Title: Clinical onset of atopic eczema: Results from two nationally representative British birth cohorts followed through mid-life

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Abstract (224/250 words)

Background: Atopic eczema onset is described primarily in early childhood; the frequency and characteristics of adult-onset disease remain controversial.

Objective: To determine the proportion of individuals who report atopic eczema symptoms between birth and mid adulthood, and to examine demographic, immunologic, and genetic factors associated with period of symptom onset.

Methods: We conducted a longitudinal study using data from two nationally representative community-based birth cohorts from the United Kingdom: the British Cohort Studies 1958 and 1970. Individuals were followed from birth through age 42-50. The primary outcome was the age period of self-reported atopic eczema symptom onset based on repeated measures of self-reported atopic eczema at each survey wave.

Results: The annual period prevalence of atopic eczema ranged from 5-15% in two cohorts of over 17,000 participants each followed from birth through mid-age. There was no clear trend in prevalence by age, and among adults reporting active atopic eczema during a given year, only 38% had symptom onset reported in childhood. When compared with individuals whose eczema started in childhood, those with adult-onset disease were more likely to be women, from Scotland or Northern England, of lower childhood socio-economic group, smokers in adulthood, and less likely to have a history of asthma. In a sub-analysis using data from the 1958 cohort only, genetic mutations previously associated with atopic eczema, including filaggrin null mutations, and allergen-specific IgE were more common among those with childhood-onset disease.

Conclusion: Rates of self-reported atopic eczema remain high after childhood, and adult-onset atopic eczema has different risk factor associations than childhood-onset eczema.

Clinical Implication: Adult-onset eczema is common and may be less likely to present with other atopic disease.

Capsule Summary (29/ 30 words): In two nationally representative birth cohorts followed through mid-life, adult-onset eczema was most common, and the strength of association with demographic, immunologic and genetic factors differed from childhood-onset disease.

Key words: atopic eczema, atopic dermatitis, natural history, epidemiology

Abbreviations:
BCS: British Cohort Study
CI: Confidence interval
OR: Odds Ratio
UK: United Kingdom

Introduction

Atopic eczema (also known as atopic dermatitis or just eczema) is the leading cause of skin-related disability,(1) but most epidemiological research has focused only on incidence early in life or patterns of disease in childhood.(2) Recent data suggest that atopic eczema is also common among adults, but whether these trends are due to increasing persistence of disease or new-onset disease later in life is unclear.(3-5) Atopic eczema is known to wax and wane over time, yet there are limited longitudinal data on patterns of disease activity over the life course. Cross-sectional studies have reported proportions of adult-onset atopic eczema ranging from 13-60%.(6-15) The validity of these estimates have been questioned because of the potential for recall bias (adults may not accurately recall whether they had eczema as children) or the possibility that disease expression in adulthood is due to migration from low to high prevalence climates.(16) In addition, studies of dermatology clinic populations suggest that there may be important genetic and phenotypic differences in adult-onset disease, but these may not be representative of the general population and are controversial for the reasons stated above. Data from population-based longitudinal birth cohorts are needed to understand the patterns and predictors of atopic eczema presentation across the life course.

It is important to understand the epidemiology of adult-onset atopic eczema for a number of reasons. First, since most diagnostic criteria specify that disease begins early in childhood, patients and providers may feel uncertain of the diagnosis in adults with new onset disease. While additional testing is often appropriate to rule out differential diagnoses,(17) if many adults don't meet the diagnostic criteria developed for children, they may be subject to anxiety about the lack of a clear diagnosis, excessive testing, and limited access to new treatment options.(18) Second, if risk factors for adult-onset atopic eczema differ, this raises the possibility of a different subtype of atopic eczema and could help to elucidate differences in disease pathophysiology and drivers of disease activity. Finally, understanding if childhood-onset and adult-onset atopic eczema differ is important for refining preventative and treatment strategies. The latter is particularly timely because many new small molecules and biologic agents are currently under development and clinical testing for atopic eczema.(18)

Using two large cohorts followed from birth for 4-5 decades that are representative of the general UK population, we sought to determine the proportion of individuals who develop symptoms of self-reported atopic eczema in childhood and adulthood, and examine factors associated with period of onset.

Methods

We performed a longitudinal cohort study using data from the 1958 and 1970 British Cohort Studies (BCS 1958 and BCS70), which are ongoing, multidisciplinary studies that include 17,196 and 17,415 babies born in Great Britain during one week in March 1958 and March 1970, respectively.(19, 20) There have been 8-9 subsequent waves of follow up in each cohort at approximately 5-10 year intervals (Figure 1). In the 1958 study, waves at ages 33, 46, and 55 did not include data on atopic eczema and thus were not included in the analysis. Additional information on response patterns in both cohorts has been reported elsewhere.(21, 22)

Outcomes

The primary outcome was parental or self-reported period prevalence of atopic eczema, based on a standardized question asking about "eczema" during or prior to the past year or since the last survey at each wave of follow up (Supplemental Table 1). In descriptive analyses, this measure coincided well with standardized clinical exams among children in the 1958 birth cohort,(23, 24) and a similar question has been shown to have high sensitivity and specificity for physician-diagnosed atopic eczema in US children and adults.(25) We categorized individuals who reported atopic eczema into two groups: those whose first report of atopic eczema occurred in childhood (positive parental report during *or* prior to last year at age 5-7 and/or 10-11), and those with adult-onset atopic eczema (first report of atopic eczema at age 23+). For the primary analysis, we did not include atopic eczema data from age 16, because it is considered a transitional period between pediatric and adult care in the UK, and the 1958 cohort only asked about annual period prevalence (rather than period and lifetime prevalence at that age). In sensitivity analyses, data from age 16 were included.

Covariates

Additional covariates were chosen based on prior literature showing an association with atopic eczema.(23, 26, 27) These included sex, ethnic group, history of any breastfeeding, region of residence in childhood, region of residence in adulthood (at age 42), childhood smoke exposure (either parent reporting current smoking during childhood surveys), smoking in adulthood (personal report of current smoking on any of the surveys in adulthood), household size (categorized into <=3 persons and 4+ persons), in utero smoke exposure (mother reported any smoking during pregnancy), birth weight, and the Registrar General's designation of social class (a standard measure based on the father's highest occupational status reported on any survey at ages 0-10/11 for childhood, and an individuals' own occupation at ages 23-50 for adulthood). Personal history of asthma or allergic rhinitis/hay fever was based on questions repeated at multiple ages (Supplemental Table 2). Data on parental history of asthma and hay fever was only available in the 1970 cohort, and was based on either parent's report of either condition at age 5.

Primary analysis

In both cohorts, we estimated the cumulative lifetime prevalence and the age-specific period prevalence. We also calculated the proportion of individuals with childhood-onset

versus adult-onset disease among those who reported active atopic eczema in adulthood. We used multivariable logistic regression to test for differences in demographic and risk factors between 1) childhood-onset and no atopic eczema, 2) adult-onset and no atopic eczema, and 3) childhood-onset versus adult-onset atopic eczema. After examining the regression results for consistency in each cohort separately, we conducted a meta-analysis of individual participant data, assuming fixed effects across studies and accounting for the clustering of participants within cohorts.(28)

Subgroup analysis and biospecimen data

For the subgroup of the 1958 cohort who had biospecimen data available, we repeated the regressions including variables for the presence of any filaggrin (FLG) null mutation; and a non-FLG genetic risk score, total IgE, and allergen-specific IgE modeled as 3-level categorical variables derived as tertiles.

At the age of 44-45 years, 5,974 individuals in the 1958 cohort were followed up with a biomedical examination and blood sampling,(29) from which a DNA collection was established as a nationally representative reference panel. In blood samples collected at this adult follow up, the total concentration of serum IgE antibodies and the presence of specific IgE to house dust mite, mixed grass pollen and cat fur were ascertained by Hytec enzyme immunoassay, with a detection threshold of 0.35 kU/L.(30) Four common null mutations of the FLG gene that have been associated with risk of atopic dermatitis in European populations(31, 32) were genotyped directly by LGC Genomics using KASP™ genotyping technology. FLG null status was defined as the presence of one or more risk variants of rs61816761 (R501X), rs150597413 (S3247X), rs558269137 (2282del4) or rs138726443 (R2447X , formerly rs386430951). An additional 29 variants outside the FLG region were selected for inclusion in a polygenic risk score, based on previously published associations with atopic dermatitis (please see supplement for additional description of methods and full list of references). A non-FLG genetic risk score was generated as the sum of imputed allele dosages for the risk-associated variant at each of these SNPs. Additional details are provided in the supplemental methods.

Sensitivity analyses

For the primary analysis, we did not include atopic eczema data from age 16, as described above. In a pre-planned sensitivity analysis, we tested the impact of this decision on our results by including individuals who reported atopic eczema during the past year at age 16 with the childhood onset group. We also examined the potential for misclassification bias by restricting the sample to those who reported having seen a physician for their eczema in the past year, and had no history of self-reported psoriasis or contact dermatitis.

Missing data

We explored patterns of missing data throughout follow up and found that there was both intermittent missing survey data and attrition from the cohort. For the primary analysis, we included only individuals with at least one survey response in childhood and one survey response in adulthood (Figure 1). Additionally, to explore the impact of missing data, we performed multiple imputation in each cohort separately with iterative chained equations to impute missing exposure, outcome, and covariate data. Thirty imputed datasets were

generated, and the average results from repeated analyses were compared to the complete case analysis. All statistical analyses were conducted using Stata, version 14 (StataCorp, Tx).

