Identifying infants at high risk of peanut allergy: The Learning Early About Peanut Allergy (LEAP) screening study

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Background: Peanut allergy (PA) is rare in countries in which peanuts are introduced early into infants' diets. Learning Early About Peanut Allergy (LEAP) is an interventional study aiming to assess whether PA can be prevented by oral tolerance induction.

Objective: We sought to characterize a population screened for the risk of PA.

Methods: Subjects screened for the LEAP interventional trial comprise the LEAP screening study cohort. Infants were aged 4 to 10 months and passed a prescreening questionnaire.

Results: This analysis includes 834 infants (mean age, 7.8 months). They were split into the following: group I, patients with mild eczema and no egg allergy (n = 118); group II, patients with severe eczema, egg allergy, or both but 0-mm peanut skin prick test (SPT) wheal responses (n = 542); group III, patients with severe eczema, egg allergy, or both and 1- to 4-mm peanut wheal responses (n = 98); and group IV, patients with greater than 4-mm peanut wheal responses (n = 76). Unexpectedly, many (17%) in group II had peanut-specific IgE sensitization (≥0.35 kU/L); 56% of group III were similarly sensitized. In contrast, none of the patients in group I and 91% of those in group IV had peanut-specific IgE sensitization. Sensitization on skin testing to peanut (SPT response of 1-4 mm vs 0 mm) was associated with egg allergy and severe eczema (odds ratio [OR], 2.31 [95% CI, 1.39-3.86] and 2.47 [95% CI, 1.14-5.34], respectively). Similar associations were observed with specific IgE sensitization. Black race was associated with a significantly higher risk of peanut-specific IgE sensitization (OR, 5.30 [95% CI, 2.85-9.86]). Paradoxically, for a given specific IgE level, black race was protective against cutaneous sensitization (OR, 0.15 [95% CI, 0.04-0.61]).

Conclusion: Egg allergy, severe eczema, or both appear to be useful criteria for identifying high-risk infants with an intermediate level of peanut sensitization for entry into a PA prevention study. The relationship between specific IgE level and SPT sensitization needs to be considered within the context of race. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: *Peanut sensitization, peanut allergy, allergy risk factors, eczema, egg allergy, patient recruitment, allergy prevention, LEAP study*

The prevalence of peanut allergy (PA) among children in the United Kingdom, North America, and Australia has doubled in 10 years and is approximately 1.8%, 1.4%, and 3.0% respectively.[1-7] PA is a common cause of anaphylaxis and is infrequently outgrown.[8-12] The onset of IgE sensitization to peanut usually occurs during infancy, with symptomatic PA typically presenting during early childhood.[13-15]

Studies eliminating food allergens during pregnancy, lactation, and infancy have consistently failed to prevent IgE-mediated food allergy.[16] There are no recommendations aimed at the prevention of PA through avoidance or exposure to peanut during pregnancy, breast-feeding, and infancy.[17-19] The Learning Early About Peanut Allergy (LEAP) study[20] is a randomized controlled trial in infants that aims to determine which is the best strategy for the prevention of PA: introduction of peanut into the diet of young infants or complete avoidance. An intervention needs to be applied to a high-risk population before subjects become

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Abbreviations used
LEAP: Learning Early About Peanut Allergy
OR: Odds ratio
PA: Peanut allergy
PP: Per-protocol
SPT: Skin prick test

clinically allergic to be an effective prevention strategy. The LEAP study sought to enroll infants at high risk for the development of PA. A review of the literature suggested that eczema severity, early onset of eczema, and frequent use of topical corticosteroids might be useful high-risk factors for the development of PA.[14,21] There are also data showing an association between egg allergy and PA.[22] We therefore decided to use severe eczema, egg allergy, or both as inclusion criteria for the LEAP study. We anticipated that infants with a skin prick test (SPT) wheal diameter to peanut of 0 to 4 mm would not yet have established PA; children with wheal diameters of greater than 4 mm were considered likely to have PA and therefore excluded from the prevention study.[23-27]

In this article we prospectively assess whether severe eczema and egg allergy are effective inclusion criteria for the identification of infants at high risk for peanut sensitization but without established PA.

METHODS

Study design

The LEAP screening study is a single-center, prospective, observational study that includes infants who underwent screening for an interventional trial termed the LEAP study (see the Methods section in this article's Online Repository at www.jacionline.org), which investigated the prevention of PA in high-risk children. Recruitment was targeted to families with young infants with eczema, egg allergy, or both. In this article the term *eczema* is identical to the term *atopic dermatitis*. Recruitment focused on (1) child health professionals, such as dermatologists, allergists, and specialist nurses; (2) a study flyer posted to parents of young infants in the United Kingdom; and (3) other avenues, such as written and electronic media and word of mouth. Interested families were asked to make contact with the study team either through an external call center or directly. Infants underwent screening for the LEAP study if the family agreed to consider participation in the study and passed a prescreening questionnaire addressing previous allergy and eczema history.

Demographics

Information about prior eczema and other allergies was gathered through interviews. Information about race was based on families' self-report. In the United Kingdom, where the study took place, subjects who identify themselves as black are predominantly Afro-Caribbean or African. Thus the black population in the current study is not identical to the American black population. Those who identify themselves as Asian are predominantly from the Indian subcontinent.

Severe eczema

Eczema was self-defined by participants' parents by a questionnaire. Severe eczema was defined as one of the following: (1) frequent need for treatment with topical corticosteroids or calcineurin inhibitors, (2) parental description of "a very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash," or (3) a severe SCORAD grade (≥40) by a clinician before or at the time of screening.

Egg allergy

Egg allergy was defined on the basis of either (1) an SPT-induced wheal diameter of 6 mm or greater with raw hen's egg white and no history of previous egg tolerance or (2) an SPT-induced wheal diameter of 3 mm or greater with pasteurized hen's egg white with a history of an allergic reaction to egg.[28]

SPTs and specific IgE measurements

SPTs to ingested allergens, including raw hen's egg white (Red Lion salmonella-free egg), pasteurized hen's egg white, peanut, cow's milk, sesame, and soya (all other SPTs sourced from ALK-Abelló, Hørsholm, Denmark), were undertaken at the baseline assessment. The lyophilized peanut extract contains 20 mg of peanut protein per vial; analysis by means of Western blotting confirmed the presence of Ara h 1, Ara h 2, and Ara h 3. By using a standardized lancet (ALK-Abelló), the skin on the forearm was pricked through a drop of the extract. Peanut SPTs were undertaken in duplicate, with the widest diameter of the wheals at 15 minutes recorded and averaged.[24] A saline control was not subtracted. Cutaneous sensitization for peanut was generally defined as an SPT response of greater than 0 mm, except in Fig E4 and Tables E2 and E3 in this article's Online Repository, in which it was defined as an SPT response of 3 mm or greater.

At baseline, specific IgE assays (Thermo Fisher Scientific, Uppsala, Sweden) were undertaken for peanut, hen's egg white, cow's milk, sesame, brazil nut, hazel nut, cashew, almond, and walnut. Three cutoffs for specific IgE levels were used. Detectable specific IgE levels were defined as greater than 0.01 kU/L. An intermediate cutoff of 0.1 kU/L or greater was used in some analyses. Sensitization by specific IgE was defined as a result of 0.35 kU/L or greater.

Sample size

The number of infants screened was based on the need to enroll 640 participants in the LEAP study. Additional details are given in the Methods section in this article's Online Repository.

Statistical analysis

We categorized all infants who were screened into groups of increasing atopy. Group I, with "mild eczema and no egg allergy," did not meet LEAP study inclusion criteria. Group II, with "severe eczema and/or egg allergy but no reaction on SPT to peanut," is the LEAP study negative SPT response stratum. Group III, with "severe eczema and/or egg allergy and a 1-4 mm peanut wheal," is the LEAP study positive SPT response stratum. Group IV have peanut wheal responses of greater than 4 mm. Groups I to IV comprise the LEAP screening study cohort. Each group was described in terms of its demographics and clinical features. Trends were examined with 2-sided Cochran-Armitage trend tests. Spearman correlation coefficients were used to assess the association between SPT responses to different foods and between specific IgE results to different foods. Participants were split into 3 severity groups based on SCORAD scores (mild, <15; moderate, 15-40; and severe, >40)[29] at screening to explore the relationship between eczema severity and sensitization. A similar methodology was followed for the peanut SPT-induced wheal diameter groups. Finally, baseline factors associated with sensitization to peanut were analyzed by using univariate and multivariate logistic regression models.

Ethical considerations

Ethical approval for the study was provided by the NRES Committee London – Fulham, formerly West London REC2 Ethics Committee (REC Reference 04/Q0403/13). Informed consent was obtained from the parents of all participants.

