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Hand eczema in adolescents and atopic dermatitis; a prospective cohort study from the BAMSE project

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Abstract

Background: There is a well-known association between atopic dermatitis and hand eczema but less is known about how age at onset, persistence and severity of atopic dermatitis influence the risk of developing hand eczema.

Objectives: To examine the role of atopic dermatitis for occurenceof hand eczema in adolescence. In addition, associations between asthma and rhinoconjunctivitis, sensitization to common airborne and food allergens and hand eczema were studied.

Methods: From the population-based birth cohort BAMSE, 2,927 adolescents that had been followed up repeatedly concerning allergy related disease were included. Questionnaires identified adolescents with hand eczema at 16 years and blood was analysed for specific IgE.

Results: A total of 152 (5.2%) adolescents had hand eczema at age 16. Many of these adolescents had a history of atopic dermatitis and asthma and/or rhinitis; 73.0% (n=111) and 54.6% (n=83), respectively. Children with atopic dermatitis (age 0-16) had more than threefold increased odds ratios (OR) for having hand eczema, those with persistent or severe atopic dermatitis had crude OR 6.1 (95% CI 4.0-9.1) and crude OR 5.3 (95% CI 2.9-9.6), respectively.

Conclusions: We confirm a strong association between atopic dermatitis during childhood and hand eczema in adolescence. Children with persistent or more severe atopic dermatitis are at greater risk of developing hand eczema. Asthma and/or rhinoconjunctivitis, positive specific IgE, or age at onset of atopic dermatitis is not associated with hand eczema in adolescence.

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Introduction

The incidence rate of hand eczema in adolescence is of the same magnitude as in adults (573/100,000 person-years) and we have recently found that the 1-year period prevalence of hand eczema is 5.2% among Swedish adolescents.[5] Hand eczema (dermatitis on the hands) is often long-lasting, severely affecting the quality of life and working capacity.[6, 7] Hand eczema has a multifactorial etiology where atopic dermatitis (AD) is one of the strongest associated factors[10-15] but data is scarce concerning how age at onset, persistence and severity of AD influence the risk of developing hand eczema. Previous studies are also often hampered by retrospective data collection of allergy related disease manifestations and likely influenced by recall bias or not based on the general population. In addition, it remains unclear how symptoms of asthma, rhinoconjunctivitis, IgE sensitization to common allergens and heredity of parental allergy related disease influence the risk of developing hand eczema.

In the present study, we used data from a Swedish birth cohort[16] to examine the role of allergic disease in childhood in the occurrence of hand eczema in adolescence. The prospective design, where information on symptoms of AD, asthma, rhinoconjunctivitis and IgE sensitisation have been collected repeatedly through childhood, enabled us to explore the influence of age at onset, persistence and severity of AD as well as occurrence of asthma and rhinoconjunctivitis.

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Materials and Methods

Study population

The BAMSE project is a closed population-based birth cohort where children were consecutively recruited at birth and prospectively followed up to 16 years of age.[16] All children born between 1994 and 1996 in predefined areas of Stockholm, Sweden were invited to participate. The included children (n=4,089) represented 75% of the eligible children.[16] Data on parental history of allergy related disease, children's environmental exposure and life style factors were obtained shortly after birth (mean age two months). Thereafter, parents answered detailed questionnaires concerning manifestations of AD, asthma and rhinoconjunctivitis at one, two, four, eight, 12 and 16 years of age.[16] At the follow-ups at 12 and 16 years of age the children also answered a questionnaire, and at 16 years of age questions about hand eczema were also included.[5] In all the follow-up questionnaires the response rate has been high (retention through to age 16 was 78%, n=3,181).[8]

We defined the present study population according to all adolescents where both the adolescent and a parent had answered the question about ever having experienced hand eczema. "Have you/has your child ever had hand eczema (itching eruption, vesicles or itching rash)?".[5] For the occurrence of hand eczema during the past 12 months at the 16 years follow-up the children's response was used "Have you had hand eczema on any occasion during the past 12 months?" (this question has been previously validated).[18]

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Definition of allergy related disease variables

For definitions of AD, asthma and rhinoconjunctivitis see Table 1. Onset of AD, asthma and rhinoconjunctivitis were divided into two time periods: onset before four years of age and onset from four years of age up to 16 years of age. These time intervals were based on the fact that a majority of the children with AD had symptoms before four years of age, and after that the number of children with new onset of symptoms was rather constant.

