

# Food Challenge and Community-Reported Reaction Profiles in Food-Allergic Children Aged 1 and 4 Years: A Population-Based Study



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**What is already known about this topic?** Little is known about clinical reaction profiles in infants and young children undergoing food challenges irrespective of skin prick test wheal size and community-based history of reaction.

**What does this article add to our knowledge?** Urticaria is the most common presenting symptom following food challenges in 1- and 4-year-old children, although there is a shift to more angioedema at age 4 years. Anaphylaxis during food challenges in this age group is rare, as are parent-reported breathing problems on accidental exposures.

**How does this study impact current management guidelines?** Food challenges in this age group rarely result in severe reactions and anaphylaxis. High serum food-specific IgE levels are associated with moderate to severe reactions during food challenges.

**BACKGROUND:** Oral food challenge is the main tool for diagnosing food allergy, but there is little data on the reaction profiles of young children undergoing challenges, nor how these reactions compare to reactions on accidental ingestion in the community.

**OBJECTIVES:** To compare reaction profiles from food challenges and parent-reported reactions on accidental ingestion, and assess predictors of severe reactions.

**METHODS:** HealthNuts is a longitudinal population-based cohort study of 5276 1-year-old infants. Infants underwent skin

prick tests and those with identifiable wheals were offered food challenges. Food challenges were repeated at age 4 years in those with previous food allergy or reporting new food allergies. Community-reported reactions were ascertained from parent questionnaires.

**RESULTS:** Food challenges were undertaken in 916 children at age 1 year and 357 children at age 4 years (a total of 2047 peanut, egg, or sesame challenges). Urticaria was the most common sign in positive challenges at both ages (age 1 year, 88.7%, and age 4 years, 71.2%) although angioedema was

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*Abbreviations used*

DBPCFC- double-blind placebo-controlled food challenge  
sIgE- serum food-specific IgE  
SPT- skin prick test

significantly more common at age 4 years (40.1%) than at age 1 year (12.9%). Anaphylaxis was equally uncommon at both ages (2.1% and 2.8% of positive challenges at ages 1 and 4 years, respectively) but more common for peanut than for egg (4.5% and 1.2% of positive challenges at ages 1 and 4 years, respectively). The patterns of presenting signs reported during community reactions were similar to those observed in formal food challenges. Serum food-specific IgE levels of 15 kU/L or more were associated with moderate to severe reactions but skin prick test was not.

**CONCLUSIONS:** There was a shift from the most common presenting reaction of urticaria during food challenges toward more angioedema in older children. Serum food-specific IgE levels were associated with reaction severity. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:398-409)

**Key words:** Food allergy; Egg allergy; Peanut allergy; Sesame allergy; Oral food challenge; Reaction profiles; Anaphylaxis; Community reactions; Urticaria; Angioedema; Skin prick test; Specific IgE

The prevalence of food allergy is reported to have increased over the past 20 years.<sup>1-3</sup> Formal food challenges are currently the main tool for diagnosing food allergy, with double-blind placebo-controlled food challenges (DBPCFCs) being the criterion standard.<sup>4</sup> Nonetheless, the use of food challenges in both clinical practice and research settings has been limited by restraints in available resources and concerns of placing children under unnecessary risk of severe or even fatal allergic reactions. Most children with a large skin prick test (SPT) wheal size do not undergo a food challenge, because perceived benefits are not sufficient to offset potential risks. Because of these limitations, data on patterns of food challenge outcomes, irrespective of SPTs, which require a large number of tests to be performed and systematically examined across time, are limited.

The objective clinical end points of food challenges include noncontact urticaria, angioedema, vomiting, and anaphylaxis. However, differences in food challenge stopping criteria across different centers have hindered the ability to compare results between studies, particularly where studies include subjective symptoms.<sup>5,6</sup> Previously there was no standard definition for a positive food challenge although a consensus on a standardized criteria for stopping food challenges has recently been developed as part of the PRACTALL guidelines, which reduces these limitations.<sup>7</sup> However, there is little data on the actual reaction profiles of children undergoing food challenges irrespective of SPT wheal size and reaction history and as such, it is not known whether the signs and symptoms of infants undergoing food challenges differ from those of older children and whether their outcomes should be interpreted in the same manner. In addition, previous research shows that SPT and serum food-specific IgE (sIgE) level cannot predict the type or severity of reaction elicited during a food challenge,<sup>8-11</sup> although a limited number

of studies have suggested that increasing sIgE levels may be associated with more severe reactions.<sup>12-14</sup> This question has not been comprehensively assessed in a population-representative cohort of children undergoing food challenges at specific ages irrespective of SPT, sIgE, and reaction history. Finally, it is not clear whether reactions observed in controlled food challenges reflect those that may occur in a community setting on accidental allergen ingestion. These will be important to clinicians in deciding the management plans for children presenting with food allergy at different ages and risks of exposure.

The HealthNuts study, a longitudinal population-based cohort study of infants in Melbourne, Australia, is uniquely placed to examine these questions because food challenges were undertaken in all sensitized participants irrespective of SPT wheal size, with challenge staff blinded to SPT result. The aim of this study was to compare clinical reaction profiles from food challenges to peanut, egg, and sesame in infants and young children at age 1 and 4 years and assess whether SPT wheal size or sIgE level could predict the type of reaction. In addition, parental-reported reaction patterns following allergen ingestion in the community setting were examined.

## METHODS

### Study design

**Recruitment.** The HealthNuts study is a longitudinal population-based cohort study of childhood food allergy in Melbourne, Australia. The recruitment methods have been described in previous publications.<sup>15,16</sup> A total of 5276 (out of 7134 approached, 74% participation rate) 12-month-old infants were recruited at council-run immunization sessions, and had SPTs performed to 4 common food allergens, including peanut, egg, and sesame. All children with a detectable wheal size of greater than 1 mm were invited to undergo supervised food challenges at a specialist clinic at Melbourne's Royal Children's Hospital. SPT was repeated on the day of the food challenge, and blood was also taken to measure sIgE level.

**Questionnaires.** During recruitment, parents completed a questionnaire that collected information on demographic characteristics, family history of allergy, and environmental and dietary exposures, including whether the child had ever had a reaction and type of reaction to a food. Reactions occurring within 4 hours of ingestions were categorized into urticaria, facial swelling/angioedema, vomiting, and breathing problems, corresponding to the 4 signs in our food challenge stopping criteria (see below).

**SPTs and serum samples.** SPTs were administered with a single-tine lancet (Stallergenes, Antony, France) on the child's back using allergen extracts (ALK-Abello, Madrid, Spain), along with a positive control (10 mg/mL histamine) and a negative control (saline). Wheal size was measured after 15 minutes and calculated as the average of the longest diameter and the diameter perpendicular to that, after subtracting the negative control. Blood samples were collected, and plasma was isolated for specific IgE assays to individual food items using the ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden).

**Oral food challenges.** The protocol and predetermined cessation criteria of food challenge have been described previously.<sup>17</sup> All challenges were performed with staff blinded to both SPT results

