



Patterns of allergen sensitization and self-reported allergic disease in parents of food allergic children



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ABSTRACT

Background: Sensitization in adults has not been extensively studied.

Objective: To investigate patterns of allergen sensitization in parents of food allergic children and to compare self-report of allergic disease with specific IgE (sIgE) measurements.

Methods: A total of 1,252 mothers and 1,225 fathers of food allergic children answered standardized questionnaires about demographics, home environment, history of atopic diseases, and food allergy. Skin prick testing and sIgE serum tests were performed to 9 foods and 5 aeroallergens.

Results: A total of 66.1% of parents were sensitized to either a food or aeroallergen. Mean sIgE levels were low for all foods tested. A total of 14.5% of mothers and 12.7% of fathers reported current food allergy. Only 28.4% had sensitization to their reported allergen. Fathers had significantly higher rates of sensitization to both foods and aeroallergens ($P < .01$) than mothers. Logistic regression evaluating predictors of self-reported food allergy revealed statistically significant positive associations in fathers with self-reported asthma, environmental allergy, and eczema. For mothers, significant positive associations were found with environmental allergy and having more than 1 food allergic child.

Conclusion: This cohort of parents of food allergic children found higher rates of sensitization to foods and aeroallergens compared with the general population. However, food sIgE levels were low and correlated poorly with self-reported food allergy. Sex differences in sensitization to foods and aeroallergens were seen.

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Introduction

Similar to other allergic diseases, the prevalence of food allergy has been increasing for the last several decades.^{1,2} Although the cause for this increase in food allergy has not yet been elucidated, an interaction between genetic and environmental factors, including the timing and route of allergen exposure, has been implicated.^{3–7} Sensitization, or the presence of allergic antibody, is a prerequisite for development of an allergic response to an allergen. Patterns of sensitization to environmental and food allergens have previously been studied in children in an effort to

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better understand allergy development. Notably, differences in sex have been observed, with a higher prevalence of sensitization in boys, although this finding is not consistent in all age ranges.^{8,9}

Previous studies have assessed patterns of allergen sensitization in adults and differences in sex among families. In the United States, the prevalence of allergen sensitization in the adult population has previously been estimated using the National Health and Nutrition Examination Survey (NHANES). NHANES 2005–2006 measured serum specific IgE (sIgE) concentrations to multiple food and environmental allergens. Individuals were tested to 15 inhalant allergens and 4 food allergens (egg, milk, peanut, and shrimp). Nearly half (44.6%) of those surveyed had sIgE to at least 1 of the 19 allergens tested, highlighting a high prevalence of allergen sensitization in the United States.⁹ High prevalence has been reported in other nations as well. A European multicountry survey of adults aged 20 to 54 years found a high prevalence of sIgE to foods (range, 6.6%–23.6%).¹⁰ In this study, higher prevalence of sensitization was specifically noted to food allergens that are related to pollen allergens, such as apple (6.5%), peach (7.9%), and hazelnut (9.3%).¹⁰

Our family-based population study of food allergic children and their parents provided a unique opportunity to assess sensitization to foods and aeroallergens in an atopic population. This cohort was previously used to investigate familial aggregation of food allergy. Significant positive associations between parents and offspring were observed for total IgE and sIgE to all the examined food allergens and aeroallergens. Estimated heritability correlation coefficients ranged from 0.15 to 0.35 for food sIgE and 0.24 to 0.38 for aeroallergens.¹¹ Our objective was to use this population of parents of food allergic children to investigate patterns of food and aeroallergen sensitization and sex differences in sensitization.

