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CLINICAL REPORT

Factors Associated with Remission of Eczema in Children: A Population-based Follow-up Study

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The aim of this study was to analyse factors associated with remission of atopic dermatitis (AD) in childhood. A population-based AD cohort of 894 children aged 1–3 years from a cross-sectional baseline study in 2000 was followed up in 2005. The association between remission, background, health, lifestyle, and environmental variables was estimated with crude and multivariable logistic regression. At follow-up, 52% of the children had remission. Independent factors at baseline predicting remission were: milder eczema (adjusted odds ratio (aOR), 1.43; 95% confidence interval (95% CI) 1.16–1.77); later onset of eczema (aOR 1.40; 95% CI 1.08–1.80); non-flexural eczema (aOR 2.57; 95% CI 1.62–4.09); no food allergy (aOR 1.51; 95% CI 1.11–2.04), and rural living (aOR 1.48; 95% CI 1.07–2.05). Certain aspects of AD and rural living were important for remission, but despite the initial hypotheses to the contrary, the environmental factors examined in this paper were not substantial predictors of remission. Key words: atopic dermatitis; epidemiology; longitudinal study; preschool child; prognosis.

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The prevalence of atopic dermatitis (AD), used synonymously with eczema (1) in this report, has increased to a level of public health concern in the Western world, where AD affects 15–20% of pre-school children (2). As the most common inflammatory condition in childhood, AD is characterized by typical flares and itching (3), with an impact on physiological and psychological wellbeing (4). The impairment of quality of life has been estimated to be comparable to that of chronic illnesses such as diabetes or neurological disorders (5). Children with AD have an increased risk of developing asthma and rhinitis (6). Childhood AD leads to substantial social and financial costs (7, 8).

Studies have shown that approximately 50% of childhood AD heals before adolescence (9, 10). However,

there is little knowledge regarding determinants of remission, especially in children (11). The few prospective cohort studies that investigated early childhood AD and later remission have focused on health conditions associated with remission (9, 12–14). Atopic sensitization (9, 14) and wheezing (9, 12) were found to be associated with remission of eczema in 2 studies each, but there were conflicting results regarding rhinitis (9, 12). Heredity was assessed in 1 study and was associated with remission (9). Thus, further evidence is needed about the impact of allergic diseases and health conditions on remission of eczema. Beyond this, there has been little investigation into the impact of other issues, such as environmental factors and lifestyle. To our knowledge, only one study has assessed the influence of gender, parental smoking, breastfeeding, and antibiotic consumption, and this found no association with remission (9).

To make recommendations on how to increase the chance of eczema remission, more information is needed on modifiable environmental and behavioural factors as well as health factors associated with remission. Given the lack of evidence about non-health variables, we hypothesized that factors that are associated with the prevalence and incidence of allergic diseases might also be inversely associated with remission of AD.

In terms of environmental factors, it has been shown that the prevalence of AD was higher in children living in an urban area, or in a home with polyvinyl chloride (PVC) flooring (15–17). The prevalence of AD was also greater in children attending day-care (18). Lifestyle factors that have been suggested as predictors of AD prevalence are parental smoking, short period of breastfeeding (19), and antibiotic consumption (20), but the evidence is not conclusive (21, 22), and the only study to our knowledge assessing the impact of these factors on the prognosis of eczema found no association (9). Examination of non-modifiable factors is important to identify risk groups. There is no evidence as yet whether gender, socioeconomic status (SES), and birth order predict remission, although they are associated with eczema prevalence (9, 15–17, 21). Therefore, this study aimed to determine factors associated with remission of AD in childhood, and the strength of selected modifiable factors in predicting remission.

METHODS

Study design and study population

The Swedish Dampness in Building and Health (DBH) study, started in 2000 with a baseline questionnaire, based on an International Study of Asthma and Allergies in Childhood (ISAAC) protocol (23), to parents of all children aged 1–5 years living in the county of Värmland (DBH-I), with follow-up in 2005 of children aged 1–3 years at baseline in 2000 (DBH-III). In total 4,779 (4,779/7,509, 63.6%) children were included in both baseline and follow-up questionnaires, of whom 894 (18.7%) had eczema during the 12 months prior to the baseline interview and constituted the population for this study (Fig. S1[†]).