Results

At birth, 17,196 individuals were recruited to the 1970 cohort and 17,415 individuals were recruited into the 1958 cohort. There was intermittent missing data and attrition in both cohorts over time; 56-57% of the original birth sample responded to the last wave of follow up (Figure 1). Data on atopic eczema in both childhood and adulthood were available for 11,886 members of the 1970 cohort and 13,143 members of the 1958 cohort; demographic characteristics and missing covariate data are shown in Supplemental Table 3.

Consistent with international trends, atopic eczema was more common in the 1970 cohort: the cumulative lifetime prevalence of atopic eczema was 28% in the 1970 cohort and 18% in the 1958 cohort. Among those with atopic eczema at any time point, 40% and 43% reported disease for the first time in adulthood in the 1970 and 1958 cohorts, respectively. The period prevalence of atopic eczema ranged from 7-14% during any given period childhood and 5-12% during any given period in adulthood (Supplemental Table 1), and there was no clear trend across ages in either cohort (Figure 2). Among those who reported atopic eczema activity at each survey wave in adulthood, the majority (mean 62%) did not have a report of eczema during childhood (Figure 3).

The strength of association from multivariate regression models comparing individuals with childhood-onset atopic eczema and adult-onset atopic eczema to individuals without atopic eczema differed, as is evidenced by the results of the regression model directly comparing those with adult-onset to childhood-onset disease (Table 2). We found that individuals with adult-onset were more likely to be women, from Northern geographic areas in the UK, from lower social class in childhood, and smoke during adulthood; but were less likely to have a history of asthma (Table 2).

In a sub-group analysis using data from 3,365 individuals in the 1958 cohort who were part of the biomedical follow up at age 44-45 and had atopic eczema, genetic, IgE, and covariate data available, we examined rates of known risk alleles for AD and both total IgE and allergen-specific IgE. We found that 21% of those with childhood-onset disease, 13% with adult-onset disease, and 10% of those without any history of atopic eczema had at least one FLG null mutation (Table 1). Both childhood-onset and adult-onset atopic eczema were associated with FLG null mutations, but the association was stronger for childhood-onset than adult-onset in multivariable analyses (OR 2.73, 95%CI 2.06-3.63, and OR 1.49, 95%CI 1.01-2.19, respectively; Table 3). A high non-FLG genetic risk score predicted childhood-onset atopic eczema, but there was little evidence for an association between the non-FLG genetic risk score and adult-onset disease (OR 1.81 95% CI 1.37-2.40, and OR 1.18, 95%CI 0.85-1.64, respectively; Table 3). Similarly, a high allergen-specific IgE predicted childhood-onset atopic eczema, but there was little evidence for an association between the allergen-specific IgE and adult-onset disease (OR 1.90, 95%CI 1.32-2.74, and 0.86, 0.54-1.36, respectively; Table 3).

Analyses after multiple imputation to address missing data showed similar results (Supplemental Table 4). In a sensitivity analysis using data from age 16, we found that an additional 260 individuals would be classified as having childhood-onset disease in the 1970 cohort and an additional 193 children in the 1958 cohort. The overall proportion with childhood-onset disease remained near 60% in both cohorts, and the results of the regression analyses did not change (Supplemental Table 5). Finally, when we excluded patients who had a history of contact dermatitis or psoriasis, or did not report seeing a physician in the past year for their atopic eczema (Supplemental Table 6), we again found similar results (Supplemental Table 7).

Discussion

Using two large population-based cohorts followed from birth into midlife, we found the period prevalence of self-reported atopic eczema was 5-14%. One of the defining characteristics of childhood atopic eczema is early age at onset; however, the majority of those reporting symptoms in adulthood did not have disease onset in childhood. When comparing those with childhood-onset and adult-onset atopic eczema, we found differences in demographic characteristics, atopic comorbidities, IgE profile in adulthood, and genetic risk factors. Our findings help to address the gap in knowledge about the epidemiology of adult atopic eczema, and suggest that there may be different subtypes of adult disease that warrant additional characterization.

Strengths and limitations

Our study is unique in that there is prospective follow up of individuals residing in the UK from birth through mid-age. The data come from two large community-based cohorts broadly representative of the UK general population. Consistent with previous reports and international trends,(33-35) we found that the overall prevalence of atopic eczema increased between 1958 and 1970; but there did not appear to be a difference in trends across calendar year (Supplemental Figure 1). Two population-based mail surveys in the US and Italy also found high rates of adult-onset disease (54% and 60% of the population respectively,(7, 36)), but have been questioned because of the possibility for poor recall of childhood disease or migration to new climates.(16) These biases are unlikely to affect our estimates since individuals in our cohorts were born in the UK and followed with repeated assessments from birth through mid-life. We likely found a lower proportion of individuals with early-onset disease because our data included a longer duration of prospective follow-up than prior studies.(37) For example, an older study using data available through age 23 from the 1958 BCS concluded that of the 870 cases by the age of 16 years, 66% had age of onset by the age of 7 years.(38) By comparison, using the same initial data, now with extended follow-up through age 50, we found only 41% had onset of symptoms by age 7. Longitudinal studies of asthma have similarly found higher rates of late-onset and recurrent disease with longer periods of follow up.(39, 40)

A limitation of our study is that our outcome of atopic eczema was based on parental- or self-report and it is likely that some patients were misclassified. Misclassification could include other forms of eczema, including stasis dermatitis and irritant contact dermatitis in

adults. Nearly all of the population-based epidemiologic literature on atopic eczema has relied on self-reported assessment of disease, and prior studies have shown that self-report performs reasonably well, though better in children than adults (positive predictive value for physician-diagnosis was 0.87, 95% CI 0.78-0.96 in children and 0.76, 95% CI: 0.64-0.85 in adults in a multi-center US study).(25) Additional analyses to examine the potential for misclassification including restricting our sample to those who reported having seen a physician for their atopic eczema and never reported contact dermatitis and psoriasis were similar to the primary regression results (Supplemental Table 7). While these results do not rule out the potential for misclassification bias, they suggest that the magnitude of bias is likely to be small. Furthermore, as described in more detail below, our findings on filaggrin mutations, IgE, and demographic factors are similar to smaller studies of clinical populations with physician-diagnosed atopic eczema. (15, 16, 41, 42)

An additional limitation of our study is that surveys were fielded at multi-year intervals and we cannot rule out the possibility that atopic eczema may be underreported. For example, some parents may not recall a history of early or mild atopic eczema when asked at age 5-7 of their child's life; however, the recall is likely to be superior to surveys of adults asked about their own early childhood disease decades later.(43) Similarly, many of the adult surveys only asked about atopic eczema during the past year (as shown in supplemental table 1), and our results may underestimate adult-onset atopic eczema. Detailed phenotypic assessments of participants to detect atopic eczema at frequent intervals would be desirable, but they are impractical in large population-based cohorts followed for over 40 years.

Finally, as with any long-term study, the data are limited by attrition over time. Prior research has shown that in the 1970 cohort, there is a weak predictive effect of sex and socioeconomic status on response: men from lower social backgrounds with less educated parents are less likely to respond, which has previously been described in detail.(44) Because the cohort was not explicitly designed to study atopic disease, it is unlikely that attrition was differential by atopic eczema status. Nonetheless, to address missing data issues, we performed multiple imputation and found results that were consistent with the complete-case analysis.

Implications for research and clinical practice

Our results highlight the need for additional research to better characterize adult eczema and understand whether the pathophysiology differs by age of onset. Atopic eczema is known to have a multifactorial etiology, and we found genetic, immunologic, demographic, and risk factor differences between childhood onset and adult onset disease. Only a few other smaller studies have explicitly addressed age-associated differences in atopic eczema, and their findings are largely consistent with our results. Studies from dermatology clinic populations in Germany and the US also found that those with self-reported adult-onset disease were more likely to be female(42) and less likely to have a personal or family history of atopic disease(41, 42) elevated IgE levels;(41, 45) or filaggrin mutations,(46, 47) but did not find differences by smoking or socioeconomic status.(42) In contrast, a small case-control study from Taiwan found both current and ever smoking were strong independent risk factors for adult-onset disease,(48) and a recent meta-

analysis found high rates of smoking in adults with AD overall, but did not differentiate by age of onset.(49)

Atopic eczema is considered to be a clinical diagnosis, and the most widely used diagnostic criteria (the Hanifin and Rajka criteria, the UK Working Party criteria refinement of the Hanifin and Rajka criteria, and the American Academy of Dermatology criteria) all include early age at onset and history of atopy.(50) Clinicians evaluating adults with a potential diagnosis of atopic eczema should recognize that the majority of patients may not have symptom onset in childhood. Moreover, while individuals with adult-onset disease have a higher probability of having a history of other atopic disease than individuals without atopic eczema, asthma is only present in about 1/3 and allergic rhinitis in about ½ of atopic eczema patients (Table 1). Diagnostic criteria were developed based on expert opinion among dermatologists whose clinical experience may not reflect the distribution of disease in the general population, and none have been validated in a population-based study of adults.(51) Our data highlight the need to better understand what is adult "atopic" eczema and to refine diagnostic criteria for use in the general adult population. In the meantime, clinical trials of adult "atopic" eczema should describe the method by which physicians made the diagnosis (if any) and whether validated diagnostic criteria were used that would permit exploration or study heterogeneity and subgroup analyses in future meta-analyses."

