

Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort

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Summary

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Conflicts of interest

None declared.

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Background Filaggrin (FLG) mutations are major genetic determinants for eczema, but their role in eczema severity needs further investigation. Children with eczema are at higher risk of having asthma and rhinitis but it is not known if this risk is associated with the severity of eczema.

Objectives To investigate eczema severity in relation to sex, FLG mutations, asthma, rhinitis and topical treatment among preadolescent children in a population-based cohort.

Methods Parental questionnaires were used to obtain data on symptoms of eczema, asthma, and rhinitis among 3301 preadolescent children. Eczema severity was evaluated based on sleep disturbance, extent of disease and total time with eczema the previous year. Genotyping was performed in 1854 individuals for three common FLG mutations (R501X, R2447X and 2282del4).

Results Eczema was more prevalent among girls (14.5%) than boys (9.4%). FLG mutations were detected in 13.1% of children with mild eczema and 12.5% with moderate-to-severe eczema. Of children with moderate-to-severe eczema, 45.1% had rhinitis and 22.0% had asthma compared with 32.7% and 13.8% of children with mild eczema, respectively. Children with moderate-to-severe eczema used moisturizers and topical glucocorticoids more frequently than children with mild eczema. Boys used moisturizers less frequently than girls.

Conclusions More preadolescent girls than boys had eczema. FLG mutations did not influence eczema severity in our population-based cohort. Prevalence of rhinitis and asthma was associated with eczema severity, with the highest prevalence among boys with moderate-to-severe eczema.

Eczema¹ (atopic dermatitis) affects 15–38% of children and represents a growing public health problem in many areas of the developing world.^{2–4} A large number of studies, both in children and adults, have investigated the association between eczema and related diseases such as asthma and rhinitis. Research consistently shows that the presence of eczema, as well as a history of eczema, is associated with an increased risk of having asthma and rhinitis.^{5–11} Recently reported data from the Swedish population-based BAMSE birth cohort showed that many children with eczema had concomitant asthma and/or rhinitis during

childhood, with the highest prevalence among preadolescent children.⁴

Filaggrin (FLG) mutations confer a genetic predisposition for dry skin and eczema, as well as predisposing persons with eczema to asthma.^{12–15} Most studies on the role of FLG mutations in the severity of eczema have shown weak associations,^{16–20} although one study found no association.²¹

The issue of FLG mutations as risk factors for eczema disease severity needs to be explored further; to our knowledge no studies have yet examined the association between asthma and rhinitis, in relation to the severity of eczema. Therefore we

investigated eczema severity in the Swedish population-based birth cohort BAMSE, in relation to sex, *FLG* mutations, asthma, rhinitis and topical treatment.

Materials and methods

Study subjects

The BAMSE project is a longitudinal population-based cohort from Stockholm in which children were included at birth and prospectively followed throughout childhood. The BAMSE cohort comprised 4089 infants, corresponding to 75% of the eligible subjects.²² When the child was aged 1, 2, 4 and 8 years, the parents completed postal questionnaires focusing on background factors and on symptoms of eczema, asthma and rhinitis during the previous 12 months. For the 12-year follow-up, all questionnaires were sent out on one occasion in 2008 when the children were aged 12 years (range 11–14 years). The response rate was 82% ($n = 3366$), with a mean age of the children of 13 years at the time when the questionnaires were filled in. For 3301 of the children, complete data on eczema, asthma and rhinitis were available and these children were included in the present study.

DNA was available for 1854 individuals from blood obtained at 4 and 8 years of age. No blood or DNA was collected at the 12-year follow-up. Genotyping was performed for the *FLG* mutations that are common in Scandinavia using TaqMan allelic discrimination for R501X and R2447X on the ABI Prism 7500 detection system according to the manufacturer's protocol (Applied Biosystems, Foster City, CA, U.S.A.) and MALDI-TOF (matrix-assisted laser desorption/ionization-time of flight; Sequenom GmbH, Hamburg, Germany) for 2282del4. Primer sequences, amplification conditions and allele sizes are available on request. Children with a mutation in any of these positions were classified as having a loss-of-function mutation. The STROBE guidelines for cohort studies were used.