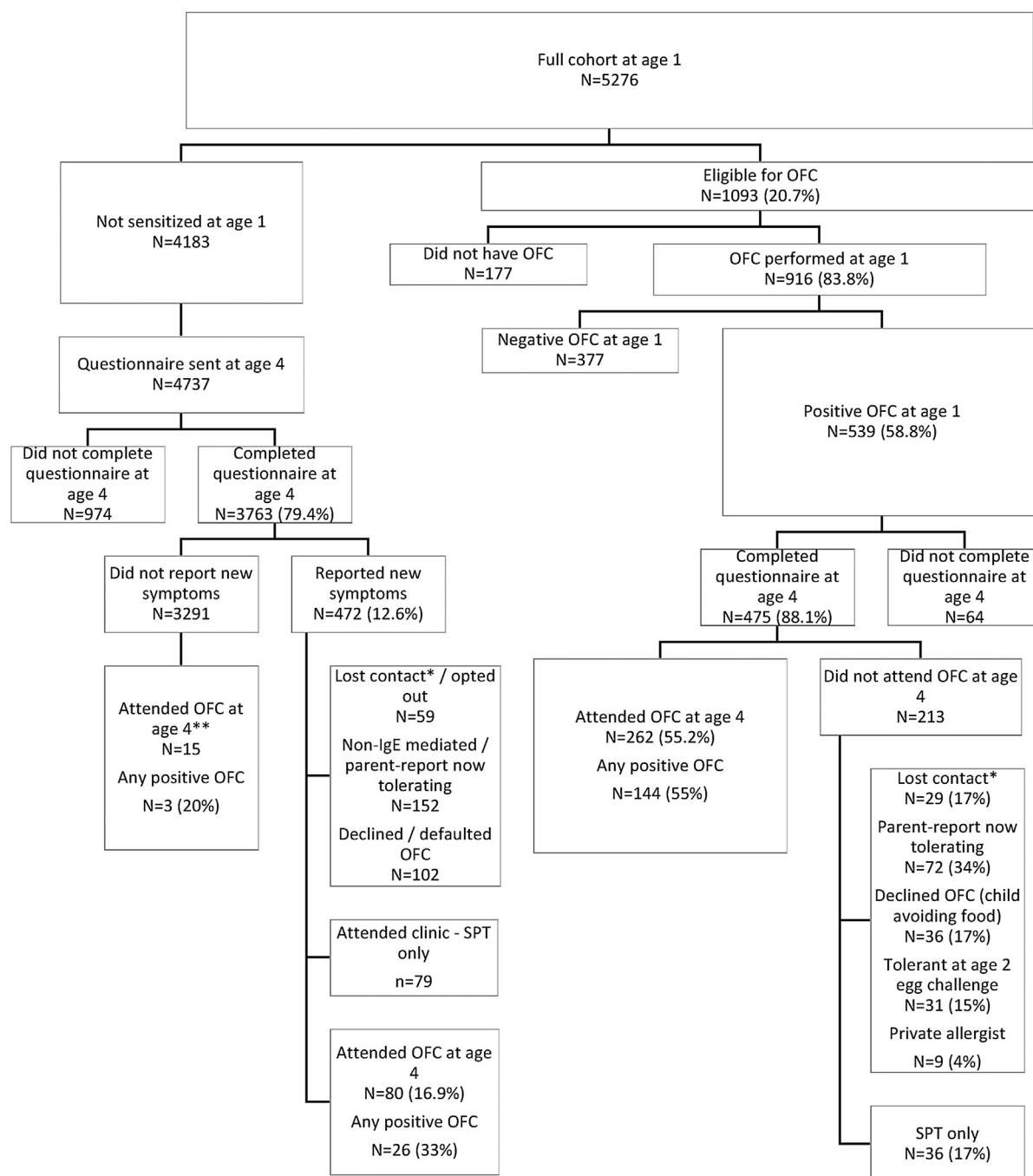


**FIGURE 1.** Participation in HealthNuts OFCs at age 1 and 4 years. OFC, Oral food challenge. \*If parents reported new symptoms in questionnaire, they were phoned by research nurses to clarify the history. If they could not be reached after 6 phone attempts, they were categorized as “lost contact.” \*\*Reasons for these children attending OFCs included inconclusive OFC at age 1 year, negative OFC at age 1 year with subsequent new sensitization, or avoiding food because of family history of food allergy.

and history of reactions. Food challenges were considered positive if any of the following signs occurred within 2 hours of ingestion at the last dose: 3 or more concurrent noncontact urticaria persisting for at least 5 minutes, perioral or periorbital angioedema, vomiting (excluding gag reflex), or *anaphylaxis*, defined as evidence of circulatory or respiratory compromise (eg, hypotension, persistent cough, or wheeze).<sup>15</sup> Upon discharge, a single serving of the challenged food at the highest challenge dose was administered to continue the

challenge at home for 7 days, and research nurses contacted parents for any late reactions. If late reactions were reported, and it was compatible with a food challenge stopping criteria, the challenge was considered positive. If the child did not have any reaction on day 1, nor reported a late reaction, the food challenge was considered negative. If a child had a recent reaction to the food (1 month for egg and 2 months for peanut and sesame), which was consistent with the food challenge stopping criteria, and also demonstrated evidence of

**TABLE I.** Demographic characteristics of children who underwent food challenges at age 1 and/or 4 y

| Characteristic                                        | OFC at age 1 y<br>only (n = 620) | OFC at age 1 and<br>4 y (n = 296) | OFC at age<br>4 y only (n = 61) | P     |
|-------------------------------------------------------|----------------------------------|-----------------------------------|---------------------------------|-------|
| Sex (male)                                            | 51%                              | 61%                               | 61%                             | .01   |
| Socioeconomic status                                  |                                  |                                   |                                 |       |
| Quintile 1 (most disadvantaged)                       | 18%                              | 15%                               | 18%                             | .68   |
| Quintile 2                                            | 20%                              | 22%                               | 18%                             |       |
| Quintile 3                                            | 21%                              | 21%                               | 13%                             |       |
| Quintile 4                                            | 19%                              | 21%                               | 26%                             |       |
| Quintile 5                                            | 22%                              | 21%                               | 25%                             |       |
| Family history of any allergy                         | 74%                              | 80%                               | 72%                             | .08   |
| Asthma                                                | 36%                              | 38%                               | 46%                             | .32   |
| Eczema                                                | 34%                              | 43%                               | 43%                             | .02   |
| Hay fever                                             | 53%                              | 61%                               | 57%                             | .07   |
| Food allergy                                          | 12%                              | 16%                               | 22%                             | .08   |
| Parents' countries of birth                           |                                  |                                   |                                 |       |
| Both Australia                                        | 50%                              | 52%                               | 66%                             | .25   |
| One or both Asian                                     | 24%                              | 24%                               | 17%                             |       |
| Others                                                | 26%                              | 23%                               | 17%                             |       |
| Maternal age at child's birth (y), mean $\pm$ SD      | 33.0 $\pm$ 4.7                   | 33.4 $\pm$ 4.1                    | 34.4 $\pm$ 4.6                  | .04   |
| Premature birth                                       | 6%                               | 3%                                | 8%                              | .08   |
| Exposure to tobacco smoke in first year               | 18%                              | 18%                               | 13%                             | .62   |
| Any siblings at recruitment                           | 45%                              | 46%                               | 48%                             | .86   |
| Eczema diagnosis in child's first year                | 43%                              | 67%                               | 58%                             | <.001 |
| Reported food allergy to egg in child's first year    | 18%                              | 31%                               | 14%                             | <.001 |
| Reported food allergy to peanut in child's first year | 4%                               | 8%                                | 5%                              | .04   |
| Egg SPT community 1 y                                 |                                  |                                   |                                 |       |
| Median (IQR)                                          | 2 (1-4)                          | 4 (2-6)                           | 0 (0-0)                         | <.001 |
| Sensitized $\geq$ 2 mm                                | 64%                              | 75%                               | 11%                             | <.001 |
| Egg SPT clinic age 1 y                                |                                  |                                   |                                 |       |
| Median (IQR)                                          | 1 (0-3)                          | 3 (2-5)                           | —                               | <.001 |
| Sensitized $\geq$ 2 mm                                | 48%                              | 76%                               | —                               | <.001 |
| Egg SPT 4 y                                           |                                  |                                   |                                 |       |
| Median (IQR)                                          | —                                | 0 (0-2)                           | 0 (0-0)                         | .02   |
| Sensitized $\geq$ 3 mm                                | —                                | 22%                               | 12%                             | .08   |
| Peanut SPT community 1 y                              |                                  |                                   |                                 |       |
| Median (IQR)                                          | 0 (0-3)                          | 2 (0-7)                           | 0 (0-0)                         | <.001 |
| Sensitized $\geq$ 2 mm                                | 35%                              | 52%                               | 6%                              | <.001 |
| Peanut SPT clinic 1 y                                 |                                  |                                   |                                 |       |
| Median (IQR)                                          | 0 (0-2)                          | 2 (0-7)                           | —                               | <.001 |
| Sensitized $\geq$ 2 mm                                | 28%                              | 53%                               | —                               | <.001 |
| Peanut SPT 4 y                                        |                                  |                                   |                                 |       |
| Median (IQR)                                          | —                                | 0 (0-10)                          | 0 (0-2)                         | .01   |
| Sensitized $\geq$ 3 mm                                | —                                | 42%                               | 23%                             | .01   |
| Sesame SPT community 1 y                              |                                  |                                   |                                 |       |
| Median (IQR)                                          | 0 (0-0)                          | 0 (0-0)                           | 0 (0-0)                         | .02   |
| % $>$ 2 mm                                            | 7%                               | 12%                               | 2%                              | .01   |
| Sesame SPT clinic 1 y                                 |                                  |                                   |                                 |       |
| Median (IQR)                                          | 0 (0-0)                          | 0 (0-0)                           | —                               | <.001 |
| $\geq$ 2 mm                                           | 5%                               | 15%                               | —                               | <.001 |
| Sesame SPT 4 y                                        |                                  |                                   |                                 |       |
| Median (IQR)                                          | —                                | 0 (0-0)                           | 0 (0-0)                         | .74   |
| % $>$ 2 mm                                            | —                                | 11%                               | 10%                             | .87   |

IQR, Interquartile range; OFC, oral food challenge.

sensitization, the child did not undergo a food challenge and was considered food allergic.

**Baked egg challenges.** Halfway through the study, the baked egg substudy was initiated. Infants with challenge-confirmed egg allergy at age 12 months were invited to undergo an additional baked egg challenge. Protocol and participation in the baked egg substudy have been previously described in detail.<sup>18</sup>

**Age 4-year follow-up.** Participants' parents were sent a questionnaire when their child turned 4 years of age, which included questions on whether the child had adverse reactions to any food between age 1 year and age 4 years. The reactions were categorized in the same manner as the age 1-year recruitment questionnaire. Children who attended the study clinic as age 1 year were invited to undergo a clinical allergy assessment at age 4 years, which included SPT, sIgE, and a food challenge for tolerance in those deemed food allergic at age 1 year. Parents of children who reported a new adverse reaction to food between age 1 year and age 4 years were telephoned by a study nurse and if the history was compatible with IgE-mediated food allergy, the child was invited to the clinic for assessment, which included SPT and food challenge if indicated. In addition, if a child demonstrated sensitization to a food and there was no history of ingestion and tolerance, a food challenge was offered. At age 4 years, oral food challenges were conducted to a wider range of foods than at age 1 year but in the present article results are reported only for egg, peanut, and sesame, because these challenges were undertaken at both ages.

