

Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants

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Background: Several indicators suggest that food allergy in infants is common and possibly increasing. Few studies have used oral food challenge to measure this phenomenon at the population level.

Objective: To measure the prevalence of common IgE-mediated childhood food allergies in a population-based sample of 12-month-old infants by using predetermined food challenge criteria to measure outcomes.

Methods: A sampling frame was used to select recruitment areas to attain a representative population base. Recruitment occurred at childhood immunization sessions in Melbourne, Australia. Infants underwent skin prick testing, and those with any sensitization (wheal size ≥ 1 mm) to 1 or more foods (raw egg, peanut, sesame, shellfish, or cow's milk) were invited to attend an allergy research clinic. Those who registered a wheal size ≥ 1 mm to raw egg, peanut, or sesame underwent oral food challenge.

Results: Amongst 2848 infants (73% participation rate), the prevalence of any sensitization to peanut was 8.9% (95% CI, 7.9-10.0); raw egg white, 16.5% (95% CI, 15.1-17.9); sesame, 2.5% (95% CI, 2.0-3.1); cow's milk, 5.6% (95% CI, 3.2-8.0); and shellfish, 0.9% (95% CI, 0.6-1.5). The prevalence of challenge-proven peanut allergy was 3.0% (95% CI, 2.4-3.8); raw egg allergy, 8.9% (95% CI, 7.8-10.0); and sesame allergy, 0.8% (95% CI, 0.5-1.1). Oral food challenges to cow's milk and

shellfish were not performed. Of those with raw egg allergy, 80.3% could tolerate baked egg.

Conclusion: More than 10% of 1-year-old infants had challenge-proven IgE-mediated food allergy to one of the common allergenic foods of infancy. The high prevalence of allergic disease in Australia requires further investigation and may be related to modifiable environmental factors. (*J Allergy Clin Immunol* 2011;127:668-76.)

Key words: Food allergy, anaphylaxis, infant, peanut, egg, sesame, cow's milk, skin prick testing, population, prevalence, oral food challenge, eczema

Recently there has been much debate about the increase in food allergies leading to concerns in the community especially among families, school staff, the food industry, and health care providers. To date, these concerns are largely unsubstantiated because of a lack of prevalence studies with sufficient methodologic rigor.

Results of population studies examining prevalence or incidence of pediatric food allergy have been hampered by several factors including small size, selection bias related to sampling methodology and response rates, and use of parental report of allergy and/or skin prick test (SPT) as a proxy for food allergy diagnosis. Even those that have used the gold standard of oral food challenge (OFC) have been limited by the lack of predetermined objective criteria to define the outcome.¹

The 12-month age group provides an interesting developmental window for prevalence studies of food allergy because infants are undergoing a rapid development in their immune systems at a time when new foods are being introduced.² Investigation of food allergy prevalence in infants at 12 months of age, rather than at a later age, is likely to reduce self-selection based on knowledge of food reactions because the initial screening of infants for sensitization to foods will take place at a time when some infants will not have previously consumed the food in question. Foods such as peanut are often introduced after the first birthday.³ Recruiting participants before knowledge of food allergy will also prevent recall bias when collecting data on environmental risk factors. The logistics of using a birth cohort can prove inhibitory as a methodology because SPT has not been shown to be accurate in those under 6 months of age⁴ and could potentially be biased in follow-up, where participants may be lost. Screening at 12 months of age also has the advantage that parents are likely to be interested in knowing their child's status as having food allergies because this age tends to be a time when a variety of new foods are introduced, encouraging higher response rates. Despite

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Abbreviations used

OFC: Oral food challenge
RCH: Royal Children's Hospital
SEIFA: Socio-Economic Indexes for Areas
SPT: Skin prick test
UK: United Kingdom

these advantages, assemblage of studies of this age group is rare because of the difficulty in finding populations of 12-month-olds to recruit in a timely and economic fashion, as opposed to school-age children.

The aim of this study was to describe the prevalence of food allergy in infants (12-month-olds) in Melbourne, Australia, to a variety of foods known to be potentially allergenic in childhood by using a sampling frame designed to recruit a representative population sample and predetermined challenge criteria to assess food allergy outcomes at OFC.

METHODS

Population-based recruitment

Melbourne is the second largest city in Australia with a population of almost 4 million⁵ and is located on the coast of southeastern Australia. The HealthNuts study methods have been previously described elsewhere.⁶ Briefly, parents of infants aged between 11 and 15 months (inclusive) attending childhood immunization (recommended to take place at 12 months) at over 120 locations across Melbourne were approached to take part in the HealthNuts study. Parents were not informed before attending the immunization session that the study would be taking place, and attendance at clinics was in a random fashion. After written consent was obtained, parents completed a questionnaire. A short interview (7 questions) was used for nonparticipants to assess potential participation bias.

SPT screening

Infants were subsequently skin prick–tested to 4 of 5 foods (raw hen's egg, peanut, sesame, cow's milk, or shellfish [*Pandalus borealis*] (ALK, Madrid, Spain) and a positive control (10 mg/mL histamine) and negative control (saline). Tests were performed using single-tine lancets (Stallergenes, Antony, France) on the infant's back. Cow's milk SPT was initially not conducted because of failure to gain ethics committee approval because of fears that a high prevalence of sensitization would be observed in infants already tolerating cow's milk, leading to unnecessary anxiety among parents and possibly extending Royal Children's Hospital (RCH) Allergy Department waiting lists. This ruling was subsequently reversed when a pilot study found low cow's milk sensitization rates at age 12 months and SPT for cow's milk in place of shellfish commenced in October 2009. Shellfish SPT was ceased because accurate estimates of the low sensitization rate to shellfish had been obtained.

