

ORIGINAL ARTICLE

Clinical Mechanisms in Allergic Disease

Relevance of low specific IgE levels to egg, milk and peanut in infancy

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Abstract

Background: IgE sensitization is usually associated with allergy-related diseases, but may also occur in asymptomatic individuals. The clinical importance of IgE antibody concentrations in the interval 0.1-0.34 kU/L in early life in relation to allergy development is poorly evaluated.

Objective: To assess the relevance of low specific IgE (s-IgE) to hen's egg, cow's milk and peanut at 6 months of age for development of sensitization and allergy-related disease during early childhood.

Methods: s-IgE concentrations to relevant allergens from blood samples taken at 6 months and 1, 2 and 5 years from children in the prospective ALADDIN cohort were divided into three categories: non-sensitized (<0.1 kU/L), low sensitized (0.1-0.34 kU/L) and sensitized (≥ 0.35 kU/L) and allergy-related disease assessed.

Results: A total of 372 children were included in this study. Compared with non-sensitized children at 6 months of age, children with low levels of allergen specific IgE (0.1-0.34 kU/L) to food allergens, especially to egg, at 6 months of age were associated with development of sensitization to aeroallergens at 5 years of age (10/14 [71%] vs 39/250 [15%]). In addition, children with low levels to egg or milk at 6 months were more often sensitized to the respective allergen at 1 year of age and, regarding low levels to egg, also to the development of eczema (6/18 [33%] vs 29/292 [10%]).

Conclusion & Clinical Relevance: IgE antibody concentrations in the interval 0.1-0.34 kU/L to food allergens in infancy seem to increase the probability of sensitization to aeroallergens and, regarding low levels to egg, also of eczema during early childhood. Thus, IgE levels during the first year of life, although below 0.35 kU/L, can provide additional allergy-related prognostic information.

KEYWORDS

birth cohort, food allergy, immunoglobulin E, infancy, lifestyle, relevance

1 | INTRODUCTION

The presence of allergen specific IgE antibodies (s-IgE), that is IgE sensitization, is common in early infancy and related to clinical allergy.¹ Sensitization during infancy commonly concerns food allergens, especially hen's egg (egg) and cow's milk (milk).^{1,2} Such antibodies are

often down-regulated over time by the developing immune system,^{3,4} and consequently, clinical tolerance to egg and milk is usually achieved around school start.^{2,5} Therefore, monitoring changes in IgE levels in allergic individuals over time is important and has been proposed as a diagnostic tool to study the development of tolerance or further sensitization/s and emergence of allergy-related symptoms.^{1,6}

There is a quantitative relationship between s-IgE concentration and allergic symptoms, with the probability of IgE-related allergic symptoms increasing with higher s-IgE levels.⁷ Most published studies use 0.35 kU/L as a cut-off to define sensitization. However, routine IgE antibody quantification is today able to detect concentrations down to 0.1 kU/L. The association between IgE concentrations to common food allergens in the interval 0.1–0.34 kU/L and allergic disease is not well understood.¹

The present study examined IgE to common food allergens in the interval 0.1–0.34 kU/L in infancy by following the development and variation in s-IgE concentrations to egg, milk and peanut prospectively in children within a birth cohort from 6 months of age and at 5 years of age, in relation to IgE to food and aeroallergens and doctor's diagnosis of allergy-related disease.

2 | METHODS

2.1 | Study design

This study was based on the ALADDIN cohort, described in detail by Stenius et al.^{8,9} In brief, a total of 552 families were recruited between 2004 and 2011 at anthroposophic and conventional Maternal Healthcare Centres in the Stockholm area, Sweden. Children were excluded from the cohort study if they were born preterm (<gestational week 36). The families were divided into three groups, anthroposophic, partly anthroposophic and non-anthroposophic, depending on degree of adherence to an anthroposophic lifestyle.⁹ The families completed detailed questionnaires about lifestyle, background, diet and health at enrolment and repeatedly thereafter at health examinations of the children at 2 and 6 months and 1, 2 and 5 years of age.

2.2 | Inclusion and outcomes

For inclusion in this prospective study, a child had to contribute with a blood sample at 6 months and for comparison as primary outcome at least at one other follow-up at 1, 2 and 5 years of age for assessment of changes in s-IgE antibody concentration. Doctor's diagnosis of allergy-related disease was used as secondary outcome, based on parental report at the 5-year follow-up: "Has your child ever got an asthma, eczema, allergic rhinoconjunctivitis or food allergy diagnose by a doctor?"

The study was approved by the local ethics committee in Stockholm (approval numbers 474/01, 07-01-2002 and 329-32, 21-02-2012). Written informed consent was obtained from all parents.

2.3 | Blood samples

Blood samples from the children were obtained at 6 months and 1, 2 and 5 years of age and from the parents at inclusion, during the third trimester or early infancy. All blood samples were collected in sodium heparin tubes, and plasma was separated and stored at

–20°C. Specific IgE for milk, egg, peanut, cat, dog, birch and timothy was analysed in child plasma by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) at 6 months and 1 and 2 years. Child samples at 5 years were analysed for a mixture of food allergens (egg, milk, peanut, soy, cod and wheat) by fx5 (Thermo Fisher Scientific, Uppsala, Sweden) and aeroallergens (birch, timothy, mugwort, cat, dog, horse, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Cladosporium herbarum*) by Phadiatop™ (Thermo Fisher Scientific, Uppsala, Sweden). If fx5 and/or Phadiatop™ value was ≥ 0.35 kU/L, IgE levels for the aforementioned allergens were analysed separately in the sample when plasma was available. Parental samples were analysed for aeroallergens by Phadiatop™.

