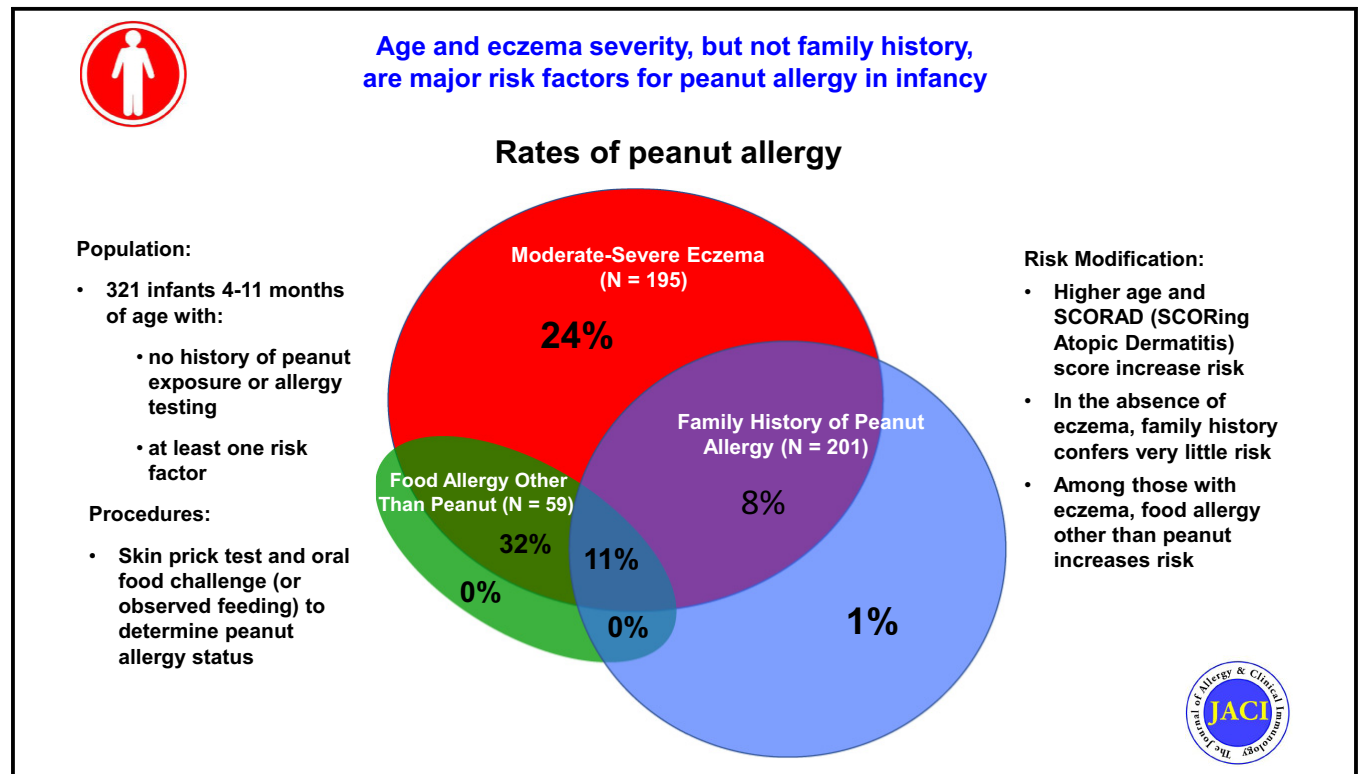


Age and eczema severity, but not family history, are major risk factors for peanut allergy in infancy

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GRAPHICAL ABSTRACT



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Background: Whether to screen high-risk groups before early peanut introduction is controversial.

Objective: We sought to determine the risk of peanut allergy (PA) before peanut introduction for infants with (1) moderate-severe eczema, (2) another food allergy (FA), and/or (3) a first-degree relative with peanut allergy (FH).

Methods: Infants aged 4 to 11 months with no history of peanut ingestion, testing, or reaction and at least 1 of the above risk factors received peanut skin prick test and, depending on skin prick test wheal size, oral food challenge or observed feeding.

Results: A total of 321 subjects completed the enrollment visit (median age, 7.2 months; 58% males); 78 had eczema only, 11 FA only, 107 FH only, and 125 had multiple risk factors. Overall, 18% of 195 with eczema, 19% of 59 with FA, and 4% of 201 with FH had PA. Only 1% of 115 with FH and no eczema had PA. Among those with eczema, older age (odds ratio [OR], 1.3; 95% CI, 1.04-1.68 per month), higher SCORing Atopic Dermatitis score (OR, 1.19; 95% CI, 1.06-1.34 per 5 points), black (OR, 5.79; 95% CI, 1.92-17.4 compared with white), or Asian race (OR, 6.98; 95% CI, 1.92-25.44) and suspected or diagnosed other FA (OR, 3.98; 95% CI, 1.62-9.80) were associated with PA.

