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Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study

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Clinical and Experimental Allergy

Summary

Background Studies of Australian infants have reported that more than 80% of those with moderate atopic eczema (AE) have high levels of IgE food sensitization (IgE-FS) that are commonly associated with IgE food allergy.

Objectives To explore the relationship between high levels of IgE-FS and AE in a large cohort of young children with eczema participating in a multi-centre, international study.

Methods Two thousand one hundred and eighty-four subjects (mean age 17.6 months, range 11.8–25.4; 1246 males) with active eczema from atopic families from 94 centres in 12 countries were studied. Clinical history, Scoring Atopic Dermatitis index as a measure of eczema severity and CAP-FEIA measurements for total IgE and IgE antibody levels to cow milk, egg and peanut were entered into a database. If CAP-FEIA levels exceeded previously reported age-specific cut-off levels for 95% positive predictive values (PPVs) for food allergy, subjects were defined as having high-risk IgE-FS (HR-IgE-FS).

Results Serum was available from 2048 patients; 55.5% were atopic. The frequency of HR-IgE-FS to milk, egg and/or peanut was the greatest in patients whose eczema developed in the first 3 months of life and the least in those whose eczema developed after 12 months ($P < 0.0001$). In a regression analysis to allow for potential confounding factors, children with HR-IgE-FS had the most severe eczema and the youngest age of onset ($P < 0.001$); 64% of infants with severe eczema of onset-age < 3 months had HR-IgE-FS.

Conclusion Early-onset severe eczema in infancy was associated with HR-IgE-FS.

Clinical implications Food allergies should be routinely assessed in infants with moderate or severe eczema.

Capsule summary In eczematous infants, the earlier the age of onset, and the greater the severity of eczema, the greater the frequency of associated high levels of IgE-FS.

Keywords atopic eczema, food hypersensitivity, food-specific serum IgE antibody, IgE food sensitization, infants

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Introduction

Infantile atopic eczema (AE) is a chronic, relapsing and pruritic inflammatory disease of the skin that is frequently associated with allergic sensitization, raised serum IgE levels and a family history of atopic diseases [1]. AE affects 28% of Australian infants [2], and 9.4% of infants have AE of moderate severity requiring at least 6 weeks of topical steroid treatment in the first 12 months of life [2]. This prevalence is similar to that in European [3, 4] and

British studies [5, 6]. The impact of AE on families and the cost of treatment are greater than for juvenile diabetes mellitus [7].

In Australian infants with AE, the risk of having IgE-mediated food allergy (IgE-FA) is increased 5.9-fold when compared with control subjects [2] and more than 80% of those with severe AE have IgE-FA to cow's milk, egg and/or peanut [8]. The strength of this association between IgE-FA and AE increased with increasing severity of AE [2]. The association between high levels of IgE food

sensitization (IgE-FS) and AE was confirmed in a further study of infants referred to a Dermatology Department [9]. Ninety percent of these infants had high levels of IgE-FS to milk, egg or peanut, levels invariably associated with challenge-proven food allergy, when assessed by *in vivo* or *in vitro* methods [9]. Despite these findings and an earlier report from a university-affiliated dermatology clinic that demonstrated IgE-FA in about one-third of young children with AE [10], the relationship between IgE-FA and AE has remained an area of debate [11, 12].

In vivo and *in vitro* methods are being increasingly used as a surrogate for the diagnosis of IgE-FA. These rely on the association between large skin prick test (SPT) weal diameters and/or high levels of IgE antibodies to specific foods and the presence of challenge-proven IgE-FA. These novel diagnostic criteria are accepted as markers of IgE-FA in centres where these levels have been validated against food challenges [13, 14]. Their use has significantly reduced the need to undertake diagnostic food challenges [10, 13–20].

In the present investigation, we used *in vitro* markers of IgE-FA validated by three centres experienced in the investigation of infants and young children with food allergy [13, 16–18] to measure the strength of association between high levels of IgE-FS and eczema. However, because these markers had not been validated as evidence of IgE-FA by all the centres in this study, we designated such patients as having high-risk IgE-FS (HR-IgE-FS).

We tested the validity of the strong association between HR-IgE-FS, the early onset and the severity of eczema found in Australian infants [2, 8, 9] on a large cohort of young children with eczema enrolled in an international study.

