

The predictive value of early life total immunoglobulin E measurement in identifying atopic children in a population-based birth cohort study

Perkin MR, Strachan DP, Williams HC, Lack G, Golding J and the ALSPAC Study Team. The predictive value of early life total immunoglobulin E measurement in identifying atopic children in a population-based birth cohort study.

Pediatr Allergy Immunol 2006; 17: 118–124.

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Atopy is common and the prevalence amongst children is rising. Measurements in early childhood that can predict subsequent development of atopy could be clinically useful for targeting preventive measures. We used the Children in Focus (CiF) subgroup of a large population-based birth cohort study (the Avon Longitudinal Study of Parents and Children) to investigate whether total immunoglobulin E (IgE) measured at 12 and 18 months could predict subsequent development of atopy at 5 yr of age. Atopy was determined by positive skin prick test (≥ 3 mm wheal) to one or more of 14 inhalant and food allergens. Prevalence of skin prick positivity to any allergen was 14.5% (104 of 715; 95% CI: 12.0–17.1%). Total IgE levels were significantly higher at 12 months of age ($p < 0.0005$) but not 18 months of age in those children subsequently atopic. The highest positive predictive value was 41% with an IgE measurement of > 51 kU/l, with a sensitivity of 13.5% and a specificity of 95.8%. Although significant differences in early life IgE measurements were seen, the extent of overlap was great, such that the overall performance of IgE at 12 months as a screening test for atopy was poor.

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Key words: atopy; child; immunoglobulin E; natural history; predictive value of tests; screening; skin prick tests

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Accepted 28 November 2005

Reliably identifying those children with a propensity to become atopic would be valuable and trials have already been undertaken to try and ameliorate the risk of developing atopic disease amongst high-risk children using pharmaceutical (1) and environmental interventions (2). However, screening studies are complicated by the different ways in which atopy can be defined. Atopy was first introduced as a term in 1923 to describe a 'phenomena of hypersensitiveness' (3). Nomenclature has been a source of debate ever since. A revised nomenclature for allergy for global use was recently proposed by the Nomenclature Review Committee of the World Allergy Organization (WAO; 4). They suggested that atopy be defined as, 'a personal and/or familial

tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema'.

Parameters used for screening have included total immunoglobulin E (IgE) levels. Cord blood is relatively easy to obtain, but studies using it as a screening tool have yielded conflicting results (5–10). Few studies have looked at IgE measurements in early life (5, 11). This study uses data from the Avon Longitudinal Study of Parents and Children (ALSPAC) which has serial measurements of early life total IgE. We investigated whether it was possible to identify children at

high risk of atopy at 5 yr of age based on these measurements.

Methods

Study participants

The methodology of the ALSPAC study has been described in detail elsewhere (12) and the protocol is available on the internet (<http://www.alspac.bris.ac.uk/protocol/default.shtml>). Briefly, the ALSPAC study invited all pregnant mothers resident in Avon with an expected date of delivery between 1 April 1991 and 31 December 1992 to participate. 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. 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).

We have described the recruitment of the Children in Focus (CiF) group previously (13). In summary, a subsample of approximately 10% of the children (the CiF) was identified from ALSPAC births that occurred from 1 June to the end of December 1992. A standard number of children per week were chosen at random from

the list of births within the study. The aim of the CiF study was to examine these children in a way that could not be undergone using questionnaires up to the age of 7 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. About 1509 infants were invited at 4 months of age of whom 1023 attended (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 (14, 15).

Outcomes

At 5 yr of age the CiF children underwent skin prick testing to 14 food and inhalant allergens: cat hair, dog hair, horse dander, peanut, cow's milk, hen's egg, fish (cod), six grass mix (*Avena elatior*, *Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*), three moulds (*Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*), two house dust mites (*Dermatophagoides pteronyssinus* and *fari-nae*), *Penicillium notatum* and positive (histamine 10 mg/ml) and negative (50% glycerol, 50% buffered saline) controls (ALK, Horsholm, Denmark). Prick tests were undertaken with 1 mm ALK lancets (ALK). Twenty-four children who did not respond to the positive control solution and the one child who responded to the negative control solution (with a 6 mm wheal) were excluded from the analysis. Atopy was defined using the standard EAACI criterion of a wheal diameter of 3 mm or more to any of the allergens (16).

The exposure variables of interest were derived from the obstetric record and questionnaire data. Maternal and paternal asthma, eczema and hay fever status was derived from the self-reported responses to questionnaires administered at 12 wk gestation ('Have you ever had the condition'). Parents were determined 'atopic' if they reported one or more of these conditions. Social class was determined using the United Kingdom Registrar General's 1990 classification (17).

