Kinetics of early peanut allergy development and resolution in the EAT, LEAP, and PAS cohorts

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Background: Little is known about the development and resolution of early peanut allergy (PA).

Objective: We examined the natural history and biomarkers of PA longitudinally in 3 cohorts.

Methods: PA development was examined in the Enquiring About Tolerance (EAT), Learning Early About Peanut (LEAP), and Peanut Allergy Sensitization (PAS) cohorts. Early PA was defined by skin prick test result of >4 mm by 12 months or oral food challenge at study entry. PA was confirmed by oral food challenge at study end point (36 months for EAT, 60 months for LEAP/PAS). Four groups were defined: early PA development with persistence (EP); early PA development with resolution (ER); late PA development (LA); and never peanut allergic. Clinical characteristics and biomarkers were compared between the groups.

Results: A total of 56.3% of peanut-allergic children developed PA by 12 months; 32.1% had early PA resolution by study end point. The rate of early PA resolution was 54.2% in EAT, 41.4% in LEAP, and 18.6% in PAS cohorts. Median skin prick test wheals for EP, ER, and LA were 6, 2, and 0 mm at baseline, and 10, 0, 9 mm at study end point. Median peanut-specific IgE (sIgE) levels for EP, ER, and LA were 5.9, 0.4, and 0.3 kU_A/L ($P < .001$) at baseline; 4.7, 1.3, and 0.9 kU_A/L ($P < .001$) at 12 months; and 20.1, 0.2, and 5.1 kU_A/L ($P < .001$) at study end point. LA had slower component expansion (number of components Ara h 1–sIgE, Ara h 2–sIgE, Ara h 3–sIgE > 0.1 kU_A/L) compared to EP. ER showed component expansion from baseline to 12 months but component retraction by study end point. Absence of eczema and egg allergy, low peanut-sIgE, or skin prick test result were predictive of PA resolution.

Conclusion: A significant proportion of PA resolves in early childhood. Different phenotypes of PA display different biomarkers trajectories. (J Allergy Clin Immunol 2025;■■■: ■■■-■■■.)

Key words: *Peanut allergy, resolution, persistence, prevalence, Ara h 2, specific-IgE, skin prick test*

Peanut allergy (PA) affects 2% of children in the Western world.[1-3] The onset of peanut IgE sensitization usually occurs during infancy with symptomatic PA occurring in early childhood.[4]

In 1989, Bock and Atkins[5] looked at challenge-proven PA in children aged 2 to 14 years and reported that PA is rarely outgrown. However in 1998, Hourihane et al[6] reported an 18% PA resolution rate in preschool children with a clinical history of PA. More recently, in the HealthNuts cohort that assessed PA in a general population of children reported that 22% of children with challenge-confirmed PA at 1 year of age had outgrown their PA by 4 years of age,[7] and when followed up again at 6 years of age, one third had PA resolution.[8]

There has been increasing interest in strategies to prevent PA and reduce the risk of severe reactions for those with PA. Randomized control trials, such as the Learning Early About Peanut (LEAP) and the Enquiring About Tolerance (EAT) studies, have resulted in a change in practice regarding introducing allergenic foods to infants.[9,10] The key findings from the LEAP study were that early introduction and regular ongoing consumption of peanut resulted in 81% relative risk reduction in PA at 60 months of age compared to children who avoided peanut. One of the 6 allergenic foods introduced early in the EAT study was peanut; in the per-protocol analysis, the prevalence of PA at 36 months of age was significantly lower in those children to whom peanut was introduced early (ie, from 4 months of age) compared to those to whom it was not (0 vs 2.5%, $P = .003$).

The LEAP and EAT cohorts also reported that approximately 60% of participants with PA at study end point were allergic by the 12-month visit, according to skin prick test (SPT) wheal sizes of >4 mm, which was a SPT cutoff determined from various studies that was highly predictive of PA (80% positive predictive value).[11-15]

The aim of this study was to describe the kinetics of PA development, resolution, and persistence in the LEAP and Peanut Allergy Sensitization (PAS) (high-risk populations) and EAT (general population) cohorts using changes in peanut SPT, peanut-specific IgE

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Abbreviations used
CI: Confidence interval
EAT: Enquiring About Tolerance
EP: Early persistent group
ER: Early resolution group
LA: Late-onset group
LEAP: Learning Early About Peanut
MALT1: Mucosa-associated lymphoid tissue lymphoma translocation protein 1
NA: Never allergic group
OFC: Oral food challenge
OR: Odds ratio
PA: Peanut allergy
PAS: Peanut Allergy Sensitization
SCORAD: SCORing Atopic Dermatitis
sIgE: Specific IgE
SPT: Skin prick test

(sIgE), and peanut component-sIgE. *Staphylococcus aureus, MALT1* (mucosa-associated lymphoid tissue lymphoma translocation protein 1), and HLA-DQA1*01:02 genes have previously been shown to be associated with PA,[16,17] and their relationship with resolution and persistence of PA is described.

METHODS

Patient cohorts

Longitudinal data from the LEAP, PAS, and EAT cohorts were standardized and integrated into a single database. The LEAP screening population included participants aged between 4 and 11 months who were assessed for severe eczema, egg allergy, or both.[18] A group of 118 participants (PAS group I) did not have severe eczema and egg allergy at screening and were excluded from LEAP. Conversely, a group of 76 participants (PAS group IV) at screening had SPT > 4 mm and were deemed peanut allergic and therefore ineligible for the LEAP intervention.[18] Eligible participants with severe eczema, egg allergy, or both were enrolled onto the LEAP study and randomly assigned to either peanut consumption or peanut avoidance. The peanut consumption group underwent a baseline oral food challenge (OFC). PAS groups I and IV were assessed again at 60 months of age by OFC. The EAT study recruited exclusively breast-fed infants at 3 months of age and randomly assigned them to early introduction of 6 allergenic foods (including peanut) or to UK guidance to introduce solids at 6 month of age. The early introduction group underwent a baseline peanut OFC. Biomarker data and OFCs were performed as per the LEAP and EAT study protocols.[9,10]

Ethical considerations

Ethical approval for the LEAP study was provided by the NRES Committee London–Fulham, formerly West London REC2 Ethics Committee (REC reference 04/Q0403/13).[9] The EAT Study was approved by the St Thomas' Hospital research ethics committee (REC reference 08/H0802/93).[10] Written informed consent was obtained from all participants' parents or caregivers.

Study groups and end points

We compared participants from LEAP, PAS and EAT cohorts who fit the following criteria:

- *Early development and persistence of PA (EP):* Baseline positive OFC or peanut SPT > 4 mm (before or at 12 months of age) who at study end point (36-60 months of age) had challenge-proven PA and were not consuming peanut.
- *Early PA developers with PA resolution (ER):* Baseline positive OFC or peanut SPT > 4 mm (before or at 12 months of age) who at study end point either had negative OFC or had negative peanut SPT and were consuming peanut (consumption of ≥2 g of peanut protein in a single portion in the last month or history of ever consuming ≥2 g of peanut protein on at least 3 occasions).
- *Late PA developers (LA):* Baseline negative OFC and/or peanut SPT between 0 and 4 mm (before and at 12 months of age) who at study end point had challenge-proven PA.
- *Never peanut allergic (NA):* Baseline negative OFC and/or peanut SPT ≤ 4 mm (before and at 12 months of age) who at study end point did not have PA (negative OFC or were consuming ≥2 g of peanut protein in a single portion in the last month or history of ever consuming ≥2 g of peanut protein on at least 3 occasions, irrespective of SPT).

