

Sensitization patterns to food and inhalant allergens in childhood: A comparison of non-sensitized, monosensitized, and polysensitized children

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The clinical interpretation of children sensitized to numerous allergens is challenging. We examined differences between children sensitized to zero, one, or more allergens. This was a retrospective analysis of all specific IgE tests in children 0–18 yrs of age sent to our laboratory by general practitioners and hospital-based specialists for allergy testing between 1990 and 2003. Of all 9044 children tested, 5439 (60.1%) were not sensitized to any of the aeroallergens or food allergens tested. Three thousand six hundred and five children (39.9%) had one or more positive specific IgE tests, 1120 of which (31.1%) were monosensitized (73% to aeroallergens and 27% to food allergens), 1709 (47.4%) were sensitized to two to four allergens, and 776 (21.5%) to five or more allergens (polysensitization). Polysensitization was more common in children 4–11 yrs of age (24.8%) than in younger (18.7%) or older children (18.3%, $p < 0.001$), and more common in boys (9.8%) than in girls (7.3%, $p < 0.001$). Median total IgE values increased with increasing number of positive specific IgE tests ($p < 0.001$). House dust mite more commonly showed monosensitization (22.2%) than other aeroallergens (grass pollen 10.5%, tree pollen 3.6%, cat 2.9%, and dog 1.5%); cow's milk (27.6%) more commonly than other food allergens (hen's egg 9.7%, peanut 4.6%, wheat 0.8%, soy 0.7%). Between 55.7% (cow's milk) and 87.9% (soy) of children sensitized to food were co-sensitized to aeroallergens, while only 25.4% (house dust mite) to 39.5% (dog) of children sensitized to aeroallergens were co-sensitized to food. Polysensitization is common in children, in particular in boys. It is most common in school-aged children. The strong association with total serum IgE values and the striking co-sensitization between biologically unrelated allergens suggest that polysensitization is the expression of a distinct clinical, more severe, atopic phenotype, and not of biologic cross-reactivity to similar allergens.

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The prevalence of allergic disease in childhood has increased considerably in the past 25 yrs (1–5). Early and persistent sensitization to food allergens in the first years of life is a major risk factor for the development of aeroallergen sensitization and asthma (6–8). Consequently, the need of allergy testing has increased. Assessment

of allergic sensitization is considered to be important in the diagnosis and management of allergic disease throughout childhood (9).

Some atopic subjects are sensitized to only one allergen (monosensitization) while others show sensitization to more than one allergen in screening tests of allergy. Although this is widely

recognized by clinicians, few studies have specifically examined polysensitization in children. Three population studies (10–12) and two clinical studies (13, 14) showed that the prevalence of monosensitization and polysensitization in children was more or less comparable. Reviews on specific immunoglobulin E (IgE) testing do not discuss this phenomenon or its interpretation (9, 15, 16). The clinical interpretation of polysensitization is challenging. It is not clear whether polysensitization is the result of cross-sensitization to similar allergens, of cosensitization to allergens found in the same environment, or simply is an expression of the underlying atopic potential of the patient (11).

We retrospectively analyzed all specific IgE tests at our laboratory over a 14-yr period to assess the prevalence of polysensitization and monosensitization in children in whom allergy testing was requested by their physician. The influence of age, sex, and total serum IgE levels was examined, and patterns of sensitization to different allergens were assessed.

Methods

This was a retrospective analysis of all specific IgE tests carried out in children aged 18 or younger at our hospital's Clinical laboratory between January 1, 1990, and December 31, 2003. The clinical laboratory of the Isala klinieken, a large (900 beds) district general teaching hospital in Zwolle, the Netherlands, is the only laboratory in the catchment area of the hospital which performed specific IgE testing for general practitioners (GPs) and hospital-based specialists (pediatricians, dermatologists, and ear–nose–throat specialists) throughout the study period. In the Netherlands, sick children primarily visit the GP and can only be seen by a specialist after referral by the GP. Assessment of specific IgE is the single most commonly used method of allergy testing in the Netherlands. Skin prick testing was hardly used as a screening tool for allergy in children during the study period.