RESULTS

Demographics of screened subjects

Infants were recruited for the LEAP study from November 2006 to May 2009. A total of 2829 potential participants

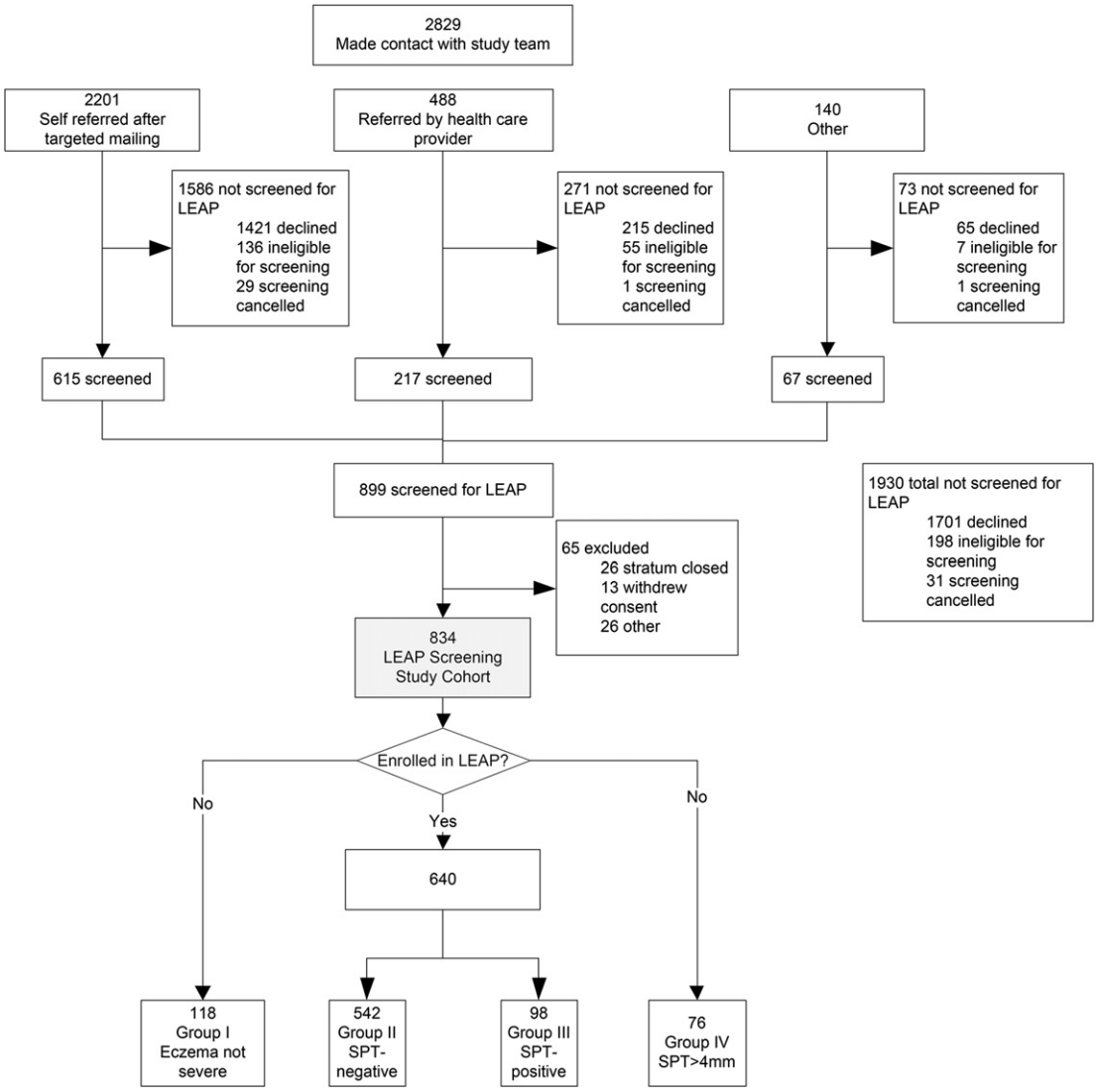

FIG 1. Flow of participants into the LEAP screening study.

contacted the clinical trials unit, and 899 underwent screening (see Fig 1 for details). Of these, 65 were not considered further because the appropriate LEAP stratum was closed or they withdrew consent or for other reasons. The remaining 834 subjects comprise the LEAP screening study cohort. For these, mean age was 7.8 months (range, 4-10 months), with slightly more male subjects (61%) and diverse race (Table I). Atopy significantly ($P < .001$) increased in ascending order from groups I to IV in terms of severe eczema, SCORAD scores, rates of egg allergy, and eosinophil levels (Table I). The mean age of those screened also increased from groups I through IV. The majority of the infants in the LEAP screening study cohort had severe eczema (77%) and met the study definition of egg allergy (57%). Further details are shown in Table I.

Specific IgE sensitization to peanut

From groups I to IV, there was a general increase in the rate and level of specific IgE sensitization to peanut (Fig 2, *A*). As expected, the majority in groups III and IV had peanut-specific IgE levels of 0.35 kU/L or greater (56% and 91%, respectively) because these groups by definition had at least some reaction on SPTs. The high median specific IgE level to peanut of 8.0 kU/L in group IV, with a median SPT response of 7.5 mm, suggests a high likelihood of pre-existing PA in this group at assessment. None of the subjects in group I had peanut-specific IgE levels of 0.35 kU/L or greater. Surprisingly, there was a high level of specific IgE sensitization in group II (17%) despite the lack of response to peanut on SPTs (Fig 2, *A*). Furthermore, 58% had at least some detectable (defined as >0.01 kU/L) peanut-specific IgE in group II.

As expected, increasing SPT-induced wheal diameters to peanut were associated with an increased percentage of children producing specific IgE to peanut (Fig 2, *B*). There was a moderate correlation between SPT responses and peanut-specific IgE levels (Spearman = 0.55, $P < .001$). Among infants with SPT responses to peanut of 0 mm, 24% (n = 153) had IgE levels of 0.1 or greater. In contrast, of those with IgE levels of less than 0.1, only 4.7% (24) had SPT responses of greater than 0 mm (see Table E1 in this article's Online Repository at www.jacionline.org). There is a high rate of SPT sensitization (≥3 mm) to individual foods and a high rate of polysensitization to multiple foods in groups

TABLE I. Baseline characteristics for the LEAP screening study cohort

	Group I: mild eczema and no egg allergy (n = 118)	Group II: SPT response–negative stratum (n = 542)	Group III: SPT response–positive stratum (n = 98)	Group IV: SPT response >4 mm (n = 76)	*P* value*
Age at screening (mo), mean (SD)	7.5 (1.83)	7.7 (1.74)	8.1 (1.62)	8.3 (1.88)	<.001
Male sex (no.)	65.3% (77)	59.4% (322)	63.3% (62)	57.9% (44)	.552
Race, (no.)					
White	72.0% (85)	74.4% (403)	68.4% (67)	64.5% (49)	
Black	9.3% (11)	7.7% (42)	6.1% (6)	14.5% (11)	
Other					
Mixed	8.5% (10)	13.7% (74)	15.3% (15)	13.2% (10)	
Asian†	7.6% (9)	3.0% (16)	8.2% (8)	5.3% (4)	
Chinese, Middle Eastern, or other	0.8% (1)	1.1% (6)	2.0% (2)	1.3% (1)	
Missing	1.7% (2)	0.2% (1)	0	1.3% (1)	
Severe eczema,‡ (no.)	0	88.9% (482)	90.8% (89)	96.1% (73)	<.001
Definition 1	0	38.6% (209)	52.0% (51)	46.1% (35)	<.001
Definition 2	0	86.2% (467)	88.8% (87)	90.8% (69)	<.001
Definition 3	0	40.2% (218)	42.9% (42)	44.7% (34)	<.001
Age at onset of eczema (mo), mean (SD)	2.6 (1.84)	2.3 (1.63)	2.2 (1.54)	1.6 (1.12)	<.001
Duration of eczema at screening (mo), mean (SD)	4.6 (2.06)	5.4 (2.03)	5.9 (1.89)	6.5 (2.08)	<.001
SCORAD score at screening, mean (SD)	9.9 (6.98)	34.2 (19.12)	35.7 (17.42)	39.3 (18.65)	<.001
Egg allergy‡ (no.)	0	61.4% (333)	76.5% (75)	86.8% (66)	<.001
Definition 1	0	60.7% (329)	74.5% (73)	85.5% (65)	<.001
Definition 2	0	53.1% (288)	72.4% (71)	76.3% (58)	<.001
Percentage eosinophilia, mean (SD)	2.5 (1.30)	4.6 (3.81)	5.6 (3.83)	5.7 (4.12)	<.001
Total IgE (kU/L), mean (SD)	17.9 (34.99)	85.7 (261.0)	211 (482.1)	505 (1263)	<.001
Peanut sensitization					
Specific IgE (kU/L), median (IQR)	0.01 (0.01-0.02)	0.02 (0.01-0.13)	0.55 (0.11-4.42)	8.0 (2.11-20.2)	<.001
SPT 0 mm, median (IQR)	0 (0-0)	0 (0-0)	2.0 (2.0-3.0)	7.5 (6.0-9.0)	<.001

The groups are defined in the Statistical analysis section.
IQR, Interquartile range.
**P* values are trend tests across groups.
†Subjects with origins in the Indian subcontinent.
‡Definitions are shown in the Methods section.