To study persistence of AD another set of variables were created based on if the children had symptoms of AD during one or both of the two different time periods mentioned above. If they only had symptoms during one of the time periods they were defined as having occasional AD and if they had symptoms during both time periods they were defined as having persistent AD.

History of parental allergy related diseases was considered positive if mother and/or father had ever had a doctor´s diagnosis of asthma and/or rhinitis in combination with allergy to furred pets and/or pollen allergy, and/or AD according to the questionnaires at 0 and/or eight years of age.[8]

Serologic allergy testing to common food and airborne allergens was performed at follow-ups at four, eight and 16 years of age. IgE-value for Phadiatop ≥0.35 kU_A/L and/or IgE-value for food mix ≥0.35 kU_A/L at four and/or eight and/or 16 years of age were considered as positive. The analysis of IgE antibodies was performed with Pharmacia CAP system Phadiatop® and fx5® that analyse mixtures of 14 common airborne and food allergens, respectively.[17, 19]

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Severity of hand eczema and AD

The BAMSE Eczema Severity Score (BESS) was used for evaluation of severity of AD. BESS was developed from the questions used at the follow-up at 12 years of age in the BAMSE project.[4] BESS was constructed based on responses to three questions: number of months with active AD during the past year, how the child´s sleep was affected by the AD during the past year, and the number of body sites involved during the past year (1-6 body sites). BESS scale is 3-14 with BESS 3-7 graded as mild, BESS 8-10 as moderate, and BESS 11-14 as severe AD.[4]

BESS was measured for the first time in the BAMSE project at 12 years of age.[4] Thus, data for evaluation of eczema severity was not available for the previous follow-ups. We therefore used BESS at 12 years of age to examine if severity of AD influenced the risk of having hand eczema at 16 years of age.

Ethics

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. The Declaration of Helsinki principles were followed and all parents gave their written informed consent that their children were allowed to participate in the clinical examination.

Statistical Analysis

Groups were compared using Student's *t* test for parametric data and the χ^2-test for non-parametric data. We compared our study population with the study base on a number of background factors and calculated 95% confidence intervals (CIs) where we adjusted the variance for finite population sampling. The Venn diagram in Fig. 1 is drawn using software from the Department of Energy (PNNL, Richland, WA).[20]

First a univariate logistic regression analysis was used to examine how the different allergy related diseases influenced the risk of having hand eczema at age 16. Then a multivariate

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logistic regression model was performed; prior knowledge was used to choose the included variables in order to study which factors influenced the prevalence of hand eczema at age 16 (dependent variable). Onset of AD before age four, onset of AD from age four up to age 16, onset of asthma and/or rhinoconjunctivitis before age four and from age four up to age 16, any manifestation of these diseases at some time point between age 0 to 16, positive IgE at four and/or eight and/or 16 years of age, and parental allergic disease were used as independent variables.

A separate uni- and multivariate logistic regression was used to examine the role of AD severity at 12 years of age on the occurenceof hand eczema at 16 years of age.

These logistic regressions are presented as crude and adjusted odds ratios (ORs) with 95% CIs, respectively.

Analyses were performed with STATA Statistical Software (release 11.1; StataCorp, College Station, TX, USA). Differences were considered significant at $P < 0.05$.