The ImmunoCap system (Pharmacia Diagnostics, Uppsala, Sweden) was used for specific IgE assessment throughout the study period. As the detection limit of the assay was 0.35 kU/l, sensitization was defined as a specific IgE concentration ≥ 0.35 kU/l. Screening tests were performed for the major allergens for children in the Netherlands. Food allergens comprised cow's milk, hen's egg, wheat, soy, fish, peanut, and tree nuts. Inhalant allergens comprised house dust mite, grass and tree pollen, dog and cat dander, and fungi.

The study was approved by the hospital's ethical review board. Because this was a retrospective analysis of stored laboratory data, the need for informed consent was waived by the ethical review board.

Data were analyzed with Statistical Package for the Social Science (SPSS, Chicago, Illinois, USA) for Windows, version 15. Differences between proportions were analyzed by χ^2 test, differences between means by Student's *t* test or oneway analysis of variance, as appropriate.

Results

Over the 14-yr period, specific IgE tests were carried out in a total of 9044 children (4632 boys, 51.2%). Clinical data on these children (symptoms, diagnosis, management) were not available for analysis. One or more positive specific IgE tests were found in 3115 children (39.9%), 1120 of which (31.1%) were monosensitized (Table 1). Monosensitization was more common for aeroallergens than that for food allergens ($p < 0.001$). Sensitization to 2–4 allergens was found in 1709 children (47.4% of sensitized children) and polysensitization (to five or more allergens) in 776 (21.5%).

When each allergen was considered separately, house dust mite more commonly showed monosensitization (516 of all 2323 children sensitized to house dust mite, 22.2%) than other aeroallergens: grass pollen 206/1971 (10.5%), tree pollen 42/1152 (3.6%), cat 34/1157 (2.9%), and dog 22/1440 (1.5%). For food allergens, cow's milk more commonly showed monosensitization (208/754, 27.6%) than the other allergens: hen's egg 53/545 (9.7%), peanut 32/693 (4.6%), wheat 4/506 (0.8%), and soy 3/414 (0.7%).

Age differences between different sensitization groups were highly significant ($p < 0.0001$) but small (Table 2). The number of children in each sensitization group at different ages is presented

Table 1. Number of children sensitized to only one allergen (monosensitized children)

Aeroallergens		Food allergens	
Allergen	Number (%)	Allergen	Number (%)
House dust mite	516 (46.1)	Cow's milk	208 (18.6)
Grass pollen	206 (18.4)	Hen's egg	53 (4.7)
Tree pollen	42 (3.8)	Peanut	32 (2.9)
Cat	34 (3.0)	Wheat	4 (0.4)
Dog	22 (2.0)	Soy	3 (0.3)
Total	820 (73)		300 (27)

The percentages in the table represent the proportion of all monosensitized children.

Table 2. Age distribution in children with different sensitization patterns

Sensitization group	Mean age (yrs)*	s.e.m.
Monosensitized (n = 1120)	8.5	0.2
Sensitized to 2–4 allergens (n = 1709)	9.7	0.1
Sensitized to five or more allergens (n = 776)†‡	9.0	0.2

*Oneway analysis of variance showed highly significant age differences between groups ($p < 0.0001$).

†Significantly older than monosensitized children ($p < 0.001$).

‡Significantly younger than children sensitized to 2–4 allergens ($p < 0.001$).

in Fig. 1. Polysensitization was more common in children aged 4 through 11 (435/1752, 24.8%) than in younger (106/567, 18.7%) and older children (235/1268, 18.5%, $p < 0.001$). This relationship of polysensitization to age was largely explained by sensitization to multiple inhalation allergens (Fig. 2). Sensitization to food allergens was most common in children younger than 4 yrs (448/2187, 20.5%), and lower in 4- to 11-yr-olds (670/4249, 15.8%) and children aged 12 and older (186/2608, 7.1%). In children sensitized to one or more food allergens, however, sensitization to multiple allergens was more common than sensitization to a single food allergen, and this difference increased with age (54.5% in 0- to 3-yr-olds, 59.5% in 4- to 11-yr-olds, and 75.3% in 12- to 18-yr-olds).