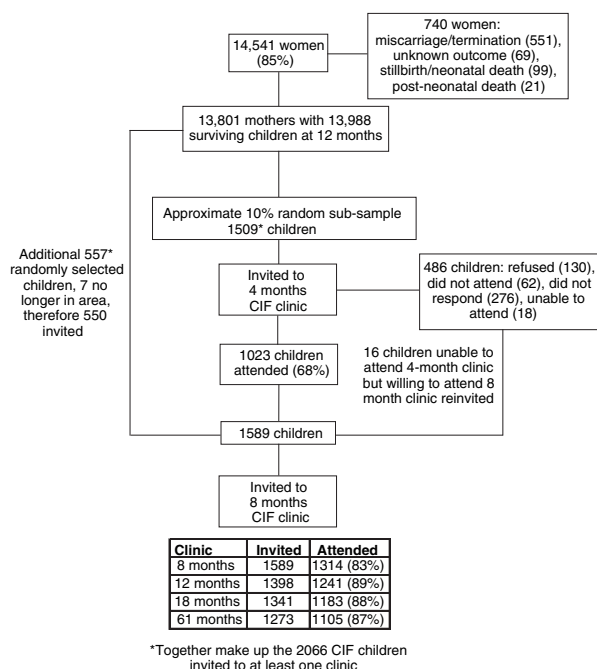


Fig. 1. Recruitment flow chart for the Children in Focus of Avon Longitudinal Study of Parents and Children (ALSPAC).

The children had a heel prick blood sample taken at 12 and 18 months for measurements of haemoglobin and ferritin. Where sufficient plasma remained, children had their total IgE levels measured. All the total IgE measurements were measured in the same laboratory using a fluorescence enzyme immunoassay (Pharmacia CAP, Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions.

Statistical analysis

Immunoglobulin E levels were not normally distributed and therefore the geometric mean value was used in the analyses. Differences in geometric mean IgE between sensitized and non-sensitized children were 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 skin prick positivity at 5 yr of age (18). The following screening parameters were also calculated. Sensitivity – proportion of truly positive (skin prick-sensitive) children who were test positive (IgE greater than given level); specificity – proportion of truly negative (skin prick-negative) children who were test negative (IgE less than the given level); positive predictive value (PPV) – proportion of test positive (IgE greater than given level) children who were true positives (skin prick-sensitive); likelihood ratio for a positive test result (LR+) – the ratio of the probability of a positive test (IgE greater than a given level) among the truly positive (skin prick-sensitive) children to the probability of a positive test among the truly negative (skin prick-negative) children; likelihood ratio for a negative test result (LR–) – the ratio of the probability of a negative test (IgE less than a given level) among the truly positive (skin prick-sensitive) children to the probability of a negative test among the truly negative (skin prick-negative) children.

Logistic regression was used to assess whether IgE was associated with skin prick positivity at 5 yr. IgE was incorporated into the model log-transformed to base 2. By doing this, the odds ratio (OR) generated could be interpreted as the change in risk for a doubling in IgE measurement. Also included in the model were other potential confounding variables known to be strongly associated with atopy: male sex (19–21), family size (bigger families have decreased risk; 22), parental atopy (23) and socioeconomic group (poorer families have decreased risk; 24). The analysis was performed using STATA 8.0 (25).

Results

Skin prick positivity – prevalence

The prevalence of skin prick positivity to any allergen at 5 yr of age was 14.5% (104 of 715; 95% CI: 12.0–17.1%; Table 1). Skin prick positivity was more common in boys than girls: 16.0:12.9% ($p = 0.25$). Positivity for individual allergens varied from 0% for *P. notatum* to 6.5% for *D. pteronyssinus* and was higher for the inhalant allergens than the food allergens.

For the 700 children with skin prick results for all the allergens, the number of children with positive reactions to the three most common allergens (cat, grass mix and house dust mite – *D. pteronyssinus*) was 72 (10.3%). Sixteen (2.3%) children reacted to the other inhalant allergens (dog, horse, *D. farinae*, *A. alternata*, *C. herbarum* and *A. fumigatus*) but not the common or food/drug allergens. Finally, an additional 15 children (2.1%) were positive to food/drug allergens (milk, egg, peanut, fish and *P. notatum*) but not the common or other inhalant allergens. In total therefore, 103 (14.7%) of 700 children were positive to any allergen. Thus, 70% of all the atopic children (72 of 103) were identified from their reactions to the three common allergens alone.

