Association of *Staphylococcus aureus* colonization with food allergy occurs independently of eczema severity

Olympia Tsilochristou, MD,[a,b] George du Toit, MB, BCh, FRCPCH,[a,b,c] Peter H. Sayre, MD, PhD,[d] Graham Roberts, FRCPCH, DM,[e,f] Kaitie Lawson, MS,[g] Michelle L. Sever, MSPH, PhD,[g] Henry T. Bahnson, MPH,[h] Suzana Radulovic, MD,[a,b,c] Monica Basting, MA,[a,b,c] Marshall Plaut, MD,[i] and Gideon Lack, MB, BCh, FRCPCH,[a,b,c] for the Immune Tolerance Network Learning Early About Peanut Allergy Study Team *London, Southampton, and Isle of Wight, United Kingdom; San Francisco, Calif; Chapel Hill, NC; and Bethesda, Md*

GRAPHICAL ABSTRACT

From [a]the Peter Gorer Department of Immunobiology, School of Immunology & Microbial Sciences, and [b]the Pediatric Allergy Group, Department of Women and Children's Health, School of Life Course Sciences, King's College London; [c]the Children's Allergy Service, Guy's and St Thomas' NHS Foundation Trust, London; [d]the Division of Hematology-Oncology, Department of Medicine, University of California, San Francisco; [e]the University of Southampton and Southampton NIHR Biomedical Research Centre, Southampton, and [f]the David Hide Centre, Isle of Wight; [g]Rho Federal Systems Division, Chapel Hill; [h]the Immune Tolerance Network, San Francisco; and [i]the National Institute of Allergy and Infectious Diseases, Bethesda.

Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award numbers NO1-AI-15416, UM1AI109565, HHSN272200800029C, and UM2AI117870. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Additional support came from Food Allergy Research & Education (FARE; McLean, Va), the Medical Research Council & Asthma UK Centre, and the UK Department of Health through the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. The clinical trials unit is supported by the National Peanut Board (Atlanta, Ga). The UK Food Standards Agency provided additional support for the costs of phlebotomy. G.L. acknowledges the Davis Foundation for academic support. O.T. received a research fellowship from the Clemens von Pirquet Foundation (Geneva, Switzerland).

Disclosure of potential conflict of interest: O. Tsilochristou reports grants from the Clemens von Pirquet Foundation, Geneva, Switzerland, during the conduct of the study. G. du Toit, S. Radulovic, M. Basting, and G. Lack report grants from National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH), grants from UK Food Standards Agency (FSA), and other support from Food Allergy Research & Education (FARE), MRC & Asthma UK Centre, the UK Department of Health through the National Institute for Health Research, the National Peanut Board (NPB), and Osem. P. H. Sayre, K. Lawson, and M. L. Sever report grants from the NIAID/NIH during the conduct of the study. G. Roberts reports grants from the NIH during the conduct of the study. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 8, 2018; revised April 6, 2019; accepted for publication April 29, 2019.

Available online May 31, 2019.

Corresponding author: Gideon Lack, MB, BCh, FRCPCH, Children's Allergy Service, 2nd Floor, Stairwell B, South Wing, Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Rd, London SE1 7EH, United Kingdom. E-mail: gideon.lack@kcl.ac.uk.

0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2019.04.025

Background: *Staphylococcus aureus* has been implicated in the pathophysiology of eczema, allergic rhinitis, asthma, and food allergy. *S aureus* is a marker of more severe eczema, which is a risk factor for food sensitization/allergy. Therefore it might be that the association between *S aureus* and food allergy in eczematous patients is related to eczema severity.
Objective: We sought to investigate the association of *S aureus* colonization with specific IgE (sIgE) production to common food allergens and allergies in early childhood independent of eczema severity. We additionally determined the association of *S aureus* colonization with eczema severity and persistence.
Methods: In Learning Early About Peanut Allergy (LEAP) study participants eczema severity was assessed, and skin/nasal swabs were cultured for *S aureus*. Sensitization was identified by measuring sIgE levels. Peanut allergy was primarily determined by means of oral food challenge, and persistent egg allergy was primarily determined by using skin prick tests.
Results: Skin *S aureus* colonization was significantly associated with eczema severity across the LEAP study, whereas at 12 and 60 months of age, it was related to subsequent eczema deterioration. Skin *S aureus* colonization at any time point was associated with increased levels of hen's egg white and peanut sIgE independent of eczema severity. Participants with *S aureus* were more likely to have persistent egg allergy and peanut allergy at 60 and 72 months of age independent of eczema severity. All but one of the 9 LEAP study consumers with peanut allergy (9/312) were colonized at least once with *S aureus*.
Conclusion: *S aureus*, independent of eczema severity, is associated with food sensitization and allergy and can impair tolerance to foods. This could be an important consideration in future interventions aimed at inducing and maintaining tolerance to food allergens in eczematous infants. (J Allergy Clin Immunol 2019;144:494-503.)

