

Natural history of atopic dermatitis and its relationship to serum total immunoglobulin E in a population-based birth cohort study

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We investigated the natural history of atopic dermatitis (AD) in a population-based birth cohort and assessed whether children at risk of visible eczema at 5 years of age can be identified from total immunoglobulin E (IgE) levels measured at 8, 12 and 18 months. AD data collected included a whole body examination for visible eczema at 49 months (4 years) and 61 months (5 years) of age and parent completed questionnaire data throughout their early lives. Children were divided into four groups based on their natural history of early AD: persistent (AD at 1, 6, 18, 30 and 42 months, $n = 34$), intermittent early onset (before 18 months of age, $n = 495$), intermittent late onset (18–42 months of age, $n = 273$) and unaffected ($n = 429$). Visible eczema at 5 years of age was present in 12.2% (117/957) (95% confidence interval [CI] 10.1–14.3%) of the children. Levels of total IgE at 8, 12 and 18 months of age were associated with early onset of AD, but not with AD of later onset. For all four natural history groups, the geometric mean total IgE at 12 months was higher in those who subsequently had visible eczema than those who did not. However, the degree of overlap was such that total IgE at 12 months of age was a poor predictor of eczema at age five. A cutoff point of 78 kU/l had the highest positive predictive value for visible eczema at 5 years of age of 28.6%, with a sensitivity of 12% and specificity of 95%.

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The International Study of Asthma and Allergy in Childhood found that the lifetime prevalence of atopic dermatitis (AD) varied between 2 and 16% among 6 to 7-years olds around the world (1). A number of studies have investigated the possibility of identifying children at risk of developing atopy (2, 3) (usually defined as skin prick positivity) or asthma (4) using parameters measured in early life. Less common have been studies to predict development of AD (5–7). Parameters used include total immunoglobulin E (IgE) (2–3), specific IgE (3) and most recently, differences in stimulated cytokine production (6). Because of the relative ease of obtaining a sample, studies have used cord blood measurements, but with conflicting results (2, 7–9). Studies involving blood collection in early

life tend to have been restricted to one or two sampling points (4). Studies have divided between those predicting subsequent AD or atopy from a high-risk population (with, for example, a family history of atopy) (10, 4) and those using an unselected population of infants or children (3, 5).

There has also been significant variation in the presentation of results in predictive studies. Some have simply compared the incidence of AD above and below a particular IgE threshold (5), while others have calculated the positive and negative predictive value of such measurements (3). The odds ratio for a measurement can be misleading, in that a highly statistically significant result can be obtained despite the measurement having a poor predictive value (7).

Very few have used receiver operating characteristic curves to summarize the predictive ability of a measurement (11).

Little is known about short to medium term fluctuations in AD disease activity (12). This study uses data from the Avon Longitudinal Study of Parents and Children (ALSPAC) which has both measurements of visible eczema at 4 and 5 years of age and questionnaire ascertained skin signs and symptoms throughout the first 5 years of life. The ALSPAC study is ideally suited to address the criticism of the dearth of studies investigating the natural history of AD (12). Studies of well-defined cases suggest that most (70%) AD cases become manifest within the first 5 years of life (12). We investigated whether it was possible to identify children at high risk of visible eczema at 5 years based on serial measurements of total IgE in early life.

Methods

Study participants

The ALSPAC study was set up with the aim 'to determine which biological, environmental, social and psychological factors are associated with the survival and optimal health of the fetus, infant and child and the ways in which causal

relationships might vary with the genetic composition of the mother and/or child' (13). The ALSPAC study invited all pregnant mothers resident in Avon with an expected date of delivery between April 1, 1991 and December 31, 1992 to participate (14). The number of pregnancies enrolled in the study was 14,541. The enrolment rate is estimated to be between 80 and 90% of eligible mothers (13). Seven hundred and forty women dropped out, the majority being for miscarriage and late fetal/early infancy death. In all, by 12 months of age, 13,801 mothers were being followed, together with their 13,988 children (Fig. 1).