Inclusion criteria in the baseline survey were all children in Värmland aged 1–5 years registered on the 2000 Census whose parents were Swedish-speakers and who consented to participate. The methods of data collection for DBH are described elsewhere (23, 24). We excluded from the analysis 65 (7.3%) children for whom data were missing for the variables analysed, leaving 829 children in the study (details on missing values are given in Appendix S1[†]).

The sample size was determined by the number of eligible children and participation rate, but power calculations were undertaken to determine whether this was sufficient to validate our planned analysis. Based on the results of Illi et al. (9), a sample size calculation for the theoretically most important explanatory factors, severity, asthma, and heredity, and their association with remission of eczema was performed with a power of 90% and alpha error of 5%. Assuming the ratio of exposed/unexposed to be 1:2, the maximum number needed would be 232. Allowing for all 19 covariates 380 children were needed in the analysis. Thus, the sample size of the current study of 829 children should be sufficient to detect associations between these factors and remission.

Variables and model structure

All the data were extracted from the parental questionnaires (24). For the disease variables (eczema, asthma and rhinitis) the original ISAAC questionnaire was used (23), i.e. “Has your child ever had an itchy rash which was coming and going for at least 6 months?” In addition, questions on doctor-diagnosed asthma and doctor-diagnosed rhinitis were included. The additional questions were: “Has your child been diagnosed with asthma by a physician?” and “Has your child been diagnosed with rhinitis by a physician?” Medical records were not cross-checked. We did not differentiate between atopic and non-atopic eczema in accordance with the World Allergy Organization’s definition of eczema (1).

Children included were assessed as having AD at baseline, and thus parents answering yes to the 2 questions: “Has your child ever had an itchy rash which was coming and going for at least 6 months?” and “Has your child had this itchy rash at any time in the last 12 months?” The main outcome in the study was remission of eczema. Remission was defined as having an answer “yes” to the ISAAC question “Has your child had this itchy rash at any time in the last 12 months?” at baseline in 2000 ($n=829$), and an answer “no” at follow-up in 2005. Possible explanatory variables are described in Table S1[†] for predefined risk factors for the main analysis. The severity of eczema was indicated by the ISAAC question “In the last 12 months, how often, on average, has your child been kept awake at night by this itchy rash?” Sleep loss several times per week was considered to indicate severe eczema (23, 25). Onset of eczema was determined from the question “At

what age did this itchy rash first occur?” Location of the eczema was indicated from the question. “Has this itchy rash at any time affected any of the following places: the fold of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?”

Food allergy was assessed via questionnaire, and parents were asked: “Has the child at any time had allergic irritations, such as eczema, nettle-rash, diarrhoea, rhinitis, swollen lips or swollen eyes caused by the following foods: milk or dairy products, eggs, fish, peanuts, nuts, almond, soya, peas, beans, fruit, vegetables or other?”

A hierarchical *a priori* model was built based on factors that have been associated with the prevalence and incidence of eczema, e.g. lifestyle, gender, home environmental factors, socioeconomic status (SES), and birth order (15–19, 21), as shown in Table S1[†]. We assumed that these factors might be inversely associated with remission of eczema. The model was later used to structure the statistical analysis, and hierarchical interrelationships were taken into account when exploring the effect of such factors (26). To determine how to build our final model we grouped together factors that were related (e.g. asthma and rhinitis). We then put these groups in a hierarchical order; factors that were earlier in a pathway or considered less influential were distal, while those with a more immediate influence on eczema were proximate (e.g. breastfeeding was present in time before any asthma or rhinitis occurred so breastfeeding was more distal). Table S1[†] explains how, in the model, possible predictors of remission of eczema are hypothetically related. In Table S1[†], the rows indicate factors that are grouped together conceptually. The model assumes that heredity and concomitant allergic diseases (9, 12) are associated both with eczema, asthma and rhinitis (27). Socioeconomic factors affect birth outcome, home environment, lifestyle, day-care attendance, environmental tobacco smoke, antibiotic consumption, and breastfeeding (28–32). The home environment possibly influences birth outcome (33). These variables, as well as birth-weight influence allergic diseases (11, 12, 15, 21, 34–36). All factors cited above might influence remission of eczema (9, 20, 21, 37–40).