Conclusions: PA is common in infants with moderate-severe eczema, whereas FH without eczema is not a major risk factor, suggesting screening only in those with significant eczema. Even within the first year of life, introduction at later ages is associated with a higher risk of PA among those with eczema, supporting introduction of peanut as early as possible. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

Key words: Food allergy, peanut allergy, prevention, early introduction

In 2015, the Learning Early About Peanut Allergy (LEAP) study was published, showing that introduction of peanut at age 4 to 11 months in infants with severe eczema and/or egg allergy reduced the risk of peanut allergy by more than 80% compared with peanut avoidance.¹ The LEAP study reversed previous thinking that earlier introduction of allergenic foods led to food allergy, prompting nearly immediate changes in guidelines for food introduction in infants around the world.^{2,3} Although most countries, public health authorities, and professional societies now recommend “early” introduction of peanut and, sometimes, other allergenic foods, there are many areas of controversy about how to practically implement early introduction of peanut for prevention of allergy.⁴⁻⁹ In the United States, addendum food allergy guidelines sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) were published in 2017 and followed the LEAP protocol closely in terms of target populations for implementation and screening. These guidelines recommended that in those with severe eczema, egg allergy, or both, screening with skin prick test (SPT) and/or peanut-specific IgE should be done before peanut introduction.² For infants with mild-moderate eczema, they recommended introduction without screening at around 6 months. In contrast, countries in Europe and Australasia do not generally recommend any screening before peanut introduction, and many infant feeding guidelines do not differentiate recommendations by risk factor.^{3,10-14} Whether to screen any subgroups of infants before peanut introduction is one of the major controversies surrounding early peanut introduction.

Abbreviations used

LEAP: Learning Early About Peanut Allergy
NIAID: National Institute of Allergy and Infectious Diseases
OFC: Oral food challenge
OR: Odds ratio
SCORAD: SCORing Atopic Dermatitis
SPT: Skin prick test

Although no current guidelines recommend screening children on the basis of family history alone, previous guidelines have included infants with a family history as “high-risk.”^{7,11,15} In practice, parents are often reluctant to introduce peanut when they have an older child who is peanut allergic, and providers commonly perform screening tests in these infants.^{16,17} However, the true magnitude of risk of peanut allergy in young infants with a first-degree relative with peanut allergy is unclear.^{15,18,19}

For successful implementation of earlier peanut introduction, more data are needed to inform guideline refinement and ensure buy-in across key stakeholders. The goal of this prospective cohort study was to quantify the risk of peanut allergy in infancy for 3 risk factors: moderate-severe eczema, family history of peanut allergy, and presence of another physician-diagnosed food allergy.

METHODS

Population

Infants aged 4 to 11 months were recruited to Johns Hopkins Hospital and MassGeneral Hospital for Children using social media advertisements; direct mailing to general pediatric, pediatric allergy, and dermatology practices; My-Chart letters to Johns Hopkins patients; and direct recruitment in the Pediatric Allergy and Dermatology Clinics. Inclusion criteria included no known history of peanut exposure or reaction, no history of peanut IgE or SPT testing, and at least 1 of the following risk factors:

1. Moderate-severe eczema as defined by
 - a. an objective SCORing Atopic Dermatitis (SCORAD)²⁰ score of at least 25 on present or previous evaluation, *or*
 - b. a rash that required the application of topical creams or ointments containing corticosteroids or calcineurin inhibitors and occurred on at least 7 days on 2 separate occasions, *or*
 - c. being described by the parent or guardian as having been at any time “a bad rash in joints or creases” or “a bad itchy, dry, oozing or crusted rash,”
2. physician diagnosis of food allergy other than peanut, *or*
3. a first-degree relative with a history of either a physician diagnosis of peanut allergy *or* reported history of symptoms consistent with peanut allergy.

Exclusion criteria included history of a feeding disorder that would make oral food challenge (OFC) difficult, history of eosinophilic gastrointestinal disease, and significant medical history aside from eczema, food allergy, or wheeze. Enrollment started at Johns Hopkins Hospital on December 21, 2016, and expanded to MGH on July 17, 2019. The accrual goal was 400, but because of the severe acute respiratory syndrome coronavirus 2 pandemic, enrollment was halted in March 2020 at 325 infants.

Infants were brought to the Pediatric Clinical Research Unit at either Johns Hopkins or Massachusetts General Hospital for the baseline visit, which included informed consent and screening for eligibility, physical examination with quantification of objective and total SCORAD score,²¹ SPT to peanut extract, histamine, and saline, blood draw, and, depending on the results of the SPT as outlined below, peanut observed feeding, OFC, or referral to allergy clinic with a diagnosis of peanut allergy. For logistical reasons, the observed

feeding or OFC could occur up to 2 weeks after the initial screening visit, but typically occurred on the same day. Details of the methods can be found in this article's [Methods](#) section in the Online Repository at www.jacionline.org.