Key words: *Food sensitization, food allergy, peanut allergy, egg allergy, eczema, atopic dermatitis,* Staphylococcus aureus*, prevention, Learning Early About Peanut Allergy, microbiome*

There are many studies that implicate *Staphylococcus aureus* in the pathophysiology of eczema and other atopic outcomes. Epicutaneous sensitization with staphylococcal enterotoxin B (SEB) elicits local cutaneous inflammation consistent with eczema in mice[1] and subjects with normal and atopic skin.[2] Prospective population-based birth cohorts report that skin[3] or nasal[4] colonization by *S aureus* precedes the clinical diagnosis of eczema in infancy. Patients with eczema are more likely to be colonized with *S aureus* than healthy control subjects, and disease severity is associated with *S aureus* colonization on lesional skin.[5] Additionally, patients with allergic rhinitis are more frequently colonized with nasal *S aureus*[6,7] or sensitized to *S aureus* enterotoxins[8] than healthy control subjects, and those with positive *S aureus* results have more severe allergic rhinitis than those with negative *S aureus* results.[6,7] Furthermore, *S aureus* enterotoxins trigger airway inflammation and increased airway responsiveness,[9] and SEB facilitates allergic sensitization in murine asthma models.[10] Clinically, nasal *S aureus* or serum IgE to *S aureus* toxins are associated with wheeze, asthma, or both in children and adults.[11-13] Finally, the presence of *S aureus* or IgE to *S aureus* toxins is related to asthma severity,[12-14] poor asthma control,[15] and greater prevalence of aeroallergen sensitization.[14] Therefore there are indications that *S aureus* is associated with the development, severity, or both of these atopic outcomes.

Abbreviations used
LEAP: Learning Early About Peanut Allergy
LEAP-On: Twelve-month extension of the LEAP study: Persistence of Oral Tolerance to Peanut
OR: Odds ratio
SEB: Staphylococcal enterotoxin B
sIgE: Specific IgE
SPT: Skin prick test

Interestingly, *S aureus* colonization has also been associated with food sensitization and allergy. Jones et al[16] retrospectively analyzed skin culture results from eczematous children aged 0 to 18 years and report that those with skin *S aureus* had peanut-, egg-, and milk-specific IgE (sIgE) levels that correlated to a greater than 95% positive predictive value of oral food challenge reactions to the respective allergen. Because eczema and eczema severity are risk factors for food sensitization and allergy[17,18] and *S aureus* is a marker of more severe eczema, it might be that the association between *S aureus* and food allergy in patients with eczema is related to eczema severity.

In the Learning Early About Peanut Allergy (LEAP) study, we sequentially recorded eczema severity and tested for *S aureus* colonization at 4 different time points in 640 children.[19] This design provides a unique opportunity for the detailed investigation of the relationship between *S aureus* and food allergy. In an exploratory secondary analysis we aimed to investigate the association of *S aureus* colonization with sIgE production to common food allergens and food allergy in early childhood independent of eczema severity. In addition, we sought to determine the association of *S aureus* colonization with eczema severity and persistence.

METHODS

Study population, design, and procedures

This is a secondary analysis of LEAP and 12-month extension of the LEAP study: Persistence of Oral Tolerance to Peanut (LEAP-On) study[20] outcomes that includes all participants recruited to these studies. Full study details have been published previously.[19,20] The LEAP study enrolled infants aged 4 years or more to less than 11 months with severe eczema, egg allergy, or both. Participants were randomly assigned to avoid (LEAP study avoiders) or consume (LEAP study consumers) peanut. Assessments were undertaken at the baseline (age 4-11 months) visit and at age 12, 30, and 60 months. They included eczema clinical evaluation, acquisition and culture of skin and nasal swabs, food allergen skin prick tests (SPTs), and measurements of both sIgE and total IgE levels. The LEAP-On study assessments were undertaken at 72 months of age, after 12 months of peanut avoidance in both groups. Concurrent and past medication use were recorded at all LEAP and LEAP-On study visits.

Clinical assessment of eczema severity

Eczema was clinically evaluated by a pediatric allergist at baseline and at 12, 30, 60, and 72 months of age; eczema severity was determined according to the SCORAD index. Mild, moderate, and severe eczema were defined as SCORAD scores of less than 15, greater than 15 to 40, and greater than 40, respectively. Persistent eczema was defined as eczema in which the severity did not decrease over sequential time points.

