Patterns of tree nut sensitization and allergy in the first 6 years of life in a population-based cohort

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Background: Longitudinal population-based data regarding tree nut allergy are limited.
Objectives: We sought to determine the population prevalence of tree nut allergy at age 6 years and explore the relationship between egg and peanut allergy at age 1 year and development of tree nut allergy at age 6 years.
Methods: A population-based sample of 5276 children was recruited at age 1 year and followed up at age 6 years. At age 1 year, allergies to egg and peanut were determined by means of oral food challenge, and parents reported their child's history of reaction to tree nuts. Challenge-confirmed tree nut allergy was assessed at age 6 years.
Results: At age 1 year, the prevalence of parent-reported tree nut allergy was 0.1% (95% CI, 0.04% to 0.2%). Only 18.5% of infants had consumed tree nuts in the first year of life. At age 6 years, challenge-confirmed tree nut allergy prevalence was 3.3% (95% CI, 2.8% to 4.0%), with cashew the most common (2.7%; 95% CI, 2.2% to 3.3%). Of children with peanut allergy only at age 1 year, 27% (95% CI, 16.1% to 39.7%) had tree nut allergy at age 6 years compared with 14% (95% CI, 10.4% to 17.9%) of those with egg allergy only and 37% (95% CI, 27.2% to 47.4%) of those with both peanut and egg allergy.
Conclusions: Tree nut allergy is uncommon in the first year of life, likely because of limited tree nut consumption. At age 6 years, tree nut allergy prevalence is similar to peanut allergy prevalence. More than a third of children with both peanut and egg allergy in infancy have tree nut allergy at age 6 years. Understanding how to prevent tree nut allergy should be an urgent priority for future research. (J Allergy Clin Immunol 2018;■■■:■■■-■■■.)

Key words: *Food allergy, sensitization, tree nut allergy, prevalence, population*

Tree nut allergies are usually lifelong and together with peanut allergy are the most common cause of food-induced anaphylaxis and related fatalities.[1,2] Unlike peanut allergy, population-based data regarding tree nut allergy are limited.

Recently, we reported that 2.3% of 10- to 14-year-old Australian children had clinic-confirmed tree nut allergy[3]; however, prevalence estimates using challenge confirmation remain limited at less than 10 years of age. To date, studies in younger children of challenge-confirmed food allergy outcomes have been limited to regions reporting very low overall rates of food allergy (<1%)[4-6] or where low numbers of tree nut food challenges were performed.[7]

Development of tree nut allergy in childhood is also understudied, with little understanding of the role of early tree nut sensitization and food allergy type. The first presentation for children with food allergy is often through reactions to peanut or egg in infancy. Children with peanut allergy are thought to be at increased risk of tree nut allergies, with around 30% of pediatric patients presenting with peanut allergy reported to have allergies to tree nuts.[8-12] To date, no study has explored this clinical observation at the population level nor systematically assessed the association using protocolized challenges. The current clinical dilemma remains: What should be done regarding tree nut allergy testing and introduction advice for those with either peanut allergy or other forms of food allergy in infancy?

The objectives of this study were to estimate the population prevalence of clinic-confirmed tree nut allergies during the first 6 years of life and describe the patterns of coexisting allergies to

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Abbreviations used
OFC: Oral food challenge
SPT: Skin prick test

peanut and other tree nuts. We also aimed to explore the relationship between food allergy at age 1 year and the subsequent development of tree nut allergy at age 6 years.

METHODS

The HealthNuts study is a population-representative longitudinal study of 5276 children recruited at age 1 year and followed up to age 6 years. The study methods have been described in detail previously.[13-15] To summarize, between 2007 and 2011, 5276 infants aged between 11 and 15 months were recruited from immunization clinics around Melbourne, Australia. At recruitment, all infants underwent skin prick tests (SPTs) to egg, peanut, and sesame, and parents completed a questionnaire. The first half of the cohort also had SPTs to shrimp, whereas the second half of the cohort had SPTs to cow's milk.[13]

SPTs were performed with single-tine lancets (Stallergenes, Antony, France) on the infant's back using allergens from ALK-Abelló (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 by subtracting the negative control from the average of the longest diameter and the diameter perpendicular to it. Parental report of the history of allergic reactions in the first year of life was determined by means of questionnaire.

All children who showed any reaction on SPTs (wheal size ≥1 mm), as well as a random sample of those with negative SPT responses, were invited to attend a study clinic at the Royal Children's Hospital for repeat SPTs and oral food challenges (OFCs). At age 1 year, OFCs were performed only for egg, peanut, and sesame.

Those attending the clinic had additional SPTs performed for tree nuts (almond, cashew, and hazelnut). No OFCs were performed for tree nuts at age 1 year. For those with negative SPT responses to tree nuts, home introduction was advised. For those with positive SPT responses, avoidance was recommended.

Follow-up methods at 4 and 6 years of age have been described previously.[14] To summarize, at age 4 years, all participants were followed up by means of questionnaire, and those who reported a new food-induced allergic reaction and those who had any food allergy at age 1 year were invited for clinic assessment that included SPTs and OFCs.

At age 6 years, the entire cohort (n = 5276) was invited to participate in questionnaire and SPT assessment. Questionnaires were mailed to all participants, capturing demographic details, history of food allergy and new food reactions, common allergen exposure information, and history of asthma/wheeze and eczema. All participants were invited for an allergy/health assessment that included SPTs to a predetermined panel of 8 foods (milk, egg, peanut, wheat, sesame, cashew, almond, and hazelnut) and was conducted either in the child's home or at the Royal Children's Hospital. Those with positive SPT responses (>1 mm) or parent-reported reactions to foods consistent with an IgE-mediated allergy were invited for a clinic appointment with a specialist allergy nurse, and OFCs were conducted when indicated by using a standardized protocol (see Fig E1 in this article's Online Repository at www.jacionline.org). Those who were sensitized to almond, cashew, or hazelnut had additional tree nut SPTs performed to all nontolerated tree nuts at the second clinic visit, including Brazil nut, macadamia, pecan, pistachio, and walnut. OFCs were conducted, as previously described,[16] and results were deemed positive if they met at least 1 of the following predefined criteria: (1) 3 or more concurrent noncontact urticarias lasting at least 5 minutes; (2) severe persistent vomiting; (3) perioral or periorbital angioedema; or (4) anaphylaxis (evidence of circulatory or respiratory involvement) within 2 hours of the last challenge dose in the presence of IgE sensitization.

Definitions

Age 1 year. *Sensitized tolerant to egg, peanut, or sesame* was defined as an SPT response of 2 mm or greater and a negative OFC result to that food.

Egg, peanut, or sesame allergy was defined as an SPT response of 2 mm or greater and a positive OFC result to that food.