Statistical analysis

Drop-out analyses were performed with respect to background, health and socioeconomic factors using the χ^2 test. First, crude odds ratios (ORs) were calculated for each variable with the category expected to have the lowest effect on remission as reference. Linear effects were evaluated for ordered categorical variables with 3 or more categories. A p -value ≤ 0.05 was used to indicate significance. Then, within conceptual groups with multiple variables, factors were identified that remained associated when adjusted for other factors within the group. These were thereafter taken to represent that group. Specific factors were retained even if the p -value was not low if there were strong theoretical reasons to believe they could be risk factors, so that their contribution could be judged in this data-set. The final model was built by sequentially adding in the retained factors from each group according to the framework of the way in which the factors were presumed to operate. If a parameter altered in value when more variables were added into the model, this could be taken as an indication of confounding or of a pathway, depending on the conceptual model used. Factors might influence remission differently in children with mild vs. severe eczema, because severity might convey susceptibility toward these influences due to more impaired skin function. In addition, the impact of severity might itself vary by age of onset because the window of opportunity for environmental factors priming immunological pathways could appear early in infancy. We therefore tested whether the effect of several factors differed across severity groups, and if there was an interaction between severity and age of onset. In the adjusted

[†]<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1681>

model, the interaction was explored between severity of eczema and each of heredity, problems with paying bills, home location, age of onset, and location of eczema. The Hosmer-Lemeshow goodness-of-fit test (41) provided evidence that the final full logistic model accounted well for the outcome of remission of eczema ($p=0.25$).

We undertook a sensitivity analysis comparing the relationship across both subjective (symptom-orientated) and objective (disease terms) measures of asthma and rhinitis with remission. This was performed in case the respondents' perceptions of symptoms were stronger indications of health status than the disease terms.

The children belonged to 812 households, but no clustering effects were detected after statistical assessment, and therefore no adjustment was made for clustering. The study was approved by the regional ethics committee in Örebro, Sweden.

RESULTS

The study population was evenly divided by sex, with most children aged 2 years (or older). Most children were breastfed longer than 6 months (68%), were a first-born child (73%), had non-smoking parents (80%), lived in urban or suburban surroundings (72%), and attended day-care (92%). A high proportion of children had at least one parent with a history of allergic disease (62%). The prevalence of physician-diagnosed asthma at baseline eczema was 11%, and physician-diagnosed rhinitis was 3.4%. Of the 829 children with eczema at baseline and complete information at follow-up, 484 (52%) reported no eczema during the 12 months preceding their follow-up interview in 2005. Table I shows the characteristics of the study population.

Drop-out analysis

There was no difference in baseline age or health factors (prevalence of asthma, wheezing, rhinitis, and food allergy, eczema features, parental history of allergic disease) ($p>0.1$; χ^2 test) between drop-outs and included subjects. Drop-outs showed a higher prevalence of girls (61% vs. 50%; $p=0.002$), parental smoking (33% vs. 20%; $p<0.001$), single-parent family (18% vs. 9%; $p<0.001$), and living in a multi-family house (30% vs. 20%; $p=0.001$) compared with participants.

Associations between factors and remission of eczema in a crude analysis during a 5-year period

The crude analyses shown in Table I identified factors at baseline that were clearly associated with remission and those which, contrary to our hypotheses, were not associated. All groups with milder or later eczema (onset of eczema after the age of 1 year, mild and moderate eczema, non-flexural eczema), and absence of other allergic diseases (absence of diagnosis of asthma, rhinitis, and food allergies) had higher odds of remission. Testing for trend showed that the milder the eczema and the older the age at onset, the higher

the odds of remission (odds ratio (OR) 1.64; 95% confidence interval (95% CI) 1.34–2.00; OR 1.66; 95% CI 1.30–2.11, respectively), and there was no evidence for deviation from trend ($p=0.720$; $p=0.637$, respectively). Regarding family lifestyle, there were higher odds of remission if living rurally. Other factors were also associated with remission, such as having no or only one parent with a history of allergic disease (heredity), and age (birth environment). Other factors related to the birth environment (birth order, sex, problems paying bills, or parental smoking) or family lifestyle groups (bedrooms with PVC flooring material, home construction, breastfeeding, antibiotic consumption and kindergarten attendance) were not associated with remission and neither was birth-weight.

Group adjustments

The following factors were statistically significant when adjusted for other factors in their group and were therefore taken forward to the full model: parental history of allergic disease, place of residence, physician-diagnosed rhinitis, age at onset, severity, and location of AD. In addition, difficulty paying bills, although not statistically significantly associated, was retained *a priori*, as socioeconomic status is known to influence many aspects of health. The factors of physician-diagnosed asthma, age and birth-weight were not associated with remission at this stage and therefore were not retained in the model.

