# Eczema in early childhood increases the risk of allergic multimorbidity

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**Abstract**

*Background:* Eczema in early childhood is associated with developing subsequent allergic diseases, including food allergy, asthma and hay fever. However, eczema has a heterogenous presentation regarding age of onset and persistence, which may lead to different allergic outcomes during childhood/adolescence. Recently, sub-phenotypes of eczema have been suggested as predictor for allergic multimorbidity. *Objective:* To identify associations of eczema phenotypes with food allergy, asthma and hay fever during childhood/adolescence. Additionally, we aimed to describe the trajectories of eczema, asthma and hay fever, stratifying by food allergy presence. *Methods:* TRACKER (Trajectories of Allergy in Children in Real Life Databases) is a prospective cross-sectional population-based cohort study of 6,852 children/adolescents from the Lifelines cohort. We investigated associations of seven eczema phenotypes, based on age of onset and persistence, with food allergy, asthma and hay fever using logistic regression, adjusted for appropriate covariates. Disease trajectories were determined by calculating prevalence at different ages. *Results:* Participants who suffered from eczema throughout childhood showed higher risks of developing food allergy, hay fever and asthma. "Very early onset – persistent" eczema showed the strongest associations with food allergy, asthma and hay fever. The prevalence of eczema, asthma and hay fever at all ages were significantly higher in participants with food allergy, compared to those without. *Conclusion:* The largest cohort study on this topic to date shows that (very) early onset and persistent eczema increases the risk for allergic multimorbidity. Identification of infants at risk for developing (very) early onset eczema is of utmost importance to prevent allergic multimorbidity.

## 1 Introduction

Trajectories of allergic diseases follow the paradigm of the atopic march, which describes the idea of sequential development of allergic diseases, namely atopic dermatitis (AD), food allergy (FA), allergic asthma (AA) and allergic rhinitis (AR), in early life.[1] AD, also known as eczema, is a chronic, recurrent skin disease, characterized by chronic skin barrier impairment, inflammation of the skin, eczematous lesions and pruritus.[2] AD usually emerges in infancy, arising in the first year in about 60 % of affected children.[3]Similarly, primary FA, characterized by IgE-mediated responses to foods,[4] generally arises during infancy and early childhood.[5] AA and AR typically show a later onset and are thus viewed as the latter manifestations in the trajectory of allergic diseases.[1,5]

Dysfunction of the skin barrier, a hallmark of AD, plays an important role in the aetiology of comorbid allergic diseases. The systemic sensitization against food allergens and inhalant allergens at a young age are thought to be promoted by skin barrier impairment (epicutaneous sensitization), increasing the likelihood for later development of FA, AA and AR.[6]

Lately, studies focusing on childhood AD have established the importance of differentiating between phenotypic subclasses of AD. Typically, these disease phenotypes are being stratified according to age of onset, persistence and severity of AD.[7-10] Differences in underlying pathophysiological pathways which might cause

this heterogeneity of AD are yet to be described.[8] However, pinpointing the phenotype at highest risk for developing allergic multimorbidity and identifying phenotype-specific risk factors is needed for developing personalized prevention and treatment strategies for children with AD.

Thus, we hypothesize that children with early onset and persistent eczema are at highest risk for sensitization against food and/or inhalant allergens and the subsequent development of allergic multimorbidity. The current TRACKER (Trajectories of Allergy in Children in Real Life Databases) study aims to identify the associations of eczema phenotypes with presence of FA, asthma and hay fever. In addition, we aimed to describe the trajectories of eczema, asthma and hay fever, differentiating between children with and without FA.

## 2 Material and Methods

### 2.1 Study design and population

Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. Baseline examinations in individuals aged 6 months to 93 years took place between 2006 and 2013 with follow-ups visits every 5 years and follow-up questionnaires in between.[11] The Lifelines cohort study was approved by the Medical Ethics Committee of the University Medical Center Groningen, Groningen, The Netherlands (2007/152). All subjects gave written informed consent.

For the TRACKER study, subjects between 4 and 18 years of age at baseline, who had completed the questionnaire about allergic diseases and a follow-up questionnaire concerning food allergies, were included.

