

Dynamic evolution of serum immunoglobulin E to airborne allergens throughout childhood: results from the Multi-Centre Allergy Study birth cohort

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Summary

Background Allergic rhinoconjunctivitis and asthma evolve dynamically throughout childhood. Yet, data on the evolution of serum levels of IgE antibodies against airborne allergens throughout the first decade of life are scarce.

Objective To describe the patterns of new and persistent sensitization against airborne allergens including remission from birth to 10 years of age and the long-term clinical outcomes up to the age of 13 years.

Methods In 273 children from the Multi-Centre Allergy Study, a German birth cohort, IgE levels were determined against airborne allergens (*Dermatophagoides pteronyssinus*, cat and dog dander, birch and grass species pollens) at 2, 5, 7, and 10 years of age (ImmunoCAP, Phadia); allergic rhino-conjunctivitis and asthma were ascertained at the 13 years of age through a standardized questionnaire (International Study of Asthma and Allergies in Childhood).

Results The prevalence of sensitization to each allergen increased steadily throughout childhood, and a hierarchy of sensitization prevalence (grass > birch > mites > cat > dog) was maintained from 5 years of age onwards. A mono-sensitization state was relatively short (measurable half-life = 3 years) as additional sensitizations were acquired frequently, and relatively soon after the first one. Remission of weak sensitization (UNICAP classes 1–2) was also quite frequent, especially before 5 years of age. By contrast, stronger IgE responses (> 3.5 kU/L) were invariably persistent. Early sensitization was associated with a higher tendency for poly-sensitization at 10 years of age and allergic rhino-conjunctivitis and/or asthma at 13 years of age.

Conclusions IgE responses against airborne allergens undergo dynamic changes throughout childhood, with a high frequency of new sensitization or remission. The long-term persistence and the clinical impact of IgE responses are affected by the intensity of IgE sensitization and the age of its onset.

Keywords childhood, IgE, MAS, Multi-Centre Allergy Study, natural history, respiratory allergies

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Introduction

Allergic rhinitis (AR) and asthma evolve dynamically throughout childhood and are strongly associated with

IgE responses against common airborne allergens [1]. Owing to cohort studies, longitudinal patterns of wheezing [2, 3] and lung function [4, 5] have been described, early risk factors have been identified [6], and a diagnostic algorithm has been proposed for the prediction of asthma and for targeting early preventive intervention [7]. By contrast, less information has been obtained on the

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natural history of allergen-specific IgE responses. This is probably due to the greater invasiveness of blood drawing, the higher costs of IgE testing, and the availability of alternative diagnostic methods such as skin prick tests (SPTs). Through the latter approach, a study from Tucson (Arizona, USA) recently described multiple dynamic changes in skin sensitization to aeroallergens in a cohort of children examined at 6 and at 11 years of age [8]. A high rate of new sensitization onset, remission, and bi-directional variations in the intensity and hierarchy of existing reactions clearly indicated that a single-point assessment of skin test reactivity is of limited value at the individual level in childhood [8].

This dynamic property of allergic sensitization in childhood is probably clinically relevant, especially for the first evaluation of a child. A single significant determination of atopy, defined as the propensity to produce IgE antibodies, does provide important clinical information as, once atopy has been convincingly demonstrated, the atopic child is at a risk of developing further sensitizations and at a risk of developing downstream allergic disease. However, a single-point assessment of allergic sensitization does not tell the clinician whether the sensitization is transient or persistent, whether it started years before or recently, and whether it is on the increase or on the decrease. Thus, recent findings have highlighted a need for epidemiological studies to provide more insights on the longitudinal trends of allergic sensitization throughout childhood [8]. Interestingly, a Swedish birth cohort study has recently shown that there is a prominent, dynamic process of sensitization at the pre-school age to inhalant allergens, which, in Scandinavia, is dominated by sensitization to birch pollen, with a probable impact on the development of allergic disease in the growing child [9].

