

Abbreviations used

EAT: Enquiring About Tolerance
 HREC: Human Research Ethics Committee
 LEAP: Learning Early About Peanut Allergy
 OFC: Oral food challenge
 sIgE: Specific IgE
 SPT: Skin prick test

infants with a greater than 4 mm peanut SPT wheal size (the cutoff used in the LEAP study to define likely peanut allergy) are truly peanut allergic, and thus whether this group should potentially undergo formal oral food challenge (OFC) before recommending peanut avoidance.

Interim guidelines have also been released as a result of the LEAP study findings, based on consensus among multiple allergy organizations worldwide. These recommend introduction of peanut between age 4 and 11 months in infants with severe eczema or egg allergy in countries where peanut allergy is prevalent. The guidelines also suggest that infants with severe eczema or egg allergy in the first 4 to 6 months of life might benefit from evaluation by an allergist or physician trained in management of allergic disease—including potentially SPT and in-office observed peanut ingestion.⁸ Data characterizing SPT and specific IgE (sIgE) values to peanut in the high-risk population of infants, and their relationship to peanut allergy, may help to define the impact on the allergy workforce if this advice is followed, and inform strategies for determining which infants require supervised peanut challenges. Finally, data on the likelihood of reactions, particularly severe reactions, in young infants exposed to peanut in early life are also likely to be useful in addressing these questions.

In a recent companion study to the LEAP trial, the Enquiring About Tolerance (EAT) randomized trial compared early introduction (from age 3 months) of allergenic foods including peanut with standard introduction (from age 6 months) in infants recruited from the general population.⁹ The EAT trial included infants with and without existing allergic disease (eczema), and infants in the control (standard introduction) arm were required to avoid allergenic foods only until age 6 months. In comparison, in the LEAP trial, the control arm avoided peanut until age 5 years. Compliance with the intervention in the EAT trial was also lower than in the LEAP trial. There was no evidence of a statistically significant difference in food allergy prevalence at age 1 to 3 years between the early and standard introduction arms in the primary intention-to-treat analysis. The failure to demonstrate efficacy of early introduction of allergenic foods in the EAT trial could potentially be due to low compliance with the early introduction intervention (consumption of sufficient doses of the allergenic foods), or because the age at allergen introduction in the intervention (median reported age ~5 months) and control arms (introduced from 6 months, actual age not reported) might not have been different enough to have a biological impact.

We aimed to use data from the HealthNuts study, a population-based cohort of 5300 infants in Australia, to understand the implications and generalizability of the LEAP trial's findings regarding the introduction of peanut at the population level. The HealthNuts study population provides an ideal opportunity to examine these issues because all infants underwent SPT screening to peanut using the same technique, device, and extract

as was used in the LEAP study and infants with any detectable wheal underwent an OFC to peanut, irrespective of SPT wheal size or history of ingestion or reaction, unless a clear reaction had occurred in the past month.

METHODS**The HealthNuts study population**

The HealthNuts study is a large-scale, population-based cohort study undertaken to assess the prevalence and risk factors for allergic disease in early childhood.^{10,11} Briefly, by using a predetermined population-based sampling frame drawn from local government-led immunization clinics in Melbourne, Australia (population 4 million), infants were recruited at their 1-year immunization visit. All infants aged between 11 and 15 months (inclusive) were eligible for recruitment (74% response rate). Parents completed a questionnaire before SPT that included questions about the child's history of peanut consumption and food reactions, and history of eczema (including whether diagnosed, age at diagnosis, and history of medication use).

Infants were skin prick tested to 4 foods including peanut and hen's egg (ALK-Abelló, Madrid, Spain), with a positive control (histamine 10 mg/mL), and a negative control (saline) using single-tine lancets on the infant's back. All participants with a detectable wheal to 1 or more foods were invited to a hospital-based clinic where staff administered repeat SPTs and diagnostic OFCs, blinded to the infant's SPT wheal size and history of ingestion. A positive challenge was defined on the basis of prespecified objective criteria¹²: hives (≥ 3 hives lasting at least 5 minutes); vomiting; and angioedema or anaphylaxis (evidence of circulatory or respiratory involvement), occurring within 2 hours of ingestion of the food. We chose any detectable wheal size as our entry criterion to assess the food allergy status of participants to minimize the chances of missing cases of food allergy. A random sample of infants with negative SPT results was also invited to undergo a food challenge (negative controls for the clinic study). SPT was performed with peanut extracts purchased from the same company used in the LEAP study (ALK-Abelló) and the same lancet device. Blood samples were obtained at clinic attendance and total and sIgE levels to peanut, egg, and other relevant foods based on clinical history were measured using ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden).

Ethics

Ethical approval was obtained from the Office for Children Human Research Ethics Committee (HREC; ref no. CDF/07/492), Department of Human Services HREC (ref no. 10/07), and Royal Children's Hospital HREC (ref no. 27047). Parents/guardians of all participants provided written informed consent.

Definitions

Eczema in the first year of life was defined as a diagnosis of eczema, to identify those infants who would already be identified through the medical system.

Early moderate/severe eczema was defined as diagnosed eczema starting in the first 6 months of life and treated with topical steroids (either over-the-counter or prescribed). Severity of eczema is defined variably with SCORing Atopic Dermatitis or by ill-defined doctor-specific grading. Therefore, for the purposes of this analysis, we used early onset eczema (before 6 months) and requirement for topical steroid therapy to identify more severe eczema. This would also offer a consistent approach to identifying these infants in practice if the international consensus recommendations are to be adopted.

Egg allergy was defined as challenge-proven egg allergy at age 1 year, in the presence of sIgE to egg detected either by SPT (wheal size ≥ 2 mm above saline control) or by serum sIgE levels (≥ 0.35 kUA/L).

Peanut allergy was defined as challenge-proven peanut allergy at age 1 year. All infants with a positive peanut challenge had peanut sIgE detected by either SPT or serum sIgE.

The following definitions were used for risk stratification:

High-risk infants were defined as those with either *egg allergy* or early onset (≤ 6 months) moderate/severe *eczema*—these infants would potentially have been eligible for inclusion in the LEAP study,¹ depending on the age of manifestation of egg allergy and the severity of eczema. A comparison of definitions of high risk used in the LEAP study and accompanying editorial and consensus guidelines is presented in Table E1 in this article's Online Repository at www.jacionline.org.

Low-risk infants were defined as those with no egg allergy and no early onset (≤ 6 months) moderate/severe eczema. It should be noted that this category of infants includes those with late-onset or mild forms of eczema.

Statistical methods

We calculated the proportion of participants in the HealthNuts study cohort who were classified as “high risk” and “low risk” and had challenge-proven peanut allergy in each of the high-risk and low-risk groups and then calculated the proportion of all peanut allergy cases that occurred in high-risk and low-risk infants. Proportions were calculated as percentages, with 95% CIs calculated assuming a binomial sampling distribution.