II to IV, with rates increasing as one moves from group I to group IV (see the Results section and Fig E4 and Table E2 in this article's Online Repository at www.jacionline.org).

Association of eczema and sensitization

Screened subjects were split into 3 levels of severity based on SCORAD scores at screening (see Tables E6 and E7 in this article's Online Repository at www.jacionline.org). As eczema severity increases, so does the corresponding rate of cutaneous sensitization to peanut, hen's egg, and sesame, with 76.0% of screened infants in the highest SCORAD category having a positive SPT response to any food (see Table E6 in this article's Online Repository at www.jacionline.org). A similar pattern was seen for specific IgE sensitization (Fig 2, *C* and see Table E7 in this article's Online Repository at www.jacionline.org).

Predictors of sensitization to peanut in infancy

Egg allergy, sex, race, severe eczema, duration of eczema, and percentage eosinophilia were assessed for association with sensitization to peanut defined either by peanut-specific IgE levels or SPT responses. Logistic regression models were then fitted with all available data. No imputation was performed. Table II presents unadjusted and adjusted estimates for predictors of specific IgE sensitization. Table III presents these estimates for sensitization measured by SPT response, comparing the 1- to 4-mm and greater than 4-mm categories with the reference 0-mm category. These categories are consistent with the use of SPTs for stratification (0 or 1-4 mm) and exclusion from the LEAP study (>4 mm).

For egg allergy and severe eczema, there were strong and significant associations with sensitization in unadjusted models (Tables II and III). These findings confirm the utility of these clinical variables for the selection of patients at high risk for sensitization without the need for laboratory assessments. These variables retain their significant associations with specific IgE sensitization after adjustment for all variables (Table II) and similarly for SPTs with adjustment for all variables except peanut-specific IgE level (Table III). Peanut-specific IgE levels and SPT responses were highly correlated (Tables II and III); when specific IgE levels were taken into account, egg allergy and eczema lost their independent predictive value for sensitization by SPT (Table III). Duration of eczema was moderately associated with sensitization, as assessed by using both measures.

Black race is strikingly associated with sensitization measured based on peanut-specific IgE levels, with an odds ratio (OR) of 4.26 (95% CI, 2.49-7.29; Table II); this association was similar after adjustment for all variables except SPT response (OR, 5.30; 95% CI, 2.85-9.86). Similar results (not shown) were obtained when the peanut-specific IgE level was treated as a continuous rather than dichotomous outcome. In line with the association between black race and sensitization based on specific IgE levels, Fig 3 shows that black participants had significantly higher

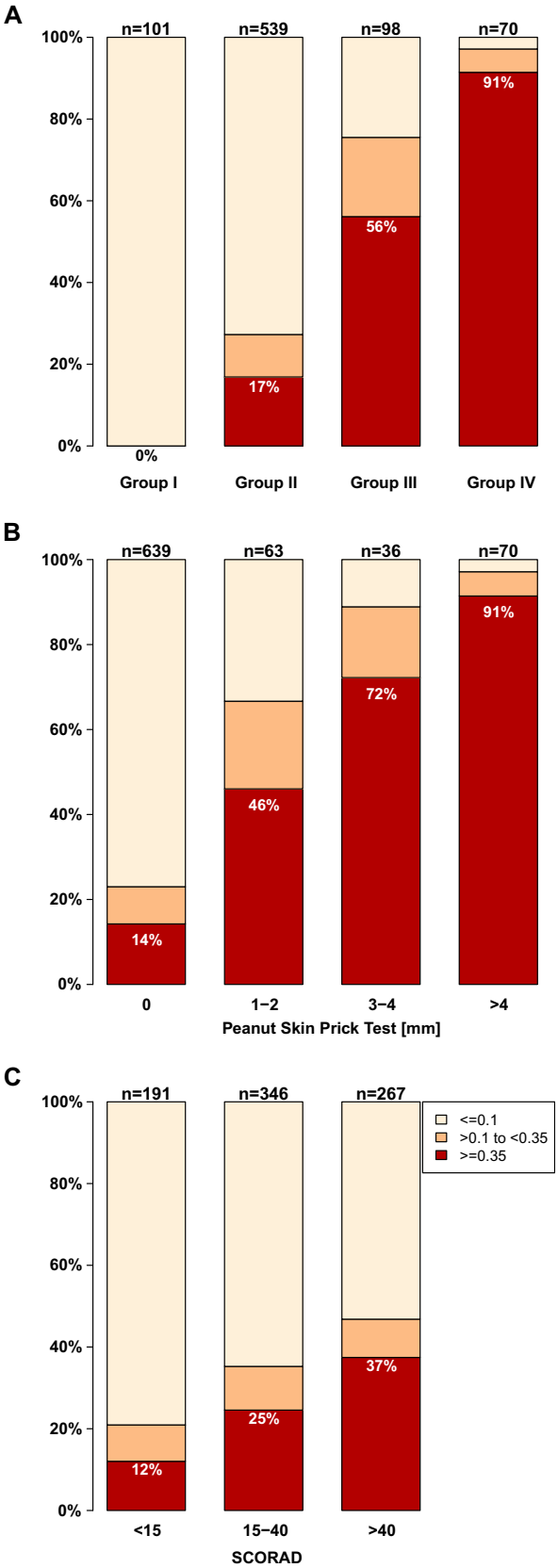

FIG 2. Peanut-specific IgE levels by group **(A)**, SPT responses **(B)**, and SCORAD scores **(C)**. Each *bar* represents the percentage of infants in each range of peanut-specific IgE level. Numbers within *bars* represent the percentage of participants in each group with IgE values at or above 0.35 kU/L.

TABLE II. OR estimates (95% CIs) for predictors of peanut-specific IgE comparing 0.35 kU/L or greater to less than 0.35 kU/L

Variable	Unadjusted	Adjusted for all variables except peanut SPT response	Adjusted for all variables including peanut SPT response
Female (yes vs no)	0.81 (0.58-1.14)	0.82 (0.56-1.19)	0.72 (0.46-1.12)
Race (black vs white)	4.26 (2.49-7.29)	5.30 (2.85-9.86)	7.13 (3.58-14.21)
Egg allergy (yes vs no)	5.97 (3.87-9.21)	4.67 (2.95-7.40)	4.08 (2.45-6.82)
Duration of eczema (quarters)	1.40 (1.10-1.78)	1.31 (0.99-1.75)	1.02 (0.73-1.42)
Severe eczema (yes vs no)	4.35 (2.35-8.06)	3.21 (1.65-6.25)	2.23 (1.09-4.57)
Eosinophilia percentage	1.16 (1.11-1.22)	1.11 (1.06-1.17)	1.12 (1.06-1.18)
Peanut SPT-induced wheal, 1-4 mm (vs 0 mm)	7.35 (4.64-11.64)	—	6.69 (3.97-11.28)
Peanut SPT-induced wheal >4 mm (vs 0 mm)	55.02 (21.30-142.13)	—	51.96 (18.88-142.97)

TABLE III. OR estimates (95% CIs) for predictors of skin test–induced wheal sizes in models comparing 1- to 4-mm and greater than 4-mm wheals with 0-mm wheals

	Unadjusted		Adjusted for all variables except peanut-specific IgE level		Adjusted for all variables including peanut-specific IgE level	
Variable	1-4 vs 0 mm	>4 vs 0 mm	1-4 vs 0 mm	>4 vs 0 mm	1-4 vs 0 mm	>4 vs 0 mm
Female sex (yes vs no)	0.89 (0.57-1.38)	1.29 (0.73-2.27)	0.93 (0.59-1.46)	1.38 (0.76-2.51)	1.06 (0.64-1.75)	2.43 (1.03-5.76)
Race (black vs white)	0.82 (0.34-1.98)	1.83 (0.77-4.33)	0.79 (0.32-1.96)	1.87 (0.75-4.70)	0.26 (0.09-0.72)	0.15 (0.04-0.61)
Egg allergy (yes vs no)	2.86 (1.74-4.69)	5.71 (2.54-12.87)	2.31 (1.39-3.86)	4.03 (2.00-10.57)	1.10 (0.62-1.97)	1.12 (0.36-3.51)
Duration of eczema (quarters)	1.50 (1.09-2.05)	2.29 (1.50-3.50)	1.38 (0.98-1.93)	2.05 (1.31-3.22)	1.40 (0.95-2.04)	1.79 (0.91-3.51)
Severe eczema (yes vs no)	3.07 (1.45-6.49)	14.08 (1.93-102.85)	2.47 (1.14-5.34)	12.53 (1.69-93.14)	1.72 (0.76-3.90)	8.64 (0.92-81.09)
Eosinophilia percentage	1.07 (1.02-1.12)	1.05 (0.99-1.12)	1.04 (0.99-1.09)	1.02 (0.95-1.09)	0.96 (0.91-1.03)	0.88 (0.79-0.99)
Peanut-specific IgE (kU/L), log10	3.17 (2.51-3.99)	8.19 (5.20-12.9)	—	—	3.53 (2.65-4.71)	14.55 (7.61-27.83)

median values for total IgE, peanut-specific IgE, and hen's egg white–specific IgE compared with white participants. These findings suggest that black participants might have a higher level of allergic reactivity than white participants.