The gender distribution in the four sensitization groups is shown in Table 3. While the proportion of boys and girls was comparable in non-sensitized children, boys were more commonly sensitized to one or more allergens than girls ($p < 0.001$), and the gender difference increased with increasing number of positive specific IgE tests (Table 3). Polysensitization was more common in boys (455/4632, 9.8%) than in girls (322/4412, 7.3%, $p < 0.001$).

Fig. 1. Percentage of children sensitized to at least one allergen within each year of age sensitized to one (open bars), two to four (hatched bars) or five or more allergens (solid bars).

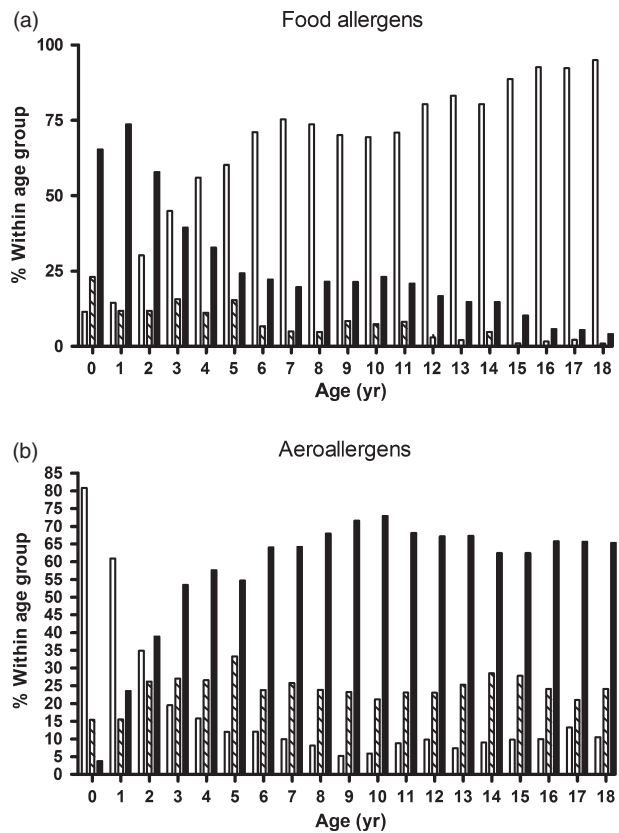
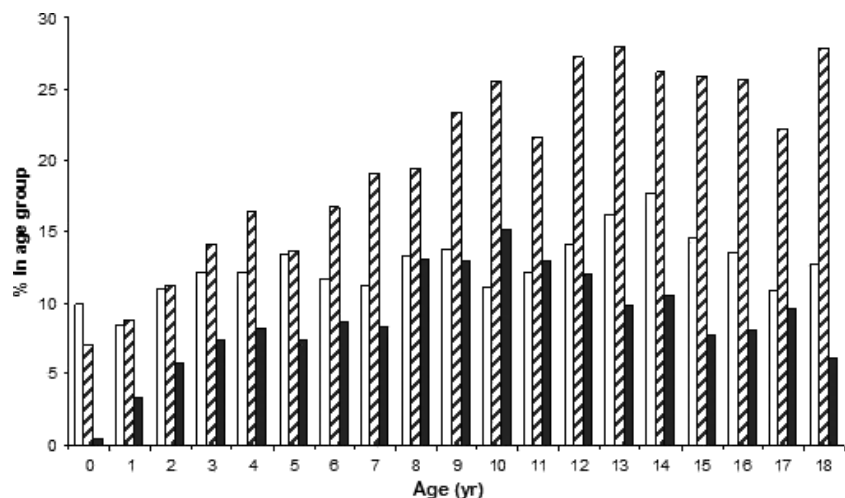


Fig. 2. Percentage of children, who were sensitized to at least one food or aeroallergen, within each year of age sensitized to no (open bars), one (hatched bars) or two or more aeroallergens (top panel), or food allergens (bottom panel).