2.4 | Statistical analysis

Comparisons were done separately for s-IgE antibody concentrations to egg, milk and peanut, and to IgE to fx5 and Phadiatop™. The concentrations were divided into three categories: children with a s-IgE antibody concentration below the limit of quantification (0–0.09 kU/L) were defined as non-sensitized, children with s-IgE in the interval 0.1–0.34 kU/L were defined as having low IgE sensitization, and children with IgE concentration ≥ 0.35 kU/L were defined as sensitized.

We used Fisher's exact test to compare the proportion of sensitized individuals (≥ 0.35 kU/L [blue in Figure 1–3]) at 1, 2 and 5 years between the groups that at 6 months were classified as low sensitized (0.1–0.34 kU/L [yellow]) compared with non-sensitized (0–0.09 kU/L [grey]) and sensitized (≥ 0.35 kU/L [blue]). In the same way, pairwise comparisons of the proportion of allergy-related doctor's diagnoses [Yes vs No] were made between children who at 6 months had IgE values 0.1–0.34 [yellow in Figures 1–3] vs <0.1 [grey] and 0.1–0.34 [yellow] vs ≥ 0.35 kU/L [blue], respectively. Data analyses were performed using IBM SPSS Statistics, version 23, Illinois, USA, and <http://www.socscistatistics.com/tests/fisher/Default2.aspx>. A *P*-value < 0.05 was regarded statistically significant.

3 | RESULTS

Of the 552 children in the cohort, 372 met the inclusion criteria for this study, and information on doctor's diagnosis was available for 332 of them. Demographic data on the participating parents and children are presented in Table 1. The study population did not differ from the non-included population regarding heredity for allergic disease, maternal smoking during pregnancy, maternal age, maternal education, older siblings or outcome in child sensitization (data not shown). However, compared with the non-included population, significantly fewer anthroposophic families were included in the study, since a blood sample at 6 months was not obtained to the same extent in that group (data not shown). Thus, as exclusive breastfeeding is more common among anthroposophic mothers in the ALADDIN cohort,¹⁰ significantly fewer mothers breastfeeding fully at 6 months were included in