SPT wheal sizes and peanut sIgE levels were classified for analysis into groups according to a combination of clinical cutoffs and those used in the LEAP study¹ to define the SPT-positive group (SPT wheal size 1–4 mm) and the likely peanut allergy group (SPT wheal size, >4 mm). Thus, SPT results were grouped into 0 mm (not sensitized); 1 to 2 mm (SPT-positive according to the LEAP study but not generally considered sensitized by clinical criteria); 3 to 4 mm (sensitized according to both the LEAP study and standard clinical cutoffs), and more than 4 mm (likely peanut allergic according to the LEAP study). sIgE to peanut was grouped into less than 0.1 kUA/L (below the limit of detection); 0.1 to 0.34 kUA/L (detectable but below usual clinical cutoffs for sensitization); 0.35 to 17.4 kUA/L (sensitized), and 17.5 kUA/L or more (high positive). The proportion of positive challenges in each SPT or sIgE category was calculated with 95% CIs as above.

To investigate factors associated with age at introduction of peanut into the infant diet, the cohort was divided into groups according to the risk factors: family history of eczema or food allergy, infant eczema, and infant history of reaction to egg or milk. Challenge-confirmed egg allergy was not used in this analysis because SPT and challenges to egg occurred after parents had already made the decision on when to introduce peanut to their child. Chi-square *P* values were calculated comparing the distribution of age at peanut introduction in each risk group to the baseline group of “no risk factors.”

We modeled the potential proportion of peanut allergy cases in the community that might be prevented by applying the LEAP intervention findings to the general population using the following steps:

1. We used a hypothetical population of 1000 infants to represent the general population.
2. We used the actual prevalence of early onset eczema and/or egg allergy in the HealthNuts study to split the population into “low-risk” and “high-risk” groups.
3. We assumed that the LEAP intervention would be applied only to the high-risk group (as per the current consensus guidelines⁸). We used the HealthNuts study data to estimate the prevalence of peanut allergy in the low-risk group without intervention (ie, the HealthNuts study observed prevalence of peanut allergy among low-risk infants).
4. We used direct percentages from the LEAP study¹ to estimate the proportion of high-risk infants who would have an SPT wheal size of more than 4 mm to peanut at age 4 to 11 months.
5. We used the HealthNuts study data to estimate the proportion of infants with an SPT wheal size of more than 4 mm who would be peanut allergic (80%) because these data were not available from the LEAP study.
6. We used direct percentages from the LEAP study control arm to estimate the prevalence of peanut allergy without intervention (17%) and direct percentages from the LEAP study intervention arm to estimate the prevalence of peanut allergy with timely peanut introduction between 4 and 11 months (3%), and thus calculated the proportion of cases that could be prevented.

RESULTS

Characteristics of the HealthNuts study cohort

Study participation is shown in Fig E1 in this article's Online Repository at www.jacionline.org. Relevant characteristics of the HealthNuts study cohort are described in Table I. Our previous work has shown that the HealthNuts study participants are generally representative of the infant population of metropolitan Melbourne as compared with the state-mandated Victorian perinatal database.¹⁰

Proportion of peanut allergy cases in the general population occurring in high- and low-risk infants

Table II presents peanut allergy prevalence by eczema and egg allergy status. Overall, 84% of the population was classified as “low risk” (no early moderate/severe eczema or egg allergy), with 0.8% of these infants having challenge-confirmed peanut allergy (Table II). This represents 23% of all peanut allergy cases in the population, who would be missed by targeting only high-risk infants. The remaining 16% of the population was classified as “high risk” by this definition, and 14% of these infants were peanut allergic. This represents 77% of all peanut allergy cases in the population. The highest risk of peanut allergy was in infants with both early moderate/severe eczema and egg allergy (who represented 3.5% of the general population), with 35% of these infants having peanut allergy. Peanut allergy was more common in infants with egg allergy than in those without egg allergy, irrespective of their eczema status.

Characterizing SPT and sIgE levels to peanut at the population level

The distribution of SPT wheal sizes and sIgE levels in the cohort is shown in Fig 1. Compared with low-risk infants, high-risk infants were more likely to have a detectable wheal on peanut SPT: 29% (95% CI, 25.8–32.4) versus 4% (95% CI 3.4–4.7), $P < .001$. Among high-risk infants with a 0-mm SPT wheal to peanut, 34% had detectable levels of sIgE to peanut. No infants with a negative (0 mm) SPT result or peanut sIgE below the limits of detection had a positive peanut OFC in either the high-group or the low-risk group; however, some positive peanut challenges occurred in infants with an SPT wheal size or sIgE level below the traditional cutoffs for sensitization (3 mm for SPT and 0.35 kUA/L for sIgE) (Fig 1, C and D).

Using the SPT cutoff values defined in the LEAP study as “likely peanut allergy” (SPT wheal size, >4 mm), 70.3% (95% CI, 54.8–85.7) of low-risk infants and 80.2% (95% CI, 73.0–87.4) of high-risk infants were allergic on OFC (Table III).

Prevalence and types of adverse reactions to peanut in the first year of life among infants introduced to peanut at home before study participation

Overall, 30% of infants were introduced to peanut by their parents before age 12 months (predominantly in the form of peanut butter, data not shown). Infants with eczema or a personal history of reactions to other foods (egg or milk) were less likely to be given peanut before age 12 months, whereas a family history of food allergy or eczema had little impact on the age of peanut introduction in the absence of any clinical signs of allergy in the infant (Table IV). Only 13% of infants with both early eczema and a history of reaction to milk or egg were introduced to peanut by age 12 months.

TABLE I. Characteristics of the HealthNuts study cohort

Characteristic	Negative (0 mm) SPT result to peanut at 12 mo			
	Attended HealthNuts clinic as controls* (N = 197)	Did not attend HealthNuts clinic (N = 3857)	Attended HealthNuts clinic because of sensitization to other food(s) (N = 428)	Detectable wheal on peanut SPT (≥ 1 mm) and attended clinic (N = 417)
Age at recruitment (mo), mean $\pm$ SD	12.6 $\pm$ 0.7	12.7 $\pm$ 0.7	12.6 $\pm$ 0.7	12.7 $\pm$ 0.7
Age at clinic attendance (mo), mean $\pm$ SD	14.6 $\pm$ 1.2	—	14.4 $\pm$ 1.3	14.3 $\pm$ 1.2
Sex: male (%)	48	50	50	60
Eczema (%)†				
None	68	77	55	36
Eczema starting ≤ 6 mo treated with topical steroids	11	6	20	35
Eczema starting ≤ 6 mo no topical steroids	10	6	9	12
Eczema starting > 6 mo of age	7	4	7	7
Age at egg introduction (%)‡				
≤ 6 mo	22	25	18	23
7-12 mo	70	68	71	62
Not yet given	5	3	5	10
Egg allergic (%)‡	—	—	51	47
Peanut sIgE measured (%)	77	—	83	86
Peanut OFC completed	68	—	—	90

*Negative SPT result to all tested foods at recruitment.

†Percentages may not add up to 100% because of missing data.