The distribution of total serum IgE levels in the sensitization groups is shown in Fig. 3. Despite considerable overlap between the four sensitization groups, differences in total serum IgE levels between groups were highly significant ($p < 0.0001$).

Table 3. Gender distribution in children with different sensitization patterns

Sensitization group	Number (%) of boys
Monosensitized (n = 1120)	598 (53.4)
Sensitized to 2–4 allergens (n = 1709)	957 (56.0)
Sensitized to five or more allergens (n = 776)*†	455 (58.6)
Total: 9044	4632 (51.2)

*Significantly more boys than in monosensitized children ($p = 0.002$).

†Difference in gender distribution with children sensitized to 2–4 allergens not significant ($p = 0.118$).

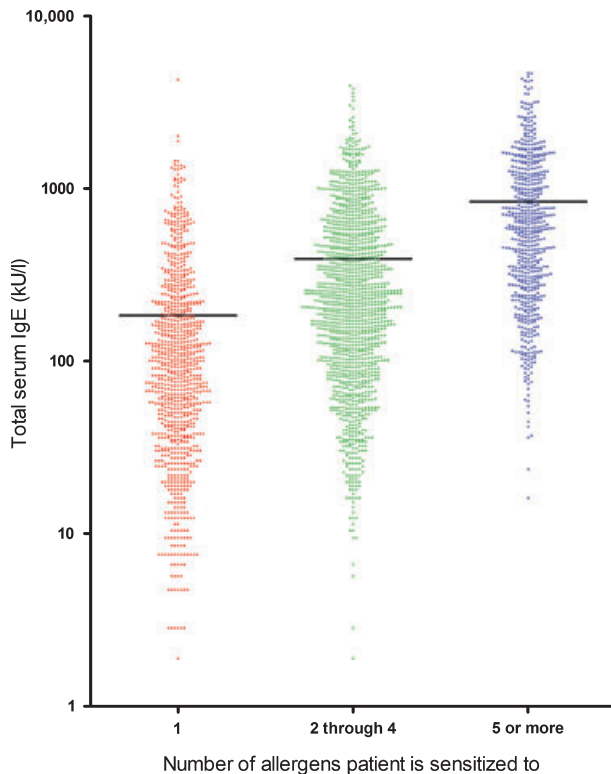


Fig. 3. Distribution of total serum IgE levels in different sensitization groups (see text). Horizontal bars represent median values.

The cosensitization patterns of the five most common food allergens to the five most common aeroallergens are presented in Table 4. Cosensitization to aeroallergens was common in all children sensitized to food allergens, but the degree of cosensitization varied between the different food allergens. Most children sensitized to food were cosensitized to aeroallergens, varying from 55.7% for cow's milk to 87.9% for soy (Table 4, upper panel).

Similarly, cosensitization to food allergens was common in children sensitized to aeroallergens, in particular those sensitized to tree pollen, cat, and dog (Table 4, lower panel). Overall, children sensitized to food allergens more commonly

showed sensitization to aeroallergens than vice versa ($p < 0.001$).

Table 5 shows the frequency of individual allergen sensitization rates in the 776 polysensitized children. Sensitization to aeroallergens (98.3%) was much more common than sensitization to food allergens (74.2%, $p < 0.001$), but if food allergen sensitization was present, it almost always included peanut. Of all 693 children sensitized to peanut, 484 (69.8%) were polysensitized.

