

Sex-specific developmental trajectories of eczema from infancy to age 26 years: A birth cohort study

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Abstract

Background

Eczema is a common inflammatory skin disease with varying developmental trajectories/patterns that are influenced by different risk factors. The aim of this study was to investigate eczema development from infancy to early adulthood by identifying distinct developmental trajectories that describe disease patterns over time and evaluate the role of prenatal and early-life risk factors.

Methods

The Isle of Wight Birth Cohort ($n = 1456$) was prospectively assessed at birth, 1, 2, 4, 10, 18 and 26 years. In all assessments, eczema was defined as chronic or chronically relapsing itchy dermatitis lasting >6 weeks with characteristic morphology and distribution in the past 12 months. Developmental trajectories of eczema between 1 or 2 and 26 years were identified separately for males and females by applying semiparametric mixture models. Associations were assessed by applying a modified Poisson regression to estimate adjusted risk ratios (aRR) and 95% confidence intervals (CI).

Results

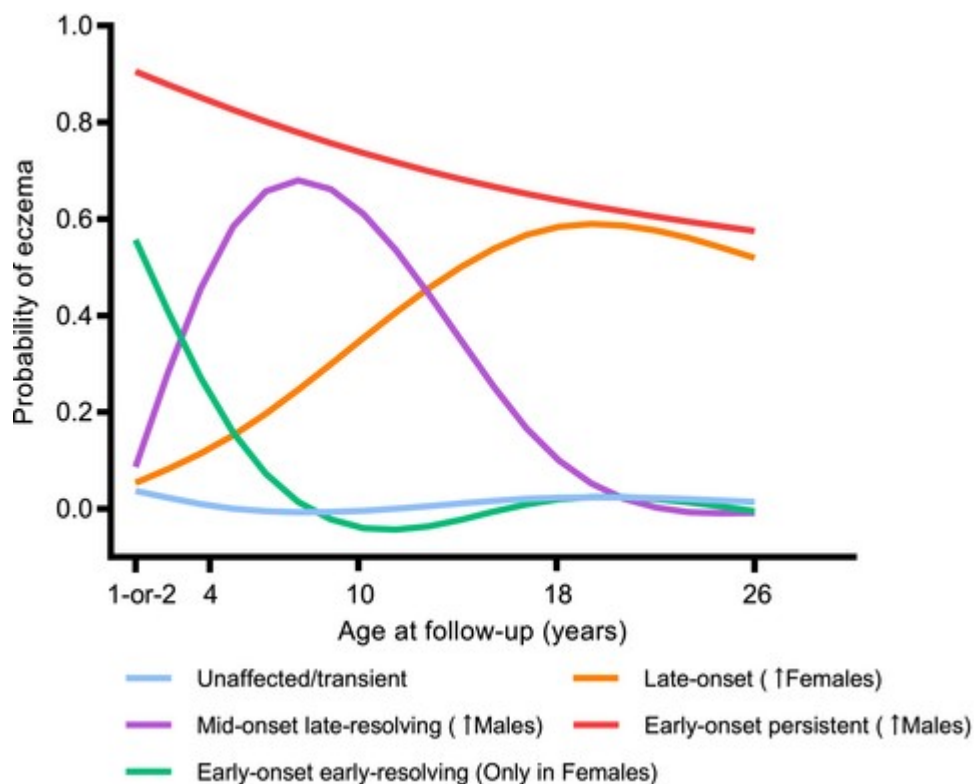
In both males and females, the following eczema developmental trajectories were identified: unaffected/transient (males: 77.7% vs. females: 73.0%), mid-onset late-resolving (males: 7.8% vs. females: 4.4%), late-onset (males: 5.2% vs. females: 9.5%) and early-onset persistent (males: 9.3% vs. females: 5.4%). In females, an additional trajectory was identified as follows: early-onset early-resolving (7.7%). Among males, filaggrin gene (*FLG*) variants (aRR = 2.45, 95% CI: 1.34–4.46) and paternal eczema (2.66, 1.39–5.08) were associated with the early-onset persistent trajectory. Among females, maternal eczema (2.84, 1.42–5.70) and high birthweight (2.25, 1.08–4.69) were associated with the early-onset persistent trajectory.

Conclusions

Four and five trajectories represented eczema development among males and females, respectively, with different predisposing risk factors. Our results indicate that males and females may experience a different course of eczema.

Abstract

Males and females follow different developmental trajectories of eczema from infancy to 26 years of age, with more males than females following an early-onset persistent trajectory and a mid-onset late-resolving trajectory. In contrast, more females than males followed a late-onset trajectory and only females were in the early-onset early-resolving trajectory. Moreover, males and females have distinct risk factors that influence the developmental trajectories of eczema. Hence, it is important to considered sex-stratified clinical management of the disease.



Key messages

Males and females experience different developmental trajectories of eczema, with sex-specific risk factors.

Males are more likely than females to follow an early-onset persistent eczema trajectory.

Females are more likely than males to develop eczema in adolescence and early adulthood.

1 INTRODUCTION

Eczema, also known as atopic dermatitis and atopic eczema, is a common and chronic inflammatory skin disease that often follows a relapsing-remitting course. It has been estimated that up to 20% of children and 10% of adults are affected by eczema.^{1, 2} The disorder is characterized by a heterogeneous clinical presentation that includes erythematous, scaly, pruritic, and acute oozing and crusting lesions.^{3, 4} The pathophysiology of eczema is multifactorial, with immune system dysregulation and epidermal barrier dysfunction being the major hallmarks of the disease.^{5, 6} Although eczema is not life-threatening, it poses a significant impact on healthcare resources and patients' and their relatives' overall health, including quality of life and psychosocial well-being.^{7, 8}

There is a consensus in the scientific literature that most cases of eczema develop during early childhood^{7, 9, 10}; however, the long-term natural history of the disease is less understood. It has been widely accepted that most early childhood cases resolve later in childhood, with few cases developing in adolescence and adulthood, but this view has been challenged as adulthood onset is not rare, and some childhood cases may relapse later in life (relapsing-remitting nature) or even follow a persistent course of the disease.¹¹⁻¹³ A meta-analysis estimated adult-onset eczema to be 26.1% (95% CI: 16.5–37.2%), that is, around 1 in 4 adults with eczema report adulthood-onset of their disease.¹⁴ Hence, this heterogeneity indicates that different trajectories of eczema development exist that may be influenced by different determinants. One strong risk factor that has been related to eczema development, and a more persistent and severe phenotype is carrying loss-of-function (LOF) variants in the filaggrin gene (*FLG*), which encodes an important structural protein involved in the epidermal barrier formation and integrity.¹⁵⁻¹⁹

