

*Original article***Patterns of sensitization to food and aeroallergens in the first 3 years of life**

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Background: There is a paucity of longitudinal studies of allergen sensitization in childhood.

Objective: To investigate the pattern of sensitization in early childhood.

Methods: A nested cohort of children ($n = 543$) were followed up from birth and given a skin prick test (SPT) at 1, 2, and 3 years of age. A detailed clinical history was obtained.

Results: The prevalences of sensitization to aeroallergens were 1.3%, 6.4%, and 10.7% at 1, 2, and 3 years of age. The figures for food allergens were 2.8%, 3.9%, and 3.7%. There was a statistically significant increase in the prevalence of sensitization to ≥ 1 allergen between years 1 and 2 ($P < .001$) and years 2 and 3 ($P = .032$). Among those with a positive SPT at 1 year, 29% tested positive to additional allergens at 2 years ($P = .0054$).

Sensitization to milk or egg at 1 year was a predictor for increased sensitization to peanut at 3 years (odds ratio, 34.8; $P < .0001$).

Sensitization to egg at 1 year was associated with increased sensitization to aeroallergens at 3 years (odds ratios, house dust mite, 27.1, $P < .001$; cat, 8.9, $P < .01$; grass, 11.8, $P = .005$). For peanut and cat allergens, wheal size increases with the age of the child ($P = .009$ and $P = .017$, respectively).

Conclusion: Sensitization to allergens as demonstrated by positive SPT tends to increase with age, and this change can be detected in the first 3 years of life.

Clinical implications: The high predictive value for early sensitization and a linear increase in SPT reactivity provide an opportunity for early intervention. (*J Allergy Clin Immunol* 111:1111-1117, 2003.)

Key words: Sensitization, food and aeroallergens, early childhood, atopy

The skin prick test (SPT) is safe, low-cost, and easy to perform for the assessment of specific sensitization to allergens.¹ It is considered to be the test of choice in

Abbreviations used

FHS: Food hypersensitivity
HDM: House dust mite
SPT: Skin prick test

clinical practice² and is usually supplemented by a spectrum of additional information obtained through the clinical history. SPT is also often used in epidemiologic studies in which the incidence of sensitization to allergens is usually one of the main outcomes.

This common use of SPT is based on the assumption that it has a high reproducibility—that is, there is a strong agreement between independent results obtained with the same method on identical patients. Although evidence suggests that this may be the case in the short term (day to day, week to week^{3,4}), very little information is available on its longitudinal variability.

Historical population-based studies⁵⁻⁸ have shown a high long-term stability of sensitization to some specific aeroallergens. However, these findings are based on cohorts followed nearly 20 years ago.

Skin prick test positivity (sensitization) is a risk factor for the development of allergic disease.⁹ In addition, because doctor-diagnosed IgE-mediated food allergy is more prevalent among the very young,¹⁰ if SPT is to be used as a common instrument, it is important for clinicians to know what the predictive values are for subsequent tests. This in turn will help with treatment of this group indicating the predictive value of a single testing for subsequent SPTs.

Therefore, the aim of this study was to investigate the pattern of sensitization in early childhood. We aimed to evaluate the longitudinal changes of SPT reactivity to common aeroallergens and food allergens in a community-based population of children followed from birth for 3 years and to assess the stability of the SPTs over this period.

METHODS**Population**

The children reported on in this article were taking part in a population-based cohort study of the prevalence of food hypersensitivity, the details of which are reported in full elsewhere.¹¹ The birth

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cohort was recruited through antenatal clinics and included all babies born on the Isle of Wight (United Kingdom) between September 2001 and August 2002. Ethical approval for the study was obtained from the Isle of Wight, Portsmouth and South East Hampshire Local Research Ethics Committee (Ref: 09/01). Within this original cohort, a nested subgroup of children consented to skin prick testing at 1, 2, and 3 years of age. These form the basis of the findings described here.

A detailed clinical history, using a standardized questionnaire, was obtained at recruitment and at each of the follow-up points. The questionnaire included information on family structure, family history of atopy, smoking habits, pet ownership, reported symptoms of atopy, and physician-diagnosed symptoms.

