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Primary versus secondary immunoglobulin E sensitization to soy and wheat in the Multi-Centre Allergy Study cohort

P. M. Matricardi*, A. Bockelbrink†, K. Beyer*, T. Keil†, B. Niggemann*, C. Grüber*, U. Wahn* and S. Lau*

*Department of Pediatric Pneumology and Immunology, Charité University Medical Centre, Berlin, Germany and †Institute for Social Medicine, Epidemiology and Health Economics, Charité University Medical Centre, Berlin, Germany

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Summary

Background IgE sensitization to soy and wheat is classified as 'primary' when generated by food ingestion and 'secondary' when it is a consequence of primary sensitization to cross-reacting pollen antigens via inhalation. The age-specific relevance of these categories of sensitization throughout childhood is unknown.

Objective To monitor the natural course of IgE sensitization against common food allergens in childhood in relation to sensitization against cross-reactive airborne allergens.

Methods The German Multi-Centre Allergy Study with follow-up from birth to age 13 recruited initially 1314 children. IgE antibody levels against cow's milk, hen's egg, soy, wheat, mites, cat and dog dander, birch and grass pollens were tested. Longitudinal data were analysed from the 273 children with sera obtained at age 2, 5, 7 and 10 years of age.

Results The point prevalence of sensitization (>1.0 kU/L) to milk and egg allergens progressively decreased from about 4% at 2 years to $<1\%$ at 10 years. By contrast, the prevalence of IgE to wheat and soy progressively increased with age, from 2% to 7% (soy) and from 2% to 9% (wheat). At 10 years of age, IgE to grass pollen was detected in 97% and 98% of the children reacting against soy and wheat, respectively; IgE to birch pollen was observed in 86% and 82% of the children reacting against soy and wheat, respectively. Early IgE sensitization to soy or wheat preceded that to grass or birch pollen in only 4% and 8% of participants sensitized to soy and wheat, respectively.

Conclusion IgE sensitization to soy and wheat is relatively uncommon and mostly primary in early infancy, more frequent and mostly secondary to pollen sensitization at school age.

Clinical Implications Awareness should be raised to avoid unnecessary diet restrictions due to the high frequency of clinically irrelevant, secondary sensitization to soy and wheat in schoolchildren with pollinosis.

Keywords atopy, birch pollen, childhood, cross-reactivity, food allergens, grass pollen, IgE, MAS, Multi-Centre Allergy Study, natural history, sensitization, soy, wheat

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Correspondence:

Paolo Maria Matricardi, Department of Pediatric Pneumology and Immunology, Charité Medical Center, Augustenburger Platz 1, D-13353, Berlin, Germany.
E-mail: paolo.matricardi@charite.de

Introduction

The epidemic trend of allergic rhino-conjunctivitis and asthma has been sustained throughout the last century by a parallel increase in IgE sensitization against airborne allergens [1]. By contrast, a parallel epidemic trend of IgE sensitization to food allergens has never been clearly demonstrated [2]. The route, dose, frequency of exposure, and mucosal sites of priming of ingested and inhaled allergens are totally different. Therefore, it is not substan-

tiated to conclude that an epidemic of IgE sensitization to food allergens is in progress just because we observe an epidemic of sensitization to airborne allergens. Yet, many airborne allergens induce IgE, which cross-reacts with food allergens, [3] and many adult patients affected by pollinosis also suffer from different kinds of food allergies [4]. On this basis it can be easily postulated that the prevalence of IgE sensitization to certain food allergens should increase at the population level in parallel with sensitization to certain cross-reactive pollens.

It is also conceivable that primary sensitization to certain pollens during childhood may result in the formation of cross-reacting IgE to food allergens. At the pre-school age, however, most manifestations of food allergy are generated through *primary* food-specific sensitization. Thus both primary *and* secondary sensitization to plant-derived food allergens can be observed in childhood. However, the actual sequence of events leading to sensitization to pollens and cross-reacting food allergens and the relative age-specific frequency of primary and secondary sensitization to plant-derived food allergens have never been formally examined in prospective studies in children.