Full model

The parameters for the successive steps to the full model are shown in Table SII¹. In the final sequence of modelling in multivariable analysis, the eczema variables "milder eczema", "later onset" and "non-flexural eczema" were the strongest predictors of remission; the other allergic diseases variables of absence of "physician-diagnosed rhinitis", and "food allergy" were associated with greater odds of remission, but the association of physician-diagnosed rhinitis/remission had a p -value >0.05 because of small numbers. The family lifestyle variable "rural living" remained strongly associated with remission (Table SII¹).

The strength of the association between the distal heredity variable "parental history of allergic disease" and remission decreased when adjusted for variables related to "aspects of eczema" and "other allergic diseases". For the birth environment variable "problems paying bills", the attenuation came when "aspects of eczema" were added. In total, the parameters did not change substantially across the models, which suggests that the groups were largely independent.

There was no statistical interaction between severity of eczema and the following factors: heredity, problems paying bills, home location, age of onset and location

Table I. Description of 829 children with eczema^a aged 1–3 years in 2000 in Värmland, Sweden and crude associations between factors at baseline and remission of eczema^b during 5-year follow-up

Variables	Subjects <i>n</i> (%)	With remission <i>n</i> (%)	Crude OR (95% CI)	LRT <i>p</i> -value
<i>Heredity</i>				
Parental history of allergic disease				
Both parents	146 (17.6)	63 (43.2)	1.00 (–)	0.020
One parent	364 (43.9)	207 (56.9)	1.74 (1.18–2.56)	
No parent	319 (38.5)	168 (52.7)	1.47 (0.99–2.17)	
<i>Birth environment</i>				
Birth order				
First	608 (73.3)	325 (53.5)	1.00 (–)	0.550
Second and third	212 (26.7)	113 (50.0)	0.91 (0.67–1.24)	
Age				
1 year	212 (25.6)	109 (51.4)	1.00 (–)	0.021
2 years	304 (36.7)	179 (58.9)	1.35 (0.95–1.93)	
3 years	313 (37.8)	150 (47.9)	0.87 (0.61–1.23)	
Sex				
Girl	410 (49.5)	209 (51.0)	1.00 (–)	0.289
Boy	419 (50.5)	229 (54.7)	1.16 (0.88–1.52)	
Problems paying bills ^c				
Yes	107 (12.9)	52 (48.6)	1.00 (–)	0.347
No	722 (87.1)	386 (53.5)	1.22 (0.81–1.82)	
Parents smoke				
Yes	167 (20.1)	92 (78.1)	1.00 (–)	0.513
No	662 (79.9)	346 (13.0)	0.89 (0.63–1.26)	
<i>Birth outcome</i>				
Birth-weight				
>4,200 g	115 (14.0)	58 (50.4)	1.00 (–)	0.261
2,500–4,200 g	683 (83.1)	366 (53.6)	1.13 (0.76–1.68)	
<2,500 g	24 (2.9)	9 (37.5)	0.59 (0.24–1.46)	
<i>Family lifestyle</i>				
Breastfeeding				
>6 months	561 (68.1)	300 (53.5)	1.00 (–)	0.104
3–6 months	171 (20.8)	81 (47.7)	0.78 (0.56–1.10)	
<3 months	92 (11.2)	56 (60.9)	1.35 (0.86–2.12)	
Antibiotic consumption				
Yes	633 (76.4)	334 (52.8)	1.00 (–)	0.942
No	196 (23.6)	104 (53.1)	1.01 (0.73–1.40)	
House location				
Urban	593 (71.5)	297 (50.1)	1.00 (–)	0.001
Rural	236 (28.5)	141 (59.8)	1.48 (1.09–2.01)	
House built, year				
>1984	121 (15.5)	68 (56.2)	1.00 (–)	0.027
1960–1984	313 (40.0)	148 (47.3)	0.70 (0.46–1.07)	
<1960	349 (44.6)	200 (57.3)	1.05 (0.69–1.59)	
Number of bedrooms with PVC flooring-material				
2	314 (39.0)	167 (53.2)	1.00 (–)	0.941
1	159 (19.8)	82 (51.6)	0.97 (0.67–1.42)	
0	333 (41.3)	174 (52.3)	1.04 (0.76–1.41)	
Day-care attendance				
No	60 (8.3)	35 (47.0)	1.00 (–)	0.221
Yes	659 (91.7)	349 (53.5)	1.30 (0.85–1.97)	
<i>Aspects of eczema</i>				
Age at onset of eczema				
<1 year	471 (56.8)	222 (47.1)	1.00 (–)	<0.001
1–2 years	320 (38.6)	188 (58.8)	1.60 (1.20–2.13)	
>3 years	38 (4.6)	28 (74.4)	3.14 (1.49–6.61)	
Flexural eczema				
Yes	715 (86.3)	353 (49.4)	1.00 (–)	<0.001
No	114 (13.8)	85 (74.6)	3.01 (1.92–4.70)	
Awake at night due to eczema (per week)				
Several nights	105 (12.7)	35 (33.3)	1.00 (–)	<0.001
≤1 night	157 (18.9)	74 (47.1)	1.78 (1.07–2.98)	
Never	567 (68.4)	329 (58.0)	2.76 (1.78–4.29)	