### 2.2 Questionnaires

At baseline and follow-up, questionnaires were completed by the parents/guardians, while children older than 13 years, completed questionnaires themselves (in addition to questionnaires completed by a parent/guardian). At baseline, different versions of the questionnaire covered predefined age brackets ***(Supplementary Table 1)*** . The version that participants received was dependent on the participants age at time of the questionnaire (ageQ). Presence of eczema, asthma, and hay fever within each age bracket was reported at baseline. Presence of FA was reported at follow-up.

### 2.3 Definitions

#### Eczema presence and eczema phenotypes

AD was operationalized as self-/guardian-reported eczema. Within each age bracket, eczema presence was determined using three parameters: presence, medication and treatment by a doctor. Eczema presence was confirmed if presence was reported or if presence was denied, but either medication or treatment were reported. Eczema was not confirmed if all three parameters were reported negatively. Ever eczema was defined as eczema presence in at least one of the age brackets.

Eight longitudinal phenotypes were defined, based on presence, age of onset and persistence of eczema ***(Table 1)*** . This stratification of eczema subclasses had been first described by Paternoster *et al.* , who identified them from two longitudinal birth cohorts using a latent-class analysis.[7] Age of eczema onset was defined as "Very early" if the first presence was reported before the age of 6 months, "Early" between 6 months and 4 years and "Late" after the age of 4 years ***(Supplementary Figure 1)*** . Persistence/remission of eczema was defined by assessing eczema presence in the most recent age bracket available. When persistence/remission could not be determined due to incomplete data, subjects were classified into phenotypes with "no info on persistence". Very young children (age $<$ 4 years at baseline) provided no information about persistence/remission and were excluded.

**Food allergy presence**

Presence of FA was assessed at follow-up and participants were assigned to one of three groups, previously reported by Westerlaken-van Ginkel *et al.* in adults.[12] The groups represented those who did not report FA (*noFA* ), those likely to have a food allergy (*likelyFA* ) and those who could not be assigned to either of those groups, termed indeterminate (*indeterminateFA* ). In short, participants were classified as *likelyFA* if they stated:

at least one food AND at least one symptom consistent with immediate allergic reactions to food AND

other characteristics of FA consistent with immediate allergic reactions to food

Further details on the definitions are provided in the supplement.

**Hay fever**

The definition of hay fever presence was identical to the definition of ever eczema presence described above. Presence of hay fever was assessed for each age bracket and over the whole study period.

**Asthma**

Presence of asthma was based on the medication and treatment parameters. If either question for medication or treatment by a doctor had been answered with "yes", presence of asthma was confirmed. Again, presence within the age brackets and ever asthma was assessed.

**Age of onset**

Age of onset was defined as the mid-point of the age bracket in which presence was first reported. For example, if eczema presence was first reported in the period 4– 7 years, age of eczema onset was taken as 5.5 years. In cases of age brackets where the end was defined as ageQ, the age of onset represented the mid-point of the age at start of the period and ageQ (4 years – ageQ, age 5 at time of questionnaire, age of onset: 4.5 years).

**Covariates**

Multiple potentially confounding variables were assessed to correct for biases in the statistical analysis:

- basic characteristics: age at baseline, age at follow-up, sex
- information about the pre-natal phase: smoking during pregnancy and passive smoking during pregnancy
- information about the post-natal phase: the location of residency in the first six months (*farm, rural village, small town/large village, suburb or large city, inner city, do not remember, unknown* ), exposure to a furry/hairy pet in the first six months, whether the infant was breast-fed and the duration of breastfeeding (*not breast-fed, up to 3 months, more than 3 months, breastfed but do not remember duration, do not know if breast-fed* )
- parental characteristics: asthma presence among parents, their income level /month (*no information on income, < 1500 \euro, 1500 – 3000 \euro, > 3000 \euro* ) and their education level (*low, medium, high, other/unknown* )