## Definitions

**Food sensitization:** SPT wheal of 2 mm or more and/or sIgE level of 0.35 kU/L or more at age 1 year and SPT wheal of 3 mm or more and/or sIgE level of 0.35 kU/L or more at age 4 years. At age 1 year, a lower SPT threshold of sensitization was used ( $\geq 2$  mm) because evidence suggests that skin reactivity is lower in infants.<sup>19-21</sup>

**Food allergy:** Positive food challenge ( $\geq 3$  concurrent noncontact urticaria, angioedema, vomiting, or anaphylaxis, within 2 hours of ingestion at the last dose) in conjunction with evidence of sensitization.

## Ethical conduct in human research

Approval to conduct the HealthNuts study was obtained from the Victorian State Government Office for Children (reference no. CDF/07/492), the Victorian State Government Department of Human Services (reference no. 10/07), and the Royal Children's Hospital Human Research Ethics Committee (reference no. 27047). Parents provided informed consent for their child to participate in the study and food challenges.

## Statistical methods

Binary variables are summarized as observed proportions as an estimate of the corresponding population proportion; comparisons for binary variables were conducted using Pearson chi-square test. Nonparametric numerical variables are summarized using the median and interquartile range and samples compared using the Mann-Whitney *U* test (2-sample comparison) or Kruskal-Wallis rank test (3-sample comparison). Parametric numerical variables are summarized as the mean and SD and compared using either student *t* test (2-sample comparison) or ANOVA (3-sample comparison). To assess whether SPT wheal size or sIgE level was associated with the type of reaction occurring during food challenges, we classified the reactions

into a binary outcome of "mild," defined as skin manifestations only (hives and/or angioedema), and "moderate-severe," which included gastrointestinal and/or respiratory reactions with or without skin reactions (hives and angioedema). SPT wheal size and sIgE levels were also categorized into a binary variable on the basis of the magnitude of results (small SPT wheal size 2-7 mm vs large SPT wheal size  $\geq 8$  mm and sIgE small 0.35-14.9 kU/L and large  $\geq 15$  kU/L). The diagnostic capacity of SPT and sIgE level to predict the type of reaction was assessed using receiver-operating characteristics analysis and the area under the curve was calculated to quantify the accuracy of the test. A logistic regression model was used to quantify the magnitude of association between SPT and sIgE levels and the binary outcome of reactions on food challenges. All statistical analyses were performed using Stata release 14.0 (StataCorp, College Station, Texas).

## RESULTS

### Participation and demographic characteristics of the sample

Participation in the HealthNuts study has been described in detail previously. Figure 1 describes participation in food

**TABLE II.** OFC results of peanut (A), raw egg (B), sesame (C), and baked egg (D) at age 1 and 4 y, respectively

| <b>A: Peanut</b>                  |                              |                              |
|-----------------------------------|------------------------------|------------------------------|
|                                   | <b>Age 1 y<br/>(n = 598)</b> | <b>Age 4 y<br/>(n = 147)</b> |
| <b>Total challenges performed</b> |                              |                              |
| OFC positive and sensitized       | 151 (25.3%)                  | 92 (62.6%)*                  |
| Inconclusive†                     | 23                           | 5                            |
| Negative                          | 424                          | 45                           |
| <b>B: Raw egg</b>                 |                              |                              |
|                                   | <b>Age 1 y (n = 756)</b>     | <b>Age 4 y (n = 191)</b>     |
| <b>Total challenges performed</b> |                              |                              |
| OFC positive and sensitized       | 453 (59.9%)‡                 | 57 (29.8%)§                  |
| Inconclusive                      | 19                           | 13                           |
| Negative                          | 263                          | 105                          |
| <b>C: Sesame</b>                  |                              |                              |
|                                   | <b>Age 1 y (n = 114)</b>     | <b>Age 4 y (n = 36)</b>      |
| <b>Total challenges performed</b> |                              |                              |
| OFC positive and sensitized       | 30 (26.3%)                   | 20 (55.6%)                   |
| Inconclusive                      | 7                            | 3                            |
| Negative                          | 74                           | 13                           |
| <b>D: Baked egg</b>               |                              |                              |
|                                   | <b>Age 1 y (n = 186)</b>     | <b>Age 4 y (n = 19)</b>      |
| <b>Total challenges performed</b> |                              |                              |
| OFC positive and sensitized       | 27 (14.5%)                   | 8 (42.1%)                    |
| Inconclusive                      | 7                            | 1                            |
| Negative                          | 152                          | 10                           |

OFC, Oral food challenge.

\*Two additional children had a positive OFC, but were not sensitized and were excluded from the analysis.

†OFC was considered inconclusive if the child refused to eat the challenge food, parents reported a late reaction that was not consistent with challenge stopping criteria but led the parent to remove the food from the infants diet.

‡Twenty-one additional children had a positive OFC, but were not sensitized and were excluded from the analysis.

§Sixteen additional children had a positive OFC, but were not sensitized and were excluded from the analysis.

||Three additional children had a positive OFC, but were not sensitized and were excluded from the analysis.

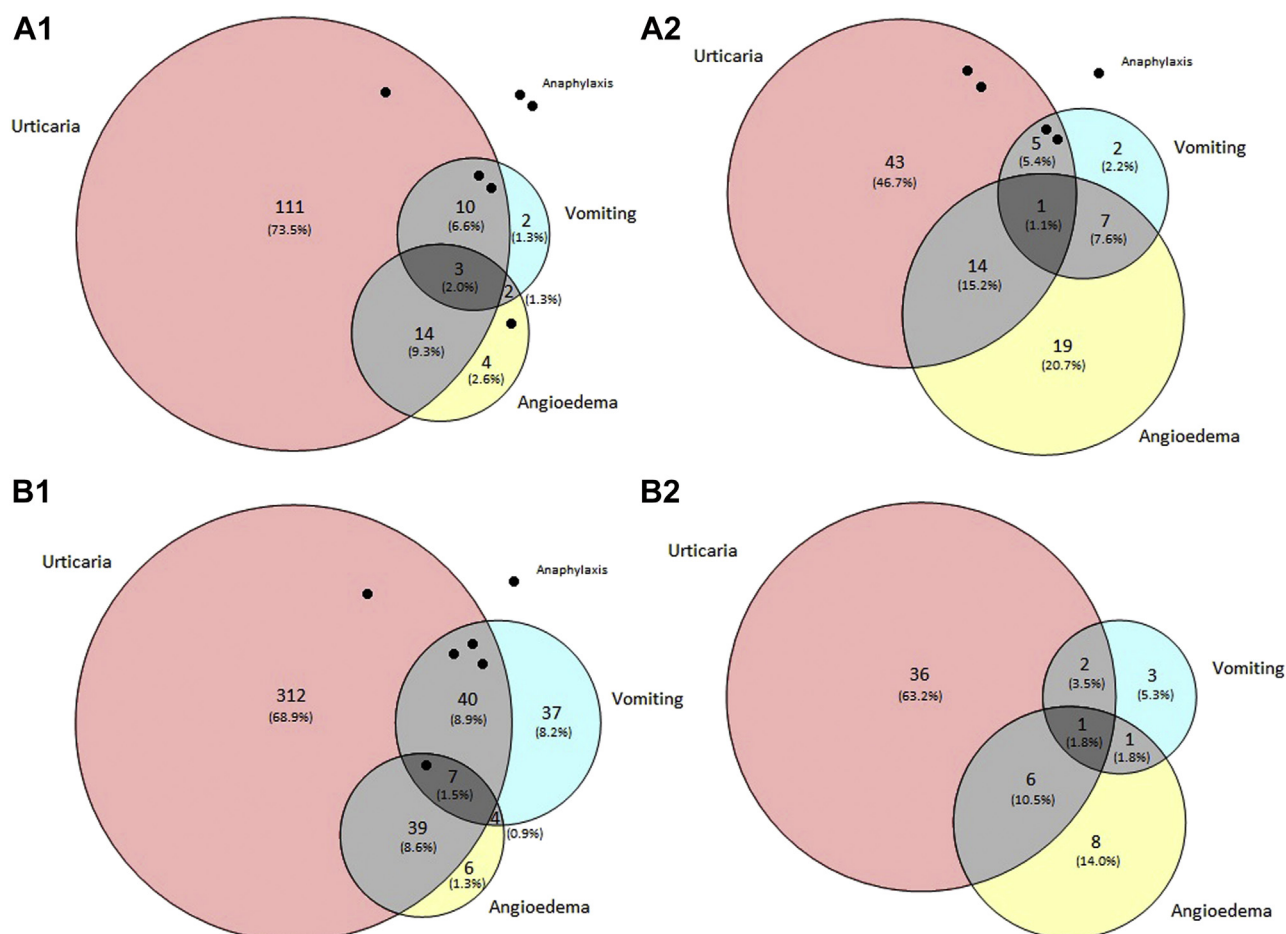


**FIGURE 2.** Reaction profile observed in positive OFCs for peanut (A), raw egg (B), sesame (C), and baked egg (D) at age 1 and 4 years, respectively. Solid circles represent individual cases of anaphylaxis. A1: Peanut OFC at age 1 year (n = 151); multiple signs: 19.2% (29 of 151). A2: Peanut OFC at age 1 year (n = 92); multiple signs: 29.3% (27 of 92). B1: Raw egg OFC at age 1 year (n = 453); multiple signs: 19.9% (90 of 453). B2: Raw egg OFC at age 4 years (n = 57); multiple signs: 17.5% (10 of 57). C1: Sesame OFC at age 1 year (n = 30); multiple signs: 16.7% (5 of 30). C2: Sesame OFC at age 4 years (n = 20); multiple signs: 40.0% (8 of 20). D1: Baked egg OFC at age 1 year (n = 27); multiple signs: 3.7% (1 of 27). D2: Baked egg OFC at age 4 years (n = 8); multiple signs: 0%.