The definitions of the groups are mutually exclusive and are defined in greater detail in Table E1, available in the Online Repository at www.jacionline.org.

Clinical characteristics (including sex, ethnicity, eczema status determined by SCORing Atopic Dermatitis [SCORAD] scores, and egg allergy) and immunologic markers (peanut-sIgE, components [Ara h 1, Ara h 2, Ara h 3]) were compared with a focus on comparisons between PA resolution or persistence.

Statistical analysis

All statistical analyses were conducted by SAS 9.4 and JMP Pro 17 (both SAS Institute). Imputations were performed for missing baseline SPT and sIgE to Ara h 1, Ara h 2, and Ara h 3 (Table E1). A logistic regression model was used to understand how clinical characteristics and early biomarkers are associated with the natural resolution of PA. The covariates included the presence of any eczema in the first 12 months of life, egg allergy, baseline peanut SPT, and baseline peanut-sIgE.

RESULTS

Study population

A total of 2137 participants were eligible; baseline characteristics for each group are listed in Table I. A total of 7.7% (164/2137) participants were excluded from the analysis because they were not evaluated at the study's end point. Of those not evaluated at study end point, 89.6% (147/164) were unlikely to have PA and had no or mild eczema (with low SCORAD) and negative or low SPT to peanut; 10.3% (17/164) participants had baseline SPT ≥ 4 mm; these subjects are compared against the EP and ER groups in Table E2, available in the Online Repository at www.jacionline.org.

Characterization of PA phenotypes

There was a significant difference between the groups, with male subjects being more likely to have a phenotype of PA at any time point compared to female subjects. There was a higher percentage of non-White children in the groups with any phenotype of PA compared to White children (Table I). Children with PA at any time point were significantly more likely to have

TABLE I. Patient characteristics of peanut phenotype groups

Characteristic	EP (n = 76)	ER (n = 36)	LA (n = 59)	NA (n = 1802)	Total (N = 2137)	*P* value
Cohort						<.001*
EAT	11 (14.5)	13 (36.1)	11 (18.6)	1133 (62.9)	1168 (59.2)	
LEAP	17 (22.4)	12 (33.3)	47 (79.7)	552 (30.6)	628 (31.8)	
PAS	48 (63.2)	11 (30.6)	1 (1.7)	117 (6.5)	177 (9.0)	
Randomized treatment						<.001*
Avoidance	19 (25.0)	17 (47.2)	50 (84.7)	825 (45.8)	911 (46.2)	
Consumption	9 (11.8)	8 (22.2)	8 (13.6)	860 (47.7)	885 (44.9)	
NA	48 (63.2)	11 (30.6)	1 (1.7)	117 (6.5)	177 (9.0)	
Age at baseline (months)						<.001†
Mean (SD)	7.36 (2.39)	5.94 (2.44)	6.87 (2.51)	5.02 (2.37)	5.18 (2.44)	
Median	7.67	5.73	6.80	3.61	3.65	
Q1, Q3	5.75, 9.20	3.50, 8.08	4.86, 8.80	3.32, 6.60	3.32, 6.93	
Range	3.09, 10.94	3.06, 10.74	3.15, 10.97	2.96, 10.97	2.96, 10.97	
Sex						.056*
Female	25 (32.9)	13 (36.1)	22 (37.3)	826 (45.8)	886 (44.9)	
Male	51 (67.1)	23 (63.9)	37 (62.7)	976 (54.2)	1087 (55.1)	
Ethnicity						<.001*
Asian	2 (2.6)	4 (11.1)	4 (6.8)	46 (2.6)	56 (2.8)	
Black	8 (10.5)	6 (16.7)	6 (10.2)	77 (4.3)	97 (4.9)	
Chinese/other	5 (6.6)	0 (0.0)	1 (1.7)	17 (0.9)	23 (1.2)	
Mixed	12 (15.8)	2 (5.6)	12 (20.3)	182 (10.1)	208 (10.5)	
White	49 (64.5)	24 (66.7)	36 (61.0)	1480 (82.1)	1589 (80.5)	
Baseline eczema‡						<.001*
No	3 (3.9)	9 (25.0)	6 (10.2)	899 (49.9)	917 (46.5)	
Yes	73 (96.1)	27 (75.0)	53 (89.8)	902 (50.1)	1055 (53.5)	
Egg allergy at baseline						<.001*
Missing	1	1	5	85	92	
Not allergic	11 (14.7)	13 (37.1)	18 (33.3)	1339 (78.0)	1381 (73.4)	
Allergic	64 (85.3)	22 (62.9)	36 (66.7)	378 (22.0)	500 (26.6)	
SCORAD at baseline						<.001†
No.	76	36	59	1801	1972	
Mean (SD)	37.59 (19.27)	28.60 (25.12)	32.79 (23.38)	12.52 (18.25)	14.39 (19.58)	
Median	36.50	25.00	31.00	3.50	3.60	
Q1, Q3	24.55, 52.75	1.85, 48.25	12.50, 50.00	0.00, 20.50	0.00, 24.90	
Range	(0.00-81.00)	(0.00-80.50)	(0.00-82.60)	(0.00-78.50)	(0.00-82.60)	
SCORAD screening groups						<.001*
No eczema (SCORAD = 0)	3 (3.9)	9 (25.0)	6 (10.2)	899 (49.9)	917 (46.5)	
Mild eczema (0 < SCORAD < 15)	9 (11.8)	4 (11.1)	11 (18.6)	361 (20.0)	385 (19.5)	
Moderate eczema (15 ≤ SCORAD < 40)	32 (42.1)	10 (27.8)	19 (32.2)	342 (19.0)	403 (20.4)	
Severe eczema (SCORAD ≥ 40)	32 (42.1)	13 (36.1)	23 (39.0)	199 (11.0)	267 (13.5)	
SCORAD (12 months or LOCF if missing)						<.001†
No.	76	36	59	1801	1972	
Mean (SD)	32.89 (21.23)	23.49 (22.38)	22.39 (19.20)	8.60 (12.57)	10.22 (14.53)	
Median	31.00	15.25	19.50	0.00	3.60	
Q1, Q3	17.00, 52.40	0.00, 41.00	5.00, 36.00	0.00, 13.50	0.00, 16.00	
Range	0.00, 81.00	0.00, 80.50	0.00, 67.00	0.00, 69.50	0.00, 81.00	
SCORAD groups at 12 months (LOCF if missing)						<.001*
No eczema (SCORAD = 0)	7 (9.2)	10 (27.8)	8 (13.6)	905 (50.2)	930 (47.2)	
Mild eczema (0 < SCORAD < 15)	10 (13.2)	7 (19.4)	18 (30.5)	479 (26.6)	514 (26.1)	
Moderate eczema (15 ≤ SCORAD < 40)	35 (46.1)	9 (25.0)	22 (37.3)	352 (19.5)	418 (21.2)	
Severe eczema (SCORAD ≥ 40)	24 (31.6)	10 (27.8)	11 (18.6)	65 (3.6)	110 (5.6)	
Nasal or skin *Staphylococcus aureus* at any point during LEAP Study§						.026†
Missing	59	24	12	1250	1345	
Negative	3 (17.6)	5 (41.7)	21 (44.7)	290 (52.5)	319 (50.8)	
Positive	14 (82.4)	7 (58.3)	26 (55.3)	262 (47.5)	309 (49.2)	
MALT1 carrier status¶‖						<.001*
Missing	18	14	13	1231	1276	
Carrier	12 (20.7)	4 (18.2)	15 (32.6)	65 (11.4)	96 (13.8)	
Noncarrier	46 (79.3)	18 (81.8)	31 (67.4)	506 (88.6)	601 (86.2)	