Results

Study population and representativeness

A total of 2,927 16-year-old adolescents (51.0% girls, n=1,494) were included in our study, comprising 72% of the original birth cohort (2,927/4,089). Background characteristics of individuals in the study population and in the original cohort (n=4,089) were regarded as comparable.[5]

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Hand eczema and allergy related disease

At age 16, 5.2% (n=152) of the adolescents had symptoms of hand eczema. Of the adolescents with hand eczema, 73.0% (n=111) had symptoms of AD and 54.6% (n=83) had symptoms of asthma and/or rhinoconjunctivitis at some point during follow-up (age 0-16) (Table 2). The proportions of adolescents with hand eczema at age 16 that had AD and asthma and/or rhinoconjunctivitis sometime before age 16 years are shown in Figure 1. A total of 43.4% (n=66) of the adolescents with hand eczema had symptoms of both AD and asthma and/or rhinoconjunctivitis and 15.8% (n=24) had no symptoms of either AD or of asthma and/or rhinoconjunctivitis.

A majority of the adolescents with a history of AD and hand eczema at age 16 had symptoms of AD for the first time before four years of age (80.2%, 85/106).

More than half of the adolescents (55.0%, 61/111) with hand eczema and AD had persistent AD and 45.0% had occasional AD according to our definitions. In the univariate analysis, adolescents with persistent AD had significantly higher odds ratios for having hand eczema at age 16 compared to adolescents with no or occasional AD (Table 2).

More than half of the adolescents with hand eczema (57.1%) had positive IgE at one or more time points at four, eight and/or 16 years of age. About half of the adolescents (56.0%) had parental allergy related disease (82.3% had simple and 17.7% had double parental history of allergy related disease) (Table 2).

Associations between hand eczema and allergy related disease variables

A total of 2,276 adolescents were included in the multivariate logistic regression; 651 adolescents were excluded since they had some missing value on one or more of the included variables (Table 3). Adolescents having had AD at some time point (0-16 years) had significantly increased odds ratios for having hand eczema at 16 years of age: more than

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threefold increase when adjusted for the possible confounders shown in Table 3. No differences in odds ratios were seen for different onset ages of AD.

Asthma and/or rhinoconjunctivitis during childhood showed no associations with hand eczema at 16 years of age when adjusted for the possible confounders (Table 3). Neither did positive specific IgE during childhood or parental history of allergic disease. Airborne and food allergens were also tested separately from each other but neither showed any statistically significant associations.

Associations between hand eczema and severity of AD at age 12

At the follow-up at age 12, 350 children were graded as having mild/moderate or severe AD according to BESS and 2,436 children graded as not having active AD during the past year (Table 4). At the follow-up at age 16, 141 of the 152 adolescents with symptoms of hand eczema had been evaluated according to BESS at 12 years of age. Of the 141 adolescents with hand eczema at age 16, 72.3% (n=102) did not have AD at 12 years of age, 17.0% (n=24) had mild AD and 10.6% (n=15) had moderate/severe AD. Increasing odds ratios were found with increased severity of AD. After adjusting for possible confounders, a threefold increased odds ratio for hand eczema at age 16 was shown for moderate/severe AD compared with no AD (OR 3.0, 95% CI 1.5-6.0) at age 12 (Table 4).

Discussion

In this large population-based cohort study we found that AD during childhood is strongly related with hand eczema in adolescence. Adolescents with persistent and more severe AD showed a greater risk of developing hand eczema while age at onset of AD seems to be of less importance. No associations between hand eczema and childhood asthma and/or

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rhinoconjunctivitis, positive specific IgE during childhood or parental history of allergy related disease were found.

High prevalence figures were found for AD and asthma and/or rhinoconjunctivitis in adolescents without hand eczema, and even higher figures for the adolescents with hand eczema. Although allergy related disease manifestations are common in the general population, the figures we found are higher than in most other studies,[14, 15] which could be due to the repetitive follow-ups during childhood and also different definitions for AD, asthma and rhinoconjunctivitis between studies. However, a couple of recent studies from Sweden found similar high figures: prevalence of AD (75.9%), rhinoconjunctivitis (67.1%) and asthma (34.9%) for young adults with hand eczema[21] and self-reported prevalence of 43.2% for eczema, 28% for rhinitis and 9.7% for asthma in adults from the general population.[22, 23] These studies are not directly comparable to ours due to different study designs and somewhat different age groups.

