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Most associations of early-life environmental exposures and genetic risk factors poorly differentiate between eczema phenotypes: the Generation R Study

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Summary

Background Childhood eczema is variable in onset and persistence.
Objectives To identify eczema phenotypes during childhood, and their associations with early-life environmental and genetic factors.
Methods In this study of 5297 children from a multiethnic population-based prospective cohort study, phenotypes based on parent-reported physician-diagnosed eczema from age 6 months to 10 years were identified using latent class growth analysis. Information on environmental factors was obtained using postal questionnaires. Four filaggrin mutations were genotyped and a risk score was calculated based on 30 genetic variants. Weighted adjusted multinomial models were used for association analyses.
Results We identified the following five eczema phenotypes: never (76%), early transient (8%), mid-transient (6%) and late transient (8%) and persistent eczema (2%). Early transient and persistent eczema were most common in first-born children, those with a parental history of eczema, allergy or asthma and those with persistent wheezing [range of odds ratio (OR): 1.37, 95% confidence interval (CI) 1.07–1.74 and OR 3.38, 95%CI 1.95–5.85]. Early transient eczema was most common in male children only (OR 1·49, 95% CI 1·18–1·89). Children with late transient or persistent eczema were more often of Asian ethnicity (OR 2·04, 95% CI 1·14–3·65 and OR 3·08, 95% CI 1·34–7·10, respectively). Children with early, late transient and persistent eczema more often had a filaggrin mutation or additional risk alleles (range OR: 1.07, 95%CI 1.02–1.12 and OR 2.21, 95%CI 1.39–3.50). Eczema phenotypes were not associated with maternal education, breastfeeding, day care attendance and pet exposure.
Conclusions Five eczema phenotypes were identified in a multiethnic paediatric population with limited differences in risk profiles, except for sex and ethnicity.

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Conflicts of interest
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What's already known about this topic?

- Two previous studies in longitudinal birth cohorts identified four and six different eczema phenotypes, predominantly in children of European ethnicity.

What does this study add?

- Five eczema phenotypes were identified in a multiethnic paediatric population using latent class growth analysis.
- Children with early transient and persistent eczema were most often first-born children and had persistent wheezing, filaggrin mutation or additional risk alleles.

- Previously known eczema risk factors had limited differentiating capabilities for eczema phenotypes, except for the association of early transient eczema with male children, and late transient and persistent eczema with Asian ethnicity.

Childhood eczema is a major common chronic health problem with a prevalence of up to 25%.[1] The age of onset and the persistence of eczema during childhood vary. There is a need to define more detailed eczema phenotypes and to understand their specific underlying risk factors in order to make better predictions about the natural course of eczema and to prevent the onset and worsening of eczema. Defining eczema as a dichotomous trait is an oversimplification. Eczema phenotypes that take into account the age of onset and persistence over time may enable better identification of specific environmental exposures and genetic mechanisms that might play a role in the development of eczema.[2–4] Previous studies suggest that higher maternal education, non-European ethnicity, having older siblings, shorter duration or nonexclusivity of breastfeeding, day care attendance and no pet exposure are associated with an increased risk of childhood eczema.[5–11] In addition, loss-of-function mutations in the gene encoding filaggrin (*FLG*), an indispensable protein for epidermal differentiation and maintenance of an optimal skin barrier, are well known to be associated with eczema.[12] Furthermore, genome-wide association (GWA) studies identified 31 variants that were associated with childhood eczema.[13–15] It is unclear whether these early-life exposures and genetic variants are related to the various eczema phenotypes. Two previous longitudinal birth cohorts identified different eczema phenotypes with sex, parental history of eczema, asthma or allergies, breastfeeding, pet exposure, *FLG* mutations, genetic risk score, asthma and other allergenic comorbidities as determinants.[15,16] However, those cohorts consisted predominantly of children of European ethnicity, did not take repeated measurements of eczema into account in the cluster analysis, or only explored the risk of early-life exposures and genetic variants in unadjusted analyses.

Therefore, in order to predict and prevent the natural course of eczema, we aimed to identify eczema phenotypes in a multiethnic population-based prospective cohort study among 5297 children. We further examined the associations of socioeconomic and lifestyle exposures in early-life and genetic risk factors with the identified eczema phenotypes.