The German Multi-Centre Allergy Study (MAS) provides a rare opportunity to address these questions. Indeed, in this birth cohort study, peripheral blood drawing was proposed to participants at several time-points up to puberty [5]. A preliminary analysis of the incidence and prevalence of IgE sensitization in this cohort was published many years ago and included data on food allergens up to 6 years of age only [6], a stage at which sensitization to aeroallergens is in most cases not fully developed. We therefore aimed at describing the natural history of IgE sensitization to animal (cow's milk and hen's egg) and plant (soy and wheat) food allergens of animal or plant source in relation to IgE sensitization to airborne allergens up to puberty.

Methods

Study population

The German MAS, a population-based prospective observational birth cohort, recruited 1314 of 7609 infants born in 1990 in six German Obstetric Departments in five German cities. A detailed description of the stratified sampling scheme and study subjects is given elsewhere [5, 7]. Briefly, 499 newborns with presumed 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 hospital's ethics committee. Each child's parents gave written informed consent at the time of enrolment. A blood drawing was proposed at 1, 2, 3, 5, 6, 7, 10, and 13 years of age but the acceptance rate was low and varied throughout the study follow-up period. Therefore, for the purposes of the present study, we focused mainly on a subset of the MAS cohort composed of the 273 children with a complete set of sera and IgE data at times 2, 5, 7, and 10 years. In addition, for specific analyses, we also used data obtained from the 577 participants whose serum was available at age 10 years,

and from the whole set of sera ($n = 4558$) obtained from the 1081 participants who consented to blood drawing at least once between 1 and 13 years of age.

Immunoglobulin E assays

A full set of IgE testing was performed in all the available peripheral blood samples up to 10 years of age. Specific IgE antibodies (Ab) to four food allergens (cow's milk, hen's egg, soy and wheat) and five airborne allergens [house dust mite (*Dermatophagoides pteronyssinus*), cat and dog dander, timothy grass, and birch pollen] were determined using the ImmunoCAP FEIA (Phadia A/S, Freiburg, Germany). Dog dander was not tested at age 2. Results were expressed in kU/L in quantitative analyses and classified as positive or negative according to the cut-off levels of 1 kU/L. In our hands, specific IgE responses against pollens with values below 1.0 kU/L are very often clinically irrelevant, transient and non-specifically elevated, especially at the pre-school age (Matricardi PM, unpublished).

Statistical analysis

We performed descriptive statistics and calculated point prevalences of sensitization to four food allergens as proportions of children with specific IgE > 1.0 kU/L to cow's milk, hen's egg, wheat, and soy at ages 2, 5, 7, and 10 years. The calculations were done on the subset of 273 participants with complete data at these time-points. The course of sensitization over time was tested by trend test, in which P -values < 0.05 were considered statistically significant. To express the interdependency of sensitization to different food and inhalant allergen sources, we calculated the relative frequency of sensitization to the other allergen sources within the group of sensitized children to each individual allergen. These calculations were based on all 577 available sera at the 10-year follow-up examination. Associations of the levels of IgE-Ab against food and inhalant allergens were expressed by Spearman's correlation coefficients. We considered correlations of wheat and soy at ages 1, 3, 5, and 10 years, as well as wheat/grass, wheat/birch, soy/grass and soy/birch at age 10 years. The latter calculations again were done on the subset of 577 participants. All analyses were performed using SPSS statistical software package version 13.0.

Results

Prevalence of immunoglobulin E sensitization to food allergens from birth to puberty

The point prevalence of IgE sensitization to cow's milk and hen's egg allergens progressively decreased from about 4% at 2 years to $< 1\%$ to 10 years, while the one to

wheat and soy progressively increased with age, from 2% for both allergens at 2 years up to 7% for soy and 9% for wheat at 10 years (Fig. 1). 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 sex ratio (boys 53% vs. 52%, $P=0.69$), older siblings (43% vs. 41%, $P=0.51$) and 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%, $P=0.01$).