Early total IgE predicting skin prick positivity

Immunoglobulin E levels were significantly higher at 12 months of age (*t*-test, $p < 0.0005$) but not 18 months of age in those subsequently skin

Table 1. Atopy prevalence amongst the Children in Focus (CiF) cohort

Skin prick status at 5 yr	Number tested	Wheal ≥ 3 mm, % (n)
<i>Dermatophagoides pteronyssinus</i>	703	6.5 (46)
<i>Dermatophagoides farinae</i>	704	4.6 (32)
Cat	714	4.5 (32)
Grass mix	703	4.0 (28)
Dog	713	1.8 (13)
Horse	713	1.7 (12)
Milk	713	1.5 (11)
Egg	713	1.3 (9)
<i>Alternaria alternata</i>	702	1.4 (10)
Peanut	712	0.8 (6)
<i>Cladosporium herbarum</i>	701	0.4 (3)
<i>Aspergillus fumigatus</i>	701	0.4 (3)
Fish	701	0
<i>Penicillium notatum</i>	700	0
Combinations		
<i>D. pteronyssinus</i> , cat, grass	703	10.2 (72)
Other inhalant allergens*	701	7.0 (49)
Food and drug allergens†	700	3.6 (25)
All allergens	715	14.5 (104)

*Dog, horse, *D. farinae*, *A. alternata*, *C. herbarum* and *A. fumigatus*.

†Milk, egg, peanut, fish and *P. notatum*.

Table 2. Relationship between skin prick status at 5 yr and total IgE levels at 12 and 18 months, by sex

Skin prick status at 5 yr	Wheal ≥ 3 mm	Skin prick-negative	t-test for heterogeneity between groups (p-value)
Geometric mean total IgE (kU/l; 12 months*)			
All	13.06 (n = 50)	5.73 (n = 231)	<0.0005
Male	13.48 (n = 33)	6.72 (n = 133)	0.006
Female	12.28 (n = 17)	4.61 (n = 98)	0.003
t-test male vs. female	p = 0.80	p = 0.03	
Geometric mean total IgE (kU/l; 18 months*)			
All	9.91 (n = 33)	6.99 (n = 244)	0.17
Male	6.37 (n = 17)	8.19 (n = 130)	0.48
Female	15.86 (n = 16)	5.84 (n = 114)	0.006
t-test male vs. female	p = 0.06	p = 0.05	

*Data on immunoglobulin E (IgE) and skin prick status available for 153 children (12 and 18 months), 128 children (12 months only) and 124 children (18 months only).

prick-positive than those skin prick-negative (Table 2). Amongst females, total IgE levels were significantly higher in those skin prick-positive compared with skin prick-negative at 12 and 18 months, whereas the difference was only statistically significant for males at 12 months of age. Assessing sex differences in total IgE independent of skin prick status (amongst those skin prick-negative), levels were higher in males at both ages, but only reaching statistical significance at 12 months of age ($p = 0.03$).

Receiver operating characteristic curves

Receiver operating characteristic curves for the total IgE measurements at 12 and 18 months predicting skin prick positivity status at 5 yr of age were generated (Fig. 2). The ROC area was greater at 12 months of age than at 18 months of age. Only the ROC curve at 12 months of age was statistically significant (lower confidence interval > 0.50). However, the difference in area under the two ROC curves was not statistically significant ($p = 0.16$; this comparison is confined to 153 children with data for skin prick status, and IgE measurements at both 12 and 18 months).

The ROC area was larger for girls than boys, although this difference only reached statistical significance for the measurements at 18 months of age (0.69 vs. 0.46; $p = 0.03$). ROC areas were the same or larger for those children with a positive parental history of atopy at either age, but none of the differences was statistically significant.

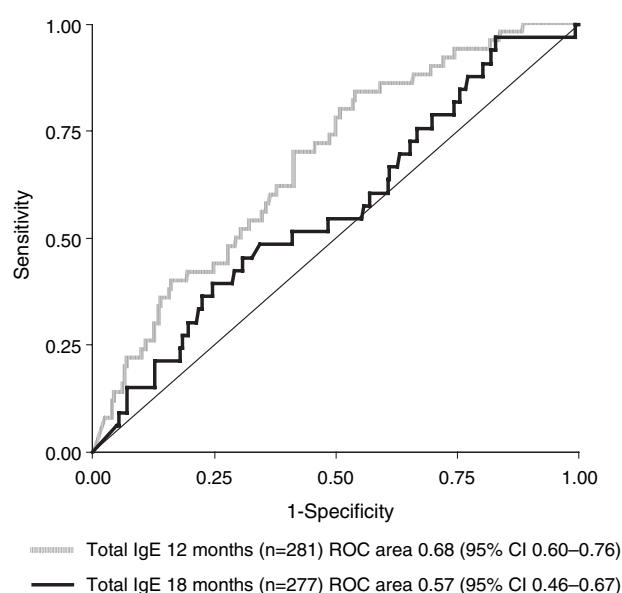


Fig. 2. Receiver operating characteristic (ROC) curve for total immunoglobulin E (IgE) at 12 and 18 months predicting skin prick positivity status at 5 yr of age.