challenges at age 1 year, and subsequent follow-up at age 4 years for food-allergic and nonallergic children. Among 5276 children from the full cohort, 1093 (20.7%) fulfilled the criteria for having a food challenge performed at age 1 year, of which 916 (83.8%) participated. Infants who participated in food challenges were more likely to have a higher socioeconomic status, Australian-born parents, a parent-reported reaction to egg (but not peanut) and be sensitized to peanut (but not egg or sesame) at age 1 year, and less likely to have a diagnosis of eczema in the first year of life, compared with nonparticipants (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

The mean age at the first food challenge was  $13.9 \pm 1.3$  months and, on average, children underwent 1.8 challenges. Food challenges were positive for 539 infants (58.8%) and of these, 475 (88.1%) participated in age 4-year follow-up by completing a questionnaire; 262 (55.2%) of these children attended the clinic for food challenge. Characteristics of children who were food allergic at age 1 year and did or did not undergo subsequent food challenges as age 4 years were similar; however, children who participated in age 4-year food challenges were

more likely to be male, have a diagnosis of eczema in the first year of life, and be sensitized to peanut or sesame at age 1 year compared with nonparticipants (see Table E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

For those who did not have a positive food challenge at age 1 year, 3763 (79.4%) completed a questionnaire at age 4 years and 472 (12.5%) reported adverse reactions to food. After verification of history over the phone by research nurses to rule out unlikely IgE-mediated reactions, 80 (16.9%) underwent a food challenge. Reasons for not attending food challenge in both groups included declining/defaulting follow-up, parent-report of tolerance to the food, and losing contact or opting out of the study. There were an additional 15 children who attended the study clinic for food challenge at age 4 years because they had an inconclusive food challenge at age 1 year, negative food challenge at age 1 year with subsequent new sensitization at age 4 years, or were avoiding food because of family history of food allergy.

A total of 357 children received food challenges at age 4 years and children underwent on average 1.4 challenges. Overall 2047 challenges were undertaken to egg, peanut, and sesame; 2189

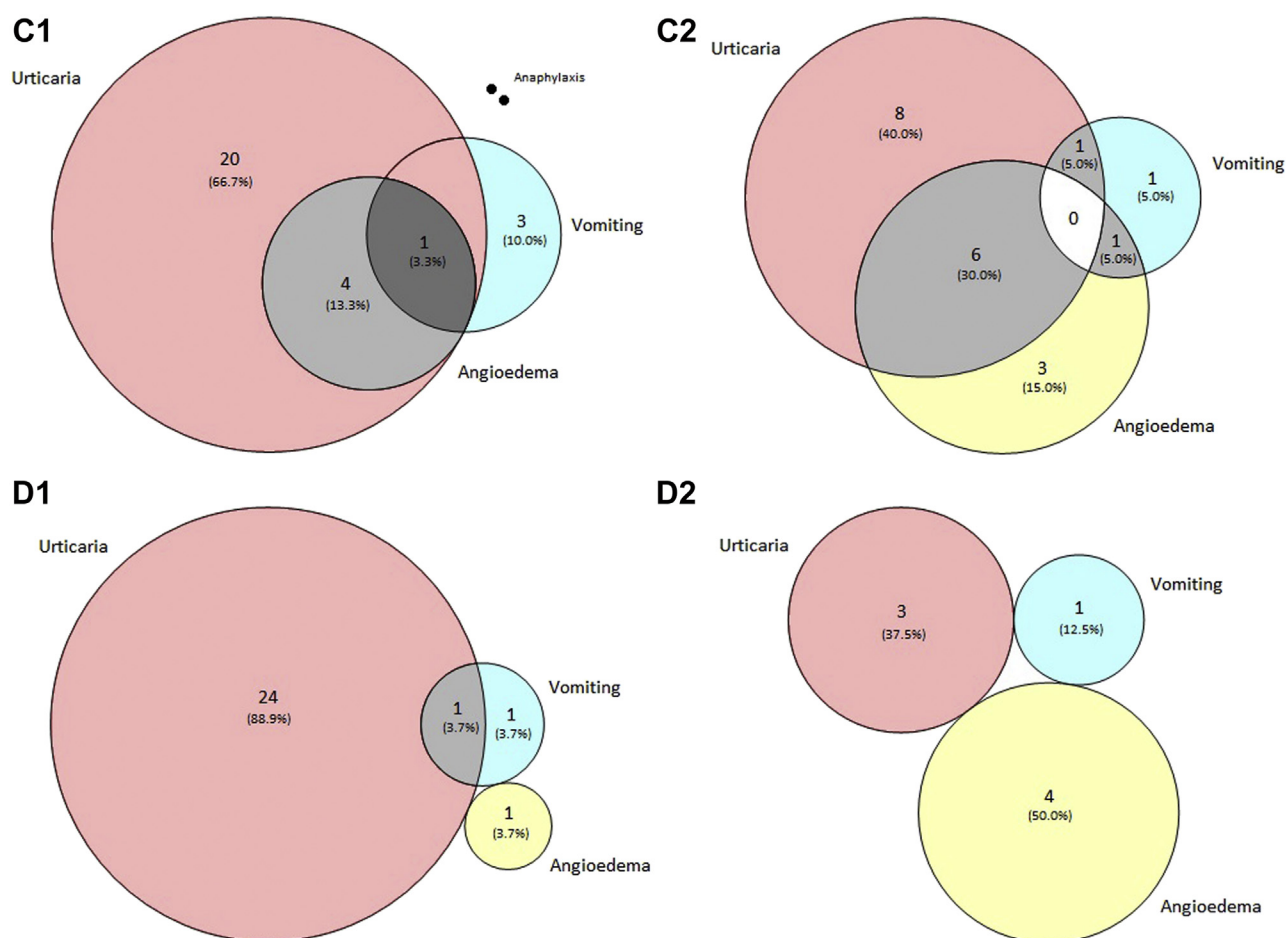


FIGURE 2. (CONTINUED).

challenges were conducted in total when including challenges to other foods at age 4 years. The mean age at which the first food challenge at age 4-year follow-up was performed was  $4.3 \pm 0.3$  years. The demographic characteristics of children who participated in food challenges at age 1 and 4 years, including those who underwent challenges at both ages, are summarized in Table I.

### Reaction profiles in food challenges

The number and results of food challenges for peanut, raw egg, sesame, and baked egg at age 1 and 4 years are reported in Table II. The reactions that were observed in positive food challenges for each food are described in Figure 2. Urticaria was the most common presenting sign for all foods across all ages (except baked egg challenge at age 4 years, where angioedema was the most common), presenting in 83.3% to 92.6% of all positive food challenges at age 1 year, and 68.5% to 78.9% at age 4 years (excluding baked egg), either alone or in conjunction with other signs. There was a notable increase in the proportion of children presenting with angioedema from age 1 year to age 4 years, from between 4% and 16.7% of food challenges at age 1 year to between 28.1% and 50.0% at age 4 years. Despite the small number of total food challenges performed, the increase was most notable in baked egg food challenges, from 4% (1 of 27) at age 1 year to 50.0% (4 of 8) at age 4 years. Figure 2

includes all participants who had positive food challenges. Table III includes only those participants who participated in food challenge to the same food at both age 1 and 4 years, to assess whether the differences observed were influenced by age rather than by different participants. A decrease in urticaria and increase in angioedema was statistically significant for both egg and peanut. At both ages, most children reacted, with only 1 sign during positive food challenges.

A total of 14 anaphylaxis cases were observed in food challenges at age 1 year. It occurred in 4.0% (6 of 151), 1.3% (6 of 453), and 6.7% (2 of 30) of positive peanut, raw egg, and sesame challenges, respectively. At age 1 year, no anaphylaxis cases were observed for baked egg challenges. At age 4 years, a total of 5 cases of anaphylaxis were observed, all occurring in peanut challenges, making up 5.4% (5 of 92) of positive challenges.