Milk allergy was defined as an SPT response of 2 mm or greater and a history of reaction consistent with IgE-mediated food allergy.

Parent-reported tree nut allergy was defined as parental report of a reaction consistent with IgE-mediated food allergy to 1 or more tree nuts (any acute onset of skin rash, facial swelling, vomiting, or breathing difficulties within 1 hour of food ingestion).

Tree nut sensitization was defined as an SPT response of 3 mm or greater to almond, cashew, or hazelnut.

Tree nut tolerance was defined as a history of tolerance on ingestion or a negative SPT response when undertaken.

Age 6 years. *Tree nut sensitization* was defined as an SPT response of 3 mm or greater to almond, Brazil nut, cashew, hazelnut, macadamia, pecan, pistachio, or walnut.

Definite tree nut allergy was defined as any of the following: (1) positive OFC result and IgE sensitization at age 6 years; (2) history of objective reaction in the past 12 months consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest and evidence of IgE sensitization at 6 years; or (3) a positive OFC result at age 4 years and SPT response of 8 mm or greater at 6 years of age.

Probable tree nut allergy was defined as any of the following: (1) SPT response of 8 mm or greater but no age 4 years OFC or recent reaction history and no known tolerance or (2) SPT response of 3 to 7 mm at age 6 years and one of (A) positive OFC result at age 4 years, (B) history of objective reaction more than 12 months ago consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest, or (C) parental report of food avoidance because of allergy.

Tree nut tolerant was defined as any of the following: (1) negative OFC result; (2) SPT response of 0 to 2 mm; (3) SPT response of 3 to 7 mm and parent-reported ingestion history (eaten >1 time since age 4 years); or (4) no reaction since age 4 years and no parental report of food avoidance.

Statistical methods

The prevalence of tree nut allergy was calculated among those who completed an allergy assessment at age 6 years (n = 3232) and limited to the tree nuts included in the screening SPT panel (cashew, hazelnut, and almond). Those with negative SPT responses were deemed tree nut tolerant.

To assess whether these estimates were influenced by characteristics that were associated with participation in allergy assessment at age 6 years, we adjusted for differences in risk factors between participants with and without missing data at age 6 years by using the inverse probability weighting method.[17] This reweighting was used to reflect the distribution of risk factors among those approached but did not participate versus those who underwent a full allergy assessment. Weights were the inverse of the predicted probability of participation obtained after fitting a logistic regression model including covariate risk factors that were associated with completing an assessment rather than questionnaire only or nonparticipation (socioeconomic status, family history of allergy, parent country of birth, and whether the child had challenge-confirmed food allergy or eczema at age 1 year). This generated a propensity score for each participant.[17]

As a sensitivity analysis, tree nut allergy prevalence was calculated as the number of children with tree nut allergy (definite or probable tree nut allergy) to 1 or more tree nuts expressed as a proportion of the entire HealthNuts cohort (n = 5276). It was assumed that those with no SPT data and no known food allergy were tree nut tolerant. This provides the most conservative prevalence estimate. All prevalence estimates are reported as the observed proportion with 95% CIs calculated by using the normal approximation to the binomial distribution.

The proportion of those with nut allergies (definite and probable allergy) with coallergy to other tree nuts was calculated. As a sensitivity analysis, this proportion has also been calculated with all those sensitized at between 3 and

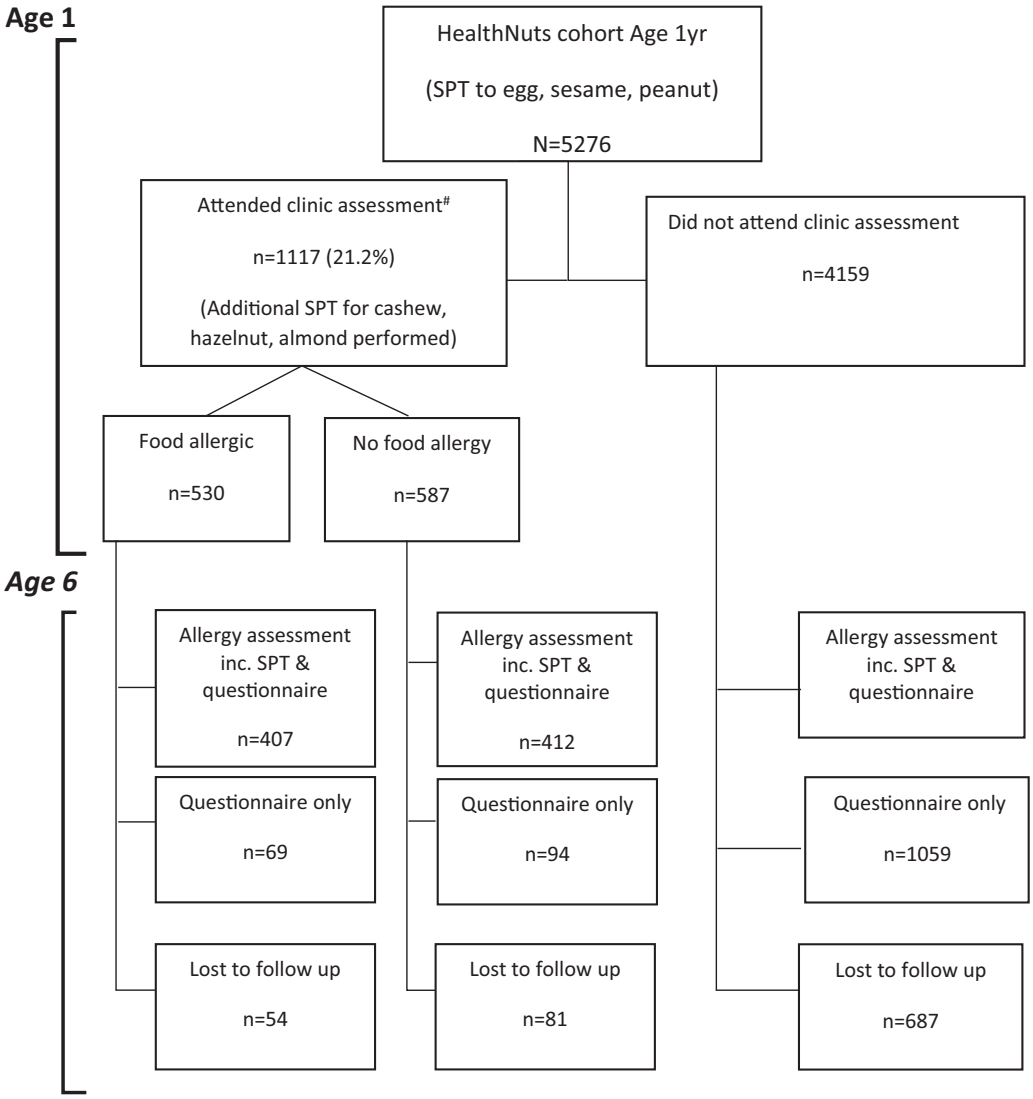

FIG 1. Overview of HealthNuts study participation at age 1 and 6 years.

