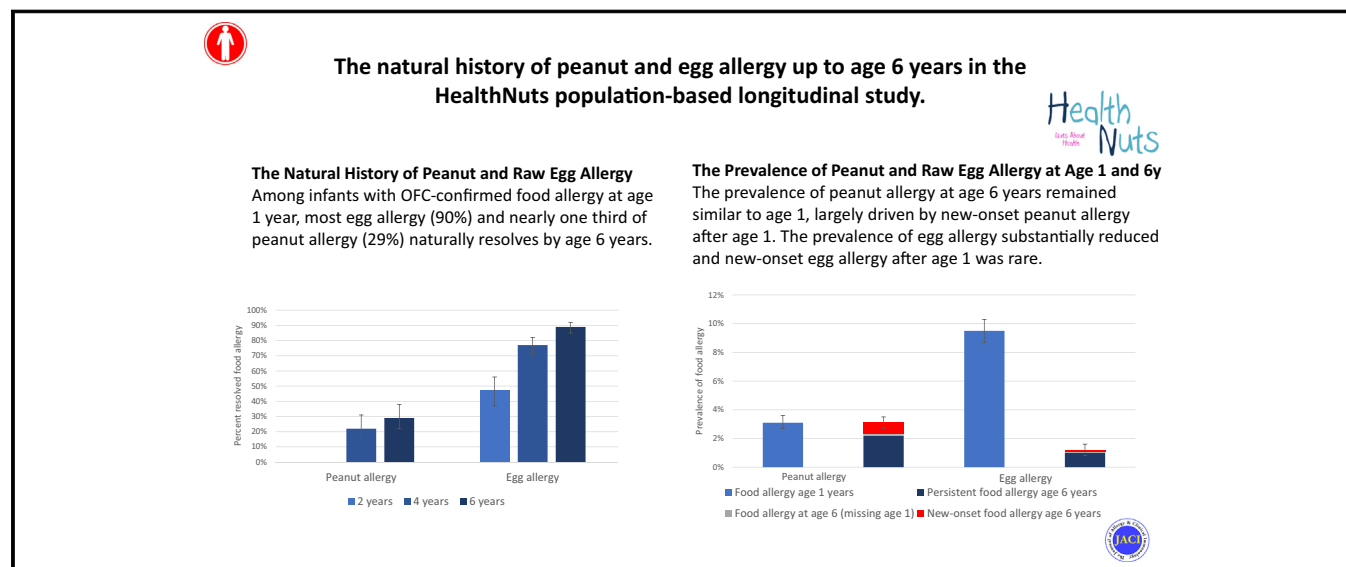


The natural history of peanut and egg allergy in children up to age 6 years in the HealthNuts population-based longitudinal study



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GRAPHICAL ABSTRACT



Background: Prospectively collected data on the natural history of food allergy are lacking.

Objective: We examined the natural history of egg and peanut allergy in children from age 1 to 6 years and assessed whether a skin prick test (SPT) result or other clinical factors at diagnosis are associated with the persistence or resolution of food allergy in early childhood.

Methods: The HealthNuts cohort consists of 5276 children who were recruited at age 1 year and have been followed prospectively. Children with food allergy at age 1 year (peanut [$n = 156$] or raw egg [$n = 471$] allergy) and children who developed new sensitizations or food reactions after age 1 year

were assessed for food sensitization and allergy (confirmed by oral food challenge when indicated) at the 6-year follow-up.

Results: New-onset food allergy developed by age 6 years was more common for peanut (0.7% [95% CI = 0.5%-1.1%]) than egg (0.09% [95% CI = 0.03%-0.3%]). Egg allergy resolved more commonly (89% [95% CI = 85%-92%]) than peanut allergy (29% [95% CI = 22%-38%]) by age 6 years. The overall weighted prevalence of peanut allergy at age 6 years was 3.1% (95% CI = 2.6-3.7%) and that of egg allergy was 1.2% (95% CI = 0.9%-1.6%). The factors at age 1 year associated with persistence of peanut allergy were peanut SPT result of 8 mm or larger (odds ratio [OR] = 2.35 [95% CI 1.08-5.12]),

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Supported by funding from the National Health and Medical Research Council (NHMRC) of Australia (grants 491233 and 1006215 and awards to R.L.P., J.J.K., S.C.D., and A.J.L.), the Ilhan Food Allergy Foundation, AnaphylaxisStop, the Charles and Sylvia Viertel Medical Research Foundation, and the Victorian Government's Operational Infrastructure Support Program.

Disclosure of potential conflict of interest: M. L. K. Tang has received research funding from Prota Therapeutics, is an employee of Prota Therapeutics, has received consultancy fees from Pfizer, and is an inventor on patents owned by MCRI and titled "A Method for Inducing Tolerance to an allergen" and "Allergy Treatment." K. P. Perrett is chair of the scientific advisory board for AllergyPal; her institution has received research grants from DBV Technologies, Novartis, and GSK and consultant fees from Aravax outside the submitted work. S. C. Dharmage and A. J. Lowe have received

investigator-initiated grants from GSK for unrelated work and S. C. Dharmage holds a similar grant from AstraZeneca. A. J. Lowe has received in-kind contributions of study intervention (EpiCeram) from Primus Pharmaceuticals for unrelated research. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication December 1, 2021; revised March 8, 2022; accepted for publication April 8, 2022.

Available online May 18, 2022.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2022.04.008>

sensitization to tree nuts (adjusted OR [aOR] = 2.51 [95% CI = 1.00-6.35]), and early-onset severe eczema (aOR = 3.23, [95% CI 1.17-8.88]). Factors at age 1 associated with persistence of egg allergy at age 6 were egg SPT result of 4 mm or larger (OR = 2.98 [95% CI 1.35-6.36]), other (peanut and/or sesame) food sensitizations (aOR = 2.80 [95% CI = 1.11-7.03]), baked egg allergy (aOR = 7.41 [95% CI = 2.16-25.3]), and early-onset severe eczema (aOR = 3.77 [95% CI = 1.35-10.52]).

Conclusion: Most egg allergy and nearly one-third of peanut allergy resolves naturally by age 6 years. The prevalence of peanut allergy at age 6 years was similar to that observed at age 1 year, largely owing to new-onset food peanut allergy after age 1 year. Infants with early-onset eczema, larger SPT wheals, or multiple food sensitizations and/or allergies were less likely to acquire tolerance to either peanut or egg. (J Allergy Clin Immunol 2022;150:657-65.)

Key words: Peanut allergy, egg allergy, natural history, persistence, incidence, prevalence, resolution, late-onset food allergy

IgE-mediated food allergy remains a significant public health burden, with ongoing research efforts aiming to identify effective prevention and treatment strategies. Although it is believed that approximately 80% of egg and milk allergy and 20% of peanut and tree nut allergy resolve by adulthood, previous estimates are potentially biased, as findings were based largely on retrospective data in patients presenting to specialist allergy clinics.¹⁻⁸ In these scenarios, children may not have repeat food challenges for tolerance until sensitization test results are negative, or conversely, children who develop tolerance may not return to a tertiary setting for follow-up.^{9,10} Furthermore, food allergy was often defined by using sensitization data rather than oral food challenges (OFCs), and food allergy in tertiary allergy clinics is rarely confirmed at both baseline and end point with the criterion standard OFC.¹⁰

Little is known about prognostic biomarkers and risk factors for persistence of food allergy, and clinicians are currently unable to accurately predict whether food allergy presenting in infancy will resolve naturally or persist into adolescence and beyond.⁹ Consequently, children may undergo multiple unnecessary costly reviews and tests, or conversely, they may have unnecessarily prolonged dietary restrictions and associated impairments to quality of life.¹¹ Presence of allergen-specific IgE is established via skin prick tests (SPTs) or serum-specific IgE level tests. Few studies however, have established whether these tests performed at diagnosis can predict the persistence or resolution of food allergy, and reported thresholds are variable.^{1,2,10,12,13} Similarly, selected clinical factors have been associated with an increased risk of persistent food allergy; however, the findings have been inconsistent.^{14,15} Prognostic indicators identifying those children who are unlikely to acquire tolerance naturally, and hence, will benefit most from early treatment with emerging approaches that induce remission, are also needed. There are no studies that prospectively examine the occurrence of newly incident food allergy beyond infancy, and moreover, none that apply the criterion standard of challenge-confirmed allergy. Population-based longitudinal studies with clinical assessments, including OFCs at regular intervals, offer a robust approach to understanding the natural history of food allergy.

HealthNuts is a population-based longitudinal study that tracks the prevalence and natural history of allergic diseases. The

Abbreviations used

aOR: Adjusted odds ratio
AUC: Area under the curve
OFC: Oral food challenge
PPV: Positive predictive value
SPT: Skin prick test

HealthNuts study previously reported challenge-confirmed peanut allergy in 3.1% of infants at age 12 months, with natural resolution in 22% by age 4 years.^{16,17} Challenge-confirmed egg allergy was found in 9% of infants at age 12 months, with 50% of cases resolving by age 2 years.^{17,18} The HealthNuts study has now completed further follow-up of the cohort at age 6 years. The aims of the present study are to describe the natural history of food allergy across the first 6 years of life and to assess whether demographic or clinical factors present at diagnosis are predictive of the persistence or resolution of food allergy.

METHODS

Study design

The HealthNuts study's methods for recruitment and the age 2 years, age 4 years, and age 6 years follow-up visits have been described in detail in previous publications.¹⁷⁻²⁰ A brief overview is provided here and in Fig 1.