Discussion

This study shows that sensitization to multiple allergens is considerably more common than monosensitization in children referred to a GP or hospital-based specialist for allergy testing. Polysensitization (sensitization to five or more allergens) is more common in school-aged children than in preschool children or in adolescents, and this age relationship appears to be largely determined by a high prevalence of sensitization to multiple aeroallergens in this age range; sensitization to multiple food allergens was more equally spread throughout childhood. Polysensitization was more common in boys than in girls, and it was strongly related to high total serum IgE levels. Cosensitization between food and inhalant allergens was very common, in particular for soy, wheat, and peanut.

Polysensitization has received little attention in the pediatric allergy literature to date. Studies in adults and mixed adult-child groups suggest that polysensitized individuals have more severe atopic disease (17) and a lower health-related quality of life than monosensitized subjects (18). In one of the few studies in the pediatric age range, children with polysensitization had higher symptom scores and a poorer response to immunotherapy than monosensitized children (13). It appears, therefore, that polysensitization points to a more severe clinical atopic phenotype than monosensitization, although the underlying pathophysiology is unclear. The only study examining immunologic parameters in monosensitized and polysensitized children showed similar interleukin 10 values between these groups (13). Both genetic and environmental factors should be considered in the pathogenesis of polysensitization. In our study, boys were more likely to be polysensitized than girls (Table 3); this has also been observed by others (13, 19, 20). Polysensitized children are more likely to have polysensitized parents than monosensitized children (20), but children are more likely to be polysensitized than their parents (19, 20). This

Table 4. Cosensitization patterns between food allergens and aeroallergens in children sensitized to one or more allergens

Cosensitization to In children sensitized to	House dust, %	Grass pollen, %	Tree pollen, %	Cat dander, %	Dog dander, %	Percentage of children cosensitized to one or more aeroallergens, %
Cow's milk (n = 754)	40.5	36.3	24.0	31.7	37.3	55.7
Hen's egg (n = 545)	49.5	39.4	30.3	39.4	45.5	64.2
Peanut (n = 693)	56.6	62.9	53.7	46.8	61.0	79.2
Wheat (n = 506)	63.6	75.1	64.8	50.6	68.6	85.8
Soy (n = 414)	63.5	74.6	70.3	52.9	70.5	87.9

Cosensitization to In children sensitized to	Cow's milk, %	Hen's egg, %	Peanut, %	Wheat, %	Soy, %	Percentage of children cosensitized to one or more food allergens, %
House dust mite (n = 2323)	13.1	11.6	16.9	13.9	11.3	25.4
Grass pollen (n = 1971)	13.9	10.9	22.1	19.3	15.7	29.4
Tree pollen (n = 1152)	15.7	14.3	32.3	28.5	25.3	38.5
Cat dander (n = 1157)	20.7	18.6	28.0	22.1	18.9	38.2
Dog dander (n = 1440)	19.5	17.2	29.4	24.1	20.3	39.5

Example: 754 children were sensitized to cow's milk; 305 (40.5%) of these were also sensitized to house dust mite, 274 (36.3%) to grass pollen. Sensitization to house dust mite was found in 2323 children, 304 of which (13.1%) were cosensitized to cow's milk, 269 (11.6%) to hen's egg, etc.

Table 5. Individual allergen sensitization rates in 776 polysensitized children (sensitized to five or more allergens)

Allergen	Number	%
House dust mite	643	82.9
Grass pollen	682	87.9
Tree pollen	609	78.5
Cat	578	74.5
Dog	675	87.0
At least one aeroallergen	763	98.3
Cow's milk	294	37.9
Hen's egg	268	34.5
Peanut	484	62.4
Wheat	414	53.4
Soy	360	46.4
At least one food allergen	576	74.2

suggests that environmental factors are also important.

Given the fact that regulation of specific IgE synthesis is orchestrated by polarization of antigen-presenting cells responding to microbial exposure through toll-like receptors (21), it is likely that environmental exposure to bacteria and other micro-organisms (or lack thereof) plays a role in the development of polysensitization, either through polyclonal stimulation of specific IgE synthesis or through elevating the propensity to generate IgE in general. The latter mechanism seems more likely, because of the strong link observed between total serum IgE levels and the degree of polysensitization (Fig. 3). This association has also been observed in a previous study in Korea (13).