Patients and methods

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards.[17] Written informed consent was obtained from parents or legal guardians. Of 7893 live-born children participating after birth, those without data on physician-diagnosed eczema available for at least three time points were excluded, leaving a total of 5297 children for the current analyses.

Eczema definition

Information on eczema was obtained from parental questionnaires at age 6 months, and at ages 1, 2, 3, 4 and 10 years (response rates 72–76%). Physician-diagnosed eczema was defined as a positive response to the question 'Was your child diagnosed with eczema in the last 6 months/last year by a physician?' (no/yes).[7] This question was adapted from the core questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC).[18]

Early-life environmental exposures

Information on parity (nulliparous/multiparous), maternal education (primary or secondary school/higher than secondary school), and parental history of eczema, allergy or asthma (no/ yes) was available from parental questionnaires obtained at enrolment. Information on the sex of the child was obtained from midwives and hospital records. Ethnic origin (European/non-European) of the child was based on the parents' country of birth according to Statistics Netherlands.[17] Postnatal questionnaires provided information on breastfeeding (never/ever) at 2, 6 or 12 months after birth, pet exposure at ages 2 months and 6 months (no/yes, exposure to cat, dog, rodent or bird at home) and day care attendance at age 12 months (yes/no). Questionnaires adapted from the ISAAC study were used to determine wheezing at ages 1–6 years (no/yes).[18] Wheezing patterns were classified based on time of onset and persistence as 'never', 'early' (wheezing at age $\leq$ 3 years only), 'late' (wheezing at ages $>$ 3–6 years only), or 'persistent wheezing' (wheezing at age $\leq$ 3 years and at age $>$ 3–6 years) for children with data on wheezing available for at least two time points.[19]

Genetic risk factors

The most prevalent *FLG* mutations in European populations (2282del4, R2447X, R501X and S3247X) were genotyped by modified Taqman allelic discrimination assays using previously described primers.[20,21] Children without any mutant alleles were classified as wild-type. As we observed only two cases of homozygous *FLG* mutations, we created a combined *FLG*

genotype (no mutation/one mutation or more).[22] A recent and large GWA study identified and replicated 30 single-nucleotide polymorphisms (SNPs) that were associated with childhood eczema.[13] Information on these SNPs was available from the GWA screening performed on DNA isolated from cord blood leucocytes or, in a small minority of children with missing cord blood samples, at age 6 years using the Illumina 670K platform.[17] Genotype data were imputed for all polymorphic SNPs into the 1000 Genomes panel. A genetic risk score for each individual was calculated by summation of the number of eczema-increasing risk alleles (between 0 and 2 for each SNP) across all SNPs.[13]

Statistical analysis

Firstly, we compared characteristics of individuals included in our study with those who were not included by using independent sample t-test, Mann–Whitney U-test and Pearson's χ^2-tests. Secondly, eczema phenotypes were identified using latent class growth analysis based on parent-reported physician-diagnosed eczema data. This type of analysis assumes that a number of different latent classes exist in the study population, which describe the variation of observed responses over time, and clusters individuals with similar patterns while taking into account correlations between measurements from the same individual.[23–25] Details on model selection are provided in the Supporting Information. For comparison with previous studies on eczema subgroups, we performed longitudinal latent class analysis to identify eczema phenotypes.[15,16] Thirdly, we examined the associations of early environmental exposures and genetic risk factors with the identified eczema phenotypes using weighted mutually adjusted multinomial regression models. Multiple imputation using chained equations was used to impute missing values of environmental exposures (range 0–30% per variable). Twenty completed datasets were created and the results were pooled using Rubin's rules.[26] Physician-diagnosed eczema, *FLG* genotype and the calculated genetic risk score were not imputed as they could not be appropriately predicted from the available data.[27] Finally, in order to examine the associations between different ethnicities and eczema phenotypes in more detail, we divided ethnicity into European (European, American or Oceanian), Mediterranean (Turkish or Moroccan), Asian (Asian, Indonesian, Surinamese–Hindustani or Surinamese–mixed) and African (African, Dutch–Antillean or Surinamese–Creole) subgroups based on similarities in skin type and cultural background.[11,28] All measures of association are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Latent class analyses were performed using Mplus (version 7·11) for Windows (Muthén and Muthén, Los Angeles, CA, U.S.A.), imputation and weighted multinomial regression analyses were performed using the packages 'mice' (version 2·46·0)[29] and 'nnet' (version 7·3·12) in R version 3·4·3,[30] respectively.