Systematic analysis of simultaneous immunoglobulin E reactivity to food and airborne allergens

We performed a systematic analysis of simultaneous IgE reactivity to pairs of allergens at 10 years of age (Table 1). In participants reacting to any given allergen source,

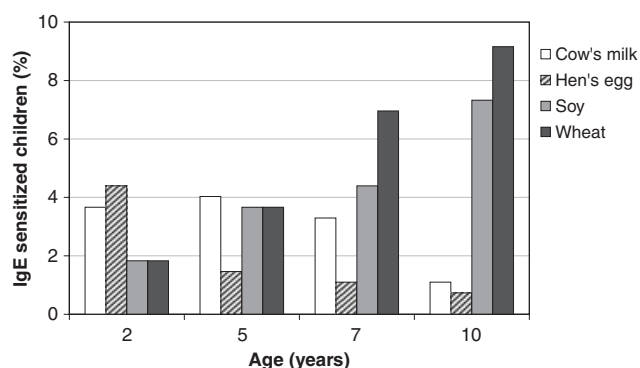


Fig. 1. Prevalence of sensitization from birth to 10 years. Point prevalence of IgE sensitization (cut-off 1 kU/L) to four common food allergens from birth to 10 years in 273 children participating in MAS. P -values for trend in sensitization at age 2, 5, 7, 10 years are the following: cow's milk $P=0.037$; hen's egg $P=0.001$; soy $P<0.001$; wheat $P<0.001$. MAS, Multi-Centre Allergy Study.

simultaneous reactivity to a specific, second allergen source ranged from as low as 2% up to 98%. This matrix generated 72 possible comparisons; in 44 (61%) simultaneous reactivity to both allergen sources considered was <40%, in 25 (35%) between 41% and 90%, and only in three (4%) above 90%. In particular, IgE reactivity against grass pollen was detected in 97% and 98% of the reactions against soy and wheat, respectively; IgE reactivity against wheat was detected in 91% of the sera reacting to soy; IgE reactivity against birch pollen was observed in 86% and 82% of the sera reacting against soy and wheat, respectively; finally, 84% of the children reacting against birch pollen also reacted against grass pollen.

Quantitative and age-specific associations among immunoglobulin E-antibody levels

We compared IgE levels against grass or birch pollens with IgE levels against soy or wheat. The corresponding scattergrams were quite similar (Fig. 2) as they were all characterized by (1) a significant level of the correlation coefficient (Spearman) ($P<0.001$); (2) the virtual absence of sera with high IgE levels against wheat or soy and low or no IgE levels against birch or grass pollens; (3) the presence of two major groups of 'bi-reactive' sera, the first elongated around the identity line, the second with low levels of IgE against wheat or soy and high levels of IgE against birch or grass pollens. These data indicate that the observed qualitative associations were also quantitative.

We also tested whether the observed associations were age-specific (Table 2). Interestingly, simultaneous reactivity between pollens and food allergen sources were absent or low in the first 2 years of life, became evident at 3 years of life and increased very fast up to 97–98% at age 10; values were slightly higher when sensitization to wheat (instead of soy) was taken into consideration. These data

Table 1. Frequency (%) of concordant positive IgE responses in 577 children (age 10 years) (MAS cohort)*

		Milk	Egg	Soy	Wheat	Mite	Cat	Dog	Birch	Grass
	<i>N</i> possible	6	5	35	51	102	56	41	94	133
Milk	6		20	6	2	3	7	5	2	2
Egg	5	17		9	2	2	5	7	4	3
Soy	35	33	60		63	8	23	29	32	26
Wheat	51	17	20	91		9	38	41	45	38
Mite	102	50	40	23	18		43	46	36	38
Cat	56	67	60	37	41	24		73	38	32
Dog	41	33	60	34	33	19	57		34	25
Birch	94	33	80	86	82	33	64	78		59
Grass	133	50	80	97	98	50	77	80	84	

*Numbers are % of sera with IgE-Ab (>1 kU/L) to the allergen in the row among sera with IgE-Ab (>1 kU/L) to the allergen in the column (e.g.: 98% of the sera positive to wheat were also positive to grass); in bold values above 90%.