Several birth cohorts have investigated the course of eczema during the first two decades of life, and in a few instances up to early adulthood, as synthesized in a prior systematic review, which concluded that the prevalence of eczema was similar before and after childhood, with some observed heterogeneity between studies.²⁰ Of the five studies reporting eczema prevalence beyond 20 years of age, three studies reported that eczema

prevalence is lowest in early adulthood,²¹⁻²³ whereas two studies showed that eczema prevalence was higher in early adulthood^{13, 24} as compared to assessments during adolescence. Few studies have investigated the longitudinal trajectories of eczema development, where distinct developmental trajectories, such as early-onset persistent, early transient and late onset, and their determinants have been identified.²⁵⁻²⁷ These studies have investigated eczema development up to 6 years,²⁵ 10 years²⁷ and 16 years,²⁶ and hence, there is a need to investigate eczema trajectories beyond adolescence. Another study has incorporated eczema severity phenotypes while investigating eczema development up to age 14 years.²⁸

The participants of the Isle of Wight Birth Cohort (IOWBC) study have been seen on six occasions over the course of 26 years, at 1, 2, 4, 10, 18 and 26 years, with eczema being assessed at each follow-up.²⁹ Using data from the IOWBC, this study aims to investigate the natural course of eczema development from infancy to early adulthood in terms of identifying distinct developmental trajectories that describe disease patterns over time. Given that male and female subjects experience different course of the disease, with eczema prevalence being equal or slightly higher among males during childhood and becoming preponderant among females after puberty,^{23, 24, 30-32} our analysis was stratified by sex. In addition, effects of prenatal and early-life risk factors on eczema trajectories were assessed.

2 METHODS

2.1 Study design and participants

The IOWBC is a whole population-based prospective study that recruited all children ($n = 1536$, ~98% Caucasian) born between 1 January 1989 and 28 February 1990 on the Isle of Wight, UK, to study the natural history and aetiology of allergic and respiratory conditions.^{29, 33} Parental informed consent was obtained to enrol 1456 newborns to participate in the ensuing follow-ups that occurred at the ages of 1, 2, 4, 10, 18 and 26 years, with >80% retention at all assessments up to 18 years and 71% retention at age 26 years.^{29, 34} In the current analysis, participants who had three or more valid eczema status information (i.e. not missing) across the follow-ups were included; hence, 1381 (94.8%) participants satisfied our inclusion criteria. All participants provided informed consent and ethical approval was obtained from the local/national Research Ethics Committee at recruitment and at each assessment. At age 26, ethical approval was granted by National Research Ethics Committee, West Midlands (15/WM/0071). Phenotypic and environmental information was collected using questionnaires and a wide range of clinical assessments and measurements were carried out as detailed by Arshad et al.²⁹

2.2 Eczema ascertainment

In all assessments of the IOWBC, investigators determined the presence of eczema based on

symptoms over the last 12 months, which was defined as chronic or chronically relapsing itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution,^{29, 35} according to the criteria of Hanifin and Rajka.³⁶ Since the 1- and 2-year follow-up data on eczema were collected in a relatively narrow time window, we have combined them for analytic purposes and reported them hereafter as 1 or 2 years.

2.3 Prenatal and early-life variables

In the current report, we have assessed the effect of prenatal and early-life risk factors on the development of eczema, including *FLG* LOF variants, maternal and paternal history of eczema, birthweight (low/normal <4000 g; high $\geq$ 4000 g; the low (<2500 g) birthweight group was analysed with the normal birthweight group due to a small proportion (3.5%, 48/1360) of participants were born with low birthweight), birth order, duration of breastfeeding reported in weeks, and whether the child's family owned a cat and/or a dog at the time of the child's birth. A total of 1150 participants were genotyped for *FLG* variants R501X, 2282del4, S3247X, 3702delG and R2447X, with the latter two variants were not informative in our study population due to minor allele frequencies <0.1%. Individuals carrying the minor allele for at least one of the *FLG* variants R501X, 2282del4 or S3247X were classified as carrying *FLG* LOF variants. *FLG* variants genotyping was performed using the GoldenGate Genotyping Assays (Illumina, Inc.) on the BeadXpressVeracode platform (Illumina, Inc.) per Illumina's protocol, detailed information is provided by Ziyab et al.³⁷

2.4 Measures of disease occurrence

To investigate the natural course of eczema across the five analytical follow-ups (1 or 2, 4, 10, 18, 26 years), different measures of disease occurrence were estimated. The 12-month period prevalence was calculated at each follow-up as the number of existing cases divided by the total number of subjects participating in the respective follow-up. Incidence, to measure newly developed eczema, was defined at the 10-, 18- and 26-year follow-ups as the number of new cases at the respective follow-up divided by the total cohort at risk (i.e. disease-free in all preceding follow-ups).³⁸ Remission, to estimate the proportion of cases that outgrew eczema, was defined at the 10-, 18- and 26-year follow-ups as the number of cases that outgrew eczema at the respective follow-up divided by the cohort who had eczema in preceding follow-ups.³⁸ Moreover, given the relapsing-remitting course of eczema, disease transition measures were estimated to describe the change in a person's disease status between two consecutive assessments, regardless of whether it was the first such occurrence or whether prior data were missing.^{30, 38, 39} Hence, four transition periods were considered in our analysis: 1 or 2 to 4 years, 4 to 10 years, 10 to 18 years, and 18 to 26 years. Positive transition (change from disease-free to diseased) was defined as the number of eczema cases at the end of the transition period divided by the number of subjects that were disease-free at the beginning of the transition period. Negative transition (change from diseased to disease-free) was defined as the number of eczema-free subjects at the end of the transition period divided by the number of subjects with eczema at the

beginning of the transition period. It is worth noting that positive transition may capture some incident cases and negative transition may capture some remitting cases (i.e. some overlap may exist).

2.5 Trajectory analysis

Developmental trajectories (i.e. distinct subgroups within the total sample that follow similar disease patterns over time) of eczema across ages 1 or 2, 4, 10, 18, and 26 years were identified separately for males and females by applying semiparametric mixture models using PROC TRAJ macro in SAS 9.4 (SAS Institute).^{40, 41} See the Methods section: Appendix [S1](#) for more details.

2.6 Statistical analysis

All statistical analyses were conducted using SAS 9.4. The statistical significance level was set to $\alpha = .05$. Descriptive analyses were conducted to calculate frequencies and proportions of categorical variables and median and interquartile range (IQR) were used to describe continuous variables. Chi-square (χ^2) tests were used to assess differences in proportions across sex. To control for false-positive results, we applied the false discovery rate (FDR) method to estimate adjusted *p*-values for the sex comparisons.⁴² Adjusted associations were assessed by applying a modified Poisson regression with robust variance estimation to estimate and infer risk ratios (RR) and their 95% confidence intervals (CI).⁴³ Adjusted associations between prenatal and early-life risk factors (predictors) and eczema trajectories (outcome variable) were assessed separately for males and females. The “unaffected/transient” trajectory was set as the reference group and a series of three and four regression models were evaluated among males and females, respectively, to assess the associations.

3 RESULTS

3.1 Description of the study population

In total, information on eczema status was available for 1377 (700 males), 1214 (619 males), 1359 (688 males), 1307 (651 males) and 1029 (469 males) study participants at ages 1 or 2, 4, 10, 18 and 26 years, respectively. The total enrolled study sample and the analytical study sample were similar with respect to all characteristics under study (Table [1](#)). The combined proportion of carrying the minor (loss-of-function) allele(s) of *FLG* variants R501X, 2282del4, and/or S3247X was 10.3% (116/1,129) in the analytical study sample. No individuals were homozygous for the minor allele of any *FLG* variants. One person had a compound heterozygous genotype for R501X and 2282del4, and this person was analysed with the heterozygotes.