Despite the significant association of black race with specific IgE levels, however, Table III shows that before adjustment, black versus white race was not significantly associated with a positive SPT response. In a model adjusted for sex, race, egg allergy, duration of eczema, severe eczema, and eosinophilia, race was also not significantly associated with SPT reactivity.

Additional adjustments to the logistic regression models were undertaken to further examine the relationship between race and sensitization based on specific IgE levels and SPT responses. After adjustment for all variables, including SPT responses, the association of black race with sensitization based on specific IgE levels did not change markedly and remained strong and significant (OR, 7.13; 95% CI, 3.58-14.21), indicating that black subjects have higher specific IgE levels even after accounting for differences in SPT responses. Strikingly, however, after adjustment for all variables, including peanut-specific IgE levels, a strong negative association emerged between black race and sensitization based on SPT responses, with an OR of 0.26 (95% CI, 0.09-0.72) for the 1- to 4-mm versus 0-mm comparison and an OR of 0.15 (95% CI, 0.04-0.61) for the greater than 4-mm versus 0-mm comparison (Table III). This means that after controlling for peanut-specific IgE levels, black race was associated with decreased SPT reactivity. Thus the fully adjusted models demonstrate that the relationship between race and sensitization by SPT response, for which black race is protective, is opposite to that between race and sensitization by specific IgE level, for which it is a risk factor. This suggests that the generally higher peanut-specific IgE levels observed in black subjects might not be associated with higher rates of clinical allergy, assuming SPT response is a more accurate predictor of clinical allergy than specific IgE level.[30] Consistent with this, Fig 4 demonstrates that among participants with high peanut-specific IgE levels, 56% of black subjects had SPT responses of 0 mm, whereas only 40% of white subjects had 0-mm results; in comparison, 41% of "other" participants have an SPT response of 0 mm, which is very similar to that seen in white participants.

DISCUSSION

An intervention needs to be directed at a population that is at high risk of PA, without having already had allergy, to successfully prevent PA. The study definition of "high risk" included egg allergy, severe eczema, or both. Our analysis demonstrates that the LEAP study recruitment strategy was able to identify an appropriate atopic population of young infants because the majority of enrolled infants had detectable peanut-specific IgE levels at screening. Our data demonstrate that the specific IgE level is a more sensitive indicator of immunologic reactivity than skin test results in infants between 4 and 11 months of age. The most important clinical risk factors for peanut sensitization based on SPT responses and specific IgE levels were egg allergy and severe eczema (Table III), thus validating the inclusion criteria and approach to the LEAP study. Black race was associated with a significantly higher risk of peanut sensitization by specific IgE level but a significantly lower risk of sensitization by SPT response.

The current study supports the concept that the specific IgE level is a more sensitive indicator of peanut sensitization than the

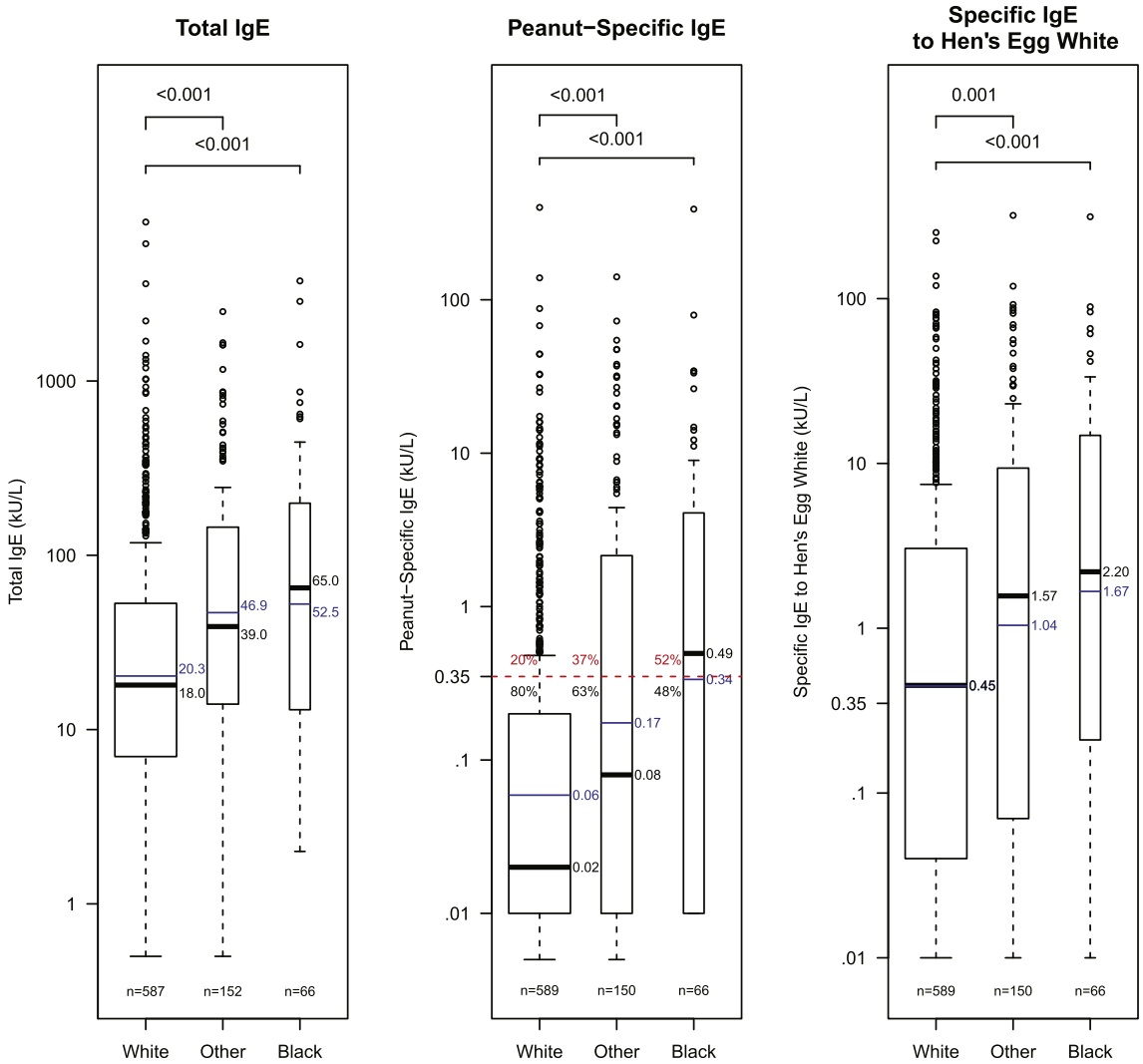

FIG 3. Total, peanut-specific, and hen's egg white–specific IgE levels compared with race. *Black lines* denote medians, and *blue lines* denote geometric means. *P* values are the Tukey HSD between categories using log-transformed values. The sensitization threshold of 0.35 kU/L and percentages greater than and less than the threshold value have been added to the peanut-specific IgE plot.

SPT response. It remains to be seen which measure or combination of measures is the better predictor of future PA. The high proportion of infants with detectable peanut-specific IgE levels (58% in group II) suggests that the process of sensitization starts in the first few months of life. For these children with pre-existing peanut-specific IgE, the strategy of oral tolerance induction evaluated in the LEAP study represents secondary rather than primary prevention of PA because the intervention is occurring after the biologic onset of the disease. We have identified many infants with large wheals and high specific IgE levels to peanut, which, together with the increasing mean age in groups I to IV (Table I), suggests that PA develops rapidly in this age group and that there is a relatively narrow age window of opportunity to intervene and prevent PA.

Eczema is thought to be an important risk factor for PA.[14] The current study confirms that severe eczema is associated with sensitization by specific IgE levels and SPT responses. As eczema increases from mild to severe, as determined by using the SCORAD score, the risk of sensitization by specific IgE level or SPT response increases more than 3-fold. We also found that duration of eczema was an important variable associated with an SPT response of greater than 4 mm. Similarly, we found that egg allergy is the most important risk factor for sensitization to peanut (Tables II and III). Egg and peanut are allergenically diverse foods, suggesting that cross-sensitization is not the explanation as it might be for the strong associations of sensitization to allergenically homologous foods, such as tree nuts.[29] The association between egg allergy and peanut sensitization is more likely due to shared risk factors for food allergy, such as severe eczema. This raises the possibility that eczema might be involved in the pathogenesis of egg allergy, as it seems to be for PA.