7 mm who did not have an OFC performed included as allergic. Both calculations have been reported.

Ethics

Ethics approval was obtained for the HealthNuts study 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).

RESULTS

An overview of the HealthNuts study is provided in Fig 1. A total of 5276 one-year-old infants participated in the HealthNuts study at age 1 year (74% participation). Of these, 924 had positive SPT responses to egg, peanut, sesame, or shrimp/cow's milk; attended the OFC clinic; and had SPTs to tree nuts (cashew, almond, and hazelnut). An additional 193 control subjects with negative results attended the clinic for SPTs. At age 1 year, 530 participants were given a diagnosis of OFC-confirmed food allergy to egg, peanut, or sesame.

At age 6 years, 84.4% of the cohort participated in follow-up, with 61.3% (n = 3232) completing both a questionnaire and allergy assessment, including tree nut SPTs, and 23.1% (n = 1222) completing a questionnaire only. Participants with a family history of allergy and children with eczema or food allergy at age 1 year were more likely to participate in the follow-up at age 6 years (Table I).

Parent-reported tree nut allergy at age 1 year

At age 1 year, 6 parents reported a reaction to tree nut consistent with an IgE-mediated food reaction, representing an overall prevalence of 0.1% (95% CI, 0.04% to 0.2%) among the whole cohort of 5276 infants. The low prevalence of reactions might be due to the low consumption of tree nuts in the first year of life, with only 18.5% of parents reporting that their infants had consumed any tree nut by age 1 year.

TABLE I. Demographic and clinical characteristics of the HealthNuts study cohort by participation status at age 6 years

	Assessment cohort (n = 3232 [%])	Questionnaire only (n = 1222 [%])	Did not participate (n = 822 [%])	*P* value†
Sex (male)	52	50	48	.187
SEIFA*				.003
Quintile 1 (least disadvantaged)	18.8	20.3	25.3	
Quintile 2	20.0	20.3	19.2	
Quintile 3	21.9	20.3	18.2	
Quintile 4	19.7	19.5	17.8	
Quintile 5	19.6	19.4	19.4	
Parents' country of birth				<.001
Both Australian	61.8	59.8	49.4	
One East Asian	4.4	4.5	4.1	
Both East Asian	5.8	5.0	9.8	
Other	28.0	30.7	36.6	
Mode of delivery				.601
Vaginal	66.4	67.9	66.1	
Cesarean	33.6	32.1	33.9	
Premature birth	6.2	6.0	5.4	.470
Any siblings	49.9	49.1	50.1	.450
Family history of any allergy	72	66	63	<.001
Family history of food allergy	12	10	9	.007
Family history of asthma	33	27	29	<.001
Family history of eczema	32	28	26	.001
Eczema diagnosis by age 1 y	29	21	24	<.001
Wheeze by age 1 y	18	15	21	.010
Any food allergy at age 1 y	13	7	6	<.001

*Socioeconomic status was assigned on the basis of home postcode by using socioeconomic indexes for areas *(SEIFA)* measures derived from the 2006 Australian census, which accessed relative socioeconomic advantage/disadvantage, economic resources (income, assets, and expenditure) and educational and occupational characteristics.

†χ^2 *P* value refers to any difference between columns 1, 2, and 3.

Tree nut sensitization at age 1 year among those with food allergy

Among those with challenge-confirmed food allergy at age 1 year, 31% (95% CI, 26.6% to 34.7%) were sensitized to 1 or more tree nuts. Tree nut sensitization was less common in infants who were sensitized to 1 or more foods but not allergic (sensitized tolerant; 12% [95% CI, 9.4% to 16.6%]) and in infants with no food sensitization (5.2% [95% CI, 2.7% to 9.3%; Table II).

Tree nut sensitization was more common in infants with both peanut and egg allergy (48.4% [95% CI, 38% to 58.9%]) compared with that in infants with single egg or peanut allergies (23.6% [95% CI, 19.7% to 28.9%] and 33.3% [95% CI, 21.7% to 46.7%], respectively; Table II).

Tree nut allergy at age 6 years

At age 6 years, 234 children were sensitized, and 154 children were allergic to 1 or more tree nuts. Of those with an SPT to tree nuts at age 6 years (n = 3232), the observed prevalence of tree nut sensitization was 7.3% (95% CI, 6.4% to 8.3%), and that of tree nut allergy was 4.3% (95% CI, 3.8% to 5.2%; see Table E3 in this article's Online Repository at www.jacionline.org). After reweighting this estimate for differences in characteristics of subjects who did and did not participate in assessments at age 6 years, the weighted prevalence of tree nut allergy was 3.3% (95% CI, 2.8% to 4.0%). Cashew was the most common tree nut allergy (2.7% [95% CI, 2.2% to 3.3%), followed by hazelnut (0.9% [95% CI, 0.7% to 1.3%) and then almond (0.3% [95% CI, 0.1% to 0.5%]; Fig 2).

All other individual tree nut allergies were diagnosed in less than 1.0% of participants (pistachio, n = 50; walnut, n = 28; macadamia, n = 12; pecan, n = 8; and Brazil nut, n = 5; Table III).

Among the whole cohort of 5276 children, the prevalence of tree nut sensitization was 4.4% (95% CI, 3.9% to 5.0%) and that of tree nut allergy was 3.1% (95% CI, 2.6% to 3.6%). This estimate is likely to be conservative because it assumes that all children who were lost to follow-up did not have tree nut allergy. Collectively, tree nut allergy prevalence (3.3%) was similar to peanut allergy prevalence (2.8% [95% CI, 2.4% to 3.3%). A summary of the SPT and OFC outcomes at age 6 years is included in Fig E2 in this article's Online Repository at www.jacionline.org.

Coallergy patterns among tree nuts

Coallergy patterns among those with any nut allergy are outlined in Table III. Of the 154 children with any tree nut allergy at age 6 years, 42.9% (n = 66) also had peanut allergy at age 6 years. Eighty-four (52.2%) were allergic to only 1 tree nut, 26.7% to 2 tree nuts, 12.4% to 3 tree nuts, and 8.7% to more than 3 tree nuts. Of those with cashew allergy, 36% had coexisting pistachio allergy, and if all those with pistachio sensitization results of between 3 and 7 mm who did not have an OFC were deemed allergic, this increased to 46%.

Of the 147 children with peanut allergy at age 6 years, 45% also had 1 or more tree nut allergies. The most common tree nut coallergy for those with peanut allergy at age 6 years was to cashew (36.7%; Table III).