Table I contd.

<i>Other allergic diseases</i>				
Food allergy				
Yes	323 (39.0)	143 (44.3)	1.00 (–)	< 0.001
No or do not know	506 (61.0)	295 (58.3)	1.76 (1.33–2.33)	
Wheezing during last 12 months				
Yes	273 (33.4)	132 (48.4)	1.00 (–)	0.074
No	544 (66.69)	299 (55.0)	1.33 (0.97–1.74)	
Asthma, physician diagnosis				
Yes	91 (11.1)	38 (41.8)	1.00 (–)	0.026
No	728 (88.9)	394 (54.1)	1.65 (1.06–2.56)	
Rhinitis symptoms during last 12 months				
Yes	156 (19.1)	75 (48.1)	1.00 (–)	0.206
No	661 (80.9)	355 (53.7)	1.25 (0.88–1.78)	
Rhinitis, physician diagnosis				
Yes	28 (3.4)	7 (25.0)	1.00 (–)	0.002
No	801 (96.6)	431 (53.8)	3.50 (1.49–8.31)	

All children without missing data were included in the analysis. ^aEczema during the last 12 months in 2000; ^beczema during the last 12 months in 2000, but not during the last 12 months in 2005; ^cduring the last 12 months in 2005. OR: odds ratio; CI: confidence interval; LRT: likelihood ratio test.

of eczema (interaction *p*-values: $p_{\text{heredity/severity}} = 0.289$; $p_{\text{financial problems/severity}} = 0.786$; $p_{\text{home location/severity}} = 0.035$; $p_{\text{age of onset/severity}} = 0.572$; $p_{\text{location of eczema/severity}} = 0.245$).

Sensitivity analysis

As with the physician diagnoses of asthma, wheezing symptoms showed no relationship with remission in the adjusted analysis (aOR 1.18; 95% CI 0.86–1.60).

DISCUSSION

This study demonstrated that approximately half of the children with eczema in early childhood at baseline did not have eczema during a 1-year period prior to follow-up in 2005. Aspects of eczema that dominated the predictors of remission 5 years later were mildness, later onset, and non-flexural location. The environmental factors that were explored in this study had surprisingly low association with remission. Heredity and proneness to allergic diseases were also predictors; those with no or only 1 parent with eczema, and those without rhinitis or food allergies had higher odds of remission than others. The strongest environmental factor was rural living. Non-modifiable factors of birth order and gender were not predictive, nor were behavioural factors such as parental smoking, breastfeeding, antibiotic consumption and day-care attendance. Regarding the home environment, PVC flooring in the home, a factor associated with the incidence of asthma (36), was also not associated with eczema remission.

A major advantage of this study was the prospective design, which made the results less vulnerable to recall bias and allowed assessment of a temporal relationship. The large sample size minimized chance as the source of the findings for the predefined main analysis; however,

given that multiple tests were conducted, chance cannot fully be excluded. The population-based design made results less prone to selection and ascertainment bias. Another reason for data quality is the high response rate and limited loss to follow-up. There were no differences between the analysed sample and drop-outs in health-related variables, and there was only higher prevalence in non-responders regarding parental smoking, single-parent family and living in a multi-family home, which should not have biased results. We did not observe that siblinghood influenced our results. However, most children were first-born in our study population because they came from single-child families. Therefore, it cannot be excluded that birth order might have influenced our results if we had a study population with more siblings. For example, AD has previously been shown to develop more commonly in second-born than in first-born children (42), but there are also conflicting results (43). Further studies will be needed to determine whether incidence and remission of eczema are associated with the same factors.