Statistical analysis

The analytical data set used for this report involves only the baseline evaluations and not the outcomes assessed longitudinally until age 30 months. Study data were collected and managed using Research Electronic Data Capture (REDCap, Vanderbilt, Tenn) tools hosted at John Hopkins School of Medicine. Peanut allergy status was tabulated by risk factor, stratified into overlapping groups. Infants meeting the entry criteria for eczema were compared with infants not meeting the entry criteria using *t* test or chi-square test as appropriate to the variable of interest. Multivariable logistic regression was used to estimate associations between risk factors and peanut allergy. All models included age, race, and sex and were restricted to infants who met the inclusion criteria for eczema, hereafter called "moderate-severe eczema." SCORAD score was included as indicated, and an interaction term between age and SCORAD score was created to assess for interaction. All analyses were done using STATA 14 (College Station, Tex).

The study was funded by the NIAID as a cooperative agreement. The protocol was approved by the NIAID Division of Allergy, Immunology and Transplantation Clinical Research Committee, and the institutional review boards of Johns Hopkins School of Medicine and MassGeneral Hospital for Children (Partners institutional review board). The protocol was monitored by an NIAID-appointed Data and Safety Monitoring Board.

RESULTS

Participants

Three hundred twenty-five children were enrolled (307 at Johns Hopkins and 14 at MassGeneral Hospital for Children). Two withdrew consent before study procedures, 1 was a screen failure after consent and 1 did not complete the observed feeding and did not introduce peanut at home so could not be evaluated, leaving 321 in the analysis population: 78 with moderate-severe eczema only, 107 with family history of peanut allergy only, 11 with personal history of other food allergy only, and 125 with multiple risk factors, for a total of 195 with moderate-severe eczema, 201 with family history of peanut allergy, and 59 with a personal history of food allergy other than peanut. Of those with a first-degree relative with peanut allergy, in 164 (82%) it was a sibling who was allergic, in 33 (16%) it was the parent, and in 4 (2%) both. The mean age at evaluation was 7.2 ± 1.7 months, 58% were males, 74% white, 8% black, 7% Asian, and 12% multiracial or of other racial background. Among those with moderate-severe eczema according to the inclusion criteria, the mean objective SCORAD score was 21 ± 16 (Table I). Among those without moderate-severe eczema meeting inclusion criteria, 34% had a parental report of a history of a skin rash and 5% had a physician's diagnosis of eczema. Compared with infants without moderate-severe eczema, those with eczema were significantly older and more likely to be black or Asian (see Table E3 in this article's Online Repository at www.jacionline.org).

In addition to the 59 with physician-diagnosed nonpeanut allergy, there were 64 with suspected food allergies, for a total of 123 with either a physician-diagnosed or a suspected nonpeanut allergy (Table I). The most common nonpeanut allergies were to milk (66%), egg (23%), soy (20%), or "other" (ie, foods other than milk, egg, soy, sesame, wheat, tree nut, fish, or shellfish, 37%) (see Table E4 in this article's Online Repository at www.jacionline.org).

Prevalence of peanut allergy at first introduction by risk factor

Of 321 children included in the analysis, 69 (21%) had a positive SPT result, of whom 57 underwent OFC, and 252 (79%) had a negative SPT result, of whom all underwent observed feeding. Thirty-seven children (11% of the total) were found to be peanut allergic at the baseline visit. Of these, 25 (68%) were diagnosed by positive food challenge (22 [59%]) or observed feeding (3 [8%]), and 12 (32%) were deemed peanut allergic by SPT wheal size, including 1 with a peanut SPT size of 8.5 mm, peanut-specific IgE of 1.49 kU/L, and Ara h 2 specific IgE of 1.39 kU/L whose parents refused the food challenge. Of the 284 who were not found to be peanut allergic, 35 (12%) had negative OFC, 237 (83%) had negative observed feeding, and 12 (4%) did not consume sufficient quantity of challenge material, but introduced peanut at home without problems. As above, 1 did not consume sufficient challenge material during the observed feeding and did not introduce peanut so could not be evaluated.

In the overlapping risk factor groups, peanut allergy was diagnosed in 36 of 195 (18%; 95% CI, 13%-25%) with moderate-severe eczema, 8 of 201 (4%, 95% CI, 2%-8%) with a family history of peanut food allergy, and 11 of 59 (19%; 95% CI, 10%-31%) with another food allergy. Of 126 infants who did not meet the inclusion criteria of moderate-severe eczema (107 with family history alone, 8 with family history and food allergy other than peanut, and 11 with food allergy other than peanut), only 1 infant was determined to be peanut allergic (0.8%; 95% CI, 0.02%-4.3%) (Table II and Fig 1). Detailed descriptions of the eczema, age, family history, and food allergy status of those with peanut allergy and those without peanut allergy can be found in Table III.