A sub-sample of approximately 10% of the children (the *Children in Focus – CiF*) was identified from ALSPAC births that occurred from June 1st to the end of December 1992. A standard number of children per week was chosen at random from the list of births within the study (14). The aim of the CiF study was to examine these children in a way that could not be performed using questionnaires up to the age of seven when ALSPAC clinics for the whole cohort began. Parents of this 10% sample were invited to bring their children to a clinic at intervals between 4 and 61 months. Of 1509 infants invited at 4 months of age, 1023 attended

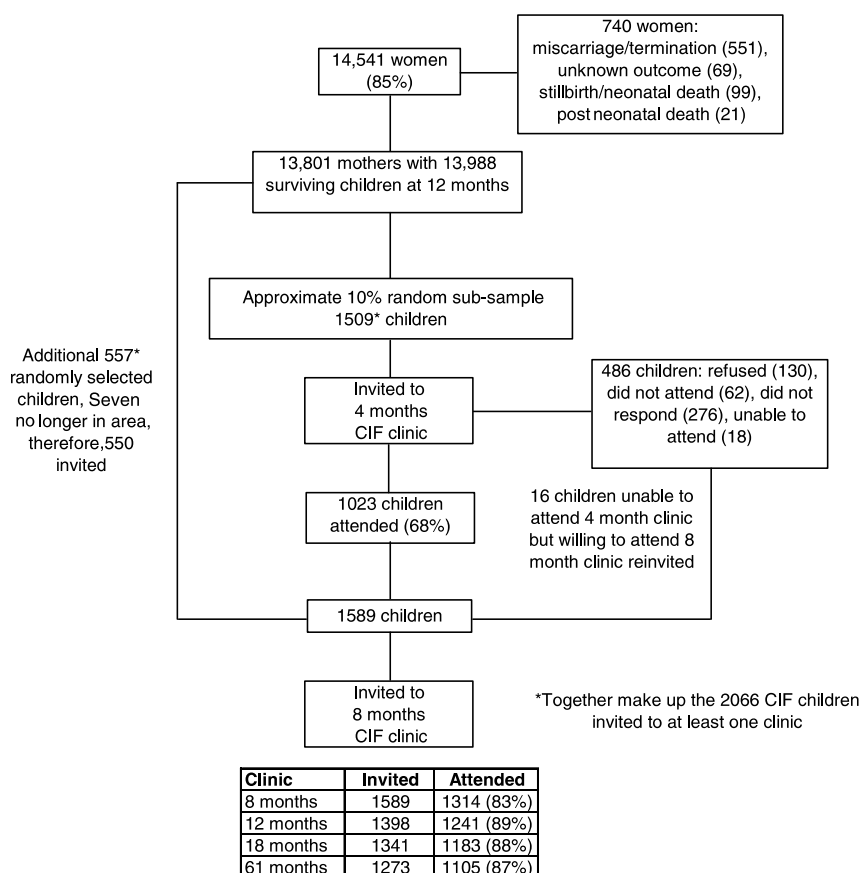


Fig. 1. Recruitment flow chart for the Children in Focus of ALSPAC.

(68%). A further randomly selected group of 550 children was invited at 8 months to increase the size of the cohort. Children who attended at 4 and/or 8 months formed the CiF cohort that was invited to subsequent clinics. In all, mothers of 2066 children were invited to one or more clinics but because of the study design, the number invited to each individual clinic was less (Fig. 1). This analysis was restricted to the 2009 singleton pregnancies.

All projects undertaken with the ALSPAC cohort have obtained both local research ethics committee and ALSPAC ethics committee approval (15, 16).

Definitions of atopic dermatitis

All ALSPAC parents were asked a series of questions about rash (Table 1). The AD questions were based on the work of Hanifin and Rajka (17, 18) with some modifications. The questions were formulated before the UK working party proposed diagnostic criteria for AD (19). They found that a question asking whether 'rash affected skin creases' had 90.0% sensitivity and 74.5% specificity (19). A child was deemed to have had AD at 4 weeks, 6 and 18 months if the response was positive to either of the two questions. At the 4 and 5-year clinics the children were examined for visible eczema with a whole body examination by a trained observer. The observers were given an illustrated tutorial on common skin conditions in childhood, including the manifestations of AD. They attended outpatient clinics and ward rounds at the Bristol Royal Hospital for Sick Children and were given a clinical slide based examination to ensure they could recognize the common conditions. A sketch of the front and back of a child was divided into 30 segments and the observers ticked which segment had visible eczema. Observers were blind to the questionnaire responses. The age at onset of AD was determined by the time

when the mother first reported AD in either a questionnaire or the 4-year examination for visible eczema. AD frequency was determined by the number of times the mother reported AD out of the five questionnaires and the 4-year examination. AD frequency was confined to those children with data from all six sources.