Infants were invited for a food challenge if they had never previously knowingly eaten a large amount of the food to which they had a positive SPT or if they had a previous adverse reaction to foods regardless of their SPT result. Food challenges were conducted with all foods except peanuts and sesame, because it is thought that infants should not be exposed to these foods in the first year of life (Sampson H et al, Personal communication, May-July 2001). Children were challenged within a maximum period of 6 weeks to ensure food hypersensitivity (FHS) was diagnosed as early as possible.

Challenges were performed following an algorithm. Procedures for both 1-day and 1-week challenges have been described previously.¹²

SPT procedure

Children were given an SPT to a standard battery of predefined foods (milk, egg, wheat, peanut, sesame, and cod fish) and aeroallergens (house dust mite *Dermatophagoides pteronyssinus* [HDM], cat, and grass). SPTs were conducted with commercial extracts of standard food and aeroallergens (Soluprick SQ allergens; ALK Allergologisk Laboratorium A/S, Hørsholm, Denmark) placed on the forearm in a standardized order. Two experienced allergy nurses performed all the tests during the whole study using the same standardized procedure. The wheal perimeter was transferred to paper from the skin by using translucent tape. Measurement was undertaken in standard fashion, measuring the largest wheal diameter and that perpendicular to it, and recording the mean of these 2 values. Results were classified as positive if the mean diameter was 3 mm or more in the presence of a negative control (0.9% saline, Soluprick SQ allergens) and a positive histamine (10 mg/mL, Soluprick SQ allergens) reaction after 15 minutes.

Data analysis

Frequency tables were produced at each time point, from which prevalence rates were computed for each allergen together with 95% CIs. Changes in prevalence rates over time were tested for significance using the McNemar test for paired samples. Comparisons between independent population subgroups were made using the Fisher exact test.

RESULTS

The original birth cohort consisted of 969 children (91% of the target population). Of these, 807 (83.3%) children were seen at 1, 2, and 3 years of age. They were all approached to be skin tested on each occasion. Overall, the consent rate to skin prick testing was high, with three quarters or more of children being skin tested at any 1 time point. Lack of parental consent was the main reason that other children were not tested.

TABLE I. Characteristics of the study population

	All subjects (N = 543) Percentage	Sensitized	
		Yes (N = 78) Percentage	No (N = 465) Percentage
Sex			
Male	52	63	50
Female	48	37	50
Sibship			
First born	46	53	44
Subsequent child	54	47	56
Pet ownership			
Yes	73	66	75
No	27	34	25
Reported family history of atopy			
Yes	84	93	92
No	16	7	8
Reported maternal asthma			
Yes	22	31	20
No	78	69	80
Reported maternal atopy			
Yes	58	65	56
No	42	35	44
Exposed to smoke			
Yes	48	47	49
No	52	53	51

The analysis presented here was confined to the 543 children (284 boys, 52.3%) who were given SPTs on all 3 occasions. These children did not differ from those who were tested less frequently in terms of sex, reported family history of atopy, or rate of sensitization to individual allergens the occasions that they were tested. Table I shows some of the basic characteristics of this nested cohort.

The prevalence of sensitization to any of the predefined allergens tested was 3.1% (95% CI, 1.8% to 5.0%) at year 1, 8.7% (6.4% to 11.3%) at year 2, and 11.4% (9.0% to 14.4%) at year 3. The corresponding figures for aeroallergens were 1.3% (0.5% to 2.6%), 6.4% (4.5% to 8.8%), and 10.7% (8.2% to 13.6%). For food allergens, the rate of sensitization was 2.8% (1.5% to 4.5%), 3.9% (2.4% to 5.8%), and 3.7% (2.2% to 5.6%) at 1, 2, and 3 years of age, respectively (Fig 1).

Of the 15 children sensitive to food at 1 year of age, 5 (33.3%), 7 (46.6%), and 12 (80.0%) were sensitive to aeroallergens at 1, 2, and 3 years of age, respectively.