Results

Parental and child characteristics

Maternal and child characteristics are presented in Table 1. The prevalence of eczema declined from 16% (n = 662) at age 6 months to 7% (n = 347) at age 10 years. Individuals who were not included in the current analyses had somewhat less favourable socioeconomic and environmental factors (Table S1; see Supporting Information).

Eczema phenotypes

In children with data on physician-diagnosed eczema available from at least three time points (n = 5297), latent class growth analysis identified the model with five eczema phenotypes as the best fit (Fig. 1, Tables S2, S3; see Supporting Information). The five eczema phenotypes were described as never eczema (76%), early transient eczema (8%), mid-transient

Table 1 Characteristics of children and their mothers after multiple imputation

	Individuals (N = 5297)
Parental characteristics	
Parity (nulliparous)	3096 (59)
Maternal education (higher)	3009 (57)
History of eczema, allergy and asthma (yes, at least one parent)	3189 (60)
Child characteristics	
Sex (male)	2632 (50)
Ethnicity (non-European)	1359 (26)
Breastfeeding (ever)	4885 (92)
Day care attendance (yes)	3145 (59)
Pet exposure (yes)	2038 (39)
Wheezing pattern	
Never	2887 (55)
Early	1495 (28)
Late	261 (5)
Persistent	655 (12)
FLG genotype (≥ 1 mutations)[a]	247 (8)
Genetic risk score, mean ± SD[a]	31 ± 3·45
Physician-diagnosed eczema[a]	
6 months	662 (16)
1 years	637 (13)
2 years	719 (14)
3 years	442 (9)
4 years	378 (8)
10 years	347 (7)

Data are presented as n (%) unless stated otherwise. Values are based on 20 imputed datasets. [a]Data on *FLG* genotype, genetic risk score and physician-diagnosed eczema were not imputed. Data were missing for *FLG* genotype [n = 2186 (41%)], genetic risk score [n = 1880 (36%)], and physician-diagnosed eczema at 6 months [n = 1569 (30%)], 1 year [n = 730 (14%)], 2 years [n = 457 (9%)], 3 years [n = 726 (14%)], 4 years [n = 789 (15%)] and 10 years [n = 1418 (27%)].

eczema (6%), late transient eczema (8%) and persistent eczema (2%). Similar results were observed in children with data on physician-diagnosed eczema available at all six time points (n = 1975) (Table S2; see Supporting Information). To compare our results with previous studies, we used longitudinal latent class analysis and identified that the model with three, not five, eczema phenotypes was the best fit for our data (Table S3, Fig. S1a, b; see Supporting Information). The three phenotypes were similar in pattern to the never, early transient and persistent eczema phenotypes identified using latent class growth analysis.

Early environmental exposures and eczema phenotypes

No major differences in the magnitude or the direction of the effect estimates were observed between analyses with imputed data and analyses with complete cases only. Here, we present only the results based on imputed data. Nulliparity and parental history of eczema, allergy or asthma were positively associated with early transient and persistent eczema compared with never eczema and reference groups (OR range 1·37, 95% CI 1·07–1·74 and OR 2·01, 95% CI 1·20–3·36, respectively) (Table 2). Boys were significantly more likely to have early transient eczema (OR 1·49, 95% CI 1·18–1·89), while non-European ethnicity was associated with late transient (OR 1·35, 95% CI 1·03–1·78) and persistent eczema (OR 1·74, 95% CI 1.09–2.79). Children with late-onset wheezing had higher risks for early transient and persistent eczema (OR 2·65, 95% CI 1·67–4·20 and OR 3·63, 95% CI 1·71–7·71, respectively) than children classified as 'never wheezing' and 'never eczema'. Children with persistent wheezing more often had early and late transient, and persistent eczema (OR 2·67, 95% CI 1·94–3·69; OR 1·89, 95% CI 1·36–2·65 and OR 3·50, 95% CI 2·03–6·04, respectively) than children classified as 'never wheezing' and 'never eczema'. No other significant associations of early environmental exposures with eczema phenotypes were observed.