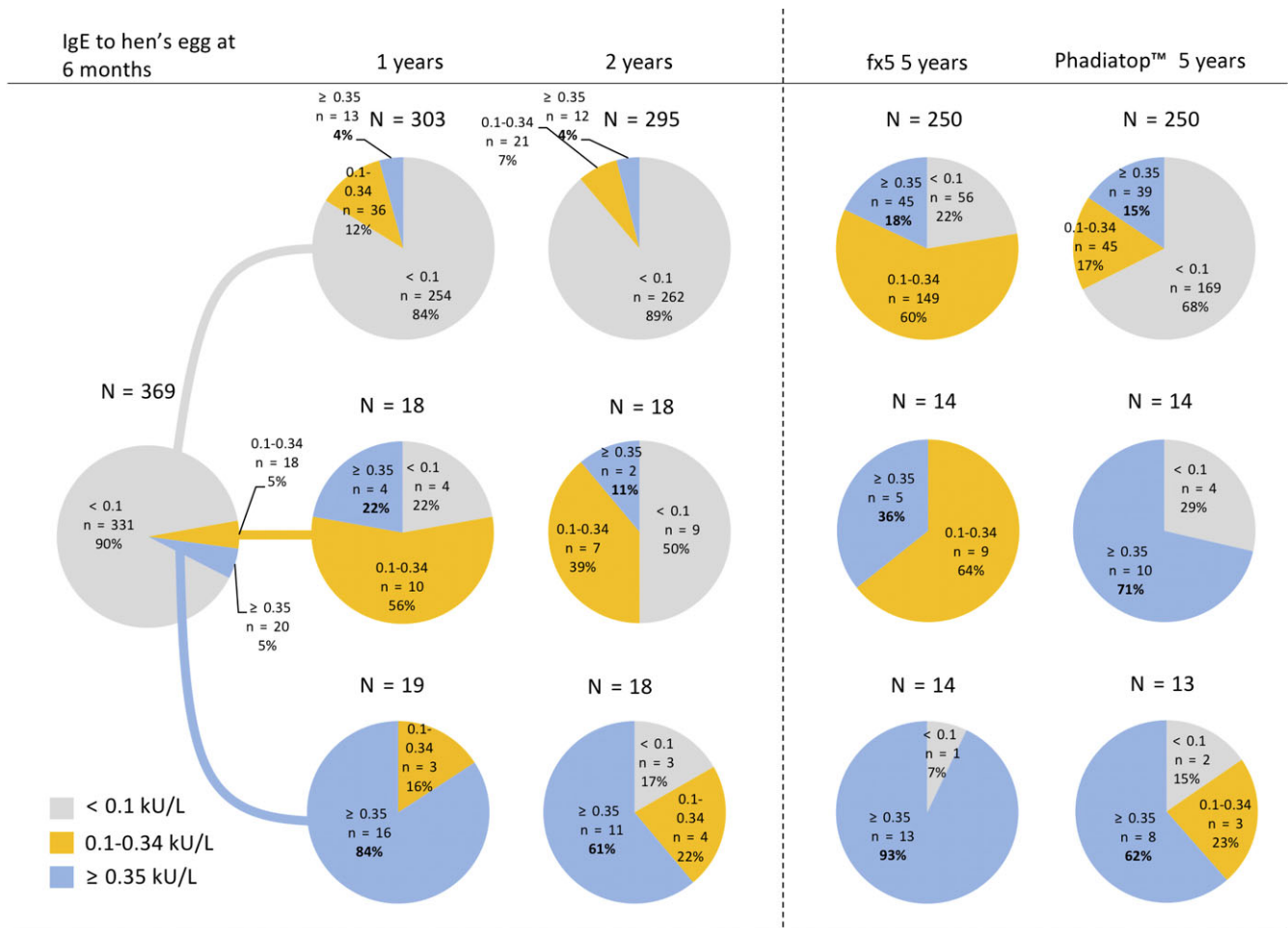


FIGURE 1 Development of IgE to egg during the first 2 y of life in children in three s-IgE concentration categories: non-sensitized <0.1 kU/L, low sensitized 0.1-0.34 kU/L and sensitized ≥0.35 kU/L. Circle diagram at 6 mos shows the distribution of these categories in the cohort. All other diagrams show the development into the same s-IgE categories from each of the original categories for egg, at 1 and 2 y, and for food allergens (fx5) and aeroallergens (Phadiatop™) at 5 y of age

this study (26% exclusively and 56% partly among those included; 45% exclusively and 77% partly among those non-included).

At 6 months, 11% of the children were sensitized to at least one of the seven allergens analysed. The proportion of sensitized children increased over time: 17% at 1 year, 18% at 2 years and 35% at 5 years of age (Table 1). About 10% of the children had ever got a doctor's diagnosis of asthma, eczema or food allergy, and 3% a doctor's diagnosis of allergic rhinoconjunctivitis (Table 1).

3.1 | Development of s-IgE to egg

3.1.1 | Children with IgE levels in the interval 0.1-0.34 kU/L to egg at 6 months

Eighteen children had s-IgE to egg in the interval 0.1-0.34 kU/L at 6 months, two of them also s-IgE to aeroallergens (Figure 1). At 1 year, four of these children had developed sensitization (≥0.35 kU/L) to egg, but thereafter the proportion of children both with low levels (0.1-0.34 kU/L) and being sensitized (≥0.35 kU/L) to egg

decreased. At 5 years, blood samples were available for 14 of the 18 children. None of them were sensitized (≥0.35 kU/L) to egg. However, 5 of 14 were sensitized (≥0.35 kU/L) to another food allergen, commonly to milk (3/14). Moreover, 10 of 14 children were sensitized (≥0.35 kU/L) to an inhalant allergen (six to cat and/or dog and four to birch, timothy and/or mite) at 5 years of age.

3.1.2 | Children with s-IgE ≥0.35 kU/L to egg at 6 months

At 6 months, 20 children were sensitized (≥0.35 kU/L) to egg. They were also to a high extent sensitized to egg up to 5 years, although the proportion decreased from 16/19 at 1 year of age to 6/14 at 5 years. In contrast to the group of children with IgE levels to egg in the interval 0.1-0.34 kU/L at inclusion, all but one of the children with IgE levels ≥0.35 kU/L to egg at 6 months had a sensitization ≥0.35 kU/L to any food allergen in the fx5 analysis at 5 years of age, with milk (8/13), egg (6/13) and wheat (6/13) being the most prevalent allergens. All six children sensitized to egg at 5 years were