**2.4 Statistical analysis**

Descriptive analysis of the baseline characteristics, disease phenotypes and covariates of the study population was performed, stratifying by presence of FA. Continuous and categorial variables were tested using one-way ANOVA and $Chi^2$-test, respectively. To investigate the associations of ever eczema and eczema phenotypes with FA presence, multinomial logistic regression analysis with and without adjustment for all covariates (excluding age at baseline) was conducted. Association of ever eczema and eczema phenotypes with presence of asthma and hay fever were analyzed using logistic regression analysis with and without adjustments for all covariates (excluding age at follow-up). The trajectories of the different allergic diseases in the study population, stratified by FA presence, was based on the prevalence of eczema, asthma and hay fever within

each age bracket. Differences in prevalence of each allergic disease between the FA groups were tested using a $Chi^2$-test with post-hoc group-wise comparison within each age bracket.

Data management tasks and statistical analysis were carried out using R Studio (2022.02.0443, based on R version 4.1.2, RStudio Team (2022), RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/). Relevant packages are listed in the supplement. The significance level for all tests conducted was a p-value of 0.05.

## 3 Results

### 3.1 Study population

Data on eczema and FA was available for 6,852 participants. Of these, 6,638 could be assigned to one of the eczema phenotypes***(Figure 1)*** . Among the included 6,852 children, 27.0 % reported eczema, 9.9 % asthma and 8.2 % hay fever. The distribution of eczema phenotypes and covariates is presented in ***Table 2(Supplementary Figure 2A)***. "Very early onset – remitting" eczema showed the highest prevalence, followed by "Early onset – remitting" and "Late onset". In total, 6.2 % of participants were classified as having *likelyFA* and 1.2 % as having*indeterminateFA* ***(Supplementary Figure 2B).*** The average onset age for eczema, asthma and hay fever was 2.7 (SD 2.7) years, 3.4 (SD 3.9) years and 7.4 (SD 4.4) years, respectively.

### 3.2 "Very early onset- persistent" eczema shows the highest risk for likelyFA

Participants who suffered from eczema at any point in childhood showed a 3.8 times higher odds of developing *likelyFA* and a 2.6 times higher risk for *indeterminateFA* ***(Supplementary Table 2)***. The risk of developing *likelyFA* was significantly higher across all eczema phenotypes when compared to "Never eczema". Figure 2 shows that "Very early onset – persistent" eczema displayed a 10.4 times higher odds for developing*likelyFA* , followed by "Early onset – persistent" eczema with a 3.9 times higher odds ***(Figure 2)*** . Additionally, "Very early onset – persistent", "Early onset – remitting" or "Early onset – persistent" eczema phenotypes showed a significantly higher risk of *indeterminateFA* . The results of both "no info on persistence" groups ("Very early onset – no info" N = 23; "Early onset – no info" N = 22) can be found in Supplementary Table 3 , together with comprehensive results for all eczema phenotypes.

### 3.3 "Very early onset – persistent" eczema shows the highest risk for both asthma and hay fever

Ever eczema was associated with the presence of asthma and hay fever***(Supplementary Table 2)*** . All eczema phenotypes besides the "Late onset" group showed significantly higher risks of having asthma ***(Supplementary Table 4)*** . The "Very early onset – persistent" group with a 4.1-times higher odds observed the highest risk for having asthma ***(Figure 3A)*** . All eczema phenotypes showed significant associations with hay fever presence***(Supplementary Table 5)*** . The "Very early onset – persistent" group observed the highest risk of having hay fever with 6.6-times higher odds ***(Figure 3B)*** .

### 3.4 Allergic disease trajectories

The reported prevalences of eczema, asthma and hay fever within each age bracket, stratified by FA presence, are presented in Figure 4 and Supplementary Table 6 . In all FA groups the peak in prevalence of eczema was observed in the age bracket 6 months – 3 years, followed by a steady decline over the later age brackets. Regarding asthma, the highest prevalence over all groups was observed in the age bracket 4 – 7 years and for hay fever in the age bracket 8 – 12 years. Generally, prevalence of eczema was higher than prevalence of asthma and hay fever, at least until the age bracket of 4 – 7 years. Comparing eczema prevalence between the FA groups at each age bracket showed significant differences between the *noFA*and *likelyFA* groups over all age brackets. When comparing eczema prevalence of the *noFA* group to *indeterminateFA* , only the last age bracket did not show a significant difference. The asthma prevalence showed significant differences across all age brackets, when comparing *noFA* and *likelyFA* , but no significant differences were observed between

*noFA* and*indeterminateFA.* The same was seen for hay fever, with significant differences between *noFA* and *likelyFA* , but not between *noFA* and *indeterminateFA* .