Recruitment at age 1 year. HealthNuts is a population-based, prospective study that recruited 5276 infants (aged 11-15 months; 74% participation) from council-run immunization sessions across Melbourne from 2007 to 2011. At recruitment, infants underwent SPTs (ALK-Abelló, Madrid, Spain) to 4 common food allergens: peanut, egg, sesame, and either cow's milk or shellfish. Infants with a detectable SPT wheal (≥ 1 mm) to egg, peanut, or sesame were offered OFC (83% accepted) along with additional SPTs to a larger panel of allergens (milk, egg, peanut, wheat, sesame, cashew, almond, and hazelnut). Blood samples were also collected, and plasma was isolated for specific IgE assays by using the ImmunoCAP System fluoroenzyme immunoassay (Phadia AB, Uppsala, Sweden).¹⁹

Age 2-year egg allergy substudy. Recruitment into this egg allergy substudy began halfway through the HealthNuts study. All infants with challenge-confirmed raw egg allergy at 12 months of age who had been recruited after February 2010 (n = 264) were invited to participate in an additional baked egg OFC at age 1 year and follow-up at age 2 years with repeat raw egg OFCs.¹⁸

Age 4 years follow-up. At age 4 years, all enrolled participants were invited to complete a questionnaire (n = 4291 participated). Additionally, those with a history of food allergy at age 1 year and those reporting new food allergy symptoms since age 1 were invited to attend a study visit for assessment that included an SPT and possible OFC (n = 592).¹⁷

Age 6 years follow-up. At age 6 years, all participants who remained contactable were invited to complete a full written questionnaire and participate in a comprehensive health assessment. If parents did not complete the full assessment or questionnaire, a short telephone questionnaire was administered to capture key details on allergy history. The full assessment included physical measurements, spirometry, and SPTs to food and aeroallergens (a combination of tests from ALK-Abelló, Immunotek S.L.—Australasian Medical and Scientific Ltd [Madrid, Spain] and Greer-Stallergens Greer Ltd on account of supply issues over the course of the study). OFC was offered to children who had a food allergy at a previous wave, those reporting new food reactions suggestive of new-onset IgE-mediated food allergy, and those who had a new food sensitization and were not consuming and tolerating the index food.²⁰

Ethics approval was obtained from the Victorian Department of Human Services (reference no. 10/07), the Office for Children (reference no. CDF/07/492), and the Royal Children's Hospital Human Research Ethics Committee

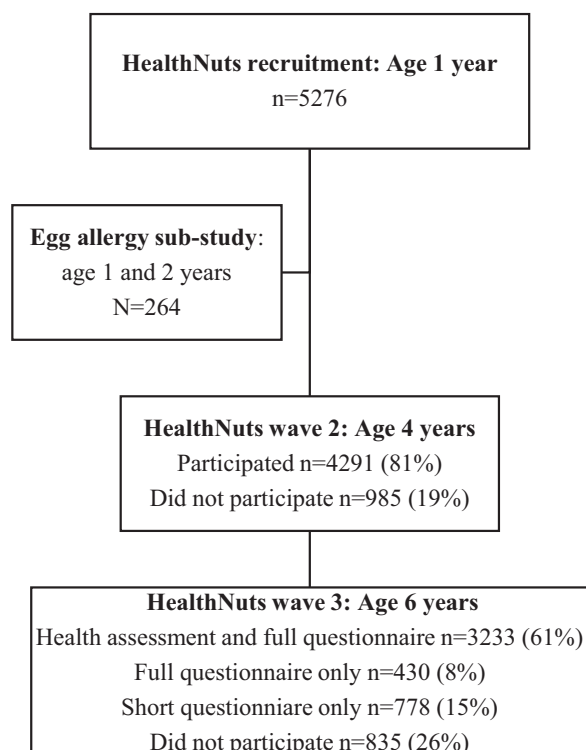


FIG 1. Longitudinal follow-ups of the HealthNuts study.

(reference nos. 27047 and 32294). Parents provided informed consent on behalf of their children.

Definitions of food allergy outcomes and eczema.

Food sensitization at age 1 year was defined as an SPT wheal size of 2 mm or larger and/or a specific IgE level of 0.35 kU/L or greater. At the age 6 years follow-up, food sensitization was defined as a SPT wheal size of 3 mm or larger and/or a specific IgE level of 0.35 kU/L or greater. A lower SPT threshold of 2 mm or larger was used at age 1 year, as infants aged 12 months may have lower skin reactivity.²¹

A positive OFC result was defined as having at least 1 of the following: 3 or more concurrent, noncontact hives lasting at least 5 minutes; perioral and/or periorbital angioedema; vomiting; or anaphylaxis.²²

Food allergy at age 1 year was defined as a positive OFC result in conjunction with a positive test of sensitization. Children were also classified as having a food allergy without challenge at age 1 year if they had a reaction that met the OFC stopping criteria within the previous month for egg and previous 2 months for peanut and had a positive test of sensitization. Food tolerance at age 1 was defined as a negative OFC result or negative SPT result. At age 4 years, food allergy was defined as previously described and informed by OFC, SPT, and clinical history.¹⁷ Food allergy at age 6 years was defined as per Table 1 and informed by OFC, an SPT, and clinical history.

Eczema was defined as a parental report of a doctor's diagnosis of eczema in the first year of life and was further categorized as no eczema, early-onset severe eczema (onset occurring at age <6 months and requiring topical steroid use), or other eczema (onset occurring at any age and not requiring topical steroid use or onset occurring at an age older than 6 months and requiring topical steroid use).

Statistical methods

We described the prevalence and incidence of food allergy at age 6 years by using probable and definite definitions in the assessment subgroup and possible food allergy in the questionnaire-only subgroup. Prevalence and incidence are reported as the observed proportion with 95% CI and assumption

of a binomial distribution. Baseline characteristics were compared between those who did and did not participate in the allergy assessment or questionnaires at age 6 years; to account for possible attrition bias, prevalence estimates at age 6 years were reweighted by use of propensity scores to reflect differences in characteristics between those who and did not participate (see Table E1 in the Online Repository at www.jacionline.org). Weights were the inverse of the predicted probability of participation obtained after fitting a logistic regression model in which characteristics associated with participation were included as covariates.²³

The natural history of food allergy is described as the proportion of persistence or resolution among those with challenge-confirmed food allergy at age 1 year. The "definite food allergy" outcome definition for age 6 years was used for all subsequent analyses. Risk factors for persistent food allergy were modeled by using logistic regression, adjusting for confounding variables selected on the basis of considering separate directed acyclic graphs for each exposure, and adjusting for factors associated with both the exposure and outcome (see Fig E1 in the Online Repository at www.jacionline.org). The ability of the SPT performed at age 1 year to discriminate between persistent and resolved food allergy at age 6 years was assessed by using receiver operating characteristic curves; the Youden index identified the optimal cut point. Logistic regression was used to estimate the odds of persistent or resolved allergy at the optimal threshold. We also examined whether a threshold for an SPT at age 1 with 95% positive predictive value (PPV) to persistent food allergy could be identified, as 95% PPVs are a tool frequently used in clinical practice. As per the methods developed in our previous publications, logistic regression was used to model the association between the risk of food allergy at age 6 years and SPT thresholds determined by assuming a linear relationship between the log of the proportion of patients with persistent food allergy and the numeric measure of sensitization. A fitted probability of persistent food allergy was produced from the logistic regression model for each of the participants given their SPT wheal size, and these were used to replace the observed outcome in the standard formula for the PPV; 95% CIs were estimated from 100 bootstrap replications.^{16,24}

RESULTS

Participation

Of the original cohort of 5276 infants, 84% participated at age 6 years by completing either a health assessment and questionnaire (n = 3233) or questionnaire only (n = 1222). Participation in the assessments and determination of allergy outcomes at age 6 years is described in detail in Fig E2 (available in the Online Repository at www.jacionline.org).

The natural history of food allergy by age 6 years

There were 156 children with peanut allergy at age 1 year. By 6 years of age, peanut allergy had resolved in 29% of cases (95% CI = 22%-38%; n = 37 of 127) or in 27% of cases (95% CI = 20%-35%; n = 37 of 137) with use of the definite or probable food allergy definitions, respectively. There were 471 children with raw egg allergy at age 1 year. Resolution of egg allergy was more frequent than resolution of peanut allergy, resolving in 89% (95% CI = 85%-92%; n = 287 of 323) or 87% (95% CI = 83%-90%; n = 287 of 331) of cases for definite or probable food allergy, respectively. Fig 2 presents the proportion of food allergy resolution across the first 6 years, incorporating results published in previous articles at the time of the age 2 years and age 4 years follow-ups.¹⁶⁻¹⁸ Resolution rates using a best- and worst-case scenario were calculated under the assumption that all children lost to follow-up had either a persistent allergy or a resolved allergy and are presented in Tables E2 and E3 (available in the Online Repository at www.jacionline.org).

TABLE I. Definitions of food allergy and food tolerance in 6-year-old children

Group	Food-tolerant	Food allergy		
		Definite food allergy	Probable food allergy	Possible food allergy
Assessment group*	● SPT result < 3 mm ● Negative OFC result at age 6 y ● SPT result of 3-7 mm and ingestion history indicative of tolerance (had eaten the index food >3 times, no recent reactions, and not avoiding the index food; alternatively, negative OFC result at age 4 y)	● Positive OFC result and sensitized ● Reaction consistent with IgE-mediated food allergy within the previous 12 mo and sensitized (no OFC) ● SPT result ≥ 8 mm at age 6 y and positive OFC result at age 4 y (no OFC at age 6 y)	● SPT result ≥ 8 mm (no OFC at age 4 y or age 6 y, no known tolerance) ● SPT result of 3-7 mm and either a positive OFC result at age 4 y or a reaction consistent with IgE-mediated food allergy since age 4 y	N/A
Questionnaire only group†	Full questionnaire: child is eating the index food, and no reported allergic reactions Short questionnaire: child is not avoiding the index food because of allergy and no recent reactions to the index food	N/A	N/A	Parent-reported reaction consistent with IgE-mediated food allergy since age 4 y or parent report that the child is avoiding the index food because of an allergy

Children were classified into each group on the basis of meeting any of the listed criteria.

N/A, Not available.

*Completed full assessment at age 6 years.

†Completed only questionnaires at age 6 years (no SPT data available).