Of the 17 children sensitized to any allergen at year one, 13 (76.5%) remained sensitive at year 2, and 11 (64.7%) continued to remain sensitive to year 3.

Among the 21 sensitive to food at 2 years of age, 9 (42.9%) were also sensitive to aeroallergens. By year three, 14 (66.6%) of these were sensitive to aeroallergens.

Of the 47 sensitive to any allergen, 33 (70.2%) remained sensitive at year 3.

At 3 years of age, among the 20 sensitized to food, 16 (80.0%) were also sensitive to aeroallergens.

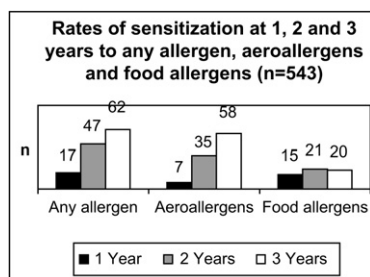


FIG 1. Rates of sensitization at 1, 2, and 3 years to any allergen, aeroallergens, and food allergens.

There was a statistically significant increase in the prevalence of sensitization to 1 or more allergen between year 1 and year 2 (McNemar test, $P < .001$) and also between year 2 and year 3 ($P = .032$).

Children with early-onset sensitization to allergens (at year 1) were more likely to show increased sensitivity to allergens later in life. Of the 526 children who tested negative to all allergens at 1 year, 35 (6.7%) subsequently tested positive to 1 or more allergens at year 2. Among the 17 children who tested positive to at least 1 allergen at year one, 5 (29%) subsequently tested positive to additional allergens at year 2 ($P = .0054$). Similar results emerged between years 2 and 3. Among those children who tested negative in year two, 5.6% became positive to 1 or more allergens by year 3. Of those already positive at year two, 19% subsequently tested positive to additional allergens the following year ($P = .0025$). Transient loss of reactivity was observed in 1 child who had a positive SPT to grass allergen at 1 year. At 2 years, his SPT data to grass were negative, and at 3 years, he had a positive reaction to grass.

The positive predictive value of sensitization at 1 year of age for sensitization at 3 years of age to 1 or more allergen was 76.5% (13/17; 95% CI, 50% to 93%). The negative predictive value of sensitization at 1 year of age for sensitization at 3 years of age was 91% (477/526; 95% CI, 87.9% to 93%).

The rate of sensitization to individual food and aeroallergens at 1, 2, and 3 years of age and the associated clinical symptoms of atopy are summarized in Table II.

At 3 years of age, the prevalence of sensitization was greater among boys (Fisher exact test, $P = .022$). There was no significant association between sensitization and sibship (coded as first born or not, $P = .280$) or family history of smoking ($P = 1.000$). In addition, we did not find any association between sensitization to cat and cat ownership. We did not find any association between sensitization and any reported family history of atopy (defined as reported history of atopy in mother, father, or the sibling). However, when reported maternal atopy was considered on its own, we did find a significant difference at 1 and 2 years of age ($P = .045$ and $.032$, respectively) between the sensitized and unsensitized children. This difference was not present at 3 years or if the first 3 years of life were considered cumulatively.

Sensitization to milk or egg at 1 year of age was a predictor for increased sensitization to peanut at 3 years

of age ($P < .0001$; odds ratio, 34.8; 95% CI, 9-129; $P < .0001$). In addition, sensitization to egg at 1 year of age was strongly associated with increased sensitization to HDM, cat, and grass at 3 years of age (odds ratios, HDM, 27.1, 7.3-112.5, $P < .001$; cat, 8.9, 1.4-39.3, $P < .01$; grass, 11.8, 1.9-53.7, $P = .005$).

Changes in sensitization during the first 3 years are presented in Table III. With the exception of egg allergen, there was an increase over time in the rate of positive reactions. Seven children converted from positive to negative skin test to egg between year 1 and year 3. Three children consumed egg throughout without any adverse reaction. Three had a positive double-blind, placebo-controlled food challenge at 1 year of age but had introduced egg to their diet by 3 years of age without any adverse effect. In 1 case, the oral challenges could be completed at 1 or 2 years of age, but by the age of 3 years, this child had a positive open food challenge to egg.