Methods

Study Population and Data Collection

This study was part of a family-based food allergy study in Chicago, Illinois. Local families were recruited from both hospital clinics and the community setting from August 2005 through May 2008. Eligible families had 1 index child (aged 0–21 years) with any food allergy and 2 or more family members (biological parents and/or siblings). Clinical criteria for food allergy in the child were met if positive test results (sIgE or skin test to that food) corroborated typical symptoms of an allergic reaction to a food with onset within 2 hours of ingestion. A positive test result or sensitization to a food was defined as a positive ImmunoCAP result or a positive skin prick test result. Symptoms included any 1 of the following: skin (hives or angioedema), respiratory tract (difficulty breathing, shortness of breath, repetitive coughing, wheezing, or chest tightness), oropharyngeal (throat tightness, choking, or difficulty swallowing; tongue swelling), cardiovascular (fainting, dizziness, light-headedness, or decreased level of consciousness), or gastrointestinal (vomiting).¹² Parents of children with chronic health conditions other than asthma, eczema, or allergic rhinitis in the index child were excluded. Information regarding home environment, history of atopic diseases, and food allergy of each family member was collected via questionnaire-based self-report. Skin prick testing was performed. Venous blood samples were obtained from each participating family member. Allergen sensitization was defined as having an sIgE level greater than 0.35 kUA/L or a positive skin test result. The institutional review board of the former Children's Memorial Hospital (now the Ann & Robert H. Lurie Children's Hospital of Chicago) approved the study. All participating adults and children older than 12 years provided written informed consent or assent per institutional review board guidelines before entry.

Total and sIgE Measurement

Total serum IgE, sIgE for 9 food allergens (egg white, sesame, peanut, soy, milk, shrimp, walnut, cod fish, and wheat), and sIgE for 6 perennial environmental allergens (cat dander, dog dander, cockroach, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Alternaria alternata*) were measured for each participant using Phadia ImmunoCAP. Total serum IgE was reported to range from 2.0 to 5,000 kU/L. sIgE was reported to range from 0.1 to 100 kUA/L, with a level higher than 0.35 kUA/L considered positive. All total and sIgE assays were performed by the Clinical Immunology Laboratory at Children's Memorial Hospital. Quality control and recalibration for the assays were performed as previously published.¹¹ Allergen sensitization was defined as having an sIgE level greater than 0.35 kUA/L or a positive skin test result.

Skin Prick Testing

Skin prick tests were performed on participants using the Multitest II device (Lincoln Diagnostics, Decatur, Illinois) to 9 food allergens (cow milk, soy, egg white, wheat, fish mix [cod, flounder,

halibut, mackerel, tuna], shellfish mix [clam, crab, oyster, scallops, shrimp], peanut, sesame, and English walnut) and to 5 perennial environmental allergens (cat hair, dog epithelia, cockroach mix [American and German cockroach], house dust mite mix [equal parts mixture of *D farinae* and *D pteronyssinus*] and *A alternata*). Any skin test with a mean wheal diameter at least 3 mm greater than the saline control was considered a positive result. Histamine was used as a positive control.

Statistical Analysis

We compared the sensitization rates in our population of adults for 4 food allergens with publically available NHANES 2005–2006 sensitization data using 1-sample binomial tests for the matching sex and age groups. Fisher exact tests or χ^2 tests with a significance level of .05 were performed to compare the sensitization rates to each allergen between mothers and fathers. A pairwise analysis was also performed. The χ^2 tests were used to compare parents who self-reported food allergy with those who did not self-report food allergy. Finally, we looked at the potential predictors of self-report of food allergy in fathers and mothers by fitting 2 separate logistic regression models. All statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, North Carolina), IBM SPSS Statistics, version 22 (SPSS Inc, Chicago, Illinois), and GraphPad Prism, version 6.03 (GraphPad Software Inc, San Diego, California).

Results

Full data were available for 1,252 mothers and 1,225 fathers of food allergic children. Demographic information for the population is provided in Table 1. A total of 13.7% of all parents reported current food allergy, with 3.6% reporting allergy to shellfish, 2.1% to milk, 2.1% to peanut, 2.1% to tree nuts, 1.4% to fish, 1.1% to egg, 1.0% to soy, 0.9% to wheat, and 0.3% to sesame. Two-thirds of adults (66.1%) were sensitized to a food or aeroallergen. Table 2 gives the prevalence of allergen sensitization (positive skin prick test result or sIgE level >0.35 kUA/L) for mothers and fathers. A total of 14.5% of mothers and 12.7% of fathers reported current food allergy. For mothers and fathers combined, the prevalence of sensitization to peanut (15.1%) and sesame (14.4%) was substantially higher than milk (4.4%), egg (3.3%), and fish (1.2%). In their children, the most prevalent allergen was peanut (37.3%) followed by milk (29%) and egg (22.1%).