‡Defined as challenge-proven egg allergy at age 1 year, in the presence of sIgE to egg detected either by SPT (wheal size ≥ 2 mm above saline control) or serum sIgE levels (≥ 0.35 kUA/L).**TABLE II.** Proportion of peanut allergy cases in the HealthNuts study population-based sample occurring in high- and low-risk infants

Clinical profile	Eczema status	Egg allergy	N	% (95% CI)		
				Proportion of the population with this risk profile	Proportion with peanut allergy at age 1 y	Proportion of peanut allergy cases captured (total n = 137*)
Low risk	None	No	3338	72.2 (70.9-73.5)	0.6 (0.3-0.8)	13.9 (8.6-20.8)
	Later onset or mild eczema†	No	535	11.6 (10.7-12.5)	2.4 (1.1-3.7)	9.5 (5.1-15.7)
Low-risk group: total			3873	83.8 (82.7-84.8)	0.8 (0.5-1.1)	23.4 (16.6-31.3)
High risk	None	Yes	167	3.6 (3.1-4.2)	10.8 (6.0-15.5)	13.1 (8.0-20.0)
	Later onset or mild eczema†	Yes	82	1.8 (1.4-2.2)	20.7 (11.8-29.7)	12.4 (7.4-19.1)
	Early moderate/severe eczema‡	No	338	7.3 (6.6-8.1)	3.8 (1.7-5.9)	9.5 (5.1-15.7)
	Early moderate/severe eczema‡	Yes	164	3.5 (3.0-4.1)	34.8 (27.4-42.1)	41.6 (33.3-50.3)
High-risk group: total			751	16.2 (15.2-17.3)	13.9 (11.5-16.5)	76.7 (68.7-83.4)

*Of the cases that could be classified into high-risk group or low-risk group (complete data on eczema and egg allergy status).

†Diagnosed eczema starting at age > 6 months and treated with topical steroids or eczema (at any age) without topical steroid treatment.‡Diagnosed eczema starting at age ≤ 6 months and treated with topical steroids.

Of those infants introduced to peanut by their parents by age 12 months, 3% reported a possible reaction, with most of these (82%) occurring within 1 hour of ingestion, consistent with IgE-mediated reactions. Reactions occurred more commonly in high-risk infants (10.6% vs 1.4%; $P < .001$). Table V presents the types of reactions. Only 1 infant had a history consistent with possible anaphylaxis (wheeze/difficulty breathing), with peanut being the reported food causing this reaction (when given at age 12 months); however, this child was later shown to tolerate peanut on OFC at age 14 months.

Prevalence and types of adverse reactions to peanut during hospital-based OFC

The most common reaction to peanut OFC, irrespective of SPT wheal size or risk profile, was urticaria (Table VI). Anaphylaxis occurred in 6 challenges (4% of positive

challenges), with cases of anaphylaxis seen in both high- and low-risk groups.

Applying the proportion of peanut allergy cases that may be preventable by applying the LEAP intervention to the general population

We used the best available data from either the HealthNuts study or the LEAP intervention to model the proportion of peanut allergy cases that might be preventable if the LEAP intervention findings were applied to a hypothetical population of 1000 infants (Fig 2), with the following assumptions:

1. A total of 84% of the population belongs to low-risk and 16% to high-risk groups (the HealthNuts study data).
 - Of the low-risk infants, 0.8% are peanut allergic without intervention (the HealthNuts study data).

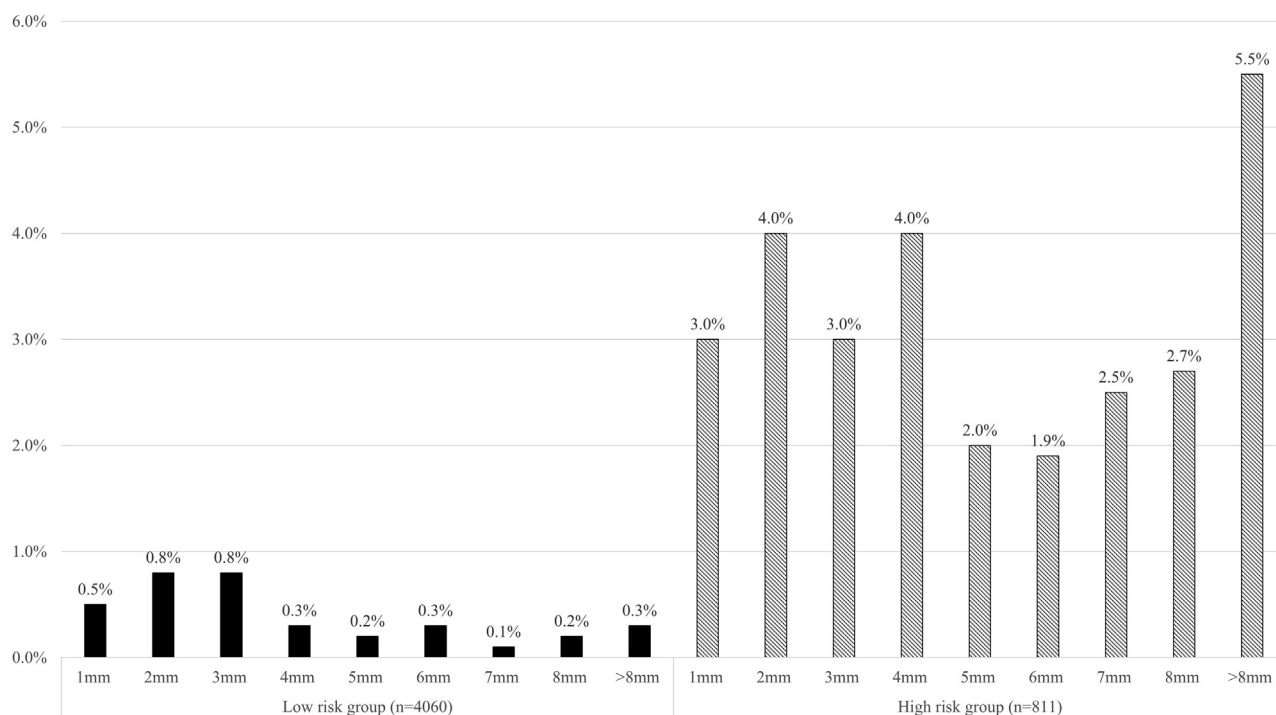
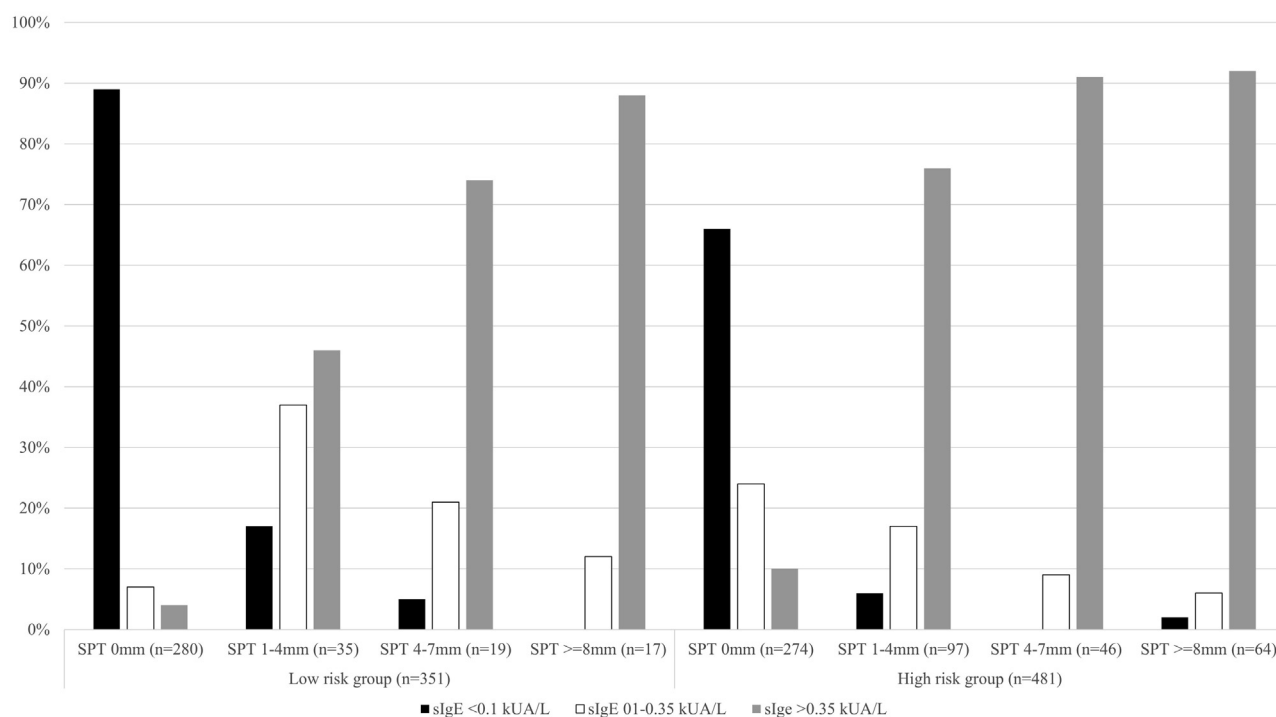
A**B**