### Reaction patterns upon accidental ingestion reported by parents

Figure 3 shows the parent-reported community reactions consistent with IgE-mediated food allergy upon accidental ingestion for peanut, egg, and sesame at age 1 and 4 years. Among 1-year-old infants who had been introduced to the food in question, 3.6% (55 of 1527), 5.2% (256 of 4881), and 0.3% (7 of 2517) reported a reaction consistent with IgE-mediated

**TABLE III.** Comparison of symptoms elicited from food challenges at age 1 and 4 y, restricted to those who underwent food challenge to the food at both ages

| Reaction    | Age 1 y          | Age 4 y*       | P     |
|-------------|------------------|----------------|-------|
| Peanut      |                  |                |       |
| Urticaria   | 96% (89 of 93)   | 69% (56 of 81) | <.001 |
| Angioedema  | 17% (16 of 93)   | 43% (35 of 81) | <.001 |
| Vomiting    | 11% (10 of 93)   | 16% (13 of 81) | .30   |
| Anaphylaxis | 4% (4 of 93)     | 6% (5 of 81)   | .58   |
| Raw egg     |                  |                |       |
| Urticaria   | 86% (134 of 155) | 75% (42 of 56) | .05   |
| Angioedema  | 15% (23 of 155)  | 30% (17 of 56) | .01   |
| Vomiting    | 23% (35 of 155)  | 14% (8 of 56)  | .19   |
| Anaphylaxis | 0.6% (1 of 115)  | 0              | —     |
| Sesame      |                  |                |       |
| Urticaria   | 77% (17 of 22)   | 80% (12 of 15) | .84   |
| Angioedema  | 18% (4 of 22)    | 47% (7 of 15)  | .06   |
| Vomiting    | 18% (4 of 22)    | 20% (3 of 15)  | .89   |
| Anaphylaxis | 9% (2 of 22)     | 0              | —     |
| Baked egg   |                  |                |       |
| Urticaria   | 100% (7 of 7)    | 0              | —     |
| Angioedema  | 0                | 100% (2 of 2)  | —     |
| Vomiting    | 0                | 0              | —     |
| Anaphylaxis | 0                | 0              | —     |

\*Although this analysis was restricted to those who had food challenge at both ages to the food in question, the total number who had challenges at age 4 y is lower because not all children had a positive challenge at age 4 y. For example, 119 children had a peanut challenge at both age 1 and 4 y, but data from only 93 positive challenges at age 1 y and 81 positive challenges at age 4 y are included in this table.

peanut, egg, and sesame allergy, respectively. Most children reporting reactions in the community before age 4 years had a confirmed food allergy (72% for peanut, 89% for egg, and 50% for sesame). Only 1 child each who reported a reaction to egg or peanut in the community was assessed as tolerant at both age 1 and 4 years; the remaining had an inconclusive allergy status.

The patterns of reactions occurring on accidental exposure are similar to those as observed in food challenges. Urticaria was the most commonly reported community reaction, occurring in 90% to 100% of food reactions at age 1 year and 66% to 84% of reactions at age 4 years. As observed in food challenges, there was an increase in reported angioedema, from 20% to 40% for peanut and 8% to 26% for egg between age 1 and 4 years. Few children reported reactions to sesame in the community, 7 and 10 at age 1 and 4 years, respectively.

Reported breathing problems such as cough and wheezing were recorded among community reactions. A total of 13 cases were reported at age 1 year, occurring in 9% (5 of 55) and 3% (8 of 256) of peanut and egg reactions in the community, respectively. There were 15 cases at age 4 years, occurring in 28% (9 of 32), 11% (6 of 56), and 20% (2 of 10) for peanut, raw egg, and sesame reactions, respectively.

### Can SPT and sIgE predict the type of reaction?

At both age 1 and 4 years, there was no significant difference between the median SPT wheal size among participants who had mild compared with moderate to severe reactions and the area under the curve indicated that SPT was not an accurate test for

predicting the type of reaction (see Tables E3 and E4 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). In addition, the logistic regression model demonstrated that there was no significant increase in the risk of having a moderate to severe reaction compared with mild reaction among children who had large SPT responses ( $\geq 8$  mm) (Table IV).

In contrast, there was evidence that higher sIgE levels were associated with the severity of reaction to peanut, egg, and sesame at age 1 year and peanut at age 4 years. Children who had moderate-severe reactions on average had significantly higher sIgE levels than children who had mild reactions at both age 1 and 4 years (see Tables E3 and E4). High peanut sIgE levels ( $\geq 15$  kU/L) were associated with a 4-fold greater risk of having a moderate to severe reaction during peanut challenges at both age 1 and 4 years. High egg sIgE levels were associated with a 3-fold increased risk of having a moderate to severe reaction during egg challenges at age 1 year only. At age 4 years, there were only 3 children with egg sIgE level of 15 kU/L or more and they all had mild reactions (Table IV).

## DISCUSSION

This is the first study to investigate the reaction profiles of children undergoing food challenges in a longitudinal population-based cohort, and compare the reactions observed at different time points for the same cohort of children. Our findings have identified differences between the types of signs presented during food challenges between age 1 and 4 years. Although urticaria remained the most common type of reaction observed as the end point in food challenges, the proportion of children presenting with urticaria decreased from age 1 year to age 4 years, whereas those presenting with angioedema increased. A similar pattern was found when comparing parent-reported reactions upon accidental ingestion between age 1 and age 4 years, and was similar for both peanut and egg. To our knowledge, this is the first study to report such observations of differences in food allergy reactions among the same group of children at different ages.

A higher proportion of children were reported to have breathing problems in the community setting, compared with the occurrence rate of anaphylaxis observed in hospital-based food challenges. However, parental report of "breathing problems" in the questionnaire, which included cough, wheezing, and shortness of breath, may not be reliable and also may not fulfill the clinical criteria for respiratory compromise in anaphylaxis as observed in food challenges. Alternatively, in contrast to the controlled setting of a food challenge where escalating doses were used and the challenge ceased at the minimum dose at which a reaction occurred, the amount of food that the child consumed in an accidental setting was uncontrolled and possibly larger, which may result in more severe reactions.

The strengths of the study are the population sampling and high participation rates, which resulted in the study having good external validity to the general population.<sup>15</sup> Because recruitment into the study was done at the population level, the full clinical spectrum of food allergy is represented with minimal selection or referral bias, and avoids overrepresentation of severe disease, which is more commonly seen in tertiary referral centers. We also offered food challenges to all children with detectable SPT wheals irrespective of wheal size, compared with other studies, which often do not offer challenges to children with SPT wheals greater

than 95% positive predictive values. This reduced the false-positive rate because of wrongly including those without allergies, and also allowed us to capture the full spectrum of reaction profiles across different wheal sizes. Longitudinal follow-up in this cohort study also allowed comparison of the same group of patients at different ages, reducing interpatient variability contaminating results had different patients been used for different ages.

A potential limitation of our study is that some children who were eligible for a food challenge did not participate. Our study design allowed for comparison of the groups of children who attended and did not attend the study clinic and assess for potential bias and our present analysis. At age 1 year, 84% of infants eligible for food challenge participated and participants were more likely to have a higher socioeconomic status, Australian-born parents, report a reaction to egg, and less likely to have eczema. Among children who were challenge-confirmed food allergic at age 1 year, 88% participated in the age 4-year follow-up by completing a questionnaire. All these children were invited for a repeat oral food challenge to test for tolerance and of those 55% attended. The most common reason for parents declining for their child to participate in challenges at age 4 years was because the child was now eating and tolerating the food (49%). Other parents declined to participate because their child was under the care of a private allergist (4%) or because they believed their child was still allergic and avoiding the food in question (17%). Participants were more likely to be male, have older siblings, and eczema in the first year of life. In addition, participants were more likely to be sensitized to peanut and sesame (but not egg) at age 1 year, which suggests that the sample undergoing repeat food challenges may have been biased toward those with persistent allergic disease. Because this analysis primarily addressed reactions occurring among those with food allergy, it should not significantly affect the current results as those who had developed tolerance are not contributing data to the present analysis.

Another potential limitation was that in our study, open food challenges were used as opposed to DBPCFC, which is the current criterion standard. However, previous studies have shown that open food challenges are an acceptable substitute for DBPCFC in young children.<sup>22</sup> In addition, our study challenge staff members were blinded to both the reaction history and SPT wheal sizes, thus minimizing any observational bias, and our stopping criteria included only objective clinical signs. Our study did not include challenges to cow's milk, which is a common childhood food allergy; however, sensitization to cow's milk is low in this cohort<sup>23</sup> and current knowledge of cow's milk allergy suggests that the majority will outgrow their reactivity early in life.<sup>24</sup>

Few studies have characterized reaction profiles during food challenges at specific ages, especially during infancy, nor compared repeated challenges in the same population. This is important to assess the safety, acceptability, and outcomes of food challenges in infants and young children. Similarly, few studies compare reaction profiles from controlled food challenges to accidental exposures in the community, in the same population.