TABLE 1. Characteristics of the total enrolled study sample and the analytical study sample

Characteristic	Enrolled study sample	Analytical study sample ^a
Sex, % (n/total)		
Male	51.2 (786/1536)	50.4 (696/1381)
Female	48.8 (750/1536)	49.6 (685/1381)
FLG genotype, % (n/total)		
Loss of function	10.3 (118/1150)	10.3 (116/1129)
Maternal eczema, % (n/total)		
Yes	12.1 (147/1213)	12.1 (144/1191)
Paternal eczema, % (n/total)		
Yes	6.4 (78/1213)	6.5 (77/1191)
Birthweight, % (n/total)		
Low/normal ^b	88.0 (1329/1511)	87.6 (1192/1360)
High ^c	12.0 (182/1511)	12.4 (168/1360)
Birth order, % (n/total)		
First	42.1 (510/1212)	42.0 (500/1189)
Second	34.6 (419/1212)	34.5 (410/1189)

Abbreviation: IQR, interquartile range.

^a Includes participants who have three or more valid eczema status information (i.e. not missing) across the five analytical follow-ups.

^b Low/normal birthweight: <4000 g. ^c High birthweight: ≥4000 g

3.2 Measures of disease occurrence

Estimates of the 12-month period prevalence, positive transition, incidence, negative transition and remission of eczema from 1 or 2 to 26 years of age are shown in Table 2. The 12-month prevalence of eczema was highest at 1 or 2 years (14.2%) and lowest at 26 years (10.2%). Among males, eczema was most prevalent at 1 or 2 years (14.6%) and lowest at 18 years (8.3%) and 26 years (8.5%). Among females, eczema was most prevalent at 18 years (16.3%) and lowest at 26 years (11.6%; Table 2, Figure S1). Only minor differences in the prevalence were detected between males and females up to 10 years of age; however, eczema was statistically significantly more common among females compared to males at age 18 years (16.3% vs. 8.3%, $p < .001$, FDR-adjusted $p < .001$) and slightly higher at 26 years

(11.6% vs. 8.5%, $p = .104$, FDR-adjusted $p = .395$; Table 2).

TABLE 2. Prevalence (12-month), positive transition, incidence, negative transition and remission of eczema from infancy to 26 years of age in the total study sample and according to sex

	Age at follow-up (years), % (n/total)				
	1-or-2	4	10	18	26
Prevalence					
Overall	14.2 (196/1377)	11.9 (145/1214)	13.7 (186/1359)	12.3 (161/1307)	10.2 (105/1029)
Male	14.6 (102/700)	12.6 (78/619)	13.4 (92/688)	8.3 (54/651)	8.5 (40/469)
Female	13.9 (94/677)	11.3 (67/595)	14.0 (94/671)	16.3 (107/656)	11.6 (65/560)
<i>P</i> -value ^a	.715	.472	.733	<.001	.104
Positive transition					
Overall		5.9 (57/962)	8.6 (88/1025)	6.9 (73/1063)	4.9 (42/850)
Male		6.4 (31/488)	8.3 (43/518)	4.3 (23/532)	4.0 (16/404)
Female		5.5 (26/474)	8.9 (45/507)	9.4 (50/531)	5.8 (26/446)
<i>P</i> -value ^a		.569	.743	.001	.209
Incidence					
Overall			6.9 (60/865)	5.7 (42/743)	3.0 (16/539)
Male			6.7 (29/435)	3.0 (11/365)	1.6 (4/249)
Female			7.2 (31/430)	8.2 (31/378)	4.1 (12/290)

^a Calculated using chi-square (χ^2) tests to compare proportions across sex. If any cell count was less than 5 observations, Fisher's exact test was used.

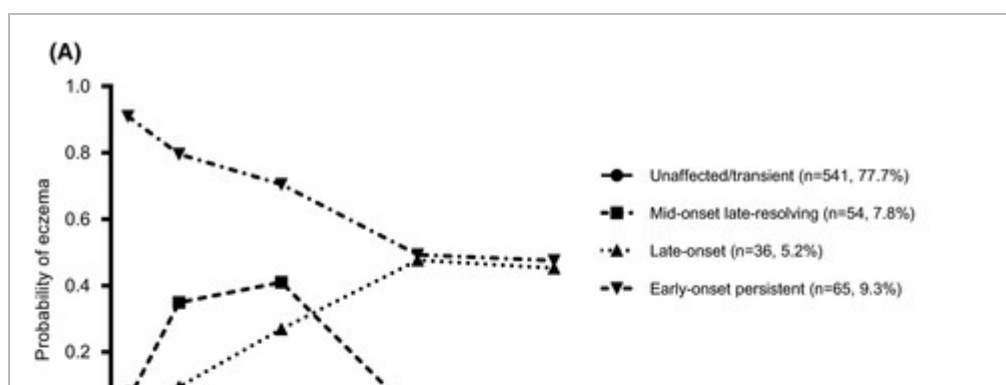
Positive transition (i.e. change in eczema status from “no eczema” to “yes eczema” in two consecutive follow-ups) was highest in males between 4 and 10 years (8.3%) and lowest between 18 and 26 years (4.0%; Table 2). Among females, positive transition was highest between 10 and 18 years (9.4%) and lowest between 1 or 2 and 4 years (5.5%) and between 18 and 26 years (5.8%). Positive transition between 10 and 18 years was statistically significantly higher in females compared to males (9.4% vs. 4.3%, $p = .001$, FDR-adjusted

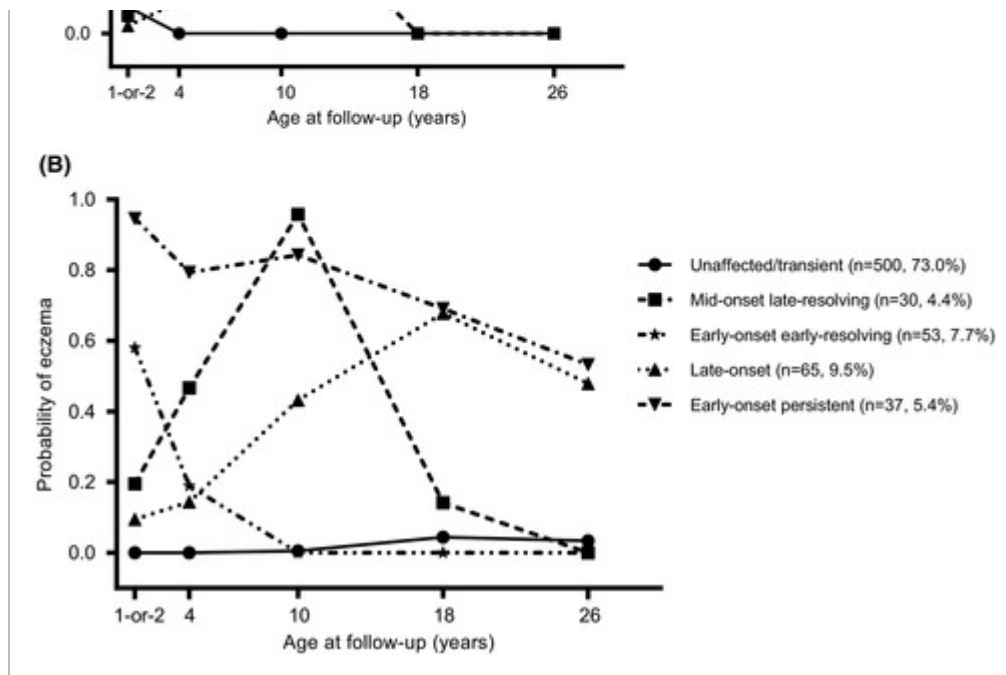
$p = .009$). Incidence (i.e. the first occurrence of eczema) of eczema decreased over the ages from 6.9% at age 10 to 3.0% at age 26 years. Similar to the finding of positive transition measure, incidence at age 18 years was higher in females than males (8.2% vs. 3.0%, $p = .002$, FDR-adjusted $p = .013$), a trend, which partially continued at age 26 years (Table 2).