Genetic risk factors and eczema phenotypes

Children with one or more *FLG* mutations had increased risks of early and late transient eczema (OR 2·21, 95% CI 1·40–3·49 and OR 2·09, 95% CI 1·30–3·34, respectively) compared with children without *FLG* mutations and those classified as 'never eczema' (Table 3). For each additional risk allele in the genetic risk score, children had increased risks of early transient and persistent eczema (OR 1·08, 95% CI 1·03–1·13 and 1·09, 95% CI 1·01–1·18, respectively). The size and the direction of the effect estimates of the associations of genetic risk factors with eczema phenotypes remained similar when we additionally adjusted for all early environmental exposures. Also, the size and the direction of the effect estimates of the associations of early environmental exposures with eczema phenotypes remained similar, although some were attenuated to nonsignificant when we additionally adjusted for *FLG* genotype and the genetic risk score (Table S4; see Supporting Information).

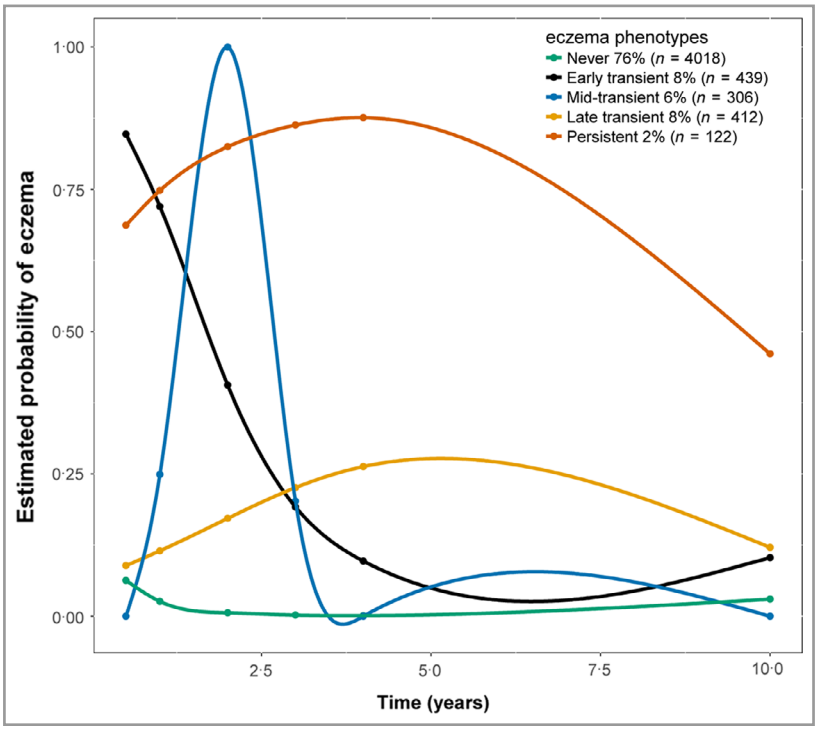

Fig 1. Eczema phenotypes trajectories from latent class growth analysis.

Table 2 Associations of early environmental exposures with eczema phenotypes

	Early transient eczema, n = 439	Mid-transient eczema, n = 306	Late transient eczema, n = 412	Persistent eczema, n = 122
Environmental exposure model, n = 5297				
Parity (nulliparous)	**1·37 (1·07–1·74)**	1·38 (0·98–1·95)	1·10 (0·88–1·39)	**1·65 (1·06–2·55)**
Maternal education (higher)	1·04 (0·80–1·36)	1·11 (0·76–1·61)	1·04 (0·80–1·35)	0·70 (0·44–1·12)
Parental history of eczema, allergy or asthma (yes)	**1·71 (1·29–2·25)**	1·14 (0·79–1·64)	1·20 (0·93–1·55)	**2·01 (1·20–3·36)**
Sex (male)	**1·49 (1·18–1·89)**	0·98 (0·71–1·35)	0·83 (0·66–1·04)	1·21 (0·80–1·83)
Ethnicity (non-European)	1·02 (0·76–1·36)	1·04 (0·69–1·58)	**1·35 (1·03–1·78)**	**1·74 (1·09–2·79)**
Breastfeeding (ever)	0·90 (0·58–1·39)	0·83 (0·45–1·53)	0·91 (0·59–1·40)	0·69 (0·34–1·39)
Child day care(yes)	1·06 (0·81–1·39)	1·22 (0·82–1·80)	1·21 (0·92–1·58)	1·49 (0·88–2·50)
Pet exposure (yes)	0·88 (0·68–1·14)	0·82 (0·57–1·19)	1·10 (0·85–1·42)	0·67 (0·41–1·11)
Wheezing pattern (early)	1·20 (0·88–1·62)	1·05 (0·71–1·55)	1·14 (0·85–1·52)	0·87 (0·47–1·58)
Wheezing pattern (late)	**2·65 (1·67–4·20)**	1·23 (0·54–2·80)	1·23 (0·68–2·25)	**3·63 (1·71–7·71)**
Wheezing pattern (persistent)	**2·67 (1·94–3·69)**	1·27 (0·74–2·17)	**1·89 (1·36–2·65)**	**3·50 (2·03–6·04)**