Predictors of peanut allergy

Among those meeting the eczema inclusion criteria, in a multivariable model that included age, race, sex, suspected/diagnosed food allergy, and SCORAD score, the odds of peanut allergy were significantly higher for each increased month of age (odds ratio [OR], 1.3; 95% CI, 1.04-1.68; *P* = .02), for each 5-point increase in SCORAD score (OR, 1.19; 95% CI, 1.06-1.34; *P* = .003), and for black (OR, 5.79; 95% CI, 1.92-17.4; *P* = .003) or Asian race (OR, 6.98; 95% CI, 1.91-25.44; *P* = .03) compared with white race (Tables IV and V and Fig 2). As can be seen in Table IV, even moderate eczema, as defined by objective SCORAD score between 15 and 40, conferred elevated risk of peanut allergy, particularly at older ages.

Having another food allergy, whether physician diagnosed or suspected by the parents, also increased the risk of peanut allergy (OR, 2.56, 95% CI, 1.02-6.43 for physician diagnosed; OR, 3.98, 95% CI, 1.62-9.80 for suspected or diagnosed food allergy combined) in a model adjusting for race, age, sex, and SCORAD score (Table IV). Other food allergy increased risk regardless of whether the symptoms reported were immediate or nonimmediate (OR, 3.75; 95% CI, 1.47-9.58 for immediate symptoms vs OR, 5.13, 95% CI, 1.27-20.76 for only nonimmediate symptoms), and egg allergy did not increase risk compared with other foods (OR, 1.70, 95% CI, 0.56-5.13 for egg allergy vs OR, 3.20, 95% CI, 1.33-7.73 for other food allergies) (Table E4).

TABLE I. Demographic and other characteristics of the study population by risk factor

Characteristic	Overall (321)	Risk factor*		
		Moderate-severe eczema (195)	Family history (201)	FA other than peanut (59)
Age (mo), mean $\pm$ SD	7.2 $\pm$ 1.7	7.4 $\pm$ 1.7	7.0 $\pm$ 1.7	7.4 $\pm$ 1.7
Race, %				
White	74	67	75	80
Black	8	12	5	8
Asian	7	9	7	3
Multi/other	12	12	12	8
Male sex, %	58	61	54	67
Moderate-severe eczema, n (%)	195 (61)	195 (100)	86 (43)	40 (68)
Family history of peanut allergy, n (%)	200 (62)	86 (44)	201 (100)	17 (29)
Physician-diagnosed nonpeanut food allergy, n (%)	59 (18)	40 (21)	17 (9)	59 (100)
Suspected or physician-diagnosed nonpeanut food allergy, n (%)	123 (38)	88 (45)	54 (27)	59 (100)
History of suspected or physician-diagnosed nonpeanut food allergy with immediate symptoms, n (%)	91 (28)	71 (36)	34 (17)	40 (68)

*Subjects may have more than 1 risk factor.

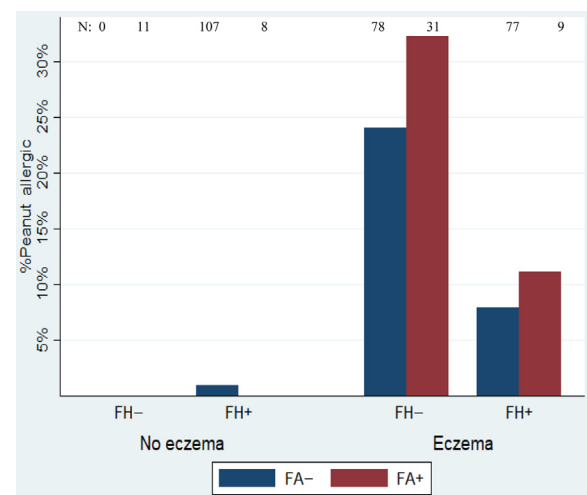
TABLE II. Peanut allergy by risk factor

Risk factor	Total N	Peanut allergic, n (%)
Overlapping groups		
Moderate-severe eczema overall (195)	195	36 (18)
Family history overall (201)	201	8 (4)
Food allergy other than peanut overall (59)	59	11 (19)
Nonoverlapping groups		
Eczema alone (79)	78	19 (24)
Eczema plus FH, no FA (77)	77	6 (8)
Eczema plus FA, no FH (31)	31	10 (32)
Eczema plus FH, plus FA (9)	9	1 (11)
FH alone (106)	107	1 (1)
FH plus FA, no eczema (8)	8	0
FA alone (11)	11	0

FA, Another (nonpeanut) food allergy; FH, family history of peanut allergy.