Negative transition (i.e. change in eczema status from “yes eczema” to “no eczema” in two consecutive follow-ups) was highest in males between 10 and 18 years (65.4%) and highest in females between 18 and 26 years (61.2%; Table 2). On the base of negative transition, males were more likely than females to experience negative transition of eczema between 10 and 18 years (65.4% vs. 50.0%, $p = .044$, FDR-adjusted $p = .187$), with no sex differences detected at other negative transition periods. Remission (i.e. outgrowing eczema) was highest in males at age 18 years (39.1%) and highest in females at age 26 years (45.5%; Table 2) without showing statistically significant differences between the sexes.

3.3 Developmental trajectories of eczema

Trajectories of eczema development across the first 26 years of age were determined separately for male and female subjects. The optimum number of trajectories was determined based on BIC as shown in Table S1. In males, the development of eczema from infancy to 26 years of age was best represented by four developmental trajectories, labelled as: (1) unaffected/transient (77.7%, $n = 541$), (2) mid-onset late-resolving (7.8%, $n = 54$), (3) late-onset (5.2%, $n = 36$), and (4) early-onset persistent (9.3%, $n = 65$; Figure 1A). In females, the development of eczema across the first 26 years of life was best represented by five developmental trajectories, labelled as: (1) unaffected/transient (73.0%, $n = 500$), (2) early-onset early-resolving (7.7%, $n = 53$), (3) mid-onset late-resolving (4.4%, $n = 30$), (4) late-onset (9.5%, $n = 65$), and (5) early-onset persistent (5.4%, $n = 37$; Figure 1B). The early-onset early-resolving trajectory was identified in females but not in males. Overall, similar proportions made up the unaffected/transient trajectories in males and females (77.7% vs. 73.0%), but the distribution of the other trajectories was different across sex. For instance, more males than females were in the mid-onset late-resolving trajectory (7.8% vs. 4.4%, $p = .009$) and in the early-onset persistent trajectory (9.3% vs. 5.4%, $p = .005$), whereas females were more often than males to be in the late-onset trajectory (9.5% vs. 5.2%, $p = .002$), which also reflects their higher incidence/positive transition of eczema at age 18 years and the lower negative transition compared to males (Table 2).



**FIGURE 1**[Open in figure viewer](#) | [PowerPoint](#)

Trajectories of eczema from 1 or 2 to 26 years of age. (A) The four trajectories represent the latent growth patterns of eczema from 1 or 2 to 26 years of age in males ($n = 696$). (B) The five trajectories characterize the latent growth patterns of eczema from 1 or 2 to 26 years of age in females ($n = 685$). The y-axis presents the predicted probability of having eczema among the participants of each trajectory at different time points

3.4 Prenatal and early-life risk factors and trajectories of eczema

Associations between prenatal and early-life risk factors and the identified developmental trajectories of eczema were assessed separately for males (Figure 2A, Table S2) and females (Figure 2B, Table S3). Among males, carrying *FLG* LOF variants was associated with increased risk for being in the early-onset persistent trajectory (aRR = 2.45, 95% CI: 1.34–4.46), so was paternal eczema (2.66, 1.39–5.08). Moreover, *FLG* LOF showed positive associations with mid-onset late-resolving (1.84, 0.84–4.03) and late-onset 1.97 (0.79–4.94) trajectories, though these associations did not gain statistical significance. Cat-keeping at child's birth showed an association with the late-onset trajectory (2.79, 1.24–6.27) among male participants (Figure 2A). Among females, carrying *FLG* LOF variants was not statistically significantly associated with eczema trajectories (Figure 2B); however, indication for possible association was present with mid-onset late-resolving (1.47, 0.54–3.96) and early-onset persistent (1.58, 0.67–3.75) trajectories. Maternal eczema (2.84, 1.42–5.70) and high birthweight (2.25, 1.08–4.69, Figure 2B) were associated with the early-onset persistent trajectory among females.



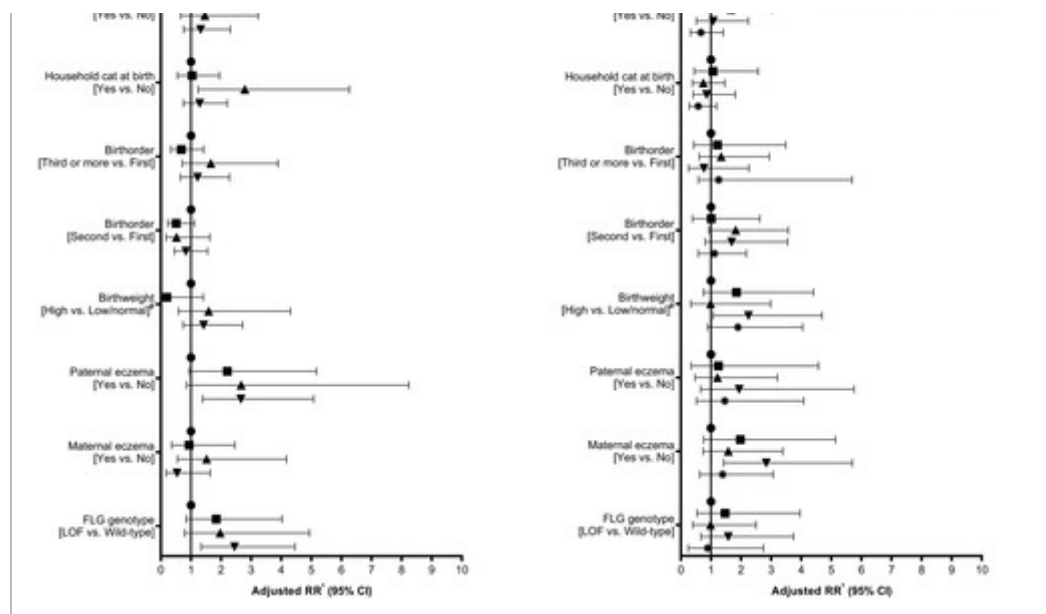


FIGURE 2

[Open in figure viewer](#) | [PowerPoint](#)