Methods

Study population

A population of 2222 infants born between April 2000 and March 2003 were screened for recruitment into a randomized clinical trial, the Early Prevention of Asthma in the Atopic Child (EPAAC) study. They were aged between 11.5 and 25.5 months (mean 17.6), had active AE and a positive family history for atopy and/or asthma. The trial was designed to test the effect of a new-generation antihistamine, levocetirizine, on the onset of asthma. The current study is an analysis of the screening data collected between March 2002 and March 2004 before randomization into the EPAAC study.

Atopic eczema and disease severity

The severity of eczema was assessed by the Scoring Atopic Dermatitis (SCORAD) index, a standard tool that measures the extent of the body area involved and the intensity of

symptoms [21]: scores <25 define mild AE; 25–50 moderate AE and >50 severe AE. Investigators were trained for using the SCORAD to ensure uniformity of the assessments. The use of SCORAD by non-dermatologists has been validated previously in a paediatric population [21]. For the purposes of this study, SCORAD results were divided into quartiles: Q1 ≤ 22.5; 22.5 < Q2 ≤ 31.2; 31.2 < Q3 ≤ 41.3; Q4 > 41.3.

Immunoglobulin E measurements

Total and specific serum IgE antibodies were measured in three central laboratories by the Pharmacia ImmunoCAP fluorescence enzyme immunoassay technology (Pharmacia Diagnostics, Uppsala, Sweden) for the following eight allergens: mixed grass pollen, mixed tree pollen, house dust mites (HDMs), cat, *Alternaria*, egg white, peanut and milk. The lower and upper detection limits were 0.35 and 100 kU_A/L for specific IgE, and 0.35–10 000 kU/L for total IgE. Unless otherwise stated, a specific IgE test was considered to be positive if ≥ 0.35 kU_A/L. The reproducibility between the central laboratories was tested by measuring IgE antibody levels on 40 samples each for grass pollen and HDM. Specific IgE antibody levels were expressed as Pharmacia classes. The results were identical, except for two samples, where the concentrations were close to the detection limit.

Definitions

Atopy: present if any allergen-specific IgE level was ≥ 0.35 kU_A/L.

IgE sensitization: the demonstration of IgE antibodies to allergens by SPT or measurement of serum IgE antibody levels.

HR-IgE-FS: high levels of IgE antibodies to common foods in subjects where no adverse reaction to a food has been reported or exposure has not taken place.

IgE-FA: a documented IgE-associated adverse clinical reaction to a food.

Acute urticaria: urticaria of rapid onset and of a short duration.

Criteria for identification of high-risk immunoglobulin E food sensitization

Three predictive reference decision points for the *in vitro* diagnosis of HR-IgE-FS by CAP-FEIA were available. These decision points were based on those validated for the diagnosis of IgE-FA to cow milk, egg and peanut by food challenge [9, 13, 16–18] in specific studies. The first, for cow milk, was based on the 90% positive predictive value (PPV) for IgE-FA in children <1 year of age: ≥ 2.5 kU_A/L (90% PPV, sensitivity 48%, specificity 95%) [16]. The second, for egg allergy for children <2 years,

was 0.35 kU_A/L (94% PPV, sensitivity 91%, specificity 77%) [17]. The diagnosis of IgE-FA to peanut was based on reference values for older children, mean age 3.8 years: ≥ 14 kU_A/L (95% PPV, sensitivity 57%, specificity 100%) [18]. It was not possible in this study to document the frequency of adverse food reactions in subjects with these levels.

Statistics

Descriptive statistics were reported in a standard manner (number and proportion, mean and/or median and standard deviation). Measures of association were estimated by multiple logistic regressions. Candidate confounding factors were selected based on the current literature. They included country, age, sex, birth weight, maternal age, a family history of atopy, presence of siblings, breastfeeding, parental smoking, day care, exposure to pet animals and SCORAD total index. The candidate factors were first evaluated by univariate analysis and were only retained in further analyses if they were statistically significant in a consistent way. In subsequent multivariable analyses, the set of confounding factors was further optimized for each outcome, separately. Odds ratios (ORs) were estimated by logistic regression (Proc Logistic, SAS 8.2, SAS Institute Inc., Cary, NC, USA), either without any factor other than exposure (raw OR) or with the confounding factors (adjusted OR).

Ethical approval: The parents of all children involved in the study gave their informed consent. The research protocol was approved by the Ethics Committees in the institutions of every participating investigator.