Tree nut allergy at age 6 years among children with egg or peanut allergy in infancy

Of those with peanut allergy only at age 1 year, 27% had tree nut allergy at age 6 years compared with 14% of those with egg allergy only. A greater proportion (37%) of those with both peanut and egg allergy at age 1 year had tree nut allergy at age 6 years (Fig 3).

Tree nut sensitization at age 1 year and development of tree nut allergy at age 6 years

Of 168 children who were sensitized to cashew at age 1 year, 39% had cashew allergy, and 35% were cashew tolerant at age 6 years (Table IV). Of those sensitized to almond at age 1 year (n = 87), 11% had almond allergy, and 59% were almond tolerant, whereas of those sensitized to hazelnut (n = 72), 19% had hazelnut allergy, and 53% were hazelnut tolerant at age 6 years.

DISCUSSION

This is the first population-based longitudinal study to characterize food challenge–confirmed tree nut allergy in

TABLE II. Cosensitization to tree nuts at age 1 year among the HealthNuts clinic cohort (n = 1117) stratified by food allergy status

Age 1 y food allergy status	Cashew, almond, or hazelnut sensitized (% [95% CI])	Cashew sensitized (% [95% CI])	Almond sensitized (% [95% CI])	Hazelnut sensitized (% [95% CI])
No food allergy/not sensitized (n = 193)	5.2 (2.7-9.3)	3.9 (1.7-7.4)	1.5 (0.3-4.1)	0.5 (0.1-2.7)
Sensitized tolerant* (n = 384)	12.0 (9.4-16.6)	9.4 (6.36-12.9)	3.6 (1.9-6.1)	3.3 (1.7-5.7)
Egg allergy only (n = 347)	23.6 (19.7-28.9)	17.7 (13.8-22.0)	8.9 (6.2-12.4)	7.5 (5-10.8)
Peanut allergy only (n = 60)	33.3 (21.7-46.7)	23.3 (13.4-36.1)	13.3 (5.9-24.6)	8.3 (2.7-18.4)
Peanut and egg allergy† (n = 96)	48.4 (38-58.9)	38.9 (29.1-49.5)	24.2 (16.0-34.1)	20 (12.5-29.5)
Any other allergies‡ (n = 37)	44.4 (27.9-61.9)	38.9 (23.1-56.5)	30.5 (16.3-48.1)	25 (12.1-42.2)

**Sensitized tolerant* is defined as an SPT response of 2 mm or greater to egg, peanut, or sesame and a negative OFC result to that food.
†Allergic to both peanut and egg, irrespective of other food allergies.
‡All other allergies: single milk, 8; single sesame, 5; milk or sesame with either egg or peanut, 23.

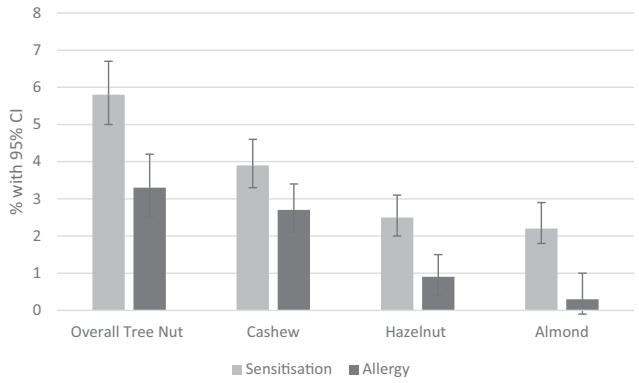

FIG 2. Tree nut sensitization and allergy prevalence at age 6 years.

childhood. It is also the first population-based study to characterize the development of tree nut allergy among children with infantile egg and peanut allergy. We found the prevalence of tree nut allergy at age 6 years (3.3%) to be as common as that of peanut allergy (2.8%), with cashew the most common individual tree nut allergy (2.7%). At age 1 year, 41% of those with challenge-confirmed allergy to egg or peanut were already sensitized to 1 or more tree nuts, and those with both allergies were at greatest risk for tree nut sensitization. Cashew was the most common tree nut sensitization at age 1 year, and around 40% of children sensitized to cashew at age 1 year were allergic to cashew at 6 years of age. Almost half (48%) of the children with both peanut and egg allergy at age 1 year had tree nut allergy at age 6 years.

The strengths of the HealthNuts study are the large population-representative sample, high participation fraction, and good internal and external validity.[13] The follow-up at age 6 years had high cohort retention (>80%). Most tree nut allergy outcomes were clinically confirmed based on objective criteria, with outcomes based on predetermined objective stopping criteria, and the remainder were determined based on large SPT wheal sizes and a history of reported objective adverse reactions consistent with IgE-mediated food allergies.

Limitations included use of open OFCs rather than double-blind, placebo-controlled OFCs, although only objective criteria were used to define a positive challenge result, and nurses were blind to SPT wheal size and history of previous reaction. Not all study participants had SPT or nut consumption data available at age 6 years. Almond, cashew, and hazelnut had more complete screening, and there are limited SPT and OFC data for the additional tree nuts. Most of those deemed allergic to Brazil nut, macadamia nut, pecan, pistachio, and walnut are based on high-level sensitization (SPT response, >8 mm) but not OFC results, and many of those with midrange sensitization (3-7 mm) did not have OFCs performed. This limits the coallergy patterns reported and is an important factor to consider for tree nut allergy studies in the future. In addition, there is also likely to be an allergic bias in participation and follow-up at age 6 years. Therefore we have reported a range of more and less conservative observed prevalence estimates and a population prevalence estimate for tree nut allergy reweighted for factors that were associated with participation at age 6 years.

There are few prevalence studies reporting challenge-confirmed outcomes for tree nut allergy. Recently, we undertook a systematic review of tree nut allergy prevalence internationally and found estimates ranged from 0.05% to 4.9%. However, there was significant study heterogeneity resulting from differences in study design and diagnostic methods. We found 7 studies in children reporting challenge-confirmed tree nut outcomes ranging from 0% to 1.4%.[18] Most of these estimates come from countries or regions with low overall food allergy prevalence.[4-6] Our SchoolNuts study of 10,000 children aged 10 to 14 years reported clinic-defined tree nut allergy of 2.3% by using the same OFC protocols as the current HealthNuts study.[3] The slightly lower prevalence in the SchoolNuts study might reflect the older age group studied.