Forest plots showing associations between risk factors and trajectories of eczema among males (A) and females (B).[#]

Low/normal birthweight: <4000 g, high birthweight: ≥4000 g; *Adjusted for all variables shown in the figure. *FLG*, filaggrin gene; LOF, loss of function

4 DISCUSSION

The current study described the natural course and developmental trajectories of eczema from infancy to early adulthood and examined factors that are associated with eczema development. The developmental trajectories of eczema were best described by four trajectories among males and five trajectories among females. In general, similar developmental patterns of eczema were observed in males and females, with two exceptions. First, an “early-onset early-resolving” trajectory that was only observed among females. Second, more males than females experienced an “early-onset persistent” and “mid-onset late-resolving” developmental trajectories, whereas females were more often than males to be in the “late-onset trajectory.” In terms of risk factors for eczema trajectories, among males, *FLG* LOF variants and paternal eczema were associated with increased risk for being in the “early-onset persistent” trajectory. In contrast, among females, maternal eczema and high birthweight were associated with higher risk for being in the “early-onset persistent” trajectory. Such results indicate that males and females may experience a different course of eczema and also sex-specific risk factors.

We have estimated different measures of disease occurrence to better understand the natural course of eczema. The 12-month prevalence captured a decreasing trend in the course of eczema in both males and females, with more females than males being affected at ages 18 and 26 years. Such an observation has been reported in the German birth cohort (the “Multicenter Allergy Study” [MAS]) that showed higher eczema prevalence in females

than males at ages 15 and 20 years with an overall decreasing trend.⁴⁴ This female predominance in eczema prevalence that starts in adolescence and persists into adulthood has been described by several prior studies.^{32, 45, 46} In a previous investigation, we reported that more females than males developed eczema between ages 10 and 18 years (positive transition), and more males than females outgrew eczema between age 10 and 18 years (negative transition), which can explain the higher prevalence among adolescent females than males.³⁰ Herein, we showed that between ages 18 and 26 years eczema prevalence did not change among males (8.3% vs. 8.5%), but it decreased among females (16.3% vs. 11.6%). This observation can be explained by the fact that more females than males experienced negative transition and remission at 26 years of age than males. Moreover, newly developed eczema (incident cases) was more common among females than males at ages 18 and 26 years, indicating that females are more likely to experience adolescence- and adult-onset eczema than males. This observation contradicts prior findings that showed adult-onset eczema to be similar among the sexes^{14, 47} and support the idea that it is more common among females than males.³¹ Moreover, we estimated the incidence of eczema to be 3.0% at age 26 years, which is much less than a previously estimated adult-onset eczema of 26.1%.¹⁴

Although few prior studies have investigated the longitudinal development of eczema²⁵⁻²⁷ (summarized in Table S4), our study is the first to extend such trajectories beyond adolescence, to age 26 years. Overall, our identified trajectories were similar in patterns to previously identified trajectories (see Discussion section: Appendix S1 for more details about the prior studies). None of the studies described in this article's "Appendix S1: Discussion section" have considered analysing the developmental trajectories separately for males and females. Our analysis identified four eczema developmental trajectories among males and five trajectories among females. Although the developmental patterns of four trajectories were similar among both sexes, we identified an "early-onset early-resolving" trajectory only among females. Nonetheless, the distribution of the common trajectories differed according to sex, with more males than females following an early-onset persistent trajectory (9.3% vs. 5.4%) and a mid-onset late-resolving trajectory (7.8% vs. 4.4%). In contrast, more females than males were in the late-onset trajectory (9.5% vs. 5.2%), which may contribute to the observed higher eczema prevalence at ages 18 and 26 among females compared to males (Table 2). It has been suggested previously that sex hormones may contribute to the observed sex dimorphism, with oestrogens inducing pro-inflammatory responses and testosterone being immunosuppressive.^{48, 49} Moreover, we identified different risk factors for male and female trajectories. For example, *FLG* LOF variants were associated with increased risk for being in the early-onset persistent trajectory among males but such an effect was moderately present among females, which did not gain statistical significance due, possibly, to limited statistical power; this potential sex-specific effect of *FLG* LOF variants on eczema development has not, up to our knowledge, been reported previously. Such findings indicate that genetic risk factors may influence the long-term development of eczema in a sex-specific manner. Moreover, paternal eczema was associated with early-

onset persistent trajectory among males, whereas maternal eczema was associated with early-onset persistent trajectory among females. Hence, indicating sex-dependent effects of parental history of allergy on offspring eczema development. Such a mother-to-daughter and father-to-son effects were reported previously for eczema and asthma in this cohort.⁵⁰ We also observed that high birthweight to be associated with early-onset persistent eczema among females only. Prior studies have shown that elevated birthweight is associated with eczema development in infancy.^{51, 52} Among males, our analysis identified that cat-keeping at birth was associated with increased risk for late-onset eczema trajectory; this observation has been reported previously.⁵³⁻⁵⁵

Comparing different studies on eczema trajectories (see Table S4) suggests that about 10%–40% of the eczema cases that develop early in life remain persistent (Generation R: 2%/24% = 8.3%; IOWBC males: 9.3%/22.3% = 41.7%); 60%–90% are resolving in late childhood, adolescence or early adulthood. It is likely that a family history of eczema/allergy or *FLG* LOF variants can help to distinguish children who have a higher risk of a persisting disease. However, future studies are needed to corroborate these findings. Moreover, the current IOW analysis and the prior investigations have consistently identified a “late-onset” trajectory, but potential risk factors for this trajectory remain to be identified. When comparing different studies (see Table S4), it is obvious that long-term cohort studies on eczema mainly originated in Europe. Such research and data are deficient in the United States and other parts of the world.

The prospective long-term follow-ups that covered childhood, adolescence and early adulthood and the high retention are major strengths to our study. In addition, analysing males and females separately provided novel insights into sex-specific inferences. Nonetheless, splitting the sample by sex might have magnified the influence of random variations on the assignment of males and females into the developmental trajectories. The trajectories we have identified are similar to those reported by previous investigation²⁵⁻²⁷; hence, further strengthening the consistency of our results. Lack of statistical power due to limited subgroup sample sizes was evident in few instances. For example, among males, *FLG* LOF variants non-statistically significantly increased the risk for “mid-onset late-resolving” and “late-onset” eczema trajectories. A similar pattern of non-statistically significant effects of *FLG* LOF variants was seen among females, which can be explained by the limited statistical power among the female subsample. Hence, such findings should not be overlooked solely due to the lack of statistical significance. We have used the Hanifin and Rajka³⁶ criteria to define eczema, which has shown high sensitivity (87.9%–96.0%) and specificity (77.6%–93.8%) as compared with clinical diagnosis as reference standard.⁵⁶ Nonetheless, a limitation of our eczema definition is not being age-adaptive to capture the evolvement of eczema over age. Moreover, the large gaps between the follow-ups is a further limitation to our estimated measures of disease occurrence, as such measures might miss cases that develop and resolve in-between the follow-ups.