Values are pooled odds ratios with their 95% confidence intervals. All environmental exposure were entered simultaneously in the model. Reference groups are 'never eczema' phenotype group (n = 4018), and multiparous, primary education, no parental history of eczema, allergy or asthma, female sex, never breastfeeding, no day care attendance, no pet exposure or never wheezing groups. Bold values indicate statistical significance at the $\alpha = 0{\cdot}05$ level.

Ethnicity and eczema phenotypes

After dividing ethnicity into more detailed subgroups in our early environmental exposure model, we observed that Asian and African ethnicity were positively associated with late transient (OR 1·83, 95% CI 1·20–2·80 and OR 1·49, 95% CI 1·00–2·23, respectively) and persistent eczema (OR 2·26, 95% CI 1·11–4·60 and OR 2·01, 95% CI 1·06–3·79, respectively), compared with 'never eczema' and European ethnicity (Tables 3, S5; see Supporting Information). When we additionally adjusted for genetic risk factors, only the associations of Asian ethnicity with an increased risk for late transient (OR 2·04, 95% CI 1·14–3·65) and persistent eczema (OR 3·08, 95% CI 1·34–7·10) remained (Tables 3, S6; see Supporting Information).

Discussion

Five eczema phenotypes were identified in a multiethnic paediatric population, which was followed from birth until age 10 years, based on age of onset and persistence of eczema. Several known risk factors for eczema were associated with distinct phenotypes, but no clear patterns emerged, which suggests that the previously known eczema risk factors have limited differentiating capacities for eczema phenotypes. Most of the associations were found in relation to early transient and persistent eczema. Early transient and persistent eczema were most common in first-born children, those with a parental history of eczema, allergy or asthma and those with persistent wheezing. Early transient eczema was most common in male children only. Children with late transient or persistent eczema were more often of Asian and African ethnicity. Eczema phenotypes were not associated with maternal education, breastfeeding, day care attendance or pet exposure. Children with early and late transient and persistent eczema more often had a filaggrin mutation or additional risk alleles in the genetic risk score. Most effect estimates did not materially change when we adjusted our analyses for both environmental and genetic factors. The explanation of why early transient and persistent eczema phenotypes share several determinants is not clear, but both patterns are dominant around the age of 1 year. This may be an important age in relation to exposure to environmental factors and the expression of genetic predisposition in the maturation of the skin and the immune system leading to the development of eczema.[31]

In our study, never, early transient and late transient and persistent eczema showed a similar pattern as those identified in a cohort study among 1038 children followed from birth until age 6 years.[16] Compared with a different study among 3652 and 9894 children followed from birth until age 11 years and 16 years,[15] higher early eczema probabilities were observed with steeper resolving curves, and no phenotype was identified with an onset after age 6 years. There was a greater degree of similarity in the patterns when we used longitudinal latent class analysis. However, this analysis does not take repeated measurements into account, which we considered relevant in this study because eczema measurements were taken at different time intervals. The remaining discrepancy in number and pattern of phenotypes might be explained by the differences in follow-up time (10 years compared with 6 years and 11–16 years in the other studies),[15,16] number of repeated eczema measurements (six measurements compared with seven and 10–12), eczema definition (physician-diagnosed eczema vs. itchy rash on specific locations) and population characteristics (multiethnic vs. mostly European ethnicity).