Definition of disease outcomes

Assessment of current diseases was based on the follow-up questionnaires: (i) eczema (at the 1, 2, 4, 8 and 12-year follow-up) – dry skin, itchy rashes with age-specific location for 2 weeks or more, and/or doctor's diagnosis of eczema in the past 12 months;²³ (ii) asthma (at the 12-year follow-up) – at least four episodes of wheeze in the past 12 months or at least one episode of wheeze in combination with occasional or regular use of prescribed inhaled glucocorticoids;²⁴ (iii) rhinitis (at the 12-year follow-up) – sneezing, runny or blocked nose, or itchy, red and watery eyes after exposure to furred pets or pollen during the past 12 months, or doctor's diagnosis allergic rhinitis from age 10 years.²⁵

Evaluation of eczema severity

The questionnaire used for the BAMSE 12-year follow-up was more extensive concerning eczema than at previous follow-

ups, and included questions modified from the Rajka and Langeland index²⁶ for evaluation of eczema severity. This explains why the present study of eczema severity was based on the 12-year follow-up only. For the current study, a BAMSE Eczema Severity Score (BESS), scale 3–14, was constructed based on the responses to three questions: (i) total time with eczema during the past 12 months; (ii) disturbed sleep; and (iii) number of affected body sites (multiple choice alternatives: face, scalp, ears, arms and/or legs, armpits, knees and/or elbows, wrist and/or ankles, hands, feet, throat and/or neck, buttocks, chest and/or abdomen and/or back and/or shoulders, groin and/or genitals). After collecting the data we found the questions in our study to be very similar to the questions used in the Nottingham Eczema Severity Score (NESS), a validated tool for evaluation of eczema severity in epidemiological studies.²⁷ We therefore took the opportunity to compare BESS with an existing validated scale. Children who fulfilled the study's definition of eczema were divided into three groups on the basis of their score: mild (BESS 3–7), moderate (BESS 8–10) and severe eczema (BESS 11–14). For evaluations of differences in comorbidity, *FLG* mutations, topical treatment and response to aggravating factors, the groups with moderate and severe eczema were merged.

Statistics

The prevalence rates of eczema, asthma and rhinitis were expressed in percentage of total number of observations available in the current group. Chi-squared tests were used for dichotomous variables, such as comparison of prevalence of asthma among children with mild vs. those with moderate-to-severe eczema. Differences in use of moisturizers and topical glucocorticoids (GCS) between groups were calculated using the Wilcoxon rank sum test, as were differences between boys and girls concerning BESS. Persistence of eczema was evaluated by calculating the mean number (range 0–4) of previous follow-up occasions (at 1, 2, 4 and 8 years) with eczema. For evaluation of differences in response to aggravating factors, eczema persistence and doctor's diagnosis of eczema, 95% confidence intervals (CI) were calculated and intervals that did not overlap were considered significantly different. All statistical analyses were performed with STATA statistical software (release 11.1; StataCorp, College Station, TX, U.S.A.).

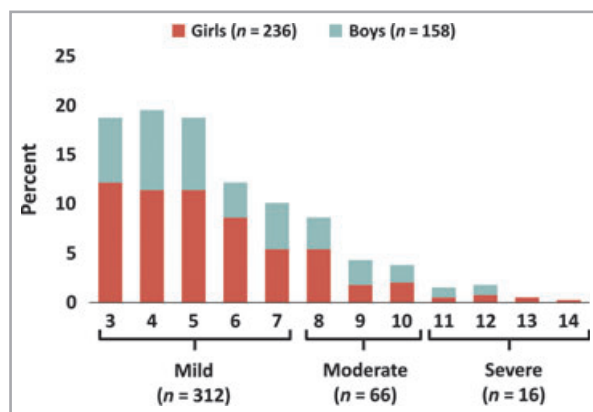
Results

Eczema and Eczema Severity Score among preadolescent children

The 12-month period prevalence of eczema at the 12-year follow-up was 11.9% (394 of 3301). Eczema was significantly ($P < 0.001$) more common among girls than boys [236 of 1627 (14.5%) vs. 158 of 1674 (9.4%), respectively]. Table 1 shows the result for each of the three questions on which BESS was based. About one-third of the children had had eczema more than a month the previous year and the same