Our study design did not include a direct assessment of atopic and non-atopic eczema by blood serum immunoglobulin E (IgE) or a skin-prick test. Future research is needed with a specific focus on possible differential effects of factors on remission in sensitized and non-sensitized children.

A questionnaire that assesses the presence of eczema can have advantages over physician diagnosis, as eczema can be intermittent (38). Although self-report can in some cases be unreliable, the term "itchy flexural rash in the last 12 months" has been shown to correlate well with diagnosis by a physician in a validation study done in the UK in children aged 3–11 years. Sensitivity was 84% and specificity 93% (25). The ISAAC questionnaire has not been validated on parental information about preschool children, and there might therefore be some risk of misclassification. However, we saw no indication for differential misclassification, e.g. age at onset of eczema (1 of the strongest predictors) did not show any indication of systematic bias; earlier onset would suggest recall bias/information bias, but the odds were higher in early onset eczema. Random misclassification would mean that any bias in our estimates was towards the null. A recently performed validation study of a parental questionnaire that was based on the ISAAC eczema questions has shown that questionnaire diagnosis of infant and preschool eczema is possible with high accuracy (44). Non-flexural sites are common in infants (45, 46), and AD prevalence in our study is in accordance with other studies (47). However, we cannot exclude that some of the infants who had non-flexural eczema had skin diseases other than AD.

As yet, no clear definition of remission of eczema exists (11). Illi et al. (9) considered cases to be in remission when disease signs were not present at follow-up.

In the current study, remission was defined as not having eczema during a 12-month period in 2005, which should minimize misclassification of children who have "repeated temporary rashes", and would also take into account seasonal variations. We may not have captured fully the effects of economic deprivation as we had to use a crude assessment of "problems paying bills."

In our models, milder eczema, later onset eczema and non-flexural eczema were the strongest predictors of remission. Aspects of eczema are proximate factors in the hierarchy; more distal factors may contribute to severity and hence to the chance of remission and thus contribute indirectly on a pathway; parameters for heredity were attenuated on addition of health variables, suggesting that having at least 1 parent without eczema is indirectly important for remission. Similar to our results in the adjusted analysis, rhinitis and asthma were not significantly associated with the remission of eczema in adults in Sandström & Faergemann's study (48).

Findings from the studies of Peters et al. (49) and Illi et al. (9), that breastfeeding, parental smoking, kindergarten attendance, gender, birth order, and number of infectious diseases were not associated with an increase in the odds of eczema persistence is supported by our findings. Low birth-weight decreased the odds of eczema during childhood (11), and to the best of our knowledge, no study has investigated the relationship between birth-weight and remission of eczema. Our analysis indicated there was no strong association.

In accordance with our results, Illi et al. (9), Gustavsson et al. (50) and Ricci et al. (51) reported that eczematous children with high severity scores were at increased odds of persistence of eczema. The effect of a parental history of allergic disease decreased in the full model; it is possible that the indirect effect of parental history of allergic disease is passed via features of eczema and concomitant allergic diseases (26). In the current study a weak association between SES and remission was seen only in the full model, suggesting a mediating effect of health factors (26). The association might have been stronger if other aspects of SES could have been included. Recently, Peters et al. (49) suggested that eczema is a "middle-class disease".

The important effect of eczema features may be explained by the presence of more impaired epithelial function in more severe cases, which may increase sensitization and IgE production (52), thus increasing the risk of a lack of remission of AD.

Knowledge of the predictors of remission could have a major impact on patient management, since eczema can lead to impairment of quality of life and health-related costs. Besides a positive effect of rural living, predictors of remission were found in health factors. The advantages of the study design and analysis may allow generalization of the results to other childhood populations in Sweden and countries with a similar

setting. Further evidence is needed to determine the underlying mechanisms of the factors associated with remission. In this regard, impaired skin function might be an explanatory factor; impaired skin promotes sensitization (52), and sensitization is a factor associated with no remission of AD (14). The effect of early and successful treatment of eczema should be explored (53, 54). Based on the data, there is no evidence to recommend that families with children with eczema should change their home environment (55).