Terminology

We choose to use the term atopic eczema based on a call for consistency in the literature.(52) There are regional variations in terminology; in the UK, the term 'eczema' is considered more precise than 'dermatitis'; while in the US, the term 'atopic dermatitis' is usually preferred.(52) In either case, use of the term 'atopic' has been debated because, even among children, not all disease is associated with elevated IgE levels or comorbid atopic conditions including asthma or rhinitis. Indeed, previous research has suggested that the majority of what is called atopic eczema is not atopic at a population-level.(53) Our findings that adult-onset disease was associated with lower rates of IgE and asthma further call into question the use of the term 'atopic' in adult disease; nonetheless, we have continued to use this terminology for consistency and clarity. Future studies may uncover subtypes of adult-onset disease that require new terminology.

Conclusion

We found that self-reported adult-onset atopic eczema is common among two community-based British cohorts. Differences in genetic, demographic, and immunologic profiles between childhood-onset and adult-onset disease suggest there may be different subtypes of atopic eczema and emphasize the need for better characterization of adult-onset disease and validation of diagnostic tools in this population. These data are particularly timely because dozens of new treatments are under development and clinical testing for AD,(18) and trial populations selected on the basis of early onset disease are unlikely to be representative of the general population of adults.

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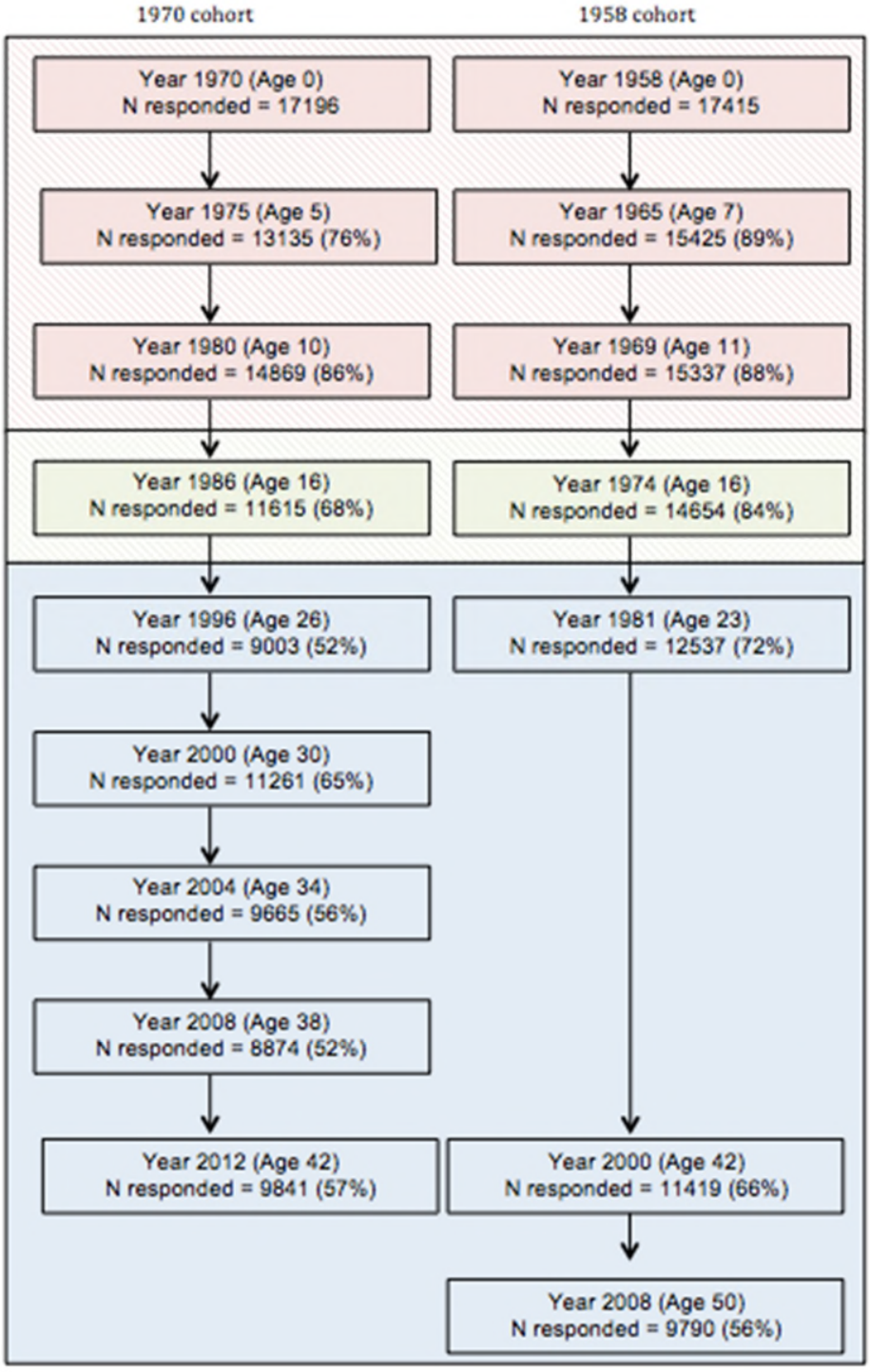
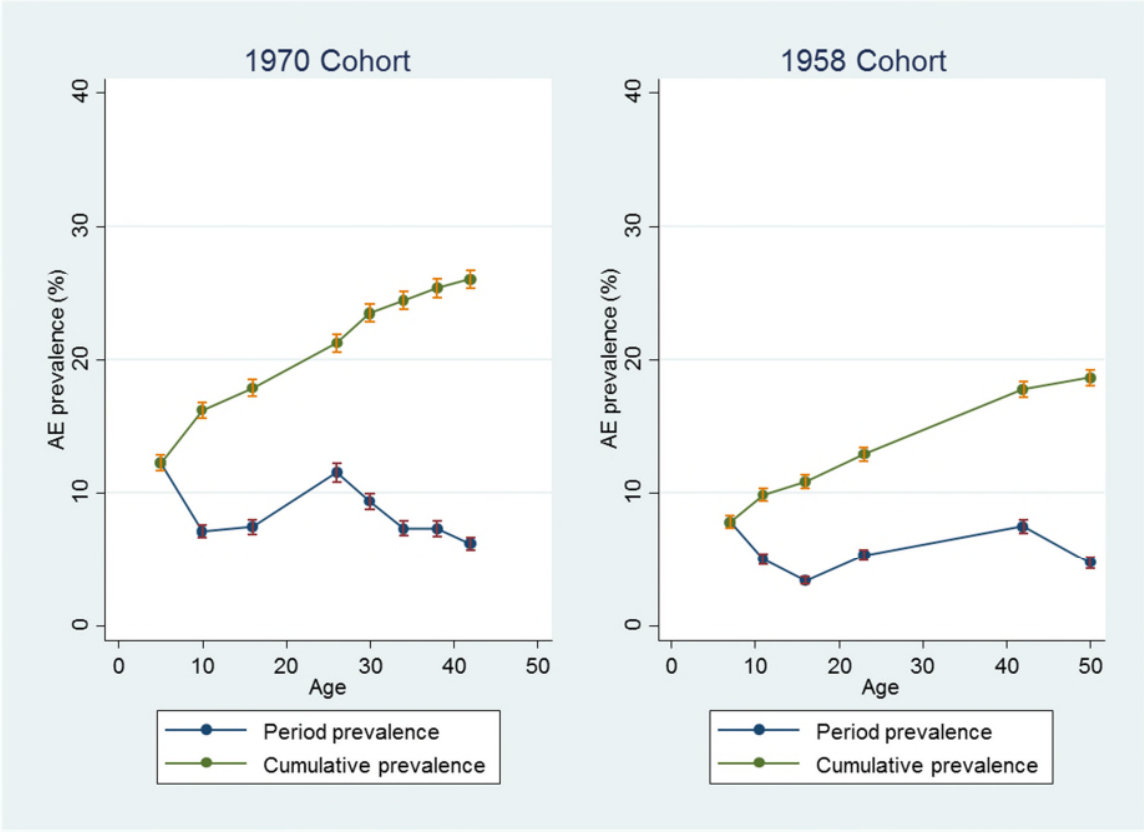
Figure 1. Flowchart of ages at which atopic eczema activity was assessed