Results

Of the 2222 children screened, 2184 children in 94 study centres from 12 countries had at least one outcome and one factor but not all results were available on all the participants; 92.1% of the study subjects were Caucasian. The mean age at the screening visit was 17.6 (range 11.8–25.4) months, and 57.1% were male. The mean age of onset of eczema was 4.3 months (median 3.1).

The mean total SCORAD index for the study population was 33 (median 31.0; range 0.6–93.8), and the proportion of children in the moderate/severe eczema category (SCORAD ≥ 25) was 68%. In Fig. 1, the distribution of the population according to their SCORAD index at the time of joining the study is shown (see Fig. 1).

Before joining the study, 68.2% of the cohort had ingested cow's milk, 68.8% egg and 23.4% peanut. There was no significant association at a country level between food consumption and IgE sensitization to these allergens but there was a negative association between ingestion rates and sensitization to cow milk and peanut.

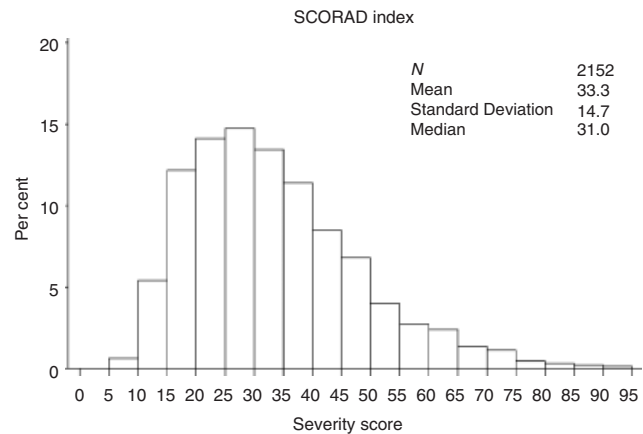


Fig. 1. Distribution of eczema severity for the study population. The mean total Scoring Atopic Dermatitis (SCORAD) index was 33 (median 31.0; range 0.6–93.8) and the proportion of children in the moderate/severe eczema category (SCORAD ≥ 25) was 68%.

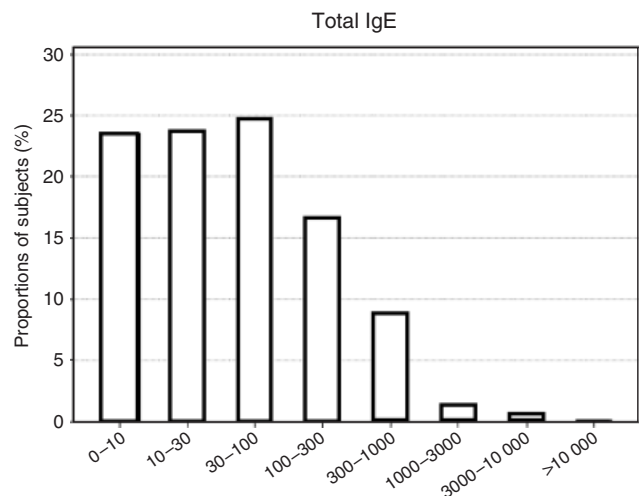


Fig. 2. Distribution of total IgE levels for the study population. Total IgE was elevated (>30 kU/L) in 52.9% of the children.

Complete specific IgE test results were available on 2048 subjects, of whom 55.5% were sensitized to at least one of the tested allergens i.e. were atopic; 48.6% were sensitized to food allergen(s) (6.9% were sensitized to inhalants alone 27.4% to milk, 41.9% to egg and 24.4% to peanut). The correlation co-efficient between total IgE and the number of positive tests for specific IgEs was high ($R = 0.70$). Total serum IgE results were available for 2116 patients. Elevated total serum IgE (>30 kU/L) was detected in 52.9% of the children. The distribution of total IgE levels in the population is shown in Fig. 2.

The frequency of HR-IgE-FS was examined according to the reported age of onset of AE (Table 1). From Table 1, the frequency of HR-IgE-FS was the greatest in patients whose eczema developed in the first 3 months of life and gradually decreased with increasing age of onset of AE.

Table 1. Proportion of children with high-risk IgE food sensitization (HR-IgE-FS) according to age of onset of atopic eczema

Age of onset	Total	Egg	Milk	Peanut	Any food
Onset <3 months	995	494 (49.7%)	135 (13.6%)	56 (5.7%)	499 (50.3%)
Onset 3–5 months	563	245 (43.6%)	62 (11.0%)	34 (6.1%)	249 (44.6%)
Onset 6–11 months	352	94 (26.7%)	19 (5.4%)	10 (2.9%)	96 (27.4%)
Onset >12 months	148	32 (21.6%)	4 (2.7%)	1 (0.7%)	32 (21.80%)
Total*	2058	865 (42.1%)	220 (10.7%)	101 (4.9%)	876 (42.7%)

*Total refers to the proportion of the total population with HR-IgE-FS.