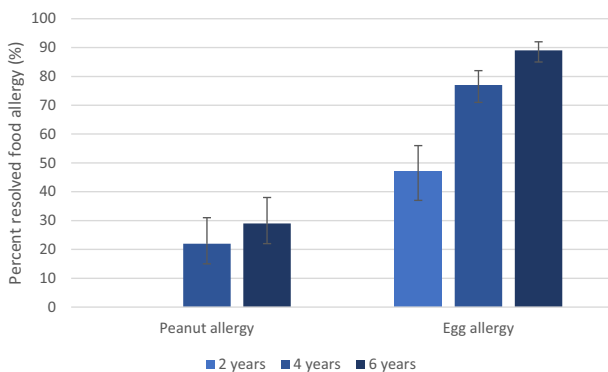


FIG 2. Proportion of definite food allergy present at age 1 year that resolves at ages of follow-up. (Some figures extracted from Savage J et al,⁹ Peters et al,¹⁰ and DunnGalvin et al.¹¹)

The incidence of new-onset food allergy at age 6 years

New-onset peanut allergy developing between age 1 year and age 6 years among those who were tolerant at age 1 year occurred in 0.7% of cases (95% CI = 0.5%-1.1%), whereas new-onset raw egg allergy was very rare, occurring at a rate of 0.09% (95% CI = 0.03%-0.3%) (Table II).

The prevalence of food allergy at age 6 years

The prevalences of peanut and egg allergy at age 6 years are reported for the different definitions (definite, probable, and possible) and samples (assessment or questionnaire only), with an overall estimate provided combining the probable and possible food allergy definitions (Table III).

The overall weighted prevalence (combining definite, probable, and possible outcomes) of peanut allergy at age 6 years was 3.1% (95% CI = 2.6%-3.7%). We previously reported the prevalence of challenge-confirmed peanut allergy at 12 months of age as 3.1% (95% CI = 2.7%-3.6%).¹⁷

The overall weighted prevalence of egg allergy at age 6 years was 1.2% (95% CI = 0.9%-1.6%). We previously reported the prevalence of egg allergy at 12 months of age as 9.5% (95% CI = 8.7%-10.3%).¹⁷

Predictors of peanut allergy persistence

Clinical and demographic characteristics at age 1 year were compared between children with persistent and resolved food allergy (Table IV). Children with persistent peanut allergy at age 6 years were more likely to have at least 1 parent who was Asian; have an eczema diagnosis at age 1 year; show sensitization to a least 1 tree nut, 1 other type of food, or house dust mite; and have a lower cumulative reaction-eliciting dose in peanut OFC at age 1 than did those with a resolved peanut allergy. Age of peanut introduction had little impact on the persistence of peanut allergy. In adjusted models (Table V), sensitization to tree nuts and early-onset severe eczema at age 1 were associated with a higher risk of persistent peanut allergy at age 6 years (adjusted odds ratio [aOR] = 2.51 [95% CI = 1.00-6.35] and aOR = 3.23 [95% CI = 1.17-8.88], respectively).

Predictors of egg allergy persistence

Children with persistent egg allergy at age 6 years were more likely to be male, have at least 1 Asian parent, an eczema diagnosis at age 1 year, sensitization to a least 1 other type of food, a lower cumulative reaction-eliciting dose, and skin reactions during initial OFC and allergy to baked egg at age 1 year than were those with resolved egg allergy (Table IV). In the adjusted models, early-onset severe eczema (aOR = 3.77 [95% CI = 1.35-10.52]), other food sensitization (aOR = 2.80 [95% CI = 1.11-7.03]), and baked egg allergy (aOR = 6.46 [95% CI = 1.88-22.19]) at age 1 year were associated with a higher risk of persistent egg allergy at age 6 years (Table V).

TABLE II. The incidence of new-onset food allergy at age 6 years among children who were tolerant to the food at age 1 year

Allergy	Definite food allergy assessment cohort*	Probable food allergy assessment cohort*†	Possible food allergy questionnaire only*	Overall food allergy*‡
	% (95% CI) [n/N]	% (95% CI) [n/N]	% (95% CI) [n/N]	% (95% CI) [n/N]
Peanut allergy: observed incidence	0.7% (0.5%-1.1%) [20/2847]	0.9% (0.7%-1.4%) [27/2854]	0.5% (0.2%-1.0%) [6/1093]	0.8% (0.6%-1.2%) [33/3947]
Peanut allergy: weighted incidence‡	0.6% (0.4%-1.0%)	0.8% (0.5%-1.2%)	0.4% (0.2%-1.1%)	0.7% (0.5%-1.1%)
Egg allergy: observed incidence	0.08% (0.02%-0.3%) [2/2600]	0.1% (0.04%-0.4%) [3/2601]	0 [0/993]	0.08% (0.03%-0.3%) [3/3594]
Egg allergy: weighted incidence‡	0.09% (0.02%-0.3%)	0.1% (0.04%-0.4%)	—	0.09% (0.03%-0.3%)

*The denominator includes only those children who were deemed to be food tolerant at age 1 year. There were children who had a food allergy at age 6 years but were missing a clear food allergy status at age 1 year, and these children are not included in the calculation of new-onset food allergy (definite peanut allergy [n = 13], probable peanut allergy [n = 6], possible peanut allergy [n = 10], definite egg allergy [n = 7], probable egg allergy [n = 5], or possible egg allergy [n = 3]).

†Probable food allergy also includes those who had definite food allergy; overall food allergy includes probable (and therefore definite) food allergy plus possible food allergy.

‡Inverse probability weighting was used to estimate a weighted prevalence of food allergy to account for differences in baseline characteristics between participants and nonparticipants at age 6 years.

TABLE III. The prevalence of food allergy at age 6 years

Allergy	Definite food allergy assessment cohort	Probable food allergy assessment cohort*	Possible food allergy questionnaire only	Overall food allergy*
	% (95% CI), [n/N]	% (95% CI), [n/N]	% (95% CI), [n/N]	% (95% CI), [n/N]
Peanut allergy: observed prevalence	4.0% (3.4-4.8%), [123/3060]	4.7% (4.0-5.5%), [146/3083]	2.2% (1.5-3.2%), [25/1145]	4.0% (3.5-4.7%), [171/4228]
Peanut allergy: weighted prevalence†	3.2% (2.6-3.8)	3.6% (3.0-4.3%)	1.2% (0.7-2.0%)	3.1% (2.6-3.7%)
Egg allergy: observed prevalence	1.5% (1.1-2.0%), [45/3035]	1.9% (1.5-2.5%), [59/3049]	1.0% (0.5-1.7%), [11/1134]	1.7% (1.3-2.1%), [70/4183]
Egg allergy: weighted prevalence†	1.1% (0.8-1.5%)	1.4% (1.0-1.8%)	0.6% (0.3-1.2%)	1.2% (0.9-1.6%)

*Probable food allergy also includes those who had definite food allergy; overall food allergy includes probable (and therefore definite) food allergy plus possible food allergy.

†Inverse probability weighting was used to estimate a weighted prevalence of food allergy to account for differences in baseline characteristics between participants and nonparticipants at age 6 years.

The ability of an SPT at age 1 year to predict the prognosis of peanut allergy

Children with persistent food allergy at age 6 years had larger SPT responses at age 1 year than did those with transient food allergy (Table IV); however, receiver operating curve analysis showed that SPT results measured at age 1 year performed poorly in predicting the prognosis of peanut allergy at age 6 years (area under the curve [AUC] = 0.64 [95% CI = 0.54-0.74] [see Fig E2]). A peanut SPT result of at least 8 mm at age 1 year was identified as the threshold that maximized sensitivity and specificity (67% and 54%, respectively [Table VI and see Table E4 in the Online Repository at www.jacionline.org]) and was associated with a 2.35-fold (95% CI = 1.08-5.12) increase in odds of persistent peanut allergy (Table V). For an SPT conducted at age 1 year, the threshold with 95% PPV for persistent peanut allergy at age 6 years was at least 17 mm; however, this threshold had very low sensitivity (Table VI). Diagnostic characteristics of a selection of SPT thresholds are presented in the Online Repository (see Table E4).

The ability of an SPT at age 1 year to predict the prognosis of egg allergy

Receiver operating curve analysis indicated that SPT results measured at age 1 year performed poorly in predicting the prognosis of egg allergy at age 6 years (AUC = 0.68 [95% CI = 0.58-0.78]) (see Fig E2). The optimal cut point identified

for egg SPT was 4 mm or larger (Table VI), which was associated with a 2.98-fold (95% CI = 1.35-6.36) increase in odds of persistent egg allergy. A threshold for SPT at age 1 year that had 95% PPV for persistent egg allergy could not be identified. Diagnostic characteristics of a selection of SPT thresholds are presented in the Online Repository (see Table E5).

DISCUSSION

This is the first study to prospectively monitor the status of food allergy by using standardized questionnaires, SPTs, and OFC. The findings showed that 29% of peanut allergy diagnosed at age 1 year resolved by age 6 years. Despite this resolution, the overall weighted prevalence of peanut allergy at age 6 years was 3.1% (95% CI = 2.6%-3.7%), which is similar to the 3.1% prevalence of peanut allergy previously reported at age 1 year in our cohort and reflects the newly incident peanut allergy observed.¹⁷ The majority (89%) of egg allergy resolved by age 6 years, resulting in a substantially lower prevalence at age 1 year (9% vs 1.2%); incident raw egg allergy after age 1 year was very rare.