AD is known to be strongly associated with hand eczema [10-13, 15, 24, 25] and several studies involving adolescents have found a positive association between AD and hand eczema, but all of them are hampered by the retrospective method of obtaining the history of AD.[14, 21, 26-28] The TOACS cohort in Denmark was followed from adolescence to adulthood and only AD and wet working conditions were associated with hand eczema.[13] They found a lower OR for the association between AD and hand eczema (1.9 (95 % CI 1.2-3.0)) than in the present study but since the independent variables were not the same ORs are not directly comparable. Since the TOACS cohort was older (about 19 years of age) variables as wet work, taking care of children and smoking were also included. A Swedish study among adults found similar OR for hand eczema and self-reported AD as we did.[15]

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Age of onset of AD has been associated with prognosis of AD,[29] however it is unclear whether age at onset of AD is associated with the risk of developing hand eczema. We have shown that age at onset of AD does not seem to influence the risk of developing hand eczema in adolescence.[30]

In the present study, adolescents with persistent and more severe AD were found to have increased risk of hand eczema. This might be related to a higher prevalence of dysfunctional skin barrier in this group. Rystedt also found a stronger association between hand eczema and severe AD than with less severe AD in dermatitis patients born in the 1950s; however this study is not directly comparable with ours.[31]

The present study did not show any associations between hand eczema and asthma and/or rhinoconjunctivitis. Some earlier studies have found slightly increased risk for hand eczema in people with asthma and rhinoconjunctivitis, while others have found no associations.[10, 11, 14, 21, 26] This discrepancy between different studies may be explained by different questions, age groups and study designs. The overall conclusion is that symptoms of asthma and/or rhinoconjunctivitis in childhood do not seem to have a strong influence on the risk of developing hand eczema in adolescence.

This study did not find any associations between IgE sensitization to common airborne and food allergens at four and/or eight and/or 16 years of age and hand eczema. To the best of our knowledge no previous studies regarding hand eczema and specific IgE have been published. IgE sensitization is influenced by age, sex, lifestyle and genetic factors[32, 33] and elevated total and/or allergen-specific IgE level is the most commonly associated laboratory feature in patients with AD. Hand eczema is strongly associated with a variety of contact allergens but potential associations with food allergy and airborne allergens are less explored.[34]

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In the present study no association between parental allergy related disease and hand eczema was found. Allergy related diseases are known to be caused by interplay between genetic and environmental factors, and genetic factors have also been shown to influence the risk of hand eczema.[24, 35] It is also well known that a positive family history of allergy related disease predisposes to AD but less is known about how a positive family history of allergy related disease influences the risk of having hand eczema. A Swedish study found a positive correlation between a family history of AD and hand eczema, but their questions differed from ours and they included the heredity of the whole family instead of just the parents.[28]

The main strengths of this study are the prospective design, the population based participants with data from birth until 16 years of age, the asset of blood samples, and that a previously used and validated question was used to determine the prevalence of hand eczema at 16 years of age.[18] This is the first study to evaluate risk factors for hand eczema where the information regarding AD/asthma/rhinoconjunctivitis has been collected in a prospective manner to minimize differential misclassification of allergic diseases. Repeated follow-ups during childhood on six occasions also create reliable data and reduce the risk of missing milder forms of AD, asthma and rhinoconjunctivitis. Furthermore, to the best of our knowledge this is the first study to examine how the age of onset of AD or positive specific IgE influence the risk of hand eczema.