Table 2. Number of children in each quartile of severity of atopic eczema (AE) (by SCORAD) with high-risk IgE food sensitization (HR-IgE-FS), according to age of onset of AE

SCORAD quartile	Age of onset (months)	Number with HR-IgE-FS	Number in quartile	% of HR-IgE-FS
Q1 ≤ 22.5 IgE = 115 kU/L	Onset <3	92	237	39
	Onset 3–5	53	138	38
	Onset 6–11	20	100	20
	Onset ≥ 12	10	42	24
	All	175	517	34
22.5 < Q2 ≤ 31.2 IgE = 126 kU/L	Onset <3	107	249	43
	Onset 3–5	54	137	39
	Onset 6–11	17	91	19
	Onset ≥ 12	9	34	26
	All	187	511	37
31.2 < Q3 ≤ 41.3 IgE = 153 kU/L	Onset <3	128	239	54
	Onset 3–5	65	142	46
	Onset 6–11	27	93	29
	Onset ≥ 12	6	36	17
	All	226	510	44
Q4 > 41.3 IgE = 355 kU/L	Onset <3	172	267	64
	Onset 3–5	77	141	55
	Onset 6–11	32	67	48
	Onset ≥ 12	7	35	20
	All	288	510	56

SCORAD, Scoring Atopic Dermatitis.

It was the least in those whose AE developed after the age of 12 months. There was a statistically significant association between the early age of onset of eczema and HR-IgE-FS (χ^2 85.6, $P < 0.0001$ for any HR-IgE-FS and age of onset of eczema). Of the children with HR-IgE-FS, 99% were to egg, 25% to cow's milk and 11.5% to peanut. There were only 11/876 (1.3%) children with HR-IgE-FS to cow's milk and/or peanut without HR-IgE-FS to egg.

In order to explore these interactions further, the SCORAD results were divided into quartiles and related to the frequency of an HR-IgE-FS and the reported age of onset of eczema. In Table 2, the number of children in each quartile of severity of AE (by SCORAD) with HR-IgE-FS, according to age of onset of AE, is shown. There was an association between eczema severity and the frequency of HR-IgE-FS in infants whose eczema developed before, but not after 12 months of age. Thus, for infants whose eczema started before 3 months, only 39% of those with mild eczema (in the first quartile) had HR-IgE-FS, whereas 64% of those with severe AE (in the fourth quartile) had

HR-IgE-FS. A similar trend between eczema severity and the frequency of HR-IgE-FS was seen for eczema age of onset 3–5 and 6–11 months, but not for those whose eczema developed after 12 months of age. The relationship between eczema severity by SCORAD quartiles and the frequency of HR-IgE-FS to any food according to the age of onset of eczema is also shown in Fig. 3. In a regression analysis to allow for the major confounding factors (age, gender, country, SCORAD, age of onset), the children with HR-IgE-FS had the most severe eczema and the youngest age of onset ($P < 0.001$), thus confirming the non-adjusted analysis. The number of parent-reported adverse food reactions was low and insufficient to present meaningful information. However, attacks of acute urticaria (commonly associated with IgE-FA in infancy) were recorded. There was an association between eczema severity and a history of urticaria and an increased risk of urticaria with sensitization. The proportion of children with urticaria was 4.7% in those not sensitized, 12.0% in those mono-sensitized and 22.25% in those