The importance of age as a factor determining polysensitization in our study was not as clear-

cut as has been suggested by others (Table 2, Figs 1 and 2) (22). In previous studies, the risk of polysensitization increased with age (13, 14, 22, 23), although polysensitization has also been found in 20–50% of children of 3–4 yrs of age (8, 10, 12). In our study, polysensitization was most common in children 4–11 yrs of age (Fig. 1). It seems unlikely, therefore, that polysensitization simply represents increasing expression of the atopic phenotype with increasing age (17). It is largely explained by increasing degrees of multiple sensitization to aeroallergens in school-aged children (Fig. 2). Although sensitization to food allergens was most common in young children, sensitization to multiple food allergens became more prevalent with increasing age in children sensitized to food allergens. Food allergen sensitization has been observed in approximately 5% of teenagers in the UK (24). Our results confirm and extend these findings by showing that sensitization to food allergens in teenagers is most commonly seen in the context of polysensitization to a mixture of several food and aeroallergens.

The clinical interpretation of multiple sensitizations in individual patients can be challenging. Although multiple sensitizations are traditionally interpreted as cross-reactivity between biologically related allergens, they can also be viewed as an unspecific expression of the underlying atopic potential of the child (11). The pattern of cosensitization observed in our study (Table 4) is comparable to that observed in population studies of polysensitized children (11, 12). For example, 45% of children sensitized to two pollen in the Swedish BAMSE study at the age

of 4 yrs were also sensitized to peanut (12). In the ALSPAC cohort in the UK, children who were sensitized to mixed grass pollen at the age of 7 were 13 times as likely to be sensitized to peanut than children who were not sensitized to grass pollen (11). Although in both these cohorts cross-sensitization between biologically similar allergens was also observed, a considerable proportion of the associations of sensitizations between different allergens could not be explained by such biologic cross-reactivity (9). This is comparable to the results in our study. Most children sensitized to food are cosensitized to at least one aeroallergen, and this is true for almost all children sensitized to wheat and soy (Table 4). It seems likely, therefore, that polysensitization cannot be fully explained by biologic cross-reactivity between allergens sharing comparable epitopes.

In our large sample of children tested for allergy, almost one-quarter of sensitized children showed polysensitization to five or more allergens. In these polysensitized children, sensitization to aeroallergens was more common than that to food allergens (Table 5). In polysensitized children sensitized to food, peanut was almost always included. The large majority of children sensitized to peanut were polysensitized (69.8%). Although it has been shown that the degree of peanut sensitization helps in predicting clinical response to peanut (25, 26), cosensitization rates to other allergens have never been described in these studies. Our results suggest that peanut sensitization is commonly encountered in polysensitized individuals, and it is our clinical experience that many of these children tolerate peanut. The clinical relevance of peanut sensitization in children with different cosensitization patterns should be explored in more detail.

The main disadvantages of our study are that it is retrospective in nature and that we do not have any clinical data of our patients. The main strengths are the large size, the use of a single laboratory, and the fact that this cohort comprised children presenting to a doctor, presumably with symptoms of allergic disease. Our data, therefore, are supplementary to the results from population-based studies.

In conclusion, polysensitization to multiple allergens occurs frequently in children referred for allergy testing. Boys are more frequently polysensitized than girls. There is no clear increase with age: polysensitization is most common in school-aged children. The strong association with total serum IgE values and the striking cosensitization patterns between biologically unrelated allergens suggest that polysensitization

is the expression of a distinct clinical, more severe, atopic phenotype, and not of biologic cross-reactivity to similar allergens. Future studies are needed to unravel the pathophysiology of this fascinating phenomenon.

Conflict of interest

None declared.

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