(Continued)

TABLE I. *(Continued)*

Characteristic	EP (n = 76)	ER (n = 36)	LA (n = 59)	NA (n = 1802)	Total (N = 2137)	*P* value
HLA-DQA1*01:02¶‖						<.001*
Missing	67	29	20	1334	1450	
Carrier	9 (100)	3 (42.9)	14 (35.9)	139 (29.7)	165 (31.5)	
Noncarrier	0 (0)	4 (57.1)	25 (64.1)	329 (70.3)	358 (68.5)	

Data are presented as nos. (%) unless otherwise indicated.
*Chi-square test.
†Kruskal-Wallis test.
‡One subject in NA group lacked eczema outcomes (SCORAD and severity group).
§*Staphylococcus aureus* was only collected in LEAP Study at baseline and at 12, 30, and 60 months of age.
¶*MALT1* carrier data were only available for participants from LEAP and PAS study participants; HLA-DQA1*01:02 was only available in LEAP study participants.
‖Further chi-square statistical analysis was performed comparing just 3 groups (EP, ER, and LA) for both genes and for *S aureus*. For *MALT1*, $P = .278$; for HLA-DQA1*01-02, $P = .002$; and for *S aureus*, $P = .139$.

egg allergy ($P < .001$), with at least 62.9-85.3% having egg allergy at baseline compared to 22% in those with no PA. This remained true when looking at the 3 PA phenotypes: a significantly higher number of children in the EP group had egg allergy ($P = .012$) (Table I).

Children with any PA phenotype were also significantly more likely to have eczema at baseline ($P < .001$), with mean SCORAD being higher in the EP and LA groups. When comparing eczema severity, children with PA at any time point (ie, EP, ER, and LA groups) had higher SCORAD compared to those without PA ($P < .001$). Specifically, the EP had a higher percentage of participants with moderate to severe eczema at baseline and at 12 months of age.

Of the children who had PA at any time point, 65.5% (112/171) had developed PA by 12 months of age. Of the children who had diagnosed PA at the study end point (EP and LA groups), 56.3% (76/135) had developed PA by 12 months of age.

For those with any PA phenotype, 78.9% (135/171) had a PA diagnosis by the study end point (EP and LA). Of the participants who had PA by 12 months of age (groups EP and ER), 32.1% (36/112) outgrew their PA by 36-60 months of age. Seventeen participants were excluded because they were not assessed at the study end point, but on the basis of SPT ≥ 4 mm at baseline, they likely had early PA. If we assume that all had persistent PA at study end point, then the rate of resolution would be 27.9% (36/129). The rates of early PA resolution for each cohort individually were as follows: 54.2% (13/24) for EAT, 41.4% (12/29) for LEAP, and 18.6% (11/59) for PAS group IV. The clinical characteristics and biomarkers based on study cohort are shown in Tables E3 and E4, which are available in the Online Repository at www.jacionline.org.

Changes in PA biomarkers over time

Peanut biomarkers were measured over 3 time points (Table II). EP had significantly higher mean SPT at baseline, 12 months, and study end compared to the ER and LA groups, and mean SPT remained significantly higher in the EP group when intergroup analysis was performed ($P < .001$) (Fig 1). The ER group had lower mean SPT at baseline that increased at 12 months, consistent with PA diagnosis, but by study end, it had decreased to 2.1 mm, consistent with no longer having PA. This differed from the LA group, who had low baseline and 12-month SPT results, which significantly increased to 9.1 mm by study end point, consistent with a PA diagnosis.

Median peanut-sIgE levels in the EP group were significantly higher at baseline and increased across time compared to all other groups (Table II, Fig 2). A similar pattern was observed in Ara h 2–sIgE levels, suggestive of PA at 12 months and confirmed PA at study end point. The ER group's baseline peanut-sIgE level was lower than the EP group but increased at 12 months before decreasing to levels suggesting PA resolution. Median Ara h 2–sIgE levels were 0.05 kU_A/L at baseline, increased to 0.35 kU_A/L, which is consistent with PA, but then by study end dropped to 0.04, which fits with outgrowing PA. The LA group also had low levels of peanut-sIgE and Ara h 2–sIgE both at baseline and 12 months, similar to levels seen in the NA group, but increased by study end point, consistent with the pattern of later-onset PA. For those with no PA at any time point, peanut-sIgE and Ara h 2–sIgE levels remained low across time. Individual data for the ER group are shown in Table E5, available in the Online Repository at www.jacionline.org.

Peanut component spreading

The trend of *component spreading,* defined as the number of components (sIgE for Ara h 1, –2, and –3 > 0.1 kU_A/L), was also compared between the groups (Fig 3). The EP group had expansion of detectable components from baseline until the study end point. Within the ER group, the number of components >0.1 kU_A/L initially expanded from baseline to 12 months but subsequently retracted, consistent with early PA and subsequent PA resolution. Within the LA group, the number of components >0.1 kU_A/L expanded later compared to the EP and ER groups, consistent with a diagnosis of later-onset PA. There was a significant difference in component spreading between the groups at 12 months and study end point ($P < .001$) (Table II). For the NA group, over 90% had no components >0.1 kU_A/L at each time point.

Staphylococcus aureus colonization

Staphylococcus aureus colonization at any point during the study duration was significantly different between the 4 groups ($P = .026$) and in the 3 PA group comparison ($P = .139$) (see Table I). A total of 82.4% of the EP group, 58.3% of the ER group, 55.3% of the LA group, and 47.5% of the NA group were colonized with *S aureus* with presence of eczema taken into account (see Fig E1 in the Online Repository available at www.jacionline.org).

MALT1 and HLA-DQA1*01:02 carrier status

There was a higher percentage of participants who had PA at any time who were carriers of the *MALT1* gene and HLA-DQA1*01:02 allele compared to those who were never PA (Table I). There was no

TABLE II. Changes in PA biomarkers across early childhood in different PA phenotype groups