Other variables

At the 5-year examination, the children also underwent skin prick testing with fourteen allergens: cat hair, dog hair, horse dander, peanut, cow's milk, hen's egg, fish (cod), six grass mix, three molds (*Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*), two house dust mites (*Dermatophagoides pteronyssinus* and *farinae*), *penicillium notatum* and positive and negative controls. A positive response was recorded if the maximum diameter of the weal for an allergen was 3 mm or more. A child was considered atopic if they had such a response to any of the allergens. One child reacted to the negative control (with a 6-mm weal), and was excluded from the analysis.

The children had a heel prick blood sample taken at 8, 12 and 18 months for measurements of haemoglobin and ferritin. Permission for blood taking decreased with each clinic: 90% (1176/1314), 78% (963/1241) and 72% (847/1183) respectively. Of those giving permission, the proportion from whom a sample was obtained was excellent: 96%, 99% and 99% respectively (13). Where sufficient plasma remained, children had their total IgE levels measured. The other exposure variables of interest were derived from the obstetric record and questionnaire data. Mothers were asked in the 6 and 18 months' questionnaires: 'Has your baby ever had wheezing with whistling on her chest when she breathed?'. Early wheezing was defined as a positive response to this question at either time point. Both mothers and their partners were

Table 1. Questions asked about atopic dermatitis

Age at questionnaire	Question wording	Variable in the analysis
4 weeks and 6 months	Has the baby had a rash in the joints and creases of her body (e.g. behind the knees, under the arms)?	Flexural dermatitis
18 months	Has she had an itchy, dry, oozing or crusted rash on the face, forearms or shins?	Convexity dermatitis
	Has she had a skin rash in the joints and creases of her body (e.g. behind the knees, elbows, under the arms) since she was 6 months old?	Flexural dermatitis
30 months	Has she had an itchy, dry, oozing or crusted rash on the face, forearms or shins since she was 6 months old?	Convexity dermatitis
	Has your child had an itchy, dry skin rash in the joints and creases of her body (e.g. behind the knees, elbows, under the arms) since she was 18 months old?	Flexural dermatitis
42 months	Has your child has an itchy, dry skin rash in the joints and creases of her body (e.g. behind the knees, elbows, under the arms) in the past 12 months?	Flexural dermatitis

asked at 12 weeks' gestation whether they had ever had eczema. Social class was determined using the U.K. Registrar General's 1990 classification of occupation (20).

Statistical analysis

Figure 2 was used to divide the cohort into four groups based on their parent reported history of AD: persistent (AD at 1, 6, 18, 30 and 42 months, 34/1231 children, 2.8%), intermittent early onset (before 18 months of age, 495 children, 40.2%), intermittent late onset (18–42 months of age, 273 children, 22.2%) and unaffected (no AD by 42 months of age, 429 children, 34.9%). These groupings were used for further analysis. The chi-squared test was used to assess heterogeneity between the four groups in the prevalence of visible eczema at 4 and 5 years of age and the percentage skin prick positive at 5 years of age. The percentage of children skin prick positive, stratified by

visible eczema status at 5 years of age, was compared in each natural history group using Fisher's exact test. IgE levels were not normally distributed and therefore the geometric mean level was used in the analyses. Differences in geometric mean IgE between the four groups were compared using analysis of variance. The difference in geometric mean IgE in those with and without visible eczema was compared using Student's *t*-test. Receiver operating characteristic (ROC) curves were used to assess the ability of total IgE at 12 and 18 months of age to predict presence of visible eczema at 5 years of age (21).

Multiple regression was used to determine the independent effects of visible eczema and natural history status on the log-transformed total IgE measurements at 8, 12 and 18 months. Tests for interaction between the visible eczema variable and the natural history variable were not significant and therefore interaction terms were not included in the final models.