FIG 1. Characterizing peanut SPT wheal size and specific IgE levels in a population-based sample of infants, stratified by high-risk group (early eczema and/or egg allergy) or low-risk group (no early eczema and/or egg allergy). **A**, Proportion of infants sensitized to peanut on community-based SPT. **B**, Relationship between skin prick and sIgE results to peanut among infants attending food challenge clinic. **C**, Relationship between peanut SPT results and challenge outcome among infants attending food challenge clinic. **D**, Relationship between peanut sIgE results and challenge outcome among infants attending food challenge clinic. *Infants with a 0-mm SPT wheal size for peanut included infants selected for challenge on the basis of previous detectable SPT wheal in the community (n = 81; 54 of these were <3 mm) or as part of a negative control group (0-mm SPT wheal to peanut in both community and clinic, n = 140). Numbers in each analysis differ because of the study design: skin prick testing to peanut was performed as a screening step for all infants, but only infants attending challenge clinic had blood taken for sIgE measurement (83% of those attending clinic agreed to give a blood sample).

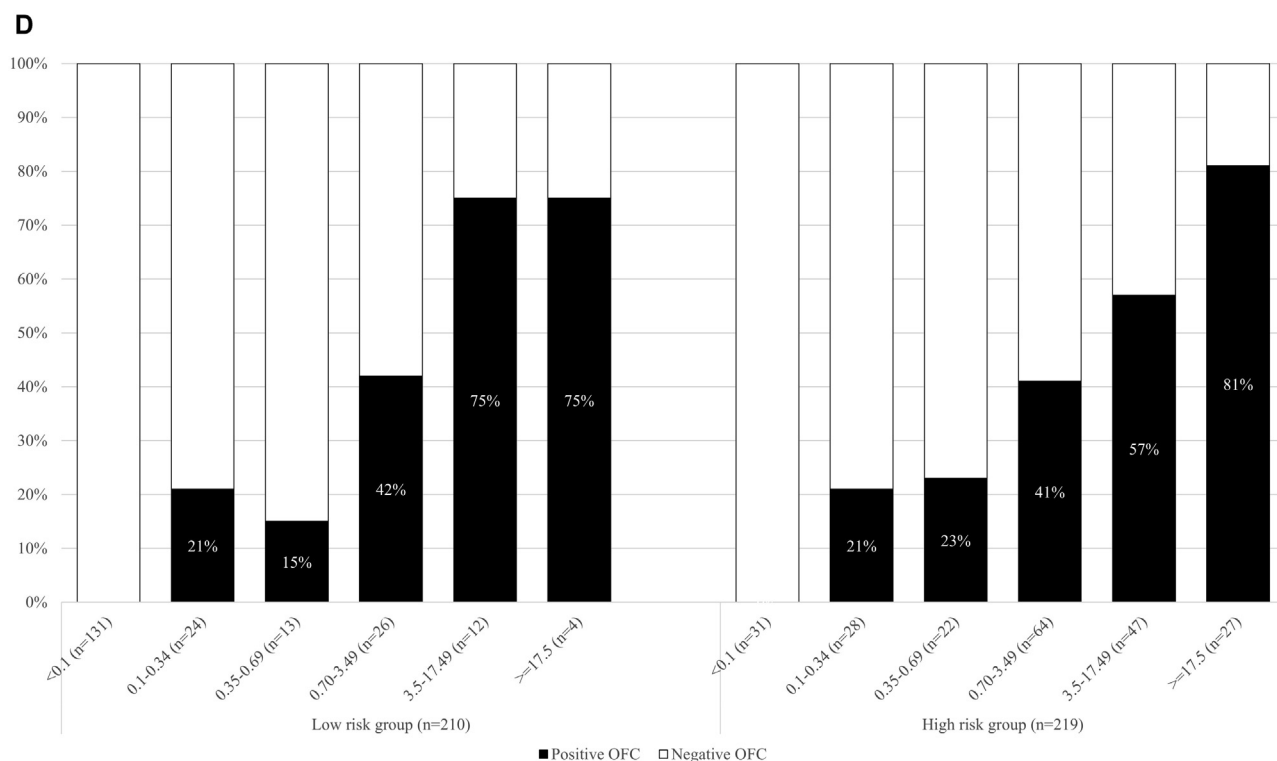
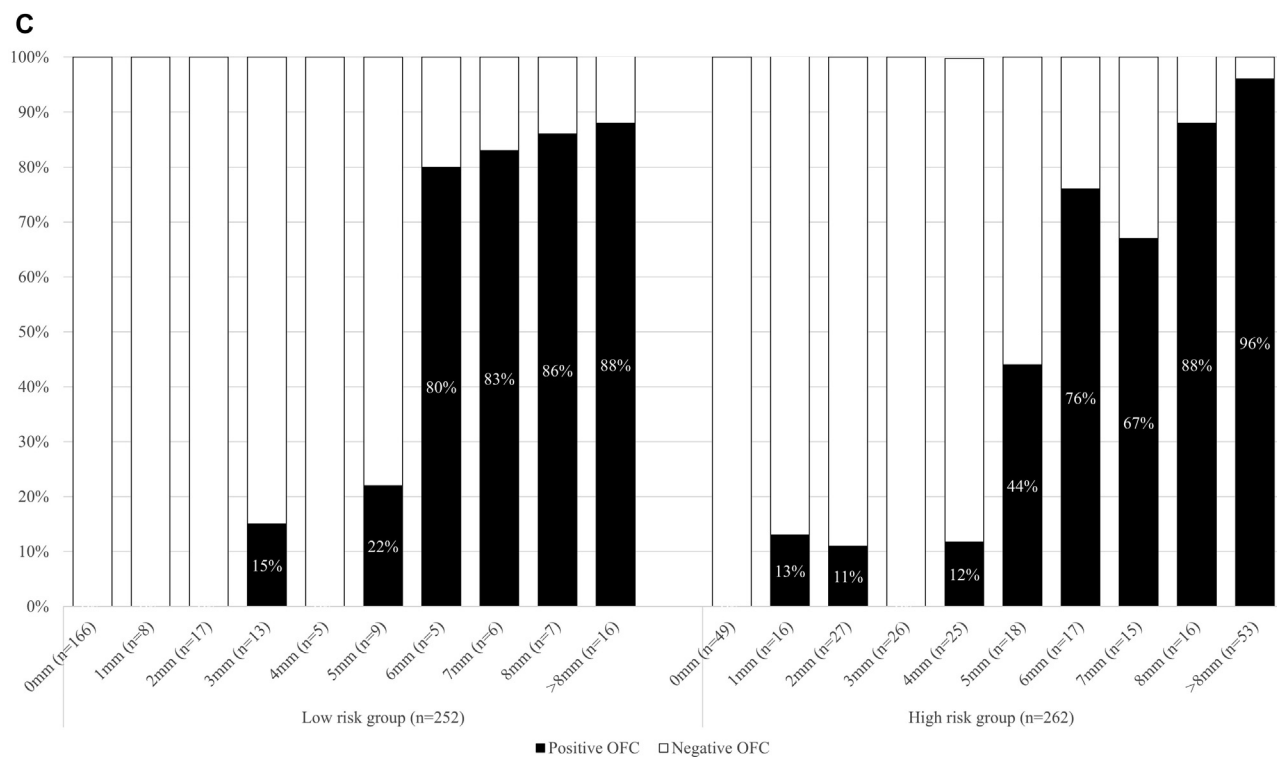