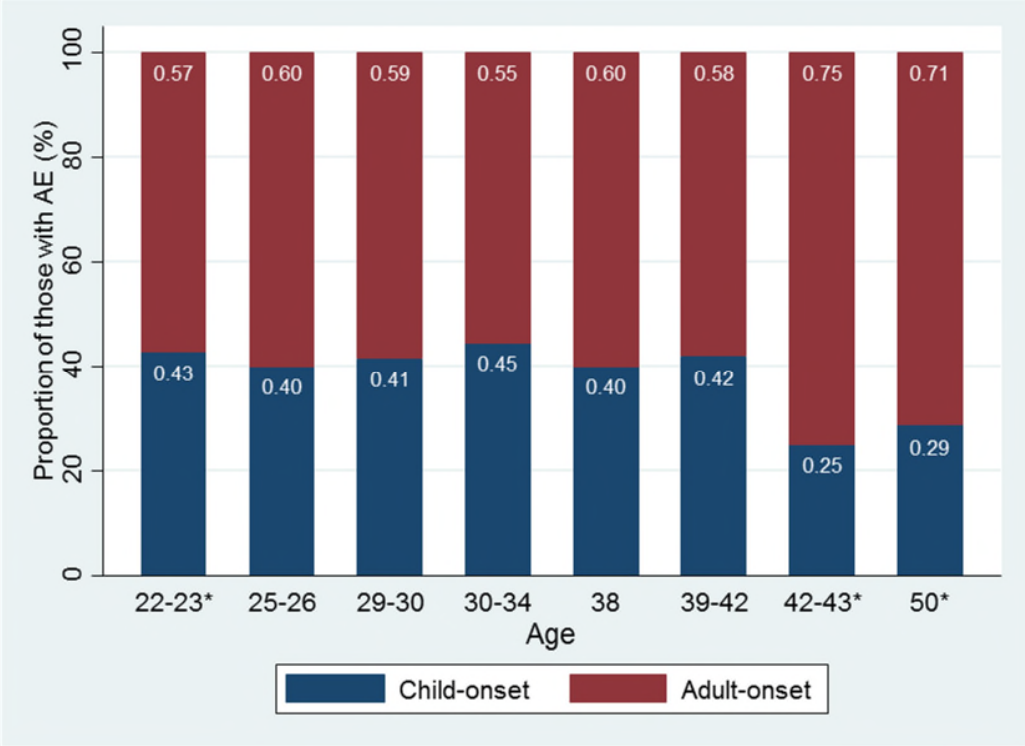
Legend: Percentages represent proportion of original sample assessed at each age. Red shading indicates ages used to define childhood-onset atopic eczema and blue shading indicates ages used to define adult-onset atopic eczema. Data from age 16 was included with childhood-onset disease in a sensitivity analysis.

Figure 2. Atopic eczema period prevalence and cumulative lifetime prevalence by age and by cohort



Legend: *Prevalence from age 0-5 for 1970 cohort and age 0-7 for 1958 cohort; bars represent 95% confidence intervals.

Figure 3. Proportion of individuals with symptom onset in adulthood among those with active atopic eczema at each survey wave in adulthood



Note: Age periods with * are from the 1958 cohort; the remainder are from the 1970 cohort. Childhood-onset disease defined as first report at age 0-11; adult-onset disease defined as first report after age 22-23

Table 1. Patient characteristics by AE and period of onset

	1970			1958		
	No AE N=8611	Any AE N=3275 (28% of cohort)		No AE N=10825	Any AE N=2318 (18% of cohort)	
		Childhood-onset N=1972 (60% of those with AE)	Adult-onset N=1303 (40% of those with AE)		Childhood-onset N=1313 (57% of those with AE)	Adult-onset N=1005 (43% of those with AE)
	N (%)			N (%)		
Sex						
Male	4406 (51.2)	996 (50.5)	467 (35.8)	5594 (51.7)	663 (50.5)	383 (38.1)
Female	4205 (48.8)	976 (49.5)	836 (64.2)	5231 (48.3)	650 (49.5)	622 (61.9)
Ethnicity						
European, Caucasian	7164 (96.3)	1709 (96.8)	1071 (96.5)	8749 (99.0)	1147 (98.7)	822 (98.9)
Other	272 (3.7)	56 (3.2)	39 (3.5)	88 (1.0)	15 (1.3)	9 (1.1)
Region of residence in childhood						
Southern England	2552 (33.4)	725 (40.3)	418 (36.5)	3193 (29.5)	431 (32.8)	311 (30.9)
Central England	2112 (27.6)	487 (27.0)	316 (27.6)	3224 (29.8)	433 (33.0)	303 (30.1)
Northern England	2988 (39.0)	589 (32.7)	411 (35.9)	4408 (40.7)	449 (34.2)	391 (38.9)
Region of residence at age 42						
Southern England	2283 (37.0)	636 (43.3)	402 (38.5)	3136 (37.1)	429 (40.5)	365 (39.9)
Central England	1671 (27.1)	404 (27.5)	290 (27.8)	2199 (26.0)	302 (28.5)	261 (28.5)
Northern England	2215 (35.9)	429 (29.2)	351 (33.7)	3115 (36.9)	327 (30.9)	289 (31.6)
Social class in childhood						
I/II	3049 (35.4)	891 (45.2)	489 (37.6)	3072 (28.5)	455 (34.7)	306 (30.5)
IIIa/b	4905 (57.0)	974 (49.4)	719 (55.2)	6597 (61.2)	749 (57.1)	603 (60.2)
IV/V	648 (7.5)	106 (5.4)	94 (7.2)	1104 (10.2)	107 (8.2)	93 (9.3)
Social class in adulthood						
I/II	4326 (53.2)	1156 (61.1)	720 (57.4)	4573 (43.7)	607 (47.6)	482 (49.6)

IIIa/b	3003 (36.9)	612 (32.3)	454 (36.2)	4671 (44.7)	536 (42.1)	402 (41.4)
IV/V	801 (9.9)	125 (6.6)	80 (6.4)	1212 (11.6)	131 (10.3)	87 (9.0)
Household size						
<=3 persons	821 (10.7)	183 (10.1)	121 (10.6)	857 (8.9)	115 (9.3)	75 (8.4)
4+ persons	6845 (89.3)	1626 (89.9)	1022 (89.4)	8766 (91.1)	1119 (90.7)	821 (91.6)
Smoking during pregnancy						
No	4635 (54.1)	1155 (58.8)	730 (56.2)	7096 (66.3)	910 (70.3)	669 (67.6)
Any	3934 (45.9)	809 (41.2)	570 (43.8)	3600 (33.7)	384 (29.7)	320 (32.4)
Childhood smoke exposure						
No	2616 (34.2)	691 (38.2)	396 (34.7)	2173 (27.2)	316 (31.9)	215 (28.4)
Any	5025 (65.8)	1117 (61.8)	745 (65.3)	5805 (72.8)	675 (68.1)	541 (71.6)
Adult smoking						
No	4647 (54.1)	1095 (55.6)	649 (49.8)	6076 (56.2)	764 (58.3)	533 (53.0)
Any	3950 (45.9)	875 (44.4)	654 (50.2)	4736 (43.8)	547 (41.7)	472 (47.0)
Atopy						
History of asthma	1451 (16.9)	627 (31.8)	378 (29.0)	2362 (21.8)	485 (36.9)	322 (32.0)
History of allergic rhinitis/hay fever	3160 (36.7)	1090 (55.3)	684 (52.5)	3070 (28.4)	648 (49.4)	416 (41.4)
Parental history of atopy	1563 (22.3)	660 (39.3)	281 (27.1)	---	-----	-----
Birth weight (kg), mean (SD)	3.3 (0.5)	3.3 (0.5)	3.3 (0.5)	3.3 (0.5)	3.4 (0.5)	3.3 (0.5)
Breastfeeding						
No	4851 (63.7)	1020 (56.9)	687 (60.5)	3193 (32.2)	338 (26.9)	283 (30.9)
Any	2766 (36.3)	773 (43.1)	449 (39.5)	6729 (67.8)	920 (73.1)	634 (69.1)
Filaggrin null mutations*						
No	---	---	---	3689 (90.3)	446 (79.1)	337 (86.9)
Any	---	---	---	398 (9.7)	118 (20.9)	51 (13.1)
Non-FLG SNPs*						
< 25 risk alleles	---	---	---	1196 (29.3)	124 (22.0)	97 (25.0)
25-28 risk alleles	---	---	---	1536 (37.6)	189 (33.5)	139 (35.8)

> 28 risk alleles	---	---	---	1355 (33.2)	251 (44.5)	152 (39.2)
Total IgE*						
<30kU/L	---	---	---	2157 (52.8)	239 (42.4)	184 (47.4)
30-99 kU/L	---	---	---	1154 (28.2)	176 (31.2)	119 (30.7)
>=100kU/L	---	---	---	776 (19.0)	149 (26.4)	85 (21.9)
Allergen-specific IgE*						
<0.35kU/L	---	---	---	3007 (73.6)	321 (56.9)	260 (67.0)
0.35-3.5 kU/L	---	---	---	369 (9.0)	51 (9.0)	37 (9.5)

Notes: *Data only available for a subset of the 1958 cohort (N=5,039)

Table 2. Multivariable regression results (complete case analysis)