Participation in food challenge clinics

All participants with SPT wheals ≥ 1 mm greater than the negative control were invited to a study clinic at the RCH for diagnosis by OFC after repeat skin prick testing. Parents were asked not to alter the child's diet (that is, not to introduce any new foods) in the interval between skin prick testing and food challenge. A 1-mm wheal size was used to select participants for food challenge to increase the likelihood of capturing all infants with food allergy. Food challenges were undertaken with clinical staff blind to the infant's SPT wheal size. Challenge protocols are included in the OFC protocols section in this article's Online Repository at www.jacionline.org. In the diagnosis of egg allergy, we used the standard clinical protocols from the Department of Allergy, RCH. Raw egg was used because it is the

most allergenic form of egg and reduces the chance of false negatives. To capture late reactions, research nurses phoned all food challenge participants the next day. Parents of infants with a negative food challenge were asked to administer a single serving of the challenge food on a daily basis at home over the next 7 days and simultaneously to complete a daily symptoms questionnaire.

Definitions

Sensitization status. Sensitization prevalence figures are reported as both SPT wheal size ≥ 1 mm (used to select infants for OFC) and as SPT wheal size ≥ 3 mm (standard clinical definition of sensitization⁷), in the context of a positive histamine control and negative saline control. Those participants with saline wheal size ≥ 1 mm (ie, dermatographism) for whom food allergens were less than the size of the saline control were excluded from the analysis ($n = 5$; 0.2%). Results of participants with wheals to food allergens greater than the saline control were included after subtraction of the negative control wheal size. Those with a negative positive control (ie, an average wheal size < 2 mm for the histamine positive control) were recorded as missing ($n = 37$; 1.6%).

Infants who had previously had a SPT by another allergist (results available from the parents) in the last 6 months ($n = 44$ for egg; 45 for peanut; 29 for sesame; 11 for shellfish; 17 for milk) were included in the analysis. These infants were all still invited for food challenge if SPT-positive.

IgE-mediated allergy to raw egg, peanut, and sesame. Positive challenge. The development of 1 or more of the following objective criteria was used to define a positive OFC: 3 or more concurrent noncontact urticaria persisting for at least 5 minutes, perioral or periorbital angioedema, vomiting (excluding gag reflex), or evidence of circulatory or respiratory compromise, occurring within 2 hours of ingestion of a dose during food challenge. This definition was also used if infants developed a reaction within 2 hours of ingestion of the food on subsequent days of home-based introduction if they had not reacted on day 1 of the challenge.

In addition, infants were considered to have food allergy (thus not offered a food challenge) if a parent reported any of these reactions occurring within 2 hours of ingestion of the food in the previous 1 month before food challenge clinic for egg, or the previous 2 months for peanut and sesame, and the infant had a positive SPT (≥ 1 mm) in the immunization clinic and was currently avoiding the food in question. If the history was equivocal either for reaction or for actual ingestion of the food in question, an OFC was recommended.

Negative or inconclusive challenges. The food challenge was deemed negative if the infant was able to complete the top dose of the challenge with no reaction and had no reactions on daily full servings of the food for the subsequent 7 days. If the infant refused to eat the challenge food, the challenge was deemed inconclusive. Participants with an inconclusive result on the day of the challenge ($n = 20$; 2.9% of all OFC) or an inconclusive reaction after ingestion of the food at home ($n = 43$; 6.2% of all OFC) were offered a second OFC ($n = 16$ participating). No reaction was inconclusive at the second attempt.

For 88 participants with raw egg allergy, a baked egg OFC was offered on a subsequent day to examine their ability to tolerate baked goods containing egg (see the OFC protocols section in the Online Repository).

Cow's milk allergy. Oral food challenge was not performed for cow's milk in our study, so to estimate cow's milk IgE allergy, we used questionnaire-derived parent report of reaction to cow's milk ever with reactions within 1 hour of definite cow's milk consumption with IgE-related symptoms (including skin rash, vomiting, diarrhea, difficulty breathing, or other symptoms such as swelling, eczema flare, angioedema, and hives). The denominator for IgE-mediated cow's milk allergy incidence was all those that had consumed cow's milk, cow's milk formula, partially hydrolyzed cow's milk formula, or dairy products at the time of interview (eg, cheese, yogurt, and so forth). We also estimated the cumulative incidence of overall adverse reactions to cow's milk (which captured a combined incidence of parent-reported IgE-mediated and non-IgE-mediated allergies as well as intolerance) by using parent-reported reaction to cow's milk ever

TABLE I. Prevalence of any food sensitization (≥ 1 mm) and challenge-proven food allergy in HealthNuts study (2848 participants)

Food tested	SPT at immunization session (n)	Missing SPT (n)*	Proportion recruited SPT (%)	SPT ≥ 1 mm (n)†	Prevalence sensitization SPT		Prevalence sensitization SPT		Attended RCH for OFC (n)‡	Positive OFC (n)	Food allergy prevalence		Weighted food allergy	
					≥ 1 mm (%)	95% CI	≥ 3 mm (%)	95% CI			(%)§	95% CI	(%)	95% CI
Peanut	2757	91	96.8	246	8.9	7.9-10.0	6.4	5.5-7.3	251	81	2.9	2.2-3.5	3.0	2.4-3.8
Raw egg	2768	80	97.2	455	16.5	15.1-17.9	11.7	10.6-13.0	383	248	9.0	7.9-10.0	8.9	7.8-10.1
Sesame	2695	153	94.6	69	2.5	2.0-3.1	1.6	1.2-2.1	65	19	0.7	0.4-1.0	0.8	0.5-1.2
Shellfish	2375	118	95.3	25	0.9	0.6-1.5	0.4	0.2-0.7	ND	ND	ND	ND	ND	ND

ND, OFC not performed for shellfish.

*Missing because positive control < 2 mm or wheal size minus negative control was a negative number or not tested.

†Number with SPT ≥ 1 mm at immunization session or SPT-positive (≥ 1 mm) previously by participant's (nonstudy) allergist.

‡The total number of participants attending OFC for peanut included 204 of the 246 with a SPT wheal size ≥ 1 mm greater than the negative control in the immunization clinic. A further group of participants received an OFC (47 for peanut challenge, 29 for egg, 18 for sesame) for 1 of the following reasons: (1) no SPT at the immunization clinic because they had recently had a SPT by their own allergist, (2) a positive SPT at the hospital clinic while visiting for another food challenge, (3) a positive SPT in the context of a negative saline control with a greater or equal wheal size, or (4) a positive SPT but a failed or missing positive histamine control.