DISCUSSION

In this study of 321 children prospectively enrolled to understand risk factors for peanut allergy in infancy, we found that among infants with moderate-severe eczema, the rate of peanut allergy before peanut introduction was 18%. In contrast, family history of peanut allergy, in the absence of moderate-severe eczema, did not confer substantial risk. Among infants with moderate-severe eczema, older age was strongly associated with increased risk of peanut allergy, as was severity of eczema, such that the presence of peanut allergy for those with severe eczema (SCORAD score >40) who entered the study at an age older than 6 months was nearly 50%. These findings support 2 important concepts: (1) in infants with moderate-severe eczema, introducing peanut-containing foods at or after age 6 months may not be as effective in preventing peanut allergy because many of them will already be peanut allergic and (2) infants with a family history of peanut allergy, but without other risk factors, do not need to be screened for peanut allergy before peanut introduction. In infants with moderate-severe eczema, our data support introduction of peanut-containing foods before age 6 months, and guidelines that encourage providers to consider screening those with severe eczema before introduction, particularly if the infant is in later infancy.

**FIG 1.** Percent peanut allergic by risk category. *Eczema*, Moderate-severe eczema by inclusion criteria; *no eczema*, includes those with eczema who did not meet the inclusion criteria; *FA*, history of a nonpeanut food allergy diagnosed by a physician; *FH*, family history, defined as a first-degree relative with peanut allergy; *N*, total number in each group.

That close to one-fifth of infants with at least moderate eczema may already be peanut allergic at a mean of age 7 months suggests that simply following the LEAP protocol may not be sufficient to prevent peanut allergy. Compared with infants with eczema or egg allergy screened for LEAP, our cohort of infants with moderate-severe eczema were of similar age (7.4 vs 7.8 months), lower mean SCORAD score (21 vs 35 in LEAP), and similar racial distribution.²² Despite these similarities between the LEAP screening population with eczema and our population, had we applied the LEAP inclusion criteria to this study, more than twice as many infants would have been excluded from attempting early peanut introduction (24% vs 11%). In fact, our population already had a rate of peanut allergy/high sensitization similar to what the LEAP “avoiders” ended up having at age 5 years; in the LEAP study, 11% were excluded from the trial for SPT wheal size and 17% of those randomized to avoidance had peanut allergy at age 5 years, for a total of 28% with either SPT wheal size more

TABLE III. Detailed characteristics of peanut-allergic and peanut nonallergic subjects

Characteristic	Peanut nonallergic (N = 284)	Peanut allergic (N = 37)
History of skin rash	201 (70.8)	36 (97.3)
History of physician-diagnosed eczema	141 (49.7)	36 (97.3)
History of skin rash occurring at least 7 d on 2 occasions	161 (56.7)	36 (97.3)
History of skin rash described as “a bad rash in joints or creases” or “a bad, itchy, dry, oozing or crusted rash”	141 (49.7)	36 (97.3)
History of skin rash treated with medicated cream or ointment	135 (47.5)	33 (89.2)
Objective SCORAD score category		
0 (none)	76 (26.8)	1 (2.7)
1-14 (mild)	123 (43.3)	11 (29.7)
14-40 (moderate)	66 (23.2)	15 (40.5)
>40 (severe)	19 (6.7)	10 (27)
Age (mo), mean $\pm$ SD	7.2 $\pm$ 1.7	8.0 $\pm$ 1.7
First-degree relative with peanut allergy	193 (68.0)	8 (21.6)
Nonpeanut allergy in subject	48 (16.9)	11 (29.7)

Values are n (%) unless otherwise indicated.

than 4 mm at baseline or peanut allergy at 5 years, which is only slightly higher than the 26% in our population who either had an SPT wheal size more than 4 mm or were found to be peanut allergic at baseline.^{1,22} This may suggest that the LEAP study identified infants less likely to be peanut allergic than would typically be found among infants with at least moderate eczema, that we recruited a population more likely to be allergic, or that there are differences between the United Kingdom and the United States in other risk factors for peanut allergy, and thus the rate of peanut allergy. Of note, our rates of peanut allergy in infants with moderate-severe eczema are similar to those in the population-based HealthNuts study of 12- to 14-month-old infants.²³ Regardless of the reason, our findings suggest that there is a group of infants with severe eczema who are at a very high risk of peanut allergy if peanut is not introduced by the second half of the first year. In addition, even “moderate” eczema raises the risk of peanut allergy and may be an indication for testing.