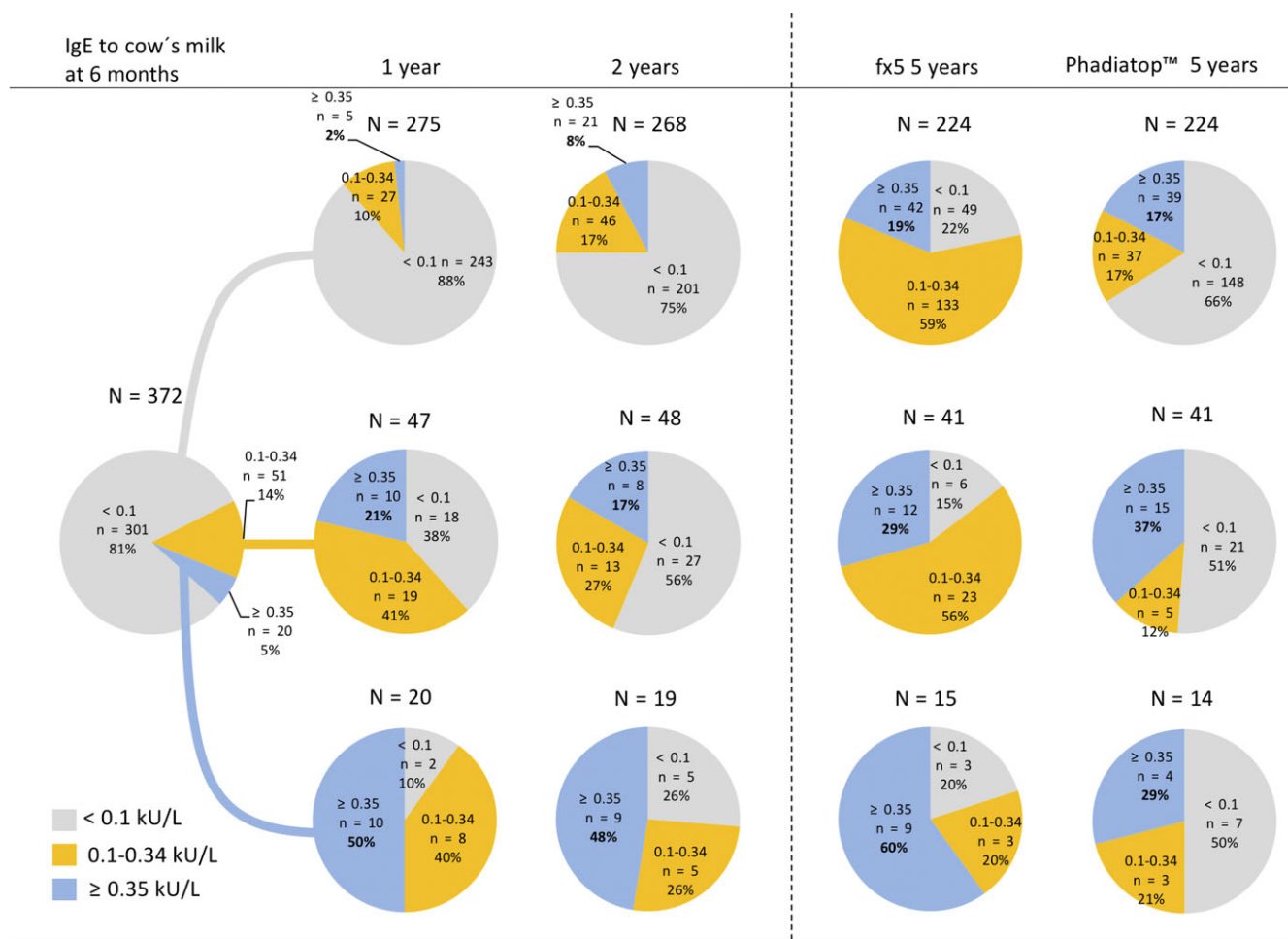


FIGURE 2 Development of s-IgE to milk during the first 2 y of life in children in three s-IgE concentration categories: non-sensitized <0.1 kU/L, low sensitized 0.1-0.34 kU/L and sensitized ≥ 0.35 kU/L. Circle diagram at 6 mos shows the distribution of these categories in the cohort. All other diagrams show the development into the same s-IgE categories from each of the original categories for milk, at 1 and 2 y, and for food allergens (fx5) and aeroallergens (Phadiatop™) at 5 y of age

also sensitized to milk. Besides, 8 of 13 children had IgE antibodies ≥ 0.35 kU/L to an inhalant allergen at 5 years of age, with birch (7/13), timothy (6/13) and/or dog (4/13) being most frequent.

3.2 | Associations between IgE to egg at 6 months of age and future sensitization

Blood from 16 of the 18 infants who had low levels (0.1-0.34 kU/L) to egg at 6 months of age could be analysed for IgE to aeroallergens at 5 years of age (Table 2). Having IgE in the interval 0.1-0.34 kU/L to egg at 6 months of age was significantly associated with being sensitized (≥ 0.35 kU/L) to egg at 1 year of age, and to aeroallergens at 5 years of age, compared to children with IgE < 0.1 kU/L to egg at 6 months of age (Table 2). Being sensitized (≥ 0.35 kU/L) to egg at 6 months of age was significantly associated with being sensitized (≥ 0.35 kU/L) to egg at 1 and 2 years of age, as well as being sensitized to any food allergen. However, IgE sensitization (≥ 0.35 kU/L) to egg at 6 months of age was not associated with sensitization to aeroallergens, at 5 years of age, in

contrast to those with IgE to egg in the interval 0.1-0.34 kU/L at 6 months of age (Table 2).

3.3 | Development of s-IgE to milk (Figure 2)

3.3.1 | Children with IgE levels to milk in the interval 0.1-0.34 kU/L at 6 months

s-IgE levels to milk in the interval 0.1-0.34 kU/L were present in 51 of 372 children at 6 months of age (three of them had also s-IgE to aeroallergens), a proportion that decreased over time. The proportion developing sensitization (≥ 0.35 kU/L) to milk at 1 year of age was 21%, and this proportion remained at around 20% throughout the follow-up period. At 5 years, blood samples were available for 41 of the 51 children of which 12 who at 6 months had IgE antibodies to milk in the interval 0.1-0.34 kU/L were sensitized (≥ 0.35 kU/L) to a food allergen, predominantly to milk (8/41), followed by egg (6/41) and wheat (5/41). At 5 years, 15 of 41 children were sensitized to an aeroallergen (eight to birch and seven to cat, dog and/or timothy).