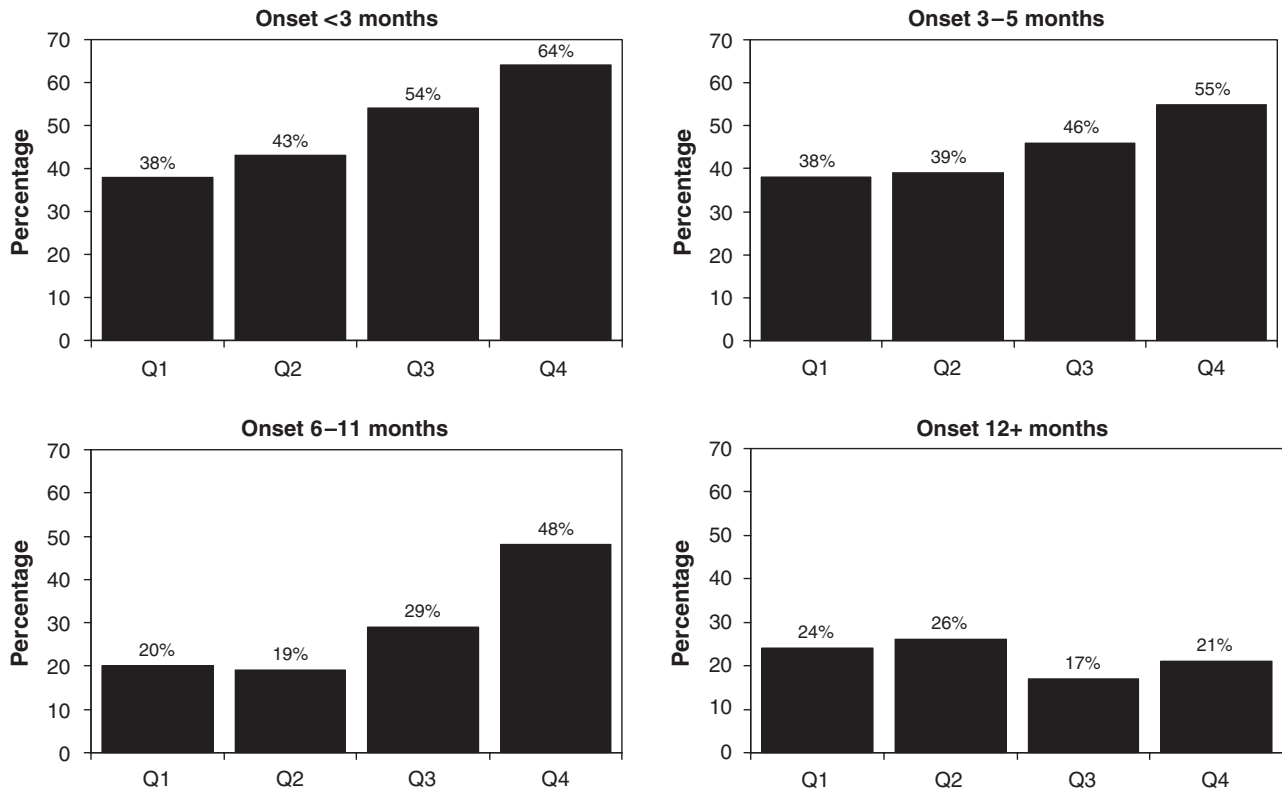


Fig. 3. The relationship between eczema severity and the frequency of high-risk IgE food sensitization (HR-IgE-FS) to foods according to the age of onset of eczema is shown. The children with the most severe eczema (Q4), and the earliest age of onset (3 months), had the greatest frequency of HR-IgE-FS.

Table 3. Proportion of children with a history of urticaria in relation to specific IgE levels

	Specific IgE < HR-IgE-FS	Specific IgE ≥ HR-IgE-FS	Odds ratio	χ^2
Egg	86/1227 (7.0%)	179/887 (20.2%)	3.4	$P < 0.001$
Milk	204/1885 (10.8%)	60/227 (26.4%)	3.0	$P < 0.001$
Peanut	220/1999 (11.5%)	33/104 (31.7%)	3.6	$P < 0.001$

Young children with high-risk IgE food sensitization (HR-IgE-FS) to milk, egg and/or peanut had a significantly higher incidence of reported acute urticaria ($P < 0.001$) than those with lower levels of sensitization.

polysensitized. Sensitization to peanut had the greatest effect on the frequency of urticaria; 27% with peanut IgE had a history of urticaria compared with 8% of those without sensitization to peanut. The frequency of reported acute urticaria was significantly greater in subjects who had HR-IgE-FS to cow's milk, egg and/or peanut than those with lower levels ($P < 0.001$) (see Table 3).

Discussion

In this international study of a large cohort of young children with eczema assessed between 11.5 and 25.5 months of age, up to 64% of those whose eczema

commenced before 3 months of age had HR-IgE-FS to egg and/or cow's milk and/or peanut. Of those whose eczema developed before 12 months of age, the frequency of HR-IgE-FS increased with increasing eczema severity. However, in those children whose eczema commenced after 12 months of age, the overall frequency of HR-IgE-FS was only 22%, and the relationship between increasing eczema severity and increasing HR-IgE-FS frequency was lost. In a regression analysis to allow for potential confounding factors (gender, country, age of onset, SCORAD), the children with HR-IgE-FS had the most severe eczema and the youngest age of onset ($P < 0.001$). Thus, it is in infants with eczema developing in the first 12 months that IgE-FS is likely to have an important role.