In conclusion, we have described the natural course and developmental trajectories of

eczema from infancy to early adulthood. Our results showed that males and females may experience different eczema course and different sets of risk factors. Specifically, *FLG* LOF variants and paternal eczema were associated with a higher risk of an early-onset persistent trajectory among males, whereas maternal eczema and high birthweight were associated with early-onset persistent trajectory among females. Hence, investigations related to the aetiology and long-term development of eczema should be sex-stratified to facilitate stratified medicine efforts. Finally, extension of the prior cohorts and their analyses into adulthood and in non-European countries are needed.

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CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

AHZ conceived the epidemiological design of the study, analysed and interpreted the data and drafted the manuscript. NM contributed to the design of the study and interpretation of the data. SHA contributed to the conception and design of the study and contributed to acquisition and interpretation of data, funding acquisition, and project administration and supervision. WK contributed to the conception and design of the study and interpretation of the data, contributed to acquisition and interpretation of data, funding acquisition, and project administration and supervision. All authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by all authors.

ETHICAL APPROVAL

All participants provided informed consent, and ethical approval was obtained from the local/national Research Ethics Committee at recruitment and at each assessment. At age 26, ethical approval was granted by National Research Ethics Committee, West Midlands (15/WM/0071).

Open Research



DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information



Filename	Description
cea14068-sup-0001-AppendixS1.pdf PDF document, 136.4 KB	Appendix S1

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Supporting Information

Sex-specific developmental trajectories of eczema from infancy to age 26 years: a birth cohort study

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SUPPLEMENTARY METHODS

Trajectory analysis

Developmental trajectories (i.e., distinct subgroups within the total sample that follow similar disease patterns over time) of eczema across ages 1-or-2, 4, 10, 18, and 26 years were identified separately for males and females by applying semiparametric mixture models using PROC TRAJ macro in SAS 9.4 (SAS Institute, Cary, North Carolina, USA).^{1,2} This trajectory analysis is one type of latent class analyses methods, noted as latent class growth analyses or group-based trajectory analyses.³ The regular latent class analysis PROC LCA is not suitable for longitudinal data, since the “responses” (eczema status) are potentially dependent across different ages. The aim of the trajectory analysis is to identify distinct latent subgroups that best resemble the developmental patterns embedded in the data, and hence model selection was performed according to established criteria.⁴ To decide on the optimum number of groups, we fitted a one group model (basic model) and increased the group size to six while setting the parameter estimates to a second order (quadratic) equation.⁵ The model with the smallest absolute Bayesian Information Criterion (BIC) value that also minimizes overlap in the confidence intervals around estimated group membership probabilities of adjacent trajectories while summarizing the distinctive features of the data in the most parsimonious fashion was selected.^{2,5} As a confirmatory step, change in the BIC value between two consecutive models was used as a measure of weight of evidence against the null model (i.e., the model with less groups): $\Delta\text{BIC} = \text{BIC}_{(\text{complex model, i.e., a model with one more group than the null model})} - \text{BIC}_{(\text{null model})}$.¹ Interpretation of $2*(\Delta\text{BIC})$ values in terms of evidence against the null model is as follows: <2, not worth mentioning; 2 to 6, positive; >6 to 10, strong; >10, very strong.¹ Moreover, we ensured that the average of group-membership probabilities for individuals assigned to each group/trajectory exceeded the

recommended minimum threshold of 0.7.⁵ After selecting the best fitting model, individuals were assigned to one of the trajectories/groups based on their highest estimated group-membership probabilities.

We assume that missing data occurred at random in our study since we did not identify any factors explaining missingness at the different time points (follow-ups). Hence, such a missing pattern is compatible with the PROC TRAJ macro, which is able to handle data that is missing at random.⁵ Moreover, to ensure that missingness does not affect the determination of the trajectories, we have focused our analysis on participants who had three or more valid eczema status information (i.e., ≥ 3 of the 5 follow-ups) across the follow-ups; hence, 1,381 (94.8%) participants satisfied our inclusion criteria. A total of 775 participants had complete eczema information across all the follow-ups.

SUPPLEMENTARY DISCUSSION

Description of prior studies investigating eczema trajectories

Analyzing data from two birth cohort studies, namely the British ‘Avon Longitudinal Study of Parents and Children’ (ALSPAC; follow-up to 16 years) and the Dutch ‘Prevention and Incidence of Asthma and Mite Allergy’ (PIAMA; follow-up to 11 years) study, compared to one unaffected latent class, Paternoster et al. identified five latent classes of eczema development,⁶ with the most prevalent latent class was the early-onset-early-resolving eczema (ALSPAC: 12.9%; PIAMA: 15.4%; see Table S4 in this article’s Online Repository). *FLG* LOF variants and parental history of allergy were associated with increased risk for being in the persistent latent classes.⁶ Moreover, following children from birth to six years, similar patterns of eczema development were identified in the ‘Protection Against Allergy Study in Rural Environments’ (PASTURE) using latent class analyses.⁷ The study identified four classes (see Table S4 in this article’s Online Repository), with the early transient class being the most common (9.2%). Parental allergies status was associated with increased risk for being in the early transient and early persistent classes.⁷ Analyzing data from the multiethnic Generation R prospective cohort study, Hu et al. identified five eczema phenotypes between 6 months and 10 years of age (see Table S4 in this article’s Online Repository), with the most common latent classes being early transient (8%) and late transient (8%).⁸ In their study, parental history of allergy was associated with increased risk for being in the early transient and persistent eczema phenotypes. Moreover, carrying *FLG* LOF variants was associated with higher risk for the early transient and late transient eczema phenotypes, and demonstrated a trend for association with the persistent eczema phenotype.⁸ A study based on the ALSPAC data have incorporated eczema severity phenotypes while investigating eczema development up to age 14 years, have identified the

following subtypes: unaffected/rare (66%), severe-frequent (4%), moderate-frequent (7%), moderate-declining (11%), and mild-intermittent (12%), with FLG LOF variants and parental history of eczema being major risk factors.⁹

Table S1. Bayesian Information Criterion (BIC) and 2(Δ BIC) of different number of groups (trajectories) of eczema development from infancy to 26 years of stratified by sex.

Number of Groups	Males			Females		
	BIC	Null model	2(Δ BIC) [§]	BIC	Null model	2(Δ BIC) [§]
1	-1291.55			-1379.66		
2	-1084.08	1	414.94	-1219.66	1	320
3	-1032.08	2	104	-1204.48	2	30.36
4	-1023.92[†]	3	16.32	-1201.66	3	5.64
5	1035.27	4	-22.7	-1151.15[‡]	4	101.02
6	1035.88	5	-1.22	-1151.28	5	0.26

[†] Among male subjects, the 4-group (trajectory) model is favored, since it has the lowest absolute BIC value. Moreover, the change in BIC (2[Δ BIC]) between the 4-group and 5-group models did not provide evidence against the 4-group model.

