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Eczema in childhood and adolescence

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ABSTRACT

Background: Eczema (atopic dermatitis) is an itchy inflammatory skin disease that affects many children and adolescents. Eczema associated with IgE antibodies is called atopic eczema (AE), while other eczema is called nonatopic eczema (non-AE). Having a filaggrin (*FLG*) mutation is associated with increased risk for eczema. Children with eczema more often develop food allergy, asthma, and rhinitis. It has been suggested that eczema is associated with non-allergic comorbidities such as ADHD.

Aims: To describe eczema in adolescence and the course of preschool eczema up to age 16 years in a population-based birth cohort, to investigate consequences of preschool eczema and *FLG* mutation later in childhood/adolescence and to study factors of importance for remission of preschool eczema.

Methods: We used data from a Swedish birth cohort recruited from the general population (n=4,089). The families provided information on background factors at inclusion when children were 2 months of age. Questionnaires regarding eczema during the preceding year were answered by parents at 1, 2, 4, and 8 years, and by parents and children at 12 and 16 years. Information on IgE sensitization at 4, 8, and 16 years and on *FLG* mutation was available for most children. Record-linkage to the Swedish prescribed drug register provided data on dispensed medication at age 10-18 years (range 8.6-19.9).

Results: The 12-month prevalence of eczema in adolescence was 10%, and of those affected 73% had mild, 17% moderate, and 10% severe eczema. The most common locations of eczema in adolescence were flexural surfaces (73%), neck (40%) and extensor surfaces of extremities (39%). Among adolescents with eczema, onset was most common before age 2 years (49%), but onset after age 12 years was also common (26%). A history of eczema at every previous follow-up was seen among 11% of the adolescents with eczema. In adolescence, AE was more common, had earlier onset and was more severe compared with non-AE, but there were no differences in seasonal variation or location of eczema.

There was no association between PSE and ADHD medication at school age (adjOR 1.12, 95% CI: 0.80-1.56). Further, PSE was not associated with dispensed antidepressants, migraine medication or antiepileptics at school age.

PSE was associated with IgE sensitization to both food and aeroallergens up to age 16 years (overall adjOR 2.30, 95% CI: 2.00-2.66). This association was significantly stronger among children with persistent PSE. Among sensitized children at age 4, 8, and 16 years, polysensitization was more common in children with PSE than those without PSE. *FLG* mutation was not associated with IgE sensitization up to age 16 years, with the exception of IgE sensitization to peanut at age 4 years (adjOR 1.88, 95% CI: 1.03-3.44).

Half (51%) of children with PSE were in complete remission of eczema at school age. In prognostic multivariate models male sex and exclusive breastfeeding ≥4 months were positively associated with complete remission of PSE at school age. Persistent PSE, severe PSE, parental allergy, parental smoking, and *FLG* mutation were associated with reduced likelihood of complete remission. The prognostic models developed had correct classification rates of 63-65%.

Conclusions: Only half of children with eczema before age 4 years are in complete remission at school age. Of adolescents with eczema, more than 10% have severe eczema. In adolescence, AE and non-AE do not differ in seasonal variation or location. No significant association was found between eczema and dispensed ADHD medication, antidepressants, migraine drugs or antiepileptics. PSE, especially if persistent, is strongly associated with IgE sensitization to both foods and aeroallergens. *FLG* mutation is associated with IgE sensitization to peanut, but not to other allergens, indicating that *FLG* mutation in the absence of PSE does not play a major role in IgE sensitization. Finally, male sex and exclusive breastfeeding ≥4 months were positively associated with complete remission of PSE at school age, whereas persistent and/or severe PSE, parental allergy, parental smoking, and *FLG* mutation were associated with reduced likelihood of complete remission.

LIST OF SCIENTIFIC PAPERS

I. **Johansson EK**, Ballardini N, Bergström A, Kull I, Wahlgren CF.
Atopic and nonatopic eczema in adolescence: is there a difference? Br J Dermatol 2015;173(4):962-968.

II. **Johansson EK**, Ballardini N, Kull I, Bergström A, Wahlgren CF.
Association between preschool eczema and medication for attention-deficit/hyperactivity disorder in school age. Pediatr Allergy Immunol 2017;28(1):44-50.

III. **Johansson EK**, Bergström A, Kull I, Lind T, Söderhäll C, van Hage M, et al. IgE sensitization in relation to preschool eczema and filaggrin mutation. J Allergy Clin Immunol 2017 Apr 26. doi: 10.1016/j.jaci.2017.04.008.

IV. **Johansson EK**, Bergström A, Kull I, Lind T, Söderhäll C, Melén E, Asad S, Bradley M, Liedén A, Ballardini N, Wahlgren CF. Prognosis of preschool eczema and factors of importance for remission. Manuscript.

LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
AE	Atopic eczema
ATC	Anatomical therapeutic chemical classification
BAMSE	Barn (children) allergi (allergy) miljö (environment) Stockholm epidemiologi (epidemiology)
BESS	BAMSE eczema severity score
CI	Confidence interval
CNS	Central nervous system
DNA	Deoxyribonucleic acid
EASI	Eczema area and severity index
FLG	Filaggrin gene
GEE	Generalized estimating equation
HDM	House dust mite
HR	Hazard ratio
IgE	Immunoglobulin E
ISAAC	International study of asthma and allergies in childhood
NESS	Nottingham eczema severity score
non-AE	Nonatopic eczema
NPV	Negative predictive value
OR, adjOR	Odds ratio, adjusted odds ratio
POEM	Patient-oriented eczema measure
PPV	Positive predictive value
PSE	Preschool eczema
RR	Relative risk
SCORAD	Severity scoring of atopic dermatitis index
SPDR	Swedish prescribed drug register
TCI	Topical calcineurin inhibitor
TGC	Topical glucocorticoid
WAO	World Allery Organization

CONTENTS

1 BACKGROUND

ECZEMA

Nomenclature

The clinical features of eczema are highly variable and there is no specific diagnostic test to verify the disease group. Because of this the nomenclature for eczema is divergent, and atopic dermatitis and atopic eczema are often use synonymously with eczema. Therefore, the nomenclature used in research, as well as in clinical practice, can be confusing.

According to the World Allergy Organization (WAO) nomenclature established in 2004, the umbrella term for local inflammation of the skin should be dermatitis. Eczema is the term describing dermatitis with certain clinical characteristics and association with atopic diseases (asthma and rhinitis). If a skin prick test or analysis of IgE antibodies in serum is performed, eczema can be classified as atopic eczema (presence of IgE sensitization) or nonatopic eczema (absence of IgE sensitization).[1]

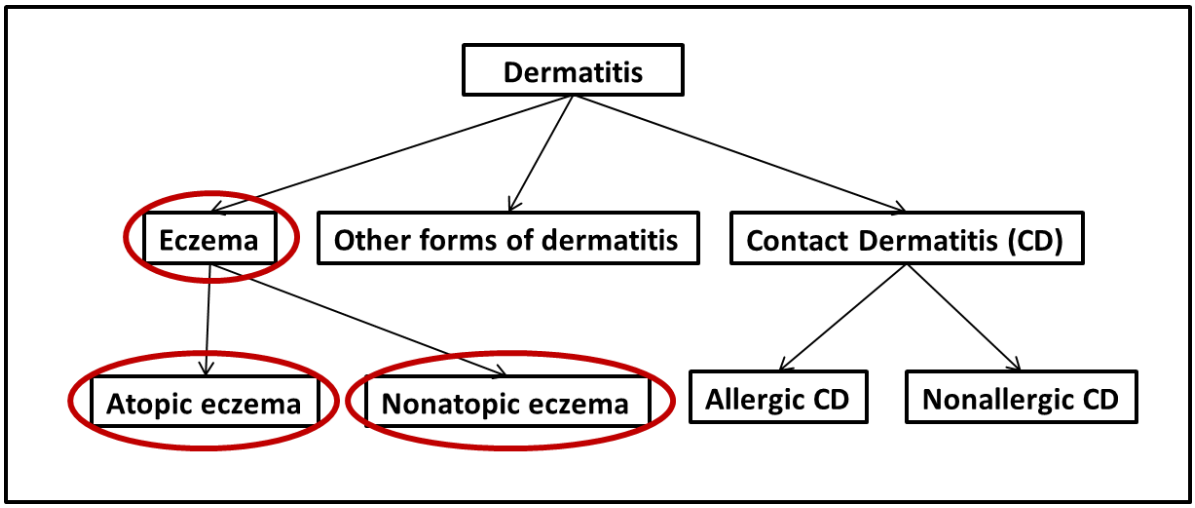

Figure 1 WAO nomenclature of eczema.[1]

In literature, the terms eczema, atopic eczema (in the UK) and atopic dermatitis (in the USA) are used synonymously, and in clinical practice atopic eczema and atopic dermatitis are often used even when a patient has not been tested for IgE sensitization.[2] Within this thesis, we have chosen to use the WAO nomenclature as no other consensus is established. In 1980, Hanifin and Rajka described the main clinical criteria of eczema (atopic dermatitis), based on patients seen in hospitals,[3] and these criteria have been widely used and refined thereafter. The most validated diagnostic criteria of eczema, often known as William´s criteria, were developed by a UK working party.[4-8] These are commonly used in every-day clinical practice, in clinical trials and in epidemiological studies, see Table 1.

Table 1 William's criteria for atopic dermatitis.

MUST have itchy skin condition in past 12 months

PLUS three or more of:

1. History of involvement of the skin creases
2. Personal history of asthma or hay fever, or if child <4 years, history of atopic disease in 1st degree relative
3. History of generally dry skin in past year
4. Visible flexural dermatitis
5. Onset below age 2 (not used if child <4 years)

The UK refinement of Hanifin's and Rajka's diagnostic criteria for atopic dermatitis (for use as 12-month prevalence measure in epidemiological studies).[9]

Clinical presentation

Eczema is a relapsing inflammatory skin disease characterized by skin dryness, scratching and itchy red rash that favors the body folds.[10] Disease onset is most common in the first two years of life but many debuts later in childhood, adolescence or in adulthood.[11, 12] Episodes with red, scaly and itchy patches or plaques are followed by periods free from symptoms. Eczema is most common early in childhood, and the episodes of symptoms in general becomes less frequent later in childhood and among adults. Rash distribution on the bodies of individuals with eczema is highly variable and age-bound. Therefore, eczema is classified into three different phases.[11, 13, 14]

- The infantile phase (up to 2 years of life); with skin lesions on the face, neck, extensor surfaces of extremities and on the trunk.
- The childhood phase (between 3 and 11 years); involvement of body folds, face (mostly perioral and not as common as in the infantile phase), as well as hands, feet, buttocks and on the back/inside of the thighs.[14]
- The adult phase (from 12 years); mainly involving body folds, face (mostly forehead/periorbital), neck and hands.[11, 15, 16]

This classification is based on patients seen in hospitals with more severe disease. However, most individuals with eczema are treated in primary care; furthermore, it has been shown that about 30% of Scandinavian school-children with eczema and other allergy-related diseases have never visited a doctor for their symptoms.[17] The characteristics of eczema among adolescents in the general population have not been described in detail, although eczema is common in adolescents.

Atopic (AE) and nonatopic eczema (non-AE)

IgE sensitization is not causative, but follows in the course of infantile eczema.[18-20] Many will never develop IgE sensitization, but still have typical signs of eczema. This non-IgE-associated form of eczema, non-AE, is not associated with atopic asthma and is more common among females.[21] The classification of AE includes presence of IgE antibodies to either food or

aeroallergens.[1] Non-AE in children may evolve into AE, and the diagnosis of AE and non-AE cannot be reached without an IgE antibody determination or skin prick test.[1] A study among 5-year-old children suggests that AE and non-AE are two different entities; (i) the AE variant is more common, presents early in infancy, has a male majority and is more persistent, and (ii) the non-AE variant goes with later onset and has no relation to asthma or hay fever.[22] Others argue that IgE sensitization is associated with an increased risk of more severe and more persistent eczema, but that it is not a useful diagnostic tool when other clinical signs have been taken into account.[23]

Differences between AE and non-AE regarding disease course, eczema severity and clinical characteristics in the general population need further exploration.

Outcome measures

The Harmonizing Eczema Outcome Measures (HOME) initiative was started in 2010 as an effort to provide consensus regarding what diagnostic criteria and outcome measures to use within eczema research, in particular in clinical trials. The outcome measures used up until then had been diverging and often not validated making it difficult to compare result from different studies.[24] The HOME initiative identified clinical signs, symptoms, quality of life, and long-term control of flares as core outcome domains for eczema trials. The most validated scales for clinical signs are the Eczema Area and Severity Index (EASI) and the objective Scoring Atopic Dermatitis (SCORAD). A recent systematic review recommended EASI for clinical signs in future studies.[25] Moreover, the HOME initiative has proposed that the Patient-Oriented Eczema Measure (POEM) be used for assessment of symptoms.[26] POEM reflects symptoms in the week before assessment and should be used in trials, but due to the intermittent course of eczema POEM does not reflect the symptoms or severity of eczema over the course of the preceding year. An alternative in epidemiological studies could be the validated Nottingham Eczema Severity Scale (NESS), assessing symptoms in the preceding 12 months.[27] NESS has an adequate interobserver reliability, but is not tested sufficiently and has not performed adequately according to a systematic review.[28] In the BAMSE project, the BAMSE Eczema Severity Score (BESS) was developed in the 12-year follow-up. BESS has not been validated, but it is similar to NESS.[29]

Epidemiology

The prevalence of eczema has increased in Sweden and in other industrialized countries during the past decades; 15-30% of children and 2-10% of adults are affected.[10, 30] The 12-month prevalence of eczema in adolescence is 7.3%-13%.[31-35] In the International Study of Asthma and Allergies in Childhood (ISAAC) phase 3, the global 12-month prevalence at 13-14 years of age was 7.3% and the Swedish prevalence 12.3%.[31] In the 12-year follow-up in the BAMSE project the prevalence of eczema was 11.9%,[29] and in a British birth cohort, from the Isle of Wight, the prevalence at 18 years of age was 12.3%.[35]

Although the natural course of eczema in children and adolescents is individual, eczema often debuts in childhood.[18, 36] More than 60% have disease onset within the first 2 years of life[11, 21] but onset can occur in any age.[12] For example, in the British National Child Development Study (NCDS) 28.4% of 16-year-old subjects with eczema reported that their eczema onset was after age 7 years.[37]

Since eczema is most common in early childhood, children are said to "grow out" of their disease. It has been suggested that about 60% of children with eczema are free from symptoms in early adolescence.[2] This has been confirmed in three European birth cohorts,[18, 35, 38] in which approximately half of children with infantile eczema were in remission later in childhood. However, up to 40-60% may have recurrence later in life, often as hand eczema.[16, 39, 40] Among adults who had visited a Swedish hospital outpatient clinic because of eczema, 59% still had eczema 24-38 years later.[41]

Factor of importance for prognosis of eczema

Knowledge of disease prognosis is important, especially for parents of small children with eczema, and several prognostic factors have been identified.[9] Early-onset eczema,[40, 41] IgE-mediated sensitization,[18, 40, 41] family history of eczema,[18, 41] and severe eczema in childhood[18, 40] have all been reported to be associated with worse prognosis. Sex has not been found to be a prognostic factor.[18, 41] In a recent systematic review and meta-analysis, Kim et al concluded that onset before age 2 years, and male sex was associated with better prognosis while persistent disease was associated with worse prognosis. Presence of IgE sensitization was not associated with persistent disease.[42] Most studies have focused on eczema early in life and subsequent disease course in childhood, but less is known about children with eczema onset later in childhood or in adolescence. The first systematic review investigating which factors that predict remission of infantile eczema was published in 2015. Only two studies were suitable for inclusion and the authors concluded that it is largely unknown which factors predict remission of infantile eczema.[43] The natural course and prognostic factors require further study.

Etiology

Briefly, two major pathophysiological aspects initiate eczema: abnormalities of skin barrier structure or function and cutaneous inflammation due to an inadequate immune response.[12] Each aspect can cause eczema alone, but in most cases eczema is probably caused by a combination of epidermal dysfunction and hyper-reactive immune response causing inflammation. Both aspects can be triggered by predisposing genetic factors and/or environmental factors.[44]

Genetics

Heredity is a known risk factor for eczema. In a Danish twin study, the concordance rate was much higher in monozygotic twins (72%) than in dizygotic twins (23%).[45] Allergic asthma and allergic rhinitis in a parent seem to be of minor importance for the development of eczema in the offspring, indicating that eczema might be inherited independently.[46] The strongest known genetic factor is loss-of-function mutation in the filaggrin gene (*FLG*),[12] see below (page 14).

Environment

Genetics alone cannot explain the increase of eczema seen over the world.[47] Environmental factors have been found to play an important role in eczema development. For example, eczema is more common in wealthy families.[48] Black Caribbean children living in London have higher prevalence of eczema than children with the same ethnicity living in Kingston, Jamaica (14.9% vs. 5.6%).[2]

In 1989, David Strachan found that eczema was less common in large families, and in younger siblings. This led to "the hygiene hypothesis", i.e. that younger siblings in large families are more exposed to infections and thereby protected from atopy and atopic disease manifestations.[49] While many studies have been conducted, the hygiene hypothesis has not been confirmed and there is no clear evidence of protective effects of early life infections on development of eczema. Flohr et al performed a systematic review including studies inspired by the hygiene hypothesis evaluating risk factors for eczema. They concluded that there was an inverse relationship between eczema and early day care, consumption of unpasteurized milk, and farm animal and dog exposure in early life. The protective effects of these, as well as the fact that use of broad-spectrum antibiotics increased the risk of eczema, was thought to be due to a general increase in exposure to non-pathogenic infections.[50] They also found that cat exposure in combination with impaired skin barrier is associated with an increased risk of eczema, and that routine childhood vaccinations are not associated with a risk of eczema. Helminth infection is protective for eczema, but bacterial and viral infections are not.[50] Several studies have investigated whether prebiotics (non-digestible food ingredients that promote the growth of beneficial microorganisms in the intestines) or probiotics (live microorganisms assumed to provide health benefits to the host when consumed) can prevent incident eczema. A systematic review and meta-analysis have shown that probiotics given to pregnant or breastfeeding women and/or infants reduced incident eczema,[51] while the evidence for prebiotics is more uncertain, though some studies indicate that prebiotics given to high-risk infants might prevent eczema.[52] Passive exposure to tobacco smoke is associated with increased risk for eczema.[53] To summarize, probiotics may be protective for eczema.[54] In contrast, small family size, high education level in household, smoking in household, and living in regions with low humidity and low exposure to ultra violet radiation are associated with increased risk for eczema.[12, 53]

Treatment

The aim of treatment is to improve symptoms and achieve long-term disease control. The main principle is continuous epidermal barrier repair with use of emollients and avoidance of individual trigger factors.[12] Use of emollients in patients with eczema extends the time to relapse, and give longer disease-free periods.[55] The hypothesis that use of emollients can prevent, or delay, eczema onset has emerged in the last few years due to increasing research evidence that epidermal dysfunction has a pathogenic role in eczema. In a randomized clinical trial, Simpson et al found that daily use of emollients in high-risk newborns (treatment started within 3 weeks of age) reduced the risk of developing eczema at 6 months of age (RR 0.50, 95% CI: 0.28-0.9).[56] Similarly, Horimukai et al showed that daily application of emollients during the first 32 weeks of life reduced the risk for eczema in high-risk infants.[57] Larger, ongoing trials to analyze the possible preventive effect of emollients will hopefully clarify this further.