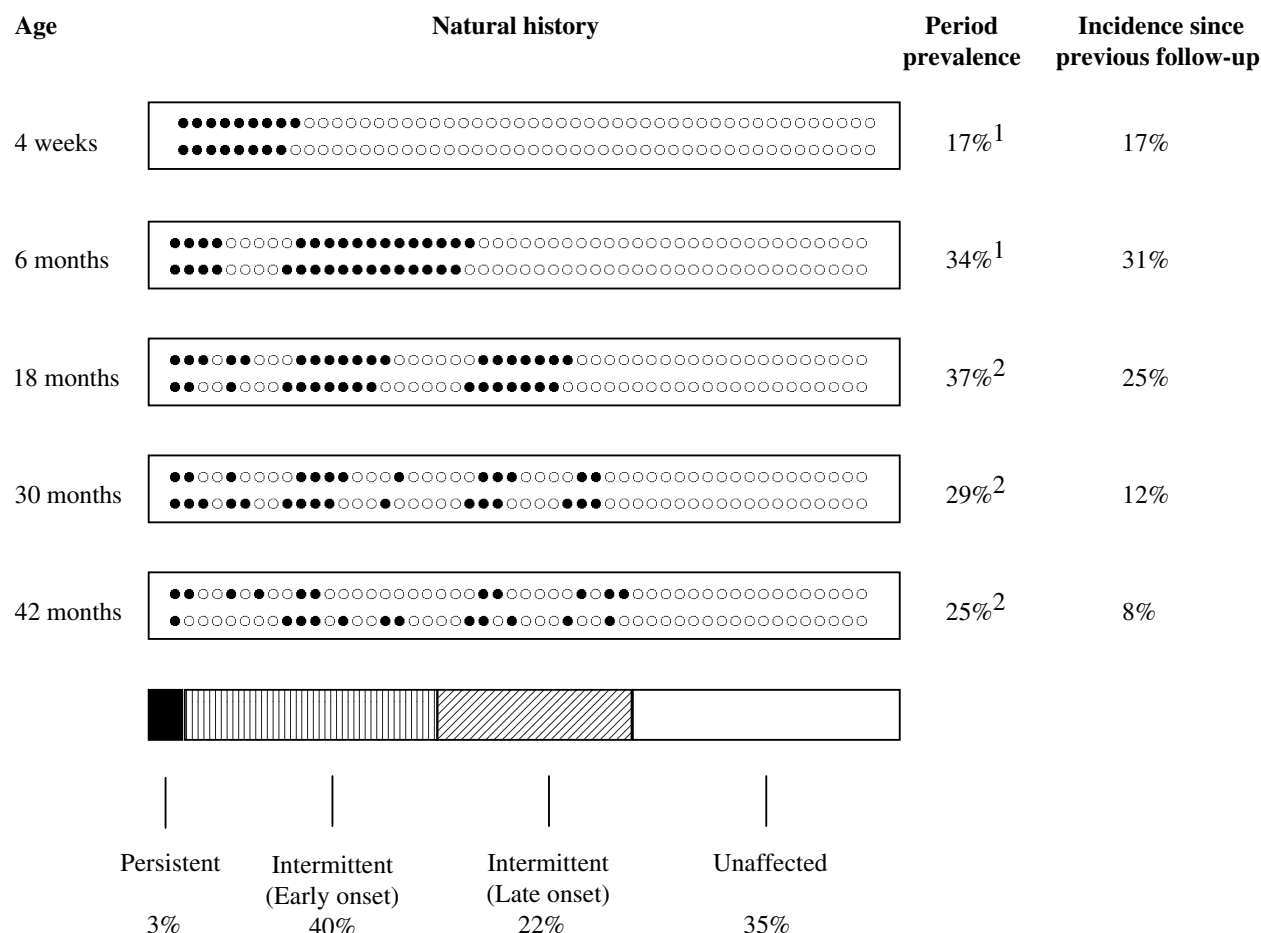


Fig. 2. Natural history of atopic dermatitis to 42 months of age in children with questionnaire data from all five age points. The 1231 children with data at all five age points are represented as 100 circles. Thus each specific circle represents the same group of approximately 12 children at each age point. Skin status is indicated as atopic dermatitis (●) or normal skin (○). Prevalence figures given are either life time prevalence (1) or twelve month period prevalence (2).

Multiple regression was also used to assess whether visible eczema *severity* at 5 years of age (determined by the number of segments ticked on the recording sheets – range 0–30) was related to the dependent variable, log-transformed total IgE measurements at 8, 12 and 18 months.

Logistic regression was used to assess whether IgE was related to visible eczema at 5 years of age. IgE was incorporated into the model log transformed to base 2. By doing this, the odds ratio generated could be interpreted as the change in risk for a doubling in IgE measurement. Adjustment was made for variables known to have strong and consistent associations with atopic eczema. These were early wheezing history, early atopic eczema onset, atopic eczema frequency, family size (22), parental eczema status (23, 24), and social class (25). The analysis was carried out using STATA 7.0 (26).