In conclusion, the most important factors for remission of early childhood eczema within 5 years were mild disease symptoms, later onset of eczema, and non-flexural location of the eczema. The only environmental factor found to be associated with remission of eczema was rural living. Thus, this study does not provide evidence for changing the modifiable lifestyle and environmental factors that were analysed in this paper. A longer follow-up of the cohort would be beneficial to determine whether remission was maintained. Given the relevance of an earlier history of eczema for remission during our year of study, treatment interventions should be studied for the effect on duration of remission.

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REFERENCES

- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113: 832–836.
- Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. Development of atopic dermatitis in the DARC birth cohort. *Pediatr Allergy Immunol* 2010; 21: 307–314.
- Bieber T. Atopic dermatitis. *N Engl J Med* 2008; 358: 1483–1494.
- Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006; 60: 984–992.
- Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; 155: 145–151.
- Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis D. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. *J Am Acad Dermatol* 2007; 58: 68–73.
- Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. *Pediatr Dermatol* 2005; 22: 192–199.
- Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child* 1997; 76: 159–162.
- Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; 113: 925–931.
- Sandstrom Falk MH, Faergemann J. Atopic dermatitis in adults: does it disappear with age? *Acta Derm Venereol* 2006; 86: 135–139.
- Williams HC. Atopic dermatitis: the epidemiology, causes and prevention of atopic eczema. Cambridge: Cambridge University Press; 2000.
- Mohrenschlager M, Schafer T, Huss-Marp J, Eberlein-König B, Weidinger S, Ring J, et al. The course of eczema in children aged 5–7 years and its relation to atopy: differences between boys and girls. *Br J Dermatol* 2006; 154: 505–513.
- Rottem M, Darawsha J, Zarfin J. Atopic dermatitis in infants and children in Israel: clinical presentation, allergies and outcome. *Isr Med Assoc J* 2004; 6: 209–212.
- Ziyab AH, Raza A, Karmaus W, Tongue N, Zhang H, Matthews S, et al. Trends in eczema in the first 18 years of life: results from the Isle of Wight 1989 birth cohort study. *Clin Exp Allergy* 2010; 40: 1776–1784.
- Larsson M, Hagerhed-Engman L, Sigsgaard T, Janson S, Sundell J, Bornehag CG. Incidence rates of asthma, rhinitis and eczema symptoms and influential factors in young children in Sweden. *Acta Paediatr* 2008; 97: 1210–1215.
- Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis? *J Allergy Clin Immunol* 2004; 114: 150–158.
- Thestrup-Pedersen K. Clinical aspects of atopic dermatitis. *Clin Exp Dermatol* 2000; 25: 535–543.
- Hagerhed-Engman L, Bornehag CG, Sundell J, Aberg N. Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. *Allergy* 2006; 61: 447–453.
- Yang Y, Tsai C, Lu C. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. *Br J Dermatol* 2009; 161: 373–383.
- Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? *Br J Dermatol* 2005; 152: 202–216.
- Apfelbacher CJ, Diepgen TL, Schmitt J. Determinants of eczema: population-based cross-sectional study in Germany. *Allergy* 2011; 66: 206–213.
- Kusel M, Klerk ND, Holt P, Sly P. Antibiotic use in the first year of life and risk of atopic disease in early childhood. *Clin Exp Allergy* 2008; 38: 1921–1928.
- Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–491.
- Bornehag CG, Sundell J, Sigsgaard T. Dampness in buildings and health (DBH): Report from an ongoing epidemiological investigation on the association between indoor environmental factors and health effects among children in Sweden. *Indoor Air* 2004; 14(Suppl 7): 59–66.
- Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999; 103: 125–138.
- Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. *Int J Epidemiol* 1997; 26: 224–227.
- Burgess JA, Lowe AJ, Matheson MC, Varigos G, Abramson MJ, Dharmage SC. Does eczema lead to asthma? *J Asthma*