New-onset peanut allergy occurred in 0.7% (95% CI = 0.5%-1.1%) of those who were tolerant at age 1 year. In the Isle of Wight birth cohort, the prevalence of peanut allergy (defined by SPT result and clinical history) remained relatively constant across the first 10 years, with the prevalence ranging from 0.1% to 0.5% at ages 1, 2, 4, and 10 years, followed by a substantial rise at 18 years (1%); however, prevalence point estimates were not

TABLE IV. Demographic and clinical characteristics present at age 1 year, by persistent and resolved peanut and egg allergy at age 6 years

Characteristic	Resolved peanut allergy (n = 37)	Persistent peanut allergy (n = 90)	Resolved egg allergy (n = 287)	Persistent egg allergy (n = 36)
Male	29%	71%	87%	13%
Female	30%	70%	93%	7%
Missing			0	1
Parents' country of birth				
Both Australian	31%	69%	87%	13%
1 or both Asian	21%	79%	91%	9%
Other	39%	61%	91%	9%
Missing, no.	0	2	6	0
FHx of any allergy: no	21%	79%	88%	12%
FHx of any allergy: yes	32%	68%	89%	11%
No eczema*	44%	56%	96%	4%
Eczema, other	36%	64%	88%	12%
Eczema, early-onset severe	19%	81%	83%	16%
Missing, no.	1	4	10	1
Introduced to peanut at age	31%	69%	—	—
4-10 mo				
11-12 mo	27%	73%	—	—
Peanut not given by 12 mo	31%	69%	—	—
Missing, no.	2	10	—	—
Introduced to egg at age	—	—	100%	0%
<4 mo				
4-6 mo	—	—	90%	10%
7-9 mo	—	—	88%	12%
10-12 mo	—	—	89%	11%
>12 mo	—	—	85%	15%
Missing, no.	—	—	12	1
SPT result to index food (mm)	7 (6-9)	8.5 (6-11)	3 (3-5)	5 (3.5-7.5)
Sensitized to tree nuts: no†	41%	59%	92%	8%
Sensitized to tree nuts: yes	17%	83%	83%	17%
Missing, no.			3	0
Sensitized to house dust mite: no	33%	59%	89%	11%
Sensitized to house dust mite yes	10%	83%	86%	14%
Missing, no.			3	0
Sensitized to other food: no‡	36%	64%	94%	6%
Sensitized to other food: yes	26%	74%	84%	16%
Missing, no.			3	0
OFC reaction: skin only	28%	72%	92%	8%
GIT/respiratory (± skin)	20%	80%	80%	20%
Missing	4	1	28	6
Other food allergy: no§	33%	67%	91%	9%
Other food allergy: yes	26%	74%	83%	17%
Cumulative dose on OFC (mL)	2.2 (0.3-4.7)	0.3 (0.01-4.7)	1.5 (0.01-8.5)	0.01 (0.01-3.5)
No baked egg OFC	—	—	91%	9%
Baked egg OFC-negative	—	—	91%	9%
Baked egg OFC-positive	—	—	60%	40%

FHx, Family history; GIT, gastrointestinal tract.

*Parental report of doctor's diagnosis of eczema in the first year of life. Other eczema (onset at any age and did not require topical steroid use or onset at more than 6 months of age and did require topical steroid use); early-onset severe eczema (onset at less than 6 months of age and required topical steroid use).

†Cashew, almond, or hazelnut SPT responses of 2 mm or larger.

‡Sesame, soy, shrimp, wheat, milk, peanut, or egg (excluding the index food) SPT responses of 2 mm or larger.

§OFC-confirmed allergy to other food (peanut, egg, or sesame, excluding the index food).

broken down into persistence versus incidence.²⁵ A recent US study found that among adults with self-reported food allergy (with at least 1 symptom consistent with IgE-mediated food allergy), half reported developing their food allergies in adulthood.²⁶ This is the first study to have methodically tracked new-onset peanut allergy by using a standardized protocol and procedures. Our data for peanut allergy highlight the fact that onset of peanut allergy beyond the first year of life is a real and

potentially increasing problem. Current strategies have focused solely on prevention of peanut allergy in early life, primarily in the first year, and our findings suggest that children are developing peanut allergy after age 12 months; therefore, the window for prevention may be wider.

The prevalence of raw egg allergy at age 6 years was 1.2% (95% CI = 0.9%-1.6%) which is substantially less than the 9% prevalence reported in this cohort at age 1, and late-onset egg

TABLE V. Risk factors present at age 1 year for persistent food allergy at age 6 years

Risk Factor	Persistent peanut allergy, aOR (95% CI)	P value	Persistent egg allergy, aOR (95% CI)	P value
Female	0.97 (0.43-2.16)	.94	0.53 (0.24-1.14)	.10
Parents; country of birth	1.0		1.0	
Both Australian				
≥1 Asian	1.74 (0.27-4.53)	.25	0.62 (0.25-1.52)	.30
Other	0.69 (0.27-1.78)	.45	0.66 (0.27-1.62)	.36
Family history of allergic disease*	0.42 (0.15-1.21)	.11	0.74 (0.31-1.75)	.49
Family history of food allergy*	0.44 (0.10-1.90)	.28	0.54 (0.16-1.85)	.33
Peanut SPT result ≥ 8 mm	2.35 (1.08-5.12)	.03	—	—
Egg SPT result ≥ 4 mm	—	—	2.98 (1.35-6.36)	.007
No eczema	1.0		1.0	
Eczema, other	1.35 (0.44-4.19)	.6	2.53 (0.77-8.27)	.12
Eczema, early-onset severe	3.23 (1.17-8.88)	.02	3.77 (1.35-10.52)	.01
Other food allergy†	1.39 (0.59-3.29)	.45	1.82 (0.84-3.93)	.13
Tree nut–sensitized‡	2.51 (1.00-6.35)	.05	1.43 (0.63-3.22)	.39
House dust–mite sensitized‡	2.77 (0.55-14.2)	.22	1.05 (0.38-2.89)	.92
Other food–sensitized‡	1.34 (0.50-3.62)	.56	2.80 (1.11-7.03)	.03
OFC reaction (GIT/respiratory vs skin only)§	2.21 (0.50-9.83)	.30	2.58 (0.75-8.82)	.13
Cumulative dose on OFC (mL [per unit dose increase])§	0.94 (0.82-1.07)	.34	0.97 (0.81-1.18)	.79
Baked egg allergy	—	—	6.46 (1.88-22.19)	.003

Risk factors for persistent food allergy were fitted in separate models and adjusted for potential confounders on the basis of consideration of a directed acyclic graph, adjusting for factors associated with both exposure and outcome. The models were not adjusted for SPT result in response to the index food.

GIT, Gastrointestinal tract.

*Adjusted for parents' country of birth and socioeconomic status.

†Adjusted for eczema, sex, parents' country of birth, socioeconomic status, and family history of allergy; other food allergy refers to challenge-confirmed egg, peanut, or sesame allergy at age 1 year, excluding the index food.

‡Adjusted for other sensitization variables (tree nut, house dust mite, or other food sensitization), eczema, sex, parents' country of birth, socioeconomic status, and family history of allergy; other food sensitization refers to other foods tested for in the SPT panel, excluding the index food and tree nuts.

§Adjusted for other OFC variable, sex, parents' country of birth, socioeconomic status, and family history of allergy; unit increase for OFC dose is per each graded dose as per OFC protocol.

||Adjusted for other OFC variable (OFC reaction or OFC dose), sex, parents' country of birth, socioeconomic status, family history of allergy, and other food allergy.

TABLE VI. The diagnostic capacity of SPTs conducted at age 1 year to predict the persistence of food allergy at age 6 years

Allergy type	n	Allergy confirmed, no.	SPT threshold	SPT threshold definition	PPV % (95% CI)	NPV % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Persistent peanut allergy	127	90	8 mm	Youden index	78 (67-87)	40 (26-55)	67 (56-76)	54 (37-71)	1.5 (1.0-2.1)	0.6 (0.4-0.9)
Persistent peanut allergy	127	90	17 mm (95% CI = 13-20)	95% PPV	—	30 (22-39)	3 (1-9)	100 (91-100)	2.9 (0.2-55.2)	1.0 (0.9-1.0)
Persistent egg allergy	323	36	4 mm	Youden index	16 (11-22)	94 (89-97)	75 (58-88)	50 (44-56)	1.5 (1.2-1.9)	0.5 (0.3-0.9)
Persistent egg allergy	323	36	13 mm (95 % CI = 11-*)	65% PPV	—	89 (85-92)	0 (0-10)	99 (98-100)	1.6 (0.08-32)	1 (0.9-1.0)

*Upper limit of CI could not be estimated. Additional data on the diagnostic capacity of SPT conducted at ages 2 and 4 years to predict the persistence of food allergy at age 6 years are included in [Table E6](#) in this article's online repository.

allergy was rare. Our findings show that 89% of egg allergy resolved by age 6, adding to our previous studies showing that around half of egg allergy cases had already resolved by age 2 years and 80% had resolved by around age 4 years.^{17,18} Both the HealthNuts and EuroPrevall studies reported that 50% of egg allergy had resolved 1 year after diagnosis (at around age 2-3 years), despite having markedly different baseline prevalence of egg allergy (9% and 1.2%, respectively).^{18,27} This contrasts with previous clinical reports, which found that only 50% of egg allergy resolved at a median age of 6 or 9 years.^{1,6} This may be because these other clinical reports did not systematically monitor the natural history of food allergy at the population level and instead relied on selected samples recruited from tertiary

allergy clinics, which may be biased toward more complex allergy cases or those with persistent disease.¹⁰

Although it is established that the majority of egg allergy cases and a subset of peanut allergy cases do resolve in childhood, the challenge remains in predicting when and in whom tolerance will occur. This information would be useful for clinical management, decisions around implementation of emerging therapies, and counseling for families. We identified several clinical factors that occurred more frequently in children with persistent peanut and egg allergy; however, in adjusted models there was no strong evidence to support many associations, which may reflect limited power owing to the relatively small sample size. The presence of sensitization to other food allergens and early-onset severe

eczema were associated with an increased risk of persistent peanut and egg allergy. Age of peanut introduction had little impact on the persistence of peanut allergy, although it should be noted that at the time this cohort was recruited, public health guidelines did not recommend early introduction of allergenic foods. We found that baked egg allergy was the strongest predictor of persistent egg allergy, similar to the findings at age 2 years in our previous reports, indicating that this remains a relevant factor for persistent disease in an older age group.¹⁸ We hypothesize that eczema and multiple sensitizations are associated with both egg and peanut allergy persistence and that this might reflect a greater degree of immune dysregulation in these individuals, making it less likely that they will naturally develop tolerance. Early-onset eczema is a key risk factor for food allergy and appears to also be an important driver of food allergy persistence. Although recent randomized controlled trials have found that strategies thought to reduce eczema (such as regular moisturization) are not effective at preventing eczema or food allergy,²⁸⁻³⁰ further recent randomized controlled trials should assess whether proactive treatment of eczema to achieve symptom control encourages the resolution of food allergy.³¹ Conversely, early-onset eczema may simply be a clinical marker of underlying immune status, identifying food allergy that is more likely to be of the persistent phenotype.