Results

Prevalence

The point prevalence of visible eczema was 13.7% (138/1001) at 4 years (95% [CI] 11.6–15.9%) and 12.2% (117/957) at 5 years (95% CI 10.1–14.3%). At 5 years of age the prevalence of visible eczema in girls was 13.6% and in boys, 11.1%. There was a clear transition in the cohort from predominantly convexity AD at 4 weeks of age to flexural AD at 18 months of age (Table 2). The prevalence of parentally reported flexural AD peaked at 30 months of age (29.3%).

Natural history of atopic dermatitis

Figure 2 demonstrates the relapsing and remitting nature of AD. The highest period prevalence was at 18 months, when 37% of the children had parentally reported AD. The highest incidence was in the first 6 months: 31% of the children had developed AD since the 4-wk questionnaire. The cumulative percentage of children with

parents ever having reported AD was 21.5% (313/1455, by 4 weeks of age), 42.9% (697/1626, by 6 months), 57.1% (837/1465, by 18 months), 61.9% (825/1332, by 30 months) and 65.2% (802/1231, by 42 months).

Table 3 shows the prevalence of visible eczema at 4 and 5 years of age based on the natural history grouping. As expected, the persistent group had the highest prevalence of later eczema (62% and 50% respectively) and the unaffected group, the lowest (2.9% and 3.8%). The visible eczema prevalence was higher at both examination points for the intermittent early onset group than the intermittent late onset group, but these differences were not statistically significant (4 years: 18.1% vs. 16.0%, $p = 0.54$; 5 years: 16.4% vs. 12.9%, $p = 0.29$).

The same trend was seen with the relationship between AD natural history and the likelihood of being skin prick positive at 5 years of age (Table 3). The overall percentage skin prick positive was 14.9% (92/617). By AD natural history grouping, the percentage skin prick positive was: 55.0% (persistent), 18.5% (intermittent early onset), 12.8% (intermittent late onset) and 7.2% (unaffected). Children with visible eczema at 5 years of age were significantly more likely to be skin prick positive than those without (32.9% vs. 12.0%, $p < 0.0005$). The same trend was seen in each of the four AD natural history groups.

Serum total immunoglobulin E

Geometric mean total IgE increased with age: 4.69 kU l⁻¹ (8 months), 6.08 kU l⁻¹ (12 months) and 6.65 kU l⁻¹ (18 months). Figure 3 shows the geometric mean total IgE at the three age points for each of the AD natural history groups. The difference in geometric mean between the four groups appears to diminish with age. As expected, mean levels were higher in the intermittent early onset and the persistent group compared with the other two groups. Compared with the unaffected group, the difference in IgE was statistically significant for the intermittent early onset group at 8 ($p = 0.006$) and 12 months of age ($p = 0.02$).

At all three age points the geometric mean total IgE was higher in those who subsequently had visible eczema at 5 years of age than those who did not. For the IgE measurement at 12 months of age, this difference was apparent within each natural history group, including the intermittent late onset group and the unaffected group, both of whom had not had any parentally reported eczema before 18 months of age.

Table 2. The number of children with atopic dermatitis at the five age points

Age at questionnaire	No rash % (n)	Convexity dermatitis % (n)	Flexural dermatitis % (n)	Convexity & flexural dermatitis % (n)	Total
4 wk	82.0 (1418)	12.8 (221)	3.8 (65)	1.5 (26)	1730
6 months	65.8 (1104)	11.2 (187)	14.4 (242)	8.6 (144)	1677
18 months	63.6 (1005)	8.3 (132)	20.4 (323)	7.7 (121)	1581
30 months	70.7 (1065)	Not recorded	29.3 (441)	Not recorded	1506
42 months	75.1 (1102)	Not recorded	24.9 (366)	Not recorded	1468

Table 3. Relationship between natural history of atopic dermatitis and visible eczema, skin prick positivity and total immunoglobulin E levels