- 2009; 46: 429–436.
28. Blumenshine P, Egerter S, Barclay CJ, Cubbin C, Braveman PA. Socioeconomic disparities in adverse birth outcomes: a systematic review. *Am J Prev Med* 2010; 39: 263–272.
 29. Flacking R, Nyqvist KH, Ewald U. Effects of socioeconomic status on breastfeeding duration in mothers of preterm and term infants. *Eur J Public Health* 2007; 17: 579–584.
 30. Mangrio E, Wremp A, Moghaddassi M, Merlo J, Bramhagen A-C, Rosvall M. Antibiotic use among 8-month-old children in Malmö, Sweden in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. *BMC Pediatrics* 2009; 9: 31.
 31. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. *Ann N Y Acad Sci* 1999; 896: 3–15.
 32. Lagerberg D, Magnusson M, Sundelin C. Child health and maternal stress: does neighbourhood status matter? *Int J Adolesc Med Health* 2011; 23: 19–25.
 33. Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, et al. Prenatal phenol and phthalate exposures and birth outcomes. *Environ Health Perspect* 2008; 116: 1092–1097.
 34. Gold DR, Bloomberg GR, Cruikshank WW, Visness CM, Schwarz J, Kattan M, et al. Parental characteristics, somatic fetal growth, and season of birth influence innate and adaptive cord blood cytokine responses. *J Allergy Clin Immunol* 2009; 124: 1078–1087.
 35. Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health* 2005; 26: 89–113.
 36. Larsson M, Hagerhed-Engman L, Kolarik B, James P, Lundin F, Janson S, et al. PVC – as flooring material – and its association with incident asthma in a Swedish child cohort study. *Indoor Air* 2010; 20: 494–501.
 37. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. *Curr Probl Dermatol* 2011; 41: 1–34.
 38. Wuthrich B. Clinical aspects, epidemiology, and prognosis of atopic dermatitis. *Ann Allergy Asthma Immunol* 1999; 83: 464–470.
 39. Peroni DG, Piacentini GL, Bodini A, Rigotti E, Pigozzi R, Boner AL. Prevalence and risk factors for atopic dermatitis in preschool children. *Br J Dermatol* 2008; 158: 539–543.
 40. Bieber T, Leung D, editors. *Atopic Dermatitis*. 2nd ed. Informa Healthcare; 2009.
 41. Lemeshow S, Hosmer DW, Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol* 1982; 115: 92–106.
 42. Olesen AB, Ellingsen AR, Larsen FS, Larsen PO, Veien NK, Thestrup-Pedersen K. Atopic dermatitis may be linked to whether a child is first- or second-born and/or the age of the mother. *Acta Derm Venereol* 1996; 76: 457–460.
 43. Böhme M, Wickman M, Lennart Nordvall S, Svartengren M, Wahlgren CF. Family history and risk of atopic dermatitis in children up to 4 years. *Clin Exp Allergy* 2003; 33: 1226–1231.
 44. von Kobyletzki LB, Berner A, Carlstedt F, Hasselgren M, Bornehag CG, Svensson Å. Validation of a parental questionnaire to identify atopic dermatitis in a population-based sample of children up to 2 years of age. *Dermatology* 2013; 226: 222–226.
 45. Halkjaer LB, Loland L, Buchvald FF, Agner T, Skov L, Strand M, et al. Development of atopic dermatitis during the first 3 years of life: the Copenhagen prospective study on asthma in childhood cohort study in high-risk children. *Arch Dermatol* 2006; 142: 561–566.
 46. Carson CG, Rasmussen MA, Thyssen JP, Menné T, Bisgaard H. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective cohort study. *PLoS ONE* 2012; 7: e48678.
 47. Ballardini N, Kull I, Lind T, Hallner E, Almqvist C, Ostblom E, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. *Allergy* 2012; 67: 537–544.
 48. Sandström MH, Faergemann J. Prognosis and prognostic factors in adult patients with atopic dermatitis: a long-term follow-up questionnaire study. *Br J Dermatol* 2004; 150: 103–110.
 49. Peters AS, Kellberger J, Vogelberg C, Dressel H, Windstetter D, Weinmayr G, et al. Prediction of the incidence, recurrence, and persistence of atopic dermatitis in adolescence: a prospective cohort study. *J Allergy Clin Immunol* 2010; 126: 590–595.
 50. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis – a prospective follow-up to 7 years of age. *Allergy* 2000; 55: 240–245.
 51. Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; 55: 765–771.
 52. Cookson W. The immunogenetics of asthma and eczema: a new focus on the epithelium. *Nat Rev Immunol* 2004; 4: 978–988.
 53. Ricci G, Patrizi A, Giannetti A, Dondi A, Bendandi B, Masi M. Does improvement management of atopic dermatitis influence the appearance of respiratory allergic diseases? A follow-up study. *Clin Mol Allergy* 2010; 8: 8.
 54. Simpson EL, Hanifin JM. Atopic dermatitis. *J Am Acad Dermatol* 2005; 53: 115–128.
 55. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; 4: 1–191.