Changes of wheal size over time were also investigated. The mean diameters for histamine were 3.3, 4.6, and 4.8 mm at 1, 2, and 3 years of age, respectively (Fig 2). A Friedman Rubin nonparametric alternative to a 1-way repeated-measures ANOVA indicated significant differences in histamine wheal diameter over time ($T = 245.3$; $P < .0001$). Subsequent multiple comparisons indicated significant year on year increases (1 vs 2, $P < .001$; 2 vs 3, $P = .0036$).

Looking at individual allergens (Figs 3 and 4), a test of linear trend suggested that only for peanut and cat allergens, wheal size increases with the age of the child (peanut allergen, $r = 0.397$, $P = .009$; cat allergen, $r = 0.283$, $P = .017$).

DISCUSSION

This is the first study to report on trends in skin test reactivity in the first 3 years of life using a birth cohort followed up prospectively. We tested the children to some of the most common United Kingdom allergens, and the reaction prevalence to any allergen increased significantly with age from 3.1% at 1 year of age to 11.4% at 3 years of age.

Frequency of sensitization to each of the aeroallergens (HDM, cat, grass) was $<1\%$ in the first year of life. By the time the children were 3 years old, approximately 7% were sensitized to HDM. Among the food allergens, egg was the most frequent allergen children were sensitized to in the first 2 years of life, and by 3 years of age, sensitizations to peanut and egg were the most common in this cohort.

This increase in the rate of sensitization as the children grow older could be a manifestation of increasing skin reactivity to histamine and thus an increase in allergen reaction size on SPT. It could also reflect maturation of the immune system with increased capacity to respond to allergens, or an increase in exposure to different allergens as the children grow and experience environmental exposures. A possible explanation for the patterns observed in terms of food to aeroallergens sensitivity could be the

TABLE II. Frequency of sensitization to individual allergens and atopic characteristics of the sensitized cases

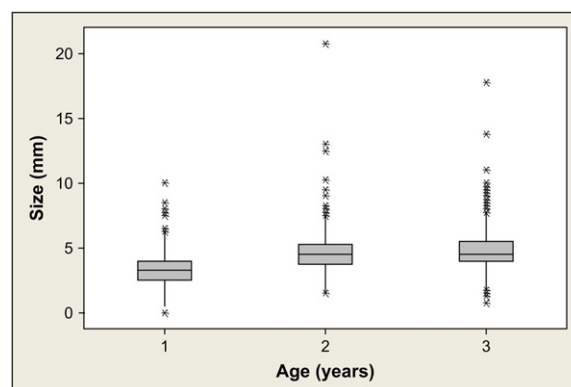
	1-Year-olds (n = 543)		2-Year-olds (n = 543)		3-Year-olds (n = 543)	
	No. sensitized	No. with atopic diseases*	No. sensitized	No. with atopic diseases*	No. sensitized	No. with atopic diseases*
Milk	2	2 (both with FHS and E)	5	5 (3 with FHS and E; 2 with E)	3	2 (1 with FHS and E; 1 with D)
Egg	13	12 (7 with FHS and E; 5 with E)	13	11 (7 with FHS and E; 4 with E)	7	7 (4 with FHS and E; 3 with E)
Fish	1	—	3	3 (all with E)	2	—
Wheat	—	—	1	1 (FHS and E)	5	3 (all with E)
Peanut‡	3	2 (1 with E and reported FHS to peanuts; 1 with E)	11	7 (all with E)	7	6 (3 with FHS; 3 with E)
Sesame‡	2	2 (both with E)	3	3 (all with E)	4	4 (1 with FHS; 3 with E)
Grass	3	3 (2 with E; 1 with RW)	4	3 (all with E)	16	11 (1 with asthma; 6 with E; 4 with RW)
HDM	3	2 (both with CoNi)	19	18 (11 with E; 4 with RW; 2 with CoNi; 1 with A)	37	30 (15 with E; 5 with A; 10 with A and E)
Cat	1	1 (A)	17	12 (2 with A; 8 with E; 2 with RW)	20	15 (2 with A; 5 with E; 4 with A and E; 2 with RW; 2 with swollen eyes)

*Atopic conditions and manifestations are defined as diagnosed FHS to the food allergen on the basis of double-blind, placebo-controlled food challenge, diagnosed eczema (E), diarrhea (D), diagnosed asthma (A), reported wheeze (RW), and cough at nighttime (CoNi).