Although several studies have reported reaction profiles in clinical cohorts of mixed ages, different presentation or classifications of reaction symptoms makes direct comparisons difficult. For example, several studies graded food challenge reactions according to severity but different body system reactions were

grouped together in their classifications of mild and severe. These studies tended to be retrospective clinical reviews of children aged 1 to 16 years.<sup>25-27</sup> Of the few studies that reported specific symptoms, skin/cutaneous manifestations were the most common presentation followed by gastrointestinal and respiratory involvement, similar to the findings in our study, despite participants' ages ranging from 1 to 16 years and retrospective study design. However, they often grouped urticaria and angioedema and it is not clear if the shift from urticaria to angioedema with age has been observed in other cohorts.<sup>12,14,28,29</sup> Subjective symptoms were also included in previous studies and reactions were not always reported by specific food, again making comparisons difficult. One study compared outcomes of repeat peanut challenges in children with a history of mild reactions, and found that reaction severity was similar at subsequent challenges in those with persistent peanut allergy.<sup>25</sup> A further study reported reactions of repeat egg challenges in 33 children and found that in nearly half the cases, subsequent reactions generally affected the same body system, although the actual symptoms were not described in detail.<sup>30</sup>

Several studies have described reactions to allergens in the community setting, to peanut and egg, although reactions are generally graded on severity, which again grouped multiple symptoms. Moderately severe reactions, which included angioedema and gastrointestinal symptoms, were most frequently described. Participants in these studies were older (mean age, 5-8 years), which is consistent with our finding that as children age from 1 to 4 years there is a shift from urticaria to angioedema.<sup>31-33</sup>

It is well established that the magnitude of SPT and sIgE responses is correlated to the likelihood of a child having a positive food challenge. However, there is little evidence to support that SPT can predict the type or severity of reaction, which is consistent with the findings in the present study.<sup>8,10,11</sup> One previous study reported that SPT wheal size of more than 6.75 mm was predictive of anaphylaxis; however, this study's control group largely comprised children who were tolerant on challenge; therefore, SPT may have been predicting the likelihood of a reaction rather than severe reaction.<sup>13</sup> Another study reported that SPT in conjunction with other factors in a scoring system (sIgE, age, and previous reactions) could predict anaphylaxis; however, this sample was older and had a higher proportion of anaphylactic reactions (24%) than the present study, so our results are not directly comparable.<sup>12</sup>

We found that sIgE level of 15 kU/L or more was predictive of moderate to severe reactions during peanut challenges at age 1 and 4 years and egg challenges at age 1 year only. Although several previous studies found no association between sIgE level and the severity of reactions,<sup>8-11</sup> several others have reported a correlation between increasing sIgE levels and the severity of clinical reactions on food challenges, including the 2 aforementioned studies assessing SPT.<sup>12-14</sup> An additional study showed a gradient of increasing sIgE level between children with no, mild, and severe reactions on egg challenges although a direct comparison between those with mild and severe reactions was not tested.<sup>14</sup>

Our study has described a previously unreported observation of differences in the reaction profiles of children with food allergy at different ages, both in food challenges and in parent-reported reactions toward accidental ingestion. Such differences are not explained by the current knowledge and understanding of the immunological aspect of food allergy, but may have important

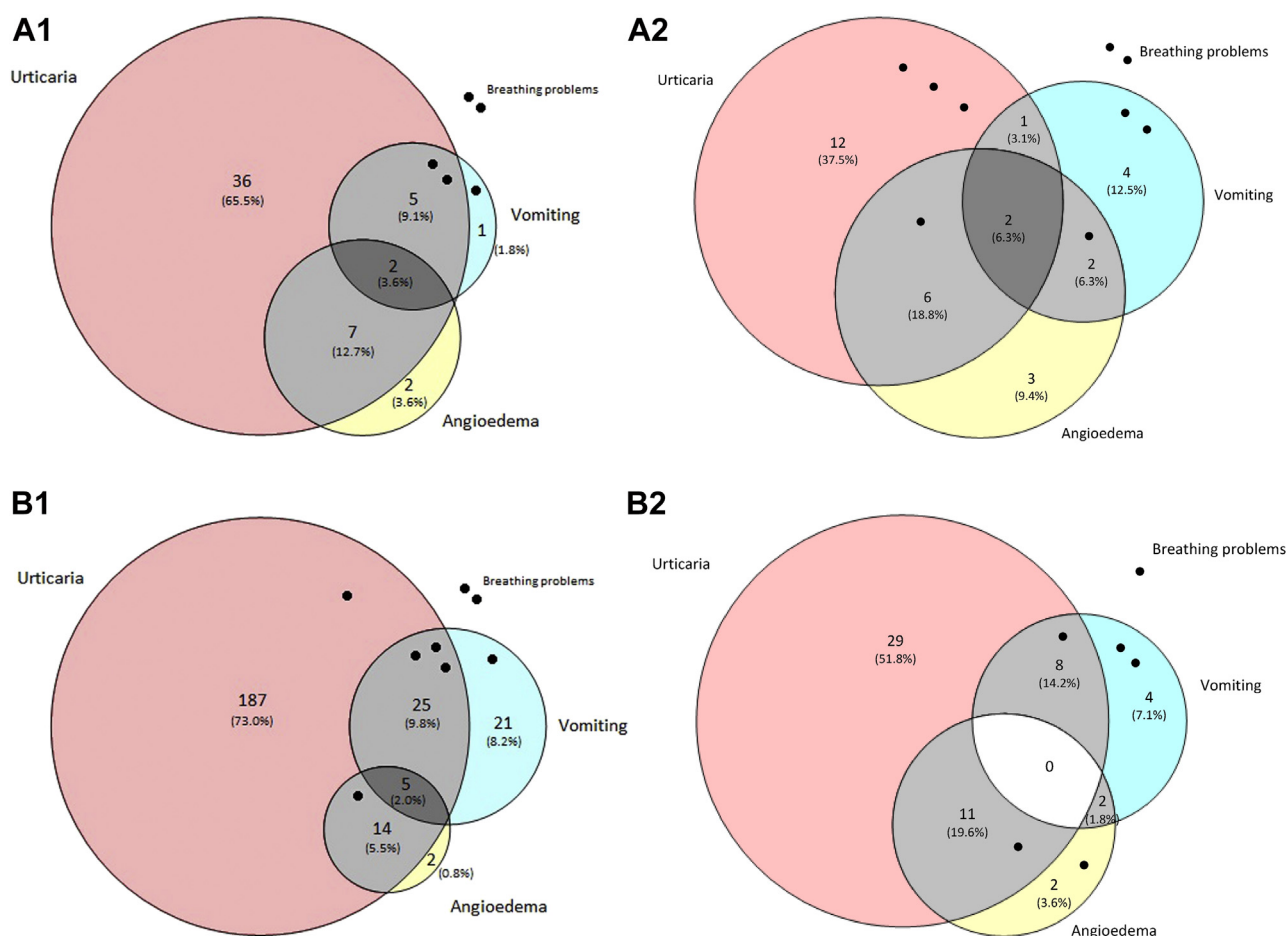


**FIGURE 3.** Parent-reported community reactions upon accidental ingestion for peanut (A), egg (B), and sesame (C) at age 1 year, and between age 1 and 4 years, respectively, before OFC. Solid circles represent individual cases of breathing problems (eg, cough, wheezing, and shortness of breath). A1: Peanut ingestion at age 1 year (n = 55). A2: Peanut ingestion between age 1 and 4 years (n = 32). B1: Raw egg ingestion at age 1 year (n = 256). B2: Raw egg ingestion between age 1 and 4 years (n = 56). C1: Sesame ingestion at age 1 year (n = 7). C2: Sesame ingestion between age 1 and 4 years (n = 10).

clinical implications on the prognosis and management for these children. It may reflect a change in the way the immune system reacts to allergens as the child grows, or it may suggest some underlying differences that lead to certain phenotypes of food allergy to resolve earlier while others persist, but currently little is known about this.

It is known that there is difference in rates of food-induced anaphylaxis across different age groups in children and adolescents as observed in the past 10 years,<sup>2</sup> but it is not known whether the reaction profiles in childhood can identify those who are at a higher risk of severe or fatal reactions. We believe that further studies on the characterization and implications of children's reaction profiles in food allergy at different ages will be useful. It will be important to understand why these changes in reaction profile occur, the immunological mechanisms underlying them, and how such differences may predict the clinical outcome or severity of food allergy.

In conclusion, we report data from a population-based cohort that identifies differences in the reaction profiles of children with food allergy between age 1 year and age 4 years. Compared with age 1 year, children with food allergy are more likely to present

with angioedema at age 4 years. Allergic reactions in the community setting resulting from accidental ingestion may be more severe than reactions seen in the clinic setting of ingestion of controlled doses of allergens. Further studies will be needed to understand the underlying mechanism of such changes and what clinical implications they carry.

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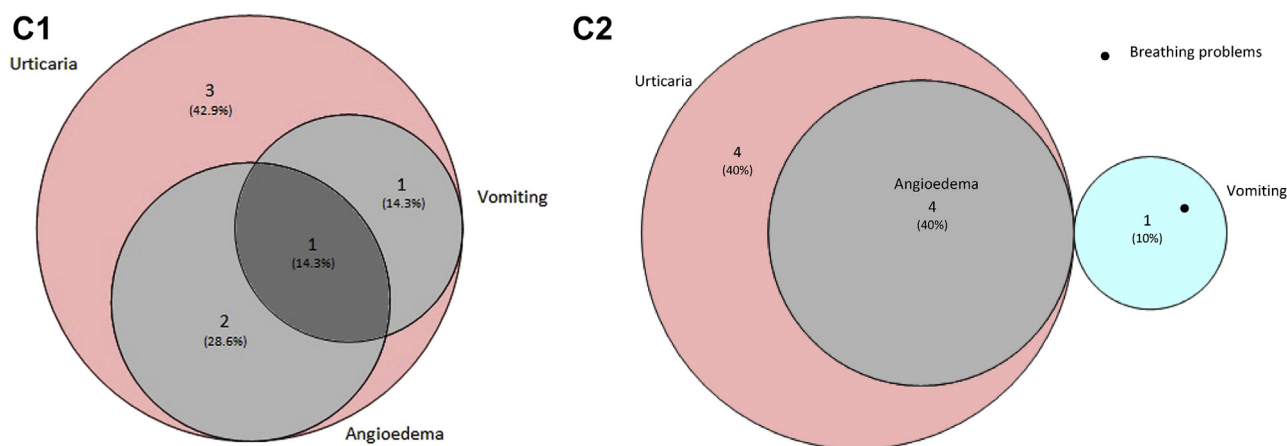


FIGURE 3. (CONTINUED).