§OFC results including immediate reactions after eating the food in question in the week after OFC (meeting the same criteria as day 1 OFC), a positive reaction on repeat of the OFC because of an inconclusive test or a parent-reported reaction to the food consistent with the OFC criteria in the previous month (egg) or 2 months (peanut and sesame) before food challenge clinic, plus a positive (≥ 1 mm) SPT plus current avoidance of the food in the infant's diet. Two inconclusive tests at the second attempt were recorded as missing data.

||Reweighted to adjust for underparticipation or overparticipation by the following factors: sex, socioeconomic status, family history of atopy, family history of food allergy, study child diagnosis with eczema, number of siblings of the study child, and whether the study child had eaten and tolerated peanuts (as per Table III).

(any reaction anytime after consumption) or parent-reported current food allergy to cow's milk.

Participant demographics

Socioeconomic status of participants and nonresponders was calculated by using Socio-Economic Indexes for Areas (SEIFA) indices, which are derived for a region from a suite of 4 summary measures including indexes of relative socioeconomic advantage and disadvantage, economic resources, education, and occupation developed by the Australian Bureau of Statistics using data from the Australian Census (last completed 2006).⁸ A socioeconomic status score was assigned to a participant by using the location of the immunization session that the participant attended (at the local government area level).⁶

Statistical analysis

Prevalence estimates for sensitization, food allergy, and other binary measures were calculated as the observed proportion with CIs on the basis of the assumption of a binomial sampling distribution. A sensitivity analysis was conducted to determine whether the prevalence estimates were likely to be influenced by differences in demographic characteristics or other risk factors between participants and nonparticipants. Weights were used to adjust the estimated prevalence to reflect the distribution of risk factors among the combined sample of participants and nonparticipants. The weights were the inverse of the probability of participation, obtained after fitting a logistic regression model including as covariates those risk factors available for both participants and nonparticipants: sex, socioeconomic status, family history of atopy, family history of food allergy, child diagnosis with eczema, number of siblings of the child, and whether the child had eaten and tolerated peanuts. This approach to handling missing data of weighting the participants that provide complete data has been referred to as "propensity weighting" by Little and Rubin.⁹ Two-sample comparisons for continuously valued data were performed by using the *t* test, and for categorical data by using the χ^2 test for contingency tables. All analyses were performed by using Stata (version 11.1; Stata Corp, College Station, Tex).

Ethics

Ethical approval was obtained from the Office for Children Human Research Ethics Committee (HREC) (reference no. CDF/07/492), the Department of Human Services HREC (reference no. 10/07), and the RCH HREC (reference no. 27047). Participants gave written voluntary informed consent both on the day of recruitment and on entry to the hospital component of the HealthNuts study.

RESULTS

Between September 28, 2007, and January 18, 2010, a total of 3898 parents/guardians were approached, and 2848 agreed to participate (73.1%). The average age of participating infants was 12.7 months (SD, 0.8). Of those who decided not to participate, 99.1% (1041/1050) completed the nonparticipant interview. Of those agreeing to participate, 1.6% (45) were not skin prick-tested at the immunization session because they had recently had a SPT performed by their own doctor.

Prevalence of sensitization to foods and history of eczema

Table I shows the prevalence of SPT ≥ 1 mm among participants (the selection criteria for OFCs). Overall, 21.0% (95% CI, 19.5-22.5) had a SPT ≥ 1 mm to 1 or more of the 4 SPT-tested foods. The prevalence of clinically relevant sensitization (ie, SPT ≥ 3 mm) to raw egg was 11.8% (95% CI, 10.6-13.0); peanut, 6.4% (95% CI, 5.5-7.3); sesame, 1.6% (95% CI, 1.2-2.1); and shellfish, 0.4% (95% CI, 0.2-0.7). Of 355 participants tested for cow's milk, 5.6% (95% CI, 3.2-8.0) were sensitized. Overall, 662 infants (26.7%; 95% CI, 25.0-28.4) reported an eczema diagnosis in the first 12 months of life.

Prevalence of IgE mediated raw egg, peanut, and sesame allergy in infancy

Over 90% of participants sensitized to peanut were seen in the clinic and food-challenged in, on average, 7.3 weeks (SD, 3.2), and 90% of participants sensitized to raw egg were seen in the clinic and food-challenged in, on average, 8.7 weeks (SD, 3.6) post-SPT. Peanut allergy was found in 2.9% (95% CI, 2.3-3.6) of participants, raw egg allergy in 9.0% (95% CI, 7.8-10.0), and sesame allergy in 0.7% (95% CI, 0.4-1.0; Table I). A total of 157 (5.6%) infants were sensitized to more than 1 of the challenge foods (peanut, raw egg, or sesame) and underwent multiple food challenges (average of 1.4 challenges per participant with any sensitization). Overall, challenge-confirmed food allergy to peanut, raw egg, or sesame was present in 10.4% (95% CI, 9.3-11.5) of participating infants.

TABLE II. Data contributing to a food allergy diagnosis in participants

Food tested	Initial SPT (mm)*	Positive OFC outcome on day 1§		Positive OFC outcome on day 2-4		Positive OFC outcome day missing or repeated OFC¶		Previous positive oral reaction (not OFC) #		Total (n)
		n	% of Total allergic	n	% of Total allergic	n	% of Total allergic	n	% of Total allergic	
Peanut	0‡	3	3.7	0	0	1	1.2	1	1.2	5
	1	0	0	0	0	1	1.2	0	0	1
	≥2	61	75.3	1	1.2	1	1.2	2	2.5	65
	Missing†	8	9.9	0	0	1	1.2	1	1.2	10
	<i>Total</i>	72	88.9	1	1.2	4	4.9	4	4.9	81
Raw egg	0‡	8	3.2	0	0	0	0	0	0	8
	1	10	3.6	2	0.8	1	(0.4)	1	0.4	14
	≥2	187	75.4	6	2.4	5	(2.4)	7	2.8	205
	Missing†	18	7.3	1	0.4	0	0	2	0.8	21
	<i>Total</i>	223	89.5	9	3.6	6	2.8	10	4.0	248
Sesame	0‡	3	15.8	0	0	0	0	0	0	3
	1	0	0	0	0	0	0	0	0	0
	≥2	10	52.6	0	0	0	0	0	0	10
	Missing†	6	31.6	0	0	0	0	0	0	6
	<i>Total</i>	19	100	0	0	0	0	0	0	19

*SPT wheal size recorded at immunization session.