FIG 1. (Continued).

- Of the high-risk infants, 89% would have an SPT wheal size of 4 mm or less and 11% would have an SPT wheal size of more than 4 mm if screened at

age 4 to 11 months (LEAP study data). *Note that this is lower than the observed proportion of high-risk infants with an SPT wheal size of more than*

TABLE III. Proportion of positive peanut challenges by SPT wheal size and specific IgE cutoffs in high- and low-risk populations

Risk group	SPT wheal size (mm)/ sIgE level (kuA/L)	No. of peanut OFC performed	% of peanut OFC that were positive (95% CI)
Low risk (no early eczema and/or egg allergy)	SPT: 0*	154	0 (0-2.4)†
	SPT: 1-2	23	0 (0-14.8)†
	SPT: 3-4	16	12.5 (0-30.7)
	SPT: >4	37	70.3 (54.8-85.7)
High risk (early eczema [$\leq$ 6 mo, requiring topical steroids] and/or egg allergy)	SPT: 0*	72	0 (0-5.0)†
	SPT: 1-2	44	11.4 (3.8-24.6)
	SPT: 3-4	51	5.9 (0-12.6)
	SPT: >4	121	80.2 (73.0-87.4)
Low risk (no early eczema and/or egg allergy)	sIgE: <0.1‡	131	0 (0-2.8)†
	sIgE: 0.1-0.34	24	20.8 (3.3-38.4)
	sIgE: 0.35-17.4	51	43.1 (29.1-57.2)
	sIgE: $\geq$ 17.5	4	75.0 (19.4-99.4)
High risk (early eczema [$\leq$ 6 mo, requiring topical steroids] and/or egg allergy)	sIgE: <0.1‡	31	0 (0-11.2)†
	sIgE: 0.1-0.34	28	21.4 (5.2-37.6)
	sIgE: 0.35-17.4	133	43.6 (35.1-52.1)
	sIgE: $\geq$ 17.5	27	81.5 (65.8-97.1)

*Selected for challenge on the basis of previous detectable SPT wheal in the community but subsequently negative on repeat SPT in clinic (n = 81; 54 of these were <3 mm initially) or as negative control group with 2 negative skin prick test results (n = 140).

†One-sided, 97.5% CI.

‡Below detection.

TABLE IV. Relationship between family history of allergy and signs of allergy in the infant and age at introduction of peanut into the infant diet

Family history of allergy and allergic symptoms in the infants before age 12 mo	N	Age at introduction of peanut (%)					P value*
		4-6 mo	7-8 mo	9-10 mo	11-12 mo	Not yet given	
No risk factors	2215	3.6	5.4	8.6	12.2	69.9	
Family history of eczema or food allergy only (parents or siblings)	1677	2.6	4.9	8.4	12.3	71.8	.32
Early eczema only (eczema $\leq$ 6 mo treated with topical steroids)	418	1.8	4.4	6.9	8.2	78.2	.014
Early eczema and infant history of reaction to milk or egg (parent-reported)	181	0.6	1.8	3.6	6.7	87.3	<.001

* χ^2 P value comparing the distribution of age at peanut introduction in each risk group to the baseline group of “no risk factors.”

4 mm in the HealthNuts study (14.6%), probably because infants in the HealthNuts study were older (12 months) at the time of SPT.

- A total of 17% of high-risk infants with a 0- to 4-mm wheal would be allergic without intervention (LEAP study data—peanut avoidance arm). Note that this is higher than the observed proportion of high-risk infants with a 0- to 4-mm wheal who are peanut allergic in the HealthNuts study, possibly because of (1) older age in the HealthNuts study and/or (2) earlier introduction of peanut in the HealthNuts study cohort compared with the LEAP study control arm.
- A total of 3% of high-risk infants with a 0- to 4-mm wheal would be allergic with intervention (LEAP study data—early peanut introduction arm).

These assumptions were used to calculate the number of cases of peanut allergy in this constructed population that would be expected with and without intervention, and therefore the proportion of peanut allergy cases that could be prevented through the early introduction of peanut. Note that the proportion of cases that would be expected in low- and high-risk infants in this hypothetical population does not match that observed in the HealthNuts study, because of the differences between the LEAP study and the HealthNuts study described in assumptions 1 to 3 above.