In this context, the German Multi-Centre Allergy Study (MAS) provides a unique opportunity for further descriptive investigation. In this birth cohort study, peripheral blood drawing was scheduled at several time-points, including pre-school age [10]. A preliminary analysis of the incidence and prevalence of IgE sensitization in this cohort was published many years ago, where the analysis was limited to 6 years of age at most [11], a stage at which sensitization to aeroallergens is, in most cases, not fully developed. By analysing the new data of the MAS cohort, we aimed to describe both the dynamic changes of the IgE-Ab serum levels against five common airborne allergens in the first decade of life.

Methods

The Multi-Centre Allergy Study

The German MAS, a prospective observational birth cohort, recruited 1314 newborns in 1990 from six delivery

wards in five German cities. A detailed description of the stratified sampling scheme and study subjects is given elsewhere [10]. Briefly, 499 newborns with risk factors for atopy [increased cord blood IgE (≥ 0.9 kU/L), at least two atopic family members, or both] and 815 newborns with none of these risk factors were included in the cohort. All children were followed up at ages 1, 3, 6, 12, 18, and 24 months and from then on yearly within 4 weeks of the child's birthday up to the age of 13 years. The study was approved by the local ethics committees. Each child's parents attended written informed consent at the time of enrolment. At 13 years of age, parents gave structured face-to-face interviews with a study physician that included questions on asthmatic and atopic symptoms, according to the International Study of Asthma and Allergies in Childhood core questions [12]. A blood drawing was scheduled at 1, 2, 3, 5, 6, 7, and 10 years of age. A detailed description of the study design is reported elsewhere [13, 14].

Study population

For the purposes of the present nested study, we examined a subset of the MAS cohort consisting of 273 children with a complete set of sera and IgE data at 2, 5, 7, and 10 years of age. The vast majority of these subjects (255/273; 93.4%) also participated in the interview and examination at 13 years. To our knowledge, this is the largest longitudinal set of sera ever examined at four different time-points up to 10 years of age for IgE responses against airborne allergens. To assess potential participation bias, we analysed the number of follow-up per child in the whole original MAS cohort, i.e. we tested whether certain children participated in more follow-ups than other children based on data collected at birth.

Immunoglobulin E assays

A full set of IgE testing was performed on all the available peripheral blood samples up to 10 years of age. Specific IgE antibodies to five airborne allergens [house dust mite (*Dermatophagoides pteronyssinus*), cat and dog dander, mixed grass, and birch pollen] were determined using the CAP-RAST FEIA (Phadia, Freiburg, Germany).

Definitions

Allergic sensitization was analysed both continuously (IgE concentration expressed in kU/L) and categorically by adopting multiple cut-off points, as indicated in the text. In particular, mono-sensitization was defined as the presence of IgE antibodies (cut-off > 1 kU/L) against only one of the five allergens examined; this cut-off was chosen to constitute a stronger atopic effect than would have been by merely choosing evidence of any detectable

specific IgE, i.e. ImmunoCAP class 1. Remission of allergen-specific sensitization was defined as the persistent absence of detectable IgE antibodies (<0.35 kU/L) in a subject sensitized at the previous follow-up point. Current asthma at 13 years of age was defined as a parent-reported wheezing in the past 12 months. Current AR at 13 years was defined as a parent-reported sneezing and itchy eyes without a cold in the past 12 months.

Statistical analysis

We performed descriptive statistics and calculated the point prevalence of sensitization to the five airborne allergens. To express the impact of age at the onset of sensitization, the data set was stratified (early: ≤ 2 years, late: >2 – ≤ 5 years, and very late: >5 years). Frequencies of clinically relevant respiratory allergies and serum IgE levels were calculated separately for the different strata. Differences between the strata were tested by the Mann–Whitney *U*-test. Differences between time-points within one stratum were tested by McNemar tests (two-related samples) and Cochran–Q tests (*k*-related samples), as appropriate. All analyses were performed using SPSS statistical software package version 15.0.