While 64% of the children with severe eczema that had developed within the first 3 months of life had HR-IgE-FS, 86% of Australian infants with eczema of similar severity had HR-IgE-FS to milk, egg or peanut [9]. However, the methodology of the two studies was different. The Australian infants were assessed for HR-IgE-FS by SPT, a more sensitive methodology [22], and at a younger age. In addition, the differences in the frequency of HR-IgE-FS between these studies may also reflect spontaneous remission of food sensitization in the second year of [23, 24] life despite persistence of eczema.

In an international study of this magnitude, many factors may influence the results. The multiple logistic regression took into account a number of potential confounding factors including age, gender and country of origin, but there are other limitations. Eczema was assessed at only one point in time and data were not available on infant feeding history, the treatment that patients received before joining the study and whether dietary exclusion had been implemented. These factors may have influenced eczema severity. In addition, the number of subjects and method of recruitment varied between centres, as did the rates of ingestion of the foods in different countries and the rates of sensitization to those foods. Because of these limitations, we pooled the data to test our hypothesis of the relationship between the age of onset, severity of eczema and sensitization to common food allergens.

Another limitation was that none of our patients underwent formal food challenges and hence it was not possible to examine directly the relation between IgE-FA and eczema. We designated our subjects as having HR-IgE-FS based on CAP-FEIA decision points for predicting positive food challenges [9, 13, 16–18]. These decision points had been validated in three centres, including one participating in this study [9, 13]. However, because of the high specificity of the cut-off points for HR-IgE-FS we have used, it is likely that some children who have IgE-FA are among those whose levels are below these cut-offs.

In children with AE, positive food challenges exacerbating eczema flares are associated with activation of eosinophils [25], mast cells [25] and circulating T lymphocytes [25], and peanut-derived epitopes have been found on T lymphocytes from skin biopsies of an infant with AE [26]. In a murine model, eczema-like lesions were induced in one-third of sensitized mice after ingestion of small amounts of cow milk and peanut allergens [27]. Clinical studies have demonstrated exacerbations of eczema during and remission following DBPCFC [25], and the benefit of a maternal low-allergen diet of breastfeeding mothers, in reducing the prevalence of eczema in breastfed infants [28]. Together, these studies highlight an important role of food allergy in the pathogenesis of eczema in childhood. Our findings using HR-IgE-FS levels as a surrogate for IgE-FA suggest that this effect is the greatest in young infants.

It is unlikely that we have overestimated the strength of the association between hypersensitivity to foods and eczema in infancy as we studied only three major food allergens. IgE hypersensitivity to other foods may have been missed. In addition, in 10% of infants and children, eczema is associated with non-IgE hypersensitivity to foods [29].

A number of genetic markers including CTLA4, TLR9/2, CD14, SPINK5, CARD4, Fc ϵ RI β , PHF11 and MCC [30]

have been linked to atopic disorders. Recent investigations point to a very strong association between eczema and two loss-of-function variants in the gene encoding Filaggrin (FLG), a regulator of keratinization [31], and thus cutaneous integrity. The FLG mutations were most strongly linked with IgE-associated eczema but were not associated with early-onset eczema [31]. Thus, this skin-barrier mechanism may not be of major significance in infants with early-onset eczema. Further studies are needed to explore the genomic markers of these eczema phenotypes. Our previous studies suggested a linkage between AE in young children and a region within 5q31 but not within the IL4 promoter polymorphism –590C/T [32, 33] but these studies did not focus on infants with early-onset eczema. The overlap between susceptibility regions for psoriasis and eczema heightens the complexity of the genetic basis of AE [30]. Our findings from this and other studies suggest that in infants with eczema, IgE-FA may be a dominant factor [2, 8, 9, 34].

The community prevalence of eczema of moderate severity in infants is about 10% [2, 4–6]. Our findings lend support to the important association between high levels of IgE sensitization to dietary antigens and eczema in early infancy [2, 8, 9]. Further studies are now required to define precisely the role of food allergens in the pathogenesis and management of eczema presenting in the first 12 months of life.

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