If the LEAP intervention findings were applied to all infants with early onset eczema and/or egg allergy, 44% of all peanut allergy cases in the community might be prevented (Fig 2; 20 of 45 = 44%). If the same magnitude of risk reduction (80%; 6 of 7 cases prevented) could be achieved in low-risk infants, a total of 58% of peanut allergy cases in the community might be prevented (26 of 45 = 58%). This would increase to 64% of cases if timely peanut introduction could also be implemented and was protective in the 20% of infants with an SPT wheal size of more than 4 mm who are negative on baseline challenge (29 of 45 = 64%). If timely peanut introduction was half as successful at preventing peanut allergy in low-risk infants compared with high-risk infants (eg, 40% of cases prevented instead of 80%), and not implemented in the SPT wheal size more than 4 mm group, a total of 51% of peanut allergy cases might be prevented (23 of 45 = 51%).

DISCUSSION

Our study extends the findings of the LEAP trial¹ to a population-based cohort. We show that using the strict criteria applied in the LEAP trial to select high-risk infants to target early introduction of peanut would miss a sizeable number of peanut allergy cases in the general community. Even using very inclusive criteria to define “high risk” (all infants with early onset eczema

TABLE V. Prevalence and types of community-based adverse reactions to peanut in the first year of life in infants introduced to peanut at home before SPT screening at age 12 months

Group	No. introduced to peanut	% reporting a reaction	Reported reaction within 1 h (possibly IgE-mediated)*							
			Skin only (hives, rash, swelling of lips, eyes, or face)		Gut only (vomiting, diarrhea)		Skin and gut		Wheeze/ difficulty breathing	
			N	Challenge-confirmed peanut allergy	N	Challenge-confirmed peanut allergy	N	Challenge-confirmed peanut allergy	N	Challenge-confirmed peanut allergy
Low-risk group (no early eczema or egg allergy)	1135	1.2	14	31% (4 of 13)	0	—	0	—	0	—
High-risk group (early eczema or egg allergy)	185	9.7	15	67% (10 of 15)	0	—	2	100% (2 of 2)	1†	0

*An additional 6 infants had a reported reaction occurring 14 hours after ingestion, with 5 involving skin only (1 positive on challenge) and 1 skin and gut (negative challenge). An additional 3 infants had a reported reaction >4 hours after ingestion, all involving skin only (2 positive on challenge).

†Reaction occurred on first reported introduction of peanut butter at age 12 months. Vomiting also reported. Child had a negative SPT result at age 12 months (1 mm) and sIgE to peanut and a negative OFC to peanut at age 14 months in clinic, and tolerated peanut (1 tsp/d) for a week at home after challenge with no reaction, so peanut allergy unlikely or outgrown. Child had positive SPT result and sIgE to hazelnut at age 14 months.

TABLE VI. Reactions to peanut on OFC at age 12 months

SPT wheal size	No. of peanut OFC	No. of positive OFC	Hives* (% of positive challenges)	Angioedema* (% of positive challenges)	Vomiting* (% of positive challenges)	Skin and gut* (% of positive challenges)	Anaphylaxis*† (% of positive challenges)
0 mm	221	0	—	—	—	—	—
Low-risk group (no early eczema or egg allergy)							
1-4 mm	43	2 (5%)‡	1 (50%)	0	1 (50%)	0	0
5-7 mm	20	11 (55%)	10 (91%)	0	0	0	1 (9%)
>8 mm	23	20 (87%)	17 (85%)	3 (15%)	1 (5%)	1 (5%)	0
High-risk group (early eczema or egg allergy)							
1-4 mm	94	8 (9%)‡	6 (75%)	0	0	0	0
5-7 mm	50	30 (60%)	24 (80%)	2 (7%)	2 (7%)	2 (7%)	2 (7%)
>8 mm	69	65 (94%)	59 (91%)	13 (30%)	10 (15%)	10 (15%)	3 (5%)

*Note that categories are not mutually exclusive; for example, all the children with skin and gut reaction also appear in both the skin (hives or angioedema) and gut (vomiting) columns.

†All infants developed respiratory symptoms (wheeze) and were treated with adrenaline (single dose in each cases) and Ventolin, ±Zyrtec.

‡Three children in this category had a negative day 1 hospital-based challenge but had a reaction on continued consumption of peanut at home, all with hives + eczema flare ± angioedema; these reactions are not presented in the table but the infants are included in the "number positive OFC" column.

and/or egg allergy) to target screening, 23% (95% CI, 16.6-31.3) of peanut allergy cases in the population would still be missed. Furthermore, 29% (95% CI, 25.8-32.4) of these high-risk infants could have a positive SPT result. If the current international consensus guidelines were followed, these infants would require clinical follow-up to assist with assessment for timely introduction of dietary peanut, which is a large proportion of the general infant population.

Using a combination of data from the LEAP study and the HealthNuts study to model the potential impact of implementing the LEAP intervention in the wider population, we show that this might prevent only up to 44% of peanut allergy cases if the intervention is restricted to high-risk infants. New strategies in addition to earlier introduction of peanut need to be investigated in future studies to prevent peanut allergy in those infants whose peanut allergy develops too early to benefit from the early introduction intervention. Further research to determine whether earlier introduction of peanut is also beneficial in low-risk infants may also be warranted. The recently published EAT trial compared peanut introduction (along with other allergenic foods) from 3 months (although actual reported median age at introduction was around 5 months) with introduction after age 6 months in

population-recruited infants (with and without eczema). The primary analysis (intention to treat) showed no significant difference in peanut allergy in the 2 groups, although there was a lower prevalence of peanut allergy in the early introduction group in a secondary per-protocol analysis. High- and low-risk infants were not analyzed separately.⁹

We add to the findings of the LEAP trial by showing that around 80% (95% CI, 73.0-87.4) of high-risk infants with an SPT wheal size of more than 4 mm, excluded from participation in the LEAP study, had challenge-confirmed peanut allergy. Conversely, 20% of infants with an SPT wheal size of more than 4 mm could tolerate peanut. Thus, if screening were implemented and this cutoff used, an inappropriate recommendation to avoid peanut might be made for these high-risk infants. Identifying peanut-tolerant infants through peanut OFC so that they can be included in the earlier introduction of peanut group could improve the proportion of peanut allergy cases prevented, although no data are currently available on the potential beneficial effect of early peanut introduction in preventing peanut allergy later in life in infants with such SPT wheal size. If a cutoff is to be used to identify infants who are highly likely to be peanut allergic, and thus reduce the need for food challenges, a more appropriate level