[‡] Among female subjects, the 5-group (trajectory) model is favored, since it has the lowest absolute BIC value. Moreover, the change in BIC (2[Δ BIC]) between the 5-group and 6-group models did not provide evidence against the 5-group model.

[§] Interpretation of 2(Δ BIC) values in terms of evidence against the null model: <2, not worth mentioning; 2 to 6, positive; >6 to 10, strong; >10, very strong.

Table S2. Associations between risk factors and trajectories of eczema among male subjects

	Trajectories of eczema among males			
	Unaffected/transient	Mid-onset late-resolving	Late-onset	Early-onset persistent
FLG genotype				
Wild-type (n = 491), % (n)	78.4 (385)	8.1 (40)	4.7 (23)	8.8 (43)
Loss-of-function (n = 63), % (n)	57.1 (36)	12.7 (8)	12.7 (8)	17.5 (11)
Adjusted RR [§] (95% CI)	1.00 (Reference)	1.84 (0.84-4.03)	1.97 (0.79-4.94)	2.45 (1.34-4.46)*
Maternal eczema				
No (n = 538), % (n)	77.3 (416)	8.0 (43)	4.1 (22)	10.6 (57)
Yes (n = 68), % (n)	76.5 (52)	8.8 (6)	8.8 (6)	5.9 (4)
Adjusted RR [§] (95% CI)	1.00 (Reference)	0.94 (0.36-2.46)	1.52 (0.55-4.18)	0.54 (0.18-1.64)
Paternal eczema				
No (n = 563), % (n)	78.7 (443)	7.6 (43)	4.4 (25)	9.3 (52)
Yes (n = 43), % (n)	58.1 (25)	14.0 (6)	7.0 (3)	20.9 (9)
Adjusted RR [§] (95% CI)	1.00 (Reference)	2.21 (0.94-5.17)	2.67 (0.86-8.24)	2.66 (1.39-5.08)*
Birthweight				
Low/normal [†] (n = 587), % (n)	77.2 (453)	8.3 (49)	5.3 (31)	9.2 (54)
High [‡] (n = 98), % (n)	80.6 (79)	4.1 (4)	4.1 (4)	11.2 (11)
Adjusted RR [§] (95% CI)	1.00 (Reference)	0.20 (0.03-1.41)	1.59 (0.59-4.31)	1.42 (0.74-2.72)
Birth order				
First (n = 248), % (n)	74.6 (185)	10.1 (25)	4.4 (11)	10.9 (27)
Second (n = 207), % (n)	80.7 (167)	7.2 (15)	2.4 (5)	9.7 (20)
Third or more (n = 150), % (n)	76.7 (115)	6.0 (9)	8.0 (12)	9.3 (14)
Adjusted RR [§] (95% CI) [2 nd vs. 1 st]	1.00 (Reference)	0.51 (0.23-1.12)	0.52 (0.17-1.63)	0.83 (0.45-1.55)
Adjusted RR [§] (95% CI) [$\geq$ 3 rd vs. 1 st]	1.00 (Reference)	0.68 (0.33-1.42)	1.66 (0.71-3.89)	1.22 (0.65-2.28)
Household cat at birth				
No (n = 459), % (n)	78.4 (360)	7.8 (36)	4.4 (20)	9.4 (43)
Yes (n = 232), % (n)	76.7 (178)	6.9 (16)	6.9 (16)	9.5 (22)
Adjusted RR [§] (95% CI)	1.00 (Reference)	1.04 (0.55-1.95)	2.79 (1.24-6.27)*	1.29 (0.75-2.21)
Household dog at birth				
No (n = 488), % (n)	78.5 (383)	7.8 (38)	4.3 (21)	9.4 (46)
Yes (n = 203), % (n)	76.3 (155)	6.9 (14)	7.4 (15)	9.4 (19)
Adjusted RR [§] (95% CI)	1.00 (Reference)	1.01 (0.53-1.95)	1.46 (0.66-3.23)	1.32 (0.76-2.31)
Breastfeeding duration				
Weeks (n = 635), Median (IQR)	8.0 (2.0-26.0)	16.0 (2.0-32.0)	9.5 (0.0-26.0)	12.0 (4.0-24.0)
Adjusted RR [§] (95% CI)	1.00 (Reference)	1.01 (0.99-1.03)	1.00 (0.97-1.03)	1.00 (0.99-1.02)

RR: risk ratio; CI: confidence interval; IQR: interquartile range; [†]Low/normal birthweight: <4000 grams; [‡]High birthweight: $\geq$ 4000 grams; [§]Adjusted for all variables shown in the table. *P-value <0.05.

Table S3. Associations between risk factors and trajectories of eczema among female subjects

	Trajectories of eczema among females				
	Unaffected/transient	Early-onset early-resolving	Mid-onset late-resolving	Late-onset	Early-onset persistent
FLG genotype					
Wild-type (n = 522), % (n)	73.0 (381)	8.2 (43)	4.4 (23)	9.0 (47)	5.4 (28)
Loss-of-function (n = 53), % (n)	69.8 (37)	5.6 (3)	7.6 (4)	7.6 (4)	9.4 (5)
Adjusted RR [§] (95% CI)	1.00 (Reference)	0.89 (0.25-2.75)	1.47 (0.54-3.96)	0.99 (0.40-2.50)	1.58 (0.67-3.75)
Maternal eczema					
No (n = 509), % (n)	74.6 (380)	8.3 (42)	3.9 (20)	8.3 (42)	4.9 (25)
Yes (n = 76), % (n)	54.0 (41)	11.8 (9)	7.9 (6)	13.2 (10)	13.2 (10)
Adjusted RR [§] (95% CI)	1.00 (Reference)	1.39 (0.63-3.07)	1.98 (0.76-5.14)	1.58 (0.74-3.39)	2.84 (1.42-5.70)*
Paternal eczema					
No (n = 551), % (n)	72.9 (402)	8.4 (46)	4.4 (24)	8.9 (49)	5.4 (30)
Yes (n = 34), % (n)	55.9 (19)	14.7 (5)	5.9 (2)	8.8 (3)	14.7 (5)
Adjusted RR [§] (95% CI)	1.00 (Reference)	1.46 (0.52-4.09)	1.25 (0.34-4.58)	1.22 (0.47-3.21)	1.94 (0.66-5.76)
Birthweight					
Low/normal [†] (n = 605), % (n)	74.9 (453)	7.1 (43)	4.3 (26)	9.1 (55)	4.6 (28)
High [‡] (n = 70), % (n)	58.6 (41)	12.9 (9)	5.7 (4)	11.4 (8)	11.4 (8)
Adjusted RR [§] (95% CI)	1.00 (Reference)	1.90 (0.89-4.05)	1.85 (0.76-4.41)	0.99 (0.33-2.99)	2.25 (1.08-4.69)*
Birth order					
First (n = 252), % (n)	74.6 (188)	8.3 (21)	4.4 (11)	7.9 (20)	4.8 (12)
Second (n = 203), % (n)	69.5 (141)	8.4 (17)	3.4 (7)	9.8 (20)	8.9 (18)
Third or more (n = 129), % (n)	70.5 (91)	10.1 (13)	6.2 (8)	9.3 (12)	3.9 (5)
Adjusted RR [§] (95% CI) [2 nd vs. 1 st]	1.00 (Reference)	1.12 (0.58-2.18)	1.01 (0.39-2.63)	1.82 (0.93-3.57)	1.69 (0.81-3.55)
Adjusted RR [§] (95% CI) [$\geq$ 3 rd vs. 1 st]	1.00 (Reference)	1.26 (0.59-2.69)	1.22 (0.43-3.49)	1.34 (0.61-2.94)	0.77 (0.26-2.27)
Household cat at birth					
No (n = 467), % (n)	71.3 (333)	9.2 (43)	4.5 (21)	10.1 (47)	4.9 (23)
Yes (n = 216), % (n)	76.4 (165)	4.6 (10)	4.2 (9)	8.3 (18)	6.5 (14)
Adjusted RR [§] (95% CI)	1.00 (Reference)	0.58 (0.28-1.19)	1.07 (0.45-2.57)	0.75 (0.39-1.46)	0.86 (0.41-1.81)
Household dog at birth					
No (n = 490), % (n)	72.9 (357)	9.2 (45)	4.3 (21)	8.4 (41)	5.3 (26)
Yes (n = 193), % (n)	73.1 (141)	4.2 (8)	4.7 (9)	12.4 (24)	5.7 (11)
Adjusted RR [§] (95% CI)	1.00 (Reference)	0.67 (0.32-1.41)	1.49 (0.66-3.38)	1.67 (0.92-3.03)	1.08 (0.52-2.24)
Breastfeeding duration					
Weeks (n = 633), Median (IQR)	8.0 (1.0-26.0)	12.0 (2.0-36.0)	21.0 (3.0-36.0)	6.0 (0.5-21.0)	6.0 (2.0-22.0)
Adjusted RR [§] (95% CI)	1.00 (Reference)	1.01 (0.99-1.03)	1.02 (0.99-1.04)	1.00 (0.98-1.01)	0.99 (0.97-1.02)