	Childhood-onset vs no AE N= 17,373	Adult-onset vs no AE N=12,956	Adult-onset vs childhood-onset AE N=12,956	
	Odds Ratio (95% CI)			p-value
Sex				
Male	Reference	Reference	Reference	
Female	1.04 (0.95, 1.13)	**1.75 (1.56, 1.98)**	**1.66 (1.44, 1.92)**	**<0.001**
Ethnicity				
European, Caucasian	Reference	Reference	Reference	
Other	0.86 (0.65, 1.15)	1.07 (0.73, 1.57)	1.23 (0.77, 1.97)	0.391
Region of early childhood residence				
Southern England	Reference	Reference	Reference	
Central England/Wales	0.91 (0.82, 1.02)	0.88 (0.73, 1.08)	0.95 (0.75, 1.20)	0.651
N. England/Scotland	**0.77 (0.70, 0.86)**	1.03 (0.83, 1.29)	**1.31 (1.01, 1.71)**	**0.045**
Region of residence at age 42				
Southern England	-----	Reference	Reference	
Central England/Wales	-----	1.17 (0.96, 1.42)	1.14 (0.90, 1.43)	0.281
N. England/Scotland	-----	0.87 (0.70, 1.09)	0.92 (0.71, 1.20)	0.551
Highest social class in childhood*				
I/II	Reference	Reference	Reference	
III	**0.80 (0.73, 0.88)**	1.00 (0.88, 1.14)	**1.23 (1.05, 1.43)**	**0.009**
IV/V	**0.70 (0.58, 0.85)**	0.99 (0.77, 1.26)	**1.38 (1.01, 1.89)**	**0.044**
Highest social class in adulthood*				
I/II	-----	Reference	Reference	
III	-----	0.92 (0.81, 1.04)	1.00 (0.86, 1.17)	0.956
IV/V	-----	**0.75 (0.58, 0.96)**	0.90 (0.66, 1.22)	0.489
Household size in early childhood				
<=3 persons	Reference	Reference	Reference	
4+ persons	1.01 (0.87, 1.17)	1.08 (0.88, 1.31)	1.10 (0.87, 1.40)	0.439
In utero smoke exposure				
No	Reference	Reference	Reference	
Any	0.93 (0.84, 1.03)	0.94 (0.82, 1.07)	0.99 (0.84, 1.16)	0.915
Childhood smoke exposure				
No	Reference	Reference	Reference	
Any	0.93 (0.85, 1.03)	1.02 (0.89, 1.16)	1.07 (0.91, 1.26)	0.400
Adulthood smoking				
No	-----	Reference	Reference	
Any	-----	**1.26 (1.13, 1.42)**	**1.20 (1.04, 1.38)**	**0.013**
Asthma				

No	Reference	Reference	Reference	
Any	**1.85 (1.68, 2.04)**	**1.45 (1.27, 1.66)**	**0.79 (0.68, 0.93)**	**0.004**
Allergic rhinitis/hay fever				
No	Reference	Reference	Reference	
Any	**1.81 (1.65, 1.98)**	**1.59 (1.41, 1.80)**	0.90 (0.77, 1.04)	0.141
Birth weight				
Per kg increase	**1.09 (1.00, 1.19)**	1.01 (0.90, 1.13)	0.90 (0.79, 1.04)	0.156
Breastfeeding				
No	Reference	Reference	Reference	
Any	**1.18 (1.07, 1.29)**	1.11 (0.98, 1.26)	0.94 (0.81, 1.09)	0.411

Notes: *Registrar General's social class: I Professional, II Managerial and technical; III Skilled; IV Partly-skilled; V Unskilled.

Table 3. Multivariable regression results from sub-analysis with genetic data from the 1958 birth cohort*

	Child-onset vs no AE N=3,444	Adult-onset vs no AE N=3,365	Adult-onset vs child-onset AE N=3,365	
	Odds Ratio (95% CI)			p-value
Filaggrin null mutations				
No	Reference	Reference	Reference	
Any	**2.73 (2.06, 3.63)**	**1.49 (1.01, 2.19)**	**0.54 (0.35, 0.83)**	**0.006**
Non-FLG SNPs				
< 25 risk alleles	Reference	Reference	Reference	
25-28 risk alleles	1.17 (0.87, 1.58)	1.07 (0.77, 1.48)	0.87 (0.57, 1.32)	0.507
> 28 risk alleles	**1.81 (1.37, 2.40)**	1.18 (0.85, 1.64)	**0.64 (0.43, 0.97)**	**0.036**
Total IgE				
<30kU/L	Reference	Reference	Reference	
30-99 kU/L	1.14 (0.83, 1.56)	1.08 (0.76, 1.54)	0.96 (0.61, 1.51)	0.866
>=100kU/L	0.93 (0.63, 1.38)	1.08 (0.68, 1.71)	1.22 (0.68, 2.17)	0.503
Allergen-specific IgE				
<0.35kU/L	Reference	Reference	Reference	
0.35-3.5 kU/L	1.09 (0.69, 1.71)	1.05 (0.63, 1.74)	0.94 (0.49, 1.78)	0.846
>=3.5kU/L	**1.90 (1.32, 2.74)**	0.86 (0.54, 1.36)	**0.44 (0.25, 0.77)**	**0.004**
Sex				
Male	Reference	Reference	Reference	
Female	0.98 (0.79, 1.22)	**1.67 (1.27, 2.19)**	**1.71 (1.23, 2.39)**	**0.002**
Region of early childhood residence				
Southern England	Reference	Reference	Reference	
Central England/Wales	0.84 (0.64, 1.10)	1.03 (0.68, 1.57)	1.17 (0.71, 1.94)	0.535
N. England/Scotland	**0.65 (0.49, 0.85)**	1.30 (0.81, 2.07)	1.64 (0.92, 2.93)	0.094
Region of residence at age 42				
Southern England	-----	Reference	Reference	
Central England/Wales	-----	1.15 (0.77, 1.70)	1.16 (0.72, 1.87)	0.550
N. England/Scotland	-----	0.67 (0.42, 1.08)	0.85 (0.47, 1.53)	0.585
Social class in childhood**				
I/II	Reference	Reference	Reference	
IIIa/b	0.99 (0.78, 1.25)	1.05 (0.78, 1.41)	1.08 (0.76, 1.55)	0.662
IV/V	0.79 (0.50, 1.26)	1.29 (0.79, 2.09)	1.61 (0.85, 3.06)	0.142
Highest social class in adulthood**				
I/II	-----	Reference	Reference	
III	-----	0.85 (0.64, 1.13)	0.77 (0.54, 1.08)	0.131
IV/V	-----	0.74 (0.44, 1.22)	0.75 (0.40, 1.41)	0.369

Household size in early childhood				
<=3 persons	Reference	Reference	Reference	
4+ persons	0.87 (0.59, 1.27)	1.14 (0.69, 1.89)	1.30 (0.71, 2.38)	0.388
In utero smoke exposure				
No	Reference	Reference	Reference	
Any	0.92 (0.71, 1.19)	0.99 (0.73, 1.35)	1.08 (0.74, 1.58)	0.697
Childhood smoke exposure				
No	Reference	Reference	Reference	
Any	0.93 (0.73, 1.19)	0.93 (0.69, 1.26)	0.98 (0.68, 1.42)	0.910
Adulthood smoking				
No	-----	Reference	Reference	
Any	-----	1.01 (0.77, 1.33)	0.94 (0.68, 1.32)	0.739
Asthma				
No	Reference	Reference	Reference	
Any	**1.53 (1.21, 1.94)**	**1.38 (1.03, 1.85)**	0.88 (0.62, 1.25)	0.482
Allergic rhinitis/hay fever				
No	Reference	Reference	Reference	
Any	**1.62 (1.26, 2.07)**	**1.54 (1.14, 2.06)**	0.95 (0.66, 1.36)	0.761
Birth weight				
Per kg increase	0.98 (0.79, 1.21)	1.03 (0.80, 1.34)	1.03 (0.75, 1.41)	0.870
Breastfeeding				
No	Reference	Reference	Reference	
Any	1.18 (0.91, 1.51)	0.97 (0.73, 1.30)	0.81 (0.57, 1.17)	0.264

Notes: *Does not include data from survey at age 50. **Registrar General's social class: I Professional, II Managerial and technical; III Skilled; IV Partly-skilled; V Unskilled.

Supplemental tables and figures

Supplemental Table 1. Summary of atopic eczema variables

Age	Format	Question	Number who answered question	Number who responded positively	
1970 Cohort					
Age 5	Parent interview	Eczema during or prior to past year?	12,183	1,495	12%
Age 10	Interview & exam	Eczema during or prior to past year? Eczema during past year?	12,389 12,373	1,795 887	14% 7%
Age 16*	Interview & exam	Eczema during past year?	8,900	668	8%
Age 26	Postal questionnaire	Eczema during past year?	8,333	963	12%
Age 30	Computer interview	Eczema during past year?	10,394	978	9%
Age 34	Computer interview	Eczema since last survey?	8,954	662	7%
Age 38	Telephone interview	Eczema currently?	8,204	604	7%
Age 42	Computer interview	Eczema since last survey?	9,093	566	6%
1958 Cohort					
Age 7	Interview and exam	Eczema during or prior to past year?	14,030	1,100	8%
Age 11	Interview and exam	Eczema during or prior to past year? Eczema during past year?	12,991 12,983	917 652	7% 5%
Age 16*	Interview and exam	Eczema in the past year?	13,701	470	3%
Age 23	Interview	Eczema in the past year?	11,838	634	5%
Age 42	Computer Interview	Eczema in the past year?	10,788	812	8%
Age 50	Postal questionnaire	Eczema currently?	9,250	442	5%