Table 3 The associations of genetic risk factors with eczema phenotypes and three separate sensitivity analysis investigating the associations between early environmental exposures, genetic risk factors and/or ethnicity and eczema phenotypes

	Early transient eczema	Mid-transient eczema	Late transient eczema	Persistent eczema
Genetic risk factor model, n = 2981	n = 258	n = 177	n = 235	n = 76
FLG genotype (≥ 1 mutations)	**2·21 (1·40–3·49)**	1·52 (0·73–3·15)	**2·09 (1·30–3·34)**	1·68 (0·69–4·09)
Genetic risk score (per additional allele)	**1·08 (1·03–1·13)**	1·06 (0·99–1·13)	1·02 (0·98–1·06)	**1·09 (1·01–1·18)**
Environmental exposure model and genetic risk factors (i), n = 2981	n = 258	n = 177	n = 235	n = 76
FLG genotype (≥ 1 mutations)	**2·21 (1·39–3·50)**	1·56 (0·75–3·24)	**2·02 (1·26–3·24)**	1·80 (0·73–4·47)
Genetic risk score (per additional allele)	**1·07 (1·02–1·12)**	1·05 (0·99–1·12)	1·01 (0·97–1·06)	**1·09 (1·00–1·18)**
Environmental exposure model in ethnic subgroups (ii), n = 5297	n = 439	n = 306	n = 412	n = 122
Ethnicity (Mediterranean)	0·78 (0·48–1·26)	0·44 (0·18–1·05)	1·12 (0·72–1·74)	1·10 (0·50–2·40)
Ethnicity (Asian)	1·27 (0·78–2·06)	1·66 (0·91–3·01)	**1·83 (1·20–2·80)**	**2·26 (1·11–4·60)**
Ethnicity (African)	1·35 (0·89–2·05)	1·11 (0·60–2·06)	**1·49 (1·00–2·23)**	**2·01 (1·06–3·79)**
Environmental exposure and genetic model in ethnic subgroups (iii), n = 2981	n = 258	n = 177	n = 235	n = 76
Ethnicity (Mediterranean)	0·99 (0·53–1·86)	0·57 (0·19–1·70)	1·41 (0·79–2·49)	1·00 (0·35–2·83)
Ethnicity (Asian)	1·43 (0·75–2·73)	1·95 (0·88–4·31)	**2·04 (1·14–3·65)**	**3·08 (1·34–7·10)**
Ethnicity (African)	1·35 (0·77–2·37)	1·68 (0·82–3·43)	1·43 (0·81–2·50)	1·80 (0·77–4·17)

Values are pooled odds ratios with their 95% confidence intervals. The genetic risk factor model was adjusted for ethnicity only. The environmental exposure model was mutually adjusted for all environmental exposures as presented in Table 1, and additionally adjusted for (i) genetic risk factors, (ii) ethnic subgroups and (iii) for genetic risk factors and ethnic subgroups. Reference groups are the 'never eczema' phenotype group, and European ethnicity, or no *FLG* mutation group. Effect estimates for the association of early environmental exposures with eczema phenotypes additionally adjusted for the genetic risk factors and ethnicities subgroups are shown in Tables S4–S6 (see Supporting Information). Bold values indicate statistical significance at the $\alpha = 0{\cdot}05$ level.

The observations in this study support the view that nulliparity, parental history of eczema, allergy and asthma, late-onset and persistent wheezing, *FLG* genotype and the genetic risk score based on previously identified SNPs are risk factors for childhood eczema.[6,12,15,16] The functions of many of these SNPs are not yet determined, but may be related to autoimmunity and skin barrier.[13] A previous study suggests that children of Surinamese–Creole and Surinamese–Hindustani origin have an increased risk of eczema.[22] In addition, this study showed that Asian and African children had an up to 3·6-fold increased risk of late transient and persistent eczema compared with European children. Possible underlying mechanisms include differences in skin barrier properties, parental psychological distress, microbiome development and other genetic factors.[11,22,32]

In contrast to the literature, no associations were observed between breastfeeding and eczema phenotypes. However, most literature focused on the presence or absence of eczema and not on distinct phenotypes, or a univariate analysis was used.[15] Even though favourable effects have been found between pet exposure and eczema, we did not find any effect between postnatal pet exposure and eczema phenotypes.[8] This is in line with previous studies on eczema phenotypes.[15,16] Differences between our study and the previous literature might be due to the timing of the measurements, different distribution of risk factors or mild severity of included eczema cases as is illustrated by the low prevalence of *FLG* mutations in our multiethnic paediatric population.[12]