‡Children were not challenged with peanut or sesame until 3 years of age.

TABLE III. Changes in sensitization during the first 3 years

Allergen	Prevalent cases		Change		
	Year 1	Year 3	– to +	+ to –	Net absolute change in prevalence (%)
HDM	3	37	36	2	+6.3
Grass	3	16	15	2	+2.4
Cat	1	20	20	1	+3.5
Milk	2	3	3	2	+0.2
Wheat	0	5	5	0	+0.9
Egg	13	7	1	7	–1.1
Fish	1	2	2	1	+0.2
Peanut	3	7	6	2	+0.7
Sesame	2	4	3	1	+0.4

**FIG 2.** Changes in histamine wheal diameter.

development of tolerance to food and an increased exposure to aeroallergens.

By 3 years of age, there was a higher prevalence of sensitization among boys. In another population-based birth cohort in Europe,¹³ the investigators reported sensitization rates of 7% and 13% at 1 and 4 years of age. Although our 3-year data (11.4%) suggest a similar rate of sensitization, our cohort had a lower rate of sensitization to any of the test allergens at 1 year (3.1%). Similar to this study,¹³ we found that the most common allergen at 1 year was egg, and at 3 years, HDM and cat appeared to be the major allergens.

In terms of persistence of the sensitization, of those who were sensitized to at least 1 allergen at 1 year, more than

70% remained sensitive at year 2, and 65% continued to remain sensitive at year 3, a finding that has been reported by others as well.¹⁴

Those sensitized to milk and egg at 1 year (and 2 years) of age were significantly more likely to be sensitized to peanut by 3 years of age. One explanation may be that this is another manifestation of the allergic march phenomenon, and indeed, as we have found, early onset of sensitization (at 1 year of age) is more likely to lead to sensitization to other allergens later. In terms of clinical allergy to these foods (ie, symptomatic and challenge-proven), we found that subjects who were allergic to either egg or milk at 1 year were about 6 times more likely to develop allergy to peanut, but the increase in risk failed to

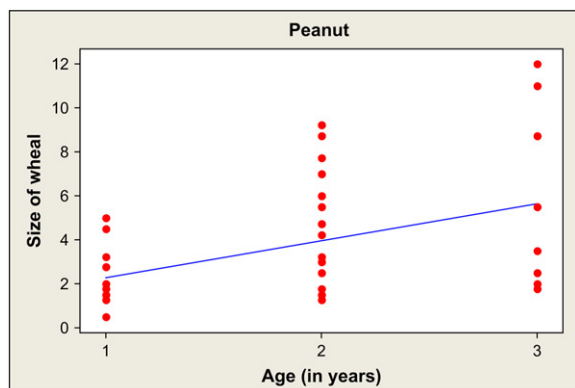


FIG 3. Changes in wheal diameter for peanut.

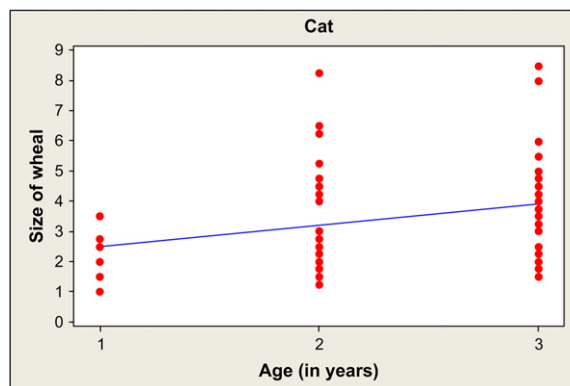


FIG 4. Changes in wheal diameter for cat.

reach statistical significance. These data need to be treated cautiously because the numbers involved are small.