Estimates of allergy prevalence for individual tree nuts are also limited. Our systematic review found high regional variation, with European studies reporting hazelnut as the most common tree nut allergy, largely because of the high rate of birch pollen allergy and its cross-reactivity with hazelnut. In the United Kingdom Brazil nut was reported as the most common tree nut allergy, and walnut and cashew were reported as the most common tree nut allergy in the United States. Here we found cashew to be the most common tree nut sensitization at age 1 year and allergy at age 6 years. Our Australian SchoolNuts study also reported cashew as the most common tree nut allergy in 10- to 14-year-olds and the most common tree nut trigger for food-induced anaphylaxis.[3] The overall nut coallergy prevalence reported in our study (45%) was greater than that of the population-representative SchoolNuts study reporting 30% of 10- to 14-year-olds with peanut allergy having 1 or more tree nut allergies and 30% of those with a tree nut allergy having 1 or more additional tree nut allergies. Several single-center allergy clinics have also reported similar rates of coallergy to 1 or more tree nuts among children with peanut allergy[10,11,19,20]; however, Fleischer et al[2] reported a higher rate of coexisting peanut allergy (68%) among 190

TABLE III. Peanut and tree nut coallergy patterns at age 6 years

	Coexisting peanut allergy (%)	Coexisting almond allergy (%)	Coexisting Brazil nut allergy (%)	Coexisting cashew allergy (%)	Coexisting hazelnut allergy (%)	Coexisting macadamia nut allergy (%)	Coexisting pecan allergy (%)	Coexisting pistachio allergy (%)	Coexisting walnut allergy (%)
Peanut allergic (n = 147)		6.1-14.2	0.7-6.8	36.7-40.8	19.1-21.8	3.4-7.5	2.7-7.5	13.6-18.4	7.5-11.6
Almond allergic (n = 17)	42.8-60		14.3-25.7	78.5-80.0	57.0-64.3	7.1-20.0	14.3-22.9	34.3-35.7	20.0-28.6
Brazil nut allergic (n = 5)	20.0-50	40.0-45.0		60.0-85.0	55.0-60.0	40.0-55.0	20.0-50.0	75.0-80.0-	60.0-60.0
Cashew allergic (n = 121)	35.5-44.8	8.9-20.9	2.4-12.7		22.6-32.1	5.6-12.7	3.2-12.7	36.3-46.2	14.5-19.4
Hazelnut allergic (n = 44)	44.6-54.2	19.1-33.9	6.4-18.6	59.6-72.9		14.9-22.0	10.6-25.4	25.5-37.2	19.1-25.4
Macadamia nut allergic (n = 12)	25.0-47.8	8.3-30.4	16.6-47.8	58.3-74.0	56.5-58.3		16.6-56.5	50.0-73.9	65.2-66.6
Pecan allergic (n = 8)	25.0-40.7	25.0-29.6	12.5-37.0	50.0-63.0	55.6-62.5	25.0-48.1		37.5-59.2	50.0-77.8
Pistachio allergic (n = 50)	30.0-40.3	10.0-17.9	8.0-22.4	90.0-92.5	24.0-32.8	12.0-25.4	6.0-23.9		30.0-38.8
Walnut allergic (n = 28)	28.5-41.5	14.3-17.1	10.7-29.3	63.4-64.3	32.1-36.6	28.6-36.6	14.3-51.2	53.6-63.4	

Screening for tree nut allergy varied for the various tree nuts. Hazelnut, almond, and cashew SPTs were performed for all study participants. The full tree nut SPT panel was only performed for those sensitized to either almond, cashew, or hazelnut. OFCs were limited for some tree nuts, and therefore the figures presented include those who had OFCs and probable allergy as the lower figure and as a sensitivity analysis those who had OFCs and probable food allergy plus those sensitized at 3 to 7 mm and no OFCs performed included as the upper percentage.

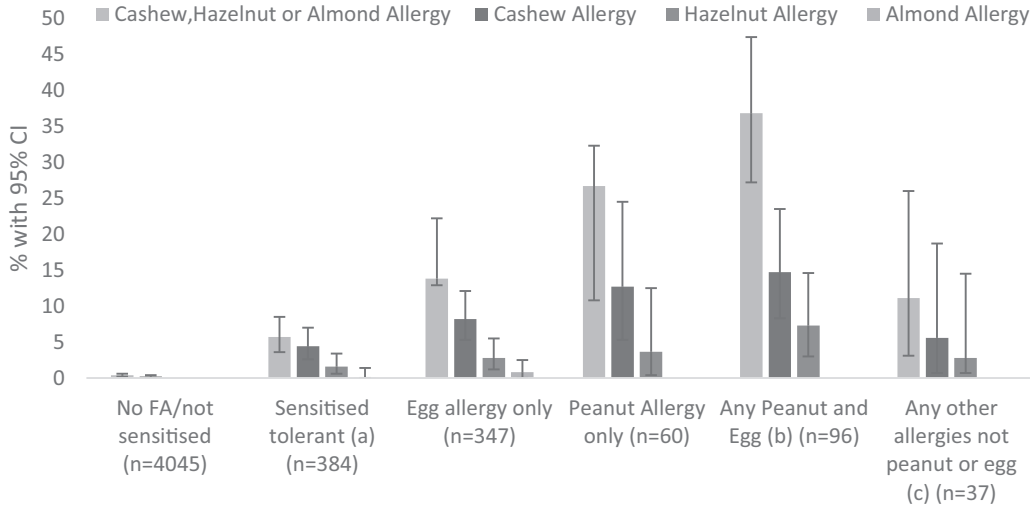

FIG 3. Tree nut allergy (cashew, hazelnut, and almond) at age 6 years by type of food allergy *(FA)* at age 1 year.

children with tree nut allergy in 2005, which might indicate that children with multiple food allergies were overrepresented in their clinics.

Cashew-pistachio and walnut-pecan belong to the same botanical families (Anacardiaceae and Juglandaceae, respectively) and have a reported high degree of serologic cross-reactivity[8,21] and coallergy. The NutCracker study, a single-center prospective cohort study of 83 children with tree nut allergy in Israel, reported two thirds of those with walnut and cashew allergy were also allergic to pecan and pistachio, respectively, whereas all those with pecan and pistachio allergy were allergic to walnut and cashew, respectively.[22] Andorf et al,[23] in a study of 60 selected patients with multifood allergy, reported all those allergic to walnut had coexisting pecan allergy. They reported a unidirectionality of the coallergies, with only two thirds of those patients with walnut and cashew allergy allergic to pecan and pistachio, respectively, suggesting that some allergenic proteins are shared, whereas others are unique to cashew and walnut, resulting in monoallergy.

We found a lower proportion of those with cashew allergy having coexisting pistachio allergy. We did not find pecan-walnut coallergy to be as common as other studies. The differences observed might be due to the limitations of tree nut screening and OFCs in our study because although a smaller study (n = 87), the NutCracker study, did complete OFCs for all sensitized tree nuts, which we were not able to achieve. The observed differences might also to be due to regional differences.