We found that an SPT at age 1 was not a good predictor of persistent food allergy at age 6 years, as indicated by poor AUC. However, we did identify SPT thresholds at age 1 year that were associated with 2- and 3-fold increases in peanut and egg allergy at age 6 years. Interestingly, these thresholds were the same as the thresholds previously identified as having 95% PPV for the diagnosis of food allergy at age 12 months. A threshold that could predict whether food allergy would persist with 95% PPV was difficult to attain and not very useful clinically. For example, an SPT result of 17 mm or larger at age 1 year had 95% PPV for persistent peanut allergy at age 6 years; however, the sensitivity of this threshold indicates that only 3% of children with allergy would be correctly identified by this threshold.

The strengths of the present study are that we have systematically monitored the natural history of food allergy in a large population-based, longitudinal study with high rates of follow-up, which overcomes limitations of previous studies (which have largely recruited from tertiary allergy clinics and may be biased toward persistent allergic disease). Food allergy was confirmed at baseline by using the criterion standard OFC, which overcomes limitations of previous studies that may have included children as having an allergy based on a high SPT result or specific IgE level alone. All children with food allergy at a previous wave were eligible for a food allergy assessment at age 6 years that included an SPT and OFC when indicated to confirm persistence or resolution of food allergy. Only a subsample of children who were sensitized were eligible for OFC at ages 4 years (70% peanut and 76% egg) and 6 years (30% peanut and 30% egg) owing to changes to the study protocol as described in the Methods section and Table I; however, the definitions of definite and probable food allergy are quite stringent, with only definite food allergy used for analyses beyond prevalence. A potential limitation of this study is that there was some loss to follow-up at age 6 years. A descriptive analysis revealed some differences between characteristics of those who participated at age 6 years and those lost to follow-up. This suggested that there may be some attrition bias in the present study, particularly toward those with a history of allergic disease. We

applied inverse probability weighting to our prevalence estimates to account for this. Follow-up of the children with peanut allergy was very high, although there was more loss to follow-up among those children who had egg allergy at age 1. This may be a reflection of more children outgrowing their egg allergy early and not being as motivated to participate in the present wave.

In a population-based cohort, despite nearly one-third of children outgrowing their peanut allergy by age 6 years, the prevalence of peanut allergy at age 6 years was similar to that observed at age 1, driven largely by new-onset peanut allergy after age 1. In contrast, there was a substantial reduction in egg allergy prevalence by age 6 years, reflecting a high rate of resolution of egg allergy and rare occurrence of new-onset egg allergy. Infants with multiple food sensitizations or allergies and early-onset severe eczema at age 1 year are less likely to outgrow their egg and/or peanut allergies at age 6 years. Infants with eczema and multiple food sensitizations and/or allergies would be appropriate targets for early intervention trials evaluating disease-modifying immunotherapies or proactive treatment of eczema to promote food allergy resolution. Prioritizing research of these and future interventions to infants less likely to naturally develop tolerance would yield the most benefit of finite health care resources and research funding.

We thank the children and parents who participated in the HealthNuts study, as well as the staff of Melbourne's Local Government Areas for access to community immunization clinics. We thank ALK Abelló, S.A. Madrid, Spain, for supplying the skin prick testing reagents and the HealthNuts safety committee: Associate Professor Noel Cranswick (Australian Paediatric Pharmacology Research Unit, Murdoch Children's Research Institute), Dr Jo Smart (Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Australia), and Associate Professor Jo Douglass (Director, Department of Allergy and Immunology, Royal Melbourne Hospital, Melbourne, Australia).

Clinical implications: Although one-third of peanut allergy in children resolved by age 6 years, the prevalence of peanut allergy remained similar to that at age 1 year, driven by new-onset peanut allergy. The majority of egg allergy resolves naturally. Infants with larger SPT wheal sizes, eczema, or multiple food sensitizations are less likely to outgrow their egg or peanut allergy by age 6 years. Disease-modifying interventions (such as immunotherapy) in early life may be best targeted to infants with a large SPT result, early-onset severe eczema, multiple food sensitization, or baked egg allergy, as they are less likely to develop tolerance naturally.

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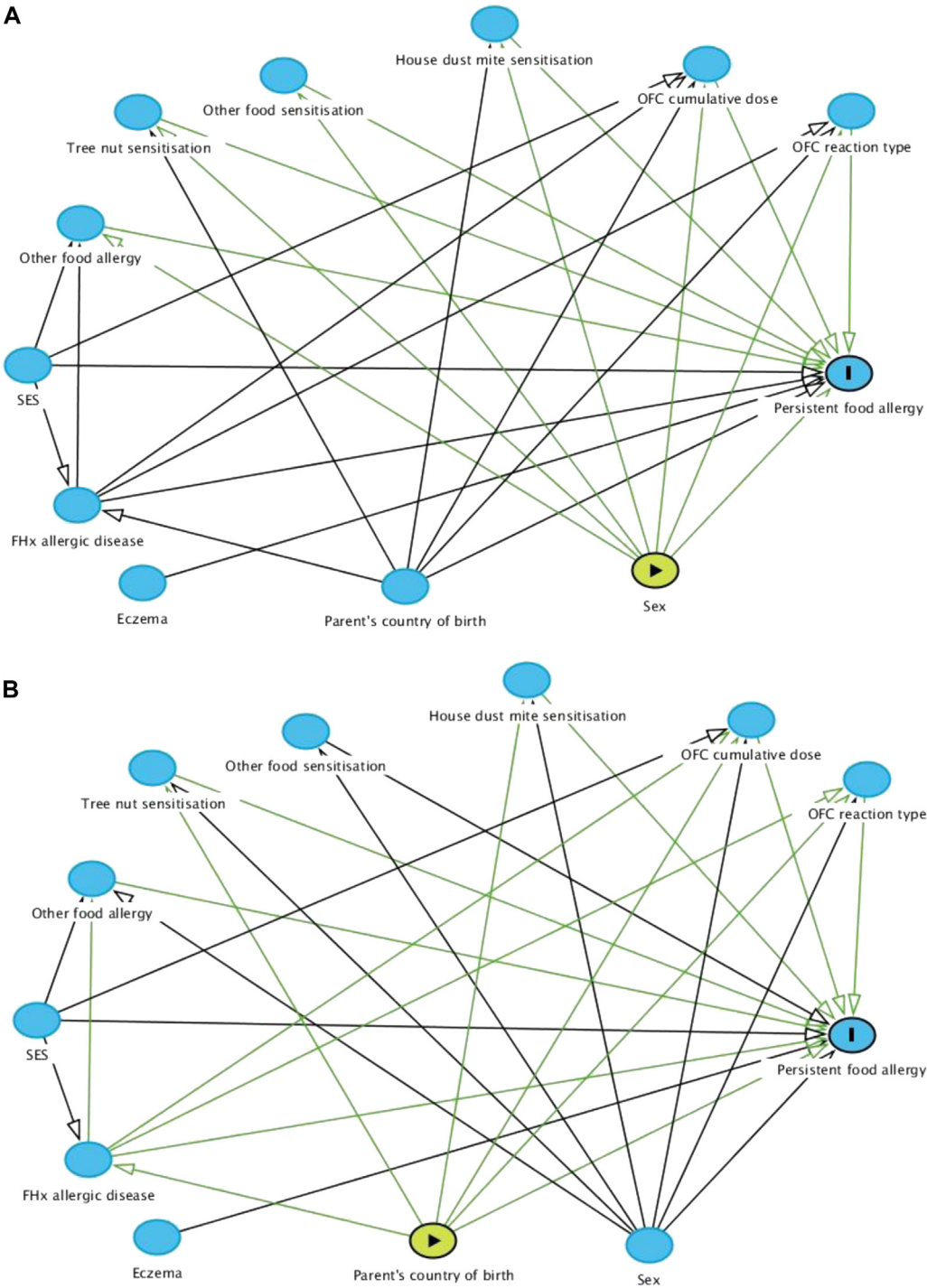
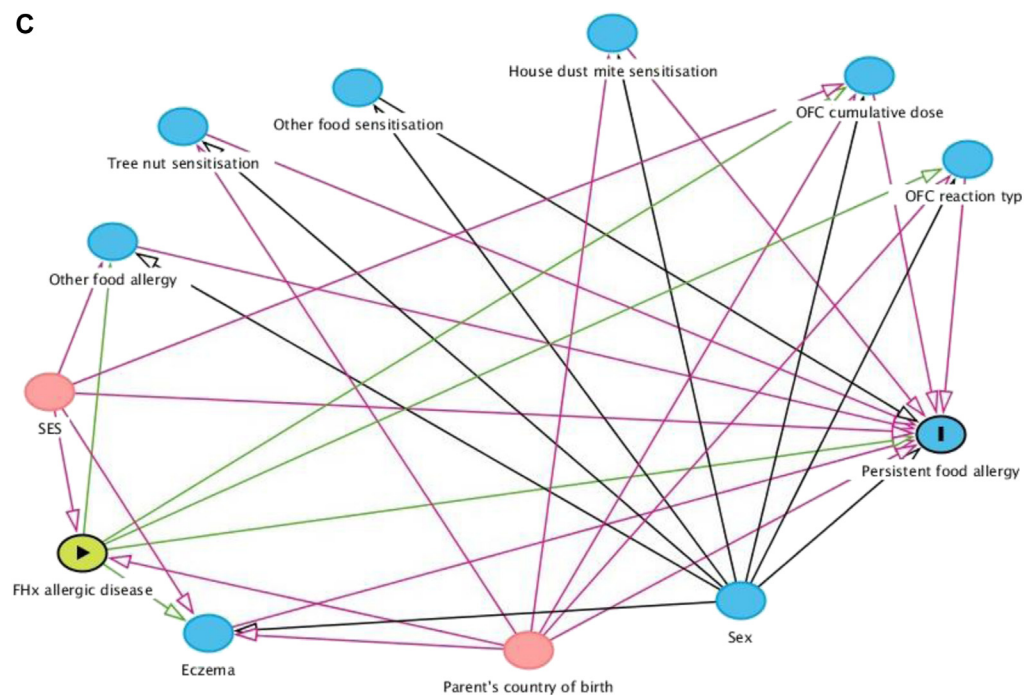