## 4 Discussion

### 4.1 Primary findings

In the largest population-based cohort study on this topic to date, including 6,852 children/adolescents, we identified the association of ever eczema and eczema phenotypes with the presence of FA, asthma and hay fever. "Very early onset – persistent" eczema showed the strongest associations across all investigated allergic diseases and thus represents the phenotype at highest risk for developing allergic multimorbidity. Moreover, participants with FA observed a significantly higher prevalence of eczema, asthma and hay fever throughout childhood, comparing them to participants without FA.

### 4.2 Interpretation

We confirmed that eczema presence represents a risk factor for FA, as shown previously.[13-16] Further, we demonstrated associations between eczema presence and presence of asthma and hay fever, reflecting findings from other studies.[13,17,18]Associations between eczema phenotypes and FA, asthma and hay fever presence revealed, that all phenotypes, especially the persistent ones, had significantly higher risks of developing subsequent allergic disease when compared to the "Never eczema" group. Other studies also reported that persistent eczema was associated with the development of FA[19] as well as asthma and hay fever.[8,20] Further, our results suggest that, the age at eczema onset plays an important role in allergic multimorbidity. Earlier onset of eczema showed a stronger association with FA, asthma and hay fever presence, with "Very early onset" showing higher aOR's (adjusted Odds Ratio) than "Early onset" and "Late onset". These findings agree with similar reports, showing eczema onset before 2 years of age to be associated with development of FA, asthma and hay fever.[20-22] Onset of eczema in the first 2 months has even been reported to have the strongest association with development of FA by age 3.[23]

Taken together, our findings suggest that individuals with disease onset before 6 months and persistent eczema are at highest risk for developing allergic multimorbidity during childhood and adolescence. This supports our hypothesis that this subpopulation might be at highest risk for sensitization against food or inhalant allergens before allergen tolerance developed. The higher likelihood of allergen sensitization and subsequent development of FA, asthma and hay fever in patients with eczema can be, at least partially, attributed to impairment of the skin's barrier function [24,25]. The dual allergen exposure hypothesis suggests that, regarding FA, the oral consumption of allergenic foods promotes immune tolerance, whereas exposure to food allergens on the skin (before oral tolerance could develop), is more likely to lead to epicutaneous sensitization through allergen penetration and cytokine dysregulation. This applies especially, but not exclusively, to eczematous skin.[4,24,26]For asthma and hay fever, evidence regarding epicutaneous sensitization with inhalant allergens is still limited.[6,27]Although, it has been reported that likelihood for inhalant allergen sensitization is higher in children with eczema, due to increased skin permeability, even when skin barrier parameters were measured on non-lesional skin. The same study described a correlation between allergy score (cumulative skin-prick-test results) and eczema duration.[28] The dual allergen exposure hypothesis has gained traction throughout the last decade and resulted in a change in management from allergen avoidance strategies towards early dietary introduction of allergenic foods, aiming for tolerance induction.[29] It is important to note, that the clinical manifestation of eczema is no driving factor for the development of FA, but rather represents a symptom indicating an underlying epithelial barrier dysfunction.[30] Thus, restoring barrier function represents a promising preventative strategy for allergic multimorbidity in children with eczema.[31,32] However, specific interventions for preventing allergic diseases, like the use of emollients, have not proven to be successful yet.[33]Still, those who experience the longest duration of skin barrier impairment, like our "Very early onset – persistent" phenotype, may benefit the most from early eczema prevention and treatment. It would be crucial to find a method or biomarker to identify this subpopulation as early as possible.