Data on rates of early tree nut sensitization are limited. In 2005, Clark and Ewan[10] reported that by 2 years of age, 19% of those with peanut allergy were sensitized to 1 or more nuts. This was a single-center allergy cohort limited to 47 patients with peanut allergy only. We have reported a markedly higher rate of tree nut sensitization among those with peanut allergy in our population cohort of 33.3%. We also report for the first time a high rate of tree nut sensitization among all those with food allergy at age 1 year and not just peanut allergy. Consideration should be given to identifying this high-risk group of infants in the general population to activate allergy prevention strategies.

This study has found that at 6 years of age, collectively, rates of tree nut allergy are almost as high as those of peanut allergy, with cashew the most common tree nut allergy. Up to half of those with

TABLE IV. Patterns of tree nut sensitization status at age 1 year and sensitization and allergy status at age 6 years (n = 5276)

		Age 6 y tree nut outcome				
				Missing allergy outcome		
Tree nut type	Age 1 y tree nut sensitization status	Allergic, no. (%)	Tolerant, no (%)	3- to 8-mm SPT response and no OFC, no. (%)	No SPT response and unknown tolerance, no. (%)	Missing, no. (%)
Cashew	Positive (n = 168)	66 (39.3)	59 (35.1)	6 (3.6)	2 (1.2)	35 (20.8)
	3-7 mm (n = 110)	26 (19.0)	49 (44.5)	2 (1.8)	2 (1.8)	31 (28.2)
	≥8 mm (n = 58)	40 (70.7)	10 (17.2)	4 (7.0)	0	4 (7.0)
	Negative, <3 mm (n = 947)	38 (4.0)	633 (66.8)	6 (0.6)	7.0 (0.7)	263 (27.8)
	Tree nut SPT not done* (n = 4161)	17 (0.4)	2358 (56.7)	1 (0.02)	39 (1.0)	1746 (42.0)
Almond	Positive (n = 87)	10 (11.5)	51 (58.6)	6 (6.9)	1 (1.1)	19 (21.8)
	3-7 mm (n = 80)	7 (8.8)	49 (61.2)	5 (6.2)	1 (1.2)	17 (21.2)
	≥8 mm (n = 7)	2 (28.6)	2 (28.6)	1 (14.3)	0	2 (28.6)
	Negative, <3 mm (n = 1030)	4 (0.4)	733 (71.0)	8 (0.8)	6 (0.6)	279 (27.1)
	Tree nut SPT not done* (n = 4159)	3 (0.07)	2376 (57.1)	4 (0.1)	29 (0.7)	1747 (42.0)
Hazelnut	Positive (n = 72)	14 (19.4)	38 (52.8)	3 (4.2)	1 (1.4)	16 (22.0)
	3-7 mm (n = 61)	7 (11.5)	35 (57.4)	3 (5.0)	1 (1.6)	15 (24.6)
	≥8 mm (n = 11)	7 (63.6)	3 (27.3)	0	0	1 (10.0)
	Negative, <3 mm (n = 1044)	24 (2.3)	719 (68.9)	10 (1.0)	8 (0.8)	283 (27.0)
	Tree nut SPT not done* (n = 4160)	6 (0.1)	2370 (57.0)	2 (0.1)	35 (0.8)	1747 (42.0)

*Not sensitized to screening foods (egg, peanut, sesame, and shrimp/cow's milk) and therefore did not attend allergy clinic for additional tree nut SPT at 1 year of age.

egg and peanut allergy can be sensitized to tree nuts as early as 1 year of age, and therefore tree nut SPT screening has the potential to impose a significant burden on allergy clinics to confirm allergy status for each tree nut. Evidence that tree nut allergy can be prevented might be required before making recommendations to identify and target children at high risk of tree nut allergy early in life.

Clinical implications: Up to 48% of those with food allergy at age 1 year were found to be tree nut sensitized, and more than a third of those tree nut–sensitized patients had tree nut allergy at age 6 years.

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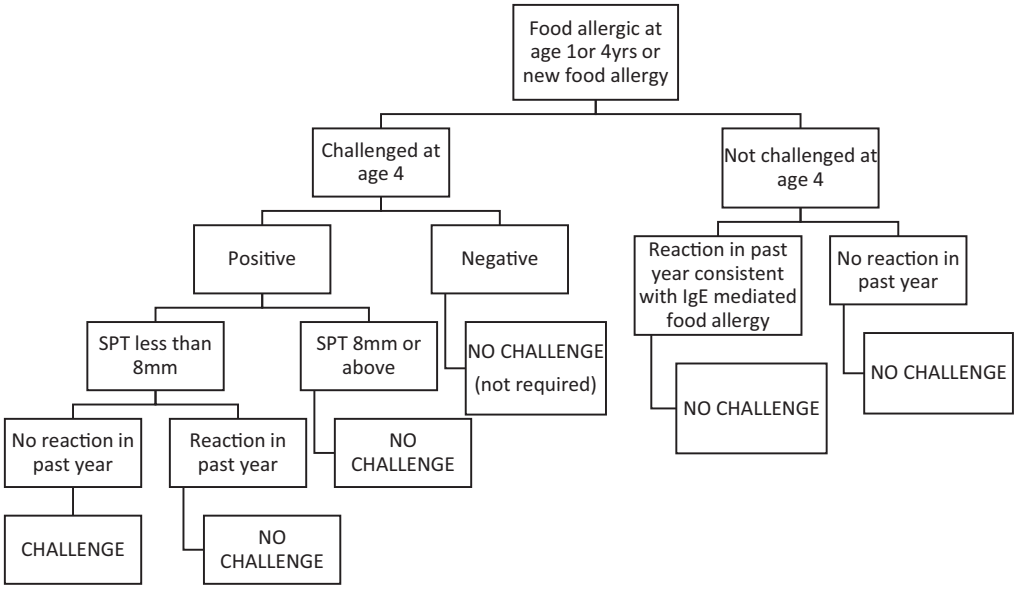

FIG E1. Flow chart of HealthNuts challenge criteria protocol at age 6 years.