MAS, Multi-Centre Allergy Study; Ab, antibody.

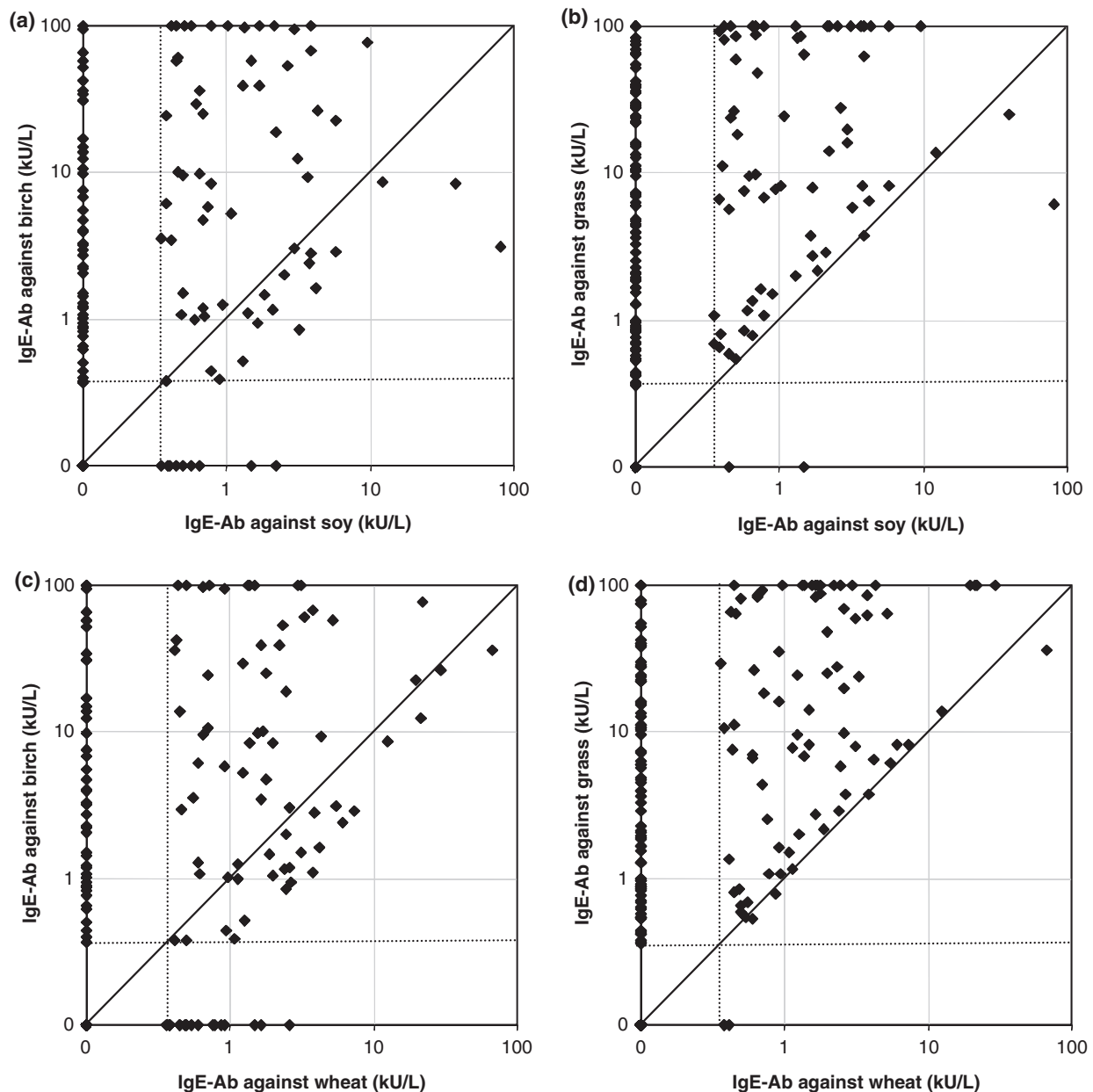


Fig. 2. Quantitative relation of serum IgE-Ab against pollen and food allergens. Relationship between the levels of serum IgE-Ab against pollen and food allergens in 577 children participating in the MAS cohort at 10 years of age: (a) birch and soy, correlation coefficient (Spearman) $r = 0.66$; (b) grass and soy, $r = 0.59$; (c) grass and wheat, $r = 0.64$; (d) birch and wheat, $r = 0.65$. All correlations are significant at $P < 0.001$. Values depicted at 100 represent values > 100 kUa/L. Dotted lines show detection threshold at 0.35 kU/L. Ab, antibody; MAS, Multi-Centre Allergy Study.

indicate that all the qualitative associations became stronger with age. Similarly, the quantitative association between the levels of IgE-Ab against soy and of IgE-Ab against wheat also became stronger with age (Fig. 3).