Atopic dermatitis natural history	All	Persistent	Intermittent (Early onset)	Intermittent (Late onset)	Unaffected	Test for heterogeneity between groups
% Visible eczema at 4 years	14.2 (120/848)	62.1 (18/29)	18.1 (64/353)	16.0 (30/187)	2.9 (8/279)	89.2 $p < 0.0005^*$
% Visible eczema at 5 years	12.8 (104/815)	50.0 (14/28)	16.4 (57/347)	12.9 (23/178)	3.8 (10/262)	57.9 $p < 0.0005^*$
% Skin prick test positive at 5 years						
All	14.9 (92/617)	55.0 (11/20)	18.5 (50/270)	12.8 (17/138)	7.2 (14/194)	37.6 $p < 0.0005^*$
Visible eczema at 5 years +ve	32.9 (26/79)	71.4 (5/7)	29.8 (14/47)	26.3 (5/19)	33.3 (2/6)	5.3 $p = 0.15^*$
Visible eczema at 5 years -ve	12.0 (64/535)	46.2 (6/13)	15.8 (35/221)	9.7 (11/113)	6.4 (12/188)	23.7 $p < 0.0005^*$
Fisher's exact test +ve vs. -ve	$p < 0.0005$	$p = 0.37$	$p = 0.04$	$p = 0.06$	$p = 0.06$	
Geometric mean total IgE kU l ⁻¹ (8 months)						
All	4.69 (n = 105)	1.61 (n = 1)	7.17 (n = 41)	3.79 (n = 24)	3.53 (n = 39)	$p = 0.21^\dagger$
Visible eczema at 5 years +ve	5.26 (n = 15)	1.61 (n = 1)	8.24 (n = 10)	2.57 (n = 3)	1.63 (n = 1)	
Visible eczema at 5 years -ve	4.30 (n = 65)	— (n = 0)	5.17 (n = 21)	3.92 (n = 14)	3.95 (n = 30)	
	$p = 0.53^\ddagger$					
Geometric mean total IgE kU l ⁻¹ (12 months)						
All	6.08 (n = 381)	8.36 (n = 18)	7.38 (n = 164)	4.65 (n = 75)	5.27 (n = 124)	$p = 0.63^\dagger$
Visible eczema at 5 years +ve	11.62 (n = 43)	15.21 (n = 6)	12.17 (n = 27)	9.05 (n = 6)	8.27 (n = 4)	
Visible eczema at 5 years -ve	5.70 (n = 280)	8.63 (n = 8)	6.81 (n = 119)	4.28 (n = 52)	5.17 (n = 101)	
	$p = 0.0006^\ddagger$					
Geometric mean total IgE kU l ⁻¹ (18 months)						
All	6.65 (n = 363)	8.77 (n = 14)	6.88 (n = 155)	6.06 (n = 80)	6.55 (n = 114)	$p = 0.68^\dagger$
Visible eczema at 5 years +ve	9.82 (n = 42)	12.70 (n = 6)	11.70 (n = 23)	5.91 (n = 9)	7.68 (n = 4)	
Visible eczema at 5 years -ve	6.24 (n = 273)	10.04 (n = 6)	6.78 (n = 111)	5.34 (n = 62)	6.08 (n = 94)	
	$p = 0.04^\ddagger$					

* χ^2 (three degrees of freedom) and p-value.

† ANOVA.

‡ t-test visible eczema +ve vs. visible eczema -ve.

Regression modelling

When natural history category and long-term outcome (visible eczema at 5 years) were modelled jointly in relation to IgE at 8, 12 or 18 months, total IgE was more strongly related to presence of visible eczema at 5 years of age than to natural history up to 42 months. At

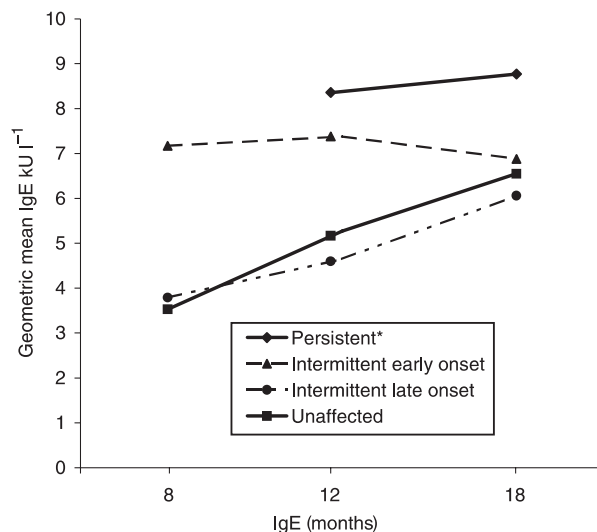


Fig. 3. Geometric mean IgE level at 8, 12 and 18 months by natural history of atopic dermatitis status. *Only one measurement of IgE at 8 months in persistent group therefore not plotted.