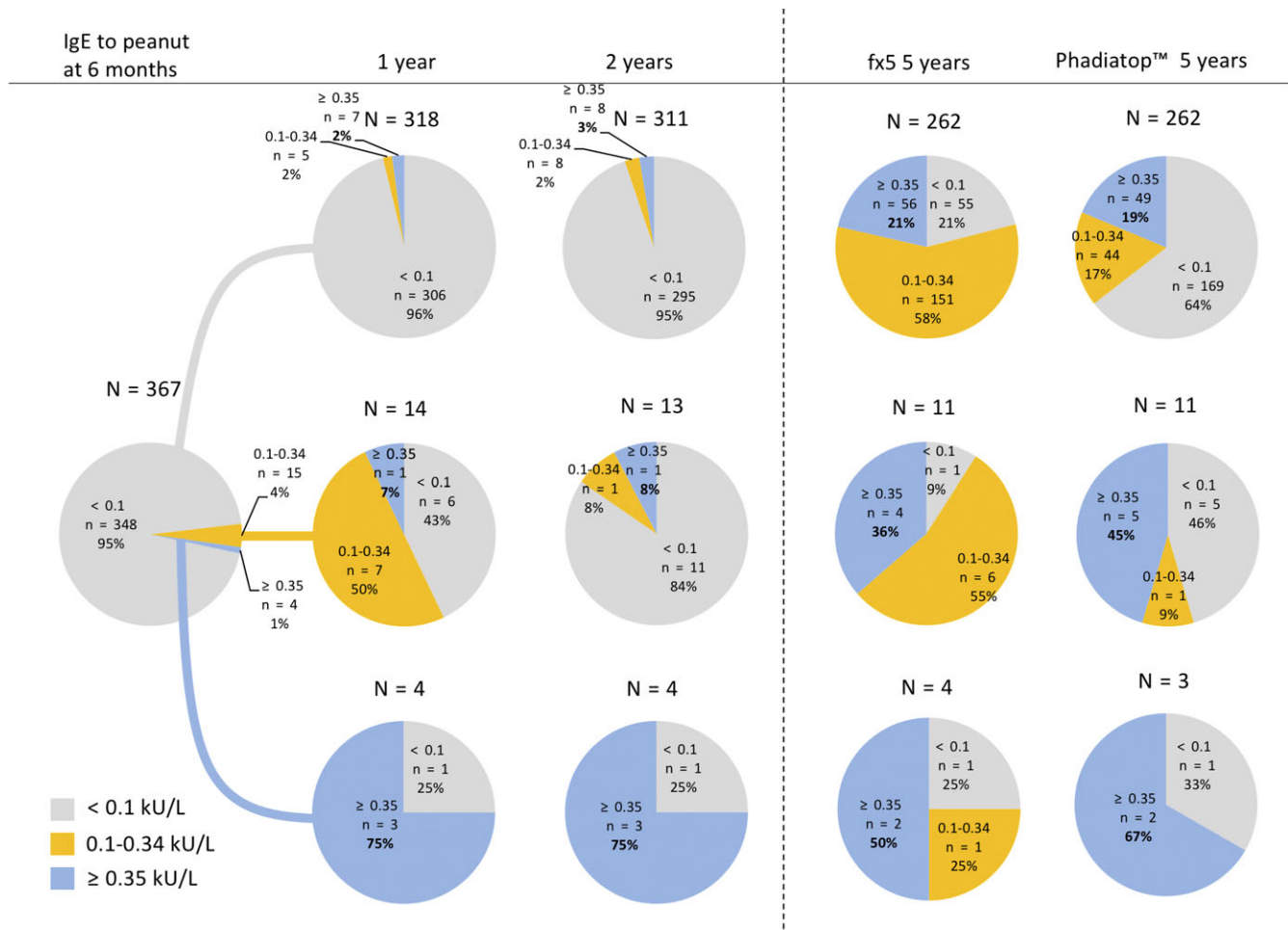


FIGURE 3 Development of s-IgE to peanut during the first 2 y of life in children in three s-IgE concentration categories: non-sensitized <0.1 kU/L, low sensitized 0.1-0.34 kU/L and sensitized ≥0.35 kU/L. Circle diagram at 6 mos shows the distribution of these categories in the cohort. All other diagrams show the development into the same s-IgE categories from each of the original categories for peanut, at 1 and 2 y, and for food allergens (fx5) and aeroallergens (Phadiatop™) at 5 y of age

3.3.2 | Children with s-IgE ≥0.35 kU/L to milk at 6 months

Twenty children were sensitized (≥0.35 kU/L) to milk at 6 months of age. Among these children, sensitization to milk decreased over time, to 4 of 14 children at 5 years. Nine of 15 children were sensitized (≥0.35 kU/L) to a food allergen at 5 years, mainly to milk (4), wheat (3) and egg (1), while 4 of 14 children with IgE ≥ 0.35 kU/L to milk at 6 months were sensitized to an aeroallergen at 5 years (including two to birch and timothy, and one to timothy only).