Our study shows that black race and the development of eosinophilia are both independent risk factors for sensitization as detected based on specific IgE levels but not SPT responses. In contrast, black race emerged as a significant protective factor for the development of sensitization defined by SPT responses.

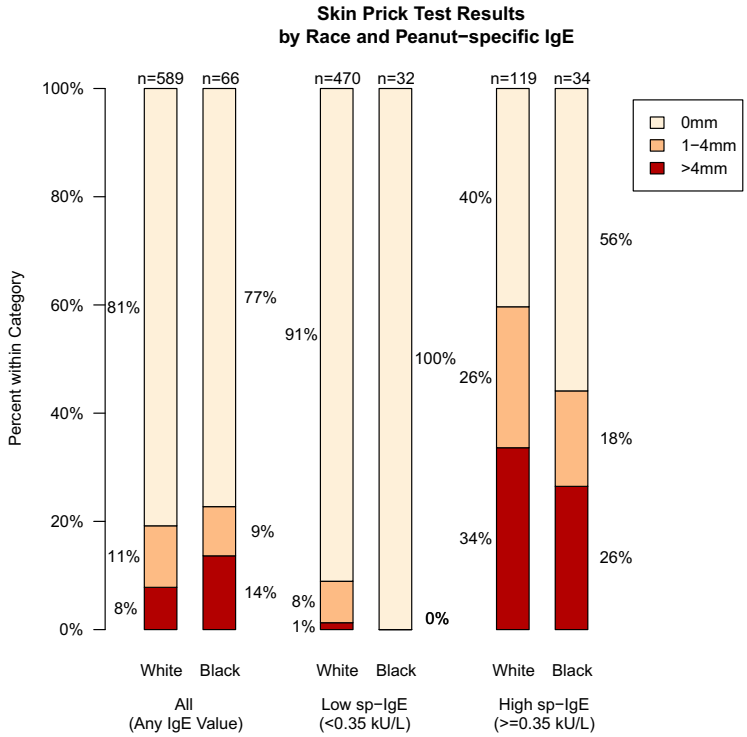

FIG 4. SPT responses stratified by race and specific IgE *(sp-IgE)* levels. Before stratification, black race appears to be associated with a higher probability of a large SPT response, but after stratifying by peanut-specific IgE level, the effect is reversed, a phenomenon known as the Simpson paradox. The relationship between SPT response and specific IgE level differs significantly by race ($P < .001$).

This poses an interesting biological paradox in which black race could potentially be associated with a higher prevalence of IgE sensitization but a lower prevalence of skin test and clinical reactivity. Two recent population studies show that American black subjects are more likely to have specific IgE sensitization to food (including peanut) and likely food allergies compared with white subjects.[3,7] Similarly Branum and Lukacs[31] found that black children were twice as likely to have detectable peanut-specific IgE levels. In contrast, the black children had the lowest rate of clinically documented food allergy in the National Health Interview Survey. These disparate findings suggest that food allergies are prevalent in the American black population yet represent an underrecognized problem.

Our findings suggest a different explanation. We demonstrate that in a population of high-risk atopic children, black race increases the risk of sensitization as measured based on specific IgE levels but is paradoxically associated with a decreased risk of sensitization to peanut, as measured based on SPT responses, and a decreased risk of likely clinical reactivity to peanut (a wheal diameter >4 mm is defined in our study as likely clinical PA at this age). This discrepancy raises important biological questions. For a given level of specific IgE, black children appear to be protected against a positive SPT response and likely clinical reactivity. We show that black children who passed the prescreening questionnaire and screened for the LEAP study are more atopic; they already make more total IgE, egg white–specific IgE, and peanut-specific IgE in the first year of life. This might reflect an evolutionary adaptation toward T_H2 responses in the face of high rates of infection with helminths. Another possibility is that IgE in black infants is directed against different allergens compared with that in white children or to different epitopes within those allergens. However, it is also possible that this difference between white and black children might not have been observed with other prescreening criteria.

These findings have important implications. First, it is not possible to estimate the prevalence of food allergy in populations of mixed race based on specific IgE levels alone. Second, the risk factors for a positive SPT response and for food allergy can differ from risk factors for specific IgE sensitization, as demonstrated by our data. Third, there are diagnostic implications for PA in the clinical setting. Our findings suggest that the same 95% positive predictive values and likelihood ratios might not be applicable to children of different racial backgrounds.[32,33] Finally, our findings raise important questions about the immunologic mechanisms of IgE sensitization as opposed to SPT sensitization and clinical reactivity.

The key limitation of this study is the lack of a clinical allergy outcome measure, such as a peanut challenge. However, there are data linking specific IgE levels and SPT responses to clinical allergy, although data are limited for infants, particularly with regard to peanuts, in whom the gold standard oral food challenge is seldom performed.[6,23-29] Data from the peanut oral food challenges performed in the LEAP study will help address this issue. We assume that the presence of at least some cutaneous reaction to peanut or, to a lesser extent, at least some level of peanut-specific IgE will be associated with a later manifestation of PA. This is biologically plausible, although we do not know of published data in the literature confirming this in a large population. Consistent with this, however, in the Australian HealthNuts study[6] 73.5% of infants with an SPT response of greater than

4 mm had challenge-proved PA (Katrina Allen, personal communication).

In conclusion, in the LEAP screening study we screened 834 infants and enrolled 640 atopic participants into the LEAP study. Even at this early age, a high proportion of children had positive peanut SPT responses, with an unexpectedly high rate of peanut-specific IgE sensitization observed even in the group with negative SPT responses, demonstrating that sensitization starts in early infancy. Our data raise questions about the previously reported higher rate of food allergy in the black population because although black participants had a higher frequency of peanut sensitization determined based on specific IgE levels and higher levels of atopy, they had less SPT response sensitivity to peanut, suggesting that they are less likely to have PA.

These early sensitization data demonstrate that our entry criteria allowed us to recruit a population with an intermediate level of sensitization. These criteria eliminated the relatively nonsensitized group I with minimal risk of allergy and also excluded the highly sensitized group IV with a likelihood of having already had allergy.

The data also indicate that the LEAP study intervention might represent a secondary prevention strategy for at least some of the enrolled infants. Follow-up for the LEAP study will be completed in 2013, when the last enrolled child reaches 60 months of age. We will then know whether the risk factors we have identified for sensitization are also risk factors for PA, as measured by using oral peanut challenges. The LEAP study will inform us of whether early consumption of peanut will successfully prevent PA.

We acknowledge the members of the LEAP study Team, including Mable Abraham, Muhsinah Adam, Michael Adamkiewicz, Tammy Amarra, Samuel Arbes, Monica Basting, Maria Rosario Caballero, Eduard Chani, Catherine Clarke, Lyn Clough, Kathryn Cockerell, Louise Coverdale, Alex Craven, Gemma Deutsch, Mary Feeney, Helen Fisher, Erica Harris, Fiona Henley, Kathryn Hersee, Saadia Hussain, Linda Irwin, Victoria Johnston, Sarah Lacey, Tom Marrs, Valerie Nelson, Lori Nirenstein, Amy Nixon, Una O'Dwyer-Leeson, Joy Panza, Alicia Parr, Deeviya Patel, Devi Patkunam, Deborah Phippard, Ewa Pietraszewicz, Audrey Plough, Jenny Romaine, Aine Sheridan, Charlotte Stedman, Alick Stephens, Asha Sudra, Ruth Towell, Natalie Witham, and Celine Wu. We also thank the participants and their families.

Clinical implications: Severe eczema and egg allergy are the strongest predictors for sensitization to peanut in infants. Many infants sensitized with specific IgE have a skin test response to peanut of 0 mm.

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METHODS

Design

The LEAP study is a single-center, randomized controlled trial enrolling children at high risk for PA. The LEAP study aims to assess whether PA can be prevented by the early introduction of peanut. Participants are randomly assigned to consume or avoid peanuts from enrollment in infancy to 60 months of age. At 60 months of age, the prevalence of PA between arms will be compared by using oral challenges.

As shown in Fig E1, participants are stratified based on the SPT responses elicited by peanut. Those with a wheal diameter of 0 mm were assigned to the SPT response–negative stratum, and those with a wheal diameter of 1, 2, 3, or 4 mm were assigned to the SPT response–positive stratum. Participants in each stratum were randomly assigned to receive a peanut-containing snack or to avoid peanut. Those assigned to receive the peanut-containing snack receive at least 2 g of peanut protein 3 times per week until they reach 60 months of age. The prevalence of PA at that time will be compared between the peanut consumption and peanut avoidance groups.

Figs E2 and E3 provide the algorithm for determination of PA. An interpretable outcome for either the double-blind, placebo-controlled food challenge or the 5-g cumulative open challenge performed in the clinic is sufficient for a determination of allergy status (Fig E2). If there is no such outcome, PA will be assessed through interpretation of dietary history, SPT-induced wheal diameters, and IgE levels (Fig E3).