The atopic trajectories for eczema, asthma and hay fever, we presented in our cohort, closely resemble the

typical trajectory of the atopic march across all FA presence groups.[5] Early peaks of eczema prevalence around the age of 2 years, followed by peaks of asthma prevalence around 5.5 years and peaks of hay fever prevalence around 10 years of age. However, multiple findings have challenged the idea of the strict sequence suggested in the atopic march, which originally stems from epidemiological studies focusing on cumulative trajectories in large cohorts. When profiles of eczema, asthma (wheeze) and hay fever (rhinitis) are analyzed based on individuals, the developmental trajectories display greater heterogeneity.[34,35] In one investigation the identified group closest to the atopic march only covered about 7 % of children who observed symptoms.[34] Another study reported early-life eczema representing the largest risk factor for allergic multimorbidity, but it only led to multimorbidity in about 25 % of cases.[35]Thus, the paradigm of the strictly sequential atopic march needs to be reconsidered and focus should lie on identifying those at highest risk for multimorbidity in early life.

### 4.3 Strengths and limitations

This study has some strengths that support the validity of our findings. First, we observed the association of eczema phenotypes with allergic multimorbidity in the largest cohort, (N = 6,852) to date. Further, all allergic diseases, which are considered in the atopic march, were included in the analysis. The overall prevalence of allergic diseases that we observed are in line with other reports.[14,15,36-39] However, eczema prevalence was slightly higher than commonly reported.[15,17,38,39]This could be, partly, due to the self-/guardian-reported factors utilized for verification of eczema presence. Prevalence of eczema phenotypes resembled the distribution of phenotypes in the cohorts that were used to define them initially, with the most prevalent phenotypes (besides "Never eczema") being "Very early onset – remitting" and "Early onset – remitting".[7] Further, our investigation covers a wide age-range (0 – 17 years) including infancy, childhood, and adolescence, while many other studies assess outcomes at a younger age. Regression models were adjusted comprehensively for confounders, known to influence allergic disease development. Lastly, due to the population-based study design, our findings are derived from real-life data and do not rely on selective sampling, leading to results representative for the general population.

However, some limitations need to be addressed. Firstly, the data used in this study was derived from self-/guardian-reported questionnaires. Additionally, the calculation of age of onset displayed some imprecision, as it was based on the age brackets which had been predefined with differing durations, resulting in estimates within those age brackets. Further, recall bias at baseline may have been present, since subjects had to report presence, treatment and medication of allergic diseases since birth. Lastly, due to the Lifelines cohort exclusively consisting of participants based in the Northern Netherlands, our results are subject to a regional bias. However, as described above, our data is in line with findings from comparable cohorts.

### 4.4 Outlook

Future investigations concerned with the effect of early-life eczema on allergic multimorbidity should consider the integration of disease severity for eczema, food allergies, asthma and hay fever, since it was repeatedly shown that eczema severity was associated with the development and severity of other allergic diseases.[13,18,21,40] Further, there seems to be a heterogenic association between eczema phenotypes and different allergenic foods.[22] This distinction could result in a more detailed understanding of the allergen specific associations present among comorbid allergic diseases, if applied to future studies.

### 4.5 Conclusion

Our findings show that ever eczema was significantly associated with food allergy, asthma and hay fever. The different eczema phenotypes observed varying degrees of association with these allergic diseases and the strongest associations were shown for "Very early onset – persistent" eczema. These results support our hypothesis that children, with very early onset and persistent eczema, are at highest risk for developing food or inhalant allergies. Ultimately, exploring methods or biomarkers which might aid in the early identification of this subpopulation could increase the efficacy of early prevention and treatment measures, leading to individual based medicine.

**Author contribution**

The study was designed and supervised by AS. LM and JV conducted the data management and statistical analysis. LM wrote the first draft of the manuscript. All co- authors provided important intellectual input and contributed considerably to the discussion and interpretation of the data. All authors guarantee that the accuracy and integrity of any part of the work have been appropriately investigated and resolved and all have approved the final version of the manuscript.

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**Conflict of interest**

The authors declare no conflict of interest.

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