3.4 | Associations between IgE to milk at 6 months of age and future sensitization

Blood from 49 of the 51 infants having IgE to milk in the interval 0.1-0.34 kU/L at 6 months of age could be analysed for IgE to aeroallergens at 5 years of age (Table 2). Similar to egg, having IgE in the interval 0.1-0.34 kU/L to milk at 6 months of age was significantly associated with being sensitized (≥0.35 kU/L) to milk at 1 year

of age as well as being sensitized to aeroallergens at 5 years of age, compared to those with IgE <0.1 kU/L (Table 2). Being sensitized (≥0.35 kU/L) to milk at 6 months of age was significantly associated with being sensitized (≥0.35 kU/L) to milk at 1 and 2 years of age, and to any food allergen. However, being sensitized to milk at 6 months was not associated with sensitization (≥0.35 kU/L) to aeroallergens at 5 years of age (only three cases), in contrast to those with IgE to milk in the interval 0.1-0.34 kU/L at the same age (Table 2).

3.5 | Development of s-IgE to peanut

3.5.1 | Children with IgE levels in the interval 0.1-0.34 kU/L to peanut at 6 months

IgE concentrations to peanut in the interval 0.1-0.34 kU/L were present in 4% of the children (15/367). A similar decreasing trend in IgE to peanut as observed for egg and milk was seen (Figure 3). At 5 years, 4 of 11 of the children who at 6 months had IgE antibodies

TABLE 1 Characteristics of the participating families and allergy-related data on the children

	%	n/N
Family		
Mother's age (years, mean [min-max])	32	[17-50]
Mother University educated	50	186/370
Mother smoking during pregnancy	5.4	20/369
Parent (any) Phadiatop™ positive	61	220/362
Older siblings	66	241/366
Lifestyle		
Anthroposophic	20	73/372
Partly anthroposophic	43	161/372
Non-anthroposophic	37	138/372
Child		
Sex (Females)	50	187/372
Birth mode (caesarean section)	17	62/371
Breastfeeding 6 mo (exclusively)	26	96/371
s-IgE ≥ 0.35 kU/L at 6 mo (any)	11	40/372
s-IgE ≥ 0.35 kU/L at 1 y (any)	17	56/325
s-IgE ≥ 0.35 kU/L at 2 y (any)	18	61/333
Phadiatop™ and/or fx5 ≥ 0.35 kU/L at 5 y	35	96/278
Reported doctor's diagnosis (ever)		
Asthma	11	36/332
Eczema	12	41/330
Allergic rhinoconjunctivitis	3	8/326
Food allergy	8	26/323

to peanut in the interval 0.1-0.34 kU/L were sensitized (≥ 0.35 kU/L) to a food allergen (one to milk, one to egg and milk and one to milk, soy, wheat and peanut) and 5 of 11 to an aeroallergen, where birch was most frequent, followed by furred animals.

3.5.2 | Children with s-IgE ≥ 0.35 kU/L to peanut at 6 months

The proportion of children who were sensitized (≥ 0.35 kU/L) to peanut at 6 months of age was 1% (4/367), a proportion that remained stable during the follow-up period.

3.6 | Associations between IgE to peanut at 6 months of age and future sensitization

Having IgE in the interval 0.1-0.34 kU/L to peanut at 6 months of age was significantly associated only with being sensitized (≥ 0.35 kU/L) to aeroallergens at 5 years of age, compared to those with IgE to peanut < 0.1 kU/L (Table 2). Being sensitized (≥ 0.35 kU/L) to peanut at 6 months of age was significantly associated with being sensitized (≥ 0.35 kU/L) to peanut also at 1 and 2 years of age, compared to those with IgE to peanut in the interval 0.1-0.34 kU/L (Table 2).

3.7 | Association between development of s-IgE at 6 months and lifestyle

When restricting the statistical analyses to children belonging to the non-anthroposophic group, in order to assess an effect of lifestyle on the prospective associations between different s-IgE-interval, a similar pattern, although less significant, was shown. The only significant difference in this subgroup was that having IgE to egg in the interval 0.1-0.34 kU/L at 6 months of age was associated also with a higher proportion of children being sensitized to food allergen at 5 years of age compared to those having s-IgE < 0.1 kU/L.

3.8 | Association between s-IgE at 6 months and clinical disease

Throughout the study, a higher IgE level to egg, milk or peanut at 6 months of age was associated with a higher proportion of doctor's diagnosis of allergy-related disease (Table 3). This was, however, significant only for those having IgE to egg in the interval 0.1-0.34 kU/L regarding eczema, and subsignificant for the same IgE level to peanut regarding food allergy (Table 3).