Topical glucocorticoids (TGCs) are the first-line anti-inflammatory treatment to control acute exacerbations.[12, 58] The treatment is used daily during flare-ups until good clinical response is achieved (reduction of itch). When the itch has disappeared, dose tapering is initiated and made gradually, so as to avoid the withdrawal rebound phenomenon.[59] Most TGCs have been used twice daily, but recent studies have shown that with potent TGCs and newer preparations, application once daily is equally effective.[60] Proper use of TGCs entails a small risk of adverse events. The risk of skin atrophy, when TGCs are used for between 4 weeks and 1 year, is 0-5%[61] and in a large systematic review of clinical trials was found to be 0.8%.[58] Twice weekly application of fluticasone reduces the risk of relapses and might be used to maintain clearance.[62]

Topical calcineurin inhibitors (TCIs) are non-steroid anti-inflammatory agents and considered as the second-line option for intermittent and short-term use.[12] TCIs do not induce skin atrophy, in contrast to glucocorticoids and are therefore suitable for certain locations, such as the face and the genital area.[59] However, few studies have compared the new TCIs with conventional therapy (TGCs). A recent systematic review showed that TGC and TCI had similar rates regarding improvement of dermatitis and successful treatment. TCI was associated with higher costs and more adverse events (skin burning and pruritus). There were no significant differences in skin atrophy or skin infections. The review concluded that TGC is the therapy of choice in eczema.[58]

If eczema cannot be controlled through topical treatment, phototherapy should be considered. When topical treatment and phototherapy fail, systemic immunosuppressive treatment is required, in both children and adults.[12] Cyclosporine, mycophenolate mofetil, methotrexate, and azathioprine are the best studied agents in children,[63] but promising newer targeted biologic therapies are under development for adults.[64]

FILAGGRIN MUTATION

For ichthyosis vulgaris, a skin disease characterized by dry and scaly skin, loss-of-function mutations in *FLG* have been identified as causal factor.[65] These mutations were also found to be strongly associated with eczema; in the families with ichthyosis vulgaris, eczema was present in 44% of individuals heterozygous for these loss-of-function mutations of the *FLG* gene and in 76% of individuals with both alleles mutant. None of the family members without *FLG* mutation had eczema. The conclusion was that *FLG* mutations leading to impaired skin barrier function are closely linked to eczema and to allergic asthma in individuals with eczema.[10, 66] Subsequent studies have confirmed *FLG* mutations as a major risk factor for developing eczema.[66-69] In addition, studies have shown that *FLG* mutation is associated with more persistent disease,[70-72] while others have not found a significant association.[73, 74] However, the majority of people with eczema do not have any *FLG* mutation and up to 60% of individuals with *FLG* mutations will never develop eczema.[12]

Having a *FLG* mutation is associated with other allergy-related diseases. For example, *FLG* mutation is associated with asthma among children with eczema or a history of eczema,[70, 75] and with allergic rhinitis in some studies.[69, 75] Furthermore, an early systematic review and meta-analysis concluded that *FLG* mutation is associated with increased risk for developing IgE sensitization.[69] It has been suggested that this association could be explained by a defective skin barrier function allowing penetration of allergens, which induces IgE sensitization.[76-78] This hypothesis is supported by the finding that *FLG* mutation in the absence of eczema is associated with both IgE sensitization to peanut and peanut allergy.[79, 80] However, more recent studies that have evaluated the relation between *FLG* mutation and IgE sensitization and included eczema as a covariate present conflicting results.[70, 81-84] Further exploration of the association between IgE sensitization and *FLG* mutation, with a possibility to adjust for eczema, is needed.

IGE SENSITIZATION

IgE sensitization occurs when the immune system produces IgE antibodies, which can be detected in the blood. This can be initiated as a response to an allergen. Proteins in foods and pollen are common allergens. If an individual with IgE-mediated allergy is exposed to the same specific allergen she has IgE antibodies against, organ-specific symptoms may occur. Rhinitis induces symptoms from the nose (itching, sneezing, increased secretion and blocking), asthma symptoms from the lungs (wheezing, cough, and forced breathing), and, if the skin is involved, eczema or urticaria will occur. IgE sensitization also exists among individuals without allergic disease.[85]

Children with eczema have increased risk for IgE sensitization to foods.[86-88] This association is even stronger with a more severe eczema,[82] and persistent eczema.[89] Less is known regarding the association between eczema and IgE sensitization to aeroallergens. The Isle of Wight cohort reported that eczema was associated with IgE sensitization to aeroallergens at age 4

years.[86] The temporal relationship between eczema and IgE sensitization is not fully established, since very few larger studies have tested for IgE sensitization before eczema is diagnosed the first time. However, a Danish population-based birth cohort followed children with regular skin examinations and measurements for IgE sensitization up to 3 years of age. Of the children diagnosed with eczema, 43% developed IgE sensitization simultaneously with their eczema, 27% showed IgE sensitization prior to or after the eczema diagnosis, and 30% did not have IgE sensitization.[20] Information on the longitudinal relationship between IgE sensitization, either to food or aeroallergens, and eczema from birth up through childhood is scarce. The pattern of IgE sensitization among children with early-onset eczema has been described,[86, 90, 91] but there is limited information on potential differences in the pattern of IgE sensitization between individuals with or without previous eczema.

COMORBIDITIES OF ECZEMA

Atopy, asthma and rhinitis

Atopy is a tendency to become IgE-sensitized (produce IgE antibodies) as a response to normal exposure to common food or aeroallergens. Individuals with atopy can develop symptoms of food allergy, asthma, rhinitis and eczema.[1] While asthma, rhinitis and eczema are often referred to as allergic or allergy-related diseases, all of them exist in individuals without IgE sensitization. As described above, persons with eczema have increased risk for IgE sensitization, and food allergy.[87] In addition, children with eczema are at increased risk of developing asthma and allergic rhinitis.[18, 92-94] In a systematic review of 4 birth cohorts, the risk for developing asthma was doubled in young children with eczema (OR 2.14, 95% CI, 1.76-2.75),[95] and in a Swedish population-based birth cohort, children with infantile eczema had an increased risk of both rhinitis (OR 2.69, 95% CI, 2.22-3.26) and asthma (OR 2.22, 95% CI, 1.65-2.98) in pre-adolescence.[38]

The course and development of allergy-related diseases in childhood have often been referred to as the atopic march. Eczema is the first clinical manifestation, followed by a typical sequence of food allergy, asthma, and rhinitis.[96] Some of the diseases persist for several years, whereas others remit with increasing age.[94] The pattern of IgE sensitization changes from food allergens to inhalant allergens.[33] In 2003, Lack et al demonstrated that use of skin preparations containing peanut oil was associated with peanut allergy in children (OR 6.8, 95% CI: 1.4-32.9). They concluded that IgE sensitization to peanut protein may occur through application of peanut oil to inflamed skin.[97] Impaired skin barrier function in patients with eczema allows penetration of allergens, irritants and bacteria.[98] Thus, IgE sensitization to allergens may occur via the defective skin barrier and initiate the atopic march.[99] Brough et al demonstrated that peanut antigen in dust was associated with increased risk of IgE sensitization to peanut and peanut allergy in atopic children. The risk was higher in children with a history of eczema and severe eczema. This supports the idea of epicutaneous IgE sensitization through an impaired skin barrier.[100] However, the atopic march does not always

follow this classic sequence. For example, patients with asthma may later develop eczema.[99] In a systematic review of several birth cohorts, only 1 of 3 children with eczema in infancy developed asthma. The authors stated that the relationship between eczema and asthma seems complex and that only a minority of children with infantile eczema follows the progression of eczema into asthma as described in the atopic march.[95] Thus, it has been debated whether the atopic march represents a causal relationship or not. The prevalence of having at least two of the diseases eczema, asthma and rhinitis (multimorbidity) varies with age. In the BAMSE cohort, the DARC cohort and the MAS cohort the prevalence of multimorbidity was 7.5% at 12 years, 12.1% at 14 years and 8.5% at 12 years, respectively.[93, 101, 102] In MeDALL (including 12 ongoing Eurpoean birth cohorts) the corresponding prevalence was 4.4% at age 8 years, and multimorbidity was seen among children both with and without IgE sensitization. MedALL concluded that IgE sensitization could not be considered as the main cause of comorbidity between eczema, asthma, and rhinitis, and that both IgE-mediated and non-IgE-mediated mechanisms are probably involved in this multimorbidity.[103]

Non-allergic related comorbidities

In recent years, several studies have shown association between eczema and non-allergic diseases, such as malignancies,[104, 105] diabetes mellitus type I, rheumatoid arthritis, inflammatory bowel disease,[106] and, in particular, disorders involving the central nervous system (CNS), for example attention-deficit/hyperactivity disorder (ADHD),[107-112] depression and anxiety disorders,[108, 110, 113] and epilepsy.[114]

ADHD

The most studied association is between eczema and ADHD and in a systematic review the OR ranged from 1.47 to 7.75. The authors stated that "studies consistently suggest a positive association between eczema and ADHD."[115] Later studies have also shown an association between childhood eczema and ADHD. For example, a large case-control study (4,692 cases and 18,768 controls, OR 1.40, 95% CI, 1.22-1.61)[112] and a population-based birth cohort study (n=770, RR 1.92, 95% CI, 1.03-3.57) showed an association between eczema at 0-4 years of age and ADHD.[111] The temporal relationship and underlying mechanisms for this association remains unclear. Several possible explanations have been suggested. Inflammatory-released cytokines that penetrate the blood-brain barrier and interfere with the maturation of the cortex and/or the transmitter system could be involved in the development of ADHD and other CNS-associated disorders.[116] Another possible explanation is shared risk factors for eczema and ADHD. Studies have shown that not only eczema, but also asthma and rhinitis, are associated with ADHD,[109, 110, 112, 117] and that low socioeconomic status, low birth weight, impaired fetal growth, and parental smoking are risk factors for both asthma and ADHD.[118] A third possible mechanism might be that children with eczema are more prone to develop mental and behavioral problems due to their illness.[112] Children with chronic disorders such as migraine, arthritis and heart diseases more often have emotional and behavioral symptoms

compared with the general population.[119] ADHD and CNS-associated disorders could be a result of the burden of chronic diseases in childhood, with eczema being one of them.[108] Finally, ADHD could be a trigger for eczema. Children with ADHD have psychosocial difficulties and higher risk for depression, anxiety, and sleep-disturbance. Psychosocial stress affects the severity of eczema.[120]

The reported prevalence of ADHD has increased in recent decades and was in a systematic review and meta-analysis estimated to 6.7-7.8%.[121] ADHD is typically diagnosed in childhood, but in most cases symptoms have been present years before diagnosis. Therefore, it is difficult to determine the age at disease onset.[122] Psychostimulant medication is used for treatment of ADHD. In a Swedish study performed in 2006-2011, 83.1-84.7% of children (age 6-17 years) with doctor-diagnosed ADHD had used psychostimulants.[123]

Most studies evaluating the association between eczema and ADHD have been cross sectional and the temporal relationship is still unclear. Large longitudinal studies with prospectively collected data are warranted.

2 AIMS

The overall aim was to describe eczema in adolescence and the course of preschool eczema up to age 16 years in a population-based birth cohort. Additional aims were to investigate consequences of preschool eczema and filaggrin mutation later in childhood and adolescence and to study factors of importance for remission of preschool eczema.

In particular:

To describe adolescent eczema and to identify potential differences in the clinical characteristics of atopic eczema and nonatopic eczema in adolescents.

To explore whether preschool eczema is associated with ADHD or other CNS-associated disorders requiring pharmacotherapy at school age, and to analyze whether eczema at other ages of childhood is associated with ADHD medication.

To examine the longitudinal relationship between preschool eczema, filaggrin mutation, or both, and IgE sensitization in childhood. In addition, to investigate if children with preschool eczema or filaggrin mutation present different patterns of IgE sensitization than children without preschool eczema or filaggrin mutation.

To study the natural course of preschool eczema up to age 16 years, and to identify factors of importance for remission of preschool eczema. Lastly, to explore whether prognostic models could be useful to predict remission of preschool eczema.

3 MATERIALS AND METHODS

STUDY DESIGN AND SETTING

All the scientific papers (I-IV) are based on material from the BAMSE (Children Allergy Environment Stockholm Epidemiology) birth cohort. The BAMSE project was initiated to study risk factors for allergy-related diseases (asthma, eczema, and rhinitis) in the general population up to age 4 years. By now, a majority of the children have participated through childhood and adolescence and were recently invited to a follow-up at age 22-24 years.

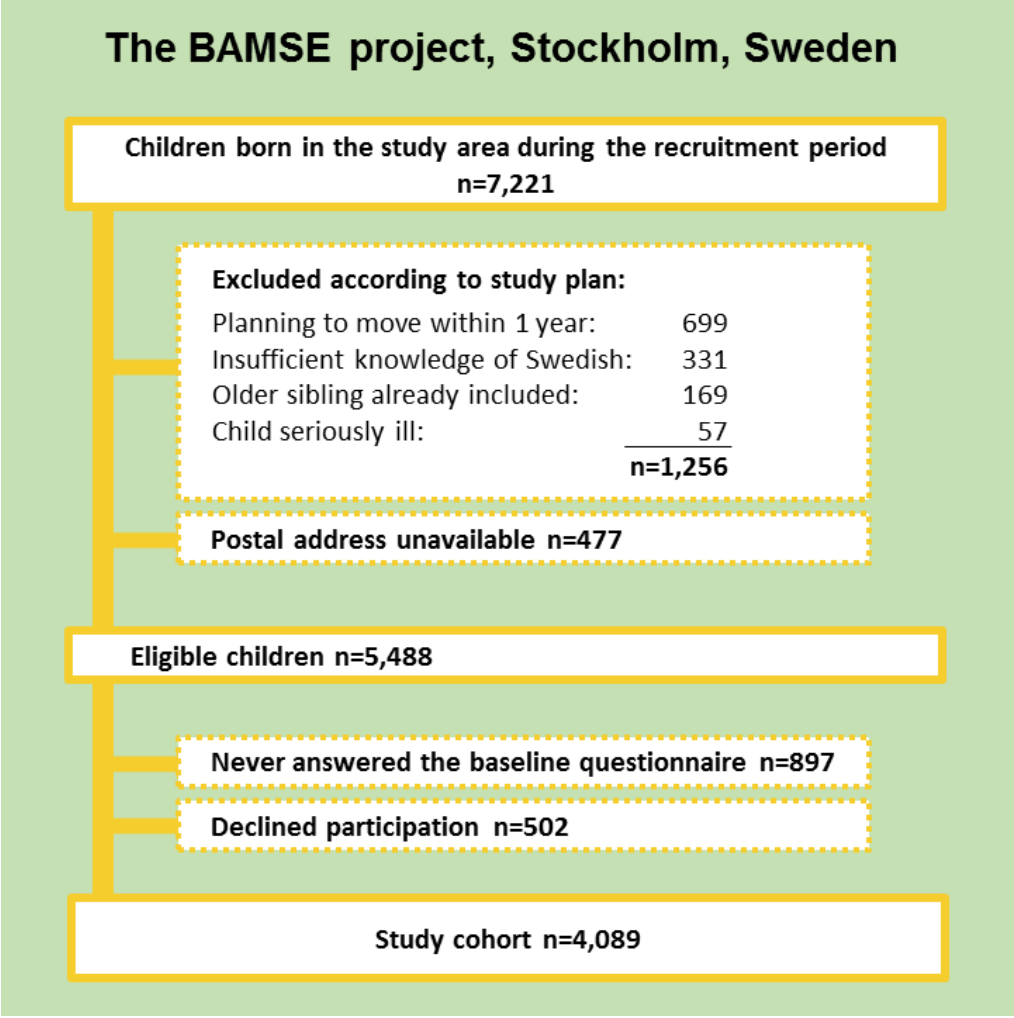

Figure 2 The BAMSE project. Flow chart for the recruitment process until final original cohort.

The BAMSE birth cohort (I-IV)

Recruitment started in February 1994 and continued until November 1996. Parents to all children born in predefined areas forming a circle sector of greater Stockholm (Northern part of inner city, Solna, Sundbyberg and Järfälla) were asked to participate. The selected districts were chosen to represent both inner city, urban and suburban households with different kinds of buildings and socio-economic status (education and profession). The children and their parents were reached through a community-based population register. During the study period, 7,721 children were born in the recruitment area. Of these 477 could not be reached,

1,256 were actively excluded and 1,399 were non-responders (502 declined to participate and 897 never answered the baseline questionnaire). The final cohort consisted of 4,089 children (75% of the eligible children) whose parents answered the baseline questionnaire when their children were aged 2 months old, at median (Figure 2).[124]

In 1996, actively excluded families and non-responders were sent a short questionnaire to study parental reasons to participate or not in relation to parental allergy, parental smoking and keeping pets at home. The response rate was 67%. Parental smoking (at age 2-4 months of the child) was more common among non-responders and actively excluded families compared with the children in the BAMSE cohort, indicating that life-style factors influenced the willingness to participate. However, the willingness to participate was not affected by parental allergy or keeping pets in household.[124]

Figure 3 Description of participation in the BAMSE birth cohort. The longitudinal design constituted regular questionnaires and, in addition, clinical examinations with blood sampling at 4, 8, and 16 years.

The baseline questionnaire (Q0) covered data on residential factors, parental allergy and environmental factors. When the children were 1, 2, 4, 8, 12, and 16 years, parents received questionnaires (Q1, Q2, Q4 etc.) regarding symptoms of asthma, eczema and rhinitis, environmental factors and lifestyle factors. In addition, the children/adolescents received questionnaires at age 12 and 16 years (Figure 3). The participants had the possibility to skip one follow-up and remain in the study, as long as they did not decline to participate further. Children whose parents completed the questionnaires at age 4, 8, and 16 years were invited to participate in clinical examinations at the corresponding age including sampling of blood specimens.

The Swedish Prescribed Drug Register (II)

The Swedish Prescribed Drug Register (SPDR) is a national health care register on all dispensed pharmaceuticals. SPDR was established in July 2005 and covers the entire Swedish population.[125] In the BAMSE cohort, information on prescribed and dispensed medication was obtained by record linkage to SPDR (from age 10 years (range 8.6-11.4)) for all children included (n=4,089). Data from this register was available through December 31 2013, when the participants in the BAMSE cohort were 18 years old (range 17.1-19.9). Linkage was performed using the Swedish personal identity numbers.[126]

STUDY POPULATIONS (I-IV)

Study I included 3,108 adolescents who filled out the questionnaire at age 16 years, and provided data on eczema (76% of the original cohort). A subpopulation had data on IgE sensitization at age 16 years available (n=2,529).

Study II included 3,606 children with complete data on eczema at age 1, 2, and 4 years (88% of the original cohort). A subpopulation encompassed 2,736 children with complete data on eczema (parental questionnaires) at age 1, 2, 4, 8, 12, and 16 years (67% of the original cohort). Data on dispensed prescribed medication was derived by record linkage to SPDR.