Sequence and intensity of sensitization to soy, wheat, grass, and birch pollen

Twenty-eight of the 273 children with a complete set of sera developed sensitization to soy and 39 to wheat during the

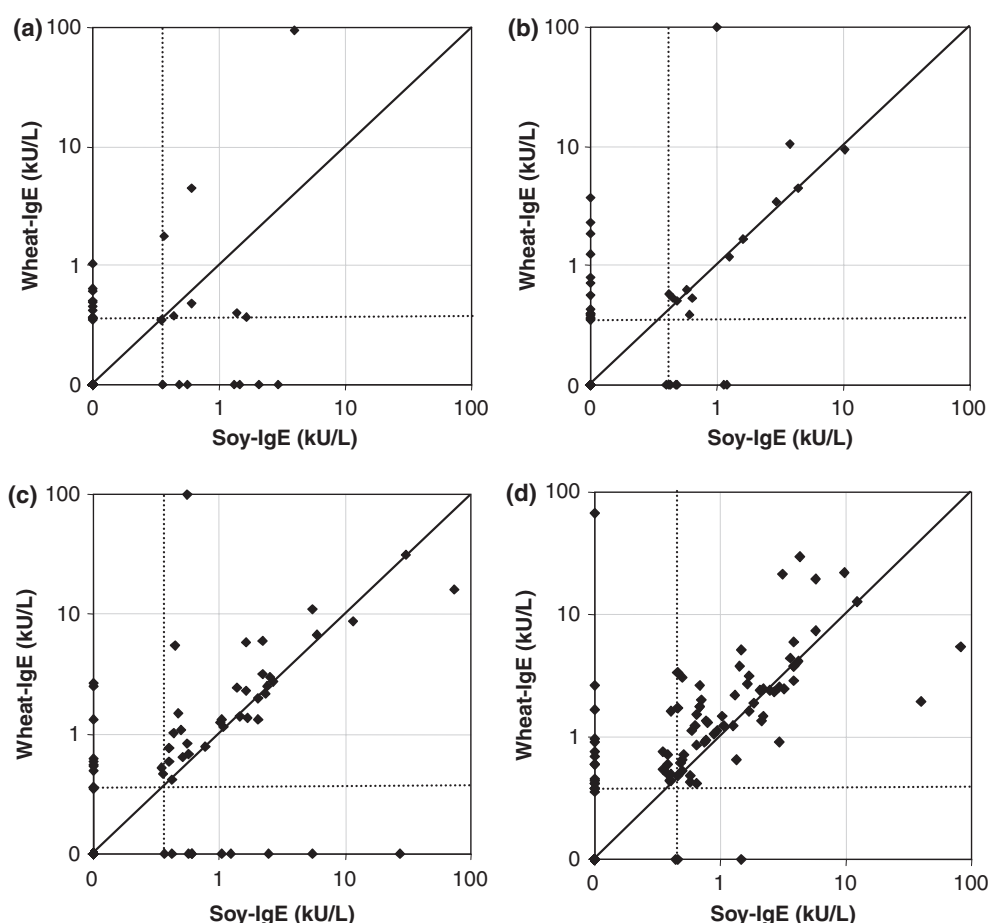
first 10 years of life. None of the 28 children (0%) sensitized to soy and only two of the 39 children (5%) sensitized to wheat *never* developed sensitization to grass or birch pollens. Similarly, only one out of 28 soy-sensitive children (4%) and only one out of 39 wheat-sensitive children (3%) started to be sensitized to soy or wheat *before* they became sensitized to grass or birch. By contrast, 15 out of 28 (54%) soy-sensitive children and 23 out of 39 (59%) wheat-sensitive children started to be sensitized to soy or wheat *after* they became sensitized to grass or birch. Finally, in