Of the parents who self-reported food allergy, only 28.4% had sensitization to the food allergen in question. The percentage of parents who reported a food allergy and who were sensitized to that food ranged from 10.7% for fish to 55.6% for peanut. We assessed the proportion of adults with sensitization (a positive skin test result or sIgE level >0.35 kUA/L) who reported food allergy to the food in question. For skin prick testing, this ranged from 11.8% for egg to 33.3% to fish and for positive sIgE result from 21.7% for egg to 72.7% for fish (eTable 1). For comparison purposes, the correlation between testing results and food allergy report in the child cohort is presented in eTable 2. Notably, the proportion of children who met stringent or probable criteria for food allergy by history with sensitization to that food was higher for milk, egg, wheat, shrimp, peanut, and walnut.

Figure 1 shows the distribution of log transformed geometric mean food sIgE concentrations. The mean sIgE levels were low. The lowest mean sensitization in mothers was to cod fish (0.65 kUA/L) and the highest mean was to peanut (1.31 kUA/L). In fathers, the lowest mean sensitization was to soy (0.73 kUA/L) and the highest mean was to shrimp (1.20 kUA/L).

Standard χ^2 tests were performed to compare the prevalence of sensitization to each specific allergen between mothers and fathers in our cohort (Table 2). Pairwise analyses were also performed for

Table 1
Demographic Characteristics of the Study Participants^a

Characteristic	Mothers (n = 1,252)	Fathers (n = 1,225)	P Value ^b
Age, mean (SD), y	38.0 (5.6)	39.6 (5.9)	NA
Race			NA
Black	3.5	4.3	
White	85.6	86.3	
Asian	6.2	5.6	
American Indian	0.2	0	
Native Hawaiian	0.2	0.3	
>1 Race	2.3	2.1	
Unknown	2.2	1.6	
Hispanic/Latino	6.9	5.2	
Annual household income			NA
<\$30,000	4.5		
\$30,000–\$60,000	8.0		
\$60,000–\$100,000	26.4		
\$100,000	57.8		
Unknown	3.3		
Highest educational level			NA
Elementary school	0	0.1	
Some secondary school	0.6	0.6	
High school graduate or GED	3.7	6.0	
Some college	11.0	10.4	
College degree	48.6	44.2	
Graduate school degree	28.3	27.2	
Postgraduate	7.8	11.6	
Comorbid asthma	15.1	14.2	.55
Eczema	19.1	14.3	.01
Environmental allergy	41.2	35.1	<.01
Self-report of current FA	14.5	12.7	.21
Self-report of outgrown FA	6.9	4.7	.03
Physician diagnosis of FA	13.3	8.9	<.01
Log ₁₀ total IgE, median (SD)	1.5 (0.6)	1.7 (0.6)	<.01

Abbreviations: FA, food allergy; NA, not applicable.

^aData are presented as percentage of study participants unless otherwise indicated.^bP values represent significant differences between mothers and fathers.

each set of parents to control for possible household or environmental confounders. No significant differences were found between the pairwise analyses and the analysis reported in Table 2.

Environmental sensitization was common in this cohort. Sensitization to dust mites and cats had the highest prevalence. Mothers and fathers who self-reported food allergy had significantly higher reports of asthma and environmental allergies compared with those who did not self-report food allergy ($P < .01$). These parents also had higher rates of sensitization to any food or environmental allergen ($P < .01$). Figure 2 shows the prevalence rates of sensitization by food allergen in parents who self-reported

Table 2
Percent Prevalence of Sensitization to Food and Aeroallergens in Mothers and Fathers

Food or Aeroallergens	Mothers (n = 1,224)	Fathers (n = 1,071)	P Value ^a
Any food	27.9	36.8	<.01
Any aeroallergen	57.7	67	<.01
Milk	3.7	5.2	.07
Egg	2.7	3.9	.10
Peanut	11.8	19.0	<.01
Walnut	6.5	11.8	<.01
Fish	0.8	1.6	.09
Shellfish	9.0	12.6	<.01
Wheat	5.7	12.0	<.01
Soy	6.9	14.0	<.01
Sesame	10.0	19.3	<.01
Dust mite	36.1	44.3	<.01
Cockroach	8.7	16.5	<.01
Dog	22	21.8	.98
Cat	34	34.4	.88
<i>Alternaria alternata</i>	24.5	32.5	<.01

^aP values represent significant differences between mothers and fathers.

food allergy compared with parents who did not self-report food allergy.