Results

Study population and participation bias

We performed an analysis of the characteristics of participants included vs. those not included in the present study. A comparison of the 273 children with complete sets of sera with the rest of the MAS cohort revealed that participating children were not significantly different from non-participants with regard to the sex ratio (boys 53% vs. 52%, $P=0.69$), older siblings (43% vs. 41%, $P=0.51$), and the level of parental school education (parents with ≥ 12 years of schooling: 55% vs. 51%, $P=0.34$), but had significantly more atopic parents (59% vs. 50%, $P=0.01$).

Prevalence of immunoglobulin E sensitization

The point prevalence of IgE sensitization (cut-off 1.0 kU/L) to each allergen increased progressively with age ($P<0.001$ for grass, birch, mite, and cat; $P=0.008$ for dog). At the age of 2 years, the prevalence of sensitization to each allergen ranged between 2% and 3% (Fig. 1). By the age of 5 years, a ranking of the prevalence of the responses against individual allergens was established, and it persisted up to 10 years of age (grass $>$ birch $>$ mites $>$ cat $>$ dog). Sensitization to at least one of the two pollens examined was always more frequent than sensitization to at least one of the three indoor allergens examined.

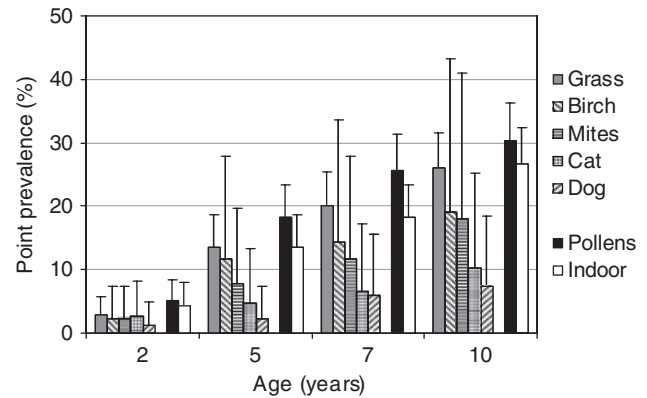


Fig. 1. Prevalence of sensitization, by age. Point prevalence of IgE sensitization (cut-off 1.0 kU/L) to five common airborne allergens, to any pollen or to any indoor allergen from birth to 10 years in 273 children participating in the Multi-Centre Allergy Study. Bars represent 95% confidence intervals (upper limits).

Mono- and poly-sensitization

Only 22 children (22/273, 8%) were sensitized to airborne allergens at 2 years of age. At each follow-up, new children with atopy were identified (48 at 5 years, 24 at 7 years, and 22 at 10 years). In most cases, these new atopic subjects were sensitized to a single allergen; this mono-sensitization state, however, was progressively lost over time. Ten out of the 19 children (53%) who were first detected as mono-sensitized at 2 years of age became poly-sensitized during the next 3 years (on average 17.7% per year); 13 out of the 31 children (42%) first detected as mono-sensitized at 5 years of age became poly-sensitized in the next 2 years (21% per year); and six out of the 18 children (33%) first detected as mono-sensitized at 7 years of age became poly-sensitized in the next 3 years (11% per year). This decrease in the prevalence of mono-sensitization was significant for the group of 2-year-olds ($P=0.002$), the group of 5-year-olds ($P=0.035$), and borderline significant for the group of 7-year-olds ($P=0.070$). Overall, a mono-sensitization state was relatively short (estimated measurable half-life approximately 36 months).