Table 2. Percentage of a positive response to birch, grass and wheat in sera with IgE responses against soy and wheat, by age, in children participating in the MAS*

Age	Soy				Wheat			
	All (n)	Birch (%)	Grass (%)	Wheat (%)	All (n)	Birch (%)	Grass (%)	Soy (%)
1	7	0	0	14	4	0	0	25
2	11	27	36	73	9	33	44	89
3	8	75	75	75	11	36	73	55
5	26	77	88	81	29	66	93	72
6	23	70	87	74	24	67	96	71
7	34	79	94	94	46	80	98	70
10	35	86	97	91	51	82	98	63
All	144	71	83	81	174	70	90	67

*Values $\geq 80\%$ are in bold.

MAS, Multi-Centre Allergy Study.

**Fig. 3.** Age-specific quantitative relation of IgE-Ab against soy and wheat. Relationship between the levels of serum IgE-Ab against soy and wheat in sera from 273 children participating in the MAS cohort study at age (a) 1 year, correlation coefficient (Spearman) $r=0.50$; (b) 3 years, $r=0.53$; (c) 5 years, $r=0.75$; (d) 10 years, $r=0.87$. All correlations are significant at $P < 0.001$. Values depicted at 100 represent values >100 kU/L. Dotted lines show detection threshold at 0.35 kU/L. Ab, antibody; MAS, Multi-Centre Allergy Study.

12/28 (43%) of the soy-sensitized children and in 13/39 (33%) of the wheat-sensitized children, IgE against grass and/or birch was detected for the first time at the same age as those against soy or wheat, respectively.

We could prospectively monitor the quantitative trends of IgE responses in each individual child: it was possible to distinguish patterns of secondary (Figs 4a and b) from those of primary (Figs 4c and d) sensitization to wheat and