Characteristic	EP (n = 76)	ER (n = 36)	LA (n = 59)	NA (n = 1802)	Total (N = 1973)	*P* value*
Peanut SPT at baseline						<.001
No.	76	36	59	1802	1973	
Missing	0	0	0	0	0	
Median	6.00	2.00	0.00	0.00	0.00	
Q1, Q3	3.00, 9.00	0.00, 5.00	0.00, 1.00	0.00, 0.00	0.00, 0.00	
Range	0.00-12.00	0.00-8.00	0.00-4.00	0.00-4.00	0.00-12.00	
Peanut SPT at 12 months						<.001
No.	28	25	52	1611	1716	
Missing	48	11	7	191	257	
Median	8.00	5.00	1.00	0.00	0.00	
Q1, Q3	6.00, 9.00	5.00, 6.00	0.00, 3.00	0.00, 0.00	0.00, 0.00	
Range	1.00-12.00	0.00-12.00	0.00-4.00	0.00-7.00	0.00-12.00	
Peanut SPT at 36-60 months						<.001
No.	74	36	59	1721	1890	
Missing	2	0	0	81	83	
Median	10.00	0.00	9.00	0.00	0.00	
Q1, Q3	8.00, 13.00	0.00, 4.00	6.00, 11.00	0.00, 0.00	0.00, 0.00	
Range	4.00-24.00	0.00-8.00	0.00-22.00	0.00-10.00	0.00-24.00	
Peanut-sIgE at baseline						<.001
No.	70	35	59	1661	1825	
Missing	6	1	0	141	148	
Median	5.89	0.36	0.29	0.03	0.03	
Q1, Q3	0.62, 14.10	0.07, 2.21	0.04, 1.22	0.02, 0.04	0.02, 0.04	
Range	0.01-400.00	0.01-87.70	0.01-79.50	0.01-54.50	0.01-400.00	
Peanut-sIgE at 12 months						<.001
No.	25	25	52	1484	1586	
Missing	51	11	7	318	387	
Median	4.74	1.34	0.90	0.03	0.03	
Q1, Q3	1.30, 17.00	0.57, 7.78	0.29, 3.25	0.02, 0.07	0.02, 0.10	
Range	0.25-219.00	0.08-58.10	0.01-50.90	0.01-34.70	0.01-219.00	
Peanut-sIgE 36-60 at months						<.001
No.	73	35	59	1578	1745	
Missing	3	1	0	224	228	
Median	20.10	0.21	5.10	0.02	0.02	
Q1, Q3	3.11, 93.80	0.07, 1.20	1.34, 36.30	0.01, 0.06	0.01, 0.11	
Range	0.01-508.83	0.01-22.98	0.14-1736.98	0.01-64.30	0.01-1736.98	
Ara h 1–sIgE (kU_A/L) at baseline						<.001
No.	28	24	57	1650	1759	
Missing	48	12	2	152	214	
Median	0.03	0.03	0.02	0.01	0.01	
Q1, Q3	0.01, 0.41	0.01, 0.36	0.01, 0.10	0.01, 0.02	0.01, 0.02	
Range	0.01-12.60	0.01-14.30	0.01-53.70	0.01-18.40	0.01-53.70	
Ara h 1–sIgE (kU_A/L) at 12 months						<.001
No.	24	24	51	1466	1565	
Missing	52	12	8	336	408	
Median	0.23	0.10	0.10	0.01	0.01	
Q1, Q3	0.04, 4.14	0.02, 0.44	0.02, 0.39	0.01, 0.02	0.01, 0.03	
Range	0.01-39.80	0.01-11.90	0.01-14.50	0.01-12.90	0.01-39.80	
Ara h 1–sIgE (kU_A/L) at 36-60 months						<.001
No.	59	34	55	1569	1717	
Missing	17	2	4	233	256	
Median	0.32	0.02	0.22	0.01	0.01	
Q1, Q3	0.05, 15.30	0.01, 0.12	0.02, 4.05	0.01, 0.02	0.01, 0.02	
Range	0.01-279.00	0.01-4.96	0.01-503.91	0.01-9.69	0.01-503.91	
Ara h 2–sIgE (kU_A/L) at baseline						<.001
No.	28	24	58	1651	1761	
Missing	48	12	1	151	212	
Median	0.07	0.05	0.03	0.02	0.02	
Q1, Q3	0.04, 0.19	0.03, 0.08	0.01, 0.06	0.01, 0.03	0.01, 0.03	
Range	0.01-7.03	0.01-2.30	0.01-0.85	0.01-2.36	0.01-7.03	
Ara h 2–sIgE (kU_A/L) at 12 months						<.001
No.	24	24	51	1466	1565	
Missing	52	12	8	336	408	

(Continued)

TABLE II. *(Continued)*

Characteristic	EP (n = 76)	ER (n = 36)	LA (n = 59)	NA (n = 1802)	Total (N = 1973)	*P* value*
Median	1.85	0.35	0.05	0.02	0.02	
Q1, Q3	0.55, 5.49	0.08, 0.79	0.03, 0.14	0.01, 0.03	0.01, 0.04	
Range	0.04-179.00	0.01-8.96	0.01-4.03	0.01-11.40	0.01-179.00	
Ara h 2–sIgE (kU_A/L) at 36-60 months						<.001
No.	59	34	55	1569	1717	
Missing	17	2	4	233	256	
Median	8.97	0.04	1.75	0.01	0.01	
Q1, Q3	1.40, 66.10	0.01, 0.20	0.26, 22.84	0.01, 0.02	0.01, 0.03	
Range	0.01-456.00	0.01-1.24	0.01-473.26	0.01-3.38	0.01-473.26	
Ara h 3–sIgE (kU_A/L) at baseline						<.001
No.	28	24	57	1650	1759	
Missing	48	12	2	152	214	
Median	0.03	0.02	0.02	0.01	0.01	
Q1, Q3	0.02, 0.16	0.01, 0.04	0.01, 0.05	0.01, 0.02	0.01, 0.02	
Range	0.01-5.15	0.01-12.40	0.01-10.70	0.01-11.40	0.01-12.40	
Ara h 3–sIgE (kU_A/L) at 12 months						<.001
No.	24	24	51	1466	1565	
Missing	52	12	8	336	408	
Median	0.03	0.10	0.05	0.02	0.02	
Q1, Q3	0.02, 0.51	0.02, 0.17	0.02, 0.25	0.01, 0.02	0.01, 0.03	
Range	0.01-8.57	0.01-4.53	0.01-12.80	0.01-46.70	0.01-46.70	
Ara h 3–sIgE (kU_A/L) at 36-60 months						<.001
No.	58	34	55	1569	1716	
Missing	18	2	4	233	257	
Median	0.07	0.03	0.08	0.01	0.01	
Q1, Q3	0.02, 1.10	0.01, 0.20	0.02, 0.47	0.01, 0.02	0.01, 0.02	
Range	(0.01-63.50)	(0.01-4.83)	(0.01-92.10)	(0.01-20.60)	(0.01-92.10)	
No. of components >0.1 at baseline						<.001
Missing	48	12	1	151	212	
0	11 (39.3)	14 (58.3)	35 (60.3)	1558 (94.4)	1618 (91.9)	
1	9 (32.1)	5 (20.8)	16 (27.6)	62 (3.8)	92 (5.2)	
2	5 (17.9)	3 (12.5)	5 (8.6)	19 (1.2)	32 (1.8)	
3	3 (10.7)	2 (8.3)	2 (3.4)	12 (0.7)	19 (1.1)	
No. of components >0.1 at 12 months						<.001
Missing	52	12	8	336	408	
0	0 (0.0)	2 (8.3)	17 (33.3)	1327 (90.5)	1346 (86.0)	
1	12 (50.0)	9 (37.5)	17 (33.3)	78 (5.3)	116 (7.4)	
2	5 (20.8)	7 (29.2)	11 (21.6)	29 (2.0)	52 (3.3)	
3	7 (29.2)	6 (25.0)	6 (11.8)	32 (2.2)	51 (3.3)	
No. of components >0.1 at 36-60 months						<.001
Missing	17	2	4	233	256	
0	2 (3.4)	15 (44.1)	7 (12.7)	1462 (93.2)	1486 (86.5)	
1	15 (25.4)	11 (32.4)	15 (27.3)	73 (4.7)	114 (6.6)	
2	15 (25.4)	4 (11.8)	14 (25.5)	17 (1.1)	50 (2.9)	
3	27 (45.8)	4 (11.8)	19 (34.5)	17 (1.1)	67 (3.9)	

Data are presented as nos. (%) unless otherwise indicated.
*Kruskal-Wallis test.

significant difference in the *MALT1* carrier rate among the 3 different phenotypes of PA. However, the carrier rate for HLA-DQA1*01:02 in the EP group was 100%, and the 3 PA group comparison was significantly different ($P = .002$).