Study III included 3,201 children with data on eczema at age 1, 2, and 4 years, who provided blood at least once at age 4, 8, and/or 16 years (78% of the original cohort). Data on *FLG* mutation was available for 1,890 children in the study population.

Study IV included children with any eczema reported during the first four years of life and data regarding eczema at age 8, 12, and 16 years (n=889). For a majority, data on IgE sensitization at age 4 years (n=671) and *FLG* mutation (n=764) were available.

DEFINITIONS

Background variables (I-IV)

Most background characteristics/exposures were based on questionnaire data reported by parents at baseline (when the children's median age was 2 months) (Table 2).

Table 2 Definitions of background factors/exposures used in studies I-IV.

Variable	Definition[a]	Study
Parental allergy	Mother and/or father with doctor's diagnosis of asthma and asthma medication and/or doctor's diagnosis of hay fever in combination with furred pets and/or pollen allergy and/or doctor's diagnosis of eczema (contact allergy among parents was excluded). (Q0)	I, II, III, IV
Parental smoking	Any parent smoking at least one cigarette per day. (Q0)	I, II, III, IV
Low socio-economic status	Both parents were blue-collar workers, or one parent blue-collar worker and the other parent was a student, housewife, on disability pension or unemployed. (Q0)	I, II, III, IV
Exclusive breastfeeding ≥4 months	Infant was breastfed for at least four months, without exposure to solid food or formula. (Q1)	I, II, III, IV
Any parent born outside Scandinavia	Any parent born outside Sweden, Denmark, Norway or Finland. (Q8)	I, II, IV
Any parent born outside Europe	Any parent born outside Europe. (Q8)	
Age of mother	Mother's age at birth of child (years). (Q0)	I
Young mother	Mother's age <25 years at birth of child. (Q0)	II, IV
Gestational age	Duration of gestation, reported in weeks. (Q0)	I
Preterm birth	Gestational age <37 weeks. (Q0)	IV
Low birth weight	Weight at birth <2,500g. (Q0)	IV
Older sibling	Any older sibling in household at birth of child. (Q0)	IV

[a]Based on parental report at baseline (at median age 2 months), at age 1 year or at age 8 years.

Eczema (I-IV)

The definition of eczema was based on parental report of either symptoms during the preceding 12 months or reported doctor's diagnosis (Table 3). The questionnaire-derived eczema definition has been validated at the pediatric open ward unit of the Department of Dermatology, Karolinska University Hospital. Fifty consecutive first-time visitors with various skin disorders at age 0-4 years were examined by a dermatologist and classified as having eczema or non-eczema in accordance with the criteria of Hanifin and Rajka. Before the visit, the parents were asked to fill out a questionnaire including the question upon which the eczema definitions in the BAMSE follow-ups are based. The questionnaire-derived eczema diagnosis, when compared with the clinical diagnosis, displayed a sensitivity and specificity of 92% and 100%, respectively.[127] In study I and study IV, the definition of eczema at age 16 years was based on symptoms of eczema reported by the adolescents (i.e. not by their parents). In contrast, the definition of eczema at age 16 years used in study II was based on parental-reported symptoms of eczema at age 16 years and/or doctor's diagnosis since last follow-up. This definition was chosen to cover the period between follow-ups at age 12 and 16 years.

Table 3 Definition of eczema used in studies I-IV based on parental report, unless otherwise stated.

Variable	Definition	Study
Eczema at age 1, 2, and 4 years	Dry skin and itchy skin rash for ≥two weeks on specific locations (face or arm/leg extension surfaces or arm/leg flexures or wrist/ankle flexures) over the last 12 months and/or doctor's diagnosis of eczema since last follow-up.	I, II, III, IV
Eczema at age 8 years	Dry skin and itchy skin rash for ≥two weeks on specific locations (face or arm/leg flexures or wrists/ankles or neck) over the last 12 months and/or doctor's diagnosis of eczema after 4 years of age up to 8 years of age.	I, II, IV
Eczema at age 12 years	Dry skin and itchy skin rash on specific locations (arm/leg flexures or wrists/ankles or neck) over the last 12 months and/or doctor's diagnosis of eczema after 10 years of age up to 12 years of age.	I, II, IV
Eczema at age 16 years	Dry skin and itchy skin rash on specific locations (arms/legs flexures or wrists/ankles or neck) over the last 12 months and/or doctor's diagnosis of eczema after 12 years of age up to 16 years of age.	II
Eczema at age 16 years	Dry skin and itchy skin rash on specific locations (arm/leg flexures or wrists/ankles or neck) over the last 12 months. Reported by adolescent.	I, IV
Atopic eczema (AE)	Eczema reported by adolescent in combination with any IgE sensitization, both at age 16 years.	I
Nonatopic eczema (non-AE)	Eczema reported by adolescent in combination with absence of any IgE sensitization, both at age 16 years.	I
Infantile eczema	Eczema at age 1 and/or 2 years.	II
Preschool eczema (PSE)	Eczema at age 1, 2, and/or 4 years.	II, III, IV
Eczema at school age	Eczema at age 8, 12, and/or 16 years.	II
Eczema ever up to age 16 years	Eczema at age 1, 2, 4, 8, 12, and/or 16 years.	II
Transient eczema	Eczema at 1, 2, and/or 4 years and no eczema at 8, 12, or 16 years.	II
Eczema with onset at school age	No eczema at 1, 2, or 4 years and eczema at 8, 12, and/or 16 years.	II
Persistent eczema	Eczema at 1, 2, and/or 4 years and eczema at 8, 12, and/or 16 years.	II
Persistent PSE	Eczema at age 1, 2, and 4 years.	III, IV
PSE with sleep disturbance	Eczema (reported symptoms and/or doctor's diagnosis) in combination with reported sleep disturbance due to itch at least once a week at 1, 2, and/or 4 years of age.	II, III, IV
Persistent eczema at school age	Eczema at age 8, 12, and 16 years.	IV
Intermittent eczema at school age	Eczema at one or two follow-ups at 8, 12 and/or 16 years.	IV
Complete remission at school age	No eczema at age 8, 12, or 16 years.	IV
Remission at age 16 years	No eczema at age 16 years.	IV
Doctor's diagnosis of infantile eczema and preschool eczema	Doctor's diagnosis of eczema at age 0-2 or 0-4 years, respectively, compared with children without doctor's diagnosis regardless of reported symptom of eczema.	II

Health outcomes other than eczema (I-IV)

The definitions of asthma and rhinitis were also based on questionnaire data (Table 4). Parental reports were used in studies II, III and IV. In study I, adolescents reported the symptoms of asthma and rhinitis at age 16 years.

While the BAMSE material primarily covers allergy-related diseases, the definitions of ADHD, depression/anxiety/phobia, epilepsy and migraine in study II were based on prescribed and dispensed medication for each particular disorder during school age (10-18 years). The drugs had to be registered as dispensed at least once between July 1 2005 and Dec 31 2013.

Table 4 Definitions of health outcomes used in studies I-IV, based on parental report unless otherwise stated.

Variable	Definition	Study
Asthma at 1 year of age	At least 3 episodes of wheeze after age 3 months and up to 1 year of age in combination with treatment with inhaled glucocorticoids and/or sign of suspected hyperactivity without concurrent upper respiratory infection.	II, III, IV
Asthma at 2 years of age	At least 3 episodes of wheeze after 1 year and up to 2 years of age in combination with treatment with inhaled glucocorticoids and/or sign of suspected hyperactivity without concurrent upper respiratory infection.	II, III, IV
Asthma at 4, 8, 12, and 16 years of age	More than 3 episodes of wheeze in the last 12 months and/or at least 1 episode of wheeze in the last 12 months in combination with inhaled glucocorticoids occasionally or regularly. Reported by adolescent at 16 years.	I, II, III, IV
Preschool asthma	Asthma at age 1, 2, and/or 4 years.	III, IV
Asthma ever up to 16 years of age	Asthma at 1, 2, 4, 8, 12, and/or 16 years of age.	II
Rhinitis	Symptoms from nose and/or eyes after exposure to furred pets or pollen.	I, II, III, IV
Rhinitis at 1 year of age	Symptoms and/or doctor's diagnosis at 0-1 year.	II, III, IV
Rhinitis at 2, 4, 8, and 16 years of age	Symptoms in the last 12 months and/or doctor's diagnosis since previous follow-up.	III, III, IV
Rhinitis at 12 years of age	Symptoms in the last 12 months and/or doctor's diagnosis at age 10-12 years.	II
Rhinitis at 16 years of age	Symptoms in the last 12 months Reported by adolescent.	I
Preschool rhinitis	Rhinitis at age 1, 2, and/or 4 years.	III, IV
Rhinitis ever up to 16 years of age	Rhinitis at 1, 2, 4, 8, 12, and/or 16 years of age.	II
ADHD medication at school age	Dispensed psychostimulants (ATC-code N06A) at age 10-18 years.	II
Antidepressants at school age	Dispensed antidepressants (ATC-code N06B) at age 10-18 years.	II
Anti-epileptics at school age	Dispensed anti-epileptic drugs (ATC-code N03A) at age 10-18 years.	II
Migraine drugs at school age	Dispensed migraine drugs (ATC-code N02C) at age 10-18 years.	II

Eczema severity (I)

To evaluate eczema severity, a modified scale of BAMSE Eczema Severity Score (BESS) was used. BESS, scale 3-14, was developed and used in the 12-year follow-up,[29] and is based on the answers to three questions. In study I, BESS was modified to BESS(3-12), scale 3-12, since one of the questions had fewer multiple choice answers in the 16-year follow-up than in the 12-year follow-up (Figure 4). The adolescents in study I were classified as having mild (3-7), moderate (8-9) or severe eczema (10-12).

BAMSE Eczema Severity Score (BESS(3-12))		
	Score	**Questionnaire, Multiple choice options**
Disease severity		
Has your sleep been disturbed by itching during the last 12 months?	1	No
	2	Less often than once a week
	3	Once a week or more often
Disease course		
For how long, in total, have you had eczema during the last 12 months?	1	<1 month
	2	1-3 months
	3	4-6 months
	4	>6 months
Extent of body surface involvement		
Where has the itchy rash been located the last 12 months?[a]	1	1 body site
	2	2 body sites
	3	3-4 body sites
	4	5-6 body sites
	5	>6 body sites
Total score	**3-12**	

Figure 4 Description of BESS(3-12) constructed and used in study I.

[a] The adolescents could choose between 14 different specified locations (scalp; face; ears; neck; trunk/back, stomach, shoulders; armpits; extensor surface of arms and legs; body folds of arms and legs; wrists/ankles; hands; buttocks; inside of the thighs; genital area/groin; feet). The number of body sites was categorized.

IgE sensitization (I, III, IV)

Analyses of serum IgE antibodies in blood collected at age 4, 8, and 16 years were performed. Airborne allergens were analyzed with Phadiatop® (dog, cat, horse, birch, timothy, house dust mite (*Dermatophagoides pteronyssinus*), mugwort, and mold (*Cladosporium herbarum*)), and food allergens with fx5® (hen's egg, cow's milk, cod, peanut, soy, and wheat), using the ImmunoCAP System (Thermo Fisher Scientific, Uppsala, Sweden). The results were expressed as positive (≥0.35 kU_A/L) or negative (<0.35 kU_A/L). To be classified as having IgE sensitization in a specific age, a child was required to be positive for Phadiatop and/or fx5 in that age. Sera with Phadiatop or fx5 results of ≥0.35 kU_A/L were subsequently analyzed for IgE antibodies to

the airborne and food allergens listed above, and in addition to *Dermatophagoides farinae* (house dust mite) in the 16-year follow-up. IgE sensitization to a specific allergen was defined as IgE ≥0.35 kU_A/L to that allergen.

In study III, children with IgE sensitization were classified as having monosensitization, oligosensitization or polysensitization. Monosensitization was defined as an IgE level ≥0.35 kU_A/L to a single allergen, or positive for Phadiatop and/or fx5 without reaching ≥0.35 kU_A/L to any of the allergens included in the mixes. Oligosensitization and polysensitization were defined as IgE ≥0.35 kU_A/L to 2-3 allergens and IgE ≥0.35 kU_A/L to ≥4 allergens, respectively.

Filaggrin mutation (III, IV)

DNA was extracted from blood collected at age 8 years (n=2,025), and 16 years (n=2,130). Genotyping was performed for the *FLG* mutations common in Sweden (2282del4, R501X, R2447X).[128] Children with a mutation in any of the positions mentioned above were classified as having a *FLG* mutation. The genotyping in the 8-year follow-up was performed using TaqMan allelic discrimination for R501X and R2447X on the ABI Prism 7500 detection system (Applied Biosystems, CA, USA) and MALDI-TOF (matrix-assisted laser desorption/ionization-time of flight; Sequenom GmbH, Hamburg, Germany) for 2282del4. TaqMan SNP Genotyping Assays for all three mutations were used in the 16-year follow-up (obtained from Applied Biosystems, CA, USA). The analysis successfully performed on blood from the 8-year follow-up (n=1,940) was available for study III. In study IV, successful analyses from both the 8- and the 16-year follow-ups (n=2,748) were accessible.

STATISTICAL METHODS

All statistical calculations were performed with Stata statistical software (release 12.1; StataCorp, College Station, TX, USA).

Confidence intervals (I, II, III, IV)

Background characteristics were expressed as percentage of the total number of individuals observed (I, II, III, IV). To compare the study population with the original cohort, 95% CIs were calculated by applying one-sample t-tests with finite population correction (I, II, III).[129]

Chi2-tests (I, II, III, IV)

To compare two groups, χ2-tests were used for dichotomous variables. P-values less than 0.05 were considered statistically significant.

Logistic regression (II, III, IV)

Logistic regression was used in study II (to investigate the association between dispensed medication for ADHD, depression/anxiety/phobia, epilepsy, migraine and PSE), in study III (to evaluate the association between PSE and mono-/oligo-/polysensitization), and in study IV (to explore the association between exposures in the first 4 years of life and complete remission at school age). First, univariate analyses were performed. In study II, different potential

confounder models were tested. The final model was adjusted for factors included due to prior knowledge, and confounders that changed the OR by >10%. Potential significant effect modification was evaluated for the same covariates (II).

Multivariate prognostic models (IV)

Multivariate models were created in study IV to analyze the possibility for complete remission of PSE (IV). Factors were included if the crude univariate logistic regression was significant or if the factor was chosen to be included a priori, based on literature. Backwards selection was performed, and factors with P >0.15 were excluded from the model. The factors that remained in the model were tested for effect modification, each factor pairwise with all other factors. The likelihood ratio test was used to compare the model with and without interaction terms and was considered significant if P <0.05. The correct classification rate was calculated as the number of correctly classified individuals divided by the total number of individuals.

Generalized estimated equations (III)

To study the longitudinal association between IgE sensitization (any, food and aeroallergens) at 4, 8, and 16 years and PSE, and/or *FLG* mutations, logistic regression models using generalized estimating equations (GEEs) with an unstructured correlation matrix to account for the correlation between repeated outcomes were used (IV). Unstructured correlation was used due to the longitudinal design and the unequal spacing to the follow-up point in time. Potential effect modifiers of the association between PSE and *FLG* mutation, respectively, and IgE sensitization, were investigated using logistic regression for each covariate separately. To analyze if associations between PSE and IgE sensitization outcomes varied with age, an interaction term was added to each model. The models were adjusted for sex and parental allergy, and additional potential confounders were included if the univariate analysis changed the OR more than 10%.

Cluster analysis (III)

In study III, cluster analysis was performed (to explore patterns of specific IgE sensitization). The k-means method with Euclidean distance between the observations was used, since this gave the most stable clusters compared with other methods tested (Jaccard and matching). This analysis was performed separately at age 4, 8, and 16 years. Moreover, 2-, 3-, 4-, and 5-cluster models were tested, and the clusters that maximized the Calinski-Harabasz pseudo-F were selected.[130]

ETHICAL APPROVAL

The BAMSE project has been approved by the regional ethical review board at Karolinska Institutet, Stockholm, Sweden (reference numbers; 93:189, 98-175, 01-478, 02-402, 2007/1634-31, 2010/1474-31/3, 2010/0177-32, and 2014/1804-32). Informed consent was provided by guardians and adolescents. The participants have regularly been informed about procedures, and their right to withdraw from participation at any stage.

4 RESULTS

ECZEMA IN ADOLESCENCE (I)

The 3,108 adolescents with data available for the diagnosing of eczema in adolescence constituted the study population and were comparable with the original cohort regarding background factors (I).

Table 5 Background characteristics of children in the original cohort and study population in study I.

	Original cohort (n=4,089)		Study population (n=3,108)		
Background factors	**n**	**%**	**n**	**%**	**95% CI**
Male	2,065/4,089	50.5	1,529/3,108	**49.2**	**(48.3-50.1)**
Low socioeconomic status[a]	695/4,072	17.1	490/3,097	**15.8**	**(15.2-16.5)**
Exclusive breastfeeding ≥4 months	3,116/3,919	79.5	2,438/3,038	**80.3**	**(79.6-80.9)**
Parental allergy[b]	1,746/4,045	43.2	1,368/3,081	**44.4**	**(43.5-45.3)**
Any parent smoking at baseline[c]	855/4,067	21.0	631/3,090	20.4	(19.7-21.1)
Any parent born outside Scandinavia[d]	543/3,398	16.0	453/2,941	**15.4**	**(14.9-15.9)**
	Mean (range)	**SD**	**Mean (range)**	**SD**	
Age of mother (years)	30.7 (16-46)	4.5	30.8 (16-46)	4.5	(30.7-30.9)
Gestational age (weeks)	39.8 (25-44)	2.0	39.8 (25-44)	2.0	(39.8-39.8)

Confidence intervals created by applying finite population correction factor. Statistically significant differences in bold.

[a]Both parents were blue-collar workers, or one parent blue collar worker and the other parent was a student, housewife, on disability pension, or unemployed.

[b]Mother and/or father with asthma and/or hay fever and/or eczema at baseline.

[c]At least one cigarette per day.

[d]Either parent not born in Sweden, Denmark, Norway or Finland.

Epidemiology (I)

The 12-month prevalence of eczema in adolescence was 9.6% (297 of 3,108). Eczema was significantly more common among girls (197 of 1,579 [12.5%]) than among boys (100 of 1,529 [6.5%]). The 12-month prevalence of asthma and rhinitis was 7.6% and 27.1%, respectively. Of the adolescents who provided blood (n=2,529), 45.9% showed some IgE sensitization. Allergy-related diseases were significantly more common (P <0.001) among children with eczema than children without eczema (Figure 5).