Positive predictive value and likelihood ratios for positive and negative test results

From the ROC analysis output the sensitivity, specificity, PPV and LR+ and LR- were calculated for different cut-off points of IgE at 12 months (Table 3). The highest PPV to determine skin prick status of 41% was achieved with an IgE level of > 51 kU/l (sensitivity 22.0%, specificity 93.1%). Thus, the PPV in this subset of children (i.e. those with IgE levels > 51 kU/l) was at best approximately double the baseline prevalence of atopy amongst all the children (increasing from 18% to 41%). However, the number of children meeting this IgE criterion is a very small proportion of the whole cohort – 27 of 281 children (Table 3). Thus, using this IgE level as a screening tool would yield 11 positive children (41% of 27) out of the 281, a poor yield given that 50 children (17.8% of 281) are positive at 12 months of age.

In this cohort, 68% of children had a maternal and/or paternal history of asthma, eczema and/or hay fever. However, despite the prevalence of atopy being higher amongst those with a positive family history (21%), the PPVs were virtually unaltered. When one considers that the yield of children with the respective IgE level and a positive family history of allergy is so small, there is no value in using family history of allergy as an additional screening tool in this cohort.

Table 3. Sensitivity, specificity, PPV and likelihood ratios for a positive and negative test result for total IgE at 12 months of age and total IgE at 12 months of age combined with a positive family history of allergy, in predicting skin prick positivity at 5 yr of age

IgE level (kU/l)	Cumulative number of children with IgE greater than this level	≥3 mm wheal				
		Sensitivity	Specificity	PPV	LR+	LR–
12 months						
All children	281	100	0	18	1.0	–
≥10	96	52	70	27	1.72	0.69
≥20	55	38	84	34	2.44	0.73
≥30	42	26	87	30	2.07	0.85
≥40	31	22	91	35	2.54	0.85
≥50	27	22	93	41	3.18	0.84
≥60	24	18	93	37	2.77	0.88
≥70	20	14	94	35	2.49	0.91
≥80	17	14	96	41	3.23	0.90
≥90	16	12	96	37	2.77	0.92
12 months and positive family history of allergy*						
All children	187	100	0	21	1.0	–
≥10	61	56	74	36	2.14	0.59
≥20	38	41	85	42	2.76	0.69
≥30	27	26	89	37	2.23	0.84
≥40	21	21	91	38	2.34	0.87
≥50	19	21	93	42	2.76	0.86
≥60	16	15	93	37	2.28	0.91
≥70	13	10	94	31	1.69	0.96
≥80	12	10	95	33	1.90	0.95
≥90	11	8	95	27	1.42	0.98

*For 5 children no maternal or paternal history of allergy.
PPV, positive predictive value; IgE, immunoglobulin E.

Atopy logistic model

Having established that the IgE measurements at 12 months predicted subsequent skin prick positivity best, log₂-transformed IgE measurement at 12 months was incorporated in a logistic model with skin prick positivity as the outcome. There was a highly statistically significant relationship (OR_{adj} 1.38, 95% CI: 1.10–1.73, $p = 0.006$). Thus, a doubling in IgE measurement at 12 months was associated with being approximately a third more likely to be skin prick-positive at 5 yr of age.

Discussion

The prevalence of skin prick positivity in this study of 14.5% compares with a prevalence of 19.6% amongst 981 4-yr-old children skin prick tested in a study from the Isle of Wight using 12 common allergens (26). The sex difference was present in the latter study as well, but reached statistical significance with 22.5% of boys being atopic compared with 16.5% of girls. The three most common positive reactions were the same in both studies: house dust mite (*D. pteronyssinus*: 6.5% in our study vs. 11.9% in the Isle of Wight),

cat (4.5% vs. 5.8%) and grass pollen mix (4.0% vs. 7.6%).

The children and parents in the ALSPAC study have been shown to be representative of the UK population in general. The 2009 CiF children could be divided into three groups: those with IgE and skin prick data, those missing IgE or skin prick data and those missing IgE and skin prick data. As expected, those who had blood taken in infancy and were skin prick tested at 5 yr of age were statistically more likely to have had earlier onset eczema and for it to have been more persistent. There was, however, no difference in parental history of atopy between the three groups.