Logistic regression model to predict PA resolution

Two logistic regression models were fit to understand PA resolution or persistence. The first model used baseline peanut SPT, egg allergy, and eczema. A significant increase in the likelihood of PA resolution was observed for every 1 mm decrease in SPT wheal size at baseline (odds ratio [OR], 1.25; 95% confidence interval [CI], 1.08, 1.45). The likelihood of PA resolution was also higher in children without egg allergy at baseline (OR, 2.12; 95% CI, 0.76, 5.89) and without eczema at baseline (OR, 2.97; 95% CI, 0.71, 15.38) (Fig 4, *A*). Similarly, a second model was fit using baseline peanut-sIgE (log_{10}), egg allergy, and eczema. A significant increase in the likelihood of PA resolution was observed for every 1 log unit decrease in baseline peanut-sIgE (OR, 1.63; 95% CI, 1.04, 2.62). The likelihood of PA resolution was also higher in children without egg allergy at baseline (OR, 1.98; 95% CI, 0.70,5.54) and no eczema at baseline (OR, 2.67; 95% CI, 0.60,14.57) (Fig 4, *B*). From these models, we created a web-based interactive prediction tool to personalize the probability of PA persistence or resolution considering any combination of predictor values using two formulas (see

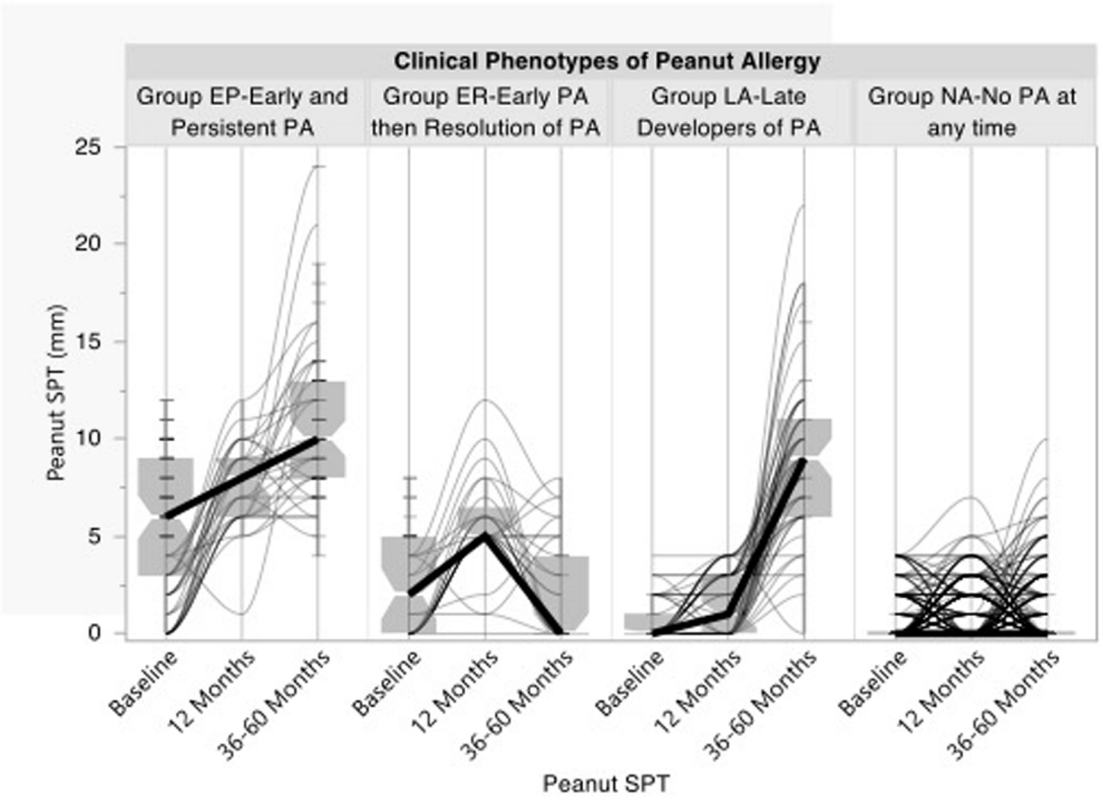

FIG 1. Individual SPT values across time by group. *Bold line* represents mean SPT across time.

Figs E2 and E3 in the Online Repository available at www.jacionline.org). Fig 4 is a static representation of the prediction tool showing the probability of PA resolution according to various risk factor combinations, including baseline levels of peanut-sIgE (Fig 4, *A*), peanut SPT (Fig 4, *B*), presence of egg allergy, and presence of eczema.

DISCUSSION

The aim of this work was to understand the development and resolution of PA in childhood in the LEAP, PAS, and EAT cohorts. We identified peanut sensitization biomarker patterns that differentiate 3 distinct PA phenotypes: those that develop early and persistent PA (EP), those that develop PA late (LA), and those that develop PA early that resolves by early childhood (ER). The EP group had biomarkers that were raised by 12 months of age and remained high at study end point that were consistent with a PA diagnosis and comparable to cutoffs for PA in the literature (ie, SPT wheal size > 6 mm and peanut Ara h 2–sIgE > 0.1 kU_A/L).[8,19,20] At baseline, the ER group had raised biomarkers that increased to levels suggestive of PA by 12 months of age, although these were lower compared to the EP group. These biomarkers then diminished over time compared to both the EP and LA groups, consistent with PA resolution, which was confirmed by peanut OFC at study end point. The LA group, who did not have a diagnosis of PA at 12 months of age, had lower biomarkers at baseline and 12 months compared to the EP and ER groups. A subsequent increase in their biomarkers seen at study end point was highly suggestive of PA, which was confirmed by positive peanut OFC. The negative biomarkers at 12 months suggest that the development of PA likely occurred after this time point—–that is, between 12 and 60 months.

Of the children who had confirmed PA at study end point, 56.3% developed it in their first year of life (EP group), and of those who had PA at any time point, 65.5% developed it in the first year of life. Consistent with the literature, we observed that male sex, presence of eczema, and egg allergy were associated with PA.[21,22]

We found that 32.1% of children who develop PA within the first 12 months of life will subsequently outgrow PA during early childhood (ER group). This is at the higher end of what has been reported in the literature.[8] Resolution may occur before the child is even evaluated for allergy and therefore may not be accounted for in the previous literature on resolution.[5,23] Even if the 17 excluded participants without study end point assessments who had baseline SPT > 4 mm suggestive of PA were counted in the analysis, the rate of PA resolution would be between 27.9% and 32.1%, which is higher than the 20% resolution rate that has previously been reported.[7,23] Only one other study has longitudinally assessed the development and resolution of PA in a normal population.[8] The HealthNuts study showed a 3.1% peak prevalence of PA at 1 year of age, with a 22% resolution rate at 4 years and a 33% resolution rate at 6 years.[8,19] However, if we looked at the rates of early PA resolution in our individual cohorts, the rates in the EAT and LEAP cohorts were higher (54.2% and 41.4%, respectively) but lower in PAS group IV (18.6%). The lower rate of PA resolution in PAS group IV may reflect earlier development of PA and higher levels of atopy (SCORAD, total peanut-sIgE, Ara h 2–sIgE) at baseline.