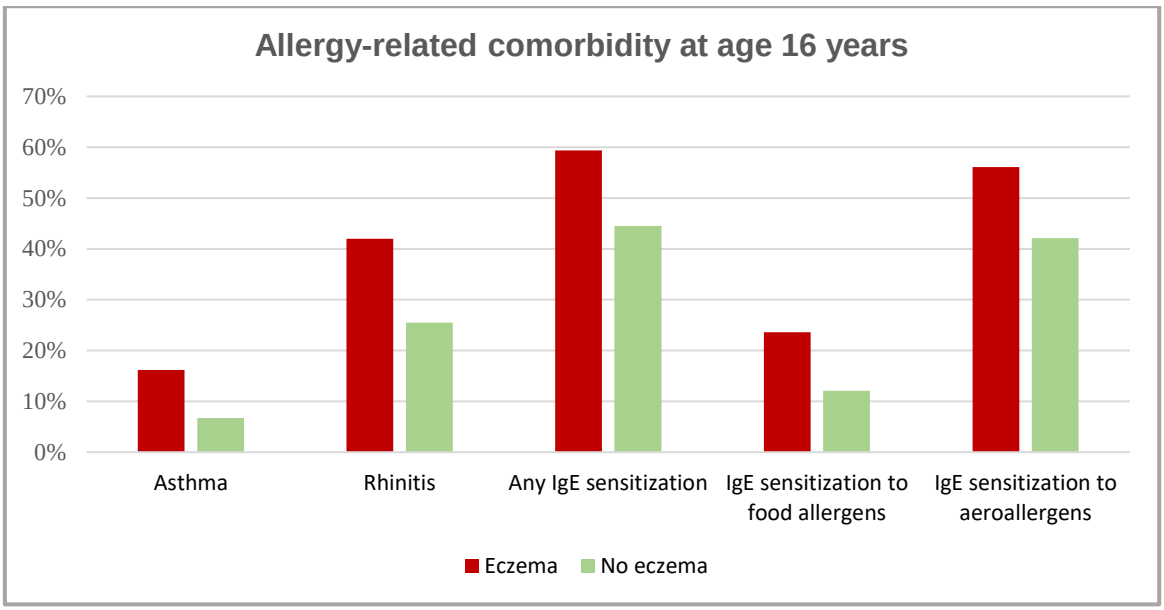

Figure 5 Prevalence of allergy-related comorbidities among adolescents with and without eczema at age 16 years. All comorbidities were significantly more common among adolescents with eczema (P <0.001).

AE vs. non-AE

Data on IgE sensitization was available for 82.8% (n=246) of the adolescents with eczema. Of these, 59.3% had AE (n=146) and 40.7% had non-AE (n=100). AE was significantly more frequent among girls than boys (7.1% vs. 4.3%, P=0.003). Similarly, non-AE was more common in girls than boys (5.8% vs. 2.0%, P <0.001).

Age at onset of eczema (I)

Onset in the first two years of life was prevalent among adolescents with eczema (48.8%). Onset after age 12 years (25.6%) was also common. Onset after age 12 years was more common among girls (P=0.016), while onset in the first year of life was more common among boys (P <0.001). There were no other significant differences between sexes regarding age of onset. The adolescents with onset after age 12 (n=76) were compared with adolescents with onset ≤12 years (n=221) regarding reported symptoms of contact dermatitis, to investigate if contact dermatitis misclassified as eczema could explain the large proportion of onset after age 12 years. There were no significant differences between the groups in reported itchy rash or eczema after contact with metal, hair dye, make-up or personal hygiene products, or latex or rubber.

AE vs. non-AE

Age at onset before age 2 years was significantly more common among adolescents with AE than among adolescents with non-AE (61.6% vs. 30.0%, P<0.001). This difference was still significant when stratifying by sex. Furthermore, onset at age 12 years or later were significantly more common among adolescents with non-AE than AE (48.0% vs. 22.6%, P<0.001), and a comparable pattern was seen when stratified for sex (Table 6).

Table 6 Age at onset among adolescents with eczema based on when eczema was reported (by adolescent or parent) the first time in the BAMSE cohort.

	AE (n=146)		non-AE (n=100)		P-value
Age at onset (years)	n	%	n	%	
Onset before age 1	**61**	**41.8**	**13**	**13.0**	**<0.001**
Onset between age 1 and age 2	29	19.9	17	17.0	0.572
Onset between age 2 and age 4	13	8.9	15	15.0	0.139
Onset between age 4 and age 8	10	6.8	7	7.0	0.963
Onset between age 8 and age 12	10	6.8	8	8.0	0.734
Onset at age 16	**23**	**15.8**	**40**	**40.0**	**<0.001**

Internal missing data ranged between 0 and 6.0%. Individuals with missing data were classified as having no disease for that particular follow-up. Significant differences in bold.

Severity of eczema in adolescence (I)

Based on BESS(3-12), adolescents with eczema were classified as having mild eczema (72.7%), moderate eczema (16.8%) or severe eczema (10.4%).

AE vs. non-AE

Severe eczema was more common in adolescents with AE than in those with non-AE (Figure 6).

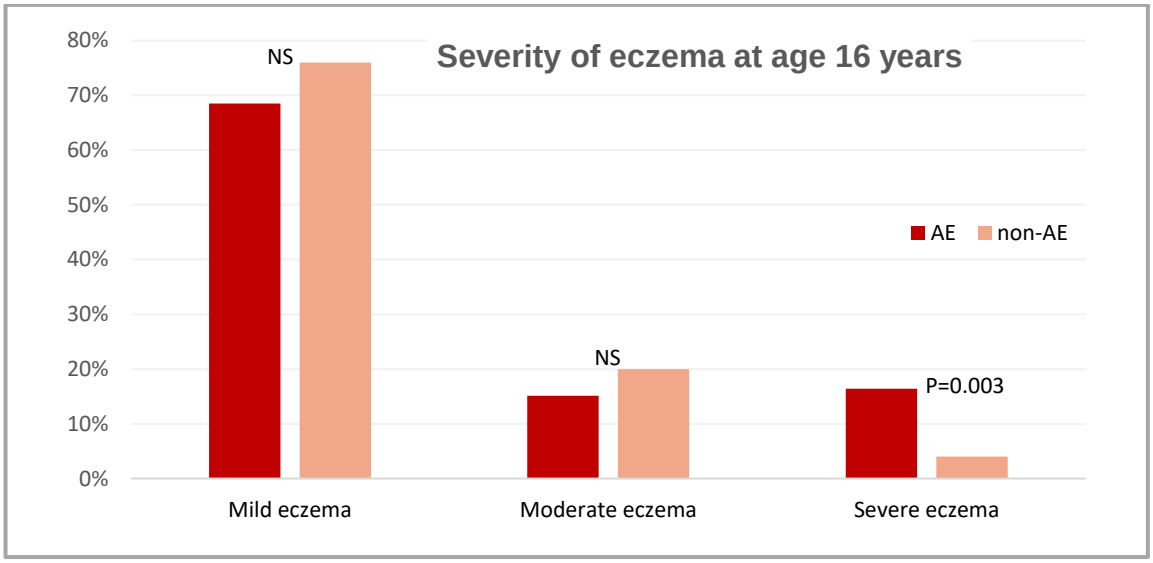

Figure 6 AE and non-AE in relation to eczema severity according to BESS(3-12) at age 16 years (n=246).

Seasonal variation of eczema in adolescence (I)

Eczema was more common in winter than in other seasons (Figure 7). There were no major differences in seasonal variation between AE and non-AE or between sexes.

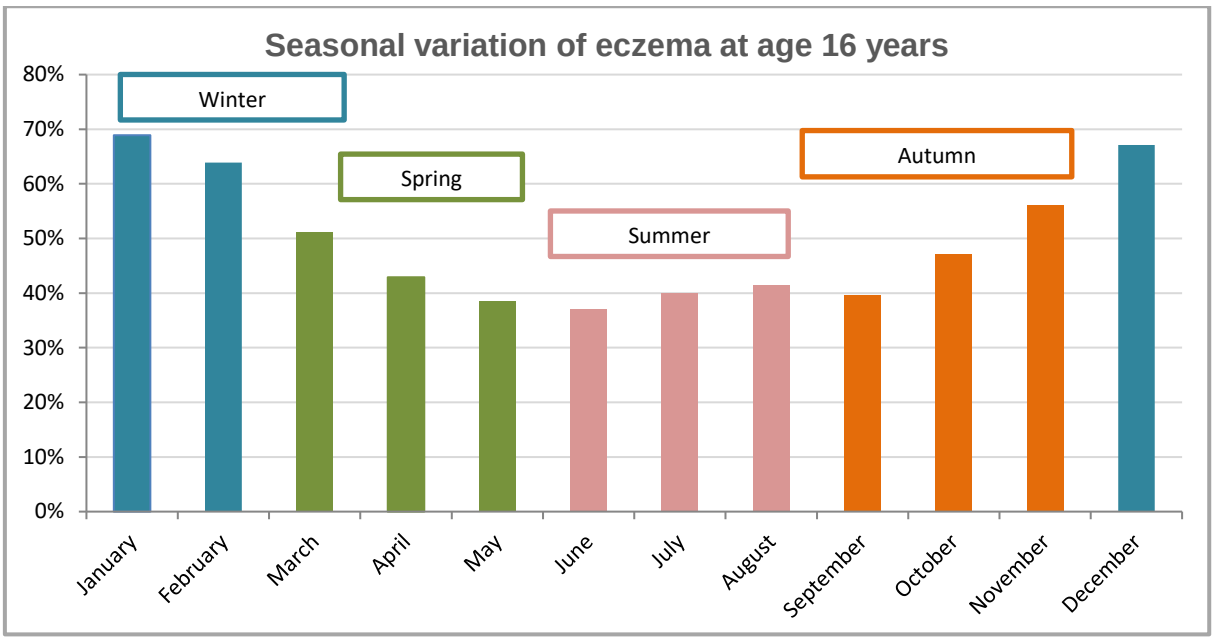

Figure 7 Reported seasonal prevalence of eczema among all adolescents with eczema at age 16 years (n=280). There were 19 adolescents with no data on seasonality.

Location of eczema (I)

Those adolescents who had eczema during the preceding year reported where the eczema had been located. The majority had eczema in 3 locations and only a few reported more than 10 locations. Flexural body areas were by far the most frequently affected (73.4%), Figure 8. More boys than girls reported eczema on extensor surfaces of extremities (47.0% vs. 34.5%, P=0.037). There were no other significant differences between sexes.

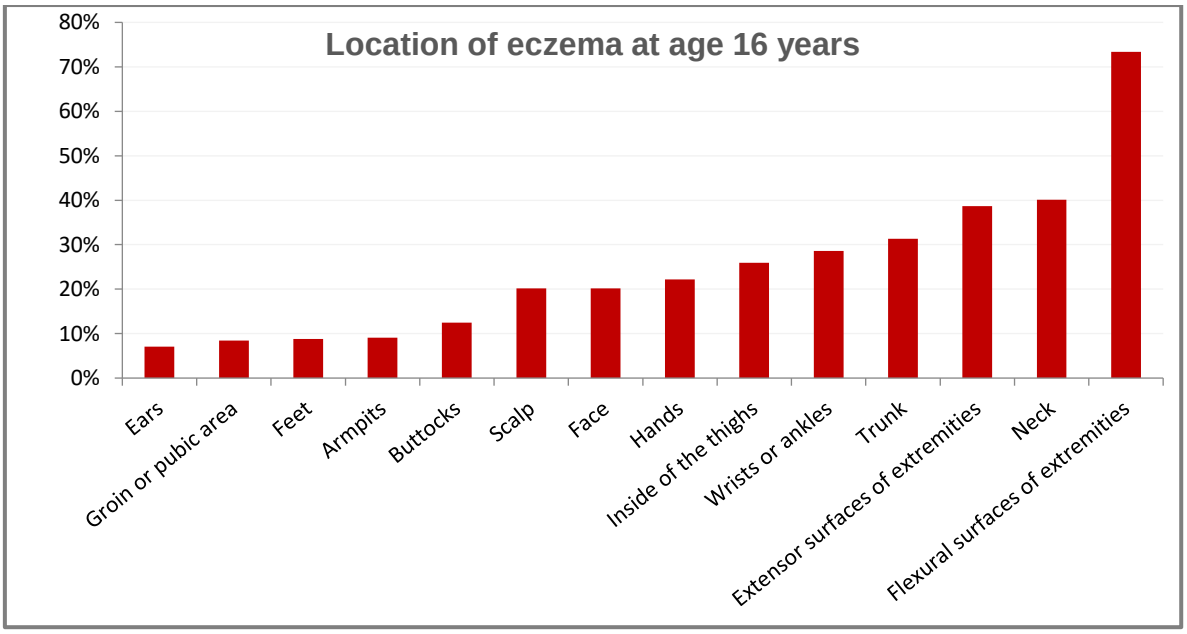

Figure 8 Proportions of adolescents with reported eczema on different body sites within the last year. Each participant could choose between 14 locations, and the adolescents reported a mean of 3.5 (range 1-14) locations each (n=297).

AE vs. non-AE

Eczema located on the ears was more common among adolescents with AE than among those with non-AE (11.0% vs. 3.0%, P=0.022). Adolescents with AE reported eczema on the face and on the inside of the thighs somewhat more often than adolescents with non-AE, but this difference was not significant. Altogether, there was no major difference in location of eczema between adolescents with AE and those with non-AE.

Eczema history among adolescents with eczema (I)

Adolescents with eczema at age 16 years, who had reported eczema in all previous follow-ups in the BAMSE cohort, were classified as having chronic eczema. Chronic eczema affected almost 11% (32 of 297) of the adolescents with eczema and was more common among boys than girls (17.0% vs. 7.6%, P=0.014).

AE vs. non-AE

When comparing adolescents with AE and non-AE at age 16 years, those with AE had significantly higher prevalence of eczema in all preceding follow-ups (at age 1, 2, 4, 8, and 12 years). One-third (32.9%) of adolescents with AE had reported eczema in four or five of the five preceding questionnaires compared with only 13.0% of the adolescents with non-AE. In contrast, 60.0% of adolescents with non-AE had reported eczema only at age 16 years or in one preceding questionnaire, twice as many as adolescents with AE (30.8%). Figure 9 shows history of eczema from birth to adolescence and illustrates the differences between adolescents with AE and non-AE.

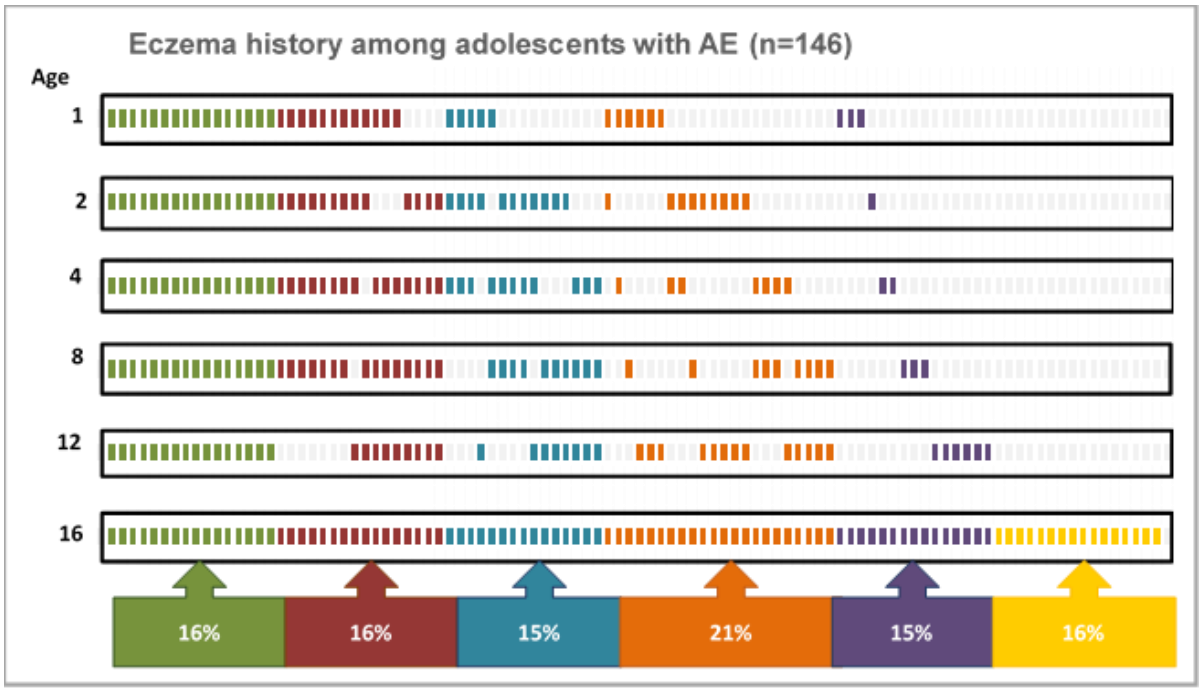

Figure 9:A Eczema history among adolescents with AE. For details, see Figure 9:B.

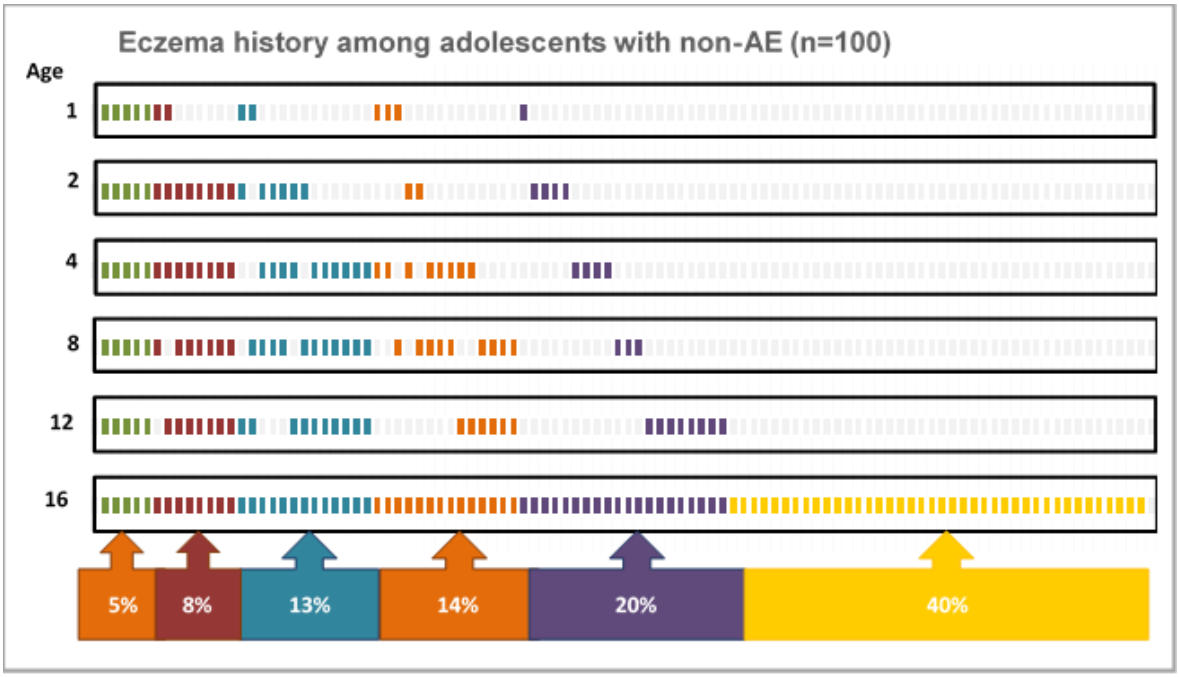

Figure 9:B Eczema history among adolescents with non-AE. Each row contains 100 squares, and each square represent 1% of the adolescents. The course of each percentage can be traced vertically, from bottom to top. Filled boxes represent children with eczema at that age. The different colors illustrate the number of preceding follow-ups (one to five) in which eczema was reported; green for chronic eczema (eczema at five of five follow-ups), red for four of five, blue for three of five, orange for two of five and purple for one of five. Yellow color represent adolescents who reported eczema for the first time at the 16-year follow-up.