Remission of sensitization

As expected, the frequency of resolution of a newly established sensitization was highly dependent on its intensity (Table 1). Low positive sensitization (in the range of 0.35–1.0 kU/L with the immunoCAP-FEIA) was often transient, especially in very young children: about two thirds of very weak IgE sensitizations observed at 2 years of age were no longer detected at 5 years of age. It is important to note, however, that this frequency dramatically declined in older children. Stronger sensitizations (range 1.0–3.5 kU/L) were more stable, as one-fourth of

Table 1. Frequency of remission of immunoglobulin E sensitization to inhalant allergens in the MAS cohort, by age*

IgE-Ab		Frequency of remissions*					
		Positive at 2 years but <.35 kU/L at 5 years		Positive at 5 years but <.35 kU/L at 7 years		Positive at 7 years but <.35 kU/L at 10 years	
		<i>n/N</i>	%	<i>n/N</i>	%	<i>n/N</i>	%
> 0.35; < 1.0	All	18/28	64.3	11/41	26.8	23/73	31.5
	Mites	3/4	75.0	0/6	0.0	5/16	31.3
	Cat	2/3	66.7	2/7	28.6	4/9	44.4
	Dog	–	–	1/7	14.3	5/16	31.3
	Birch	3/5	60.0	3/7	42.9	4/10	40.0
	Grass	10/16	62.5	11/42	26.2	5/22	22.7
> 1.0; < 3.5	All	5/20	25.0	3/35	8.6	6/59	10.2
	Mites	0/2	0.0	0/3	0.0	1/9	11.1
	Cat	1/4	25.0	0/4	0.0	0/8	0.0
	Dog	–	–	1/4	25.0	0/10	0.0
	Birch	0/6	0.0	0/12	0.0	3/13	23.1
	Grass	4/8	50.0	3/35	8.6	2/19	10.5
> 3.5	All	0/7	0.0	0/79	0.0	0/101	0.0

*Number of sera with undetectable IgE-Ab/total number of sera with the given concentration at the previous time point (2 years for 5 years; 5 years for 7 years; 7 years for 10 years) [e.g., 35 sera had a concentration of serum IgE against grass pollen at 5 years of age between 1.0 and 3.5 kU/L; three out of these (8.6%) had no detectable IgE against grass pollen at 7 years of age].

MAS, Multi-Centre Allergy Study.

those observed at 2 years of age were no longer detected at 5 years of age. Again, this frequency declined to 10% or less in older children. Not a single remission could be observed among the 187 IgE responses with an IgE serum concentration > 3.5 kU/L. Taken together these data indicate that a persistent sensitization could be discriminated on the basis of its intensity at onset. The tendency to remission of IgE responses was apparently not influenced by their allergen specificity (Table 1).

Long-term impact of early vs. delayed immunoglobulin E sensitization

We tested the longitudinal trend of serum IgE-Ab levels against individual allergens in atopic subjects, stratified by the age at first detection of sensitization (Fig. 2). Early onset of IgE sensitization to indoor allergens (mite, cat) implied a faster and greater increase in the serum concentration of IgE-Ab than late-onset sensitization to the same allergens. Explorative analysis at 7 and 10 years revealed that serum IgE-Ab levels against mite were significantly higher in early vs. very late ($P = 0.024$ at ages 7 and 10 years) and late vs. very late onset ($P = 0.003$ at age 7 and $P = 0.010$ at age 10). Differences for IgE-Ab levels against cats were not significant, with overall higher levels against mite than against cat.

We also analysed whether early, persistent sensitization (> 3.5 kU/L) had an impact on the tendency for poly-sensitization and long-term persistence of allergic respiratory symptoms. The average number of airborne allergens that the children were sensitized to at 10 years of age was

2.4 ± 1.4 , 1.8 ± 1.0 , 1.5 ± 0.7 , and 1.2 ± 0.5 , among children whose sensitization started at 2, 5, 7, and 10 years of age, respectively. These results indicate that the earlier the sensitization onset, the stronger the tendency for poly-sensitization.

Finally, the frequency of children with AR and/or asthma at 13 years of age was maximal (87.5%) among participants with persistent sensitization (> 3.5 kU/L) detected at 2 years of age and minimal (78%) among participants whose sensitization of the same level started at 10 years of age, suggesting that an earlier sensitization predicts persistence of respiratory allergic symptoms up to 13 years of age.