Table 1 Breakdown of BAMSE Eczema Severity Score results for clinical course, disease intensity and extent of disease

Score	No. of children (n = 394)	Frequency (%)
Clinical course evaluation		
In the last 12 months, for how long in total has your child had eczema?		
< 1 month	257	65.2
1–3 months	45	11.4
4–6 months	28	7.1
> 6 months	64	16.2
Disease intensity evaluation		
Has your child's sleep been disturbed by itching in the last 12 months?		
Never	255	64.7
Seldom	82	20.8
Sometimes	50	12.7
Often	5	1.3
Always	2	0.5
Extent of body surface area involvement		
Extent of eczema determined by number of involved body sites during the last 12 months		
1 body site	108	27.4
2 body sites	109	27.7
3–4 body sites	115	29.2
5–6 body sites	41	10.4
> 6 body sites	21	5.3

**Fig 1.** Distribution of BAMSE Eczema Severity Score (BESS) among preadolescent girls and boys in the BAMSE birth cohort.

proportion of children had experienced disturbed sleep due to itch. According to results on these questions each child was scored from 3 to 14 (Fig. 1). Based on the score and in agreement with NESS the children were classified into three categories of eczema severity: mild (79%), moderate (17%) and severe (4%). The severity distribution of BESS was similar to NESS (Table 2). Although there were no significant differences in eczema severity between boys and girls, Table 2 shows that the proportion of boys was somewhat higher in the group with moderate-to-severe (48%) eczema than in the group with mild eczema (38%).

Eczema severity in relation to doctor's diagnosis of eczema, disease persistence, response to aggravating factors and topical treatment

Children with mild eczema were compared with children with moderate-to-severe eczema regarding doctor's diagnosis of eczema at any time in life, persistence of eczema and reported response to aggravating factors (Table 3). Evaluation of eczema at previous follow-up occasions showed that children with moderate-to-severe eczema had had significantly more persistent eczema. Significantly more children with moderate-to-severe eczema reported worsening of eczema due to environmental factors. Moisturizers (Fig. 2) and topical GCS (Fig. 3) were more frequently used (both $P < 0.001$) by children with moderate-to-severe eczema than by children with mild eczema. There were no significant differences regarding use of topical GCS between boys and girls ($P = 0.850$), but girls used moisturizers more frequently ($P < 0.001$).

Prevalence of *FLG* mutations

FLG mutations were found in 7.3% (136 of 1854) of children, all heterozygotes (Table 4). Thirteen per cent (32 of 246) of the children with eczema and 6.5% (104 of 1608) of children without eczema at the 12-year follow-up had at least one *FLG* mutation ($P < 0.001$). *FLG* mutations were present in 26 of 198 children with mild eczema and in six of 48 children with moderate-to-severe eczema (13.1% vs. 12.5%, $P = 0.907$). One child with mild eczema and one child with moderate-to-severe eczema were compound heterozygotes (Table 4).

Prevalence of asthma and rhinitis in relation to eczema severity among preadolescent children

Of the children with eczema, 39.8% had either asthma or rhinitis. This is to be compared with 18.9% of children without eczema. Among children with moderate-to-severe eczema, rhinitis was significantly more prevalent (45.1% vs. 32.7%, $P = 0.036$) and asthma tended to be more prevalent (22.0% vs. 13.8%, $P = 0.069$) than among children with mild eczema. The combination of asthma and rhinitis was significantly more prevalent in the group with moderate-to-severe eczema (18.3% vs. 9.0%, $P = 0.016$) than in the group with mild eczema. Figure 4 shows the proportions with asthma and/or rhinitis among boys and girls with no, mild and moderate-to-severe eczema. Both asthma and rhinitis were more prevalent among boys irrespective of eczema status, and of the boys with moderate-to-severe eczema, 59.0% had asthma, rhinitis, or both diseases.