Filaggrin mutation in relation to eczema in adolescence (additional data)

Data on *FLG* mutation was available for 2,585 adolescents included in study I, and of them 6.9% (n=178) had a *FLG* mutation. Adolescents with eczema more often had a *FLG* mutation than those without eczema (13.0% vs. 6.2%, P <0.001). The likelihood of having a *FLG* mutation did not differ between adolescents with AE or non-AE (14.5% vs. 12.0%, P=0.581).

CONSEQUENCES OF PRESCHOOL ECZEMA LATER IN CHILDHOOD AND ADOLESCENCE (II, III)

In studies II, III and IV, different aspects and consequences of PSE were evaluated. The prevalence of PSE varied with the different study populations and ranged between 32.7% and 34.6%. The 12-month prevalence at age 1, 2, and 4 years was 15.1% (594 of 3,329), 19.0% (703 of 3,839) and 20.7% (769 of 3,721) , respectively (additional data).

IgE sensitization (III)

A history of PSE was associated with IgE sensitization from age 4 to 16 years (overall adjOR 2.39, 95% CI: 2.00-2.63). A similar result was found when analyzing IgE sensitization to food (adjOR 2.05, 95% CI: 1.74-2.42) and aeroallergens (adjOR 2.51, 95% CI:2.18-2.92) separately. The highest point estimate was the association between PSE and aeroallergens at age 4 years (Figure 10).

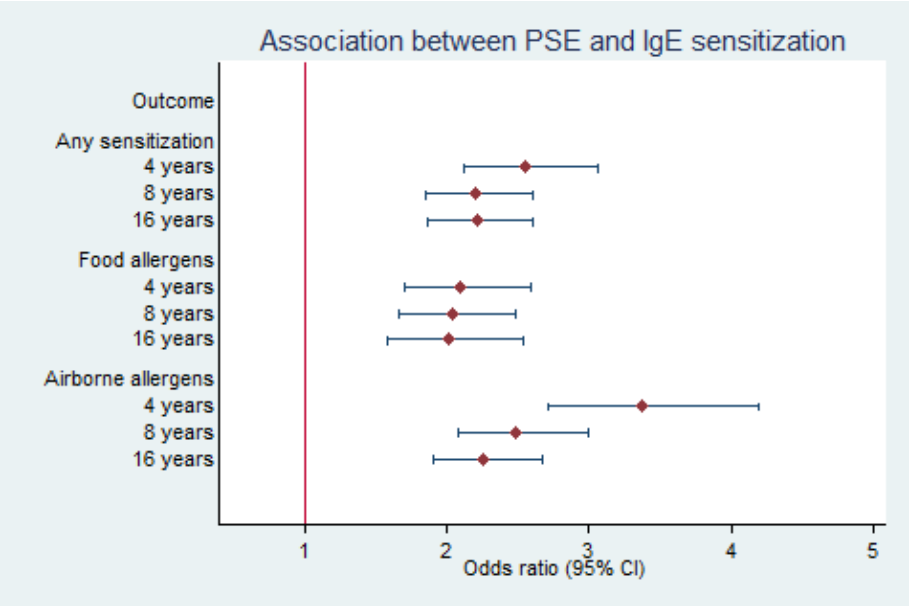

Figure 10 Association between PSE and IgE sensitization at age 4, 8, and 16 years. Children with data on PSE and who provided blood at least once were included (n=3,201). A logistic regression model with GEE adjusted for sex and parental allergy was used.

Children with PSE and sleep disturbance (here as a marker for more severe PSE) had higher point estimates than all children with PSE and those with persistent PSE had significantly higher point estimates (Table 7).

Table 7 IgE sensitization at age 4, 8, and 16 years in relation to preschool eczema (PSE), severe PSE, persistent PSE and PSE in combination with *FLG* mutation.

	PSE (n=1107)		Severe PSE[b] (n=381)		Persistent PSE[c] (n=214)		PSE and *FLG* mutation[d] (n=67)	
	adjOR[e]	95% CI	adjOR[e]	95% CI	adjOR[e]	95% CI	adjOR[e]	95% CI
Any IgE sensitization[a]								
4	2.55	2.12-3.06	3.87	3.01-4.98	6.07	4.40-8.37	2.74	1.53-4.88
8	2.20	1.85-2.60	3.08	2.41-3.94	5.04	3.62-7.02	2.06	1.24-3.43
16	2.21	1.87-2.61	3.12	2.39-4.06	4.99	3.41-7.29	2.52	1.44-4.42
Foods								
4	2.10	1.70-2.59	2.96	2.23-3.91	4.34	3.11-6.06	2.30	1.20-4.40
8	2.04	1.67-2.49	3.05	2.33-3.98	4.77	3.45-6.60	2.80	1.64-4.79
16	2.01	1.59-2.54	3.00	2.20-4.08	5.30	3.71-7.56	2.56	1.32-4.95
Airborne								
4	3.37	2.71-4.19	5.54	4.19-7.34	9.28	6.64-12.97	3.52	1.84-6.72
8	2.49	2.08-2.99	3.47	2.69-4.48	5.90	4.27-8.16	2.02	1.18-3.46
16	2.26	1.91-2.68	3.33	2.56-4.33	5.00	3.45-7.25	2.74	1.56-4.82

[a]Children with the result ≥0.35 kU_A/L were classified as having IgE sensitization, [b]Children with sleep disturbance in combination with eczema at 1, 2, and/or 4 years of age. Children with PSE without sleep disturbance and missing data at one or two ages were excluded, children without PSE (n=2,094) were the reference, [c]Children with eczema at 1, 2, and 4 years of age. Children without PSE (n=2,094) were the reference, [d]Children without PSE and *FLG* mutation (n=1,157) were the reference, [e]Logistic regression model using generalized estimating equations (GEEs), adjusted for sex and heredity. Effect modification was tested for sex, heredity, breastfeeding, parental smoking during infancy, mother's age, socio-economy and filaggrin mutation.

In addition, PSE was associated with incident IgE sensitization at age 8 years (adjOR 1.44, 95% CI: 1.08-1.91) and age 16 years (adjOR 1.48, 95% CI: 1.08-2.03). *FLG* mutation was not a significant effect modifier of the effect of PSE on IgE sensitization, and adjustment for *FLG* mutation did not change the ORs. Preschool asthma and preschool rhinitis were both significant effect modifiers of the effect of PSE on IgE sensitization. Therefore, children without asthma and rhinitis before age 4 were analyzed separately. The association between PSE and IgE sensitization up to age 16 years was still significant (overall adjOR 1.85, 95% CI: 1.57-2.19).

Preschool eczema and patterns of IgE sensitization

As a second step, children with any IgE sensitization were selected at each age (4, 8, and 16 years) and analyzed to explore if PSE was associated with specific patterns of IgE sensitization. Sensitized children with a history of PSE displayed a pattern of polysensitization in all ages. Sensitized children with no history of PSE had a pattern dominated by monosensitization (Figure 11).

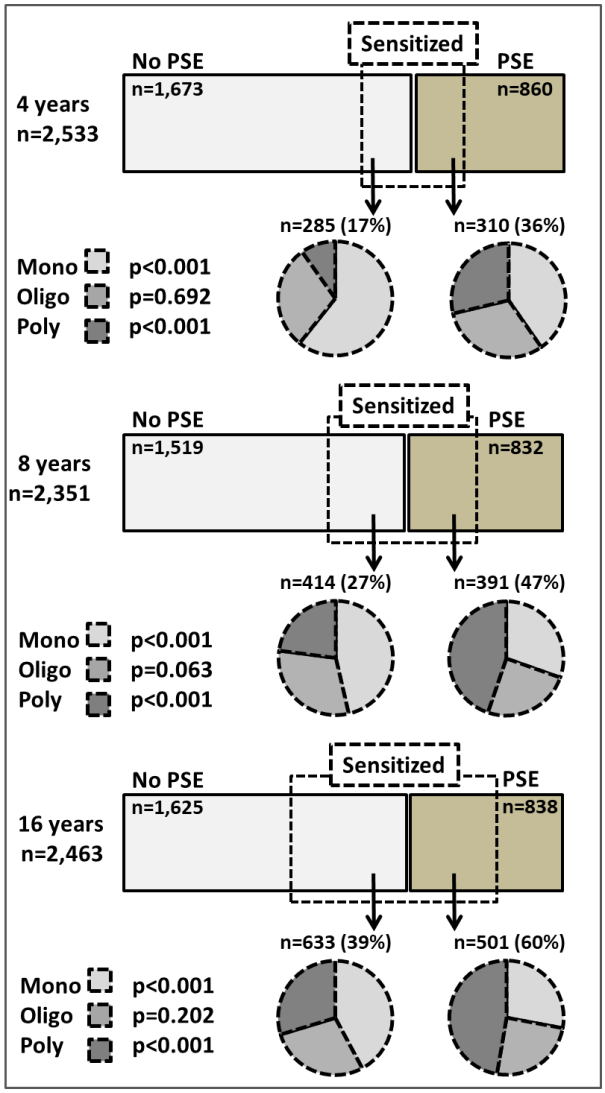

Figure 11 Proportions of mono-, oligo-, and polysensitization among IgE-sensitized children in the BAMSE cohort with and without PSE at age 4, 8, and 16 years.

Furthermore, sensitized children with PSE demonstrated a higher prevalence of IgE sensitization to almost all allergens than sensitized children without PSE (Figure 12). To analyze further, a data-driven approach was applied. Cluster analysis including children with any sensitization at each respective age (4 years, 8 years and 16 years) was used. In the analyses, IgE sensitization to each of the 14 analyzed specific allergens was included as a dichotomous variable (positive or negative). The children were stratified for PSE to analyze whether children with PSE would display a different pattern than children without PSE. The 2-cluster model was the most stable model among children with PSE. Among sensitized children without PSE, no stable clusters were found. Therefore, the sensitization patterns between sensitized children with and without PSE could not be compared. Instead, a cluster analysis including all children with IgE sensitization at 4, 8, and

16 years was performed. Altogether, the 2-cluster model was the most stable with the highest Calinski-Harabsz pseudo-F value at all ages. One cluster was larger and characterized by mono- and oligosensitization. The other, smaller cluster was characterized by polysensitization. PSE was significantly more frequent in the cluster with polysensitization at all ages (Table 8). The data-driven approach did not provide any additional patterns of IgE sensitization associated with PSE.

Table 8 Cluster analysis on IgE sensitization at 4, 8, and 16 years. Descriptive analysis in 2-cluster model among children with any IgE sensitization at each respective age.

	Cluster 1	Cluster 2	All	P-value	Missing
2-cluster model at 4 years	n=506	n=89	n=595		
Preschool eczema	**47.0%**	**80.9%**	**52.1%**	**<0.001**	**0**
FLG mutation	7.8%	8.3%	7.9%	0.89	215
Male sex	**52.8%**	**68.5%**	**55.1%**	**0.006**	**0**
Parental allergy[a]	49.4%	54.0%	50.1%	0.43	6
Parental smoking[b]	**21.0%**	**32.2%**	**22.6%**	**0.021**	**3**
Exclusive breastfeeding ≥4 months	78.0%	78.4%	78.0%	0.93	3
Monosenstization	**58.9%**	**0.0%**	**50.1%**	**<0.001**	**0**
Oligosensitization	**35.6%**	**0.0%**	**30.3%**	**<0.001**	**0**
Polysensitization	**5.5%**	**100.0%**	**19.7%**	**<0.001**	**0**
2-cluster model at 8 years	n=564	n=241	n=805		
Preschool eczema	**41.1%**	**66.0%**	**48.6%**	**<0.001**	**0**
FLG mutation	6.7%	9.6%	7.5%	0.20	141
Male sex	52.5%	57.3%	53.9%	0.21	0
Parental allergy[a]	**48.0%**	**61.8%**	**52.2%**	**<0.001**	**4**
Parental smoking[b]	20.8%	20.2%	20.6%	0.84	5
Exclusive breastfeeding ≥4 months	78.6%	80.3%	79.2%	0.59	4
Monosenstization	**55.1%**	**0.0%**	**38.6%**	**<0.001**	**0**
Oligosensitization	**39.7%**	**0.0%**	**27.8%**	**<0.001**	**0**
Polysensitization	**5.1%**	**100.0%**	**33.5%**	**<0.001**	**0**
2-cluster model at 16 years	n=663	n=471	n=1134		
Preschool eczema	**38.8%**	**54.6%**	**44.2%**	**<0.001**	**0**
FLG mutation	8.4%	6.1%	7.4%	0.22	389
Male sex	53.2%	54.8%	53.9%	0.61	0
Parental allergy[a]	**48.0%**	**58.2%**	**52.2%**	**0.001**	**11**
Parental smoking[b]	21.1%	18.3%	19.9%	0.20	6
Exclusive breastfeeding ≥4 months	79.2%	77.9%	78.7%	0.17	9
Monosenstization	**61.4%**	**0.0%**	**35.9%**	**<0.001**	**0**
Oligosensitization	**35.6%**	**14.0%**	**26.6%**	**<0.001**	**0**
Polysensitization	**3.0%**	**86.0%**	**37.5%**	**<0.001**	**0**

[a]Mother and/or father with doctor's diagnosis of asthma and/or hay fever and/or eczema (contact allergy among parents is excluded) at baseline, [b]Any of the parents smoked at least one cigarette per day at child´s birth. Significant differences in bold.

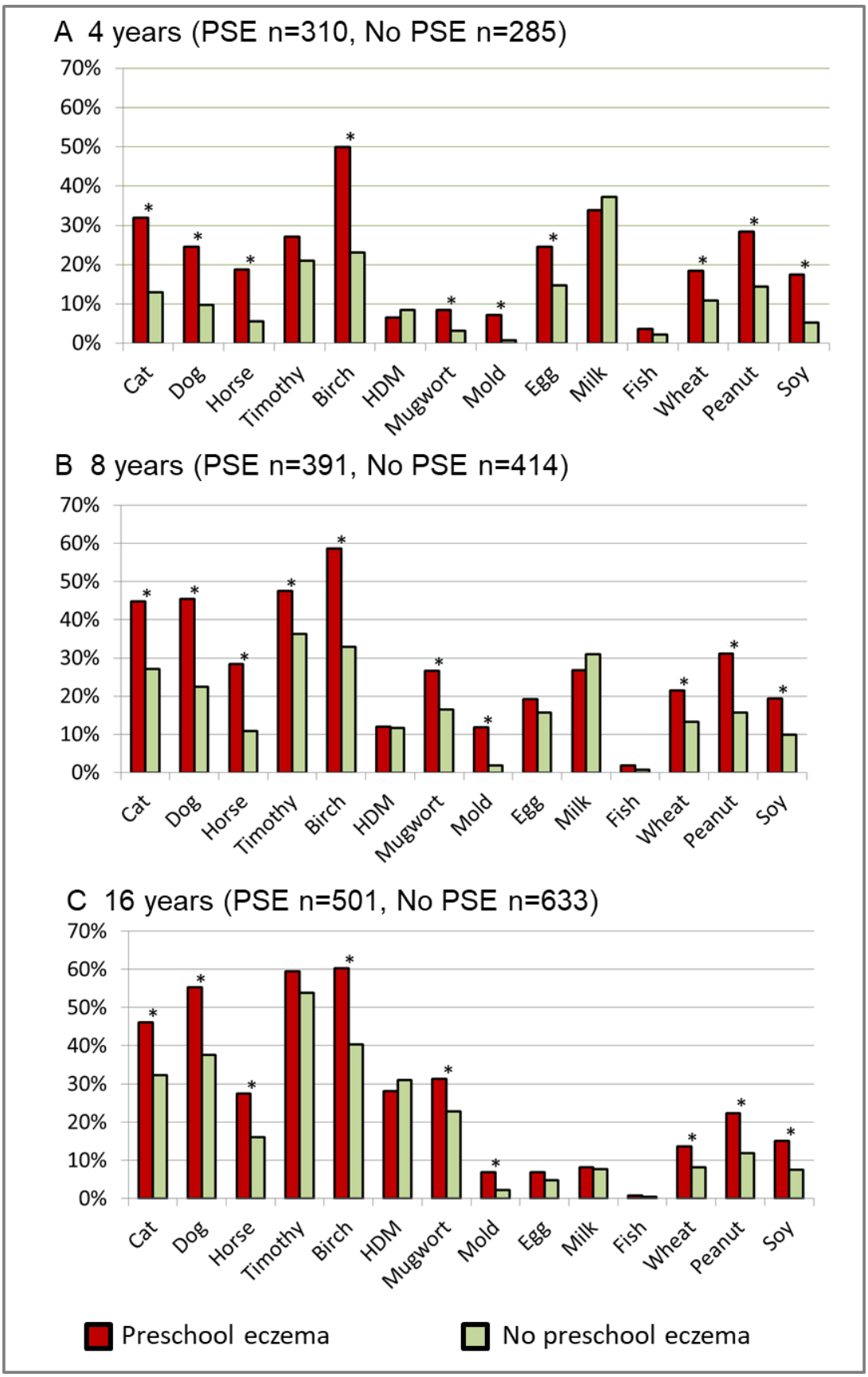

Figure 12 Pattern of IgE sensitization at age 4 (A), 8 (B), and 16 (C) years stratified by PSE. Bars represent the proportions of children with specific IgE ≥0.35 kU_A/L for each allergen. Children with any IgE sensitization and complete data on PSE and specific IgE measurement at each age were included. *Significant differences.

ADHD (II)

There were minor differences in background characteristics between the study population of study II (n=3,606) and the original cohort (n=4,089). Assuming a prevalence of ADHD medication of 5% among children without PSE and a two-sided significance level of 0.05, the study II had 80% power to detect an OR of 1.51.

Table 9 Background characteristics for children in the original cohort, the study population and the subpopulation (II).

Background factors	Original cohort		Study population (n=3,606)		Subpopulation[a] (n=2,736)	
	n=4,089	%	%	(95% CI)	%	(95% CI)
Male	2,065/4,089	50.5	50.6	(50.1-51.2)	49.9	(48.8-50.9)
Low socioeconomic status[b]	695/4,072	17.1	**16.4**	**(16.0-16.9)**	**14.8**	**(14.0-15.6)**
Exclusive breastfeeding ≥4 months	3,116/3,919	79.5	**79.9**	**(79.6-80.3)**	**81.1**	**(80.3-81.9)**
Parental allergy[c]	1,746/4,045	43.2	43.6	(43.1-44.2)	**45.0**	**(43.9-46.1)**
Any parent smoking at baseline[d]	855/4,067	21.0	**20.5**	**(20.0-20.9)**	**19.7**	**(18.9-20.6)**
Any parent born outside Scandinavia[e]	543/3,398	16.0	**15.2**	**(14.9-15.5)**	**14.3**	**(13.8-14.9)**
Young mother (<25 y)	319/4,088	7.8	**7.4**	**(7.1-7.7)**	**6.5**	**(6.0-7.0)**
ADHD medication at school age[f]	184/4,089	4.5	4.5	(4.3-4.7)	**3.7**	**(3.3-4.1)**

Confidence intervals created by applying one-sample t-tests with a finite population correction factor. Statistically significant differences in bold, [a]Including children who participated in all follow-ups up to age 16 years, [b]Both parents were blue-collar workers, or one parent blue-collar worker and the other parent was a student, housewife, on disability pension, or unemployed, [c]Mother and/or father with asthma and/or hay fever and/or eczema at baseline, [d]At least one cigarette per day
[e]Either parent not born in Sweden, Denmark, Norway or Finland, [f]Ever use of ADHD medication at age 10-18 years of age (range 8.6-19.9).