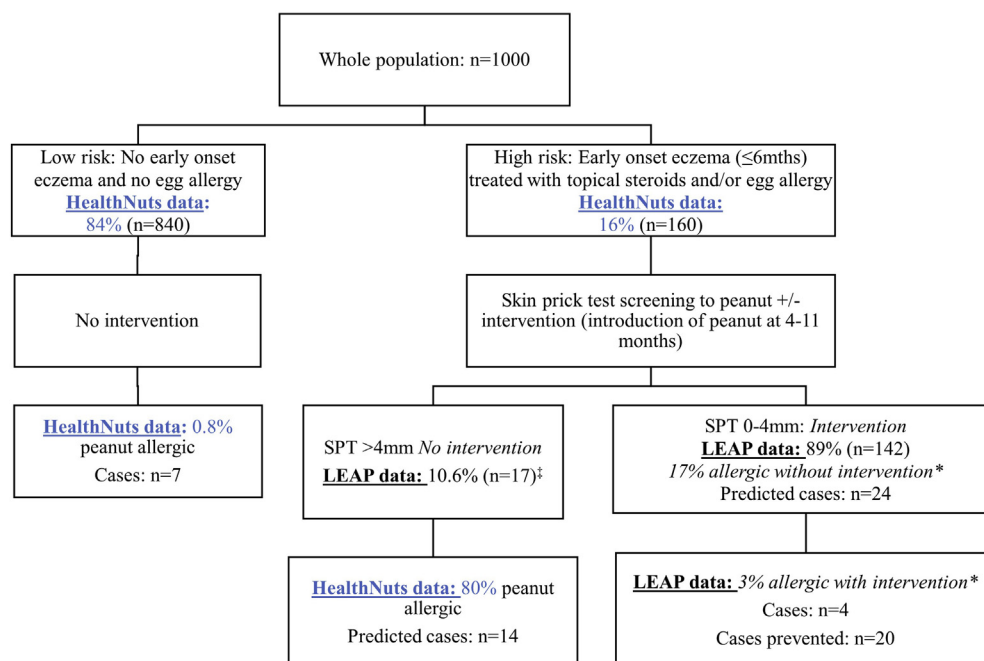


FIG 2. Cases of peanut allergy that may be theoretically preventable by applying the LEAP intervention findings to a general infant population. We used a hypothetical population of 1000 infants to represent the general population. At each step, we used the best available observed data from either the HealthNuts study (blue; this study) or the LEAP study (black)¹ to calculate the proportion of this hypothetical population that would fall into each group, and the prevalence of peanut allergy in each group. Precedence was given to data from the LEAP study where available. *The proportion of peanut allergy cases predicted to develop in the 0- to 4-mm SPT wheal group without intervention is the observed proportion of children with peanut allergy in the control arm of the LEAP study. This may be higher than actually observed in a “real-world” setting because some of these children might have been introduced to peanut earlier if they were not participating in this randomized trial and thus instructed to avoid peanut until age 5 years. The proportion of peanut allergy cases predicted to develop in the 0- to 4-mm SPT wheal group with intervention is the observed proportion of children with peanut allergy in the intervention arm of the LEAP study in the intention-to-treat analysis. ‡We used figures from the LEAP study¹ to estimate the proportion of high-risk infants who would have an SPT wheal size of 4 mm to peanut at age 4 to 11 months. This figure (10.6%) is somewhat lower than the proportion of high-risk infants in the HealthNuts study with an SPT wheal size of more than 4 mm (14.6%), possibly because infants in the HealthNuts study were older at the time of SPT (age 12 months).

might be wheal sizes of 8 mm or greater, which has previously been shown to have a 95% positive predictive value for peanut allergy in infants.¹³

Our results obtained from a general population cohort also confirm other findings from the high-risk LEAP study cohort. We showed that even high-risk infants with SPT wheal sizes of 1 to 4 mm are likely to tolerate peanut if it is introduced early in life. We also found that positive challenges occurred in some infants with a peanut SPT wheal size of 1 to 2 mm, below the traditional cutoff of 3 mm, and in infants with a peanut sIgE level between 0.1 and 0.34 kUA/L. A further interesting confirmation of the LEAP study was the finding that 34% of high-risk infants with a 0-mm SPT wheal to peanut had detectable levels of peanut sIgE—in the LEAP study cohort, 28% of SPT-negative infants had detectable peanut sIgE.¹

The strengths of this study include the careful peanut allergy phenotyping of a large cohort of infants through hospital-supervised OFCs, and the fact that the same SPT device, commercially available allergen extract, and OFC methodology as used in the LEAP study were used. In this context, it is striking that predictive values for peanut allergy in the less than 4-mm SPT

wheal size group were consistent across both studies, despite 1 study being only high-risk infants and the other population based, with 2 independent study teams performing the testing. If SPT is to be considered for screening, it is likely to be a robust methodology.

The findings of this study are likely to be generalizable to the wider Victorian population due to the population-based sampling frame and high participation rate. We have evidence that study participants are generally representative of all births in Victoria from data collected routinely in the perinatal database.¹⁰ In addition, we have previously shown that weighting prevalence estimates, using data on the prevalence of risk factors for peanut allergy in all eligible infants whose parents declined study participation, only marginally altered the prevalence estimate for peanut allergy from 3.0% to 2.9%.²

Despite the large sample size of this study, peanut allergy is a relatively uncommon outcome in the general population. As a result, some SPT and sIgE groups include only a small number of infants, resulting in wide CIs. Our findings need to be interpreted in conjunction with the magnitude of uncertainty around each of the reported estimates.

Limitations include that although study participants were peanut challenged within 4 to 8 weeks of their screening SPT at their 12-month immunization visit, our results pertain to children aged 12 to 18 months, which is an older age group than that recruited into the LEAP study. However, despite the difference in age range, key results are remarkably similar across the 2 cohorts. In addition, different definitions of eczema were used across the cohorts, with infants included in the LEAP study likely representing more severe eczema cases. Both definitions have limitations because both incorporated the somewhat subjective criteria of parental report of eczema severity and topical steroid use. Defining eczema severity remains problematic so we chose a definition that would identify infants who would be seen through the medical system, with early onset and requirement for topical steroid therapy used to identify more severe eczema. This would also offer a consistent approach to identifying these infants in practice if the international consensus recommendations are to be adopted. Restricting the definition to capture only more severe cases of eczema would increase the number of peanut allergy cases missed.

What are the implications of our findings for clinical practice and the potential to implement screening guidelines? As reported in other population-based studies of infants, eczema and egg allergy are common in infancy,^{2,14,15} although egg allergy appears somewhat more common in Australia than in Europe¹⁶; thus, even if only high-risk infants were targeted, a relatively large proportion of the population would require screening at least in some countries. Consistent with previous studies,¹⁷ we show that both SPT and sIgE to peanut have a strong negative predictive value. Screening could therefore potentially include some testing in the community setting using peanut sIgE blood tests, perhaps in combination with Ara h2 as a second step,¹⁸ making screening more feasible and reducing the number needing SPT and/or OFC. Furthermore, egg allergy was a stronger predictor of peanut allergy than eczema alone; however, because less than 25% of infants had introduced egg by age 6 months, this is unlikely to be a helpful early marker for targeting early onset allergic disease for screening as recommended by consensus guidelines.⁸ Further studies will need to be done to investigate the potential implications of implementing screening in other countries including the United States, which may have different rates of eczema and peanut allergy.