One limitation of this study is that information on the included disease outcomes were obtained from questionnaires, which might possibly lead to misclassification of some cases. However, this potential misclassification is most probably non-differential. Another limitation is that BESS which was used to classify the severity of AD has not been validated. BESS however is very similar to the Nottingham Eczema Severity Score (NESS)[36] which has been validated and the severity distribution of BESS has been shown to be similar to NESS.[4]

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Contact allergy and water exposure are other important risk factors for hand eczema but to investigate such exogenous factors were not the aim of the present study.

In conclusion, this prospective population-based cohort study confirms a strong association between hand eczema in adolescence and AD in childhood. Persistence and severity of AD strengthens the association with hand eczema, while age at onset does not seem to influence. No associations between hand eczema and asthma and/or rhinoconjunctivitis, positive specific IgE during childhood, or parental allergic disease were found.

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Table 1. Definitions of the allergy related disease variables included in the study.

Definitions

Atopic dermatitis (AD): AD at age one, two and four: dry skin and itchy rash with a typical age-specific location for at least two weeks the year before follow-up and/or doctor's diagnosis of eczema since the last follow-up. AD at age eight and 16: dry skin in combination with itchy rash and typical localization the year before follow-up and/or doctor's diagnosis of eczema since the last follow-up. AD at age 12: dry skin in combination with itchy rash and typical localization the year before follow-up and/or doctor's diagnosis of eczema since the age of 10.[1]

Occasional AD: Fulfilling the definition of AD at one or more follow-ups until age four years but not from four to 16 years or vice versa.

Persistent AD: Fulfilling the definition of AD at one or more follow-ups until age four years and at one or more follow-ups from four to 16 years.

Asthma: When the children were under two years of age this definition was used: at least three episodes of wheeze in combination with treatment with inhaled glucocorticosteroids and/or sign of suspected hyperactivity without ongoing upper respiratory infection during the last 12 months.[2-4] When the children were between age two and 16 this definition was used: at least four episodes of wheeze in the last 12 months or at least one episode of wheeze during the same period combined with prescription of inhaled glucocorticosteroids for symptoms of asthma occasionally or regularly and/or doctor´s diagnosis of asthma. [2-4]

Rhinoconjunctivitis: Symptoms of sneezing, a runny or blocked nose, or itchy, red and watery eyes after exposure to furred pets and/or pollen without having a cold or flu simultaneously and/or doctor's diagnosis of allergic rhinoconjunctivitis. [8, 9]

Onset of AD or asthma and/or rhinoconjunctivitis before age four: Fulfilled the criteria for AD/ asthma and/or rhinoconjunctivitis above at one and/or two and/or four years follow-up.

Onset of AD or asthma and/or rhinoconjunctivitis from age four to 16: Fulfilled the criteria for AD/asthma and/or rhinoconjunctivitis above at eight and/or 12 and/or 16 years follow-up.

No allergy related disease: No positive answers on any of the questions about AD, rhinoconjunctivitis and asthma at any of the follow-ups from birth until 16 years of age.

Parental history of allergy related disease: Mother and/or father with doctor´s diagnosis of asthma and/or rhinitis in combination with allergy to furred pets and/or pollen allergy and/or AD ever reported in the questionnaires at 0 and/or eight years of age.[8]

Positive IgE: IgE-value for phadiatop ≥0.35 kU_A/L and/or IgE-value for food mix ≥0.35 kU_A/L at four and/or eight and/or 16 years of age.[17]

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Figure 1. Venn diagram showing the proportions of adolescents with hand eczema at age 16 (n=152) that had atopic dermatitis (AD) and asthma and/or rhinoconjunctivitis (AR) sometime before age 16 years.