The prevalence of ADHD medication at school age was 4.5% (n=162) in the study population, and 3.7% (n=101) in the subpopulation of children who participated in all follow-ups. The group that had used ADHD medication was characterized by male sex (69.8% vs. 49.7%, P <0.001), young mother (15.4% vs. 7.0%, P<0.001), parental smoking (28.8% vs. 20.1%, P= 0.008), low socio-economy (28.0% vs. 15.9%, P <0.001), and exclusive breastfeeding less than 4 months (27.2% vs. 19.7%, P=0.02).

The prevalence of PSE was 32.7%, and 25.2% had eczema before age 2 years (infantile eczema). In the subpopulation, 41.2% (n=1,126) had eczema ever, up to age 16 years. Of these, 434 had transient eczema, 440 had persistent eczema and 252 had eczema with onset during school age.

Eczema in relation to ADHD medication at school age

PSE was not associated with ADHD medication, either in the crude analysis (OR 1.16, 95% CI: 0.83-1.61) or the analysis adjusted for sex, exclusive breastfeeding ≥4 months, parental smoking, and socioeconomy (adjOR 1.12, 95% CI: 0.80-1.56). Furthermore, PSE with sleep

disturbance (proxy for severe PSE) was not associated with ADHD medication (adjOR 1.29, 95% CI 0.80-2.08), neither was reported doctor's diagnosis of PSE (adjOR 1.07, 95% CI 0.73-1.55). In addition (not included in study II), persistent PSE tended to be associated with ADHD medication, but not significantly (adjOR 1.69, 95% CI: 0.99-2.89). Stratification by sex did not show any differences between boys and girls.

Similarly, infantile eczema (adjOR 1.31, 95% CI: 0.93-1.86), reported doctor's diagnosis of infantile eczema (adjOR1.14, 95% CI: 0.77-1.70), eczema at school age (adjOR 1.16, 95% CI: 0.74-1.83), or eczema ever up to age 16 years (Table 10) were not associated with ADHD medication. Altogether, there was no significant association between PSE or eczema at other ages up to age 16 years, and ADHD medication at school age.

Table 10 Association between eczema ever up to 16 years, and ADHD medication (any time at 10-18 years of age).

Eczema ever up to 16[a]	**ADHD medication at school age**				
	Total	Cases		Crude OR	Adjusted OR[b,c]
	n=2,736	n=101	%	OR (95% CI)	OR (95% CI)
No eczema (ref)	1,610	57	3.5	1	1
Eczema	1,126	44	3.9	1.11 (0.74-1.65)	1.09 (0.72-1.64)
Transient eczema[d]	434	15	3.5	0.98 (0.55-1.74)	0.99 (0.55-1.78)
Eczema with onset at school age[e]	252	7	2.8	0.78 (0.35-1.73)	0.87 (0.39-1.93)
Persistent eczema[f]	440	22	5.0	1.43 (0.87-2.37)	1.28 (0.75-2.16)

The analysis was performed among children in the BAMSE cohort who participated in all follow-ups, n=2,736, [a]Eczema at 1, 2, 4, 8, 12, and/or 16y, [b]Adjusted for background variables; sex, breastfeeding, parental smoking, socio-economy, [c]There were 0-15 missing values among background variables, n=2,714 [d]Eczema at 1, 2, and/or 4y and no eczema at 8, 12, or 16y, [e]Eczema at 8, 12, and/or 16y and no eczema at 1, 2 or 4y, [f]Eczema at 1, 2, and/or 4y and eczema at 8, 12, and/or 16y.

Depression/anxiety/phobia, migraine, epilepsy (II)

A history of PSE was not associated with use of antidepressants, antiepileptic drugs, or migraine drugs at school age (Table 11), neither was PSE with sleep disturbance (severe PSE).

Table 11 Association between preschool eczema and use of drugs for CNS-associated disorders at school age (10-18 years of age).

Prescribed medication	Children with eczema n=1,178		Children without eczema n=2,428		Crude OR	Adjusted OR[a,b]
	n	%	n	%	OR (95% CI)	OR (95% CI)
Antidepressants	69	5.9	168	6.9	0.84 (0.63-1.12)	0.83 (0.62-1.11)
Migraine drugs	27	2.3	48	2.0	1.16 (0.72-1.87)	1.05 (0.64-1.72)
Antiepileptics	20	1.7	38	1.6	1.09 (0.63-1.88)	1.05 (0.60-1.84)

Children in the BAMSE cohort whose parents participated in the follow-up and provided information on eczema at 1, 2 and 4, years of age, constituted the study population, n=3,606.
[a]Adjusted for background variables; sex, exclusive breastfeeding <4 months, parental smoking, socio-economy.
[b]There were 0-19 missing values among background variables, n=3,573.

NATURAL COURSE OF PRESCHOOL ECZEMA UP TO AGE 16 YEARS (IV)

The prevalence of PSE among children in the BAMSE cohort was 34.4% (1,272 of 3,700). Of these, the 889 children who participated in all follow-ups up to age 16 years constituted the study population in study IV. Onset before age 1 year was most common (46.1%), followed by onset between age 1 year and 2 years (31.7%), and onset between 2 years and 4 years (22.2%). Moreover, 18.7% (n=166) of children with PSE had persistent PSE (eczema at age 1, 2, and 4 years) and 33.2% (n=295) had PSE with sleep disturbance.

At school age, half of the children with PSE (50.8%) were in complete remission. Persistent eczema at school age was found among 8.2%, and 40.9% had eczema in one or two follow-ups (intermittent eczema at school age), Figure 13. Remission at age 16 years (no eczema at 16) was reported by 82.2% of the adolescents with a history of PSE.

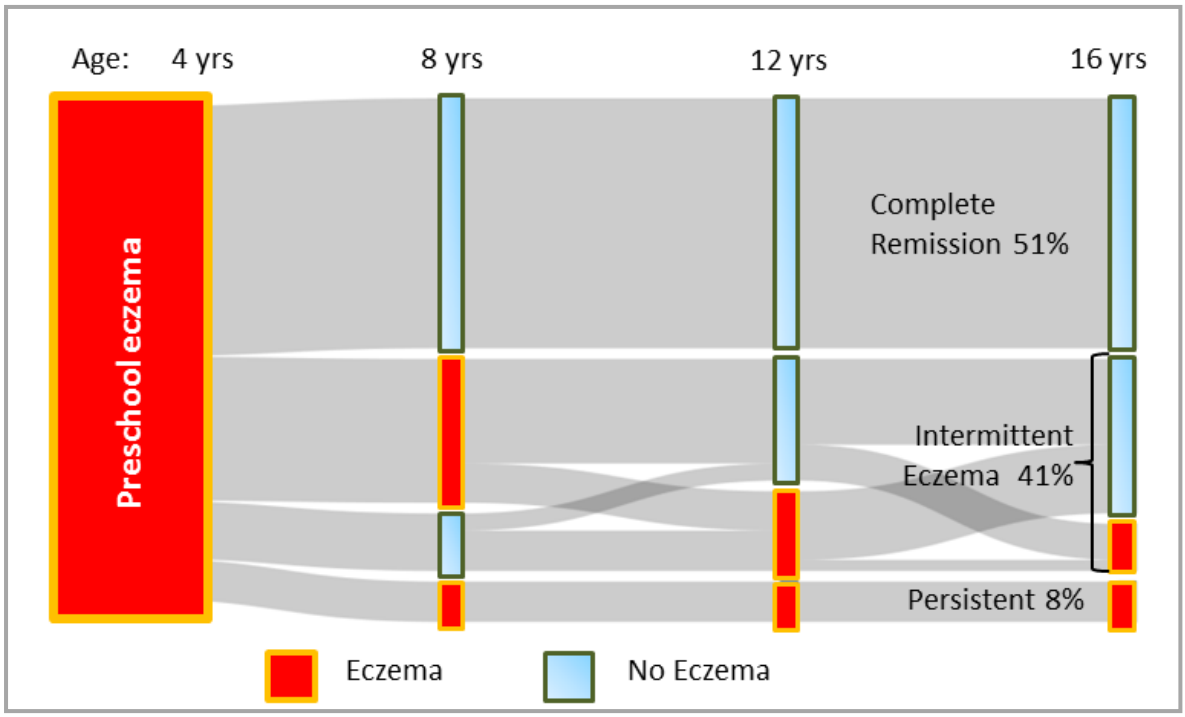

Figure 13 The course of eczema up to age 16 years among children with preschool eczema (n=889) in the BAMSE cohort.

Complete remission at school age was most common among children with onset before age 1 year (those with persistent eczema excluded), Table 12.

Table 12 The course of different phenotypes of preschool eczema[a] up to age 16 years (n=889).

	Complete remission[b]			Intermittent eczema at school age[c]			Persistent eczema at school age[d]		
PSE	n	%	95% CI	n	%	95% CI	n	%	95% CI
All (n=889)	452	50.8	47.6–54.1	364	40.9	37.7–44.2	73	8.2	6.4–10.0
Persistent[e]	39	23.5	17.0–30.0	95	57.2	49.6–64.8	32	19.3	13.2–25.3
Onset before age 1[f]	162	66.4	60.4–72.4	76	31.1	25.3–37.0	6	2.5	0.5–4.4
Onset between age 1 and 2[g]	147	52.1	46.3–58.0	114	40.4	34.7–46.2	21	7.4	4.4–10.5
Onset between age 2 and 4[h]	104	52.8	45.8–59.8	79	40.1	33.2–47.0	14	7.1	3.5–10.7

[a]Preschool eczema (PSE): Eczema at 1, 2, and/or 4 years (n=889).

[b]Complete remission: No eczema at 8, 12, and 16 years.

[c]Intermittent eczema: Eczema at one or two follow-ups at 8, 12, and/or 16 years.

[d]Persistent eczema: Eczema at 8, 12, and 16 years.

[e]Persistent PSE: Eczema at 1, 2, and 4 years (n=166).

[f]Children with onset during the first year of life; children with persistent PSE were excluded (n=244).

[g]Onset between age 1 year and age 2 years (n=282).

[h]Onset between age 2 years and age 4 years (n=197).

FACTORS OF IMPORTANCE FOR REMISSION OF PRESCHOOL ECZEMA (IV)

Exposures in the first 4 years of life of possible importance for remission of PSE were explored in relation to complete remission of PSE. Persistent PSE, PSE with sleep disturbance, *FLG* mutation, parental smoking, parental allergy, IgE sensitization to food and/or aeroallergens, and preschool rhinitis were all inversely associated with complete remission at school age. In contrast, overweight at age 4 years and exclusive breastfeeding ≥4 months were positively associated with complete remission (Table 13).

Table 13 Association between risk and protective factors in the first 4 years of life and complete remission of preschool eczema (PSE) at age 8, 12, and 16 years.

	Total		Complete remission of PSE			
Exposure	n	%	n	%	OR	95% CI
All children with PSE[a]	889	100.0	452	50.8		
Questionnaire data						
Male	434/889	48.8	234	53.9	1.27	0.98–1.66
Low birth weight	24/889	2.7	13	54.2	1.15	0.51–2.59
Preterm birth	35/889	3.9	19	54.3	1.15	0.59–2.28
Young mother	59/889	6.6	31	52.5	1.08	0.63–1.83
Parent born outside of Scandinavia	132/884	14.9	63	47.7	0.86	0.59–1.25
Older sibling in household	425/889	47.8	203	47.8	0.79	0.61–1.03
Low socio-economy	139/886	15.7	72	51.8	1.04	0.73–1.50
Parental smoking	184/881	20.9	81	44.0	**0.70**	**0.51–0.97**
Exclusive breastfeeding ≥4 months	707/878	80.5	371	52.5	**1.41**	**1.01–1.98**
Parental allergy	478/885	54.0	225	47.1	**0.73**	**0.56–0.95**
Persistent PSE	166/889	18.7	39	23.5	**0.23**	**0.16–0.34**
PSE with sleep disturbance[b]	295/889	33.2	112	38.0	**0.46**	**0.34–0.61**
Preschool asthma	141/862	16.4	67	47.5	0.84	0.59–1.21
Preschool rhinitis	204/842	24.2	85	41.7	**0.63**	**0.46–0.87**
Data based on clinical and laboratory examinations						
FLG mutation[c]	78/764	10.2	30	38.5	**0.58**	**0.36–0.93**
IgE sensitization to aeroallergens	188/670	28.1	77	41.0	**0.62**	**0.44–0.87**
IgE sensitization to food allergens	157/671	23.4	60	38.2	**0.55**	**0.38–0.79**
Overweight at age 4 years	119/763	15.6	71	59.7	**1.53**	**1.03–2.27**

Odds ratio (OR) and 95% confidence intervals (CI) calculated with crude univariate logistic regression. Significant differences in bold. [a]Preschool eczema (PSE); eczema at age 1, 2, and/or 4 years, [b]Eczema and sleep disturbance due to itch at age 1, 2, and/or 4 years, [c]Children with a mutation in any of the positions 2282del4, R501X or R2447X were classified as having a filaggrin (*FLG)* mutation.

Significant factors from the univariate analyses, and factors of possible importance based on literature (asthma, sex, socio-economy, and older sibling in household) were included in a multivariate prognostic model.

First, factors based on questionnaire data were analyzed and significant factors are shown in Table 14, Prognostic model 1. The following factors were excluded from Prognostic model 1: preschool asthma (P=0.79), low socio-economy (P=0.52), preschool rhinitis (P=0.43), and older sibling in household (P=0.20). To analyze if the association between exclusive breastfeeding ≥4 months and complete remission was affected by disease modification of exposure, we restricted the analysis by excluding children with their first symptom of eczema during exclusive breastfeeding in the first 4 months of life. The multivariate model did not change following this exclusion, and the point estimates in the full model and the restricted model were comparable.

In the same manner, Prognostic model 2 including children with data on IgE sensitization and *FLG* mutation was created. All factors explored in Prognostic model 1 were included, as was additional data from the clinical and laboratory examination. From this new multivariate model, the following factors were excluded: preschool asthma (P=0.92), overweight at age 4 years (P=0.78), low socio-economy (P=0.73), preschool rhinitis (P=0.57), IgE sensitization to aeroallergens at age 4 years (P=0.81), older sibling in household (P=0.47) exclusive breastfeeding ≥4 months (P=0.16) and parental allergy (P=0.19). The point estimates in Prognostic model 2 were comparable with and without inclusion of exclusive breastfeeding ≥4 months and parental allergy.

Table 14 Multivariate model of prognostic factors for complete remission of preschool eczema (PSE).

Prognostic model 1: Questionnaire data (n=866)			
	OR	95% CI	P value
Persistent PSE	0.27	0.18–0.41	<0.001
PSE with sleep disturbance	0.59	0.43–0.81	0.001
Male	1.37	1.03–1.82	0.029
Parental allergy	0.73	0.55–0.96	0.026
Parental smoking	0.70	0.50–0.99	0.045
Exclusive breastfeeding ≥4 months	1.44	1.01–2.05	0.046
Prognostic model 2: Data based on questionnaires and laboratory examinations (n=604)			
	OR	95% CI	P value
Persistent PSE	0.24	0.15–0.40	<0.001
PSE with sleep disturbance	0.61	0.42–0.90	0.012
Filaggrin *(FLG)* mutation	0.47	0.26–0.85	0.012
Male	1.50	1.06–2.12	0.021
Parental smoking	0.66	0.42–1.02	0.063
IgE sensitization to food allergens	0.69	0.45–1.05	0.086

Models created with multivariate logistic regression. Factors with a P value >0.15 were excluded, backwards selection.

The developed Prognostic model 1 exhibited sensitivity of 78%, specificity of 49%, positive predictive value (PPV) of 61% and negative predictive value (NPV) of 68%. The efficacy of the prognostic model (correct classification rate) was 63%. The corresponding results for Prognostic model 2 were: sensitivity 75%, specificity 54%, PPV 62%, NPV 69%, and efficacy 65%.

Absolute risk for complete remission

Persistent PSE, PSE with sleep disturbance, female sex, parental allergy, parental smoking, exclusive breastfeeding <4 months and *FLG* mutation were all significantly inversely associated with complete remission of PSE, based on Prognostic model 1 and/or Prognostic model 2. In the study population (IV), none of the participants had all seven risk factors. The probability for complete remission was 68% among children with 0-1 factors (n=273), 49% among children with 2-3 factors (n=475), and 25% among children with 4-6 factors (n=141).

Boys without any of the above listed factors had a probability of 71% to be in complete remission at school age, and the corresponding probability for girls was 60%.

CONSEQUENCES OF FILAGGRIN MUTATION (III, IV)

The *FLG* analyses performed on blood collected at the 8-year follow-up had a success rate of 95.8% (1,940 of 2,025), and were used in study III. Of these, 1,890 children were included in the study population (III). Additional analyses of blood collected at the 16-year follow-up were performed successfully in 99.8% of samples (2,126 of 2,130). In study IV, results from both the 8- and the 16-year follow-ups were used and the combined success rate was 98.5% (764 of 776) in the study population (IV).

FLG mutation in relation to preschool eczema (III, IV)

Among the 1,890 children with data on *FLG* mutation in study III, 7.3% (n=137) had any *FLG* mutation. Approximately half of them (48.9%) had PSE. *FLG* mutation was more common among children with PSE than children without PSE (10.1% vs. 5.7%, P <0.001).

When performing study IV, data on *FLG* mutation was available for 2,748 in the BAMSE cohort. In total, 7.0% (n=191) had any *FLG* mutation. Similarly, the prevalence of *FLG* mutation was 7.0% (187 of 2,656) among children with data on PSE. As in study III, *FLG* mutation was more common among children with PSE than children without PSE (10.2% vs. 5.4%, P <0.001). Children with *FLG* mutation more often developed PSE than children without *FLG* mutation (49.2% vs. 33.0%, P <0.001) (additional data).

FLG mutation in relation to IgE sensitization (III)

Having a *FLG* mutation was not associated with IgE sensitization at age 4, 8, or 16 years (Figure 14). However, when analyzing each allergen separately, *FLG* mutation was associated with IgE sensitization to peanut at age 4 years (adjOR 1.88, 95% CI: 1.03-3.44), and to house dust mite (HDM) at age 16 years (adjOR 0.47, 95% CI: 0.23-0.96), but not to other allergens. PSE was not an effect modifier, but a confounder, of the association between *FLG* mutation and IgE sensitization. Stratification by PSE and parental allergy resulted in minor differences.

