4 years. In that study 40% of the children had had an allergy-related disease at some time before reaching 4 years of age.¹⁵⁸ In our study the corresponding proportion was 45%. Moreover, a recent publication from a Danish population-based study with regular follow-ups from childhood until age 26 years found that more than half of the study participants had had an allergy-related disease.¹⁵⁹ In addition, a population-based study from northern Sweden, with a participation rate of 97%, including 4,331 seven to eight years old children found the reported lifetime prevalence of eczema to be 35%¹⁶⁰ which can be compared to the 38% found among pre-adolescents in our study.

Comorbidity of allergy-related diseases (I)

In study I we could show that comorbidity between eczema, asthma and rhinitis became more prevalent with increasing age and among 12-year-olds 7.5% have two or three of the diseases. This is in line with the findings from the ISAAC study where the corresponding proportion among 13-14-year-old children in Sweden was 6-9%.¹⁴ A recent publication from Rönmark and co-authors investigating eczema and allergy-related diseases in adults from a population-based setting in West Sweden showed that the proportion of adults having two or three of the diseases eczema, asthma and rhinitis was 7.8%.¹⁶¹ Thus, it seems that the high degree of comorbidity persists into adulthood.

Prognosis of infantile eczema (IV)

We were glad to find that half of the children with infantile eczema were free of allergy-related disease in pre-adolescence and that only 25% had eczema. The prognosis of eczema in our study is better than previously described^{19 118 162 163} which probably has to do with the population-based design, which allowed us to include even the mildest cases of infantile eczema.

Thus, the rather good prognosis is important to bear in mind when discussing public health issues and can be used to comfort the parents of infants with eczema visiting healthcare clinics. However, the prognosis is probably not equally positive for children with infantile eczema attending specialist clinics.

Eczema in relation to asthma and rhinitis (II, IV)

The risk that children with infantile eczema will develop asthma has been thoroughly investigated and the adjusted OR of 2.2 for asthma at 12 years found in study IV is comparable to what has been shown by others, even though most studies have examined the risk at earlier ages than twelve years.^{19 29 164 165} In recent years there has been an increased interest in the relation between eczema and rhinitis and studies evaluating rhinitis in relation to eczema have shown strong associations between the two diseases.^{23 121 166} This strong association has been further highlighted by the findings in this thesis. In study II we showed that rhinitis is associated with severity of eczema: the risk of rhinitis is higher among pre-adolescents with moderate to severe eczema compared to those with mild eczema. Furthermore, in study IV we could show that comorbidity of rhinitis among children with infantile eczema is associated to a worse prognosis for eczema but also with an increased risk of asthma and rhinitis in pre-adolescence.

However, we did not find concomitant asthma among infants with eczema to worsen the prognosis of eczema. This finding confirms the result from Ricci and co-workers, who studied a selected cohort of children with eczema, aged 6-36 months.¹⁶⁷ In contrast, a recent study from a selected cohort of older children with eczema (2-18 years) found a strong correlation between concomitant asthma and more persistent eczema.¹⁶⁸ This discrepancy might be explained by the different age-groups examined. Asthma in older children is often associated with atopy which in our study was strongly associated with poor prognosis for eczema, whereas wheeze and asthma in infancy has been suggested to be triggered mainly by upper airway infections.¹⁶⁹

In contrast to findings from the MAS-study by Illi and co-workers¹⁹ the increased risk of both asthma and rhinitis among children with infantile eczema in study IV remained significant after adjustment for early asthma and rhinitis. Furthermore, these increased risks remained significant even after exclusion of children with eczema at age twelve.

Infantile eczema in the first year of life only (IV)

One of the most interesting results of this thesis was that infants with eczema during their first, but not their second year of life, have almost half the risk of eczema at 12 years, but the same risk of asthma and rhinitis as compared with other infants with eczema. There is one brief report by Vickers from 1980 including 2000 English children with eczema from a population-based setting that is suggestive of poorer prognosis of eczema among children with onset between 12 and 24 months as compared with children with earlier onset.¹⁷⁰

However, our finding is in contrast to the general view that early onset is associated with worse prognosis,¹¹¹ a perception that has some support in the literature^{162 163 171} and also holds true for the children in our study with onset in the first year of life, who continued having eczema in their second year of life. Illi and co-workers followed 241 children with infantile eczema from a population-based cohort up to the age of 7 years in the MAS-study. They found no difference in prognosis of eczema when comparing children with onset of eczema in the first year of life to children with onset in their second year of life.¹⁹ However, in that study, children with infantile eczema in both their first and second years of life were analysed together with children with eczema in their first, but not in their second year of life.