With this changing pattern of PA occurring early, the predictive model of resolution focused on using covariates associated with

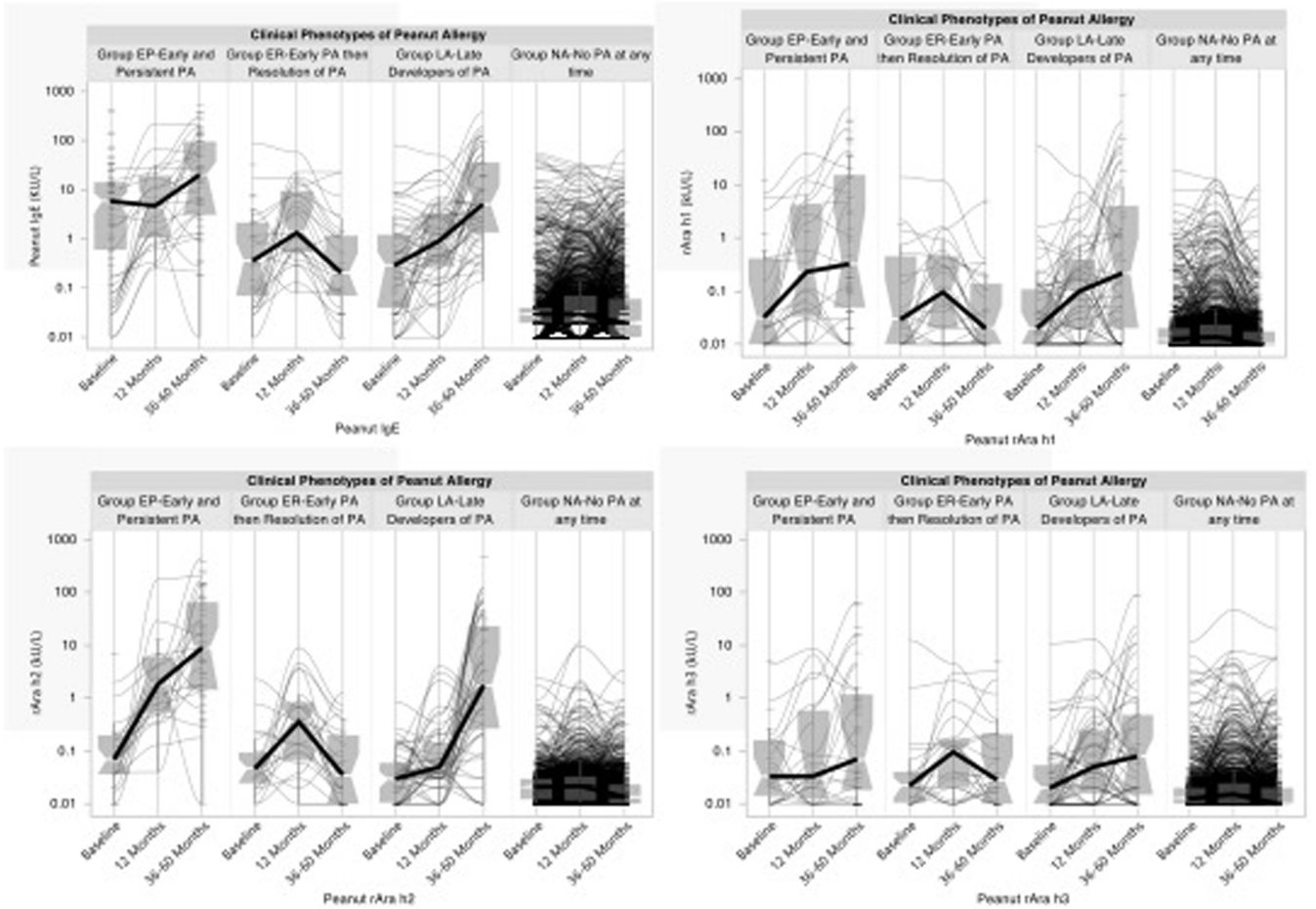

FIG 2. Individual biomarkers (peanut-sIgE, Ara h 1–sIgE, Ara h 2–sIgE, Ara h 3–sIgE) across time by group. *Bold line* represents median (sIgE and components) across time.

PA easily accessible to a wide range of clinicians. The models demonstrated that children without baseline egg allergy or eczema, low peanut SPT, and low peanut-sIgE were more likely to have PA resolution at 36-60 months of age (Fig 4). This model could be used as a clinical tool to help clinicians assess the risk of PA persistence to guide clinical decisions on when OFC, early peanut introduction, or peanut immunotherapy may be indicated.

Staphylococcus aureus colonization was significantly associated with the PA phenotypes, and although colonization was higher in those that developed early persistent PA (EP group), there was no significant difference when comparing the 3 peanut phenotype groups. Previously in the LEAP study we showed that early *S aureus* colonization was associated with persistent of eczema until age 6, persistence of egg allergy, and failure of oral tolerance induction in the peanut-consuming group. It is plausible that *S aureus* colonization initiates and maintains the PA phenotype.[20,24]

We considered genetic factors that may differentiate the 3 PA phenotypes. The *MALT1* variant, previously shown to be associated with PA in the LEAP study, did not differ significantly between the 3 PA phenotypes. The HLA-DQA1*01:02 allele, which is associated with PA in the LEAP study as well as in previous studies,[25-27] did significantly differ between the 3 PA phenotypes. Notably, 100% of the EP group were carriers of this allele, which was significantly higher than in the ER and LA groups ($P = .002$); however, sample sizes were small, as not all participants in LEAP and PAS and none in EAT had genetic data available. Nevertheless, infants with a particular HLA genotype could potentially be predisposed to both early development and persistence of PA by enhanced antigen presentation.

The key findings from the original LEAP and EAT studies have initiated a change in practice around the world for early introduction of peanut into infants' diets. The immunologic findings from the LA group, who did not have PA at baseline but were already developing it by 12 months, are perhaps those who need to be targeted as an at-risk population for early introduction and regular consumption of peanut. If children are initially seen and tested before 12 months and have negative or low biomarker results, this does not exclude the possibility of PA developing later in life. Children who have high biomarkers before age 12 months may benefit from early peanut immunotherapy. Studies found that in children who received peanut immunotherapy, being younger and having lower baseline peanut-sIgE was predictive of remission or higher response to immunotherapy, so this may be a treatment option for younger children.[28-30]

A limitation of this study was that not all those with early PA diagnosed by high baseline SPT may have had a positive OFC. Previous literature has shown that a peanut SPT wheal of ≥4 mm is