Inclusion and exclusion criteria

The study inclusion criteria are (1) children aged 4 or more to less than 11 months of age who have been weaned successfully onto solids and (2) egg allergy, severe eczema, or both. Key study exclusion criteria are a peanut-induced wheal diameter of greater than 4 mm, previous consumption of peanut protein, investigator-suspected PA, and a current household member with PA.

Statistical and sample size considerations

The intent-to-treat (ITT) group comprises all randomly assigned participants who are evaluable for PA at age 60 months. The per-protocol (PP) group comprises all participants in compliance with the dietary regimen for their assigned group and evaluable for PA at age 60 months. The main analysis will evaluate participants in the ITT sample of the SPT response–negative stratum. In an additional analysis the same comparison will be made in the PP sample. It will compare the proportion of participants with PA in the peanut and avoidance arms at 60 months of age by using a 2-tailed χ^2 test at the .05 level of significance.

PA incidence in the ITT sample will also be evaluated in the SPT response–positive stratum. The PA incidence rates at 60 months of age will be compared between the 2 groups by using a 2-tailed test at the .05 level of significance. A similar analysis will be performed in the PP sample.

For participants in the SPT response–negative stratum, the null hypothesis states that there is no difference in the proportion of subjects with PA in the peanut consumption group compared with the peanut avoidance group. We assume that the true rate of PA in the peanut avoidance group is at least 9.04% and that treatment will reduce that rate to 2% or less in the peanut consumption group. This is based on observed specific IgE levels in an early group of enrolled participants and on assumptions linking specific IgE levels with development of PA. Assuming a 20% dropout rate, enrolling 271 participants in each group will provide 89% power to detect such differences between the groups by using a 2-tailed χ^2 test (without the continuity correction).

For participants in the SPT response–positive stratum, we assume the true rate of PA in the peanut avoidance group is at least 50% and that treatment will reduce that rate to 20% or less in the peanut consumption group. Assuming a 20% dropout rate, enrolling 49 participants in each group will provide 80% power to detect such differences between the groups by using a 2-tailed χ^2 test (without the continuity correction). If the true rate in the intervention group is actually 15%, 49 participants will provide 92% power.

Ethical considerations

Ethical approval for the study was provided by the NRES Committee London–Fulham, formerly West London REC2 Ethics Committee (REC Reference 04/Q0403/13). Informed consent was obtained from the parents of all children who underwent screening for the LEAP study. A Data and Safety Monitoring Board reviews study safety data on an ongoing basis.

RESULTS

Demographics of subjects recruited into the LEAP study

The infants in the LEAP screening study cohort who were enrolled in the LEAP study comprised the SPT response–negative stratum (group II) and the SPT response–positive stratum (1- to 4-mm peanut wheal, group III). The vast majority had severe eczema (89.2%), and the majority met the study definition of egg allergy (61.6%). Group II participants (n = 542) had a mean SCORAD score of 34.2 compared with 35.7 for those in group III (n = 98, see Table I in the print text). Eosinophil levels were increased in both groups. Further details can be found in Table I in the print text.

Sensitization to other foods in screened subjects

There was a high rate of SPT responses to peanut of 3 mm or greater to individual foods and a high rate of SPT responses of 3 mm or greater to multiple foods in groups II to IV (Fig E4 and Table E2). As we move across from group I to IV, there was a significant increase in the rate of cutaneous sensitization to each individual food, and in parallel there was an increase in the rate of those with SPT responses (≥3 mm) to multiple foods. Similarly, as we move across groups I to IV, there was an increase in percentage sensitization based on specific IgE levels to each food and an increase in polysensitization based on specific IgE levels to multiple foods.

No infants in group I had SPT responses to peanut of 3 mm or greater or were sensitized based on specific IgE levels and very few had SPT responses of 3 mm or greater to other foods, which is indicative of the nonatopic status of this group and consistent with their exclusion from a study aimed at a high-risk population. In contrast, many of the infants in group IV had SPT responses of 3 mm or greater or were sensitized based on specific IgE levels to other foods, which is indicative of the highly atopic status of this group.

The correlations of SPT responses and specific IgE levels between different foods (Tables E4 and E5) are generally in the low-to-moderate range (correlation coefficients ≤ 0.6). When we looked at the relationship between peanut, tree nut, and sesame based on specific IgE values (Table E5), however, we did find some selective associations with high correlation coefficients (>0.6). In addition, there was a moderate correlation between specific IgE levels for peanut and hen's egg white (0.544), which is consistent with the expectation that egg allergy is a risk factor for PA.

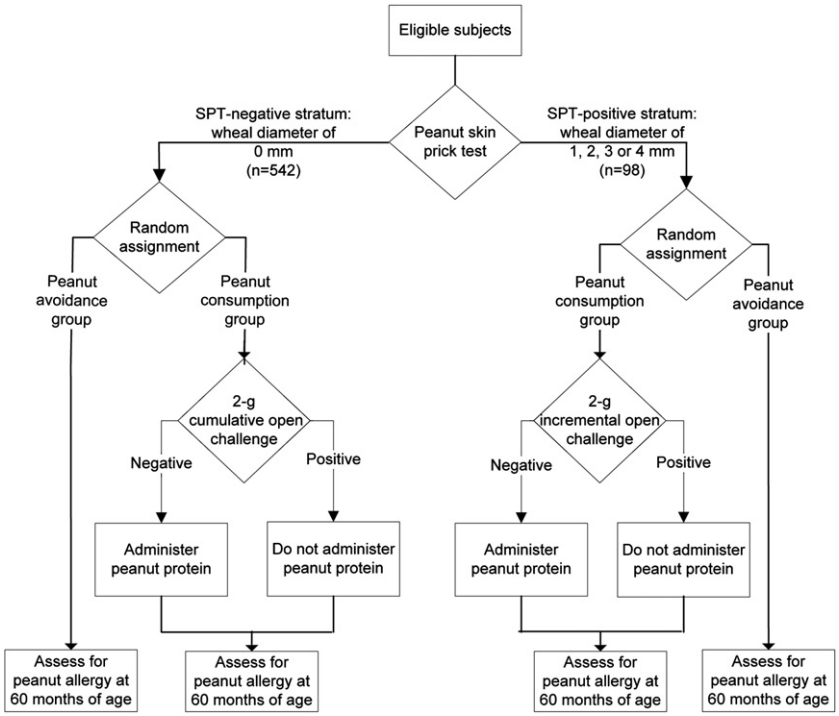

FIG E1. LEAP study design. Eligible participants were allocated to SPT response–negative or SPT response–positive strata on the basis of peanut SPT responses at screening and randomized to early or late introduction of peanuts into the diet within strata. Participants assigned to the early introduction group were first given peanut as an open challenge on the clinical trials unit. All participants will be assessed for PA at 60 months of age.

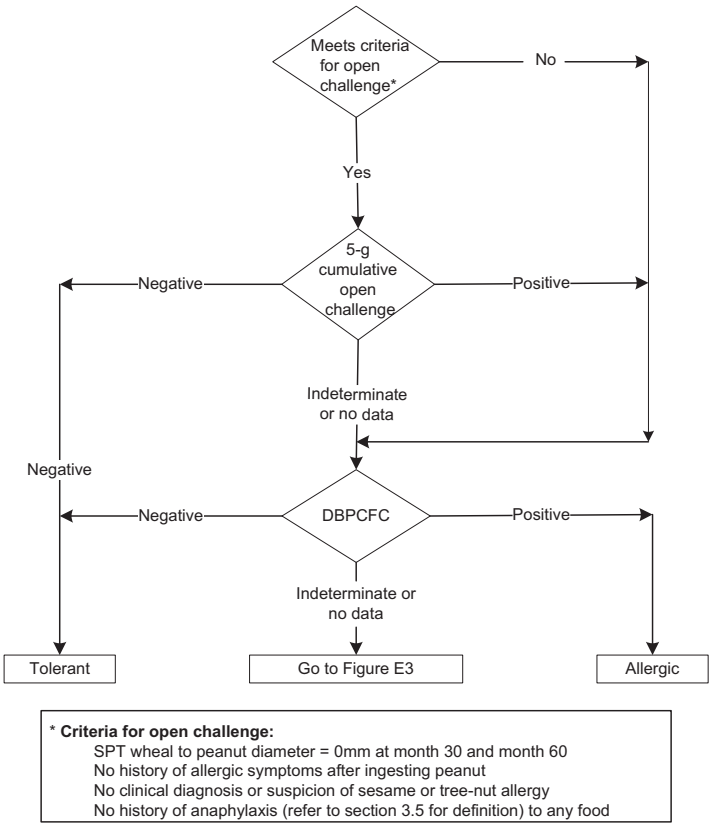

FIG E2. Determination of PA using open challenge and double-blind, placebo-controlled food challenge.