Discussion

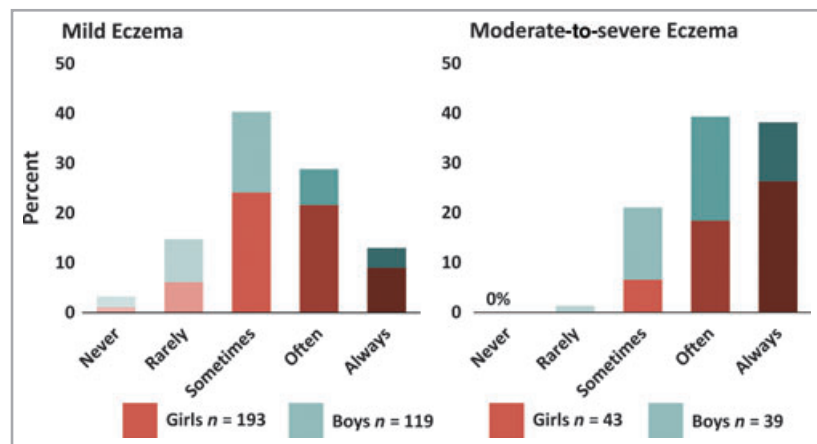
In this population-based study among preadolescent children, focusing on eczema severity, we found that *FLG* mutations were not associated with eczema severity, while prevalence of

Table 2 Comparison of BAMSE Eczema Severity Score (BESS) and Nottingham Eczema Severity Score (NESS)^a

	NESS scale 3–15	BESS scale 3–14	NESS, %	BESS, %	BESS boys/girls
Mild	3–8	3–7	82	79	119/193
Moderate	9–11	8–10	12	17	31/37
Severe	12–15	11–14	6	4	8/6

^aFor details see reference 27.**Table 3** Disease persistence, doctor's diagnosis of eczema and response to aggravating factors in relation to eczema severity among preadolescent children in the BAMSE birth cohort

	Mild eczema (n = 312)		Moderate-to-severe eczema (n = 82)	
		CI (95%)		CI (95%)
Disease persistence (range 0–4) ^a	1·47	1·33–1·62	2·26	1·94–2·57
Doctor's diagnosis of eczema ever, %	60·7	55·2–66·3	90·0	83·3–96·7
Response to aggravating factors, %				
Worsening of eczema symptoms due to				
Airway infection	2·9	1·0–4·8	11·0	4·1–17·9
Heat/sweating	12·5	8·8–16·2	48·8	37·7–59·8
Cold weather	24·4	19·6–29·1	57·3	46·4–68·3
Emotional stress	1·9	0·4–3·5	20·7	11·8–29·7
Furred pets	4·5	2·2–6·8	7·3	1·6–13·1
Leaf tree and grass pollens	5·1	2·7–7·6	9·8	3·2–16·3
Any food	4·2	1·9–6·4	17·1	8·8–25·4
Detergents	5·1	2·7–7·6	24·4	14·9–33·9
Any clothing material	4·5	2·2–6·8	19·5	10·8–28·3

CI, confidence interval. ^aDisease persistence is defined as the mean number of previous follow-up occasions at 1, 2, 4 and 8 years when the child had eczema. Significant differences are shown in bold.**Fig 2.** Frequency of use of moisturizers among preadolescent children with mild or moderate-to-severe eczema in the BAMSE birth cohort. Children with moderate-to-severe eczema used moisturizers more frequently than children with mild eczema ($P < 0·001$). Girls used moisturizers more frequently compared with boys ($P < 0·001$).

rhinitis and asthma was, with the highest prevalence rates among boys with moderate-to-severe eczema. Boys used moisturizers less frequently compared with girls, and children with mild eczema used both moisturizers and topical GCS less frequently than children with moderate-to-severe eczema. Our findings have implications for future studies of *FLG* and eczema severity as well as for physicians taking care of children with moderate-to-severe eczema.