It is possible that control of eczema may allow for more successful introduction of foods²⁴ and less food allergy, although interventions studied thus far have had mixed results.²⁵

Age of introduction is an area of controversy surrounding the US and international guidelines.²⁶⁻²⁸ The World Health Organization, the European Food Safety Association, and the Australasian Society of Clinical Immunology and Allergy recommend starting introduction of complementary foods around age 6 months, with the European Food Safety Association recently stating that there is no evidence that introduction before age 6 months is beneficial for allergy prevention.^{10,12-14,29} In contrast, both the NIAID-sponsored guidelines and the British Society for Allergy and

TABLE IV. Multivariable analysis of risk factors for peanut allergy among infants with moderate-severe eczema

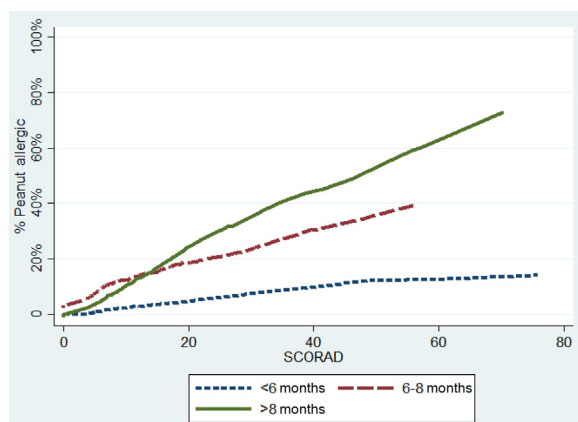
Risk factor	OR (95% CI), <i>P</i> value
Age, per month	1.3 (1.04-1.68), .02
Race,	
White	Reference
Black	5.79 (1.92-17.4), .003
Asian	6.98 (1.92-25.44), .003
Multi/other	2.09 (0.61-7.19), .24
Male sex	1.17 (0.48-2.86), .72
SCORAD score, per 5 points	1.19 (1.06-1.34), .003
Physician diagnosis of food allergy or suspected food allergy	3.98 (1.61-9.80), .003

Clinical Immunology recommend starting peanut as early as age 4 months in high-risk infants.^{2,13} Our finding that earlier age of introduction was associated with less baseline risk of allergy is in line with both the LEAP screening study, where earlier age was associated with a lower risk of SPT sensitization,^{22,28} and the Enquiring About Tolerance study,³⁰ which found a protective effect of peanut introduction before age 6 months. The accumulated evidence from these studies and the current study supports introduction of peanut before age 6 months when possible in high-risk groups, as is recommended in the United States and the United Kingdom. Pediatricians and parents should be educated on the benefits of early introduction, with the understanding that it may be difficult to introduce solid foods as early as 4 months in all infants. Although screening may be warranted for infants with severe eczema, it should not delay introduction. Additional methods of prevention of food allergy may also be required to prevent a large portion of peanut allergy.

We found a very low rate of peanut allergy among infants whose only risk factor was a family history of peanut allergy, indicating that this group does not need to be screened before peanut introduction. Of 115 children with a family history of peanut allergy but without moderate-severe eczema, only 1 child was peanut allergic. Although it is not recommended by the Peanut Allergy Prevention Guidelines, performing screening SPT or IgE testing among infants whose only risk factor is family history is common, because parents with a family history of peanut allergy may be unwilling to introduce peanut early in their child's infancy without testing.^{17,31,32} Both parental and physician fears about high sibling risk may be driven by previous small reports, which found the risk of peanut allergy in siblings to be 7% to 9%.^{15,18,19} Generally, these studies reported low rates of peanut ingestion history among siblings classified as allergic and did not verify the allergy with food challenge. Moreover, they found a much higher risk among younger siblings of the index child than among older siblings, suggesting that younger siblings may have been misdiagnosed with peanut allergy and/or had higher rates because of prolonged avoidance of peanut. In the population-based HealthNuts study, where food allergy was confirmed by OFC, the OR conferred by family history of food allergy in the study participants was low and about equal to the risk conferred by being the first-born child (OR, $\sim$ 1.3).³³ Here, we found that in the absence of moderate-severe eczema, the risk of peanut allergy with a peanut-allergic first-degree relative was less than 1%, a risk not larger than the expected baseline risk in

TABLE V. Risk of peanut allergy by age and SCORAD score category

Objective SCORAD score	Age					
	<6 mo		6-8 mo		>8 mo	
	Total N	n (%) peanut allergic	Total N	n (%) peanut allergic	Total N	n (%) peanut allergic
0 (none)	25	0 (0)	32	1 (3)	20	0 (0)
1-14 (mild)	29	0 (0)	62	8 (13)	43	3 (7)
15-40 (moderate)	21	2 (10)	36	5 (14)	24	8 (33)
>40 (severe)	10	1 (10)	11	5 (45)	8	4 (50)

**FIG 2.** Probability of peanut allergy by age and objective SCORAD score. Smoothed LOWESS curve, bandwidth(0.8).

the overall population.³⁴ Interestingly, we found that those with family history were less likely to be peanut-allergic, even adjusting for age, SCORAD score, and demographic features (data not shown). There is no clear explanation for this, but it may relate to unmeasured severity factors among those recruited with eczema. The low risk conferred by family history of peanut allergy does not mean that genetic predisposition does not play a role in peanut allergy, but instead that most genes involved may act through a shared risk of eczema,³⁵ interact with eczema susceptibility genes,³⁶ and/or manifest only with prolonged oral avoidance of peanut and/or skin exposure.³⁷ Our results should provide substantial reassurance that screening of younger siblings of peanut-allergic children before peanut introduction is not necessary.