4 | DISCUSSION

This study followed changes in IgE to egg, milk and peanut from 6 months to 5 years of age in 372 children, with a particular interest in the relevance of s-IgE in the low interval (0.1-0.34 kU/L) in infancy for further IgE sensitization and for doctor's diagnosis of allergy-related diseases. Although s-IgE had declined to below 0.1 kU/L at 2 years of age for around 50% of children with IgE in the low interval to egg or milk at 6 months, they had to a higher extent developed significant sensitization (≥ 0.35 kU/L) at 1 year of age compared to those with s-IgE below 0.1 kU/L. Around 15%-20% of the children sensitized to milk in the low interval (0.1-0.34 kU/L) at 6 months subsequently developed sensitization to egg or milk. Interestingly, none of the children sensitized to egg in this interval at 6 months had at 5 years developed egg sensitization, but to a high extent developed IgE to aeroallergens, which also was seen for children at 6 months being low sensitized to milk.

Food sensitization and allergic symptoms to food are common in infancy.¹¹ The consequence of producing s-IgE antibodies, especially low levels, early in life is poorly understood. To our knowledge, this is the first study focusing on s-IgE levels specifically below 0.35 kU/L in children from 6 months of age in a prospective design. When low s-IgE levels were investigated in a previous Swedish study, low levels were categorized as 0.1-0.7 kU/L,¹ and it was found that children with such low IgE levels to any of the studied allergens at 6 months had an increased risk of sensitization above their cut-off 0.7 kU/L at 5 years. It was also found that 81% of the children with low levels at 6 months were sensitized at 5 years.¹ Similar trends were evident in our data, statistically significant for those being low sensitized to egg or milk in infancy.

TABLE 2 Distribution of the three s-IgE concentration categories to egg, milk and peanut (0.1–0.34 [yellow]; <0.1 [grey]; ≥0.35 kU/L [blue]) at 6 mos of age in relation to the proportion of sensitized children (≥0.35 kU/L) at different ages

	Level of s-IgE at 6 mos						Yellow vs grey ^a <i>P</i>	Yellow vs blue ^a <i>P</i>
	Yellow ^a 0.1-0.34 kU/L		Grey ^a <0.1 kU/L		Blue ^a ≥0.35 kU/L			
	n/N	(%)	n/N	(%)	n/N	(%)		
IgE to egg								
1 y	4/18	(22)	13/303	(4)	16/19	(84)	0.01	<0.01
2 y	2/18	(11)	12/295	(4)	11/18	(61)	0.19	<0.01
5 y fx5	5/14	(36)	45/250	(18)	13/14	(93)	0.15	<0.01
5 y Phadiatop™	10/14	(71)	39/250	(15)	8/13	(62)	<0.01	0.69
IgE to milk								
1 y	10/47	(21)	5/275	(2)	10/20	(50)	<0.01	0.04
2 y	8/48	(17)	21/268	(8)	9/19	(48)	0.06	0.01
5 y fx5	12/41	(29)	42/224	(19)	9/15	(60)	0.14	<0.01
5 y Phadiatop™	15/41	(37)	39/224	(17)	4/14	(29)	0.01	0.29
IgE to peanut								
1 y	1/14	(7)	7/318	(2)	3/4	(75)	0.29	0.02
2 y	1/13	(8)	8/311	(3)	3/4	(75)	0.31	0.02
5 y fx5	4/11	(36)	56/262	(21)	2/4	(50)	0.27	1.0
5 y Phadiatop™	5/11	(45)	49/262	(19)	2/3	(67)	0.04	1.0

Pairwise comparisons of the proportions IgE ≥0.35 vs <0.35 kU/L [blue] to different food allergens and at different ages between children who at 6 mos had IgE values 0.1–0.34 [yellow] vs <0.1 [grey] and 0.1–0.34 [yellow] vs ≥0.35 kU/L [blue], respectively.

^aColours refer to those in Figures 1–3.

The most common food allergen to which children were sensitized at 5 years in this study was milk, as 9.7% of the participating children had IgE ≥0.35 kU/L. Sensitization to egg, rather than to milk, is generally considered to be more persistent and has been associated with subsequent sensitization to aeroallergens.^{2,6} Interestingly, in the present study, there were no children sensitized to egg at 5 years in the low interval (0.1–0.34 kU/L), while in the same group, 20% were sensitized to milk.

Overall, early sensitization to food allergens seems to increase the risk of subsequent allergic airway disease.^{12,13} A recent meta-analysis that studied the association between early food sensitization and later allergic disease supports this hypothesis.¹⁴ A similar sensitization pattern was seen in our study, where more than half of the children with egg sensitization at 6 months developed sensitization to aeroallergens at 5 years of age. Interestingly, in the group of children with IgE to egg or milk in the interval 0.1–0.34 kU/L at 6 months of age, a significantly larger proportion also had a sensitization to an aeroallergen at 5 years, compared to those with s-IgE <0.1 kU/L. This pattern was most pronounced among children with IgE antibodies to egg at 6 months of age, confirming that early egg sensitization seems to carry a worse prognosis than milk regarding further sensitization and the associated risk of allergic disease. Co-sensitization to aeroallergens, even in low levels, were relatively limited in those with s-IgE to food allergens in infancy, and could not explain the association between s-IgE to food at 6 months of age and positive PhadiatopTM at 5 years of age.