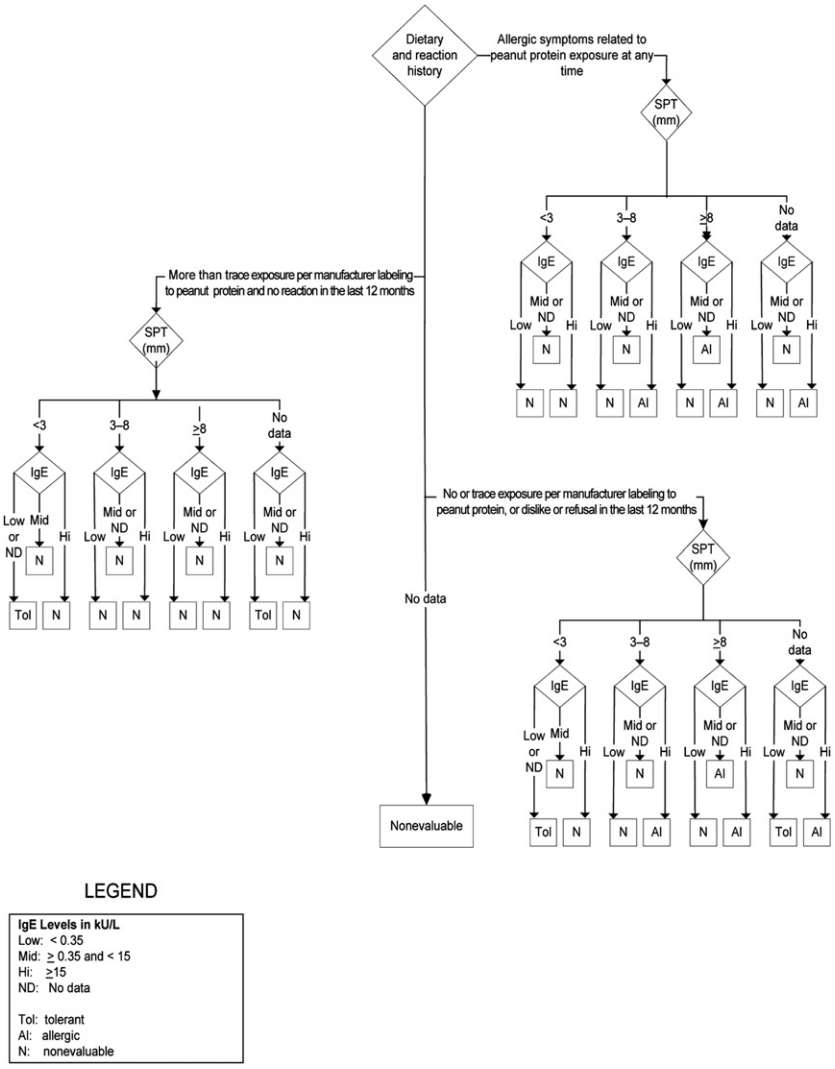

FIG E3. Determination of PA in the absence of peanut challenge results using dietary and reaction history, SPT response, and IgE level.

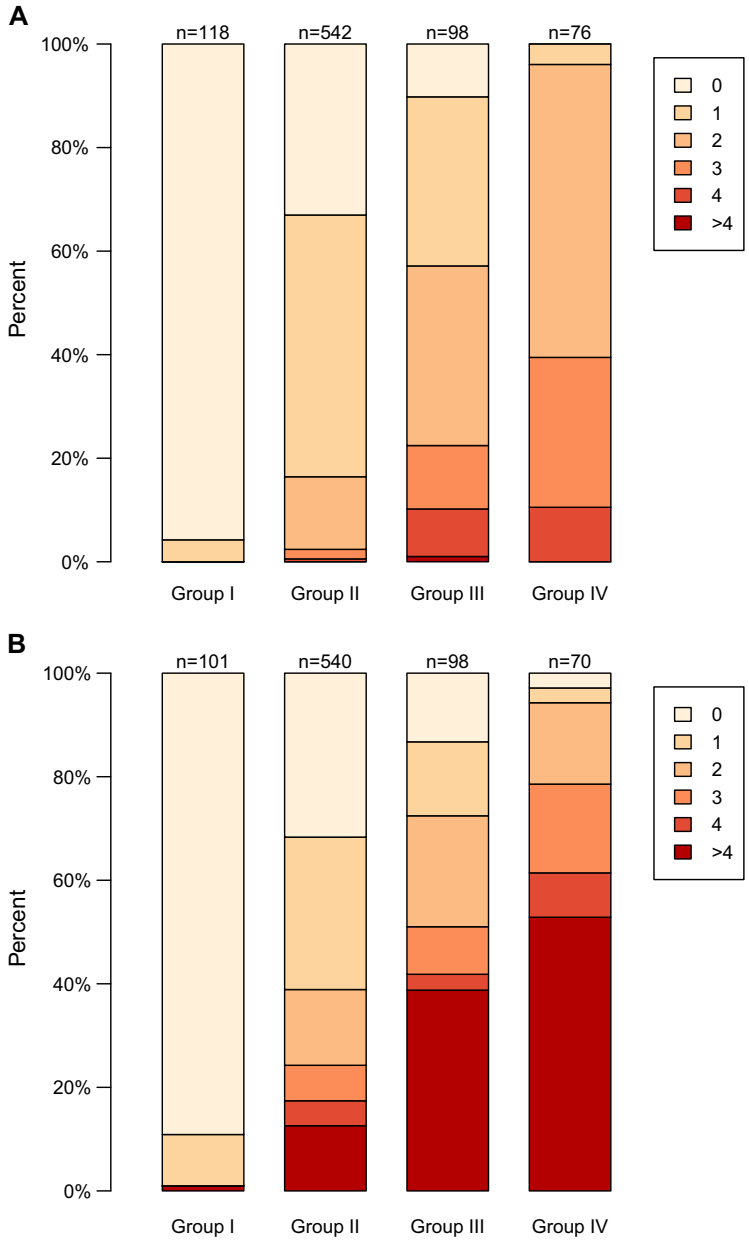

FIG E4. Five common food allergens were assessed based on SPT responses and 9 based on specific IgE levels. Each *bar* represents the percentage of infants with an increasing number of foods to which they had SPT responses of 3 mm or greater **(A)** and sensitized specific IgE levels **(B)**.

TABLE E1. SPT responses and specific IgE levels to peanut for 808 subjects in the LEAP screening study with data available for both measurements

	Specific IgE			
	<0.10 kU/L	≥0.10 to <0.35 kU/L	≥0.35 kU/L	Total
SPT				
0 mm	486	62	91	639
>0 mm	24	26	119	169
Totals	510	88	210	808

TABLE E2. Percentage of the LEAP screening study cohort by group with SPT responses of 3 mm or greater and sensitized based on specific IgE levels (≥0.35 kU/L) at baseline

	Group I (n = 118), % (no.)	Group II (n = 542), % (no.)	Group III (n = 98), % (no.)	Group IV (n = 76), % (no.)	*P* value
SPT					
Peanut	0.0	0.0	36.7 (36)	100.0 (76)	<.001
Raw hen's egg	2.5 (3)	65.3 (354)	80.6 (79)	89.5 (68)	<.001
Pasteurized hen's egg	0.8 (1)	53.9 (292)	73.5 (72)	77.6 (59)	<.001
Cow's milk	1.7 (2)	13.5 (73)	35.7 (35)	31.6 (24)	<.001
Sesame	0.0	6.1 (33)	19.4 (19)	21.1 (16)	<.001
Soya	0.0	1.5 (8)	7.1 (7)	3.9 (3)	.003
Any food allergen	4.2 (5)	67.0 (363)	89.8 (88)	100.0 (76)	<.001
No. of distinct food allergens					
0	95.8 (113)	33.0 (179)	10.2 (10)	0.0	
1	4.2 (5)	50.6 (274)	32.7 (32)	3.9 (3)	
2	0.0	14.0 (76)	34.7 (34)	56.6 (43)	
3	0.0	1.8 (10)	12.2(12)	28.9 (22)	
4	0.0	0.6 (3)	9.2 (9)	10.5 (8)	
>4	0.0	0	1.0 (1)	0	
Serum specific IgE					
Peanut	0.0	16.8 (91)	56.1 (55)	84.2 (64)	<.001
Hen's egg white	1.7 (2)	59.8 (324)	73.5 (72)	82.9 (63)	<.001
Cow's milk	6.8 (8)	28.8 (156)	46.9 (46)	51.3 (39)	<.001
Sesame	0.8 (1)	18.5 (100)	44.9 (44)	52.6 (40)	<.001
Brazil nut	0.8 (1)	12.9 (70)	32.7 (32)	46.1 (35)	<.001
Hazel nut	0.8 (1)	16.2 (88)	41.8 (41)	53.9 (41)	<.001
Cashew	1.7 (2)	17.7 (96)	39.8 (39)	50.0 (38)	<.001
Walnut	0.0	2.6 (14)	9.2 (9)	13.2 (10)	<.001
Almond	0.8 (1)	10.7 (58)	33.7 (33)	36.8 (28)	<.001
Any tree nut	1.7 (2)	22.3 (121)	48.0 (47)	60.5 (46)	<.001
Any tree nut or sesame	1.7 (2)	26.8 (145)	56.1 (55)	64.5 (49)	<.001
No. of distinct food allergens					
0	76.3 (90)	31.5 (171)	13.3 (13)	2.6 (2)	
1	8.5 (10)	29.3 (159)	14.3 (14)	2.6 (2)	
2	0.0	14.6 (79)	21.4 (21)	14.5 (11)	
3	0.0	6.8 (37)	9.2 (9)	15.8 (12)	
4	0.0	4.8 (26)	3.1 (3)	7.9 (6)	
>4	0.8 (1)	12.5 (68)	38.8 (38)	48.7 (37)	

Raw egg and pasteurized egg are treated as a single food allergen in the tabulation of multiple food allergens. *P* values are tests for trend across groups. Groups are defined in the Statistical analysis section.