12 months of age, the IgE measurement was 80.8% higher in children who subsequently had visible eczema at 5 years of age ($p = 0.006$). There was no significant heterogeneity of IgE levels across natural history categories, after adjustment for visible eczema at 5 years.

The segment score of visible eczema was significantly related to IgE at 12 and 18 months. Each additional tick was associated with the IgE being 1.082 times greater (95% CI 1.03–1.14, $p = 0.001$) at 12 months and 1.081 times greater (95% CI 1.01–1.16, $p = 0.03$) at 18 months. Thus, the IgE measurement at both 12 and 18 months of age was 8% higher for each additional segment of visible eczema at 5 years of age.

When the log (base 2) transformed total IgE at 12 months of age was included in the logistic model with visible eczema at 5 years as the outcome, the odds ratio was highly significant ($OR_{adj} 1.63$, 95% CI 1.24–2.13, $p < 0.0005$). Thus a doubling in IgE was associated with 1.6 times the risk of having visible eczema at 5 years of age.

Receiver operating characteristic curve analysis

In order to see how well total IgE measured at 12 and 18 months of age could predict subsequent visible eczema status at 5 years of age, receiver operating characteristic curves were generated

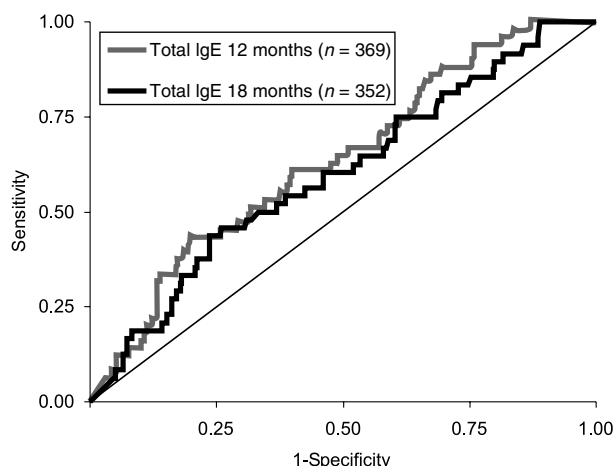


Fig. 4. ROC of visible eczema at 5 years, predicted by total immunoglobulin E level at 12 and 18 months of age. The ROC area is 0.64 (95% CI 0.56–0.71) for the 12 months' IgE data and 0.60 (95% CI 0.51–0.69) for the 18 months' data.

(Fig. 4). Total IgE predicted subsequent visible eczema slightly better at 12 months of age than at 18 months, however the difference in area for the two ROC curves was not statistically significant ($\chi^2_1 = 0.11$, $p = 0.74$). The ROC curve for total IgE at 12 months of age was only marginally statistically significant (ROC area 0.64, 95% CI 0.56–0.71). There was no statistically significant difference in predictive ability at either age point for boys or girls. Overall, the total IgE level at 12 months of age proved a weak predictor of visible eczema status at 5 years of age. The highest positive predictive value of 28.6% was achieved with a cutoff point of 78 kU l⁻¹. This cutoff point only had a sensitivity of 12% and a specificity of 95%.

Discussion

The relapsing and remitting nature of AD and the tendency for the distribution of AD to change from convexity to flexural with increasing age was confirmed in this population-based birth cohort study. Differences found in AD prevalence in previous studies may be attributable to the use of different measures of effect: the lifetime prevalence, period prevalence or point prevalence of AD or to differences in methods of recruitment. The questions about AD completed by the parents in this study did not enquire about the duration of the rash. Many studies ascertaining AD prevalence use the International Study of Asthma and Allergies in Childhood questions which enquire about an itchy rash 'coming and going for at least 6 months' (1). Consequently estimates of AD using the ISAAC criteria will

result in a lower prevalence. In order to increase the specificity of the diagnosis of AD, an analysis of AD prevalence using data from the whole ALSPAC cohort (excluding the 4-wk data), used rash reported on at least two occasions. They found that 58.0% of children reported rash at least once, but only 32.6% of parents reported AD at least twice (27). The latter figure is comparable with the 31% prevalence of doctor diagnosed AD among children in Kent, based on maternal report, in the study by Harris et al. (28), and a cumulative incidence of 32% of AD based on clinical records of 1 to 4-year-old children in Leicester (29).