Quality of life among pre-adolescents with eczema (III)

We found that eczema was associated with impaired self-perceived health both in girls with mild eczema and in girls with more severe disease. Eczema among boys was not associated with impaired self-perceived health. Even though a majority of children with eczema reported that they were completely healthy and very happy with life, the finding that eczema among girls impairs self-perceived health is important. Since eczema affects up to 20% of pre-adolescent girls⁵³ and adolescence is a critical time for the development of self-identity and self-esteem¹⁷² we believe that the findings have implications for health care providers as well as for society as a whole.

From disease-specific instruments we know that impaired HRQoL among people with eczema is due to itching, sleep deprivation and embarrassment caused by skin symptoms.^{5 129} However, it is hard to believe that these factors are the entire explanation in the group of girls with mild disease, among whom a majority did not have ongoing eczema when they answered the questionnaire.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVE

The large number of new and remitting cases found in study I for allergy-related diseases during childhood raises the question of when an outcome should be evaluated in relation to risk factors being studied. The results from study I might be of value in studies addressing risk factors for development of allergy-related diseases when deciding on what time period to use for evaluation of outcomes.

In study II we showed that prevalence of rhinitis and asthma is associated with eczema severity, with the highest prevalence among boys with moderate to severe eczema. For physicians who take care of children with eczema this is important knowledge. Eczema is a troublesome and visible disease and children and their parents notice the disease. In contrast, the symptoms of asthma and sometimes also rhinitis are more insidious and may sometimes be overlooked by children and parents, especially if the children are tired due to sleep deprivation caused by an itching eczema. Thus, based on our findings I believe that a child, and in particular a boy, who seeks advice for troublesome eczema should be asked about symptoms of both asthma and rhinitis so that comorbidities can be discovered and treated.

In view of the finding that eczema among pre-adolescent girls affects self-perceived health, it would be interesting to conduct a qualitative study with the aim of disentangling what these girls with very mild disease are troubled by. Is it the disease itself, the treatment required or other factors? Findings from such a study could possibly be used to improve management of eczema for this age-group.

Even though disputed, the concept of the atopic march is used to describe the sequential onset of allergy-related diseases in childhood, starting with eczema followed by asthma and rhinitis. The findings of study IV that infantile eczema is a risk factor for asthma and rhinitis in pre-adolescence, independent of asthma and rhinitis in infancy and of eczema in pre-adolescence, speaks in favour of the existence of the atopic march.

Furthermore, our findings in study IV confirm that atopy among children with infantile eczema is strongly associated with future risk of asthma and rhinitis. However, children with non-atopic eczema as evidenced by testing at age 2 years also had elevated absolute risks of asthma and rhinitis in pre-adolescence as compared to children without allergy-related diseases in

infancy. There is emerging evidence of the fluctuant nature of sensitization in childhood^{159 173} and it is possible that these children are truly atopic but that the sensitization was present at another age. To test this possibility it would be interesting to explore whether the increased risk for asthma or rhinitis among children with eczema is driven solely by an atopic constitution or whether a non-atopic march from eczema to asthma and rhinitis exists.

We found that children with eczema in their first but not in their second year of life have the same risk for asthma and rhinitis in pre-adolescence as other children with infantile eczema. Unexpectedly, we found that these children (with infantile eczema in their first year of life only) have a markedly better prognosis for eczema. It is important to find out whether this finding is replicable. If so, one explanation could be that these children represent a particular phenotype. Another explanation could be that treatment of eczema, or some other exposure in the first year of life, alters the risk of subsequent eczema but not the risk of asthma or rhinitis. If such an exposure exists, it is important to identify it in future studies, as it might possibly influence the clinical course of eczema in childhood.