The strengths of this study are the prospective, population-based design with a large number of participants, of whom a majority provided blood samples enabling genotyping. A weakness of the study is that information on outcomes, including assessment of eczema disease severity, was obtained from questionnaires only. The eczema definition used in this study has not been validated at the follow-up at 12 years of age. However, at age 2 years our diagnostic criteria for

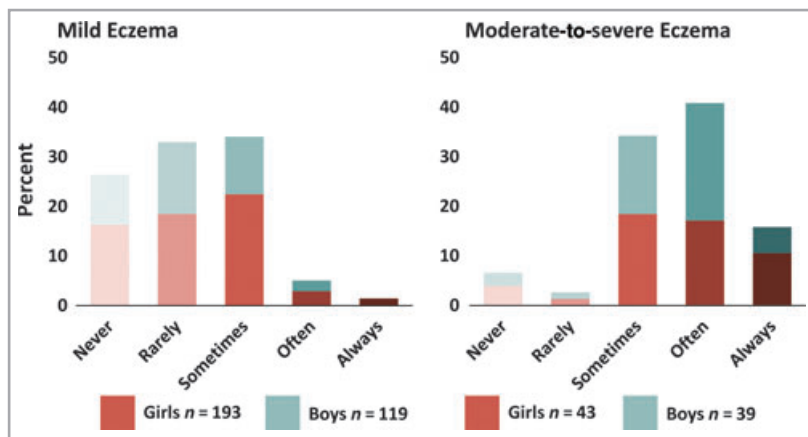


Fig 3. Frequency of use of topical glucocorticoids (GCS) among preadolescent children with mild or moderate-to-severe eczema in the BAMSE birth cohort. Children with moderate-to-severe eczema used topical GCS more frequently than children with mild eczema ($P < 0.001$). There were no significant differences between boys and girls ($P = 0.850$).

Table 4 Type of *FLG* mutation in relation to eczema status among 1854 genotyped preadolescent children in the BAMSE birth cohort

<i>FLG</i> mutation ^a	No eczema (n = 1608), n (%)	Mild eczema (n = 198), n (%)	Moderate-to-severe eczema (n = 48), n (%)	Total (n = 1854), n (%)
R501X	28 (1.7)	11 (5.6)	2 (4.2)	41 (2.2)
2282del4	62 (3.9)	11 (5.6)	5 (10.4)	78 (4.2)
R2447X	14 (0.9)	5 (2.5)	0	19 (1.0)
Any <i>FLG</i> mutation	104 (6.5)	26 (13.1)	6 (12.5)	136 (7.3)

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

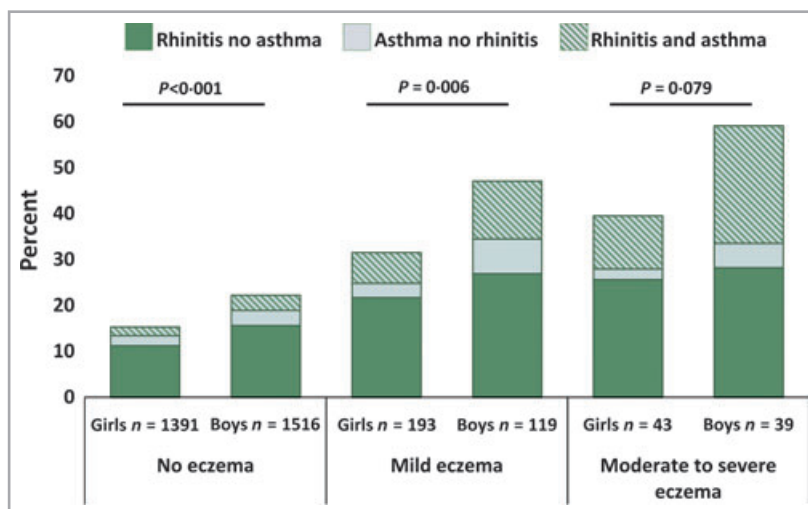


Fig 4. Proportion of girls and boys with asthma and/or rhinitis among preadolescent children with no, mild and moderate-to-severe eczema in the BAMSE birth cohort.

eczema were found to have high sensitivity (92%) and specificity (100%) in relation to clinical diagnosis by a dermatologist.²⁸