†Recruited participants may be missing a SPT and attend OFC clinic if they are already seeing an allergist.

‡Participants may have attended OFC clinic because of SPT wheal ≥1 mm for another food and on retesting registered a wheal ≥1 mm on the second SPT at the hospital clinic.

§Participant recorded a nurse-observed positive OFC meeting the predetermined criteria for the food in question.

||Participant given a positive diagnosis of food allergy as (1) parent-reported positive reaction (meeting the predetermined criteria) in the 7 days post-OFC on unequivocal exposure to the food in question or (2) returned for a second OFC at which a positive result was recorded after an inconclusive OFC result was recorded on the initial day at the clinic or sustained a reaction in the 7 days after that was deemed inconclusive.

¶Day of reaction not recorded (not day 1).

#Participants may be deemed as having food allergy if they have an unequivocal exposure to the food in question 1 month before the hospital appointment (2 months in the case of peanut or sesame) and parent reports a reaction meeting the predetermined criteria plus they have a positive SPT (this may be the second SPT at the clinic) plus they must be currently avoiding the food.

Of those diagnosed with peanut and sesame allergy, only 1.9% (n = 1) and 12.5% (n = 2), respectively, had previously consumed the food in question without a reaction. Only 10.8% (n = 25) of those diagnosed with raw egg allergy reported having previously eaten and tolerated more than a bite or taste of cooked egg (scrambled or boiled), although none of these had previously been exposed to a full serving of raw egg, the most allergenic form of egg.

Among those diagnosed as having food allergy, the vast majority (90%) were diagnosed on the basis of a nurse-observed objective reaction occurring during OFC. The remainder were diagnosed as having food allergy on the basis of either a previous reaction to the food in question (in the context of a positive SPT and current avoidance of the food in the infant's diet) or a parent-reported reaction after a dose of the food at home after a negative food challenge on day 1 (Table II). Further information on reaction types and timing observed for diagnosis of food allergy are supplied in this article's Table E1 in the Online Repository at www.jacionline.org. Only 2 (0.6%) participants were recorded as having food allergy as a result of vomiting at home after reintroduction over the next few days.

Baked egg allergy among those with raw egg allergy

Of those with raw egg white allergy who had undergone baked egg OFC (n = 88), 19.7% also had allergy to egg in this form, with the rest tolerant to 1.1 g egg protein baked in a cake. Participants

who were not able to tolerate egg baked in a cake had, on average, larger SPT wheal sizes to raw egg immediately before the baked egg OFC (5.5 mm, SD, 2.3, vs 3.7 mm, SD, 1.8; $P < .01$) and were more likely to have nurse-observed eczema on the day of the OFC (15, 88.2%, vs 40, 60.0%; $P = .02$).

Cumulative incidence of cow's milk allergy in the first 12 months of life

Of those infants who had consumed cow's milk in any form (n = 2342), an adverse reaction was reported by parents for 142 infants (6.1%; 95% CI, 5.1-7.0). However, only 2.7% (95% CI, 2.1-3.4) had a reaction consistent with IgE-mediated allergy occurring within 1 hour of cow's milk ingestion.

Differences between study participants and nonparticipants

Participants in the HealthNuts study were more likely to be boys, were more likely to have a history of eczema, and more often had a first-degree relative with a history of atopic disease compared with nonparticipants (Table III). There were also more participants from areas with higher socioeconomic status compared with nonparticipants. There was no evidence that participants and nonparticipants differed in terms of number of siblings or history of reactions to peanuts (Table III).

Despite these differences, weighting on the basis of the distribution of risk factors in participants and nonparticipants only marginally altered the prevalence estimates from 9.0 (95% CI,

TABLE III. Comparison of HealthNuts study participants (n = 2848; participation rate, 73%) with those attending immunization clinics who chose not to participate (n = 1050) and were willing to fill out a short questionnaire (>99.1% of nonparticipants approached)

Demographics	Participants			Nonparticipants			P value
	No.‡	(%)	95% CI/SD	No.‡	(%)*	95% CI/SD	
N							
Total	2848			1050			
Sex							
Male	2818	52.8	50.1-54.6	968	47.5	44.3-50.7	<.01
No. of siblings							
0	1355	48.1	46.2-50.0	224	44.2	39.8-48.6	.24
1	964	34.2	32.5-36.0	182	35.9	31.7-40.2	
2	369	13.1	11.9-14.4	80	15.8	12.7-19.2	
3 or more	130	4.6	3.9-5.5	21	4.1	2.6-6.2	
SEIFA: index of relative socioeconomic disadvantage							
Mean	2842	1051.1	54.1	946	1039.8	56.3	<.01
SEIFA quintiles (by Local Government Area)							
Least disadvantaged	773	27.2	25.5-28.8	187	19.6	17.1-22.2	<.01
2	854	30.0	28.3-31.7	271	28.4	25.5-31.4	
3	455	16.0	14.6-17.3	204	21.4	18.8-24.1	
4	336	11.8	10.6-13.0	67	7.0	5.5-8.8	
Most disadvantaged	430	15.1	13.8-16.4	226	23.7	21.0-26.5	
Parent report Food allergies							
Study child	46	1.6†	1.2-2.3	5	1.1	0.1-2.0	.39
Mother	156	5.4	4.6-6.3	17	3.6	1.9-5.2	.05
Father	94	3.3	2.6-3.9	14	3.0	1.4-4.5	.72
Eczema in study child							
Ever diagnosed	2480	26.7	24.9-28.4	497	15.9	12.7-19.1	<.01
Parent report Atopic disease§							
Mother	1245	43.7	41.9-45.5	93	25.1	20.7-29.6	<.01
Father	1072	37.6	35.8-39.4	58	17.3	13.2-21.4	<.01
Child ate and did not tolerate peanuts	20	2.6	1.5-3.8	7	2.5	0.7-4.3	.89

*Nonparticipants responded to a short questionnaire of 7 questions.