We next compared our food sensitization data to the NHANES 2005–2006 sensitization data available for 1,154 males and females aged 30 to 39 years. The mean age in our cohort was 37.9 years. For the 4 food allergens that were tested in both populations (peanut, shrimp, milk, and egg), our cohort had a significantly higher prevalence of food sensitization (slgE ≥ 0.35 kUA/L) to all 4 foods (Table 3).

Logistic regression analysis of predictors of self-reported food allergy to any food revealed a statistically significant positive association in fathers with self-report of asthma (odds ratio [OR], 1.73; 95% confidence interval [CI], 1.04–2.89; $P = .04$), environmental allergy (OR, 2.16; 95% CI, 1.40–3.33; $P = .001$), and eczema (OR, 1.94; 95% CI, 1.20–3.14; $P = .01$). For mothers, statistically significant positive associations between self-report of food allergy were found with self-report of environmental allergy (OR, 3.23; 95% CI, 2.17–4.79; $P < .001$) and having more than 1 child with food allergy (OR, 1.54; 95% CI, 1.09–2.18; $P = .01$). Maternal self-report of asthma revealed a trend toward significance (OR, 1.51; 95% CI, 0.97–2.34; $P = .07$) as did self-report of eczema (OR, 1.46; 95% CI, 0.97–2.20; $P = .07$). The other variables evaluated in the logistic regression were not significant and included age, race, ethnicity, and educational level. Prior history of asthma, eczema, and food allergy was also not associated with increased self-report of food allergy in mothers or fathers.

Discussion

Atopy is well known to have a strong hereditary component.^{13,14} A population-based survey of 3,800 Finnish children and their biologic parents found a strong association between parental allergies and positive food allergy test results in their children, with the incidence of positive test results being 2-fold higher if any allergy was reported in either parent and 3-fold higher if allergic conditions were reported in both parents.¹⁴ In this cohort, we conversely assessed prevalence of allergy self-report and sensitization to foods and aeroallergens by skin prick and slgE testing in parents of food allergic children.

This article examines sensitization in parents of food allergic children from a unique perspective. Previous studies have focused solely on the general adult population and have not looked at sensitization in a selectively atopic cohort.^{9,10} As one might expect, levels of sensitization in parents of food allergic children are higher than in the general US population.⁹ However, even though there are statistically significant differences in specific allergen sensitizations between our study population and NHANES data, these actual differences are more modest than one might expect if food allergy is highly determined by genetics. There is also a high rate of self-reported food allergies, asthma, eczema, and rhinitis in this cohort compared with the general population.^{15–17} However, when we look closely at the levels of slgE in parents who report allergy, they are very low, and clinical reactivity seems unlikely based on pediatric studies of slgE concentration and oral food challenge outcome.^{18,19} This certainly brings into question the reliability of self-report of allergy.

Adult data regarding correlation of slgE and clinical outcomes are lacking. Less than 20% of parents who reported allergy to wheat, fish, egg, or milk had positive skin test results or positive slgE test results to the food in question. The highest correlation between report of food allergy and sensitization was to peanut, yet even in this group sensitization was noted for only 55.6% of those reporting peanut allergy. This high rate of reported food allergy without sensitization may be considered surprising given the knowledge of IgE-mediated food allergy one would expect these families to have. We speculate that increased awareness of food allergy may actually