Previous studies have assessed the association between concentration of allergen specific IgE and allergic manifestations or food hypersensitivity and have found quantitative IgE to be a relatively good predictor.^{15–17} Thus, following s-IgE concentrations over time in children with suspected or verified food allergy is helpful in guiding the physician in decision-making on when provocations should be made, as there is a proven relationship between degree of decrease in s-IgE and development of tolerance.^{18,19} Our study indicates that taking s-IgE levels <0.35 kU/L into account could also be of prognostic value. Similar to Soderstrom et al¹ we found low IgE levels to egg in infancy to be associated with eczema; however, in our study, we found no such association for low IgE levels to milk. We found no differences with respect to clinical allergy-related diseases between those low-level and those significantly sensitized either to egg, milk or peanut at 6 months (Table 3). This could indicate that already low s-IgE levels in infancy are of predictive relevance.

The ALADDIN study has several strengths. The study is population-based and has a prospective design, with repeated health controls and blood sampling already in early infancy. The follow-up percentage regarding blood samples was satisfactory: 67% at 6 months, 68% at 1 year, 73% at 2 years and 61% at 5 years. In the children from families with an anthroposophic lifestyle, there were fewer blood samples available at 6 and 12 months. However, consent to blood sampling was given before parents received results of their own or their child's IgE analysis, which would

TABLE 3 Distribution of the three s-IgE concentration categories to egg, milk and peanut (0.1–0.34 [yellow]; <0.1 [grey]; ≥0.35 kU/L [blue]) at 6 mos of age in relation to doctor's diagnosis of allergy-related disease

	Level of s-IgE at 6 mos							
	Yellow ^a 0.1-0.34 kU/L		Grey ^a <0.1 kU/L		Blue ^a ≥0.35 kU/L		Yellow vs grey ^a P	Yellow vs blue ^a P
	n/N	(%)	n/N	(%)	n/N	(%)		
Doctor's diagnosis (ever)								
IgE to egg								
Asthma	1/18	(6)	32/294	(11)	3/17	(18)	0.70	0.34
Eczema	6/18	(33)	29/292	(10)	6/17	(35)	<0.01	1.0
Allergic rhinoconjunctivitis	1/18	(6)	5/288	(6)	2/17	(12)	0.31	0.60
Food allergy	3/17	(18)	19/287	(2)	4/16	(25)	0.12	0.69
IgE to milk								
Asthma	8/47	(17)	25/266	(9)	3/19	(16)	0.12	1.0
Eczema	8/46	(17)	13/247	(5)	2/19	(11)	0.33	0.71
Allergic rhinoconjunctivitis	3/46	(15)	4/261	(2)	1/19	(5)	0.07	1.0
Food allergy	3/46	(15)	19/258	(7)	4/19	(21)	1.0	0.18
IgE to peanut								
Asthma	2/12	(17)	34/312	(11)	0/4	(0)	0.63	1.0
Eczema	3/12	(25)	35/310	(11)	3/4	(75)	0.16	0.12
Allergic rhinoconjunctivitis	1/11	(9)	7/307	(2)	0/4	(0)	0.25	1.0
Food allergy	3/12	(25)	21/303	(7)	2/4	(50)	0.05	0.55

Pairwise comparisons of the proportion of doctor's diagnosis [Yes vs No] between children who at 6 mos had s-IgE values 0.1–0.34 [yellow] vs <0.1 [grey] and 0.1–0.34 [yellow] vs ≥0.35 kU/L [blue], respectively.

^aColours refer to those in Figures 1–3.

reduce the risk of selection bias. However, there are also limitations to address. The numbers of children with IgE levels in the intervals 0.1–0.34 kU/L and ≥0.35 kU/L at 6 months were low. This had consequences especially regarding estimations for egg and peanut, as the number of children with available blood samples also at 5 years was limited. This prevented longitudinal statistical analysis with adjustment for background factors, for example parental sensitization and lifestyle. Another weakness is that the separate allergens were not analysed in the blood samples at 5 years if the fx5 and/or PhadiatopTM value was below 0.35 kU/L. This makes longitudinal comparison of s-IgE beyond 2 years incomplete, as data on the allergen specific IgE levels at 5 years were available only for those children with positive fx5 and/or PhadiatopTM.

The cut-off level of 0.35 kU/L is possibly not the most appropriate level for prognostic or clinical assessments. In addition, different allergens tend to induce different immune responses.²⁰ Factors such as genetic background, age and seasonal variations in allergen exposure may also affect serum concentrations of s-IgE. Having low levels of s-IgE early in life seems to be predictive for later sensitization, but does not necessarily mean that the child will become allergic. Fluctuations in s-IgE in infancy may in some individuals also be explained by natural maturation of the immune system. As we did not have provocation data, detailed future studies, also taking s-IgE levels ≥0.1 kU/L into account, could shed light on differences in

sensitization development between common foods such as egg, milk and peanut.

4.1 | Clinical relevance

Having low levels of allergen specific IgE to egg, milk or peanut at 6 months of age was, compared with at the same age non-sensitized children, associated with development of sensitization to aeroallergens at 5 years of age. In addition, low levels to egg or milk in infancy were a risk factor for being sensitized to that allergen at 1 year of age and, regarding egg, also to development of eczema.

5 | CONCLUSION

Low IgE concentrations to common food allergens in early childhood seem to decrease over time, although may possibly increase the prevalence of sensitization to other allergens, in particular aeroallergens, and of eczema.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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