It has been suggested that impaired skin barrier function, represented by eczema in early life, may act as a catalyst for IgE sensitization and subsequent development of asthma and rhinitis.¹⁷⁴ The close relation between eczema in infancy and asthma and rhinitis later in life found in this thesis emphasises the need for further studies. A major task for the research community is to explore whether the association of eczema in early life with asthma and rhinitis later in life is merely a consequence of a genetic pre-disposition for the three diseases, or alternatively, if presence of eczema and a disrupted skin barrier constitute a step in the causal pathway in the development of asthma and rhinitis. Accordingly, the most important issue to resolve is whether development of asthma and rhinitis might be prevented by early treatment of eczema.

Reflection – eczema now and then

When reading the work of colleagues that were active before the discovery of T-cells, skin barrier defects, IgE and Filaggrin I find it striking how little impact these findings have had for the management of patients with eczema and to some extent also for what we consider important in studying the disease. Any clinician managing children with eczema can probably recognize their own reality in some of the following quotes from scientific papers from another time. I'm impressed by these physicians, the extent of their understanding and how they managed to describe what they knew or suspected without having the knowledge we today consider fundamental for the understanding of eczema and allergy-related diseases. The first quote, dated 1935, is in my opinion a good and adequate description of my own approach to severe cases of eczema in my daily practice.

Hill and Sulzberger, Archives of Dermatology and Syphilology, 1935

*“Until there is a better understanding of the fundamental variation from the normal which makes atopic sensitization possible and until this variation can be directly controlled, the best method of attack in the treatment of atopic dermatitis is symptomatic but rational local and systemic therapy plus the determination of specific sensitivities and withdrawal of the corresponding atopens from the diet or environment – or an attempt at hyposensitization in a few selected cases. The results of these procedures, while sometimes encouraging, are by no means ideal.”*¹⁷⁵

Volwes et al. British Journal of Dermatology, 1955

*“Obviously there are many degrees of severity of infantile eczema, from the mildest to the most severe; we believe, though we have no statistical proof, that as a rough guide, in a series of infants the prognosis is progressively better as the severity of eczema is less.”*¹⁷⁶

*“An attempt to assess psychological factors in the patients and the family was made, but it proved so difficult that it was regretfully abandoned.”*¹⁷⁶

Meenan, Irish Journal of Medical Science 1959

*“The asthma-eczema syndrome is a common problem. Our present methods of treating infantile eczema are, to say the least of it, not very effective. All we can do is to offer soothing creams to an irritable child and soothing words to a harassed parent.”*¹⁷⁷

*“They (the parents, my comment) are prepared to endure sleepless nights listening to the sound of steady scratching from the next room, if they can believe that the skin will eventually clear up. It is, therefore, important to know what the natural history of infantile eczema is; when and if, the eczema will disappear, and what are the chances of the child developing asthma.”*¹⁷⁷

*“The complex immunobiochemical processes which make up the eczema-asthma syndrome require much more study. There is in Boston a society known as the Wheeze, Sneeze and Itch. It is through such societies where the allergist, paediatrician and dermatologist can pool their knowledge that advances in the management of this distressing complaint will come”*¹⁷⁷

11 CONCLUSIONS

The results of this thesis stress the importance of allergy-related diseases and in particular eczema as a public health concern among children. Taken together, the findings also illustrate the strong relationships between eczema, asthma and rhinitis in childhood and show the importance of considering comorbidities between these diseases both in research and in clinical practice.

From the separate studies the following conclusions can be drawn:

Allergy-related diseases affect a majority of the paediatric population during the first 12 years of life and the development of eczema, asthma and rhinitis is a dynamic process: both new cases and remission are common throughout childhood.

Presence of asthma and rhinitis is associated with eczema severity in pre-adolescence, with the highest prevalence among boys with moderate to severe eczema.

Eczema and even mild eczema among pre-adolescent girls is associated with impaired self-perceived health.

Almost half of all children with infantile eczema will have eczema, asthma or rhinitis in pre-adolescence, but in three out of four the eczema will have remitted.