†Excludes first 113 participants because the study children were not asked whether they had a food allergy.

‡Column tallies may not equal 2848 or 1050 because of missing data or questions being introduced to the survey at a later date.

§Report of asthma, eczema, hay fever, or food allergy.

7.9-10.0) to 8.9 (95% CI, 7.8-10.1) for raw egg, 2.9 (95% CI, 2.2-3.5) to 3.0 (95% CI, 2.4-3.8) for peanut, and 0.7 (95% CI, 0.4-1.0) to 0.8 (95% CI, 0.5-1.2) for sesame.

Differences between those who participated in OFCs and those who did not

Of infants who were sensitized (SPT ≥ 1 mm) to 1 or more foods, 84% attended the study clinic at the RCH. There were no differences in mean SPT wheal size, number with multiple food sensitizations or family history of asthma, eczema, or food allergy between those who attended and those who did not attend the study clinic, although those who attended were more likely to have a mother born in Australia and were more likely to have a family history of hay fever (Table IV).

Stratification of food allergy prevalence by parental history of atopy or food allergy

Of the 2848 infants participating in the study, 26.7% had a diagnosis of eczema and 24.8% had evidence of eczema on the day of the immunization clinic recruitment. Of those with a SPT greater than the negative control to 1 of the foods, 48.7% had been previously diagnosed with eczema, and 37.6% had evidence of eczema on the day of the immunization clinic recruitment. Few (1.3%) had a history of asthma, and there were only 13 reports of allergic rhinitis at this young age

(0.5%). A further 10.3% of infants had a history of wheeze in the first year of life in the absence of an episode of bronchiolitis, and 14.4% reported an episode of bronchiolitis. In those with a SPT wheal greater than negative control to 1 of the foods, 9.8% reported a history of wheeze in the first year of life in the absence of an episode of bronchiolitis, and 11.9% reported an episode of bronchiolitis.

To assess whether parental history of either atopy in general or food allergy specifically was associated with a higher prevalence of infantile food allergy, infants were stratified by family history and food allergy outcome (Table V). Those with a family history of allergy were more likely to have challenge-proven food allergy than those who did not, but there was no difference between the groups when stratified by family history of food allergy. The latter may have been found because the question was "ever had" and parents had poor recall from an event many years ago, or results were contaminated by non-challenge-proven outcomes in adults. Sibling allergy was not taken into account because family size is not necessarily complete in families with 12-month-old infants, and biased estimates of prevalence may occur if family size affects the risk of food allergy.

DISCUSSION

We have demonstrated that in a study representative of the Melbourne population, IgE-mediated food allergy is higher than

TABLE IV. Comparison of demographic factors, risk factors for atopy, and wheal size between those who attended the hospital clinic for OFC and those who did not attend the clinic

	Attended RCH clinic			Nonattended RCH clinic			P value
	n‡	95% CI/SD		n‡	95% CI/SD		
n							
21.4% of study population	510	83.6%		100	16.4%		
Raw egg wheal							
Mean mm	367	4.1	2.8	75	3.8	2.3	.31
Peanut wheal							
Mean mm	214	5.1	3.8	31	5.2	5.0	.91
Sesame wheal							
Mean mm	53	3.4	2.3	16	3.7	2.4	.16
Multiple sensitisation*							
%	491	24.8%	21.1, 28.9	91	28.0%	19.1, 38.2	.52
Gender of study child							
% Male	506	55.5%	51.0, 60.0	99	53.5%	43.2, 63.6	.71
Preterm delivery							
% <37 wk	480	5.0%	3.2, 7.3	91	4.4%		.81
Parent reported food reaction in study child							
%	482	46.5%	42.0, 50.9	94	43.6%	33.4, 54.2	.61
Study child diagnosed with eczema							
%	450	50.0%	45.3, 54.7	86	52.3%	41.2, 63.2	.69
Parental history of atopy (ever)							
% Reporting any atopy	510	67.4%	63.4, 71.5	100	59.0%	49.1, 69.0	.10
Asthma	510	31.1%	27.1, 35.2	100	27.0%	18.2, 35.9	.41
Eczema	510	24.3%	20.6, 28.0	100	19.0%	11.1, 26.8	.25
Hay fever	510	53.7%	49.4, 58.1	100	37.0%	27.4, 46.6	.002
Food allergy	501	9.6%	7.0, 12.2	100	7.0%	1.9, 12.1	0.41
Country of birth of mother of study child							
% Australia	487	65.90%	61.5, 70.1	93	40.1%	30.7, 51.5	<.01
Maternal age at study child's birth							
Mean years	480	34.3	4.6	89	33.6	4.6	.13
Maternal tobacco use during pregnancy							
%	487	2.1%	1.0, 3.7	93	3.2%	0.7, 9.1	.48
Household member uses tobacco							
% Tobacco smokers	467	4.3%	2.6, 6.5	89	11.2%	5.5, 19.7	.08
Household income range							
<A\$50,000	58	14.9%	11.5, 18.8	10	14.1%	7.0, 24.4	.65
A\$50,001-100,000	191	49.1%	44.0, 54.2	39	54.9%	42.7, 66.8	
>A\$100,001	140	36.0%	31.2, 41.0	22	31.0%	20.5, 43.0	

*Sensitised at ≥ 2 mm average wheal size to more than 1 of the 4 foods tested at immunisation sessions.

†‡ Test between those who attended and those who did not.

‡n Includes those who had a valid SPT wheal size measured at recruitment at immunization clinics (SPT wheal size minus negative control not less than 0 mm/positive control not <2 mm etc) and/or who had answered question, who attended or did not attend RCH clinic.

expected, with over 10% of 1-year-old infants having challenge-proven food allergy to 1 of the most common 3 IgE-mediated allergies: peanut, egg, and sesame. This is in the context of unexpectedly high sensitization rates to these foods and high rates of infant-onset eczema in Australia. By contrast, the cumulative incidence of parent-reported IgE-mediated cow's milk allergy was relatively lower.