This study found a statistically significant relationship, as determined by the OR, between early total IgE levels and skin prick positivity, a relationship that has been described for cord total IgE elsewhere (10, 21). However, observing a statistically significant OR does not equate to a good screening measure. In the Isle of Wight study, Tariq et al. found that the PPV of elevated cord total IgE for the development of aeroallergen sensitization at 4 yr of age was 34.8% (27). Similarly, the MAS-90 study found the PPV to be only 48% (2). These figures are comparable with the PPV in this study of 41.2%.

There are several ways that one could attempt to improve the ability to predict which children develop subsequent atopy: (i) consider a wider range of atopic outcomes; (ii) use a better screening parameter measured in early life; or (iii) focus on a high-risk group of children.

Atopic outcomes

We have previously looked at the predictive value of these total IgE measurements on visible eczema status at 5 yr of age (13). The 12-month IgE data again performed better; however, the PPV was only 29% with a population prevalence of eczema of 13.8% in the cohort. This, perhaps, reflected the heterogeneous nature of atopic dermatitis. Flohr et al. recently concluded that up to two-thirds of persons with atopic dermatitis are not atopic (28).

Martinez et al. found no association between cord total IgE and a later history of wheezing (29). An elevated IgE level was found at 9 months of age amongst persistent wheezing children but not those with transient early wheezing or late onset wheezing. Thus, IgE at 9 months of age was related to wheezing prognosis but not to later incidence of wheezing. This finding was consistent with our eczema study

that found no association between IgE levels and late onset eczema.

We expected that total IgE might predict subsequent atopy better than eczema or wheezing given that atopy is 'a clinical definition of an IgE antibody high responder' (4). However, the predictive value in this study was not greatly higher. This may be because total IgE itself is not a sufficiently good screening tool. The WAO paper stresses that in the context of IgE-mediated allergy, IgE refers to antibody to an allergen and that 'there is no known allergy-related biological activity of non-antibody active IgE molecules: thus, allergy cannot be defined on the basis of an increased level of IgE, often referred to as total IgE...' (4). However, this is perhaps overly dismissive in that it is well recognized the proportion of specific IgE within the total IgE pool can vary considerably, from 50% to 60% in some cases of allergic rhinitis to <2% in IgE-mediated 'atopic' dermatitis (30).

Better screening parameter measured in early life

Given that total IgE performs poorly as a screening test for atopy, researchers have sought other immunological measurements. Logic would dictate that specific IgE to inhalant and/or food allergens measured early in life would predict subsequent atopy better. Other parameters investigated have included cytokine production by peripheral blood mononuclear cells (31), lymphocyte proliferation assays (32) and CD30/CD23 levels (33). Wald et al. has observed that it is not widely recognized that a risk factor must be very strongly associated with a disorder if it is to be a worthwhile screening test (34). As yet there is not a sufficient body of evidence to recommend any particular parameter.

High-risk group of children

An alternative to using a different screening parameter is to selectively screen a high-risk group. Tariq et al. used a high-risk approach by combining paternal atopy with elevated cord IgE and the predictive capacity was substantially increased (PPV: 77.8%; 27). Conversely others have found a maternal rather than a paternal history of atopy to be a stronger risk factor for subsequent atopy in a child (35, 36). In our study, combining family history and elevated IgE level made virtually no difference in improving the ability to identify children who will become atopic and this finding was consistent with the MAS-90 study where com-

binning elevated cord total IgE with a family history of allergy actually reduced the PPV (one parent atopic – 25%, both parents atopic – 30%; 7). Even if a dramatic improvement in PPV had been found, it is important to realize that this accounts for only a small proportion of children.

In conclusion, as with predicting visible eczema, early life measurements of total IgE appear to have little role in predicting subsequent atopy as defined by skin prick tests, regardless of a family history of allergy.

Acknowledgments

The authors are extremely grateful to all the mothers who took part and to the midwives for their cooperation and help in recruitment. The whole ALSPAC study team comprises interviewers, computer technicians, laboratory technicians, clerical workers, research scientists, volunteers and managers who continue to make the study possible. This study could not have been undertaken without the financial support of the Medical Research Council, the Department of Health, the Department of the Environment, the Wellcome Trust and other funders.

The ALSPAC study is part of the WHO initiated European Longitudinal Study of Pregnancy and Childhood. Dr Perkin held a Wellcome Research Training Fellowship in Clinical Epidemiology (grant number: 056906/Z/99/Z).

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