Notes: *Data used in sensitivity analysis

Supplemental Table 2. Summary of asthma and hay fever variables

Age	Format	Question	Number who answered question	Number who responded positively	
Asthma - 1970 Cohort					
Age 10	Exam	Asthma during or prior to last year?	11,984	605	5%
Age 16	Interview & exam	Asthma during or prior to last year?	5,251	649	12%
Age 26	Postal questionnaire	Asthma during or prior to last year?	8,333	1,022	12%
Age 30	Computer interview	Ever had asthma?	10,395	1,424	14%
Age 34	Computer interview	Asthma during or prior to last year?	8,954	936	10%
Age 38	Telephone interview	Asthma currently?	8,204	853	10%
Age 42	Computer interview	Asthma since last survey?	9,091	798	9%
Asthma - 1958 Cohort					
Age 7	Interview and exam	Ever had asthma?	14,036	431	3%
Age 11	Parent interview	Ever had asthma or wheezy bronchitis?	12,863	1,596	12%
Age 16	Parent interview	Ever had asthma or wheezy bronchitis?	10,744	1,257	12%
Age 23	Interview	Asthma, bronchitis since age 16?	11,877	514	4%
Age 33	Interview	Ever been told has asthma?	10,794	972	9%
Age 42	Computer interview	Ever had asthma?	10,799	1,199	11%
Age 50	Questionnaire	Asthma or wheezy bronchitis currently?	9,250	903	10%
Rhinitis/hay fever - 1970 Cohort					
Age 5	Parent interview	Hay fever during or prior to last year?	12,149	536	4%
Age 10	Interview & Exam	Hay fever during or prior to last year?	12,338	1,663	13%
Age 16	Interview & exam	Hay fever during or prior to last year?	8,928	2,285	26%
Age 26	Postal questionnaire	Hay fever during or prior to last year?	8,333	2,478	30%
Age 30	Computer interview	Ever had hay fever?	10,395	2,694	26%
Age 34	Computer interview	Hay fever since last survey?	8,954	1,984	22%
Age 38	Telephone interview	Hay fever currently?	8,204	1,640	20%
Age 42	Computer interview	Hay fever since last survey?	9,091	1,965	22%
Rhinitis/ Hay fever - 1958 Cohort					
Age 7	Parent interview	Hay fever or sneezing attacks ever?	14,020	774	6%
Age 11	Parent interview	Hay fever during the last year?	12,934	1,048	8%
Age 16	Parent interview	Hay fever during the last year?	10,553	1,279	12%
Age 23	Interview	Hay fever during the last year?	11,825	1,960	17%
Age 33	Interview	Ever suffered from hay fever	10,772	2,204	20%
Age 42	Computer interview	Ever had hay fever?	10,799	2,223	21%
Age 50	Questionnaire	Hay fever currently?	9,250	1,255	14%

Supplemental Table 3: Cohort characteristics and missing data

	1970 Cohort N (%)	1958 Cohort N (%)
Overall N	17196	17415
Sex		
Male	8908 (51.8)	9001 (51.7)
Female	8280 (48.2)	8411 (48.3)
Missing	8 (0.01)	3 (0.02)
Ethnicity		
European, Caucasian	11809 (68.7)	12019 (69.0)
African	154 (0.9)	98 (0.6)
Indian-Pakastani	178 (1.0)	32 (0.2)
Other	179 (1.0)	30 (0.2)
Missing	4876 (28.4)	5236 (30.1)
Region of residence in childhood		
Southern England	4430 (25.8)	5365 (30.8)
Central England	3465 (20.2)	5103 (29.3)
Northern England	4812 (28.0)	6947 (39.9)
Missing	4489 (26.1)	0 (0.0)
Region of residence at age 42		
Southern England	3532 (20.5)	4093 (23.5)
Central England	2460 (14.3)	2859 (16.4)
Northern England	3122 (18.2)	3878 (22.3)
Missing	8082 (47.0)	6585 (37.8)
Breastfeeding		
No	7975 (46.4)	4435 (25.5)
Any	4663 (27.1)	9587 (55.1)
Missing	4558 (26.5)	3393 (19.5)
Childhood smoke exposure[a]		
No	4347 (25.3)	2993 (17.2)
Any	8351 (48.6)	7953 (45.7)
Missing	4498 (26.2)	6469 (37.1)
Adulthood smoking		
No	6746 (39.2)	7680 (44.1)
Any	5784 (33.6)	6004 (34.5)
Missing	4666 (27.1)	3731 (21.4)
Smoking during pregnancy		
No	9210 (53.6)	11407 (65.5)
Any	7899 (45.9)	5783 (33.2)
Missing	87 (0.5)	225 (1.3)
Household size[b]		
<=3 persons	1340 (7.8)	1213 (7.0)

4+ persons	11395 (66.3)	12357 (71.0)
Missing	4461 (25.9)	3845 (22.1)
Atopic history		
Personal history of asthma	2726 (15.9)	3553 (20.4)
Missing	2911 (16.9)	1527 (8.8)
Personal history of allergic rhinitis/hay fever	5556 (32.3)	4511 (25.9)
Missing	2241 (13.0)	1533 (8.8)
Parental history of asthma or allergic rhinitis/hay fever	2961 (17.2)	N/A
Missing	5584 (32.5)	N/A
Social class in childhood		
I/II	5756 (33.5)	4737 (27.2)
IIIa/b	9592 (55.8)	10459 (60.1)
IV/V	1750 (10.2)	1990 (11.4)
Missing	98 (0.6)	229 (1.3)
Social class in adulthood		
I/II	6517 (37.9)	5864 (33.7)
IIIa/b	4300 (25.0)	5834 (33.5)
IV/V	1068 (6.2)	1520 (8.7)
Missing	5311 (30.9)	4197 (24.1)
Birth weight (kg), mean (SD)	3.3 (0.6)	3.3 (0.6)
Missing	35 (0.2)	634 (3.6)

[a] At age 5 in the 1970 cohort and age 16 in the 1958 cohort
[b] At age 5 in the 1970 cohort and age 7 in the 1958 cohort

Supplemental Table 4. Multivariable regression results for each cohort individually and imputation results

	1970				1958			
	Complete case			Imputation	Complete case			Imputation
	Child-onset vs no AE	Adult-onset vs no AE	Adult-onset vs child-onset AE	Adult-onset vs child-onset AE	Child-onset vs no AE	Adult-onset vs no AE	Adult-onset vs child-onset AE	Adult-onset vs child-onset AE
	N=9310	N=6600	N=6600	N=17196	N=7245	N=5800	N=5800	N=17415
	Odds Ratio (95% CI)				Odds Ratio (95% CI)			
Sex								
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.04 (0.93, 1.16)	**1.84 (1.56, 2.15)**	**1.79 (1.48, 2.16)**	**1.47 (1.27, 1.70)**	1.04 (0.89, 1.20)	**1.67 (1.38, 2.02)**	**1.54 (1.21, 1.96)**	**1.52 (1.30, 1.79)**
Ethnicity								
European, Caucasian	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Other	0.92 (0.67, 1.26)	0.96 (0.62, 1.50)	1.00 (0.58, 1.70)	1.17 (0.81, 1.69)	1.01 (0.42, 2.43)	1.44 (0.49, 4.22)	1.07 (0.28, 4.04)	1.04 (0.49, 2.22)
Region of early childhood residence								
Southern England	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Central England	**0.87 (0.75, 1.00)**	0.86 (0.65, 1.14)	0.95 (0.69, 1.32)	1.01 (0.79, 1.29)	1.02 (0.85, 1.23)	0.94 (0.70, 1.27)	0.93 (0.65, 1.34)	1.01 (0.80, 1.26)
Northern England	**0.79 (0.69, 0.90)**	0.91 (0.67, 1.24)	1.07 (0.74, 1.54)	1.04 (0.77, 1.41)	**0.79 (0.65, 0.95)**	1.27 (0.91, 1.76)	**1.74 (1.14, 2.66)**	1.22 (0.96, 1.55)
Region of early adulthood residence								
Southern England	-----	Reference	Reference	Reference	-----	Reference	Reference	Reference
Central England	-----	1.19 (0.90, 1.57)	1.13 (0.82, 1.56)	1.12 (0.86, 1.45)	-----	1.16 (0.87, 1.54)	1.15 (0.80, 1.64)	1.00 (0.79, 1.26)
Northern England	-----	1.05 (0.77, 1.44)	1.14 (0.79, 1.65)	1.17 (0.86, 1.60)	-----	**0.66 (0.48, 0.92)**	0.67 (0.44, 1.02)	0.87 (0.67, 1.13)
Social class in childhood								
I/II	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
IIIa/b	**0.81 (0.72, 0.91)**	0.99 (0.84, 1.17)	**1.23 (1.01, 1.50)**	**1.20 (1.04, 1.38)**	0.89 (0.75, 1.04)	1.02 (0.83, 1.25)	1.10 (0.85, 1.42)	1.18 (0.99, 1.40)
IV/V	0.78 (0.60, 1.02)	1.00 (0.71, 1.43)	1.35 (0.87, 2.09)	**1.35 (1.00, 1.81)**	0.74 (0.54, 1.01)	0.99 (0.68, 1.43)	1.19 (0.74, 1.93)	**1.36 (1.00, 1.87)**