The various scales used to measure the severity of eczema differ widely and most scales, patient-oriented or not, are constructed to evaluate current disease severity in order to measure effects of interventions and treatments.^{29–33} The NESS,²⁷ based on the Rajka and Langeland grading,²⁶ was developed for population-based research and assesses eczema severity during the past 12 months. The main difference between NESS

and BESS is that for BESS, parents evaluate disease extent over the past 12 months, whereas for NESS, evaluation of disease extent is based on a single examination. However, in the article where NESS was first presented,²⁷ Emerson and colleagues argued that evaluation of disease extent over the last 12 months might be a better approach. Furthermore, the questions in our study and NESS were not identically worded and the response alternatives were different. The question regarding total time with eczema had four response alternatives in BESS compared with five in NESS, which resulted in

BESS having 14 increments compared with 15 in NESS. Despite these differences, the proportions of children with mild, moderate and severe disease in our study and the validation study of NESS were comparable.²⁷

Studies of potential links between *FLG* mutations and eczema have been performed in different types of populations and almost all have shown a clear association. A meta-analysis of *FLG* mutations in eczema found the strongest association among moderate-to-severe cases of eczema.¹⁷ However, the effect size of *FLG* mutations varies considerably and differences in study designs and definitions of eczema complicate comparison. Studies attempting to investigate whether *FLG* mutations are associated with eczema severity show somewhat conflicting results. One study found no association²¹ while other studies found *FLG* mutations to be associated with eczema severity, albeit weakly.^{18–20,34,35} These studies have mainly been performed in selected populations dominated by moderate-to-severe cases. Based on these findings it has been suggested that patients with eczema, who also have *FLG* mutations, represent a more severe disease phenotype.³⁶ We found no association between *FLG* mutations and eczema severity in our population-based study. In our study, as well as in most other population-based studies, homozygote mutation carriers and compound heterozygote (two different mutations) individuals are few, even among cases (0–0.8%).^{14,37–39} Whereas in selected cohorts of children and adults with mainly moderate-to-severe eczema, compound heterozygote mutations and homozygote mutation carriers are found in up to 10% of cases.^{40,41} Homozygous mutation carriers and compound heterozygote individuals have been shown to have a higher risk of eczema compared with individuals carrying one mutation and some studies indicate that they also have more severe disease.^{19,34} It is possible that the presence of one *FLG* mutation influences development and presence of eczema rather than driving disease severity, while the presence of more than one *FLG* mutation might be of importance for eczema severity. More studies on the importance of *FLG* mutations for eczema severity are needed and it might be beneficial to separate individuals with one mutation from those carrying two mutations (compound heterozygotes or homozygotes) in future analyses.

We found that rhinitis was significantly more prevalent, and that asthma tended to be more prevalent, among children with moderate-to-severe eczema compared with children with mild eczema. This difference was seen for both boys and girls, although no significant differences were found when analysing boys and girls separately. It is well known that asthma and rhinitis are more prevalent among boys at this age.^{42,43} Boys in our study, regardless of whether they had no, mild or moderate-to-severe eczema, had more asthma and rhinitis than girls in the corresponding groups. The relatively large proportion of boys in the group with moderate-to-severe eczema contributes to the higher prevalence of rhinitis and asthma in this group and might have influenced the results.

In summary, we showed that *FLG* mutations did not influence eczema severity in our population-based cohort.

More preadolescent girls than boys have eczema and girls use moisturizers more frequently. Children with moderate-to-severe eczema use both moisturizers and topical GCS more frequently than children with mild disease. We also found the prevalence of rhinitis and asthma to be associated with eczema severity, with the highest prevalence among boys with moderate-to-severe eczema. Physicians who take care of children with eczema should be aware of the high degree of asthma and rhinitis among these children, and the increased risk associated with moderate-to-severe eczema.

What's already known about this topic?

- Children with eczema have a higher risk of asthma and rhinitis.
- Filaggrin mutations increase the risk for eczema.

What does this study add?

- Filaggrin mutations did not correlate with eczema severity in this population-based study.
- Rhinitis and asthma were associated with severity of eczema: the highest prevalence rates were among boys with moderate-or-severe eczema.
- More preadolescent girls than boys had eczema.
- Boys use moisturizers less frequently than girls.

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