Eczema in the first but not the second year of life is associated with good prognosis for eczema, but with increased risk of asthma and rhinitis in pre-adolescence.

12 SVENSK SAMMANFATTNING

Bakgrund

Eksem (böjveckseksem) är en kliande kronisk hudsjukdom som vanligtvis startar i barndomen. Tillsammans med astma och rinit räknas eksem till gruppen allergisjukdomar. Dessa sjukdomar blir allt vanligare och cirka en tredjedel av världens befolkning beräknas ha någon av dessa sjukdomar. Eksem kan ge försämrad livskvalitet samt ökar risken för astma och rinit.

Syfte

Det övergripande syftet med denna avhandling har varit att öka kunskapen och förståelsen av eksem i barndomen med särskilt fokus på hur det ser ut på befolkningsnivå och på eksemsjukdomen i relation till astma och rinit.

Metod

Studierna i denna epidemiologiska avhandling är gjorda med material från en populationsbaserad födelsekohort bestående av 4089 barn födda i norra Stockholm under åren 1994-1996. I BAMSE-studien har barnen därefter följts med upprepade frågeformulär och undersökningar till 16 års ålder med syfte att undersöka riskfaktorer för utveckling av allergisjukdom. I denna avhandling används enkätdata från 0, 1, 2, 4, 8 och 12 års ålder. Vid 12 års ålder svarade 82% av familjerna på enkätfrågor. DNA analyserades hos 1854 barn i blodprov som togs vid 4-års ålder och förekomsten av allergiantikroppar (IgE) i serum undersöktes vid 2 års ålder hos 137 barn med infantilt eksem.

Resultat

Avhandlingen visade att mer än var tredje barn hade eksem någon gång under uppväxten och att 58% av barnen i befolkningen hade någon av sjukdomarna eksem, astma eller rinit innan 12 års ålder. Samsjukligheten mellan dessa sjukdomar ökade med stigande ålder och 7,5% av 12-åringar hade två eller tre av sjukdomarna eksem, astma och rinit. Eksem ökade risken att ha astma och rinit och 12-åringar med medelsvårt till svårt eksem hade oftare astma och rinit jämfört med de som hade ett lindrigt eksem. Bland 12-åriga pojkar med medelsvårt till svårt eksem hade 59% någon av sjukdomarna astma och rinit jämfört med 40% bland flickorna. Vi fann att mutation i filaggrinenen var associerad till förekomst av eksem, men inte till eksems svårighetsgrad.

Eksem hos 12-åriga flickor var associerat till en negativ påverkan på självupplevd hälsa. Denna påverkan sågs även hos gruppen flickor med lindrigt eksem och kunde inte förklaras av samsjuklighet med astma eller rinit. Eksem hos pojkar i samma ålder påverkade inte den självupplevda hälsan.

Bland barn med eksem innan 2 års ålder (dvs infantilt eksem) hade hälften eksem, astma eller rinit vid 12 års ålder men hos tre av fyra barn hade eksemet försvunnit. Hos barn med infantilt eksem var förekomst av allergiantikroppar vid 2 års ålder, ärftlighet för allergisjukdom, exponering för tobaksrök tidigt i livet, rinit innan 2 års ålder och svårt infantilt eksem riskfaktorer för utveckling av allergirelaterade sjukdomar i tonåren. Hos barn med infantilt eksem enbart under sitt första levnadsår hade eksemet en god prognos. Dock hade dessa barn, i likhet med andra barn med eksem innan 2 års ålder, en ökad risk att utveckla astma och rinit.

Slutsats

Resultaten från denna avhandling har bidragit till att öka kunskapen och förståelsen gällande eksem hos barn. Avhandlingen visar att eksem, astma och rinit bland barn är ett folkhälsoproblem. En viktig lärdom från studierna i avhandlingen är att eksem, astma och rinit är sjukdomar som i hög grad är relaterade till varandra. Denna kunskap är viktig både för forskare som studerar dessa sjukdomar och för läkare och annan sjukvårdspersonal som träffar barn med eksem, astma eller rinit.

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