Social class in adulthood								
I/II	-----	Reference	Reference	Reference	-----	Reference	Reference	Reference
IIIa/b	-----	1.00 (0.85, 1.19)	1.06 (0.86, 1.29)	**1.16 (1.00, 1.36)**	-----	0.86 (0.71, 1.05)	0.97 (0.76, 1.25)	0.95 (0.80, 1.13)
IV/V	-----	**0.67 (0.47, 0.96)**	0.90 (0.58, 1.38)	1.07 (0.79, 1.45)	-----	0.86 (0.59, 1.27)	0.88 (0.54, 1.44)	0.87 (0.65, 1.17)
Household size in early childhood								
<=3 persons	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
4+ persons	1.06 (0.88, 1.27)	1.03 (0.80, 1.31)	0.97 (0.72, 1.30)	1.02 (0.81, 1.28)	0.82 (0.63, 1.06)	1.16 (0.81, 1.66)	1.50 (0.98, 2.30)	1.21 (0.92, 1.58)
In utero smoke exposure								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Any	0.99 (0.87, 1.12)	1.01 (0.85, 1.20)	0.99 (0.80, 1.21)	0.97 (0.83, 1.13)	0.90 (0.75, 1.07)	0.82 (0.66, 1.02)	0.90 (0.68, 1.19)	1.02 (0.84, 1.24)
Childhood smoke exposure								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Any	0.96 (0.84, 1.09)	1.02 (0.85, 1.21)	1.01 (0.82, 1.25)	1.07 (0.92, 1.25)	0.92 (0.77, 1.09)	1.00 (0.81, 1.24)	1.11 (0.85, 1.45)	1.11 (0.87, 1.43)
Adulthood smoking								
No	-----	Reference	Reference	Reference	-----	Reference	Reference	Reference
Any	-----	**1.35 (1.16, 1.58)**	**1.32 (1.10, 1.59)**	**1.22 (1.06, 1.41)**	-----	1.17 (0.97, 1.42)	1.09 (0.86, 1.39)	**1.20 (1.00, 1.43)**
Other atopic history								
History of asthma	**1.90 (1.66, 2.16)**	**1.58 (1.32, 1.89)**	0.85 (0.69, 1.05)	**0.81 (0.69, 0.96)**	**1.76 (1.50, 2.07)**	**1.30 (1.05, 1.60)**	**0.73 (0.57, 0.94)**	**0.79 (0.66, 0.95)**
History of allergic rhinitis/hay fever	**1.55 (1.38, 1.75)**	**1.62 (1.38, 1.90)**	1.06 (0.87, 1.29)	0.88 (0.76, 1.02)	**2.02 (1.73, 2.35)**	**1.51 (1.25, 1.84)**	**0.78 (0.61, 1.00)**	**0.74 (0.62, 0.87)**
Parental history of atopy	**1.90 (1.69, 2.15)**	1.07 (0.89, 1.27)	**0.56 (0.46, 0.69)**	**0.57 (0.49, 0.66)**	-----	-----	-----	-----
Birth weight								
Per kg increase	1.09 (0.98, 1.21)	0.93 (0.80, 1.08)	**0.82 (0.69, 0.99)**	**0.86 (0.76, 0.98)**	1.06 (0.91, 1.23)	1.13 (0.94, 1.36)	1.08 (0.86, 1.37)	0.93 (0.78, 1.10)
Breastfeeding								

No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Any	**1.19 (1.06, 1.33)**	**1.18 (1.01, 1.39)**	0.95 (0.79, 1.15)	0.88 (0.76, 1.02)	1.15 (0.97, 1.37)	1.02 (0.83, 1.26)	0.93 (0.71, 1.21)	0.84 (0.69, 1.02)

Supplemental Table 5: Sensitivity analysis: Multivariable regression results showing the odds of adult-onset vs childhood-onset AE including data from age 16 in childhood-onset group.

	1970			1958		
	Child-onset AE N (%)	Adult-onset AE N (%)	Adult-onset vs child-onset AE OR (95% CI)	Child-onset AE N (%)	Adult-onset AE N (%)	Adult-onset vs child-onset AE OR (95% CI)
	N=2232 (64% of those with AE)	N=1246 (36% of those with AE)	N=6617	N=1506 (60% of those with AE)	N=997 (40% of those with AE)	N=5800
Sex						
Male	1079 (48.3)	459 (36.8)	Reference	729 (48.4)	386 (38.7)	Reference
Female	1153 (51.7)	787 (63.2)	**1.53 (1.26, 1.84)**	777 (51.6)	611 (61.3)	**1.40 (1.10, 1.77)**
Ethnicity						
European, Caucasian	1911 (96.8)	1003 (96.4)	Reference	1310 (98.8)	783 (98.9)	Reference
Other	63 (3.2)	37 (3.6)	1.01 (0.59, 1.73)	16 (1.2)	9 (1.1)	1.36 (0.36, 5.16)
Region of residence in childhood						
Southern England	800 (39.7)	389 (36.3)	Reference	485 (32.2)	308 (30.9)	Reference
Central England	559 (27.8)	293 (27.3)	0.98 (0.70, 1.36)	493 (32.7)	295 (29.6)	0.95 (0.66, 1.36)
Northern England	655 (32.5)	390 (36.4)	1.21 (0.84, 1.74)	528 (35.1)	394 (39.5)	**1.70 (1.12, 2.57)**
Region of residence in adulthood						
Southern England	711 (42.5)	382 (38.4)	Reference	477 (39.3)	363 (40.0)	Reference
Central England	473 (28.3)	272 (27.3)	1.06 (0.76, 1.46)	346 (28.5)	257 (28.3)	1.09 (0.77, 1.55)
Northern England	489 (29.2)	341 (34.3)	1.04 (0.72, 1.51)	392 (32.3)	288 (31.7)	**0.65 (0.44, 0.99)**
Social class in childhood						
I/II	991 (44.4)	462 (37.2)	Reference	506 (33.7)	297 (29.9)	Reference
IIIa/b	1112 (49.9)	685 (55.2)	1.19 (0.98, 1.45)	869 (57.9)	597 (60.1)	1.05 (0.82, 1.36)
IV/V	127 (5.7)	95 (7.6)	1.21 (0.78, 1.86)	127 (8.5)	99 (10.0)	1.01 (0.63, 1.62)
Social class in adulthood						
I/II	1292 (60.5)	693 (57.8)	Reference	677 (46.3)	479 (50.0)	Reference
IIIa/b	697 (32.6)	431 (35.9)	1.04 (0.85, 1.28)	625 (42.8)	396 (41.3)	0.92 (0.71, 1.17)
IV/V	148 (6.9)	76 (6.3)	0.87 (0.57, 1.34)	159 (10.9)	83 (8.7)	0.79 (0.49, 1.29)

Household size						
<=3 persons	209 (10.3)	111 (10.4)	Reference	129 (9.2)	72 (8.5)	Reference
4+ persons	1813 (89.7)	959 (89.6)	1.02 (0.76, 1.37)	1269 (90.8)	780 (91.5)	1.32 (0.86, 2.01)
Smoking during pregnancy						
No	1310 (59.0)	697 (56.1)	Reference	1022 (68.9)	666 (68.0)	Reference
Any	912 (41.0)	545 (43.9)	1.00 (0.82, 1.24)	462 (31.1)	313 (32.0)	0.82 (0.62, 1.08)
Childhood smoke exposure						
No	762 (37.7)	372 (34.8)	Reference	355 (30.2)	209 (28.3)	Reference
Any	1259 (62.3)	696 (65.2)	0.99 (0.80, 1.23)	821 (69.8)	529 (71.7)	1.08 (0.83, 1.41)
Adulthood smoking						
No	1234 (55.4)	617 (49.5)	Reference	864 (57.4)	525 (52.7)	Reference
Any	995 (44.6)	629 (50.5)	**1.28 (1.06, 1.54)**	640 (42.6)	472 (47.3)	1.00 (0.79, 1.27)
Other atopic history						
Personal history of asthma	714 (32.0)	357 (28.7)	0.83 (0.67, 1.02)	541 (35.9)	320 (32.1)	0.82 (0.63, 1.05)
Personal history of allergic rhinitis/hay fever	1242 (55.6)	645 (51.8)	0.99 (0.82, 1.20)	752 (49.9)	408 (40.9)	**0.71 (0.56, 0.90)**
Parental history of asthma or allergic rhinitis/hay fever	715 (38.0)	259 (26.7)	**0.58 (0.48, 0.72)**	-----	-----	-----
Birth weight, mean (SD)	3.3 (0.5)	3.3 (0.5)	**0.82 (0.68, 0.98)***	3.3 (0.5)	3.3 (0.5)	1.07 (0.85, 1.34)*
Breastfeeding						
No	1153 (57.5)	639 (60.1)	Reference	380 (26.7)	277 (31.6)	Reference
Any	852 (42.5)	425 (39.9)	0.99 (0.82, 1.20)	1045 (73.3)	599 (68.4)	0.87 (0.67, 1.13)

Notes: *For every one kg increase in birth weight

Supplemental Table 6. Data on contact dermatitis, psoriasis, and physician-visits by cohort and age of atopic eczema (AE) onset

	1970 Cohort				1958 Cohort			
	No AE N=8611	Child-onset N=1972 (60% of those with AE)	Adult-onset N=1303 (40% of those with AE)	P-value*	No AE N=10825	Child-onset N=1313 (57% of those with AE)	Adult-onset N=1005 (43% of those with AE)	P-value
Contact dermatitis				<0.001				<0.001
No	7891 (97.8)	1755 (94.0)	1153 (90.6)		8755 (97.9)	1056 (95.0)	871 (91.6)	
Any	175 (2.2)	112 (6.0)	119 (9.4)		188 (2.1)	56 (5.0)	80 (8.4)	
Psoriasis				<0.001				<0.001
No	7651 (97.0)	1751 (95.1)	1153 (92.5)		10374 (96.3)	1220 (93.2)	925 (92.1)	
Any	233 (3.0)	91 (4.9)	94 (7.5)		402 (3.7)	89 (6.8)	79 (7.9)	
Reported seeing a physician in the past year**				0.005				0.001
No	N/A	242 (61.3)	287 (52.1)		N/A	129 (65.8)	308 (52.3)	
Any	N/A	153 (38.7)	264 (47.9)		N/A	67 (34.2)	281 (47.7)	