Because we were able to identify very few infants with a previous diagnosis of another nonpeanut food allergy who did not have moderate-severe eczema, it is difficult to assess the magnitude of the risk present in infants with food allergy who do not have eczema. At the time of evaluation for early peanut introduction, many children had very little exposure to other allergenic foods, making the presence of other food allergy of limited utility as a determinative factor for identifying infants for screening or for targeted early introduction. We found no peanut allergy in the small group of infants who had other food allergy but no eczema, but our evaluation of other food allergies was by report, not by food challenge or systematic testing, and we were unable to find very many infants who had suspected food allergies but had not yet been evaluated for peanut allergy. However, among those with moderate-severe eczema, both suspected and physician's diagnosis of food allergy were associated with increased risk of peanut allergy, suggesting that those with

evidence of food allergy and eczema are a particularly high-risk group for peanut allergy. Interestingly, immediate-type symptoms and reactions to common food allergens did not seem to confer a higher risk than nonimmediate symptoms or reactions to uncommon food allergens. Furthermore, with relevance to the US guidelines, nonegg allergy conferred at least as much risk as egg allergy, raising the question of whether egg allergy should be singled out as a risk factor in current peanut allergy guidelines.²

As has been reported for food allergy in general by other studies,³⁸⁻⁴¹ we found substantially higher rates of peanut allergy among those of black or Asian race than among those of white race, even accounting for age and eczema severity. It is not fully understood why these groups may be at a higher risk of food allergy; research in this area could help better understand the mechanism of food allergy development. Prevention measures may also need to specifically address these groups.

Limitations of this analysis include the recruitment strategy, which was not a random population-based sample. To recruit a large number of high-risk infants from a population-based sample would have required a very large sample, which, in the context of the intensive screening that included food challenge, would not have been feasible. Our strategy likely identified infants whose parents may have been more concerned about peanut allergy, inflating the prevalence estimates. However, although it was not a population-based study, we did use broad recruitment methods that likely identified a large portion of those who would seek screening by their pediatrician or allergist, making the results largely generalizable to this group. Another limitation is that not all infants classified as peanut allergic were challenged, but this was because all the first 9 children with SPT wheal size more than 10 mm reacted to the food challenge. Finally, the mobile app that we used to assess the SCORAD score⁴² does not allow for percent involvement of each given body segment, so tends to overestimate overall body surface area involvement, and thus the overall SCORAD score. This should not affect the relationships calculated between degree of SCORAD score and risk of peanut allergy, but because the SCORAD score may be overestimated here, may tend to underestimate the absolute risk of peanut allergy for a given SCORAD value.

Conclusions

Our findings suggest several considerations that may inform practices about early peanut introduction. First, among infants with moderate-severe eczema, the risk of peanut allergy before peanut introduction is high and rises rapidly over the first year of life. This finding supports the recommendation that introduction of peanut should occur as soon as possible and earlier than age 6 months in high-risk infants and that physicians consider screening

infants with severe eczema before introduction, particularly if they are older than 6 months. Second, although the utility of using food allergy in the absence of eczema as a determining factor for screening is not clear, history of symptoms with other foods is associated with increased risk of peanut allergy among those with eczema, and nonegg allergies appear to confer as much risk of peanut allergy as egg allergy. Finally, infants whose only risk factor is family history of peanut allergy do not need to be screened before peanut introduction. Our study contributes to the necessary “fine tuning” that can improve early peanut introduction guidelines, but additional work is needed to optimize approaches that will combine scientific accuracy, feasibility, and public acceptance.

We acknowledge Mharlove Andre for assistance with recruitment and data collection.

Clinical implications: Introduction of peanut in infants with moderate-severe eczema should start before age 6 months. In the absence of moderate-severe eczema in an infant, family history of peanut allergy alone is not a strong risk factor for peanut allergy.

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METHODS

Skin prick testing

Skin prick testing was done with the Greer Pick, peanut extract (Greer Laboratories, Lenoir, NC), histamine, and saline-glycerin. Wheal and flare were measured, and saline-glycerin wheal size was subtracted from the peanut wheal size. Skin prick testing was done by a separate study team member, and the study personnel performing OFCs were blinded to the size of the peanut SPT wheal.