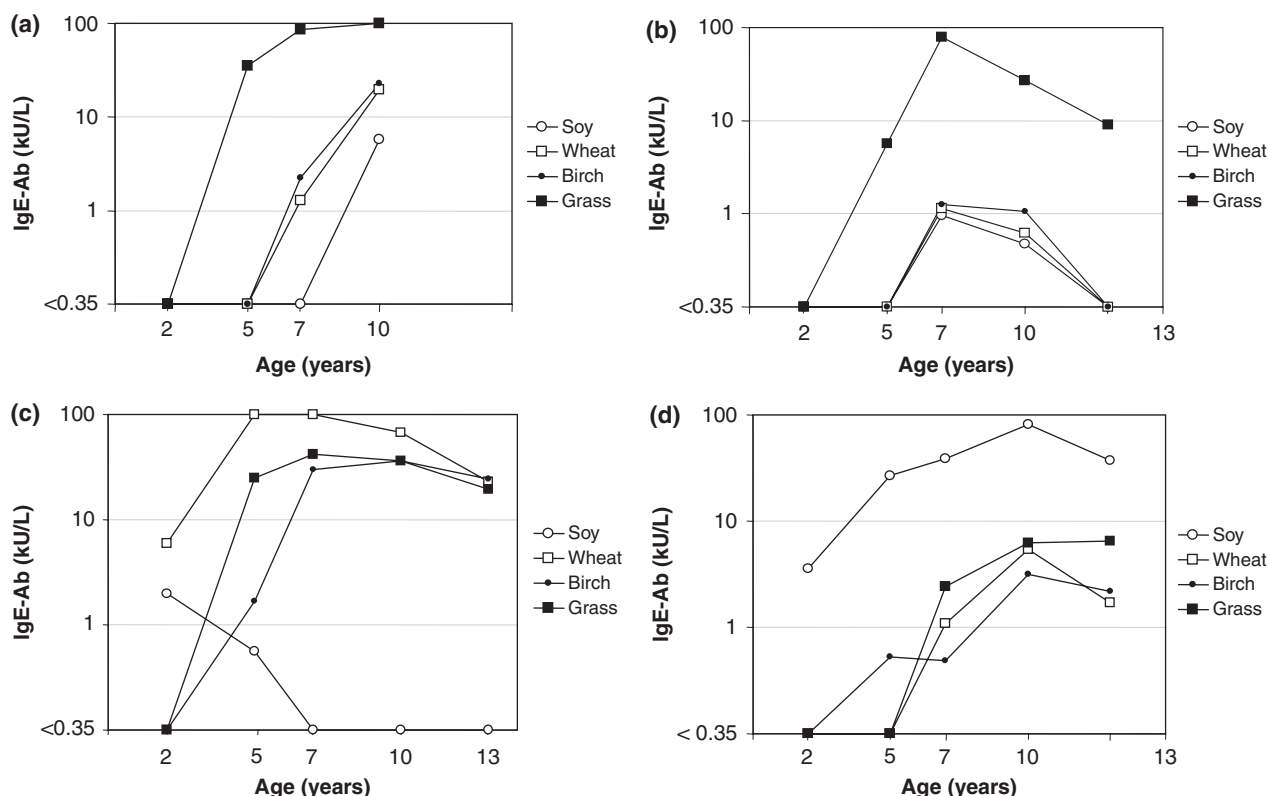


Fig. 4. Longitudinal trends of IgE responses to food and airborne allergens in individual children. Examples of longitudinal quantitative trends of serum levels of IgE-Ab to grass and birch pollens and to soy and wheat in four participants in the Multi-Centre Allergy Study cohort: (a) and (b) participants with possible primary sensitization to grass pollen and secondary IgE reactivity to soy and wheat; (c) and (d) participants with possible primary sensitization to wheat and soy, respectively. Ab, antibody.

soy. In the first group, the levels of IgE against grass pollens were in most cases 10 to 100 times higher than those against wheat and soy.

Discussion

In this data analysis of the German MAS cohort, we found that the point prevalence of IgE sensitization against two animal food allergens (cow's milk and hen's egg) declined with age, while that against two plant food allergens (soy and wheat) increased with age. We also found that sensitization to wheat and soy are highly linked to each other and that their common age related, rising trend results from the combination of two opposite components: first, a few, 'isolated' sensitizations occurring very early in life and declining or persisting over time; second, a major bulk of 'associated' sensitizations starting at any time during childhood, which are strongly linked to sensitizations to grass pollen and, to a lesser extent, to birch pollen. These findings have immunological, clinical, and epidemiological implications and a few methodological limitations.

The numerous and opposite characteristics (earlier vs. later onset, low vs. high prevalence, declining vs. rising trend, 'isolated' vs. 'associated' to pollen sensitization) of

the two components suggest that they are completely different in their aetiology. The first component is most likely due to true primary sensitization through the ingestion route; the second is most likely due to cross-reactivity to pollen antigens, having caused 'secondary sensitizations' through the inhalation route. This interpretation of our results is well supported by the existence of highly cross-reacting molecules in these four allergen sources. The strong cross-reactivity of grass pollen allergens and wheat allergens, both belonging to the same subfamily of Festucoideae, has been known for many decades [8–10]; tribes of Festuceae (including *Lolium perennis* and *Phleum pratensis*) and Triticeae (including wheat) share different groups of allergenic molecules (e.g.: profilins, LTP and grass pollen groups 2–4) (according to Allergome website. <http://www.allergome.org/> visited online on 29 May 2007) [11]. Cross-reactive molecules are shared between birch and soy [12–14]. However, it is not easy to predict whether all or only some of these cross-reactive molecules were responsible for the observed associations. A likely possibility is that we are observing a 'pseudo-association' between soy and wheat as a consequence of cross-reactivity with grass and birch pollen allergen sources. In this perspective, it is tempting to speculate that most observed cross-reactivity is due to profilins