An alternative paradigm to screening high-risk infants would be to recommend timely introduction of peanut for all infants irrespective of allergy risk, as per the current Australian guidelines.¹⁹ Our findings provide some reassurance that reactions at home when peanut was introduced as part of a weaning diet before age 12 months were uncommon overall, with no (clear) cases of anaphylaxis reported. However, there was evidence of self-selection based on risk, whereby infants with eczema or egg allergy were less likely to be introduced to peanut before age 1 year—and this group was more likely to have a reaction on introduction—thus, it is difficult to predict whether severe reactions would have occurred if peanut was introduced to all high-risk infants at home in an uncontrolled manner. The fact that peanut-allergic infants usually had mild reactions during supervised challenges provides some reassurance. Although the LEAP study did not look at whether early introduction of peanut in the low-risk group might lead to reduced risk of peanut allergy, this may be a reasonable recommendation for the population because data from the HealthNuts study suggest that

the likelihood of reaction is low and reactions were mild to moderate. The publication of the LEAP trial, resulting media coverage, and release of international consensus guidelines stating that delay in peanut introduction might be harmful are likely to encourage more parents to introduce peanut earlier in infancy, and the HealthNuts study provides baseline data against which to measure changes in timing of peanut introduction and the resulting impact on peanut allergy prevalence.

We provide data that most reactions on peanut introduction in young infants are mild, irrespective of whether peanut is introduced at home or in the hospital, and irrespective of SPT wheal size or clinical risk factors. Caution is needed in interpretation of these results because despite the large population recruited the number of peanut-allergic infants was only 150 cases—more severe reactions might still be observed in rare cases. However, in conjunction with findings from the LEAP study, our findings provide reassurance that introducing peanut in infancy is unlikely to lead to severe reactions. In fact, because infants in the HealthNuts study were already aged 1 year and had predominantly avoided peanut in infancy, thus increasing their likelihood of being peanut allergic, we would expect to see even fewer reactions if peanut was introduced earlier in the first year of life as in the LEAP study.

In conclusion, our results show that large numbers of infants would be affected if screening before introduction of peanut was implemented; thus, careful consideration of whether and how to target and/or screen infants is required before public health recommendations can be made. Despite the potential to substantially reduce the population prevalence of peanut allergy through timely introduction of peanut in high-risk infants, around 20% of peanut allergy cases in the population occur in low-risk infants and an additional 20% of cases occur in infants ineligible for participation due to an SPT wheal size of more than 4 mm at recruitment. Additional prevention strategies will be required for these infants. Further population-based intervention trials are required to determine whether timely introduction of peanut is also protective for low-risk infants, and to inform cost-effective analysis of the intervention at the population level as well as the cost-effectiveness of various screening strategies.

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Clinical implications: The LEAP study findings are of major significance for the prevention of peanut allergy. The public health and workforce implications of the LEAP study will need to be carefully considered if implemented at the population level.

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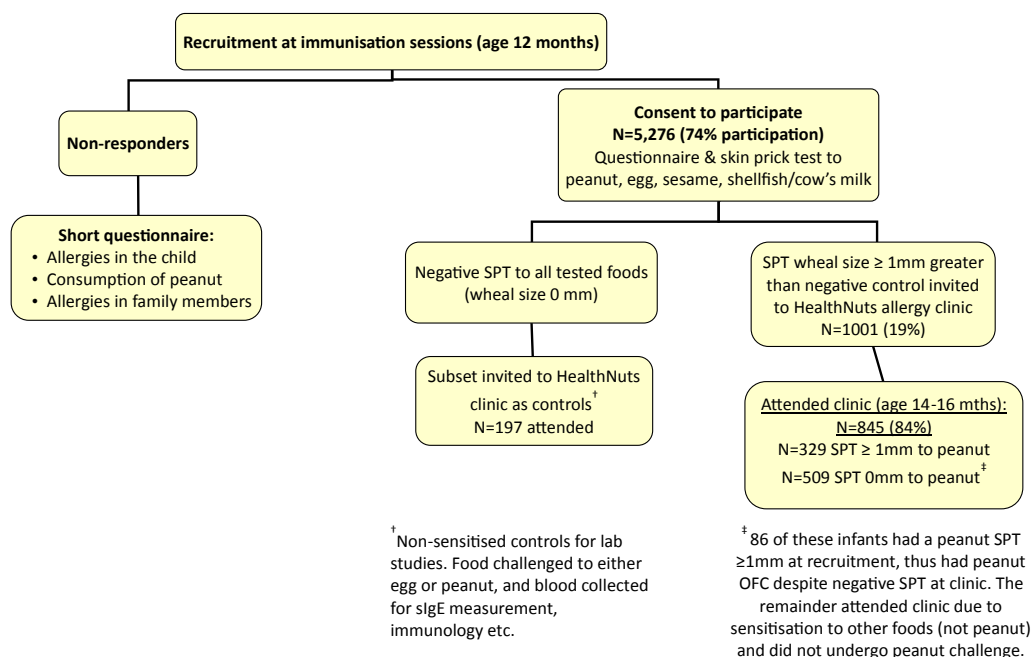


FIG E1. The HealthNuts study participation flow chart. [†]Nonsensitized controls for laboratory studies. Food challenged to either egg or peanut, and blood collected for sIgE measurement, immunology, etc. [‡]A total of 86 of these infants had a peanut SPT wheal size of 1 mm or more at recruitment; thus, they had peanut OFC despite negative SPT result at clinic. The remainder attended clinic because of sensitization to other foods (not peanut) and did not undergo peanut challenge.

TABLE E1. Comparison of definitions of high risk for development of peanut allergy used in the LEAP randomized controlled trial and subsequent editorials and consensus guidelines

Study characteristic	LEAP randomized controlled trial	Editorial accompanying the LEAP study	Consensus guidelines
Age range targeted (mo)	4-11	4-8	4-11
Eczema definition	Severe eczema (89% of participants): Requires application of topical creams, ointments, or both containing corticosteroids or calcineurin inhibitors and that, if the participant is <6 mo of age, lasted for at least 12 of 30 d on 2 occasions or, if the participant is >6 mo of age, lasted for at least 12 of 30 d on 2 occasions in the last 6 mo OR Is currently or was previously graded ≥ 40 by using the modified SCORAD evaluation	“Any infant between 4 months and 8 months of age <i>believed to be at risk of peanut allergy</i> ”	Severe eczema as per LEAP definition. If occurring in first 4 to 6 mo of life—“might benefit from evaluation by an allergist”
Egg allergy definition	Egg allergy (64% of participants): SPT wheal ≥ 6 mm to raw hen’s egg white and no history of egg tolerance OR SPT wheal ≥ 3 mm to pasteurized hen’s egg white and allergic symptoms related to exposure to hen’s egg	As above	Egg allergy as per the LEAP study definition. If occurring in first 4 to 6 mo of life—“might benefit from evaluation by an allergist”
Peanut SPT cutoffs and recommendations	0-4 mm: Included >4 mm: Excluded	0 mm: Start peanut-containing diet 1-4 mm: Peanut challenge—if negative, start peanut-containing diet >4 mm: No recommendations	Clinician can perform an observed peanut challenge for those with evidence of a positive peanut skin test response to determine whether they are clinically reactive before initiating at-home peanut introduction

SCORAD, SCORing Atopic Dermatitis.