FIG E1. Directed acyclic graphs that informed confounder selection for the risk factor analysis presented in Table V. **A**, Child's sex (no adjustment necessary). **B**, Parents' country of birth (no adjustment necessary). **C**, Family history (FHx) of allergic disease, adjusted for parents' country of birth and SES. **D**, Eczema, adjusted for FHx of allergic disease, sex, parents' country of birth, and SES. **E**, Tree nut-sensitized and fitted in a single model with additional adjustment for FHx of allergic disease, sex, parents' country of birth, SES, and eczema. **F**, Other food allergy and baked egg allergy, adjusted for eczema, FHx of allergic disease, sex, parents' country of birth, and SES. **G**, OFC reaction (gastrointestinal tract [GIT]/respiratory vs skin only) and cumulative dose in OFC (mL), fitted in a single model with additional adjustment for FHx of allergic disease, sex, parents' country of birth, and SES.

C



D

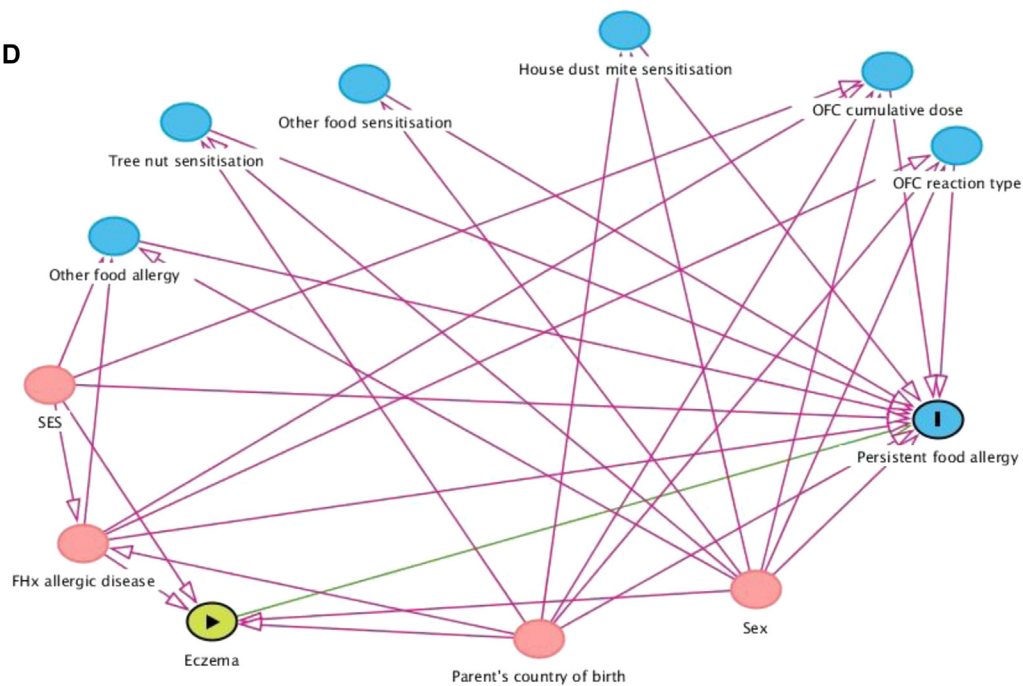


FIG E1. Continued

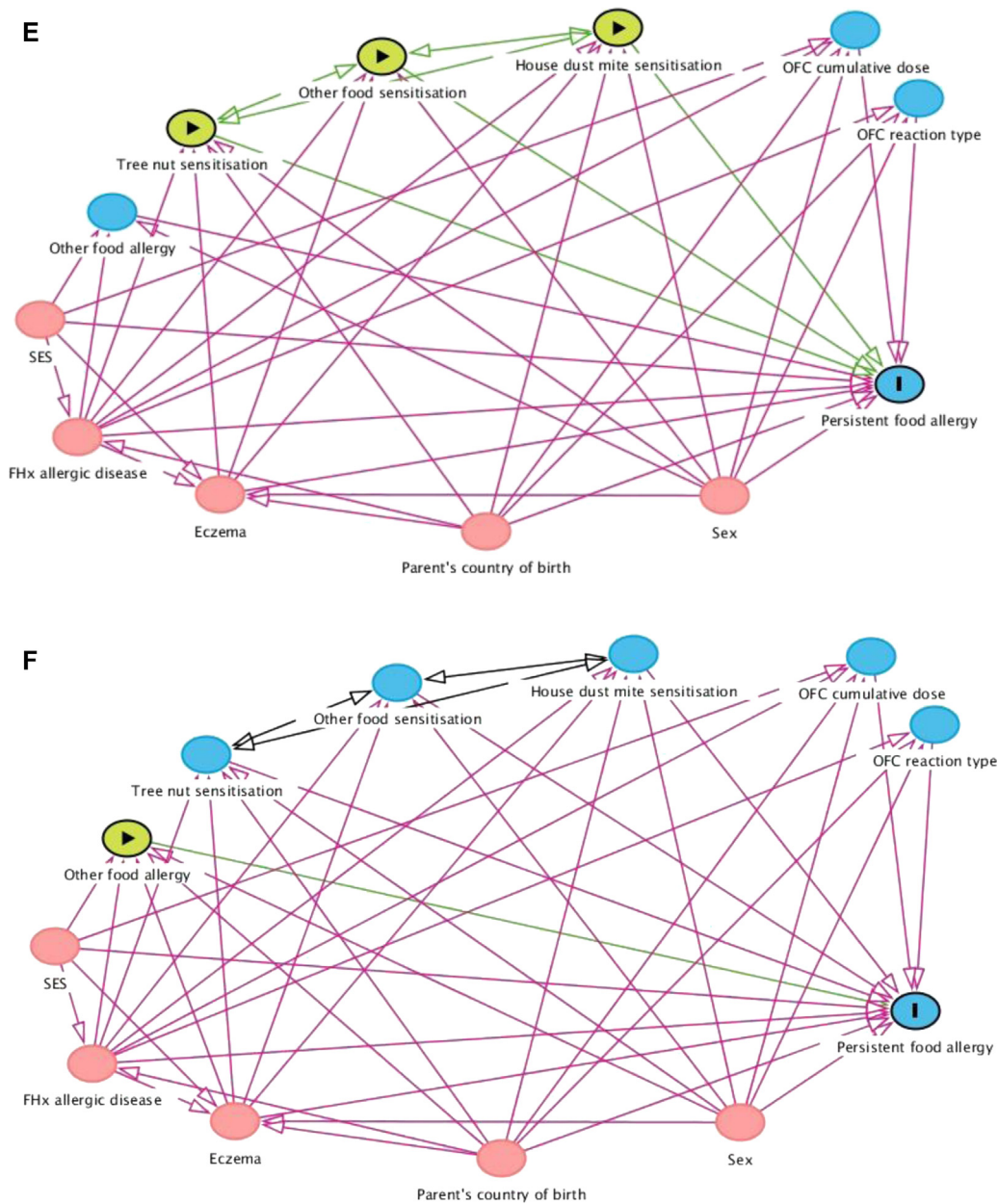


FIG E1. Continued

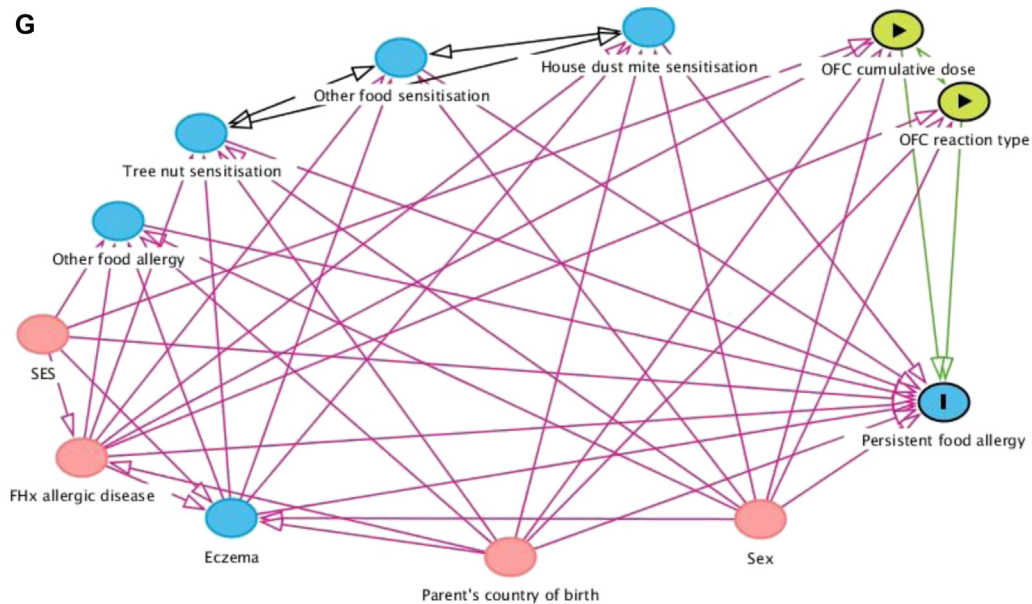


FIG E1. Continued

A

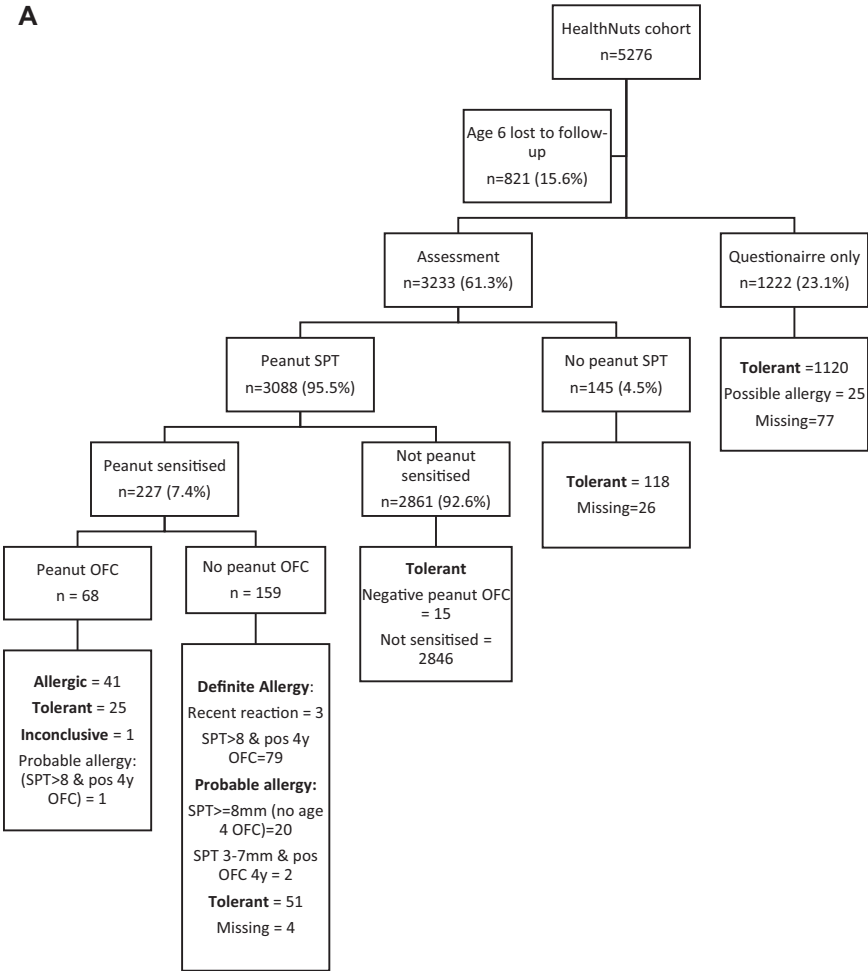


FIG E2. Participation in the HealthNuts study at age 6 years and determination of food allergy outcomes at age 6 years. **A**, Peanut. **B**, Egg.

B

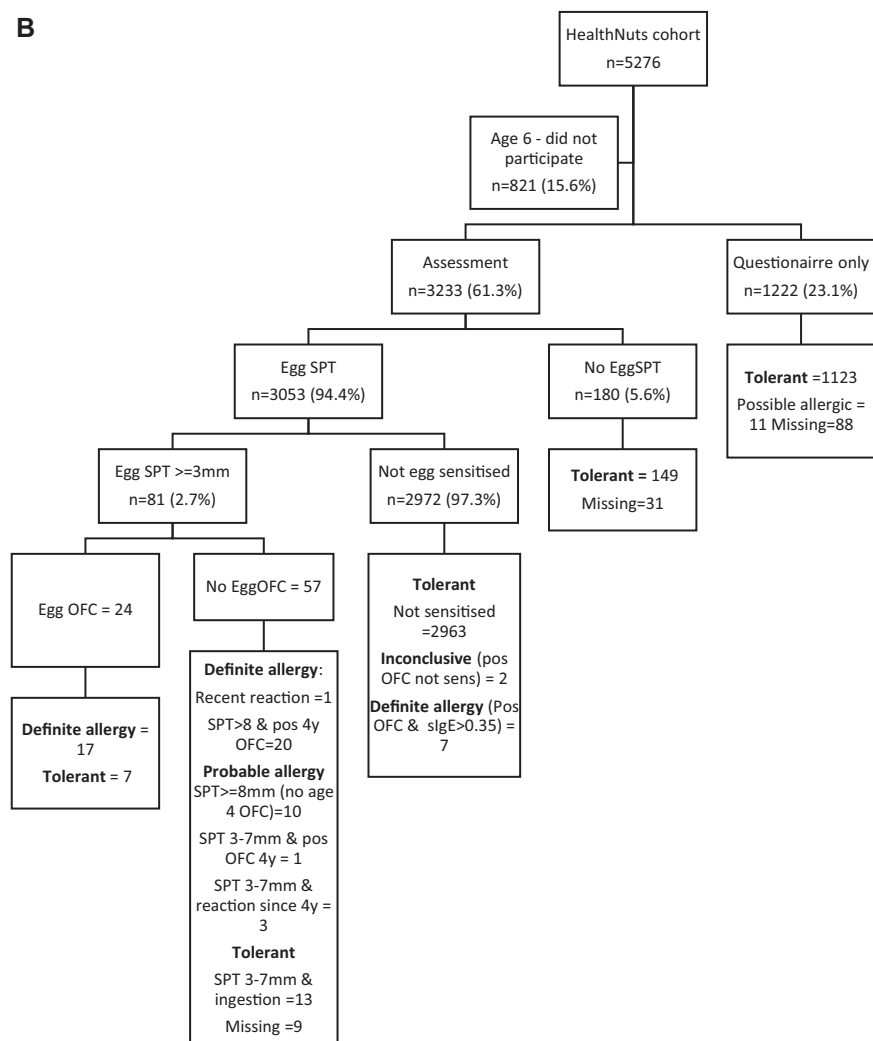


FIG E2. Continued.

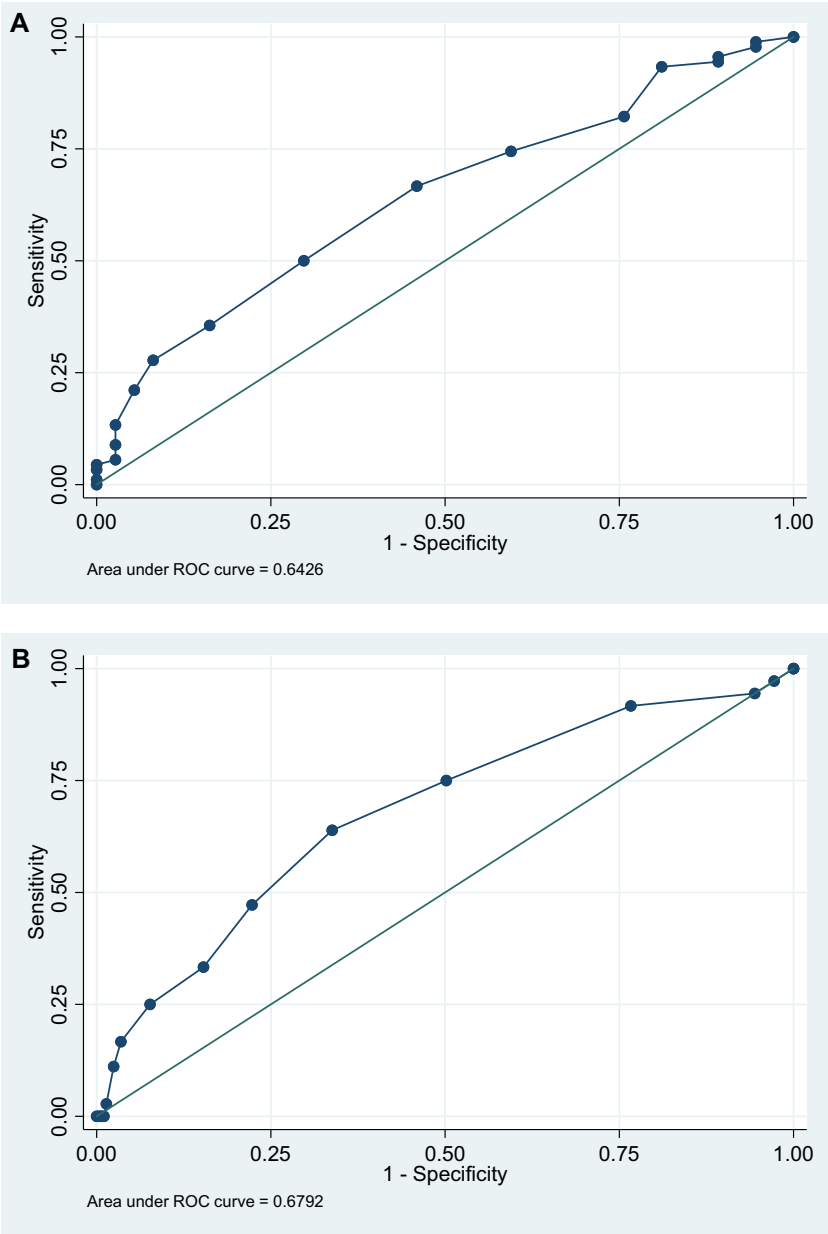


FIG E3. Receiver operating characteristic curves for SPT performed at age 1 year for predicting the prognosis of egg and peanut allergy at age 6 years. **A**, Peanut. **B**, Egg.