The primary strength of the study was the high numbers of participants oral food-challenged after initial screening with SPT, with predefined outcome criteria to call a reaction positive. Given the high participation rate (73%) of the population as well as the high attendance rate at the food challenge clinic (84%), both of which minimize the potential effect of selection bias related to the higher likelihood of those at a higher risk of allergy participating, we are confident in generalizing our prevalence estimates. This contention is further supported by the fact that prevalence estimates changed little after reweighting on the basis of characteristics that differed between participants and nonparticipants.

Even assuming that none of the nonparticipants had a food allergy (a highly unlikely scenario), prevalence estimates would still be high (raw egg, 6.4%, 95% CI, 5.6-7.2; peanut, 2.1%, 95% CI, 1.7-2.6; sesame, 0.5%, 95% CI, 0.3-0.8).

Double-blind placebo-controlled food challenges are regarded as a more rigorous measure for the presence of food allergy than an open challenge in older children; however, the children in this study were all age 14 to 18 months and were therefore not able to report the subjective symptoms (such as mouth tingling or itchy mouth) that typically complicate the interpretation of open food challenges. Our study criteria for a positive challenge included only objective symptoms, which should minimize the possibility of overcall of food challenges by the investigators. Furthermore the researchers performing the challenges were blind to both SPT wheal size and history of ingestion reaction. The validity and sufficiency of using open food challenges in young infants has recently been confirmed.¹⁰

TABLE V. Stratification of food allergy prevalence by parental history of atopy or food allergy

Parental history of allergy	With/ without allergy	Prevalence OFC food allergy (%)	95% CI	P values [§]
No parental history of atopy (37.1% of parents)				
Child peanut	21/995	2.1	1.2-2.9	.04
Child raw egg	66/953	6.4	4.9-8.0	<.001
Child sesame	5/989	0.5	0.1-0.9	.34
Child combined [‡]	80/944	7.8	6.1-9.5	<.001
Parental history of atopy* (62.9% of parents)				
Child peanut	60/1681	3.4	2.6-4.3	
Child raw egg	182/1567	10.4	9.0-11.8	
Child sesame	14/1687	0.8	0.4-1.3	
Child combined [‡]	211/1543	12.0	10.5-13.6	
No parental history of food allergy (91.5% of parents)				
Child peanut	76/2448	3.0	2.3-3.7	.5
Child raw egg	221/2313	8.7	7.6-9.8	.15
Child sesame	19/2450	0.8	0.4-1.1	.19
Child combined [‡]	261/2281	10.3	9.1-11.4	.24
Parental history of food allergy [†] (8.5% of parents)				
Child peanut	5/228	2.1	2.7-4.0	
Child raw egg	27/207	11.5	7.4-15.7	
Child sesame	0/226	0	—	
Child combined [‡]	30/206	12.7	8.4-17.0	

*Defined as either mother or father having a history of eczema, food allergy, asthma, or hay fever.

†Defined as mother or father with history of food allergy.

‡Combination of peanut egg and sesame allergies.

§ χ^2 test for individual foods or combination between parental history of food allergy and no parental history of food allergy.

This is the first population-based study to undertake food challenges in all participants irrespective of wheal size. When this study was designed (2006-2007), the medical evidence base was in a state of clinical equipoise as far as the use of SPT wheal sizes as a proxy for food allergy and the value of OFC as a diagnosis tool. We therefore decided to perform OFCs on all participants with any SPT wheal size ≥ 1 mm.

The decision to use the criterion of 3 noncontact urticaria lasting longer than 5 minutes was made for several reasons. First, the definition of a positive food challenge has not been previously published. The criteria we selected were based on clinical experience at our center and information derived from published datasets. A study of food challenges performed at the RCH Department of Allergy over a 9-year period (average age of patients, 3.0 years) revealed that at least 45% of patients diagnosed with egg allergy and at least 39% patients diagnosed with peanut allergy on the basis of a positive food challenge had developed isolated urticaria, and that the presence of isolated urticaria was the most common symptom during food challenge leading to diagnosis of food allergy.¹¹ Second, safety was paramount in our study. Health professionals administering the challenge were blind to both the SPT wheal size of the participant and the history of food ingestion and reaction. A decision had to be made to allocate a safe, predetermined

criterion to stop the challenge and declare the participant as having allergy.

Overestimation of the prevalence rates could occur as a result of including late reactions at home as indicative of food allergy because reactions at home were not observed by the researchers; however, these made up only a small proportion, and only those with the same objective reactions as used in our predetermined in-hospital challenge criteria were accepted. A further 24 reacted at home, but symptoms were insufficient to categorize these infants reliably as having food allergy. If the reactions that occurred at home immediately after ingestion of the food in question were removed, the new prevalence numbers would be reduced from 8.9% to 8.4% in the case of raw egg allergy and from 3.0% to 2.8% in the case of peanut, and there would be no change in sesame allergy prevalence.

Our sampling frame was constructed to select over 120 childhood immunization sessions,⁶ one of the few public places where there is access to a population of 12-month-old infants. A potential limitation of this study is that although overall immunization rates in Melbourne are high (>90%),¹² only 48% are immunized at council-led immunization sessions, and we have no data on those who attend other immunization locations such as general practitioners. However, infant immunization is free at both councils and general practitioners (Australia's medical system is publically funded), and if anything, participants with a history of atopic disease may have been more likely to visit their doctor for immunization, so our prevalence values are unlikely to be overestimates. We have previously reported differences in maternal age and socioeconomic status between HealthNuts participants and a census of infants born in Victoria, which may affect the generalizability of prevalence estimates.⁶ However, there is currently little evidence that either maternal age or socioeconomic status is related to risk of food allergy.