(which is shared by all these four allergen sources). By contrast, as the ImmunoCAP soy extract we used has a low abundance of the Bet v 1 homologue Gly m 4 [12, 13], this molecule may play only a minor role in the observed associations. However, we should also consider that reactivity to profilin may not explain the isolated dual reactivity of some sera against soy and wheat. Finally, we did not investigate the immunological events preceding IgE cross-sensitization to grass/birch pollen and soy/wheat allergens. The production of cross-reacting specific IgE may be preceded by the expansion of cross-reactive allergen-specific T-helper cell clones, which in turn would stimulate production of humoral responses against the inducer as well as the elicitor allergen source. Further studies are required to prove this broader concept of 'primary sensitization'.

The clinical and epidemiological implications of our observations on secondary sensitizations are self evident. Our data suggest that the increasing trend of sensitization via the inhalation route to airborne allergen sources cross-reacting with food allergen sources is likely responsible for a parallel increasing trend of sensitization to cross-reacting food allergens. Secondary sensitization to soy caused clinical manifestations of food allergy, mostly in adults [12, 13, 15–17], while primary sensitization can involve children [18]. Nevertheless, one possibility is that children sensitized to birch may develop allergic reactions to soy later in their life, during adolescence or adulthood. If this is the case, more and more adults (due to a cohort effect) may increasingly suffer from allergic reactions to soy (and wheat), as a co-morbidity of their sensitization to grass and birch pollens. In this regard, the simultaneously expanding global consumption of Asian food, containing soy, may unfortunately facilitate this trend [13]. It has been recommended that patients allergic to birch pollen be advised to be reluctant with the consumption of soy protein rich products [15]. In our opinion, the changing epidemiologic scenario will assign to clinicians two opposite tasks: first, to avoid unnecessary dietary prescriptions (especially in children) in the case of clinically irrelevant secondary sensitization to wheat and soy; second, to promptly recognize type 2 food allergy in those few patients with pollinosis whose secondary sensitization, initiated in childhood, becomes clinically relevant later in life. Finally, our data suggest that observational studies based solely on serological assays (and not on food-challenge tests) would lead to overestimation of the prevalence of children and adults allergic to soy and wheat.

One limitation of our study could be a selection bias: parents who agreed to blood samples from their children may differ from those who did not approve to this invasive procedure. They might have been more allergic, therefore more interested in objective diagnostic measurements. Thus the prevalence of sensitization shown in this study cannot be extrapolated to the general population.

In addition, our findings might be geographically biased, as patterns of sensitization may be different in Southern Europe and especially in other regions of the world, where birch is not as diffuse as in Germany. Our study was conducted using high-quality allergenic extracts produced by the same manufacturer over a long period of time. It is unlikely, however, that during this time the composition of the solid phase of the ImmunoCAPs has been significantly modified, thus affecting our results. On the other hand, ImmunoCAP may be not sensitive enough in detecting IgE-Ab against certain cross-reacting molecules such as, for example, Gly m 4 in the assay for IgE against soy [12, 13]. If this is the case, however, the associations we observed are even underestimated. Last, IgE values above the detection threshold of 100 kU/L were not exactly measured; however, the use of median values for statistical analysis minimized the impact of this limitation.

In conclusion, our findings further reinforce the need to clarify which molecules are responsible for simultaneous reactivity against related food allergens and pollens [19]. This is the only strategy that will properly guide allergen-specific prevention and therapeutic intervention. Ultimately, the whole set of our data highlights the urgent need of shifting our approach to allergy from the present use of extracts to the future use of Component Resolved Diagnostics (CRD), which allows detection of sensitization at the molecular level. Whether CRD will improve this diagnostic aspect of allergy will be seen in the future [20].

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