SCORAD score evaluation

SCORAD score assessment was done by a mobile application (SCORAD App V 4.0.2, Fondation Dermatite Atopique, Toulouse, France) that included standardized drawings of intensity in 3 different skin types (Caucasian, Asian, and black).^{E1}

Determination of observed feed versus OFC

If the average net peanut SPT wheal was less than 3 mm, observed feeding to peanut was done as detailed below. If the SPT wheal was at least 3 mm, open OFC to peanut was performed as detailed below. Initially, there was no upper limit to the SPT wheal size for OFC, but after the first 9 infants with SPT wheal size more than 10 mm failed the OFC, the protocol was amended with institutional review board and data safety monitoring board approval to deem infants with a peanut SPT wheal size of greater than 10 mm peanut allergic without challenge.

Observed feed/OFC

Both observed feedings and OFCs were done to a goal dose of 4 g of peanut protein using peanut powder or peanut butter (Table E1), depending on the child's developmental stage, feeding history, and parental preference. The dosing schedule was approximately that recommended by NIAID's addendum guidelines,^{E2} with the exception of an additional dose at the start of the challenge that was equivalent to ½ of the Guidelines first dose. The observed

feeding was done in a nongraduated manner, whereas the OFC was given as 6 escalating doses at 15-minute intervals. Challenges or feedings were deemed positive by the criteria outlined in Table E2. If the infant did not consume the minimum required (1.5 g of peanut protein for the observed feeding and 2.1 g for the OFC), the family was asked to return for another feeding or challenge; if they refused repeat feeding/challenge, but the child introduced peanut at home without symptoms, the child was considered nonallergic ($n = 12$). The 1 child whose parents refused repeat feeding/challenge and did not introduce peanut at home was deemed nonevaluable.

Peanut-specific IgE and components

Peanut IgE and IgE to peanut components (Ara h 1, Ara h 2, Ara h 3, and Ara h 8) were quantified by ImmunoCAP at the Johns Hopkins Dermatology, Allergy and Clinical Immunology Laboratory.

Subject disposition

If the infant was deemed not peanut allergic, the family was given recommendations in line with the NIAID-guidelines to continue peanut consumption at home with a minimum of 2 g of peanut protein 3 times a week. If the infant was deemed peanut allergic at baseline, referral to an allergist was made, avoidance instructions were given, and self-administered epinephrine prescribed. The study currently continues beyond the baseline visit and infants are followed to age 30 months.

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TABLE E1. OFC dosing protocol options

Dose	Option 1: peanut butter (tsp), (weight in grams)	Option 2: peanut butter powder weight (g)
1	1/16 tsp, (0.31)	0.17
2	1/8 tsp, (0.63)	0.34
3	¼ tsp, (1.25)	0.65
4	½ tsp, (2.5)	1.32
5	1 tsp, (5)	2.64
6	1½ tsp, (8)	4.2

tsp, Teaspoon.

TABLE E2. Criteria for positive food challenge

Major	Minor
Confluent erythematous pruritic rash	1-2 urticarial episodes
Respiratory signs (at least 1 of the following):	Single episode of vomiting
● Wheezing	
● Inability to speak (as appropriate for age)	
● Stridor	
● Dysphonia	
● Aponia	
At least 3 urticarial lesions	Diarrhea
At least 1 site of angioedema	Notably distressed because of nausea and/or abdominal pain with decreased activity
At least 2 distinct episodes of vomiting	Dry hacking cough that lasts for at least 4 min
Hypotension not associated with vasovagal episode	Persistent rubbing of nose or eyes that lasts for at least 5 min
Evidence of severe abdominal pain that persists for ≥ 5 min	Persistent rhinorrhea that lasts for at least 5 min
	Continuous, hard scratching that lasts for at least 3 min
	Distinct change in affect: whining, crying, and/or clinging to parent

TABLE E3. Demographic features by eczema status

Feature	Overall (321)	Moderate-severe eczema (195)	Nonmoderate-nonsevere eczema or no eczema (126)	<i>P</i> value for comparison
Age (mo), mean $\pm$ SD	7.2 $\pm$ 1.7	7.4 $\pm$ 1.7	6.9 $\pm$ 1.7	.01
Race, %				
White	74	67	86	<.001
Black	8	12	1	
Asian	7	9	2	
Multi/other	12	12	11	
Male sex, %	58	61	54	.2
SCORAD score, mean $\pm$ SD	14 $\pm$ 15	21 $\pm$ 16	4.1 $\pm$ 0.5	<.001

TABLE E4. Peanut allergy risk by specific food allergy (suspected or diagnosed combined)

Food	Overall number with the food allergy	n (%) with peanut allergy*
Milk	81	14 (17)
Egg	28	6 (21)
Soy	25	1 (4)
Sesame	3	1 (33)
Wheat	2	0
Tree nuts	3	0
Fish	0	0
Shellfish	0	0
Other	46	8 (17)

*Study diagnosed.

000 Age and eczema severity, but not family history, are major risk factors for peanut allergy in infancy

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In a study of 321 infants before peanut introduction, eczema was a strong risk factor for peanut allergy, but family history alone was not. Older age and more severe eczema increased risk.