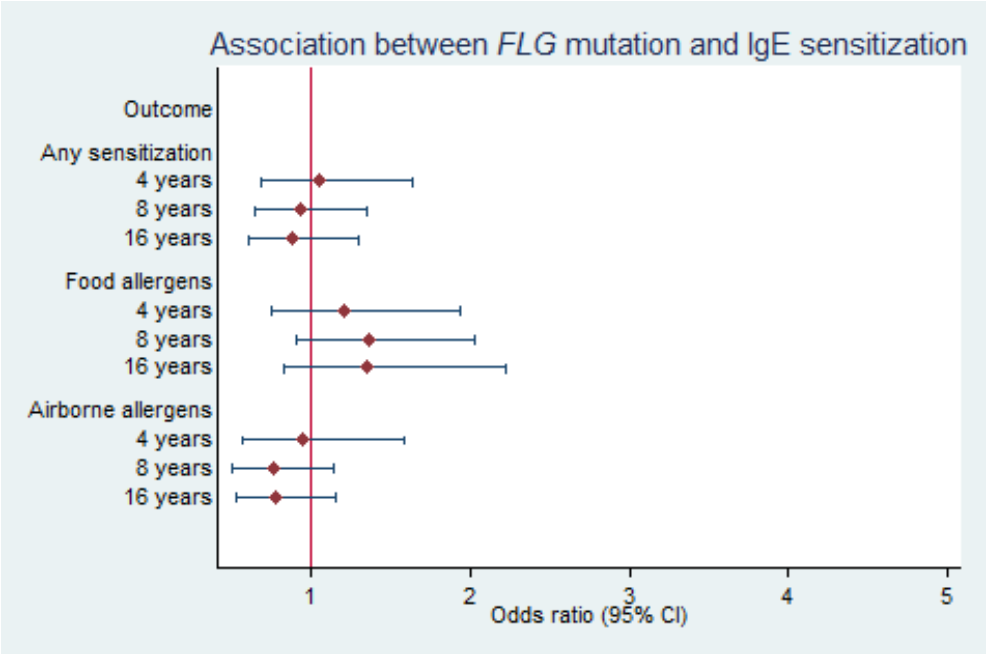

Figure 14 Association between *FLG* mutation and IgE sensitization at age 4, 8, and 16 years. Children with data on PSE and *FLG* mutation were included (n=1,890). A logistic regression model with GEE adjusted for sex, parental allergy, and PSE was used.

FLG mutation and pattern of IgE sensitization

Among children with any IgE sensitization, mono-, oligo- and polysensitization did not differ significantly between children with and without *FLG* mutation. However, IgE antibodies to peanut were significantly more common among children with *FLG* mutation at age 4 years (43.3% vs. 22.3%, P=0.010), 8 years (36.0% vs. 21.8%, P=0.022), but not at 16 years (16.4% vs. 17.1%, P=0.890), when analyzing the prevalence of IgE sensitization to each allergen separately. Children with *FLG* mutation in combination with PSE displayed the highest prevalence of IgE sensitization to peanut (Table 15).

TABLE 15 IgE sensitization to peanut at 4, 8, and 16 years among children with preschool eczema (PSE+) and/or filaggrin mutation (*FLG*+).

	4 years			**8 years**			**16 years**		
	IgE sensitization to peanut			IgE sensitization to peanut			IgE sensitization to peanut		
	N	%	95% CI	N	%	95% CI	N	%	95% CI
PSE-/*FLG*- (reference)[a]	25/161	16	10.3-22.1	48/324	15	11.1-19.2	47/387	12	9.1-15.8
PSE+/*FLG*-	53/189	28	21.8-35.0	**86/290**	**30**	**24.5-35.3**	**71/303**	**23**	**18.8-28.6**
PSE-/*FLG*+	4/11	36	10.9-69.2	6/20	30	11.9-54.3	3/19	16	3.4-39.6
PSE+/*FLG*+	**9/19**	**47**	**24.4-71.1**	**12/30**	**40**	**22.7-59.4**	6/36	17	6.4-32.8

[a]Children without preschool eczema (PSE-) and *FLG* mutation (*FLG*-) were the reference. Significant differences in bold.

There were no other differences in IgE sensitization to single allergens when comparing children with and without *FLG* mutation.

The cluster analysis performed on IgE sensitization to 14 allergens as dichotomous variables (positive or negative) did not provide any additional patterns of IgE sensitization associated with *FLG* mutation. As shown in Table 8, page 36, *FLG* mutation is equally frequent in both clusters.

FLG mutation in relation to remission of PSE (IV)

As stated above, among children with PSE *FLG* mutation is associated with reduced likelihood of complete remission at school age (crude OR 0.58, 95% CI: 0.36-0.93).

FLG mutation in relation to ethnicity (additional data)

The *FLG* mutations analyzed in studies III and IV were mutations known to be common in Scandinavia and Europe. A fraction of the children in studies III and IV had a parent born outside of Scandinavia (15.7% and 14.9%, respectively). To study this further, additional analyses were performed. In study III, 9.7% of the children had a parent born outside Europe. The analyzed *FLG* mutations were more common among children with European parents than those with a parent born outside Europe (7.8% [133 of 1,699] vs. 2.2% [4 of 183], P=0.005). The factor *any parent born outside Europe* was either a confounder, or an effect modifier, of the association between *FLG* mutation and IgE sensitization. When analyzing children with both parents being European separately a comparable result was seen (overall adjOR 0.99, 95% CI: 0.72-1.37) as among all children together (overall adjOR 0.94, 95% CI: 0.68-1.28). In study IV, the corresponding prevalence of children with a non-European parent was 10.9%. The factor *any parent born outside Europe* was either a confounder or an effect modifier of the effect of *FLG* mutation on complete remission of preschool eczema. In conclusion, about 10% in studies III and IV had a parent born outside Europe. This group of children had significantly lower prevalence of the *FLG* mutations studied. However, this finding did not influence the associations explored.

5 DISCUSSION

MAIN FINDINGS

Characteristics of eczema in adolescence (I)

In the first study, we describe eczema among adolescents recruited from the general population. The 12-month prevalence of eczema was 9.7% at age 16-years, which is comparable with reports from other studies (7.3-13%).[31-35, 131] As previously reported,[12] onset was most common before age 2 years (48.8%). However, our study shows that onset of eczema is common (25.6%) also after 12 years of age, especially among adolescents with non-AE. The British National Child Development Study have presented similar findings.[37]

Of adolescents with eczema, more than one in four was classified as having moderate-to-severe eczema. The prevalence of severe eczema (10.4%) was higher in our study compared with rates found in other population-based settings among children at preschool age (4-6%).[20, 27, 132] In these studies, severity was assessed using SCORAD and/or NESS. Previously in the BAMSE cohort, children with eczema at age 2 years were assessed using SCORAD (n=157)[133] while the 12-year-old children were evaluated with the questionnaire scoring measurement BESS. These children were classified as having severe eczema at rates of 2% and 4%, respectively. The higher rates in our study could partly be explained by the fact that both BESS(3-12) and NESS reflect the severity of eczema over the preceding year, while SCORAD assesses the severity of current eczema. It has previously been shown that NESS provides higher rates of severe eczema than SCORAD.[132] Another explanation could be that milder cases are more often in remission in adolescence and therefore the proportion of severe eczema cases may increase with age. In one American study of children 0-17 years the prevalence of severe eczema was 7%,[108] which is comparable to our findings. To summarize, adolescents with eczema seems to have a larger proportion of severe eczema than younger children with eczema.

The most common location of eczema in adolescence is flexural surfaces of extremities (creases), followed by neck and extensor surfaces of extremities. In literature, flexural location is common both in childhood and in adults, and extensor location is more common in infancy and childhood.[3, 11] In adults, as well in small children, the face is a favored location,[11, 15, 134] but in our study the face was not among the most commonly reported locations. Even though facial involvement might be less common in adolescence, as many as one in five (20%) of the adolescents reported eczema located in the face. Facial involvement is probably of major concern to the adolescents due to its visibility and affected adolescents may be more likely to visit health care providers for this reason.

AE was more common than non-AE in adolescence, and was more severe, had earlier onset and was more often connected to a history of chronic eczema throughout childhood. However, as regards to clinical signs such as location and seasonality of eczema, there were

no differences between AE and non-AE. In conclusion, in clinical practice, AE cannot be separated from non-AE without testing for IgE sensitization. Knowledge of IgE sensitization at an individual level will probably not change the management of an adolescent with eczema, unless the patient suffers from symptoms of asthma, rhinitis, contact urticarial or eczema caused by IgE sensitization, e.g., reaction to certain foods or HDM.

The course of preschool eczema (IV)

The cumulative prevalence of eczema before age 4 years (PSE) in our studies ranged between 32.7% and 34.6%, which is comparable with other findings (cumulative prevalence at age 3 years 33.5%,[135] cumulative prevalence at age 2 years 14.2-21.5%[18, 35]). Half of children with PSE (51%) were in complete remission at school age, 8% had persistent eczema (eczema at all follow-ups) and 41% intermittent eczema (eczema in one or two of three follow-ups) at school age. In this population-based cohort, only half of children with eczema before age 4 years were free of symptoms at school age. According to a recent systematic review regarding remission of infantile eczema, only two studies were suitable for inclusion. One of these was based on the BAMSE material,[93] while the other study reported complete remission up to age 7 years among 43% of children with eczema before age 2 years.[18] It is often said that small children outgrow their eczema.[2] However, according to our findings this will be true only for half of them. Furthermore, some of the remitted cases will recur later in life, often as hand eczema,[2] and the prognosis is probably even less favorable for children in specialist clinics.

Factors of importance for remission of preschool eczema (IV)

We were able to identify two factors positively associated with complete remission at school age: exclusive breastfeeding for at least 4 months and male sex. Persistent eczema before age 4 years (PSE) and severe PSE (here eczema in combination with sleep disturbance due to itch) were both strongly associated with reduced likelihood of remission at school age. In addition, having a *FLG* mutation, parental allergy, and parental smoking were also significantly associated with reduced likelihood of remission; all analyses above were in multivariate models. These findings reflect the results of a systemic review and meta-analysis, in which persistence of eczema was associated with the factors persistent childhood eczema, more severe eczema, and female sex.[42] Altogether, we identified at least two modifiable factors, parental smoking and exclusive breastfeeding ≥4 months. Encouragement to protect infants from passive smoking and to breastfeed exclusively for at least 4 months may improve the prognosis for children with PSE. Von Kobyletzki et al have highlighted the lack of knowledge regarding remission of eczema in a systematic review,[43] and previous smaller studies have not found a significant association between either breastfeeding or parental smoking and remission of eczema.[18, 136] To the best of our knowledge, our study is the largest to analyze the relationship between *FLG* mutation and prognosis of PSE in the general population, and the finding that *FLG* mutation is associated with reduced possibility for remission is novel.

The developed prognostic models for remission of PSE had a correct classification rate of 63-65%. Thus, the factors included in the models were insufficient for full prediction of complete remission. The current knowledge is limited for disease prognosis at an individual level, and therefore further studies are warranted.

Preschool eczema in relation to IgE sensitization (III)

In study III, we clearly showed that PSE is associated with IgE sensitization to both food and aeroallergens up to age 16 years, possibly through skin barrier dysfunction. In addition, sensitized children with PSE more often had polysensitization compared with sensitized children without PSE. Other studies have mainly focused on associations between eczema and IgE sensitization to food allergens, with similar findings.[87, 88] The Isle of Wight cohort explored if IgE sensitization to food and aeroallergens was associated with eczema up to age 4 years, and their findings among 4-year-olds were comparable to ours.[86] However, few other studies have analyzed IgE sensitization to aeroallergens in relation to eczema. In our study, we were surprised to find that PSE was even more strongly associated with IgE sensitization to aeroallergens than that to food allergens. Notably, this association was strongest at 4 years of age, even though IgE sensitization to aeroallergens is more frequent later in childhood. Flohr et al found that the association between eczema and IgE sensitization to food was stronger with disease severity,[82] and Perkin et al showed that persistent eczema up to age 5 years was associated with IgE sensitization to food and/or aeroallergens at 5 years.[89] We made similar findings and in our study the association was strongest between persistent PSE and IgE sensitization to food and aeroallergens. This result implies that the group with longer exposure regarding skin barrier dysfunction (children with persistent PSE) had the strongest association with IgE sensitization, which supports the idea of a causal relationship between skin barrier dysfunction and IgE sensitization.

Filaggrin mutation in relation to eczema and IgE sensitization (III)

According to the results in this thesis, having a *FLG* mutation was associated with development of eczema during childhood. Half of children with *FLG* mutation (49%) will develop eczema before age 4 years, which is significantly more than children without *FLG* mutation (33%). However, the majority (90%) of children with PSE did not have *FLG* mutation. The association between *FLG* mutation and eczema is previously well established.[67]

One of the most important results in this thesis is that *FLG* mutation is not associated with IgE sensitization up to age 16 years, with the exception of IgE sensitization to peanut at age 4 years. In contrast to our findings, an early systematic review showed that *FLG* mutation was associated with IgE sensitization,[69] and Tan et al found that *FLG* mutation was associated with IgE sensitization to food also after adjusting for eczema.[81] Furthermore, some studies have reported an association between *FLG* mutation and IgE sensitization to food allergens, but this association was not evident in the absence of prior eczema.[70, 83] In line with our result, the most recent studies have not found an association between *FLG* mutation and IgE

sensitization to food.[82, 84] However, one study has shown that *FLG* mutation is associated with peanut allergy independent of eczema.[79] Another study found that exposure to peanut allergen early in life was associated with increased risk of IgE sensitization to peanut among children with *FLG* mutation, but not among children without *FLG* mutation.[80] We found an association between *FLG* mutation and IgE sensitization to peanut at 4 years of age, but not at other ages. Altogether, these findings suggest that there is a relationship between *FLG* mutation and IgE sensitization to peanut, but not to other allergens. Our result implies that *FLG* mutation without PSE does not seem to play a major role in IgE sensitization either to food or to aeroallergens. Moreover, it is possible that skin barrier dysfunction due to *FLG* mutation is insufficient to cause IgE sensitization, with exception of peanut.

Association between eczema and ADHD or CNS-associated disorders (II)

We hypothesized that PSE, or eczema at other ages, could be associated with ADHD, as previously described by others.[107-112] However, to our surprise, we did not find any significant association between PSE and ADHD medication at school age. In addition, neither infantile eczema, reported doctor's diagnosis of PSE, severe PSE, persistent PSE, eczema at school age nor eczema ever up to age 16 years was associated with ADHD medication. On the other hand, we did not have sufficient power to detect associations with OR <1.5. Recent, larger studies among children have found significant, but weaker associations between eczema and ADHD[137] or ADHD medication[138], (adjOR 1.14, 95% CI: 1.03-1.16) and (HR 1.3, 95% CI: 1.2-1.5), respectively. Our study defined eczema based on parental report of symptoms in combination with report of doctor's diagnosis whereas the other studies' definitions were based on doctor's diagnosis (reported or obtained from registers). Far from all children with symptoms of either eczema or ADHD have visited a doctor.[17] Therefore, our results probably reflect the general population, including also milder cases of eczema, to a greater extent than the others, which might explain our findings. However, reported doctor's diagnosis of eczema was not associated with ADHD medication in our study, and we believe that our large study with prospectively collected data is valid. To summarize, among children recruited from the general population, there is no strong association between eczema and ADHD medication.

Finally, PSE was not associated with dispensed antidepressants, migraine drugs or antiepileptics. Before we started the analyses in study II only a few studies had been published regarding non-allergic comorbidities of eczema (e.g. cancer,[139] epilepsy,[114] depression[108, 113]). In the last few years, this research field has figuratively exploded. For example, studies have found that eczema is associated with increased risk for inflammatory bowel diseases and rheumatoid arthritis,[106] hypertension,[140] overweight (in North America and Asia, but not in Europe)[141], and cardiovascular disease[142, 143]. A few published studies have reported an absence of association between eczema and non-allergic comorbidities, like two European studies that did not find an association between eczema and cardiovascular disease.[144, 145] Thus, it is possible that publication bias has favored papers that found an association. Based

on these findings in observational studies, researchers now suggest that eczema, like psoriasis, is a systemic disorder.[146] Thus far, I am not convinced. While it would be appealing if new, effective treatments of eczema could prevent several of the proposed comorbidities, it is important to remember that statistical associations does not prove causality.

METHODOLOGICAL CONSIDERATIONS

In these studies, based on 4,089 children in a birth cohort recruited from the general population, we investigated associations between PSE and/or *FLG* mutation, and IgE sensitization, comorbidities, as well as remission of PSE later in childhood and adolescence. In addition, we could characterize eczema in adolescence, and explore the course of PSE up to age 16 years. The major strength was the population-based design with prospectively collected data regularly during 16 years of follow-up. Moreover, the large study size and the high number of participants that remained in the study during follow-up enabled us to perform subgroup analyses and stratification without lost power. The definition of eczema was based on questionnaire data, which can be a limitation. However, the longitudinal design with assessment of background factors and eczema at seven occasions over the course of 16 years reduces the risk of misclassification of both exposures and outcomes. The access to data on IgE sensitization at 3 different ages, and *FLG* mutation for a majority of the children, as well as data on dispensed drugs by record linkage for all participants, were major advantages.

The major considerations of this thesis are those associated with observational studies, and will be discussed below.

Random errors

Random error can occur in any study design, and originate from sampling variability. The risk for random error can be reduced by increasing the study size, which leads to a higher precision in the study. A high precision implies that there is a low risk that the observed results occurred by chance. The relatively large study population in the BAMSE cohort reduces the risk of random error. The overall narrow confidence intervals in the included studies implies good precision. In some of the stratified analyses and subgroup analyses, the results should be interpreted with caution due to small study groups. For example, when exploring IgE sensitization to peanut in relation to PSE and/or *FLG* mutation in study III, the wide confidence intervals indicate a large statistical uncertainty.

Systematic errors (bias)

In contrast to random errors, systematic errors do not depend on study size or chance. The most common systematic errors are selection bias, misclassification, and confounding. These can be introduced at all stages of the research process and lead to a reduced internal validity of the observed findings. The effects of bias is difficult to evaluate and take into account in analysis. For this reason, it is important to strive for a limited introduction of different biases during the research process, from initiating the study through evaluation of the results.

Nonetheless, systematic errors may occur and should be considered when interpreting the findings as well as the magnitude of their impact. Systematic error can cause both under- and overestimation of the associations studied.

Selection bias

Selection bias arises when the study population is not a representative sample of those theoretically eligible for the study (target population), and the association between exposure and outcome differs between those who participate and those who do not.[147] Selection bias could have been introduced at three stages of the studies in this thesis. Firstly, at recruitment, a large proportion of the children were excluded according to study plan, for example those with a seriously ill child (n=57), or planning to move within 1 year (n=699). Of the 7,221 children born in the predefined area, 76% (n=5,488) were eligible for inclusion. Secondly, of the eligible children, one in four did not respond or declined to participate, and 75% (n=4,089) were included in the study cohort. Two years after recruitment of the BAMSE project was initiated, a short questionnaire was mailed to families not included in the cohort. This additional study showed that non-participants more often reported parental smoking, but there were no other differences regarding parental allergy and other background characteristics when compared with participants.[124] A large systematic review and meta-analysis has shown that eczema is associated with passive smoking in children.[53] Therefore, selection bias might have led to a small underestimation of eczema prevalence in our studies. When exploring associations within the cohort, non-participation has likely not introduced errors in the observed associations between exposure and outcome, since the comparisons are made within the cohort. However, in study I and study IV, where we described eczema in adolescence and the natural course of PSE, respectively, the prevalence rates probably do not fully reflect the true prevalence in the target population.