The high rate of food allergy found in our population should be considered in the context of Australia's generally high rate of other allergic disease, including asthma and eczema.¹³ Comparisons between our study and others are further compounded by variation in study methodology, including the absence of sampling frames in most studies or overreliance for prevalence estimates on either parental report or sensitization status. Finally, to our knowledge, no other population-based study has used predetermined challenge criteria, which limits comparison somewhat across studies. Despite these difficulties, a recent Australian metropolitan study of 3739 five-year-old children found a similar cumulative incidence of parent-reported peanut allergy of 3.3% (95% CI, 2.8-3.9),¹⁴ which suggests that the high prevalence of food allergy in Australia is not restricted to Melbourne. Similarly, CIs of our estimates overlap with other recent estimates of peanut prevalence in the United Kingdom (UK)^{3,15} and Canada,¹⁶ although differences did appear to occur between older US,¹⁷ UK,^{18,19} and Danish research.²⁰ These may be a result of either differences in study methods (and low numbers of SPT or OFC) or reflection in the older studies of a lower prevalence at the time.

Our study is one of only a few worldwide to measure the prevalence of sesame allergy by using the gold standard of OFCs. The prevalence of sesame allergy in Melbourne, although low, was higher than that observed in Israeli infants.²¹ This is not surprising given the low prevalence of allergic disease in general in Israel.¹⁵ Our prevalence estimate is similar to that observed in a

questionnaire-based study in the UK.¹⁵ Although shellfish challenges were not performed, the rate of sensitization to shellfish was the lowest of all foods tested and suggests that shellfish allergy is low in Melbourne.

Similarly, population-based studies of the prevalence of challenge-confirmed egg allergy are rare.²² However, of those that do exist, none have reported prevalence estimates as high as those found in our study. This may be a result of several factors including use of raw egg as opposed to cooked or baked egg in both the SPT and OFC^{23,24} and the young age (11-16 months) of our participants.²⁵ The majority of infants outgrow egg allergy by 3 to 4 years of age.^{25,26} Osterballe et al²⁰ reported an egg allergy prevalence of only 1.6% (95% CI, 0.7-3.2) at an older age than our participants (3 years of age), although the use of pasteurized whole egg for challenges may have led to a reduction in allergenicity. The pilot data of our study examining consumption of baked egg products by children with raw egg allergy has suggested a high proportion (80.2%) of those who were classified as having egg allergy may be able to tolerate egg in this form, which may have significant clinical implications and would potentially align our egg allergy estimates with these other studies.

The main limitation of our cow's milk allergy estimates is that challenges were not performed. In attempt to improve the estimation of cow's milk allergy, we imposed strict criteria by history—that is, only those who had reactions usually associated with cow's milk immediate-type hypersensitivity (skin rash/redness; eczema flare; swelling of lips, eyes, or face; wheeze/difficulty breathing; hives; or a combination of these) and reacted within 1 hour of consumption. We excluded those who did not fulfill these criteria. In total, 73 of 142 participants nominated by their parents as having a reaction to cow's milk were not categorized as having cow's milk allergy, although some of these may indeed have had cow's milk allergy.

Conclusion

There was a higher than expected prevalence of challenge-confirmed raw egg, peanut, and sesame food allergies in 12-month-old infants in Melbourne, Australia. Overall, 10% of infants had IgE-mediated food allergy. Use of predefined criteria for OFCs provided an objective diagnosis of food allergy. This high prevalence of food allergy adds to the data suggesting that food allergy is an important public health issue. The high prevalence of allergic disease in Australia requires further investigation and may be related to modifiable environmental factors.

The Healthnuts investigators include Marnie N. Robinson, MBBS, Dean Tey, MBBS, Mark Nethercote, MBBS, Leone Thiele, RN, Lucy Miles, RN, Deborah Anderson, RN, BNurs/BAppSc, Tina Tan, BSc, Thanh Dang, BSc (Hons), Margaret Sutherland, RN, Helen Czech, RN, David J. Hill, MBBS, FRACP, and Giovanni Zurzolo, BSc. We thank 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, RCH, Melbourne, Australia), and Associate Professor Jo Douglass (Head of Allergy, Alfred Hospital, Melbourne, Australia). We also thank the additional members of the HealthNuts team—Kirsten Aurich, Marjolein Slaa, and Margaret Gibson—and the parents and children who participated in the study. We would like to thank ALK-Abelló, Spain, for donating food allergens for SPT.

Key messages

- There was a higher than expected prevalence of raw egg (8.9%), peanut (3.0%), and sesame (0.7%) food allergies in 12-month-old infants in Melbourne, Australia, with more than 10% of infants having challenge-proven IgE-mediated food allergy to 1 of these foods.
- A high proportion of infants with raw egg allergy could tolerate small amounts of egg in baked goods. Baked egg challenges may be warranted in the clinic setting to improve quality of life of those with egg allergy.
- Predefined criteria for OFCs will be valuable to assess differences objectively in the population prevalence of food allergies.

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OFC PROTOCOLS

Participants are seen at the hospital clinic within 8 weeks (average time, 4 weeks) of the immunization session contact and consent to the second part of the project after reading a further information sheet and having any questions answered. Skin prick testing is repeated to the initial foods (egg, peanut, sesame, shellfish, and cow's milk) as well as almond, wheat, soy, cashew, hazelnut, and house dust mite. A clinical history is taken by the supervising consultant to ensure anaphylaxis to the food being tested has not occurred in the period since the phone call, because this would preclude undertaking a food challenge to that food. The nurse performing the OFC is blind both to the SPT results and the participant's clinical history. A second questionnaire, containing questions on food exposure and symptoms, infections and treatments, family histories of allergic disease, and other environmental exposure variables, is completed.

The OFC then proceeds irrespective of whether the child is already eating the food, with doses starting with an initial smear or drop of the food being placed on the inner mucosa of the mouth of the participant, building up to a dose analogous to an amount consumed at a single sitting for a child of that age (see specific food challenge protocols for peanut, egg and sesame outlined below). After the initial dose, the allergen food is mixed with an age-appropriate previously tolerated food (eg, apple sauce or yoghurt) on the basis of preferred parental choice of food. Children are observed for 60 minutes after they have any reaction defined as a positive food challenge, or after the final dose of the challenge. Monitoring is undertaken by specialist registered nurses and supervised by a nominated study doctor. Challenges are located in the Australian Paediatric Pharmacology Research Unit, RCH. Vital signs are monitored and recorded every 5 to 10 minutes during the challenge. Medications (adrenaline and cetirizine in mg/kg) are calculated on the basis of the participant's weight and documented before commencement.