Discussion

The natural history of IgE sensitization against airborne allergens was, in our study population, a highly dynamic process characterized by (1) a steady increase and a stable hierarchy in the prevalence of sensitization, with a dominance of responses to pollen allergens; (2) a fast transition from a mono-sensitization to a poly-sensitization stage; (3) a relatively high remission rate of the weakest IgE responses; and (4) a lower association of early, compared with delayed sensitization with regard to allergic respiratory symptoms. Altogether, these four findings support the concept that a single determination of IgE sensitization against airborne allergens is not informative enough [8] and cannot represent the complex evolution of IgE responses throughout childhood.

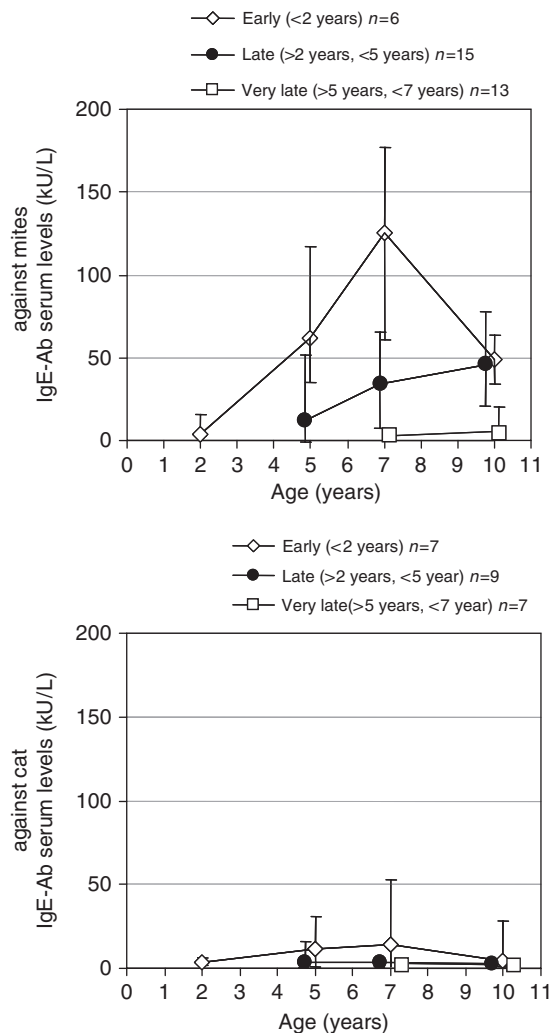


Fig. 2. Quantitative trends of IgE-Ab responses, by the age of onset and allergen. Serum levels of specific IgE-Ab against mite and cat, by the age of onset of sensitization, among 273 children participating in the Multi-Centre Allergy Study. Each line refers to the group of (*n*) subjects whose sensitization (cut-off > 1.0 kU/L) started at a 2, 5, or 7 years of age. Values are the median concentration of specific IgE in that group, by age. Error bars representing the inter-quartile range are shown.

A steady and age-related increase in the prevalence of IgE sensitization against airborne allergens was an expected outcome, which confirms previous longitudinal studies [8, 9, 15] and common experience from clinics. As also observed in the BAMSE cohort study [9], sensitization to airborne allergens frequently started in our cohort already at pre-school age. Moreover, sensitization to pollens tended to be more frequent than sensitization to indoor allergens throughout childhood. This result may be explained by the relatively low exposure to mites reported in this cohort [16] and in other studies in German children [17]. Interestingly, in countries where exposure to mites is higher, such as New Zealand [18], the prevalence of sensitization to indoor allergens in children is higher than that to pollens, and the prevalence of allergic asthma is

higher than the one observed in Germany [19]. Our data may therefore indirectly support the hypothesis that differences in exposure to mite allergens contribute towards generating differences in the prevalence of sensitization to mites and of allergic asthma in childhood [20]. Our previous work on the same cohort showed that the dynamic evolution of specific IgE is a function of both the genetic predisposition of the child, combined with their environmental exposure to risk and protective factors [13, 16].