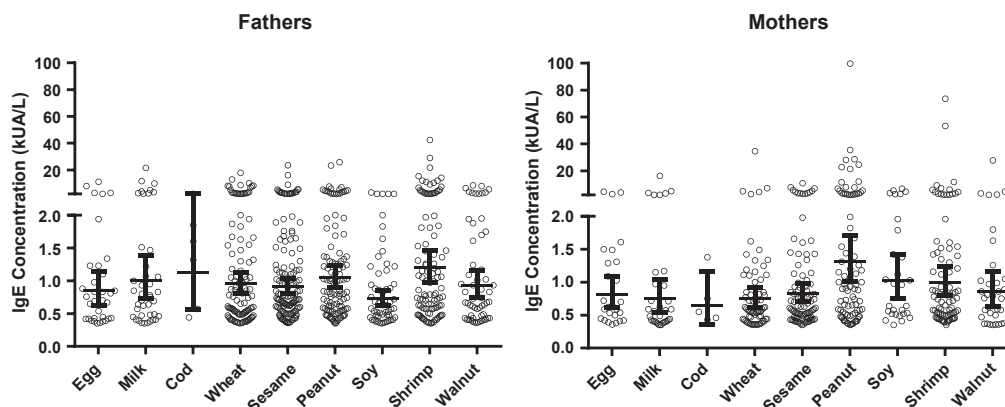


Figure 1. Distribution of mean food specific IgE concentrations in mothers and fathers.

result in increased reporting. Alternatively, it is possible that some adults were diagnosed as being allergic when young and did not seek reevaluation. Of parents who reported no food allergy, 14% had evidence of sensitization to peanut, 14% to sesame, 10% to soy, and 10% to shellfish. As has been previously illustrated, self-report of food allergy and/or sensitization is not diagnostic of food allergy prevalence.²⁰ Oral food challenges remain the gold standard to confirm or refute the diagnosis.

The highest concordance between reported allergy and sensitization was noted for peanut, sesame, and soy. High rates of sensitization to soy and peanut are consistent with other studies reporting high prevalence of sensitization to plant-related allergens.^{9,21–23} Although cross-reactivity with homologous pollen allergens likely plays a role in the high sensitization to peanut and soy allergens, we unfortunately do not have either specific pollen sensitization or protein component sIgE data in our cohort to confirm or refute this. Although sesame has not been reported to have cross-reactivity with pollens, 2 sesame allergens (Ses i 2 and Ses i 3) belong to the family of seed storage proteins and share homologic features with peanut and soybean allergens,²⁴ which may explain the high prevalence of sesame sensitization seen in this cohort. Sesame has also been noted in a European adult prevalence study to be the most common IgE sensitization in the

class of true food allergens that do not cross-react with pollen allergens, so our finding of higher sensitization to this allergen is not unique and may deserve further study.¹⁰

Interestingly, differences were noted between mothers and fathers. Although more mothers reported a physician diagnosis of food allergy (13.3% compared with 8.9% of fathers), fathers had more sensitization to environmental allergens and more food sensitization to peanut, walnut, shellfish, wheat, soy, and sesame ($P < .01$). It is possible that the higher prevalence of atopic diseases among mothers reflects some selection bias rather than an actual higher prevalence because mothers with atopy may be more likely to enroll their children in such a study as this one. The association between biologic sex and food allergy throughout life has not been as well characterized as that in childhood. A PubMed database search looking at sex disparity in food allergy previously noted most reporting of food allergy in adults to be done by women (34.82% of men and 65.18% of women older than 18 years, male to female ratio of 0.53).²⁵ The authors noted an appearance of sex reversal in food allergies at puberty and an attenuation of sex differences near menopause, suggesting a role for hormones in these differences.²⁵ It is important to distinguish biologic differences between males and females (sex) vs the social, cultural, and/or psychological traits typically associated with 1 sex (gender). Other authors have proposed that gender rather than sex differences contribute to how individuals process information, including in reporting of quality-of-life measures and in self-efficacy as related to food allergy.²⁶ Future studies of food allergy in the adult population, especially relying on self-report, should take the effect of gender on perception and reporting of symptoms into account.

The major limitations of this study include the use of self-report not only of food allergy but also of other atopic conditions. In addition the report of physician diagnosis carries its own issues unless appropriate testing, including double-blind food challenges, has been performed. There is likely bias in our high prevalence rates