Notes: *p-value for chi-square, **reported at age 30 in 1970 or age 42 in 1958

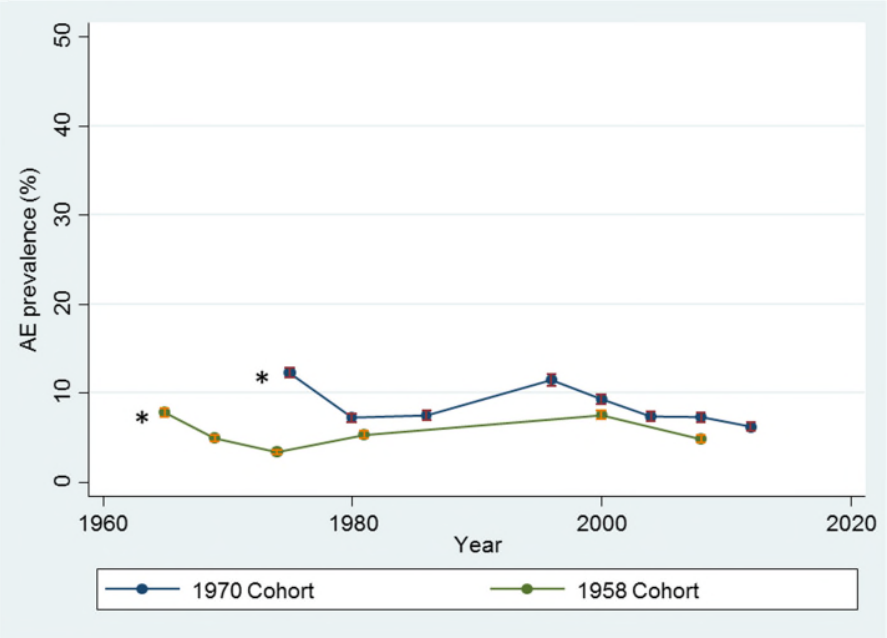
Supplemental Table 7. Sensitivity analysis results restricting to a subset of individuals with lower possibility of misclassification bias (i.e. reported seeing a MD in the last year and no history of contact dermatitis and psoriasis).

	Child-onset vs no AE N= 13,099	Adult-onset vs no AE N=10,796	Adult-onset vs child-onset AE N=10,796
	Odds Ratio (95% CI)		
Sex			
Male	Reference	Reference	Reference
Female	1.06 (0.96, 1.17)	**2.13 (1.64, 2.76)**	**2.06 (1.57, 2.71)**
Ethnicity			
European, Caucasian	Reference	Reference	Reference
Other	0.74 (0.52, 1.04)	1.16 (0.53, 2.54)	1.42 (0.61, 3.28)
Region of early childhood residence			
Southern England	Reference	Reference	Reference
Central England/Wales	0.91 (0.81, 1.03)	0.97 (0.64, 1.47)	0.98 (0.63, 1.53)
N. England/Scotland	**0.75 (0.66, 0.84)**	1.08 (0.68, 1.73)	1.28 (0.77, 2.10)
Region of residence at age 42			
Southern England	-----	Reference	Reference
Central England/Wales	-----	1.26 (0.84, 1.89)	1.26 (0.82, 1.94)
N. England/Scotland	-----	0.87 (0.55, 1.39)	1.00 (0.61, 1.65)
Highest social class in childhood*			
I/II	Reference	Reference	Reference
III	**0.82 (0.74, 0.91)**	0.94 (0.72, 1.23)	1.11 (0.83, 1.47)
IV/V	**0.72 (0.58, 0.90)**	0.99 (0.61, 1.61)	1.32 (0.78, 2.24)
Highest social class in adulthood*			
I/II	-----	Reference	Reference
III	-----	1.17 (0.90, 1.51)	1.26 (0.95, 1.66)
IV/V	-----	1.15 (0.72, 1.81)	1.45 (0.87, 2.39)
Household size in early childhood			
<=3 persons	Reference	Reference	Reference
4+ persons	1.04 (0.88, 1.23)	1.02 (0.68, 1.53)	0.99 (0.64, 1.54)
In utero smoke exposure			
No	Reference	Reference	Reference
Any	0.92 (0.82, 1.03)	1.01 (0.77, 1.33)	1.10 (0.83, 1.48)
Childhood smoke exposure			
No	Reference	Reference	Reference
Any	0.93 (0.83, 1.04)	1.09 (0.82, 1.46)	1.13 (0.83, 1.53)
Adulthood smoking			
No	-----	Reference	Reference

Any	-----	**1.58 (1.24, 2.01)**	**1.51 (1.16, 1.96)**
Other atopic history			
Asthma	**1.88 (1.69, 2.10)**	1.21 (0.91, 1.60)	**0.67 (0.50, 0.90)**
Allergic rhinitis/hay fever	**1.79 (1.62, 1.98)**	**1.63 (1.27, 2.09)**	0.92 (0.71, 1.21)
Birth weight			
Per kg increase	1.08 (0.98, 1.19)	**0.70 (0.56, 0.89)**	**0.63 (0.49, 0.82)**
Breastfeeding			
No	Reference	Reference	Reference
Any	**1.13 (1.02, 1.26)**	1.13 (0.87, 1.47)	0.96 (0.73, 1.26)

Notes: *Registrar General's social class: I Professional, II Managerial and technical; III Skilled; IV Partly-skilled; V Unskilled.

Supplemental Figure 1. Eczema prevalence by calendar year



* Prevalence from age 0-5 for 1970 cohort and age 0-7 for 1958 cohort; bars represent 95% CIs.

Supplemental Methods: British 1958 birth cohort biomedical examination and genotyping

Total and specific IgE

At the age of 44-45 years, the 1958 cohort were followed up with a biomedical examination and blood sampling [1], from which a DNA collection was established as a nationally representative reference panel. In blood samples collected at this adult follow up, the total concentration of serum IgE antibodies and the presence of specific IgE to house dust mite, mixed grass pollen and cat fur were ascertained by Hytec enzyme immunoassay, with a detection threshold of 0.35 kU/L. [2]

Filaggrin null mutations

The four common null mutations of the filaggrin (*FLG*) gene that have been associated with risk of atopic dermatitis [3,4] were genotyped directly by LGC Genomics using KASP™ genotyping technology. Filaggrin null status was defined as the presence of one or more risk variants of rs61816761 (R501X), rs150597413 (S3247X), rs558269137 (2282del4) or rs138726443 (formerly rs386430951).

Genome-wide typing, imputation and generation of non-FLG genetic risk score

Three non-overlapping subsets of the DNA collection from cohort members of white European ethnicity were genotyped by the Wellcome Trust Case-Control Consortium (WTCCC) [5]; the Type 1 Diabetes Genetics Consortium (T1DGC) [6]; and the GABRIEL consortium [7]. Genotyping was performed using the Illumina 550K array (WTCCC1 and T1DGC), the Illumina 610K array (GABRIEL) or the Illumina 1M array (WTCCC2). A set of SNPs common to these arrays were used for imputation against the March 2012 (phase 1, version 3) release of the 1000-genomes reference haplotypes for all ancestries. Pre-imputation phasing was performed using MACH v1.0.18 and imputation was performed using Minimac (version dated 16 November 2012).
The following 29 variants outside the FLG region were selected for inclusion in a polygenic risk score, based on previously published associations with atopic dermatitis:

rs7927894_T (risk-associated variant T) (*C11orf30* / 11q13.5) [8];
rs6010620_G (*TNFRSF6B* / 20q13.33) and rs7701890_G (*TMEM232* / 5q22.1) [9];
rs479844_G (*OVOL1* / 11q13.1), rs2164983_A (*ACTL9* / 19p13.2) and rs2897442_C (*KIF3A* / 5q31) [10];
rs13015714_G (*IL1RL1-IL18RAP* / 2q12), rs114764276_A (*GPSM3* / 6p21.3), rs878860_C (*OR10A3-NLRP10* / 11p15.4), rs6780220_C (*GLB1* / 3p21.33), rs12634229_C (*CCDC80* / 3q13.2), rs4722404_C (*CARD11* / 7p22), rs10995251_C (*ZNF365* / 10q21.2) and rs16999165_A (*CYP24A1-PFDN4* / 20q13) [11];
rs17389644_A (*IL2-IL21* / 4q27), rs12295535_T (*PRR5L* / 11p13), rs2041733_T (*CLEC16A-DEXI* / 16p13.13) and rs16948048_G (*ZNF652* / 17q21.32) [12];
rs12153855_T (*TNXB* / 6p21) [13];
rs7127307_T (*ETS1* / 11q24.3), rs2227483_T (*IL22* / 12q15); rs2143950_T (*PPP2R3C* / 14q13.2), rs7146581_C (*TRAF3*/14q32.32), rs17881320_T (*STAT3* / 17q21.2), rs11657987_T (*SOCS3* /17q25.3),

rs112111458_A (*CD207* / 2p13.3), rs1057258_C (*INPP5D* / 2q37.1), rs10214237_T (*IL7R* / 5p13.2) and rs6473227_C (*ZBTB10* / 8q21.13) [14].

A non-*FLG* genetic risk score was generated as the sum of imputed allele dosages for the risk-associated variant at each of these SNPs.

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