TABLE E1. Comparison of demographic characteristics between those who did and did not participate in the health assessment at age 6 years

Characteristic	Did not participate in the assessment at age 6 y (n = 2043)	Participated in the assessment age 6 y (n = 3233)	P value
Sex (male), % (no.)	49% (1004/2031)	52% (1661/3213)	.1
Mode of delivery (cesarean), % (no.)	33% (662/2026)	34% (1050/3218)	.6
Preterm birth (≤ 36 wk), % (no.)	6% (116/1936)	6% (189/3070)	.8
Birthweight (kg), mean $\pm$ SD	3.4 (0.5)	3.4 (0.6)	.04
Socioeconomic status (SEIFA), % (no.)			
1 (most disadvantaged)	22% (454/2032)	19% (608/3229)	<.001
2	20% (404/2032)	20% (646/3229)	
3	19% (396/2032)	22% (706/3229)	
4	19% (383/2032)	20% (636/3229)	
5 (least disadvantaged)	19% (395/2032)	20% (633/3229)	
Parent country of birth, % (no.)			
Both Australian	55% (1078/1954)	62% (1954/3144)	<.001
1 or both Asian	11% (215/1954)	10% (320/3144)	
Other	34% (661/1954)	28% (879/3144)	
Maternal age at birth (y), mean (SD)	32.3 (5.1)	33.3 (4.5)	<.001
Family history of allergic disease, % (no.)	65% (1318/2043)	72% (2343/3233)	<.001
Ever breast-fed, % (no.)	92% (1812/1974)	96% (3050/3176)	<.001
Overall breast-feeding duration (mo) mean $\pm$ SD	8.6 (6.1)	10.1 (5.9)	<.001
Child care in first year of life, % (no.)	20% (394/1974)	28% (872/3166)	<.001
Pet dog, % (no.)	29% (601/2042)	31% (1008/3232)	.2
Pet cat, % (no.)	17% (343/2042)	17% (550/3232)	.8
Any siblings, % (no.)	51% (1035/2032)	50% (1612/3219)	.5
Maternal smoking in pregnancy, % (no.)	6% (127/1960)	4% (112/3157)	<.001
Environmental smoking at age 1 y, % (no.)	26% (520/2018)	19% (607/3216)	<.001
Wheeze in first year of life, % (no.)	17% (307/1759)	18% (514/2844)	.6
Food allergy at age 1 y, % (no.)	7% (124/1844)	13% (410/3063)	<.001
Eczema diagnosis, % (no.)	22% (428/1929)	29% (897/3053)	<.001
Antibiotics in first year of life, % (no.)	49% (971/1988)	52% (1612/3114)	.04

Factors included in the final inverse probability weighting model for participation in the physical assessment at age 6 are as follows: sex, SEIFA, mother's age at birth, parents' country of birth, family history of any allergy, any breast-feeding, child care attendance, exposure to environmental smoking in the first year of life, and eczema or food allergy in the first year of life.

SEIFA, Socio-Economic Indexes for Areas.

TABLE E2. Comparison of demographic characteristics between those who did and did not participate in the full questionnaire at age 6 years

Characteristic	Did not participate in the full questionnaire at age 6 (n = 1613)	Participate in the full questionnaire at age 6 (n = 3663)	P value
Sex (male), % (no.)	49% (784/1601)	52% (1881/3643)	.08
Mode of delivery (cesarean), % (no.)	34% (543/1594)	33% (1199/3650)	.4
Preterm birth (≤ 36 weeks), % (no.)	6% (93/1511)	6% (212/3495)	.9
Birthweight (kg), mean (SD)	3.3 (0.6)	3.4 (0.5)	.0001
Socioeconomic status (SEIFA), % (no.)			
1 (most disadvantaged)	25% (398/1604)	18% (664/3657)	<.001
2	19% (309/1604)	20% (741/3657)	
3	19% (310/1604)	22% (792/3657)	
4	18% (283/1604)	20% (736/3657)	
5 (least disadvantaged)	19% (304/1604)	20% (724/3657)	
Parent country of birth, % (no.)			
Both Australian	53% (814/1542)	62% (2209/3556)	<.001
1 or both Asian	12% (183/1542)	10% (352/3556)	
Other	35% (545/1542)	28% (795/3556)	
Maternal age at birth (y), mean (SD)	32.2 (5.3)	33.3 (4.5)	<.001
Family history of allergic disease, % (no.)	63% (1017/1613)	72% (2644/3663)	<.001
Ever breast-fed, % (no.)	91% (1406/1551)	96% (3456/3599)	<.001
Overall breast-feeding duration (mo), mean $\pm$ SD	8.5 (6.2)	10.0 (5.9)	<.001
Child care in first year of life, % (no.)	19% (297/1558)	27% (969/3582)	<.001
Pet dog, % (no.)	28% (455/1612)	32% (1154/3662)	.02
Pet cat, % (no.)	17% (270/1612)	17% (623/3662)	.8
Any siblings, % (no.)	52% (838/1604)	50% (1809/3647)	.08
Maternal smoking in pregnancy, % (no.)	7% (113/1548)	4% (126/3569)	<.001
Environmental smoking at age 1 y, % (no.)	28% (451/1590)	19% (676/3644)	<.001
Wheeze at age 1 year, % (no.)	19% (261/1379)	17% (560/3224)	.2
Food allergy at age 1 y, % (no.)	6% (93/1433)	13% (441/3473)	<.001
Eczema diagnosis, % (no.)	23% (345/1529)	28% (980/3453)	<.001
Any allergy in first year of life, % (no.)	25% (392/1601)	32% (1159/3654)	<.001
Antibiotics in first year of life, % (no.)	50% (783/1566)	51% (1800/3536)	.6

Factors included in the final inverse probability weighting model for participation in the full questionnaire at age 6 are as follows: sex, SEIFA, mother's age at birth, parents' country of birth, family history of any allergy, any breast-feeding (fewer missing data than for breast-feeding duration), child care attendance, pet dogs, any siblings, exposure to environmental smoking in the first year of life, and eczema or food allergy in the first year of life.

SEIFA, Socio-Economic Indexes for Areas.

TABLE E3. Resolution rates calculated by using a best- and worst-case scenario

Allergy type	Observed resolution	Worst-case scenario (assumes that all children lost to follow-up still have the allergy)	Best-case scenario (assumes that all children lost to follow-up are tolerant)
Definite peanut allergy	29% (95% CI = 22%-38%); n = 37/127	24% (95% CI = 17%-31%); n = 37/156	42% (95% CI = 34%-50%); n = 66/156
Probable peanut allergy	27% (95% CI = 20%-35%); n = 37/137	24% (95% CI = 17%-31%); n = 37/156	36% (95% CI = 28%-44%); n = 56/156
Definite egg allergy	89% (95% CI = 85%-92%); n = 287/323	61% (95% CI = 56%-65%); n = 287/471	92% (95% CI = 90%-96%); n = 435/471
Probable egg allergy	87% (95% CI = 83%-90%); n = 287/331	61% (95% CI = 56%-65%); n = 287/471	91% (95% CI = 88%-93%); n = 427/471

Resolution rates were calculated under the assumption that either all children lost to follow-up had either a persistent allergy or a resolved allergy. These results should be interpreted with caution because we know that both extremes are unlikely. Some parents declined to participate because they believed that their child no longer had an allergy, as they regularly consumed the index food in their diet, whereas other parents declined to participate because they believed that their child still had an allergy.

TABLE E4. Diagnostic characteristics of a selection of thresholds for SPTs performed at age 1 year and their ability to discriminate between the persistence or resolution of peanut allergy at age 6 years

SPT wheal size (mm)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio	PPV (%)	NPV (%)
3	97	11	1.1	0.4	72	50
4	94	11	1.1	0.5	72	44
5	93	19	1.15	0.4	74	54
6	82	24	1.1	0.7	73	36
7	74	41	1.3	0.6	75	40
8	67	54	1.5	0.6	78	40
9	50	70	1.7	0.7	80	37
10	36	84	2.2	0.8	84	35
11	23	92	3.4	0.8	89	34
12	21	95	3.9	0.8	91	33

PPV, Positive predictive value.

TABLE E5. Diagnostic characteristics of a selection of thresholds for SPTs performed at age 1 year and their ability to discriminate between the persistence or resolution of egg allergy at age 6 years

SPT wheal size (mm)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio	PPV (%)	NPV (%)
3	92	23	1.2	0.4	13	96
4	75	50	1.5	0.5	16	94
5	64	66	1.9	0.6	19	94
6	47	78	2.2	0.7	21	92
7	33	85	2.2	0.8	21	91
8	25	92	3.3	0.8	29	91
9	17	97	4.8	0.9	38	90
10	11	98	4.6	0.9	36	90
11	3	99	2.0	1.0	20	89

PPV, Positive predictive value.

TABLE E6. Diagnostic capacity of SPTs conducted at ages 2 years and 4 years to predict the persistence of food allergy at age 6 years

SPT type	n	Threshold	Sensitivity	Specificity	AUC	OR
Peanut SPT at 2 y	29	8 mm	85% (62%-97%)	89% (52%-98%)	0.87 (0.73-1.0)	45.3 (4.05-506.84)
Peanut SPT at 4 y	106	10 mm	71% (60%-81%)	86% (68%-96%)	0.79 (0.71-0.87)	15.6 (4.9-50.1)
Egg SPT at 2 y	151	6 mm	67% (41%-87%)	95% (90%-98%)	0.81 (0.69-0.92)	36.0 (10.4-124.5)
Egg SPT at 4 y	209	3 mm	90% (74%-98%)	82% (75%-87%)	0.86 (0.80-0.92)	41 (11.8-143.3)

The optimal cutoffs for SPTs performed at ages 2 years and 4 years to predict the persistence of food allergy at age 6 years was determined by using the Youden index. There is some variation in the optimal SPT thresholds, which may reflect sampling variation due to the selective sampling at ages 2 and 4 years. For SPTs performed at age 2 years, an SPT was offered only to those who had egg allergy at age 1 and were recruited in the second half of the study (hence, the very low numbers for peanut allergy). At age 4 years, everyone who previously had a food allergy was invited to the study clinic, but some parents declined, particularly the parents of the 50% of children who had outgrown their egg allergy at age 2 years. Given these caveats, this table should be interpreted with caution.

OR, Odds ratio.