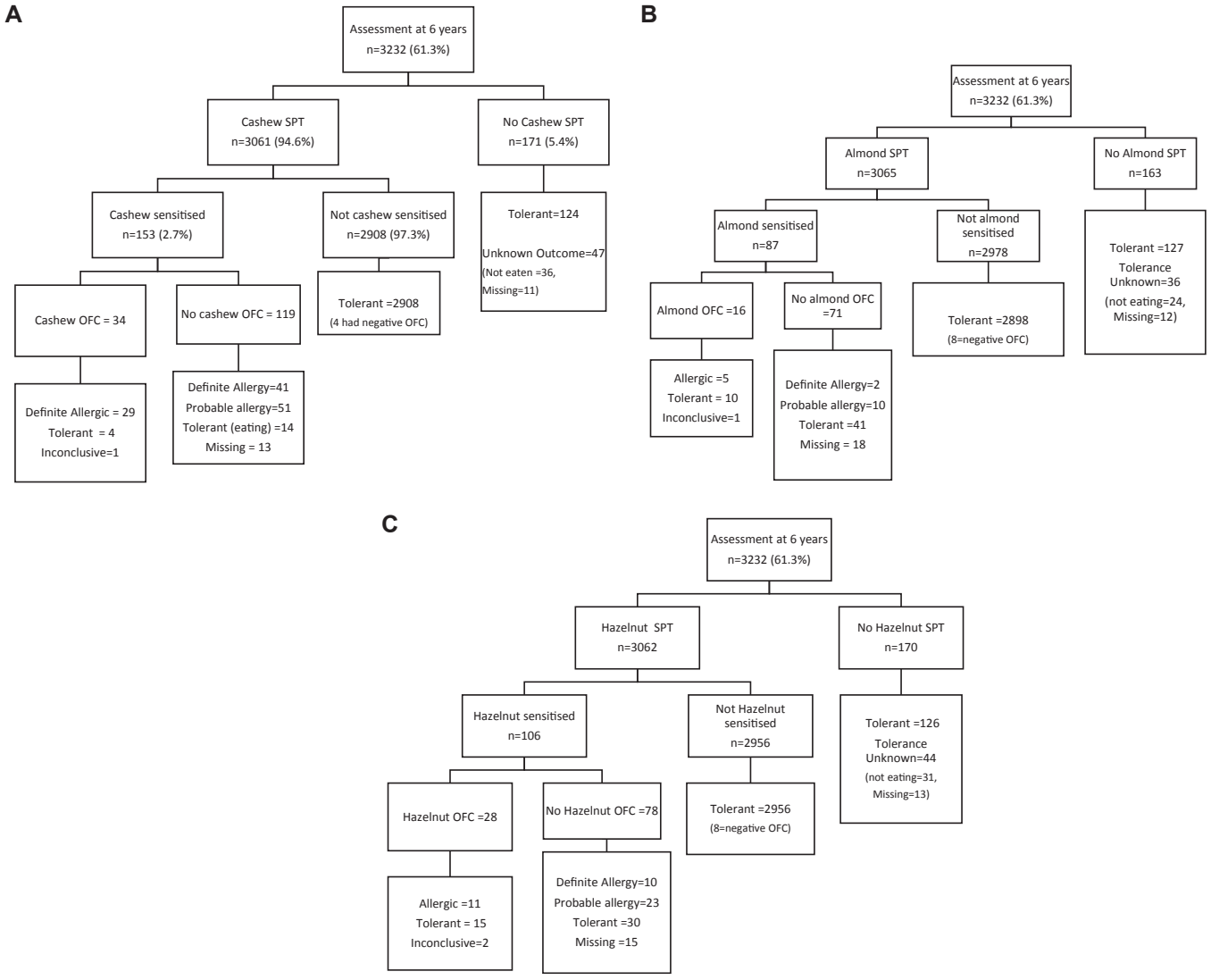

FIG E2. Summary of SPT and OFC outcomes for tree nuts (almond, cashew, and hazelnut) at age 6 years. **A,** *Definite allergy* was defined as any of the following: (1) positive OFC result and IgE sensitized at age 6 years (n = 29); (2) history of objective reaction in the past 12 months consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest and evidence of IgE sensitization at age 6 years (n = 8); or (3) positive OFC result at age 4 years and SPT response of 8 mm or greater at 6 years of age (n = 33). *Probable allergy* was defined as any of the following: (1) SPT response of 8 mm or greater but no age 4 years OFC or recent reaction history and no known tolerance (n = 48) or (2) SPT response of 3 to 7 mm at age 6 years and one of (A) positive OFC result at age 4 years (n = 3), (B) history of objective reaction more than 12 months ago consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest (n = 0), or (C) parental report of food avoidance because of allergy (n = 0). *Tolerant* was defined as any of the following: (1) negative OFC result (n = 8); (2) SPT response of 3 to 7 mm and parent-reported ingestion history (eaten >1 time since age years (n = 14 [3]) or not sensitized and no reaction since age 4 years (n = 344 [4]); and (5) no parental report of food avoidance and parent-reported ingestion history (eaten >1 time since age 4 years; n = 2684). **B,** *Definite allergy* is defined as any of the following: (1) positive OFC result and IgE sensitized at age 6 years (n = 5); (2) history of objective reaction in the past 12 months consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest and evidence of IgE sensitization at age 6 years (n = 2); or (3) positive OFC result at age 4 years and SPT response of 8 mm or greater at 6 years of age (n = 0). *Probable allergy* is defined as any of the following: (1) SPT response of 8 mm or greater but no age 4 years OFCs or recent reaction history and no known tolerance (n = 7) or (2) SPT response of 3 to 7 mm at age 6 years and one of (A) positive OFC result at age 4 years, (B) history of objective reaction more than 12 months ago consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest, or (C) parental report of food avoidance because of allergy (n = 3). *Tolerant* is defined as any of the following: (1) negative OFC result (n = 18); (2) SPT response of 3 to 7 mm and parent-reported ingestion history (eaten >1 time since age 4 years; n = 41); (3) not sensitized and no reaction since age 4 years (n = 447), no parental report of food avoidance, and parent-reported ingestion history (eaten >1 time since age 4 years; n = 2570). **C,** *Definite allergy* is defined as any of the following: (1) positive OFC result and IgE sensitized at age 6 years (n = 11); (2) history of objective reaction in the past 12 months consistent

TABLE E1. OFC protocol for tree nut challenges in the HealthNuts study

One level, 5-mL teaspoon	Average total weight in 1 level teaspoon (g)	Average total mg of nut protein in 1 level teaspoon
Almond meal	4.0	1200
Hazelnut meal	4.0	600
Crushed walnut	2-2.5	550
Crushed cashew	2.5-3.0	700
Macadamia nut	3.0	300
Pecan	2.5	250
Pistachio	3.0	600

with HealthNuts OFC stopping criteria after definite exposure to the food of interest and evidence of IgE sensitization at age 6 years (n = 6); or (3) positive OFC result at age 4 years and SPT response of 8 mm or greater at 6 years of age (n = 4). *Probable allergy* is defined as any of the following: (1) SPT response of 8 mm or greater but no age 4 years OFC or recent reaction history and no known tolerance (n = 23) or (2) SPT response of 3 to 7 mm at age 6 years and one of (A) positive OFC result at age 4 years, (B) history of objective reaction more than 12 months ago consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest, or (C) parental report of food avoidance because of allergy (n = 0). *Tolerant* is defined as any of the following: (1) negative OFC result (n = 23); (2) SPT response of 3 to 7 mm and parent-reported ingestion history (eaten >1 time since age 4 years; n = 30); (3) not sensitized and no reaction since age 4 years (n = 220); and (4) no parental report of food avoidance and parent-reported ingestion history (eaten >1 time since age 4 years; n = 2854).