TABLE IV. The association between SPT wheal size or sIgE levels and severity of reaction during food challenges at age 1 and 4 y

## A: Age 1 y

| SPT or sIgE size             | N   | Severe reactions (%) | Odds ratio         | P value |
|------------------------------|-----|----------------------|--------------------|---------|
| Egg SPT wheal 2-7 mm         | 389 | 19%                  | 1.0                |         |
| Egg SPT wheal $\geq 8$ mm    | 32  | 28%                  | 1.72 (0.76-3.88)   | .19     |
| Egg sIgE 0.35-15 kU/L        | 285 | 21%                  | 1.0                |         |
| Egg sIgE $\geq 15$ kU/L      | 37  | 46%                  | 3.26 (1.61-6.60)   | .001    |
| Peanut SPT wheal 2-7 mm      | 66  | 18%                  | 1.0                |         |
| Peanut SPT wheal $\geq 8$ mm | 80  | 13%                  | 0.64 (0.26-1.60)   | .34     |
| Peanut sIgE 0.35-15 kU/L     | 87  | 9%                   | 1.0                |         |
| Peanut sIgE $\geq 15$ kU/L   | 29  | 31%                  | 4.44 (1.52-12.97)  | .006    |
| Sesame SPT wheal 2-7 mm      | 13  | 23%                  | 1.0                |         |
| Sesame SPT wheal $\geq 8$ mm | 15  | 20%                  | 0.83 (0.14-5.08)   | .84     |
| Sesame sIgE 0.35-15 kU/L     | 19  | 5%                   | 1.0                |         |
| Sesame sIgE $\geq 15$ kU/L   | 7   | 57%                  | 24.0 (1.95-295.06) | .01     |

## B: Age 4 y

| SPT or sIgE size             | N  | Severe reactions (%) | Odds ratio        | P value |
|------------------------------|----|----------------------|-------------------|---------|
| Egg SPT wheal 3-7 mm         | 32 | 12%                  | 1.0               |         |
| Egg SPT wheal $\geq 8$ mm    | 12 | 8%                   | 0.64 (0.06-6.34)  | .70     |
| Egg sIgE 0.35-15 kU/L        | 30 | 20%                  |                   |         |
| Egg sIgE $\geq 15$ kU/L      | 3  | 0%                   |                   |         |
| Peanut SPT wheal 3-7 mm      | 12 | 17%                  | 1.0               |         |
| Peanut SPT wheal $\geq 8$ mm | 77 | 21%                  | 1.3 (0.26-6.59)   | .74     |
| Peanut sIgE 0.35-15 kU/L     | 33 | 9%                   | 1.0               |         |
| Peanut sIgE $\geq 15$ kU/L   | 17 | 41%                  | 7.0 (1.5-32.3)    | .01     |
| Sesame SPT wheal 3-7 mm      | 7  | 14%                  | 1.0               |         |
| Sesame SPT wheal $\geq 8$ mm | 13 | 15%                  | 1.09 (0.81-14.66) | .95     |
| Sesame sIgE 0.35-15 kU/L     | 8  | 12%                  | 1.0               |         |
| Sesame sIgE $\geq 15$ kU/L   | 4  | 25%                  | 2.33 (0.11-50.98) | .59     |

Note: Some participants were sensitized on only one marker but not the other. Participants who were not sensitized on the marker of interest were excluded from that analysis; therefore, some participants may have contributed data to only 1 or both analyses.

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## REFERENCES

- Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JK, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J* 2013;6:21.
- Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *J Allergy Clin Immunol* 2015;136:367-75.

3. Ben-Shoshan M, Turnbull E, Clarke A. Food allergy: temporal trends and determinants. *Curr Allergy Asthma Rep* 2012;12:346-72.
4. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126:S1-S58.
5. Wensing M, Penninks AH, Hefle SL, Koppelman SJ, Bruijnzeel-Koomen CAFM, Knulst AC. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. *J Allergy Clin Immunol* 2002;110:915-20.
6. Peeters KABM, Nordlee JA, Penninks AH, Chen L, Goodman RE, Bruijnzeel-Koomen CAFM, et al. Lupine allergy: not simply cross-reactivity with peanut or soy. *J Allergy Clin Immunol* 2007;120:647-53.
7. Sampson HA, van Wijk RG, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;130:1260-74.
8. Jarvinen KM, Amalanayagam S, Shreffler WG, Noone S, Sicherer SH, Sampson HA, et al. Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children. *J Allergy Clin Immunol* 2009;124:1267-72.
9. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
10. Sicherer SH, Wood RA, American Academy of Pediatrics Section On Allergy And Immunology. Allergy testing in childhood: using allergen-specific IgE tests. *Pediatrics* 2012;129:193-7.
11. van Erp FC, Knulst AC, Kentie PA, Pasmans SG, van der Ent CK, Meijer Y. Can we predict severe reactions during peanut challenges in children? *Pediatr Allergy Immunol* 2013;24:596-602.
12. Cianferoni A, Garrett JP, Naimi DR, Khullar K, Spergel JM. Predictive values for food challenge-induced severe reactions: development of a simple food challenge score. *Israel Med Assoc J* 2012;14:24-8.
13. Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol* 2010;21:603-11.
14. Benhamou AH, Zamora SA, Eigenmann PA. Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients. *Pediatr Allergy Immunol* 2008;19:173-9.
15. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Thiele L, Tang MLK, et al. The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. *Clin Exp Allergy* 2010;40:1516-22.
16. Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang MLK, Gurrin LC, et al. Cohort profile: the HealthNuts study: population prevalence and environmental/genetic predictors of food allergy. *Int J Epidemiol* 2015;44:1161-71.
17. Koplin JJ, Tang MLK, Martin PE, Osborne NJ, Lowe AJ, Ponsonby A-L, et al. Predetermined challenge eligibility and cessation criteria for oral food challenges in the HealthNuts population-based study of infants. *J Allergy Clin Immunol* 2012;129:1145-7.
18. Peters RL, Dharmage SC, Gurrin LC, Koplin JJ, Ponsonby A-L, Lowe AJ, et al. The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study. *J Allergy Clin Immunol* 2014;133:485-91.
19. Menardo JL, Bousquet J, Rodiere M, Astruc J, Michel F-B. Skin test reactivity in infancy. *J Allergy Clin Immunol* 1985;75:646-51.
20. Skassa-Brociek W, Manderscheid J-C, Michel F-B, Bousquet J. Skin test reactivity to histamine from infancy to old age. *J Allergy Clin Immunol* 1987;80:711-6.
21. Johannsen H, Nolan R, Pascoe EM, Cuthbert P, Noble V, Corderoy T, et al. Skin prick testing and peanut-specific IgE can predict peanut challenge outcomes in preschool children with peanut sensitization. *Clin Exp Allergy* 2011;41:994-1000.
22. Venter C, Pereira B, Voigt K, Grundy J, Clayton C, Gant C, et al. Comparison of open and double-blind placebo-controlled food challenges in diagnosis of food hypersensitivity amongst children. *J Hum Nutr Diet* 2007;20:565-79.
23. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011;127:668-76.
24. Schoemaker AA, Sprickelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children—EuroPrevall birth cohort. *Allergy* 2015;70:963-72.
25. Wainstein BK, Saad RA. Repeat oral food challenges in peanut and tree nut allergic children with a history of mild/moderate reactions. *Asia Pacific Allergy* 2015;5:170-6.
26. Rolinck-Werninghaus C, Niggemann B, Grabenhenrich L, Wahn U, Beyer K. Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE. *Allergy* 2012;67:951-7.
27. Hourihane JOB, Grimshaw KEC, Lewis SA, Briggs RA, Trewin JB, King RM, et al. Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin Exp Allergy* 2005;35:1227-33.
28. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. *J Allergy Clin Immunol* 2004;114:1164-8.
29. Thalayasingam M, Loo EX, Tan MM, Bever HV, Shek LP. A review of oral food challenges in children presenting to a single tertiary centre with perceived or true food allergies. *Singapore Med J* 2015;56:622-5.
30. Spergel JM, Beausoleil JL, Fiedler JM, Ginsberg J, Wagner K, Pawlowski NA. Correlation of initial food reactions to observed reactions on challenges. *Ann Allergy Asthma Immunol* 2004;92:217-24.
31. Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y, et al. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol* 2006;118:466-72.
32. Cherkaoui S, Ben-Shoshan M, Alizadehfard R, Asai Y, Chan E, Cheuk S, et al. Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy. *Clin Translational Allergy* 2015;5:16.
33. Boyano-Martinez T, Pedrosa M, Quirce S, Garcia-Ara C. Accidental allergic reactions in children allergic to hen's egg. *J Investig Allergol Clin Immunol* 2012;22:109-15.