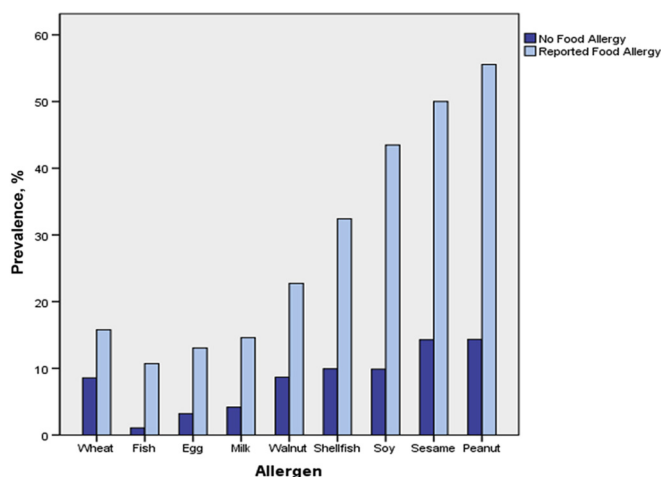


Figure 2. Prevalence of sensitization among parents with or without self-reported allergy to a food. Sensitization is defined as a positive skin prick test result and/or a specific IgE level greater than 0.35 kU/L to each specific food allergen. For each allergen, the prevalence of sensitization is higher among parents who report allergy to that food compared with those who do not.

Table 3
Sensitization in the Chicago Food Allergy Study Compared With NHANES 2005–2006

Food	Sensitization, %		P Value
	NHANES	Chicago FA Study	
Peanut	7.2	8.89	<.01
Shrimp	5.4	9.07	<.01
Milk	2.6	3.73	<.01
Egg	2.1	2.58	<.01

Abbreviations: FA, food allergy; NHANES, National Health and Nutrition Examination Survey.

of atopy. It would have been advantageous to have objective evidence of food allergy (ie, oral food challenge results) because it is well known that rates of self-report of food allergy (or perceived allergy) are higher than the rate of confirmed food allergy.²⁷ When looking at parental pairs, we used pairwise analyses to minimize the possibility of any bias related to household environmental exposures. In addition, given our specific cohort of parents of children with food allergy, it is important to note that our data are likely not generalizable to the general population.

In this cohort with a high prevalence of self-reported allergic disease, we described elevated rates of both food and aeroallergen sensitization beyond what has been seen in an unselected adult population.⁹ Notably, fathers in this cohort had higher levels of sensitization to individual foods and environmental aeroallergens and total serum IgE levels consistent with previous reports.²⁸ However, most sIgE sensitization was low, so clinical reactivity is unlikely. A high rate of food allergy report was also observed in those with no sensitization at all. This article highlights flaws in using self-report alone to determine food allergy, even in this population with heightened awareness of allergic conditions. Often in clinical practice, if a parent has food allergy, it suggests that their child is at higher risk of developing food allergy. Our study suggests that using parental report of food allergy as a risk factor is unreliable. Other known risk factors, such as infant eczema, may be better for predicting the risk of future food allergy in a child. More epidemiologic studies of food allergy in the adult population that include proper testing and food challenge outcomes are needed to better understand sensitization and heritability.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.07.042>.

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eTable 1

Proportion of Parents With a Positive Test Result (SPT Wheal >3 mm, sIgE Level >0.35 kUA/L) Who Self-report Food Allergy Separated by Food

Food	Positive SPT Result, %	Positive sIgE Test Result, %
Milk	27.0	23.0
Soy	29.0	29.4
Egg	11.8	21.7
Wheat	30.4	22.4
Fish	33.3	72.7
Shrimp	26.4	22.4
Peanut	24.5	27.9
Sesame	21.6	27.7
Walnut	21.2	25.8

Abbreviations: sIgE, specific IgE; SPT, skin prick test.

eTable 2

Proportion of Index Children With a Positive Test Result (SPT Wheal >3 mm, sIgE Level >0.35 kUA/L) Who Met the Stringent or Probable Criteria of Allergy to That Food

Food	Positive SPT Result, No. (%)	Positive sIgE Test Result, No. (%)
Milk	194 (80.4)	586 (49.8)
Soy	189 (7.4)	604 (6.8)
Egg	249 (39.4)	598 (37.5)
Wheat	34 (35.3)	566 (6.7)
Fish	41 (22.0)	77 (19.5)
Shrimp	72 (12.5)	212 (9.0)
Peanut	477 (49.7)	838 (48.6)
Sesame	231 (10.8)	660 (7.0)
Walnut	260 (29.6)	505 (27.9)

Abbreviations: sIgE, specific IgE; SPT, skin prick test.