TABLE E2. Summary of SPT, OFC, and allergy outcomes for additional tree nuts

Tree nut type (no. of SPTs performed)	Not Sensitized (<3 mm)	Sensitized (≥3 mm)		
		3-7 mm and OFC	3-7 mm, no OFC	≥8 mm
Brazil nut (n = 90)	70	0	15 (15 = missing)	5 (5 = probable allergy)
Macadamia nut (n = 101)	75	0	11 (3 = allergic, recent reaction; 8 = missing)	15 (14 = probable allergy; 1 = tolerant)
Pecan (n = 107)	80	0	19 (1 = allergic, recent reaction; 1 = tolerant; 17 = missing)	6 (6 = probable allergy)
Pistachio (n = 116)	43	5 (3 = positive; 1 = negative; 1 = inconclusive)	19 (6 = tolerant; 13 = missing)	49 (4 = tolerant; 45 = probable allergy)
Walnut (n = 111)	66	8 (5 = positive; 2 = negative; 1 = inconclusive)	17 (3 = tolerant; 14 = missing)	20 (3 = allergic at age 4 y; 17 = probable allergy)

Definite allergy is defined as any of the following: (1) positive OFC result and IgE sensitized at age 6 years; (2) history of objective reaction in the past 12 months consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest and evidence of IgE sensitization at 6 years; or (3) positive OFC result at age 4 years and SPT response at 8 mm or greater at 6 years of age. *Probable allergy* is defined as any of the following: (1) SPT response of 8 mm or greater but no age 4 years OFC or recent reaction history and no known tolerance or (2) SPT response of 3 to 7 mm at age 6 years and 1 of (A) positive OFC result at age 4 years, (B) history of objective reaction more than 12 months ago consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest, or (C) parental report of food avoidance because of allergy. *Tolerant* is defined as any of the following: (1) negative OFC result (n = 23); (2) SPT response of 3 to 7 mm and parent-reported ingestion history (eaten >1 time since age 4 years); (3) not sensitized and no reaction since age 4 years; or (4) no parental report of food avoidance and parent-reported ingestion history (eaten >1 time since age 4). *Missing* is defined as sensitized, no OFC, and unknown ingestion history of specified tree nut.

TABLE E3. Sensitization and allergy to almond, cashew, and hazelnut at age 6 years by using different definitions

	Any (almond, cashew, and hazelnut)				Almond				Cashew				Hazelnut			
	Sensitization (≥3 mm), % (95% CI)	Prob* (n = 69), % (95% CI)	Def† (n = 92), % (95% CI)	Overall‡ (n = 139), % (95% CI)	Sens (≥3 mm), % (95% CI)	Prob* (n = 10), % (95% CI)	Def† (n = 7), % (95% CI)	Overall (n = 17), % (95% CI)	Sens (≥3 mm), % (95% CI)	Prob* (n = 51), % (95% CI)	Def† (n = 70), % (95% CI)	Overall (n = 121), % (95% CI)	Sens (≥3 mm), % (95% CI)	Prob* (n = 23), % (95% CI)	Def† (n = 21), % (95% CI)	Overall (n = 43), % (95% CI)
Assessment group§ (observed prevalence [n = 3232])	7.3 (6.4-8.3)	2.7 (1.7-2.7)	2.3 (1.8-2.9)	4.3 (3.8-5.2)	2.8 (2.2-3.4)	0.3 (0.1-0.6)	0.2 (0.1-0.4)	0.5 (0.3-0.8)	5.0 (4.2-5.8)	1.6 (1.2-2.1)	2.2 (1.7-2.8)	3.8 (3.2-4.6)	3.3 (2.8-4.1)	0.7 (0.4-1.0)	0.7 (0.4-1.0)	1.3 (1.0-1.8)
Assessment group‖ (weighted prevalence [n = 3232])	5.8 (5-6.7)			3.3 (2.8-4.0)	2.2 (1.8-2.9)			0.3 (0.1-0.5)	3.9 (3.3-4.6)			2.7 (2.2-3.3)	2.5 (2.0-3.1)			0.9 (0.7-1.3)
Whole cohort¶ (n = 5276)		1.3 (1.0-1.7)	1.4 (1.1-1.8)	2.6 (2.3-3.2)		0.2 (0.1-0.3)	0.1 (0.04-0.2)	0.3 (0.2-0.5)		1.0 (0.7-1.3)	1.4 (1.1-1.7)	2.4 (2.0-2.8)		0.4 (0.3-0.7)	0.5 (0.3-0.7)	0.9 (0.7-1.2)

**Probable food allergy* is defined as any of the following: (1) SPT response of 8 mm or greater but no age 4 years OFC or recent reaction history and no known tolerance; (2) SPT responses of 3 to 7 mm at age 6 years and positive OFC result at age 4 years, (3) evidence of IgE sensitization at age 6 years with a history of objective reaction consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest and evidence of IgE sensitization, or (4) SPT response of 3 to 7 mm and parental report of food avoidance because of allergy.

†*Definite food allergy* is defined as any of the following: (1) positive OFC result and IgE sensitized at age 6 years; (2) history of recent objective reaction in the past 12 months consistent with HealthNuts OFC stopping criteria after definite exposure to the food of interest and evidence of IgE sensitization at age 6 years; or (3) positive OFC result at age 4 years and SPT response of 8 mm or greater at age 6 years.

‡*Overall any tree nut allergy*: Numbers do not add to the total of probable and definite food allergy because some participants had multiple nut allergies.

§*Assessment group (observed prevalence)*: Children who had an allergy/health assessment completed at age 6 years, which included SPTs to 8 foods (milk, egg, peanut, wheat, sesame, cashew, hazelnut, and almond). Those with negative SPT responses to all 3 tree nuts were deemed tree nut tolerant.

‖*Assessment group (weighted prevalence)*: Children who had an allergy/health assessment completed at age 6 years, which included SPTs to 8 foods (milk, egg, peanut, wheat, sesame, cashew, hazelnut, and almond). Those with negative SPT responses to all 3 tree nuts were deemed tree nut tolerant. Prevalence estimates were calculated by weighting the proportion of the participants who had a full clinic assessment at age 6 years by using sampling weights equal to the inverse probability of the family participating in the study at age 1 year.

¶*Whole cohort*: All children who participated in the HealthNuts study at age 1 year. Those who did not participate in follow-up at age 6 years or had unknown tree nut exposure at age 6 years were assumed to be tree nut tolerant (n = 1975).