Both the 4 weeks' and 6 months' questionnaires asked about presence of AD since birth. Therefore any mother responding positively at 4 weeks should have responded so again at 6 months of age. However, it is clear from Fig. 1 that, of the 212/1231 parents who reported atopic eczema at 4 weeks, 111 (52.4%) of these had presumably forgotten and responded negatively to the question at 6 months. It is unlikely that their child's condition was confused with cradle cap at 4 weeks of age in that a separate clear question about cradle cap was asked in the same questionnaire. Including these positive responses at 4 weeks of age has the effect of increasing the lifetime prevalence figures of AD by 4.6%, in that 57/1231 parents reported AD at 4 weeks of age and not in any subsequent questionnaire.

The children and parents in the ALSPAC study have been shown to be representative of the UK population in general (13). Similar to all studies where a representative sample has been attempted, the study has a slight shortfall in less affluent families and ethnic minority mothers (13). The study is a population based cohort. Thus it avoids the problem of hospital based studies of AD where patients with more severe disease are liable to be included (12).

IgE was only measured if there was sufficient serum. Those children with IgE measured at 12 months of age were significantly more likely to have parent reported AD at 4 weeks, 6 and 42 months, compared with those children who did not have IgE measured at that age. There were no statistically significant differences for those with or without IgE measurements at 8 and 18 months.

The prevalence of visible eczema at 5 years of age of 12.2% was consistent with the 11.1% prevalence found among children examined at 1 and 2 years of age in a cohort study based in Ashford, UK (28) and a 14% prevalence in a cross sectional study of 1–4-years-old children in Leicester (29).

Geometric mean total IgE increased with age. Levels were higher in those with early onset AD, whether persistent or intermittent. IgE did not predict later incidence of AD (after 18 months), in that there was no difference in IgE between the intermittent late onset and the unaffected groups. IgE levels did relate to prognosis: IgE levels were higher at all three measurement points in those who subsequently developed visible eczema. AD is a relapsing and remitting condition. By using visible eczema at one examination point as the outcome one will identify children with more severe AD, compared with a questionnaire asking about presence of a rash over a defined period. In addition children grow out of their AD (Fig. 2) so those with visible eczema at 5 years of age represent the more severe end of the spectrum of disease. This may explain why the early life IgE levels were not related to late onset AD but were related to presence of visible eczema at 5 years of age.

In the regression model incorporating IgE at 12 months of age, this relationship with visible eczema status at 5 years of age was strongly significant. Nevertheless, the ROC analysis showed that the predictive value of total IgE was poor. Bergmann et al found cord blood IgE to be a poor predictor of AD in the first 24 months of life and could not recommend it as a screening instrument for primary prevention (9). In the ETAC study of infants who already had AD, there was substantial variation in their baseline total IgE measurements. In the placebo group 52% (185/357) had normal ($< 30 \text{ kU l}^{-1}$) levels of total IgE at the baseline measurement at a median age of 16.5 months (30). In our study, based on a general population sample, the proportion of eczematous infants/children with 'normal' IgE levels was higher, for example of the children with AD at 18 months of age, 83% (129/156) had levels less than 30 kU l^{-1} .

There has been a recent resurgence in debate about the role of IgE in AD. Bos proposed that the presence of allergen-specific IgE antibodies should be a mandatory criterion for the diagnosis of AD (31). The presence of allergen-specific IgE was based on positive RAST or ELISA for specific IgE or positive skin prick testing (31). More recently, Bos proposed the term atopiform dermatitis to describe patients who have dermatitis, but who do not produce allergen-specific IgE (32). He proposed this refinement of the intrinsic (no allergen specific IgE) vs. extrinsic (IgE positive) atopic dermatitis dichotomy (33) on the grounds that the production of allergen specific IgE is the hallmark of the 'genetically

based syndrome of atopy' and thus the diagnosis of 'intrinsic atopic dermatitis' is incorrect (32). However, from this study it would seem difficult to make such a clear dichotomization. Despite the statistically significant association between total IgE levels and visible eczema severity (suggesting that IgE might, at least partly, be an epiphenomenon of disease severity), IgE levels in infancy overlapped extensively for those with skin prick positive visible eczema, skin prick negative visible eczema and no visible eczema at 5 years of age. Thus it seems right to concur with Hanifin in asking where should we draw the line and say 'no atopy' (34)?

In conclusion, despite statistically significant epidemiological associations with early incidence of AD and subsequent prognosis, it is clear from this study that early measurement of total immunoglobulin E is of little clinical use in predicting subsequent risk of visible eczema.

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