We also found that mono-sensitization is a very transient stage in a child's atopic 'career'. On the one hand, about one out of four newly sensitized subjects was already poly-sensitized at the first detection of their atopic sensitization. On the other hand, half of the mono-sensitized subjects acquired a second sensitization in just a 3-year period. This measure is a function of the frequency of the sampling and cannot be directly extrapolated to other populations. However, our observation is a foundation for future surveys in clinical settings, aimed to define the average length of a mono-sensitization stage in children with respiratory allergies, before they develop poly-sensitization. This 'mono-sensitization window period' is important from a clinical point of view, as specific immunotherapy may have a stronger efficacy if started in the mono-sensitization stage [21, 22].

Our third observation challenges the concept that sensitization against airborne allergens is inevitably persistent. This common belief has already been disclaimed by a report from the Tucson birth cohort, showing that sensitization against Bermuda grass, observed at the age of 6 years, is rather frequently lost at the age of 11 years [8]. Similarly, the BAMSE cohort study has recently shown that a proportion of sensitizations observed at the age of 4 years (birch = 3%, Timothy grass = 14%, cat = 6%, dog = 9%) were no longer observed at the age of 8 years [9]. Our results expand these observations, showing that weak sensitization (0.35–1 kU/L) detected at the age of 2 years is very frequently lost at the age of 5. In keeping with the BAMSE and Tucson data [9], however, the rates of sensitization remission declined with age in our study population. Moreover, we found no remission of sensitization if serum IgE antibody levels were > 3.5 kU/L. This threshold may have some clinical relevance, but it cannot be extrapolated to a clinical setting to predict sensitization persistence. Therefore, studies in patients cohorts are needed to test whether the 'persistence' of sensitization against airborne allergens is predictable at certain levels of serum IgE antibodies. On the other hand, the children participating in the MAS study did not undergo SPTs at each follow-up; therefore, we cannot state how the threshold of specific IgE levels (> 3.5 kU/L) relates to SPTs reactions.

Finally, our results show that earlier sensitization has a stronger impact than late sensitization in many respects.

We found that early sensitization to mite and cat allergens was characterized by a faster and steeper increase of serum-specific IgE levels than sensitizations to the same allergens starting later in childhood. We cannot totally exclude that those participating were predominantly highly allergic and/or came from allergic families and that a participation bias underlies our results. However, higher levels of IgE antibodies against common allergens have been linked to a higher risk of allergic disease at pre-school age [23, 24]. Therefore, the new finding reported here may contribute towards explaining why early sensitization to indoor allergens is associated in this cohort with a worse lung function and with asthma at school age [13]. Our data also show that early sensitization is related to a stronger tendency towards poly-sensitization and respiratory allergic disease persisting up to 13 years of age. The next question to be answered is whether an earlier sensitization is a cause or just a marker of a more severe allergic condition.

Our data analysis had some major limitations. First, it was a subgroup analysis within the MAS cohort. Participation bias has been discussed in detail previously [13, 16]. Moreover, the MAS cohort is overselected for parental atopy and is not representative of a population sample taken from the routine clinical practice; hence, that the conclusions we reached cannot be extended to the general German population of a similar age. However, to our knowledge, this is by far one of the largest sera-banks studying IgE responses at multiple time-points between birth and 10 years of age. A second limitation is that we only used extracts for the study of allergen-specific sensitization, hence, we cannot provide evidence of specific trends at the molecular level. Earlier sensitizations may be characterized by a more heterogeneous and diversified antibody repertoire, and this might explain both their faster expansion and their higher clinical relevance. Finally, a comparison of our results with those of other studies using different cut-points may be difficult.

In conclusion, this study shows that IgE responses against airborne allergens undergo dynamic changes throughout childhood, with a high frequency of new sensitization or remission. They also suggest that the long-term persistence and the clinical impact of IgE responses are affected by the intensity of IgE sensitization and the age at its onset. Longitudinal studies in patients cohorts are required to ascertain whether the changes in specific IgE responses cause, accompany, or follow modifications in clinical manifestations of allergic diseases.

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