Thirdly, in longitudinal studies selection bias might be introduced due to loss-to-follow-up. Loss-to-follow-up can bias the estimates of prevalence as well as the associations between exposure and outcome. In studies I-III, background characteristics of the study population were compared with the original cohort and there were minor differences in the prevalence of some characteristics. These differences were significant, but small, and likely did not affect the observed associations. Eczema, the main exposure/outcome of this thesis, might differ among those who continue to participate in our cohort compared with those who are lost to follow-up. Therefore, the prevalence rates in this thesis could have been either over- or underestimated due to loss-to-follow-up. However, in study I, 76% of the original cohort were included and the prevalence of eczema at age 1, 2, 4, 8, and 12 years did not significantly differ between the original cohort and the study population. Thus, the study population seems to be representative for the cohort and is probably not affected by selection bias. In the subpopulation of study II (n=2,736), PSE was more common among non-participants (n=964) compared with participants (41.3% vs. 31.9%). ADHD medication was also more

common among non-participants in the subpopulation (7.0% vs. 3.7%). This could have introduced selection bias. However, the investigated association between PSE and ADHD-medication at school age did not differ between non-participants and participants ([adjOR 0.96, 95% CI: 0.57-1.63] vs. [adjOR 1.16, 95% CI: 0.76-1.77]). Thus, the selection did not change the conclusion of study II.

Misclassification

Systemic errors in obtaining information (measurements or classifications) of the exposure and/or outcome once the participants have entered the study might lead to information bias, or misclassification. Information bias can be either differential, if the likelihood of being misclassified differs between the study groups, or non-differential. The differential information bias might either underestimate or exaggerate the association, while the effect of a non-differential information bias is random between the study groups and will dilute the true association (bias towards the null).

Differential misclassification of the exposure is minimized in our studies because of the prospective design of the BAMSE cohort, with data on background factors and potential exposures collected before disease onset. Misclassification of eczema cannot be ruled out, especially after age 4 years. The most validated diagnostic criteria for eczema is based on clinical examination and diagnosis made by physicians.[3, 4] In this thesis, the eczema definition is derived from questionnaire data. This definition has been validated at age 0-4 years and had high sensitivity (92%) and specificity (100%) when compared with clinical diagnosis by dermatologists.[127] The BAMSE definition up to age 12 years is rather strict compared with other questionnaire-based definitions (e.g. the International Study of Asthma and Allergies in Childhood [ISAAC]),[31] and require report of dry skin in combination with itchy rash on one to three specific body sites chosen among 14 specified body locations and/or reported doctor's diagnosis of eczema since the preceding follow-up. This reduces the risk for misclassification in the eczema group. On the other hand, when compared with studies using doctor's diagnosis of eczema (e.g., Genuneit et al)[111], our definition probably includes milder cases. Altogether, our definition might underestimate the prevalence of eczema due to the strict criteria but include milder cases when compared with studies using doctor's diagnosis (reported or register-based). At the clinical examination at 16 years in the BAMSE cohort, performed by trained nurses, the adolescents were asked for symptoms of eczema in the preceding week and examined for visible eczema. Almost half (48% [122 of 254]) of adolescents classified as having eczema in the questionnaire at age 16 years were diagnosed with current eczema and assessed for severity using POEM. Unfortunately, this cannot be used for validation of the questionnaire definition at the 16-year follow-up, since the disease is intermittent and the 12-month prevalence is not comparable with current eczema. However, in the ISAAC study, the questionnaire derived 12-month prevalence was compared with diagnosis of current eczema made by physician with similar findings (41.5% of children

fulfilling eczema in questionnaire had current eczema at examination). Furthermore, it was concluded that questionnaires provide adequate eczema prevalence estimates at population level.[148] We cannot rule out that some of the children have contact dermatitis misclassified as eczema. Since the adolescents with eczema only at age 16 years (onset at 16 years) did not have higher rates of reported contact dermatitis compared with adolescents with eczema at age 16 years in combination with a history of eczema, this misclassification is probably of minor importance. In summary, the eczema definition is validated up to age 4 years, and misclassification of the definition is probably limited, with minor effects on the investigated associations.

In study II, the definitions of ADHD and other CNS-associated disorders are based on dispensed drugs for each particular disease at school age (10-18 years). We have chosen to define the outcome as "ADHD medication at school age" since the definition will exclude children with ADHD medication before age 10 years, and children without medication. Misclassification can be introduced if a medication was prescribed and dispensed with some other indication (e.g. psychostimulants for rare disorders such as narcolepsy), but since such disorders are uncommon, this issue should be limited in our study.

Confounding

Confounding occurs when the association between an exposure and an outcome is attributable to a third factor (another exposure) which directly or indirectly causes the association. The confounding factor can lead to either a weaker or a stronger association. The prospective design of the BAMSE cohort, with collection of data on various background factors, and on allergy-related disorders and symptoms, enabled us to control for possible known and unknown confounders.

In study I, we hypothesized that sex could be a confounding factor when investigating different aspects of adolescent eczema in relation to AE and non-AE. To control for sex, all analyses were performed both among all adolescent and stratified by sex when comparing AE with non-AE. Stratification by sex was also performed in studies II and III, and stratification by parental allergy was performed in study III with no major differences in the investigated associations.

In studies II, III, and IV, we used logistic regression models and tested for confounding. Few factors tested changed the OR of the studied associations, and most factors were included in the adjusted model due to prior knowledge from literature. In study III, PSE was a significant confounding factor of the association between *FLG* mutation and IgE sensitization, and included in the final model. One could speculate that PSE is an intermediate link in the causal pathway between *FLG* mutation and IgE sensitization and therefore should not be classified as a confounder. However, the majority of all children with PSE (89.9%) do not have *FLG* mutations, indicating that PSE is not an intermediate link in most cases. In addition, there was

no major difference when comparing the association above with and without adjustment for PSE, and we chose to consider PSE a confounder.

As additional data in this thesis, I have explored if ethnicity/having a parent born outside Europe is a confounder of associations involving *FLG* mutation. The analyses were restricted to children whose parents were both European and the restricted analyses were comparable with the full analysis. Moreover, adjustment for the factor *Any parent born outside Europe* did not change the OR of the investigated associations.

As in all non-randomized studies, the influence of unmeasured and unknown confounders cannot be ruled out (residual confounding).

Effect modification

Effect modification, or interaction, occurs when the magnitude of the association between an exposure and an outcome depends on a third factor. In this situation, an overall estimate of the association will be misleading. To manage effect modification, the analysis can be stratified based on the third factor and the groups analyzed separately.

We tested for possible effect modification in all logistic regression models (II, III, IV). In study III, both preschool asthma and preschool rhinitis were effect modifiers of the association between PSE and IgE sensitization up to 16 years. Consequently, we restricted the analysis to children without preschool asthma and preschool rhinitis. The restricted model displayed a lower point estimate compared with the full model, but the result was not significantly different.

Generalizability

Generalizability relates to whether or not the findings in the study population can be applied to other populations (external validity). Because of the study's population-based design, good precision due to large study size, and limited selection bias, we assume that the associations found are generalizable to other urban European settings with high income, temperate climate, and comparable prevalence of eczema and background factors. On the other hand, the rates of eczema, may not reflect the area of recruitment since only 57% of children (4,089 of 7,221) were actually included at baseline, and even fewer in our studies. Therefore, the generalizability of the prevalence of eczema and other disorders to other populations should be seen with caution. However, the prevalence of eczema in our studies corresponds fairly well with rates in other Swedish,[31] Nordic,[34] and European studies.[18, 35, 89]

6 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The high prevalence of severe eczema in adolescence is a large challenge. The explanation for the high rate could be that adolescents do not treat their eczema sufficiently. Their childhood eczema has been managed by parents and pediatric heath care, but is now supposed to be managed by the adolescents themselves, and care should be transferred to a general practitioner or dermatologist. An ongoing study in the BAMSE project preliminary indicates that the adolescents do not use enough TGCs in relation to reported symptoms. If we can reduce the group of adolescents with severe eczema by only a few percent, a lot would be gained in health-related quality of life. Therefore, it would be most important to investigate the reasons for insufficient treatment by interviewing adolescents visiting health care due to eczema. Thereafter, an intervention study based on the observations in the interviews should be performed. For example, a secondary eczema educational program performed by nurses could be launched at age 12-14 years, focused on teaching eczema management. In addition, guidelines should be established for transferal from pediatric health care to suitable clinics that can support young adults with eczema.

Severe and/or persistent eczema before age 4 years is strongly associated with persistence of eczema (non-remission) and with IgE sensitization later in childhood and adolescence. It has been showed that frequent use of emollients can delay onset of eczema among infants with high risk for eczema.[56, 57] However, it is unknown whether anti-inflammatory treatment of eczema early in life affects the long-term prognosis and consequences of childhood eczema. To speculate, it is possible that new promising treatments[64] can interfere with early disease persistency, resulting in a higher degree of remission and decreased prevalence of IgE sensitization.

From a dermatologist point of view, comorbidities of eczema are seldom considered in clinical practice. Among children with eczema, I do think it is important to identify and manage symptoms of asthma and rhinitis within health care. Physicians meeting children with eczema should be aware of allergic comorbidities, ask about symptoms, and make sure that the children are treated and followed up adequately. I will have this in mind both as a physician and when I teach medical students and colleagues in the future. When it comes to non-allergic comorbidities of eczema, further research is needed before implementation in daily clinical practice. In the ongoing follow-up of the BAMSE cohort, we have asked about non-allergic disorders, including ADHD. I would like to re-evaluate the association between eczema and possible non-allergic comorbidities using data from the 22-24-year follow-up with record linkage to SPDR and national health care registers containing doctor's diagnoses.

The eczema definition used in the BAMSE cohort is not validated after 4 years of age. It would be most useful to perform a validation at the ongoing 22-24-year follow-up. For example, evaluate if William´s diagnostic criteria for atopic dermatitis performed by trained nurses or a dermatologist at the clinical examination is comparable with the eczema diagnosis derived from the preceding questionnaire. During the clinical examination at age 16 years, a patch test for common contact allergens was performed. Using this data, it would be interesting to

explore whether the adolescents with eczema have higher rates of allergic contact dermatitis than those without eczema, and if possible investigate if it is misclassified as eczema or occurs simultaneously with eczema within the BAMSE cohort.

Why peanut? My findings indicate that IgE sensitization to peanut, but not to other allergens, seems to be associated with *FLG* mutation. A future study comparing the peanut allergen with other allergens in relation to skin barrier defects could be useful for understanding the possible mechanisms behind this finding.

For me, it was a surprise to find that *FLG* mutation is not of major importance for IgE sensitization. Studies have reported that *FLG* mutation is associated not only with eczema, but also with allergy-related diseases (asthma and rhinitis).[69, 70, 75] Since eczema is strongly associated with both *FLG* mutation, and with asthma and rhinitis, it is likely that eczema is either an effect modifier or a confounder on this association. It would be interesting to investigate the relationship between *FLG* mutation and allergy-related diseases, with similar methods as those used in study III, to provide additional knowledge within this research field.

7 CONCLUSIONS

Almost 10% of Swedish adolescents report symptoms of eczema in the last year, and more than one in four has moderate-to-severe disease.

Atopic eczema and nonatopic eczema in adolescence do not differ in location or seasonality. However, atopic eczema is more common than nonatopic eczema in adolescence, and is characterized by earlier onset, chronicity and more severe current eczema. Onset in adolescence is common, especially for nonatopic eczema.

There is no significant association between preschool eczema, or eczema at any other time point up to age 16 years, and medication for ADHD at school age. In addition, there is no significant association between preschool eczema and medication for depression/anxiety /phobia, epilepsy or migraine at school age.

Preschool eczema is associated with IgE sensitization, both to food and aeroallergens, up to age 16 years. This association is even stronger with persistent preschool eczema. In children with IgE sensitization, polysensitization is more common among those with preschool eczema than among those without.

Filaggrin mutation is associated with IgE sensitization to peanut, but not to other allergens. This finding implies that filaggrin mutation without eczema early in life does not seem to play a major role in IgE sensitization.

One third of children have eczema before age 4 years, and half of them (51%) are in complete remission at school age.

Male sex and excusive breastfeeding for at least 4 months are positively associated with complete remission of preschool eczema at school age, whereas severe preschool eczema (reflected by persistency and/or sleep disturbance due to itch), parental allergy, parental smoking at child's birth, and filaggrin mutation are all significantly associated with reduced likelihood of complete remission of preschool eczema. However, prognostic models are insufficient for the prediction of complete remission of preschool eczema at school age.

8 SVENSK SAMMANFATTNING

Bakgrund

Eksem (här synonymt med atopisk dermatit eller böjveckseksem) är en hudsjukdom som orsakar torr hud och återkommande episoder av röda, kliande hudutslag och som är vanlig hos barn och tonåringar. Barn med eksem har en ökad risk att insjukna i födoämnesallergi, astma och hösnuva, och har oftare IgE-antikroppar än barn utan eksem. Eksem med samtidig förekomst av IgE-antikroppar kallas för atopiskt eksem, annars för icke-atopiskt eksem. Flera studier visar att även vissa icke-allergiska sjukdomar, såsom ADHD, depression och epilepsi, är vanligare hos dem med eksem. Individer med en mutation i genen för filaggrin har ökad risk att insjukna i eksem, och det verkar som om de oftare har IgE-antikroppar jämfört med barn utan en sådan mutation. Man känner till många faktorer som gör att man fortsätter ha eksem senare i livet, men det saknas kunskap om vilka faktorer som har betydelse för att tillfriskna.

Syfte

Det övergripande syftet med denna avhandling var att beskriva eksem hos tonåringar, och att beskriva sjukdomsförloppet upp till 16 års ålder hos dem med eksem före 4 år. Vi ville också undersöka konsekvensen av att ha eksem före 4 års ålder och att ha en filaggrin-mutation, samt studera vilka faktorer som var av betydelse för att tillfriskna från eksem.

Metoder

Vi använde data från en svensk populationsbaserad födelsekohort (BAMSE) i vilken barnen (n=4,089) rekryterades från Storstockholm under perioden 1994-1996. Vid studiens start besvarade familjerna frågor om olika bakgrundsfaktorer. Då barnen var 1, 2, 4, 8, 12 och 16 år fyllde föräldrarna i enkäter om bl.a. barnets eventuella eksem under de senaste 12 månaderna, och barnen/tonåringarna besvarade egna enkäter vid 12 och 16 år. Blodprov samlades in vid kliniska undersökningar då barnen var 4, 8 och 16 år, och information om IgE-antikroppar och filaggrin-mutation fanns för en majoritet av barnen. Registerdata för uthämtade receptbelagda läkemedel mot bl.a. ADHD och depression länkades till barnen i studien via Svenska läkemedelsregistret, och användes för att studera om dessa sjukdomar var vanligare hos barn med eksem.

Resultat

Vid 16 års ålder hade 10% (297 av 3,108) haft eksem de senaste 12 månaderna, och bland dessa klassificerades eksemet hos 73% som lindrigt, 17% som måttligt och 10% som svårt. Eksemen hos tonåringarna fanns oftast i böjveck (73%), på hals/nacke (40%) och på utsidan av armar och ben (39%). Nästan hälften (49%) av tonåringar med eksem hade fått sitt eksem före 2 års ålder, men för många debuterade eksemet först efter 12 år (26%). Hos 11% av alla tonåringar med eksem var detta kroniskt, dvs. det hade funnits vid alla tidigare uppföljningar i studien. Atopiskt eksem var vanligare än icke-atopiskt eksem. Tonåringar med atopiskt

eksem hade tidigare debut, svårare och oftare kroniskt eksem jämfört med dem som hade icke-atopiskt eksem, men det var ingen skillnad i säsongsvariation eller i eksemets lokalisation.

ADHD-medicinering i skolåldern var inte vanligare bland barn som hade haft eksem före 4 års ålder (adjOR 1,12 [95% CI: 0,80-1,56]), och inte heller bland barn som hade haft eksem i andra åldrar jämfört med barn som inte haft eksem. Andra uthämtade receptbelagda läkemedel i skolåldern i form av antidepressiva, antiepileptika samt migränläkemedel var inte heller vanligare hos barn som haft eksem jämfört med dem utan eksem.

Förekomst av IgE-antikroppar upp till 16 års ålder, både mot födoämnen och luftburna allergiframkallande ämnen, var dubbelt så vanlig hos dem som hade haft eksem före 4 års ålder jämfört med dem som inte hade haft eksem (adjOR 2,30 [95% CI: 2,00-2,66]). IgE-antikroppar var vanligast bland barn som hade haft kroniskt eksem under sina första 4 levnadsår. Hos barn med IgE-antikroppar vid 4, 8 och 16 år var förekomst av IgE-antikroppar mot flera olika allergen (polysensibilisering) vanligare hos barn som hade haft eksem före 4 år än hos dem utan eksem. Barn med filaggrin-mutation hade inte oftare IgE-antikroppar än barn utan sådan mutation, med undantag av IgE-antikroppar mot jordnöt vid 4 års ålder (adjOR 1,88 [95% CI: 1,03-3,44]).

Häften av alla barn (51%) som hade haft eksem före 4 år var eksemfria i skolåldern. Manligt kön och helamning i minst 4 månader var vanligare hos dem som var fria från eksem i skolåldern, medan kroniskt eksem och/eller svårt eksem upp till 4 års ålder, föräldrar med allergi-relaterad sjukdom, föräldrar som rökte vid tiden för barnets födelse och förekomst av filaggrin-mutation minskade chansen för att vara eksemfri i skolåldern.

Slutsats

Avhandlingen visar att endast hälften av alla barn som haft eksem någon gång under de första fyra levnadsåren är fria från eksem i skolåldern. Var tionde tonåring med eksem har svårt eksem. Till skillnad från tidigare studier hittade vi inget samband mellan eksem och uthämtat ADHD-läkemedel, antidepressiva, antiepileptika eller migränläkemedel i skolåldern. Barn med eksem före 4 år, framför allt de med kroniskt eksem, har oftare IgE-antikroppar senare i barndomen och tonåren jämfört med barn som inte haft eksem. Barn med filaggrin-mutation har oftare IgE-antikroppar mot jordnöt vid 4 års ålder, men inte mot andra vanliga allergiframkallande ämnen. Detta talar för att förekomst av en filaggrin-mutation, utan eksemsjukdom, inte verkar vara av stor betydelse för utvecklingen av IgE-antikroppar. Slutligen fann vi att manligt kön och helamning i minst 4 månader verkar öka möjligheten att tillfriskna från eksem, medan att ha haft ett kroniskt och/eller svårt eksem före 4 års ålder minskar chansen att vara eksemfri i skolåldern.

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