The number of eczema phenotypes is based on statistical fit and depends on clinical relevance. The three eczema phenotypes identified by latent class growth analysis might present a more useful model for clinical practice, because it makes a clearer distinction between transient and persistent eczema. All patients with eczema should receive optimal care, but it would be useful to identify children with a higher chance of developing persistent eczema, as they may well benefit from earlier, more aggressive, treatment.[33] For future studies, it would be clinically relevant to know whether individuals with specific eczema phenotypes are more prone to develop other atopic diseases, such as asthma and/or food allergies. From an aetiological point of view, it is important to improve the identification of specific early-life environmental exposures and genetic risk factors in the development and persistency of eczema. A sufficient number of cases of eczema and detailed information on endogenic factors are needed to compare immunological response, skin barrier defects and genetic predisposition in children with different eczema phenotypes.

The strengths of this study include the prospective population-based design, multiethnic population with detailed information on eczema, early environmental exposures and genetic factors. Our eczema phenotypes model seems valid for a multiethnic population in an ever-globalizing world. Latent class growth analysis is an objective method to identify classes within a population. More precise and unbiased effect estimates are obtained by using multivariate multinomial models based on imputed data. However, some methodological limitations to this study need to be considered. We assumed that data was missing at random. It is always a possibility that

missing data is not missing at random, which might lead to biased estimates.[34] Including children with at least 50% of the data observed ensures a more reliable model. Selection bias might be present if the associations of the selected environmental and genetic factors with eczema phenotypes were different for the children included and those who were not included in the analyses. Furthermore, we cannot rule out under-reporting or misreporting of eczema. However, there is evidence that parent-reported physician-diagnosed eczema is sufficient for epidemiological research and eczema prevalence in our study is similar to that of the Dutch population.[33,35] No information was available to determine the severity of eczema or subtypes of eczema, which could have influenced the observed effect estimates and associations, and there is a possibility that residual confounding may have occurred. Also, a longer follow-up period could influence the number and pattern of eczema phenotypes. The uncertainty of class assignment of children is only partially accounted for by using weights in the multinomial analyses. Moreover, the results were not adjusted for multiple testing. We extracted the SNPs from the most recent GWA study that included non-European populations; however, most of the genetic risk factors, including *FLG* mutations, have been discovered in European populations.[13] Although early transient and persistent eczema appear to share several determinants, most of the selected environmental and genetic factors did not strongly differentiate between the various eczema phenotypes. This may partly be explained by minimizing the number of categories per factor in order to maximize the number of factors required to maintain appropriate statistical models. Future large-scale studies examining early-life environmental exposures in more detail could provide better differentiation between eczema phenotypes.

In conclusion, five eczema phenotypes were identified in a multiethnic paediatric cohort followed from birth until the age of 10 years. Previously known eczema risk factors differentiated between the different phenotypes to a limited degree. Male sex and Asian and African ethnicity were differently associated with eczema phenotypes and therefore could be useful for prediction purposes. Further studies are needed to compare the trajectories of different eczema phenotypes and identify other potential predictive factors, ideally in a 'hypothesis-free approach' as known risk factors are relatively poor discriminators, in order to improve eczema management and prevention strategies.

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Author contributions

C.H., L.D., N.S.E. and T.N. contributed to the conception and design, acquisition of data, analyses and interpretation of the data, drafted the article, revised it critically for important intellectual content, and gave final approval of the version to be published. N.J.E., C.P., V.B., S.B., J.J., S.P. and J.F. contributed to the conception and design, acquisition of data, revised the drafted manuscript critically for important intellectual content, and gave final approval of the version to be published.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

File S1 Supplemental methods.[36]

Table S1 Characteristics of children and their mothers of those included and those not included in the analyses.

Table S2 Model fit after latent class growth analysis.

Table S3 Model fit after longitudinal latent class analysis.

Table S4 Associations of early environmental and genetic factors with eczema phenotypes.

Table S5 Associations of early environmental and eczema phenotypes with ethnicity subdivision.

Table S6 Associations of early environmental and genetic factors with eczema phenotypes with ethnicity subdivision.

Fig S1. (a) Three eczema phenotypes after longitudinal latent class analysis. (b) Five eczema phenotypes after longitudinal latent class analysis.