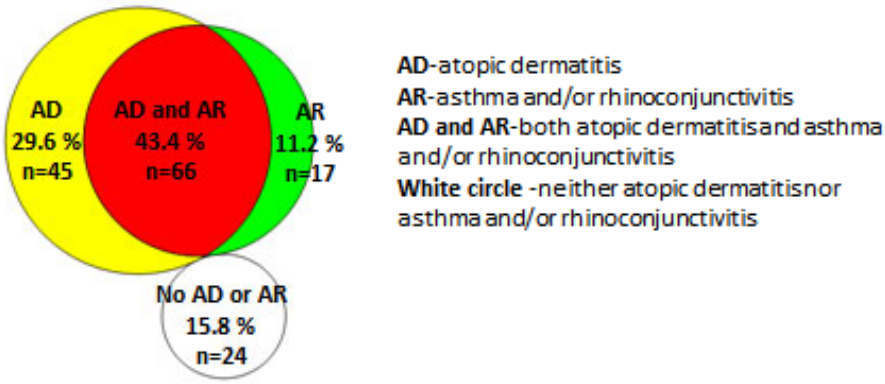

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Table 2. Distribution of atopic dermatitis, asthma and/or rhinoconjunctivitis as well as other allergy related variables in relation to hand eczema at age 16. Results of the univariate analysis on hand eczema at age 16 for the different allergy related manifestations, presented as crude odds ratios (ORs) with 95 % confidence intervals (CIs).

	Study population % (n)	**Hand eczema at age 16 % (n)**	**No hand eczema at age 16 % (n)**	**Crude OR* (95 % CI)**	***p*-value**
Total	2,927	5.2 (152)	94.8 (2,775)	-	-
Symptoms of disease during follow up (age 0-16 years)					
Atopic Dermatitis (AD), n=2,927					
No	57.3 (1,678)	27.0 (41)	59.0 (1,637)	1.0	
Yes	42.7 (1,249)	73.0 (111)	41.0 (1,138)	**3.9** (2.7-5.6)	**<0.001**
Age at onset of AD, n=2,700[a]					
No	54.6 (1,473)	24.3 (34)	56.2 (1,439)	1.0	
Onset before age 4	35.0 (944)	60.7 (85)	33.6 (859)	**4.2 (**2.8-6.3)	**<0.001**
Onset from age 4 to 16	10.5 (283)	15.0 (21)	10.2 (262)	**3.4** (1.9-5.9)	**<0.001**
Persistency of AD, n=2,927					
No AD at any time point	57.3 (1,678)	27.0 (41)	59.0 (1,637)	1.0	
Occasional	26.9 (786)	32.9 (50)	26.5 (736)	**2.7** (1.8-4.1)	**<0.001**
Persistent	15.8 (463)	40.1 (61)	14.5 (402)	**6.1** (4.0-9.1)	**<0.001**
Asthma and/or rhino-conjunctivitis (AR), n=2,927					
No	54.8 (1,605)	45.4 (69)	55.4 (1,536)	1.0	
Yes	45.2 (1,322)	54.6 (83)	44.6 (1,239)	**1.5** (1.1-2.1)	**0.02**
Age at onset of AR, n=2,588[b]					
No	48.9 (1,266)	33.6 (42)	49.7 (1,224)	1.0	
Onset before age four	26.4 (682)	40.8 (51)	25.6 (631)	**2.4** (1.5-3.6)	**<0.001**

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Onset from age four to 16	24.7 (640)	25.6 (32)	24.7 (608)	1.5 (0.9-2.5)	0.07
Any allergy related disease[c], n=2,927					
No	36.1 (1,058)	15.8 (24)	37.3 (1,034)	1.0	
Yes	63.9 (1,869)	84.2 (128)	62.7 (1,741)	**3.2** (2.0-4.9)	**<0.001**
Sensitization to airborne and/or food allergens at age four and/or eight and/or 16 years, n=2,752					
No	51.1 (1,407)	42.9 (63)	51.6 (1,344)	1.0	
Yes	48.9 (1,345)	57.1 (84)	48.4 (1,261)	**1.4** (1.02-2.0)	**0.04**
Parental allergy related disease, n=2,734					
No	50 9 (1,392)	44.0 (62)	51.3 (1,330)	1.0	
Yes	49.1 (1,342)	56.0 (79)	48.7 (1,263)	1.3 (1.0-1.9)	0.09

Bold type, 95 % CI does not include 1.00.