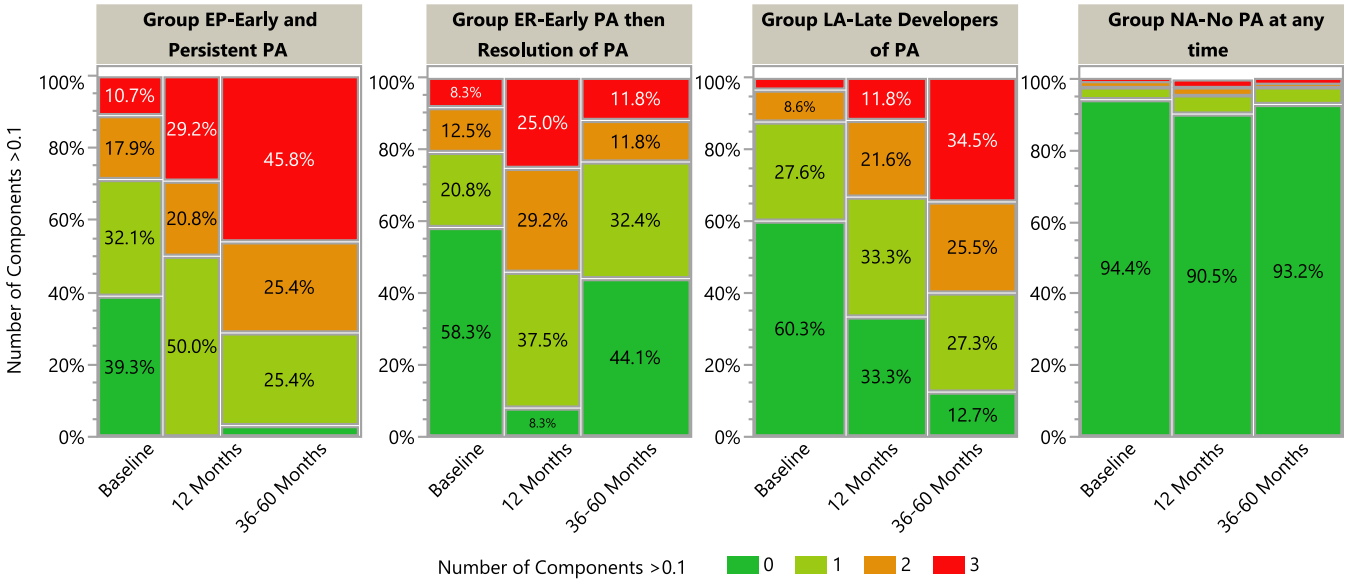

FIG 3. Proportion of Ara h 1–sIgE, Ara h 2–sIgE, and Ara h 3–sIgE components >0.1 kU_A/L at each time point for each clinical phenotype of PA.

highly predictive of challenge-proven PA at 1 year of age.[11-15] Moreover, infants with SPT > 4 mm at 12 months had a median Ara h 2–sIgE of 0.8 kU_A/L, which is highly predictive of PA. It is nevertheless possible, in the absence of challenge, that a minority of these children may not have been allergic at 12 months. There were also missing data from the PAS cohort at the 12-month time point, as these children were only seen at baseline and study end point. Additionally, a minority of participants in the NA group had biomarkers similar to those seen in the EP and ER groups. Given that 44.9% of the NA children were consuming peanut, it is possible that despite having sIgE levels that were raised, by eating peanut, they were tolerant and did not go on to develop PA. Furthermore, having data available at more time points (ie, 18 or 24 months) could have been critically important to better understand the trajectory of those who have early resolution of PA and those who develop late PA. A potential weakness is that by combining data from low- and high-risk cohorts, we could be confounding associations that would be observed within the different risk cohorts. However, Fig E4 in the Online Repository available at www.jacionline.org shows the pattern of biomarkers of the different PA phenotypes follows a similar trajectory to what we see among the risk cohorts.

Indeed, a key strength of this study is that it included children from both high-risk and low-risk populations, which is more representative of children seen in the overall population. These cohorts were derived from two large randomized controlled trials and a longitudinal observational cohort with detailed sequential follow-up over an extended period and a high retention rate. This provided us with data to study the kinetics of PA development and resolution, and we believe this is the largest group of different PA phenotypes assessed longitudinally over 3 to 5 years.

In conclusion, our study assessed the development and resolution of PA longitudinally from early infancy to 3 to 5 years of age in low- and high-risk populations, and identified and characterized unique phenotypes of PA. Better understanding of PA phenotypes may in the future help to inform clinical decision-making on peanut introduction and immunotherapy.

DISCLOSURE STATEMENT

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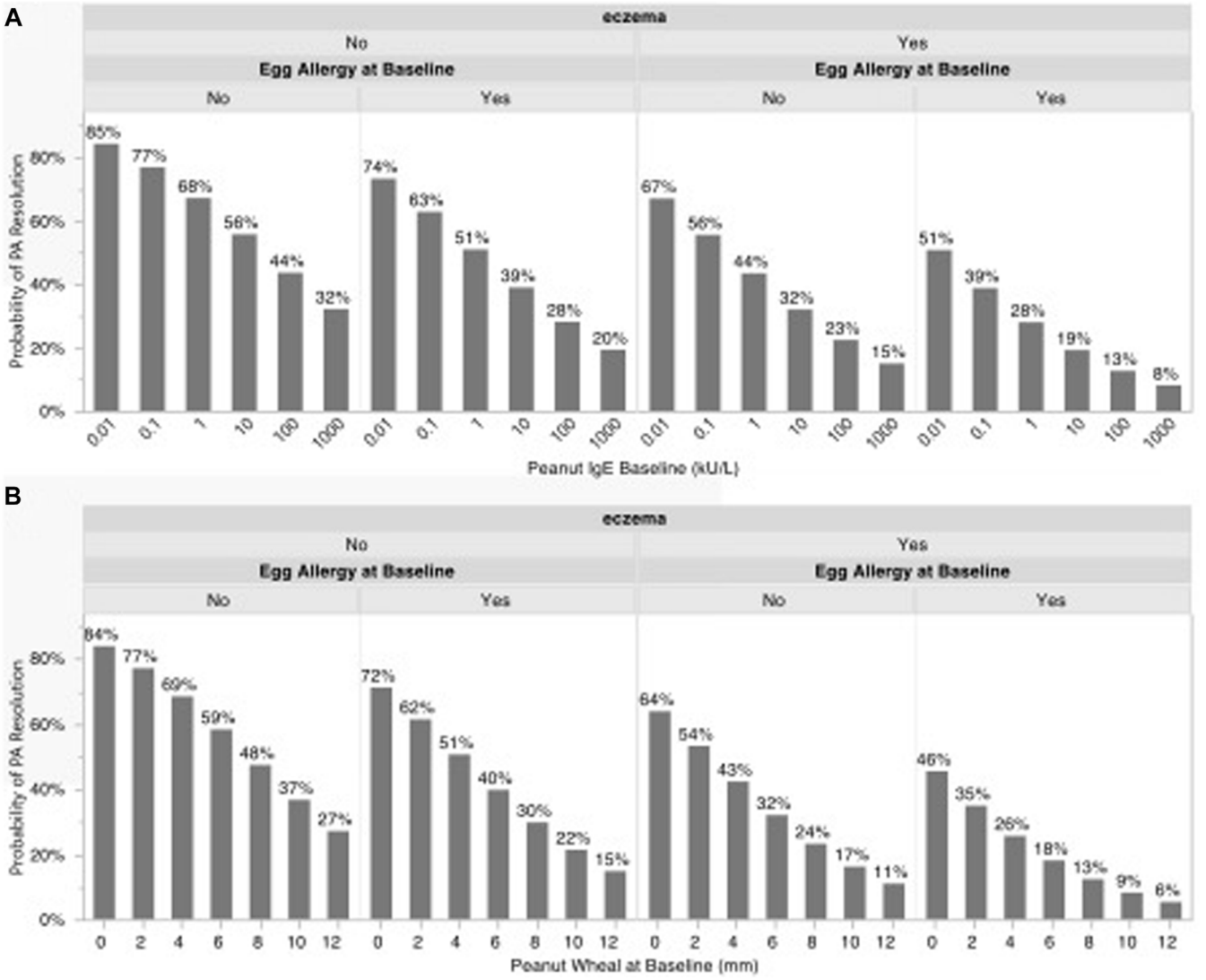

FIG 4. Predictive model demonstrating probability of PA resolution or persistence using **(A)** baseline peanut-sIgE, egg allergy, and eczema, and **(B)** baseline peanut SPT, egg allergy, and eczema.