Peanut

Smooth peanut butter paste (Kraft, Port Melbourne, Australia) is used for the challenge.

Dose number every 20 minutes to a total weight of 1.94 teaspoons of peanut butter (11.3 g):

1. Smear inside lip (not to touch outside lip)
2. 1/16 teaspoon
3. 1/8 teaspoon
4. 1/4 teaspoon
5. 1/2 teaspoon
6. 1 teaspoon

Raw egg white

A 60-g free-range egg (Coles, Glen Iris, Victoria, Australia) is used for the challenge.

Dose number every 15 minutes:

1. Drop inside lip (not to touch outside lip)
2. 0.5 mL
3. 1 mL
4. 2 mL
5. 5 mL
6. 10 mL
7. Remainder of the 60-g egg white (usually 10-13 mL)

Sesame

Unhulled tahini (Mayver's, Altona North, Victoria, Australia) is used for the challenge.

Dose number every 20 minutes to a total weight of 9.7 mL tahini (11.3 g):

1. Drop inside lip (not to touch outside lip)
2. 0.31 mL
3. 0.62 mL
4. 1.25 mL
5. 2.5 mL
6. 5 mL

If there is a suspicion of an acute allergic reaction (eg, a transient area of erythema or hives), but the criteria for a positive challenge have not been met, the next dose of the challenge protocol is administered. In the event of anaphylaxis (circulatory or respiratory involvement), intramuscular adrenaline is administered. Fully equipped resuscitation trolleys are present at all times in the unit. After anaphylaxis, the patient is monitored for a minimum of 4 hours in the unit or admitted to the RCH for observation after hours. A safety committee of independent researchers monitors the clinic, and any anaphylactic reactions are reported to the committee within 24 hours.

At discharge, patients with a positive food challenge are educated about food allergen avoidance and are given an appropriate action plan and instructions on making a follow-up appointment in 1 year's time with a consultant allergist. Patients with a negative food challenge are given instructions on continuing the challenge at home and a symptoms diary with a stamped self-addressed envelope. They are asked to return the diary to the study at the end of the week and are given ongoing instructions on introduction of the food into the diet. Study nurses telephone all participants on the day after the challenge, and participants are encouraged to contact the HealthNuts study telephone line if they have any concerns or reactions.

Protocol for baked egg challenge

Participants. The inclusion criterion is a failed raw egg challenge at the HealthNuts hospital allergy clinic—that is, diagnosed with egg allergy using predetermined criteria: 3 or more concurrent noncontact urticaria persisting for at least 5 minutes, perioral or periorbital angioedema, vomiting (excluding gag reflex), or evidence of circulatory or respiratory compromise, occurring within 2 hours of ingestion of a dose during food challenge. The baked egg challenge is offered at the HealthNuts hospital clinic within 1 month of the initial raw egg challenge.

Food test. Bake vanilla cake mix (Green's Foods Limited, Glendenning, NSW, Australia) as per packet instructions with 2 × 60-g eggs made into 12 small muffins. The total dose is equivalent to 10 g egg.

Baked egg challenge. Increase dose every 15 minutes if no allergic reaction is noted:

- A "crumb"
- 1/12 muffin
- 1/6 muffin
- 1/4 muffin
- 1/2 muffin

If the child eats the entire muffin with no reaction, then the child is deemed to have passed the baked egg challenge. Monitoring is according to the standard HealthNuts protocol.

Participants who fail the baked egg challenge are advised to exclude all egg (both raw and baked) from their diets. They will be reassessed for raw egg allergy at 24 months of age at the HealthNuts hospital clinic.

TABLE E1. Timing and type of objective signs observed for the diagnosis of food allergy and additional symptoms reported during challenge period[‡]

	Objective signs indicating a positive food challenge*	Other additional symptoms reported		Other additional symptoms reported		Other additional symptoms reported		Total
		Egg	during challenge§	Peanut	during challenge§	Sesame	during challenge§	
Positive OFC on day 1	Respiratory or circulatory compromise	6	6 (100%)	6	6 (100%)	1	1 (100%)	13
	Vomiting	45	40 (89%)	8	8 (100%)	2	2 (100%)	55
	Perioral or periorbital angioedema	21	21 (100%)	8	8 (100%)	3	3 (100%)	32
	Hives meeting criteria only	151	51 (34%)	50	24 (48%)	13	3 (23%)	214
	Subtotal	223		72		19		314
Parent report home based symptoms prior to attendance at clinic (no OFC attempted)	Respiratory or circulatory compromise	1	1 (100%)	0		0		1
	Vomiting	3	2 (66%)	0		0		3
	Perioral or periorbital angioedema	2	1 (50%)	4	4 (100%)	0		6
	Hives meeting criteria only	4	1 (25%)	0		0		4
	Subtotal	10		4		0		14
Positive OFC day 2-4 or missing day or repeat OFC	Respiratory or circulatory compromise	0		0		0		0
	Vomiting	0		2	2 (100%)	0		2
	Perioral or periorbital angioedema	3	2 (66%)	0		0		3
	Hives meeting criteria only	7	1 (14%)	2	1 (50%)	0		9
	Other [†]	5		1		0		6
Subtotal	15		5		0		20	
Total		248		81		19		348

NB, Epinephrine administered in all but 2 cases of infants having respiratory or circulatory compromise.

*More than one symptom may have been present so the most severe symptom is recorded in this table in the order epinephrine administration, wheeze, vomiting, perioral or periorbital angioedema and 3 or more hives lasting more than 5 minutes.

[†]Other included hospitalization, diarrhea on two occasions after ingestion, rash and diarrhea, redness, rash and blistering.

[‡]Participants with a past history of anaphylaxis were excluded from commencing participation at the immunization clinic.

[§]Other reactions reported (but did not necessarily contribute to participant achieving a positive diagnosis for food allergy) included less than three hives and/or not lasting for 5 minutes, diarrhea, erythema, itching, sneezing, coughing, eczema flare, as well as the 4 symptoms used as diagnostic criteria (respiratory and/or circulatory compromise, vomiting, perioral/periorbital angioedema, more than 3 hives lasting more than 5 minutes).

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