Sensitization to egg was also strongly associated with sensitization to aeroallergens at 3 years of age. This relationship between egg and aeroallergen sensitivity has also been shown by Nickel et al,¹⁵ who measured specific IgE antibodies. In parallel, Tariq et al¹⁶ showed that egg allergy in early childhood predicts respiratory allergy by the age of 4 years.

Four other studies⁵⁻⁸ have investigated the longitudinal variability of SPTs among children. Unfortunately, direct comparison with our data is difficult because the populations studied had a different age profile and focused mainly on aeroallergens, and these studies used a different definition of a positive reaction. Three of the studies⁶⁻⁸ included children who were at least 7 years old, and only the study by Barbee et al⁵ included a small number ($n = 18$) of children under the age of 5 years. In our study, we used the recommended¹⁷ 3-mm cutoff for a positive reaction, which was not the case with previous studies. Despite these differences, some aspects of our findings are similar to the earlier studies with older children. These studies reported an increased prevalence of sensitization with age.⁵⁻⁸ We have shown that this increase in sensitization prevalence can be detected in the first 3 years of life. This indicates that overall, the prevalence is greater than the disappearance of previously positive SPT results.

In this cohort, boys were significantly more likely to have a positive skin test, and maternal history of atopy was associated with an infant's sensitization in the first 2 years of life. A number of studies have shown male sex and positive family history to be significant risk factors for sensitization.^{13,14,18-20} In our cohort, there was a weak association with maternal atopy that disappeared by the time children were 3 years old. One study that was similar in design to ours¹³ and used a population-based cohort found that parental hay fever was associated with an infant's positive SPT to cat at 1 and 4 years of age and to pollen at 4 years of age. In this study, maternal hay fever was associated with sensitization to pollen in the infant at 4 years of age. Although neither our study nor this particular study

performed an SPT on the parents, we both used similar approaches to establish family history of atopy.

We attempted to minimize potential bias in our study. We feel the likelihood of sampling bias is fairly minimal because the original cohort represented 93% of the target population, and the follow-up rate was consistently above 80%. Although three quarters or more of the study population were skin tested on each occasion, for validity we report only on those who were tested at every time point. Children included in the analysis do not differ demographically or in known risk factors, such as family history of atopy, compared with the rest of the study population. The children reported on in this article appear to be from highly atopic families. However, it needs to be emphasized that this is based on reported history of atopy. When the whole cohort is considered (including those who were not skin tested on all 3 occasions), this reported rate of family history was still quite high (73%). There is likely to be a discrepancy between reported and verified history of atopy. Having said this, a recent published study²¹ used a similar approach to our study. In this study, a total of 1105 children were recruited. A positive family history of asthma, eczema, or hay fever was reported in 84% of children.

All the skin tests were performed by only 2 very experienced allergy research nurses using a standardized procedure. On each occasion, children were tested within 4 weeks of their birthdays, so any potential seasonal effect was minimized.

Reversion (change from a positive to negative SPT) has been previously reported to be extremely rare, particularly for older children and adults.^{5,6} In this study, the numbers sensitized were relatively small, and consequently, data on reversion need to be treated with caution. Nevertheless, there were a few children who had outgrown their sensitization identified at 1 year of age by the time they reached age 3 years. This was most pronounced with sensitization to egg, where nearly half of those who were sensitized at 1 year of age were no longer sensitized at 3 years. We do not feel this loss of SPT positivity is a result of measurement error, although misclassification caused by the test

performance (ie, false-positives and false-negatives) cannot be ruled out.

In conclusion, we have shown that skin sensitization tends to increase with age, and this change can be detected in the first 3 years of life. On the basis of our findings, the interpretation of pediatric population data in longitudinal studies that have used SPT is likely to be reliable in indicating changing patterns of IgE-mediated immunologic reactivity in early childhood. However, interpretation on the basis of changes of individual SPT results is less likely to be reliable in indicating changing patterns of IgE-mediated immunologic reactivity in early childhood and may occasionally be a result of transient loss of reactivity.

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