## APPENDIX

**TABLE E1.** Assessment of selection bias: Comparison of children who were eligible for food challenges at age 1 y but did or did not participate

| Characteristic                                   | Eligible but declined OFC at age 1 y (n = 178) | Underwent OFC at age 1 y (n = 916) | P     |
|--------------------------------------------------|------------------------------------------------|------------------------------------|-------|
| Sex (male)                                       | 50%                                            | 54%                                | .27   |
| Socioeconomic status                             |                                                |                                    |       |
| Quintile 1 (most disadvantaged)                  | 25%                                            | 17%                                | .05   |
| Quintile 2                                       | 20%                                            | 21%                                |       |
| Quintile 3                                       | 15%                                            | 21%                                |       |
| Quintile 4                                       | 16%                                            | 20%                                |       |
| Quintile 5                                       | 23%                                            | 22%                                |       |
| Family history of any allergy                    | 69%                                            | 76%                                | .08   |
| Asthma                                           | 33%                                            | 37%                                | .37   |
| Eczema                                           | 33%                                            | 37%                                | .37   |
| Hay fever                                        | 41%                                            | 56%                                | <.001 |
| Food allergy                                     | 16%                                            | 13%                                | .30   |
| Parents' countries of birth                      |                                                |                                    |       |
| Both Australia                                   | 36%                                            | 51%                                | <.001 |
| One or both Asian                                | 42%                                            | 24%                                |       |
| Others                                           | 22%                                            | 25%                                |       |
| Maternal age at child's birth (y), mean $\pm$ SD | 32.6 $\pm$ 5.3                                 | 33.1 $\pm$ 4.5                     | .22   |
| Premature birth                                  | 6%                                             | 5%                                 | .73   |
| Exposure to tobacco smoke in child's first year  | 20%                                            | 18%                                | .47   |
| Any siblings at recruitment                      | 53%                                            | 45%                                | .08   |
| Eczema diagnosis in first year                   | 59%                                            | 51%                                | .05   |
| Reported food allergy to egg in first year       | 14%                                            | 22%                                | .01   |
| Reported food allergy to peanut in first year    | 5%                                             | 5%                                 | .94   |
| Egg SPT community 1 y                            |                                                |                                    |       |
| Median (IQR)                                     | 3 (1-4)                                        | 3 (1-4)                            | .54   |
| Sensitized $\geq 2$ mm                           | 72%                                            | 67%                                | .26   |
| Peanut SPT community 1 y                         |                                                |                                    |       |
| Median (IQR)                                     | 0 (0-2)                                        | 0 (0-4)                            | .03   |
| Sensitized $\geq 2$ mm                           | 29%                                            | 40%                                | .01   |
| Sesame SPT community 1 y                         |                                                |                                    |       |
| Median (IQR)                                     | 0 (0-0)                                        | 0 (0-0)                            | .02   |
| % $> 2$ mm                                       | 14%                                            | 9%                                 | .07   |

IQR, Interquartile range; OFC, oral food challenge.

**TABLE E2.** Assessment of selection bias: Comparison of children who were food allergic at age 1 y who did and did not participate in OFC at age 4 y

| Characteristic                                   | No OFC at age 4 y (n = 277) | OFC at age 4 y (n = 262) | P     |
|--------------------------------------------------|-----------------------------|--------------------------|-------|
| Sex (male)                                       | 52%                         | 63%                      | .01   |
| Socioeconomic status                             |                             |                          |       |
| Quintile 1 (most disadvantaged)                  | 18%                         | 15%                      | .74   |
| Quintile 2                                       | 21%                         | 23%                      |       |
| Quintile 3                                       | 18%                         | 20%                      |       |
| Quintile 4                                       | 21%                         | 21%                      |       |
| Quintile 5                                       | 21%                         | 21%                      |       |
| Family history of any allergy                    | 75%                         | 79%                      | .23   |
| Asthma                                           | 36%                         | 37%                      | .82   |
| Eczema                                           | 38%                         | 43%                      | .19   |
| Hay fever                                        | 55%                         | 62%                      | .12   |
| Food allergy                                     | 12%                         | 14%                      | .48   |
| Parents' countries of birth                      |                             |                          |       |
| Both Australia                                   | 42%                         | 50%                      | .11   |
| One or both Asian                                | 28%                         | 26%                      |       |
| Others                                           | 30%                         | 23%                      |       |
| Maternal age at child's birth (y), mean $\pm$ SD | 32.7 $\pm$ 4.3              | 33.3 $\pm$ 4.1           | .07   |
| Premature birth                                  | 5%                          | 2%                       | .18   |
| Exposure to smoking in first year                | 0.3%                        | 0.8%                     | .54   |
| Any siblings at recruitment                      | 38%                         | 49%                      | .01   |
| Eczema diagnosis in first year                   | 54%                         | 70%                      | <.001 |
| Egg SPT clinic age 1 y, median (IQR)             | 3 (2-5)                     | 4 (2-5)                  | .27   |
| Egg sensitized 1 y SPT $\geq$ 2 mm               | 87%                         | 84%                      | .32   |
| Egg SPT 4 y, median (IQR)                        | 0 (0-0) (n = 40)            | 0 (0-3)                  | .0003 |
| Egg sensitized 4 y SPT $\geq$ 3 mm               | 5% (n = 40)                 | 25%                      | .005  |
| Peanut SPT clinic age 1 y, median (IQR)          | 0 (0-4)                     | 2 (0-7)                  | <.001 |
| Peanut sensitized 1 y SPT $\geq$ 2 mm            | 37%                         | 56%                      | <.001 |
| Peanut SPT 4 y, median (IQR)                     | 0 (0-0) (n = 40)            | 1 (0-10)                 | <.001 |
| Peanut sensitized 4 y SPT $\geq$ 3 mm            | 13% (n = 40)                | 45%                      | <.001 |
| Sesame SPT clinic age 1 y, median (IQR)          | 0 (0-0)                     | 0 (0-0)                  | .0008 |
| Sesame sensitized 1 y, SPT $\geq$ 2 mm           | 7%                          | 16%                      | .001  |
| Sesame SPT 4 y, median (IQR)                     | 0 (0-0) (n = 40)            | 0 (0-0)                  | .005  |
| Sesame sensitized 4 y SPT $\geq$ 3 mm            | 0%                          | 12%                      | .02   |

IQR, Interquartile range; OFC, oral food challenge.

**TABLE E3.** SPT and sIgE (presented as median SPT with interquartile range) and the severity of reaction elicited during food challenges at age 1 y

| Severity of reaction          | Egg SPT<br>(n = 453) | Egg sIgE<br>(n = 390) | Peanut SPT<br>(n = 151) | Peanut sIgE<br>(n = 127) | Sesame SPT<br>(n = 33) | Sesame sIgE<br>(n = 27) |
|-------------------------------|----------------------|-----------------------|-------------------------|--------------------------|------------------------|-------------------------|
| Mild                          | 3 (2.5-5)            | 1.17 (0.44-4.37)      | 8 (6-10)                | 3.05 (0.98-9.6)          | 8 (3-9.5)              | 6.8 (1.7-11.8)          |
| Moderate-severe               | 4 (2-5)              | 4.49 (1.03-13.3)      | 8 (6-11)                | 16.6 (5.01-24.7)         | 7 (4.5- 12.5)          | 25.6 (7.4-40)           |
| P value                       | .89                  | <.001                 | .57                     | .005                     | .88                    | .06                     |
| Area under the curve (95% CI) | 0.50 (0.43-0.57)     | 0.69 (0.62-0.75)      | 0.46 (0.34-0.58)        | 0.71 (0.59-0.83)         | 0.52 (0.26-0.78)       | 0.75 (0.43-1.0)         |

**TABLE E4.** SPT and sIgE (presented as median SPT with interquartile range) and the severity of reaction elicited during food challenges at age 4 y

| Severity of reaction          | Egg SPT<br>(n = 57) | Egg sIgE<br>(n = 36) | Peanut SPT<br>(n = 92) | Peanut sIgE<br>(n = 52) | Sesame SPT<br>(n = 20) | Sesame sIgE<br>(n = 12) |
|-------------------------------|---------------------|----------------------|------------------------|-------------------------|------------------------|-------------------------|
| Mild                          | 4 (3-7)             | 1.1 (0.5-3.5)        | 12 (9-16)              | 6.61 (2.04-13.6)        | 9 (7-13)               | 3.0 (1.49-19.1)         |
| Moderate-severe               | 6.5 (2-7.5)         | 3.8 (1.6-7.3)        | 12 (9-14)              | 45.6 (14.3-100)         | 10 (5-12)              | 26.1 (6.58-45.6)        |
| <i>P</i> value                | .57                 | .05                  | .77                    | .002                    | .79                    | .39                     |
| Area under the curve (95% CI) | 0.57 (0.31-0.83)    | 0.76 (0.59-0.94)     | 0.48 (0.34-0.62)       | 0.82 (0.68-0.96)        | 0.45 (0.05-0.85)       | 0.70 (0.37-1.0)         |