and The Davis Foundation, during the conduct of the study; is a shareholder in DBV Technologies and Mission MightyMe; and reports personal fees from Novartis, Sanofi-Genyzme, Regeneron, ALK-Abello, and Lurie Children's Hospital, outside the submitted work. H. A. Sampson reports funding to his institution for grants from NIH/NIAID; has received consulting fees from DBV Technologies, N-Fold Therapeutics, Alpina Biotechnology, and Siolta Therapeutics unrelated to this study; and has stock options from DBV Technologies and N-Fold Therapeutics. A. F. Santos reports grants from the Medical Research Council (MR/M008517/1; MC/PC/18052; MR/T032081/1), FARE, the Immune Tolerance Network/NIH/NIAID, Asthma UK (AUK-BC-2015-01), Biotechnology and Biological Sciences Research Council, the Rosetrees Trust, and the NIHR through the Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust during the conduct of the study; personal fees from Thermo Fisher Scientific, Nutricia, Infomed, Novartis, Allergy Therapeutics, and Buhlmann; and research support from Buhlmann and Thermo Fisher Scientific through a collaboration agreement with King's College London. R. van Ree consults for HAL Allergy, Citeq, Angany, Reacta Healthcare, Mission MightyMe, and The Protein Brewery; and has equity in Angany. The rest of the authors declare that they have no relevant conflicts of interest.

Key messages

- **Distinct phenotypes of PA are identifiable through monitoring of immunologic parameters over the first years of life.**
- **Lower SPT, peanut-sIgE, and Ara h 2–sIgE levels are associated with a greater likelihood of PA resolution.**
- **A proportion of children (32.1%) develop early PA within the first 12 months of life and subsequently outgrow PA during early childhood.**

REFERENCES

1. European Academy of Allergy and Clinical Immunology (EAACI). Food allergy and anaphylaxis public declaration. 2014. Available at: https://archiv.dgaki.de/wp-content/uploads/2014/04/FoodAllergyAnaphylaxisPublicDeclarationCombined.pdf.
2. Lange L, Klimek L, Beyer K, Blumchen K, Novak N, Hamelmann E, et al. White paper on peanut allergy—part 1: epidemiology, burden of disease, health economic aspects. Allergo J Int 2021;30:261-9.
3. Spolidoro GCI, Ali MM, Amera YT, Nyassi S, Lisik D, Ioannidou A, et al. Prevalence estimates of eight big food allergies in Europe: updated systematic review and meta-analysis. Allergy 2023;78:2361-417.
4. Lack G, Fox D, Northstone K, Golding J, Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. N Engl J Med 2003;348:977-85.
5. Bock SA, Atkins FM. The natural history of peanut allergy. J Allery Clin Immunol 1989;83:900-4.
6. Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case–control study. BMJ 1998;316(7140):1271-5.
7. Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. J Allery Clin Immunol 2015;135:1257-66.e1-2.
8. Peters RL, Guarnieri I, Tang MLK, Lowe AJ, Dharmage SC, Perrett KP, et al. The natural history of peanut and egg allergy in children up to age 6 years in the HealthNuts population-based longitudinal study. J Allergy Clin Immunol 2022;150:657-65.e13.
9. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13.
10. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med 2016;374:1733-43.
11. Koplin JJ, Peters RL, Dharmage SC, Gurrin L, Tang MLK, Ponsonby AL, et al. Understanding the feasibility and implications of implementing early peanut introduction for prevention of peanut allergy. J Allery Clin Immunol 2016;138:1131-41.e2.
12. Peters RL, Allen KJ, Dharmage SC, Tang ML, Koplin JJ, Ponsonby AL, et al. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. J Allery Clin Immunol 2013;132:874-80.
13. Roberts G, Lack G. Food allergy—getting more out of your skin prick tests. Clin Exp Allergy 2000;30:1495-8.
14. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clin Exp Allergy 2000;30:1540-6.
15. Roberts G, Bahnson HT, Du Toit G, O'Rourke C, Sever ML, Brittain E, et al. Defining the window of opportunity and target populations to prevent peanut allergy. J Allery Clin Immunol 2023;151:1329-36.
16. Tsilochristou O, du Toit G, Sayre PH, Roberts G, Lawson K, Sever ML, et al. Association of *Staphylococcus aureus* colonization with food allergy occurs independently of eczema severity. J Allery Clin Immunol 2019;144:494-503.
17. Winters A, Bahnson HT, Ruczinski I, Boorgula MP, Malley C, Keramati AR, et al. The *MALT1* locus and peanut avoidance in the risk for peanut allergy. J Allery Clin Immunol 2019;143:2326-9.
18. Du Toit G, Roberts G, Sayre PH, Plaut M, Bahnson HT, Mitchell H, et al. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. J Allery Clin Immunol 2013;131:135-43.e1-12.
19. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. J Allery Clin Immunol 2017;140:145-53.e8.
20. Savinko T, Lauerma A, Lehtimaki S, Gombert M, Majuri ML, Fyhrquist-Vanni N, et al. Topical superantigen exposure induces epidermal accumulation of $CD8^+$ T cells, a mixed Th1/Th2-type dermatitis and vigorous production of IgE antibodies in the murine model of atopic dermatitis. J Immunol 2005;175:8320-6.
21. Peters RL, Allen KJ, Dharmage SC, Lodge CJ, Koplin JJ, Ponsonby AL, et al. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. Clin Exp Allergy 2015;45:953-63.
22. Sicherer SH, Wood RA, Perry TT, Jones SM, Leung DYM, Henning AK, et al. Clinical factors associated with peanut allergy in a high-risk infant cohort. Allergy 2019;74:2199-211.
23. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. J Allery Clin Immunol 2001;107:367-74.
24. Forbes-Blom E, Camberis M, Prout M, Tang SC, Le Gros G. Staphylococcal-derived superantigen enhances peanut induced Th2 responses in the skin. Clin Exp Allergy 2012;42:305-14.
25. Hong X, Hao K, Ladd-Acosta C, Hansen KD, Tsai HJ, Liu X, et al. Genome-wide association study identifies peanut allergy-specific loci and evidence of epigenetic mediation in US children. Nat Commun 2015;6:6304.
26. Martino DJ, Ashley S, Koplin J, Ellis J, Saffery R, Dharmage SC, et al. Genome-wide association study of peanut allergy reproduces association with amino acid polymorphisms in HLA-DRB1. Clin Exp Allergy 2017;47:217-23.
27. Kanchan K, Grinek S, Bahnson HT, Ruczinski I, Shankar G, Larson D, et al. HLA alleles and sustained peanut consumption promote IgG_4 responses in subjects protected from peanut allergy. J Clin Invest 2022;132:e152070.
28. Jones SM, Kim EH, Nadeau KC, Nowak-Wegrzyn A, Wood RA, Sampson HA, et al. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. Lancet 2022;399(10322):359-71.
29. Greenhawt M, Sindher SB, Wang J, O'Sullivan M, du Toit G, Kim EH, et al. Phase 3 trial of epicutaneous immunotherapy in toddlers with peanut allergy. N Engl J Med 2023;388:1755-66.
30. Kim EH, Bird JA, Keet CA, Virkud YV, Herlihy L, Ye P, et al. Desensitization and remission after peanut sublingual immunotherapy in 1- to 4-year-old peanut-allergic children: a randomized, placebo-controlled trial. J Allery Clin Immunol 2024;153:173-81.e10.