TABLE E3. Percentage (number) with SPT responses of 3 mm or greater and median specific IgE levels to other food allergens by increasing peanut SPT–induced wheal sizes

	Peanut SPT–induced wheal size						*P* value
	0 mm (n = 659)	1 mm (n = 23)	2 mm (n = 40)	3 mm (n = 17)	4 mm (n = 19)	>4 mm (n = 76)	
Percent (no.) with SPT response ≥3 mm to the following allergens:							
Raw hen's egg	54.2 (357)	73.9 (17)	75.0 (30)	94.1 (16)	84.2 (16)	89.5 (68)	<.001
Pasteurized hen's egg	44.5 (293)	65.2 (15)	70.0 (28)	88.2 (15)	73.7 (14)	77.6 (59)	<.001
Cow's milk	11.4 (75)	26.1 (6)	30.0 (12)	41.2 (7)	52.6 (10)	31.6 (24)	<.001
Sesame	5.0 (33)	13.0 (3)	20.0 (8)	11.8 (2)	31.6 (6)	21.1 (16)	<.001
Soya	1.2 (8)	4.3 (1)	5.0 (2)	17.6 (3)	5.3 (1)	3.9 (3)	.005
Any food	55.8 (368)	78.3 (18)	85.0 (34)	100.0 (17)	84.2 (16)	96.1 (73)	<.001
Median specific IgE concentration (IQR) in kU/L to the following allergens:							
Peanut	0.02 (0.01-0.09)	0.33 (0.01-2.97)	0.33 (0.07-2.75)	2.35 (1.21-11.40)	1.54 (0.21-6.12)	8.00 (2.11-20.20)	<.001
Hen's egg white	0.38 (0.04-2.68)	0.64 (0.08-9.37)	3.79 (0.14-11.60)	4.74 (1.56-18.30)	1.51 (0.25-18.80)	5.63 (1.27-17.50)	<.001
Cow's milk	0.07 (0.04-0.35)	0.08 (0.04-0.89)	0.26 (0.10-1.93)	2.38 (0.23-23.50)	0.61 (0.04-22.00)	0.48 (0.09-6.07)	.017
Sesame	0.08 (0.06-0.15)	0.09 (0.07-0.86)	0.19 (0.09-1.88)	1.14 (0.09-4.76)	0.35 (0.09-4.24)	0.62 (0.09-3.51)	<.001
Brazil nut	0.01 (0.01-0.03)	0.03 (0.01-0.38)	0.02 (0.01-0.43)	0.58 (0.02-5.42)	0.13 (0.01-1.94)	0.30 (0.02-2.56)	.017
Hazel nut	0.01 (0.01-0.07)	0.09 (0.01-3.39)	0.08 (0.01-0.96)	2.17 (0.03-7.68)	0.16 (0.02-3.68)	0.66 (0.05-3.66)	<.001
Cashew	0.01 (0.01-0.07)	0.03 (0.01-0.78)	0.07 (0.01-0.79)	1.05 (0.10-16.30)	0.56 (0.04-8.79)	0.58 (0.04-5.83)	.002
Walnut	0.01 (0.01-0.01)	0.01 (0.01-0.04)	0.01 (0.01-0.05)	0.01 (0.01-0.15)	0.02 (0.01-0.03)	0.02 (0.01-0.10)	.002
Almond	0.01 (0.01-0.04)	0.03 (0.01-0.26)	0.01 (0.01-0.36)	0.58 (0.01-2.86)	0.14 (0.01-0.94)	0.21 (0.01-0.99)	<.001

P values test trends across wheal sizes.
IQR, Interquartile range.

TABLE E4. Correlation between foods for SPT responses in the LEAP screening study cohort

SPT-induced wheal size (mm)	Peanut	Raw hen's egg white	Pasteurized hen's egg white	Cow's milk	Sesame	Soya
Peanut	1.000	0.288 <.001 834	0.293 <.001 833	0.278 <.001 833	0.260 <.001 833	0.215 <.001 834
Raw hen's egg white		1.000	0.864 <.001 833	0.328 <.001 833	0.228 <.001 833	0.136 <.001 834
Pasteurized hen's egg white			1.000	0.373 <.001 832	0.265 <.001 832	0.156 <.001 833
Cow's milk				1.000	0.285 <.001 832	0.231 <.001 833
Sesame					1.000	0.111 .001 833
Soya						1.000

The table shows the Spearman correlation coefficient, *P* value for the test of correlation, and number of participants analyzed.

TABLE E5. Correlation between specific IgE levels in the LEAP screening study cohort

IgE (kU/L)	Peanut	Hen's egg white	Cow's milk	Sesame	Brazil nut	Hazel nut	Cashew	Walnut	Almond
Peanut	1.000	0.544 <.001 808	0.490 <.001 808	0.570 <.001 807	0.618 <.001 806	0.613 <.001 806	0.584 <.001 800	0.464 <.001 804	0.550 <.001 799
Hen's egg white		1.000	0.583 <.001 808	0.496 <.001 807	0.476 <.001 806	0.498 <.001 806	0.453 <.001 800	0.397 <.001 804	0.484 <.001 799
Cow's milk			1.000	0.504 <.001 808	0.479 <.001 806	0.506 <.001 806	0.465 <.001 800	0.443 <.001 805	0.486 <.001 799
Sesame				1.000	0.712 <.001 805	0.724 <.001 805	0.658 <.001 800	0.511 <.001 804	0.644 <.001 798
Brazil nut					1.000	0.804 <.001 806	0.798 <.001 800	0.559 <.001 804	0.762 <.001 799
Hazel nut						1.000	0.815 <.001 800	0.571 <.001 804	0.742 <.001 799
Cashew							1.000	0.533 <.001 799	0.696 <.001 797
Walnut								1.000	0.552 <.001 799
Almond									1.000

The table shows the Spearman correlation coefficient, *P* value for the test of correlation, and number of participants analyzed.

TABLE E6. Percentage (number) with SPT responses of 3 mm or greater to peanut and other food allergens by category of eczema severity, as measured based on SCORAD scores

	Eczema SCORAD score			
SPT allergen	**<15 (mild eczema [n = 204])**	**15-40 (moderate eczema [n = 354])**	**>40 (severe eczema [n = 271])**	***P* value**
Peanut	5.4% (11)	13.0% (46)	19.2% (52)	<.001
Raw hen's egg	46.6% (95)	59.6% (211)	72.0% (195)	<.001
Pasteurized hen's egg	40.7% (83)	50.0% (177)	59.4% (161)	<.001
Cow's milk	10.3% (21)	15.0% (53)	21.4% (58)	.001
Sesame	5.9% (12)	7.3% (26)	10.7% (29)	.062
Soya	2.0% (4)	0.8% (3)	4.1% (11)	.084
Any food	49.0% (100)	63.0% (223)	76.0% (206)	<.001

P values are tests for trends across eczema categories.

TABLE E7. Percentage (number) sensitized based on specific IgE levels to other food allergens by category of eczema severity as measured based on SCORAD scores

	SCORAD score			
IgE specific to food	**<15 (n = 204)**	**15-40 (n = 354)**	**>40 (n = 271)**	***P* value**
Peanut	11.3% (23)	24.0% (85)	36.9% (100)	<.001
Hen's egg white	39.2% (80)	54.5% (193)	68.3% (185)	<.001
Cow's milk	18.6% (38)	.9% (106)	38.4% (104)	<.001
Sesame	9.3% (19)	20.9% (74)	33.9% (92)	<.001
Brazil nut	4.4% (9)	16.1% (57)	26.6% (72)	<.001
Hazel nut	6.4% (13)	20.1% (71)	32.1% (87)	<.001
Cashew	5.9% (12)	20.3% (72)	33.6% (91)	<.001
Walnut	1.5% (3)	2.8% (10)	7.4% (20)	.001
Almond	3.9% (8)	14.4% (51)	22.5% (61)	<.001
Any food	47.5% (97)	64.1% (227)	76.0% (206)	<.001

P values are tests for trends across eczema categories.