Parents reported the prevalence of AD, asthma and rhinoconjunctivitis up to age 12, at the follow-up at age 16 the adolescents reported themselves. The prevalence of hand eczema is from the adolescents report at age 16.

*There were no statistically significant differences in OR between girls and boys in the univariate analysis data not shown.

[a]227 children had at least one missing value between 0 and 16 years of age concerning the questions about AD. They were therefore excluded from this analyse since we couldn´t be sure which group to categorize them into.

[b]339 children had at least one missing value between 0 and 16 years of age concerning the questions about asthma and rhinoconjunctivitis. They were therefore excluded from this analyse since we couldn´t be sure which group to categorize them into.

[c]AD or asthma or rhinoconjunctivitis at any time point between 0 and 16 years of age

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Table 3. Results of the multivariate logistic regression on 1-year period prevalence of hand eczema at age 16. Adjusted odds ratio (OR) with 95 % confidence intervals (CIs).

	Adjusted OR*[,a] **(95 % CI)** n=2,276	*p*-value
Symptoms of disease during follow up (age 0-16 years)		
Age at onset of Atopic Dermatitis (AD)		
No	1.0	
Onset before age four	**3.7** (2.0 -7.0)	**<0.001**
Onset from age four to 16	**3.7** (1.7-7.7)	**0.001**
Age at onset of asthma and/or rhinoconjunctivitis (AR)		
No	1.0	
Onset before age four	1.5 (0.8-2.5)	0.2
Onset from age four up to age 16	1.2 (0.6-2.1)	0.6
Any allergy related disease		
No	1.0	
Yes	1.0 (0.4-2.4)	1.0
Sensitization to airborne or food allergens at age four and/or eight and/or 16 years[c]		
No	1.0	
Yes	1.1 (0.7-1.6)	0.7
Parental allergy related disease		
No	1.0	

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Yes	1.1 (0.7-1.6)	0.8

Bold type, 95 % CI does not include 1.00.
*There were no statistically significant differences in OR between girls and boys in the multivariate analysis data not shown.
[a] Each variable was adjusted for all the other variables included in the table. Prior knowledge was used to choose the included variables.
[c]IgE-value for Phadiatop ≥0.35 kU_A/L and/or IgE-value for food mix ≥0.35 kU_A/L.

Table 4. Uni- and multivariate analysis of the influence of atopic dermatitis (AD) severity at 12 years of age on the 1-year prevalence of hand eczema at age 16. AD severity is based on BESS (BAMSE Eczema Severity Score), which was measured in all children with concurrent AD at age 12. 1-year prevalence of hand eczema at age16 is from the adolescents report and BESS originated from the parents report. Crude and adjusted odds ratios (ORs) with 95 % confidence intervals (CIs).

BESS at age 12 n=2,786	**Hand eczema during the last year at age 16**	**No Hand eczema during the last year at age 16**	**Crude OR*** **(95 % CI)**	***p*-value**	**Adjusted OR*,[a] (95 % CI)**	***p*-value**
No AD:	102	2,334	1.0		1.0	
Mild AD:	24	246	**2.2** (1.4-3.5)	**0.001**	1.3 (0.7-2.2)	0.4
Moderate/severe AD:	15	65	**5.3** (2.9-9.6)	**<0.001**	**3.0** (1.5-6.0)	**0.001**

Bold type, 95 % CI does not include 1.00.
*There were no statistically significant differences in OR between girls and boys in the uni- or multivariate analysis data not shown.
[a]Adjusted for age at onset of AD, age at onset of asthma and/or rhinoconjunctivitis, any allergy related disease, sensitization to airborne and/or food allergens at age four and/or eight and/or 16 years and parental allergy related disease.

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