RR: risk ratio; CI: confidence interval; IQR: interquartile range; [†]Low/normal birthweight: <4000 grams; [‡]High birthweight: $\geq$ 4000 grams; [§]Adjusted for all variables shown in the table. *P-value <0.05.

Table S4. Developmental trajectories (latent classes) of eczema identified in prior cohort studies and the current report

Classifications of eczema trajectories/latent classes [§]	Paternoster et al.* [28] ALSPAC (n = 9894; 0–16 years).	Paternoster et al.* [28] PIAMA (n = 3652; 0–11 years)	Roduit et al. [†] [27] PASTURE (n = 1038; 0–6 years)	Hu et al. [‡] [29] Generation R (n = 5297; 6 months – 10 years)	Current analysis	
					IOWBC females (n = 685; 1-or-2 to 26 years)	IOWBC males (n = 696; 1-or-2 to 26 years)
Unaffected/transient	58.0%	62.9%	79.5%	76%	73.0%	77.7%
Early-onset persistent	7.3%	4.9%	6.5%	2%	5.4%	9.3%
Early-onset late-resolving	7.0%	3.8%	NA	NA	NA	NA
Early-onset early-resolving	12.9%	15.4%	9.2%	8%	7.7%	NA
Mid-onset resolving	7.0%	6.5%	NA	6%	4.4%	7.8%
Late onset	7.9%	6.5%	4.8%	8%	9.5%	5.2%

NA: Not applicable; IOWBC: Isle of Wight Birth Cohort.

[§] Slight difference across studies in labelling/naming the trajectories exists.

* Paternoster et al. [28] analyzed data from the British ‘Avon Longitudinal Study of Parents and Children’ (ALSPAC; follow-up: 0 to 16 years) and the Dutch ‘Prevention and Incidence of Asthma and Mite Allergy’ (PIAMA; follow-up: 0 to 11 years) study.

[†] Roduit et al. [27] analyzed data from the ‘Protection Against Allergy Study in Rural Environments’ (PASTURE; follow-up: 0 to 6 years).

[‡] Hu et al. [29] analyzed data from the multiethnic Generation R prospective cohort study (follow-up: 6 months to 10 years).

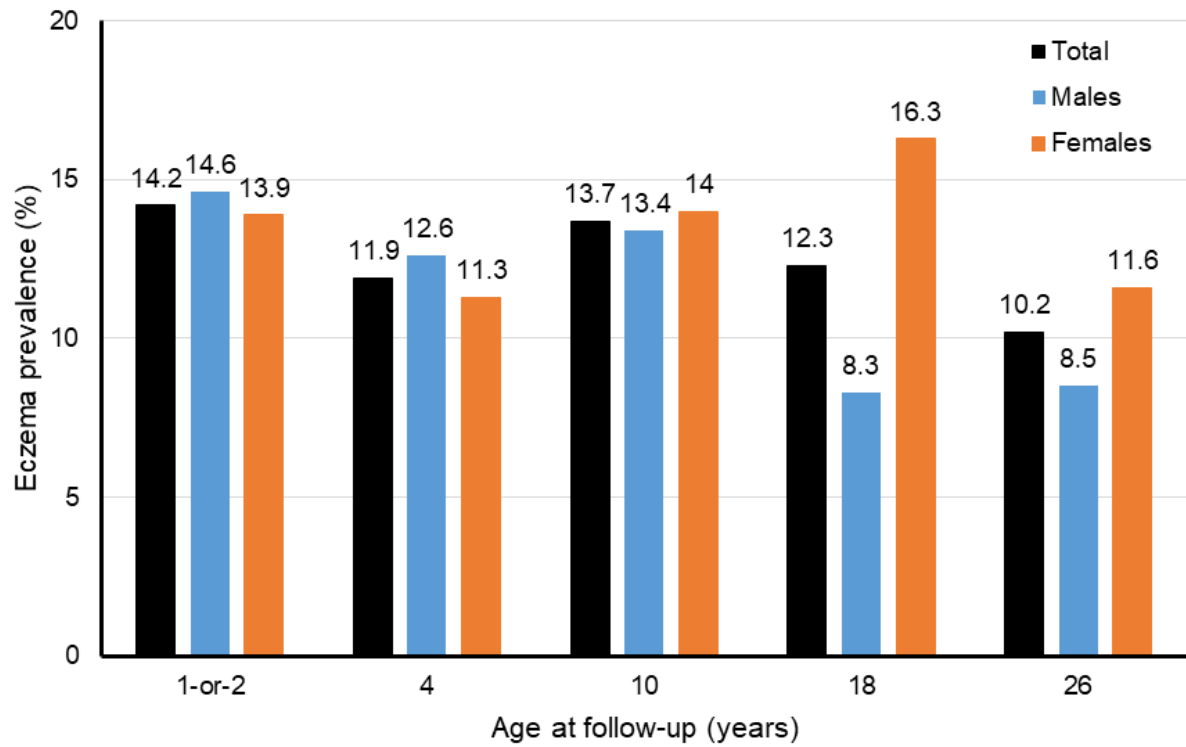


Figure S1. Prevalence estimates of eczema in the total study sample and according to sex across the study follow-ups.

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