TABLE I. Skin and nasal *S aureus* colonization prevalence over time in the LEAP study

	4-11 mo	12 mo	30 mo	60 mo	Ever colonized, 4-11 to 60 mo
Skin *S aureus*					
No.	640	626	618	630	640
S aureus	115 (18.0%)	63 (10.1%)	40 (6.5%)	45 (7.1%)	206 (32.2%)
No *S aureus*	525 (82.0%)	563 (89.9%)	578 (93.5%)	585 (92.9%)	434 (67.8%)
Nasal *S aureus*					
No.	640	626	618	630	640
S aureus	96 (15.0%)	35 (5.6%)	32 (5.2%)	94 (14.9%)	207 (32.3%)
No *S aureus*	544 (85.0%)	591 (94.4%)	586 (94.8%)	536 (85.1%)	433 (67.7%)
Skin and/or nasal *S aureus*					
No.	640	626	618	630	640
S aureus	166 (25.9%)	87 (13.9%)	66 (10.7%)	125 (19.8%)	312 (48.8%)
No *S aureus*	474 (74.1%)	539 (86.1%)	552 (89.3%)	505 (80.2%)	328 (51.3%)
Skin and nasal *S aureus* combination					
No.	640	626	618	630	
Nasal only	51 (8.0%)	24 (3.8%)	26 (4.2%)	80 (12.7%)	
Skin only	70 (10.9%)	52 (8.3%)	34 (5.5%)	31 (4.9%)	
Skin and nasal	45 (7.0%)	11 (1.8%)	6 (1.0%)	14 (2.2%)	
Neither	474 (74.1%)	539 (86.1%)	552 (89.3%)	505 (80.2%)	

Prevalence of skin, nasal, skin or nasal, and the combination of skin and nasal *S aureus* colonization for all subjects enrolled in the LEAP study at baseline (4-11 mo), 12 months, 30 months, and 60 months are shown. If a subject has at least 1 instance of *S aureus* colonization at any of the 4 LEAP study visits (4-11 mo to 60 mo), then that subject is summarized as "*S aureus*" in the ever colonized column. Analogously, if a subject never has *S aureus* at any of the 4 LEAP study visits (4-11 mo to 60 mo), then that subject is summarized as "No *S aureus*" in the ever colonized column. This definition of *ever colonized* is used in subsequent analyses.

Skin and nasal swabs and *S aureus* assessment

Skin and nasal swabs were obtained at baseline and at 12, 30, and 60 months of age. Samples were taken by using sterile cotton-tipped transport swabs suitable for isolating aerobes and anaerobes. A skin swab was obtained from the most severe eczema lesion or, in the absence of eczema, the knee flexure. If the skin was dry, a drop of sterile water was placed on the skin before the swab was taken. The skin swab was then placed in amies medium. The nasal swab was inserted into one anterior nostril and was then slowly withdrawn with a rotating motion and subsequently placed in amies medium. Swabs were incubated overnight and plated directly onto Columbia Blood Agar, CLED, or MacConkey Agar (aerobic incubation) and Chocolate Agar (CO_2). Sensitivity was reported by the British Society for Antimicrobial Chemotherapy using the bioMerieux analyzer Vitek2 (bioMérieux, Marcy l'Etoile, France).

SPT responses and sIgE and total IgE measurements

SPT responses and allergen sIgE measurements were conducted at baseline and 12, 30, 60, and 72 months of age. Total IgE levels were measured at all visits except for 12 months. Test methodologies and SPT materials have been published previously.[19-21]

Definitions of peanut allergy

Peanut allergy was determined by means of an oral peanut challenge at 60 and 72 months.[20,21] At 72 months, the allergic status of participants for whom the results of the oral peanut challenge were inconclusive or not available was determined according to a previously published diagnostic algorithm.[21]

Definitions of egg allergy

At baseline, egg allergy was defined as an SPT response of 6 mm or greater to raw hen's egg white and no history of previous egg tolerance or an SPT response of 3 mm or greater to pasteurized hen's egg white and allergic symptoms related to exposure to hen's egg. At 60 and 72 months of age, we defined persistent egg allergy as an SPT response of 6 mm or greater to raw or pasteurized hen's egg in the participants with a diagnosis of egg allergy at baseline.

Statistical analysis

Statistical analyses were performed on all LEAP and LEAP-On study participants for whom an outcome measurement was obtained. No imputation for missing data was conducted. Two separate repeated-measures longitudinal models were used to assess whether skin or nasal *S aureus* (independent variable) was associated with concurrent eczema severity, as assessed based on SCORAD scores (dependent variable). Analogously, another 2 separate repeated-measures longitudinal models were used to assess whether skin or nasal *S aureus* at the immediately preceding visit was associated with eczema persistence. Average peanut and egg sIgE levels (dependent variables) were compared between those who ever had skin *S aureus* and those who never had skin *S aureus* (independent variable) through longitudinal repeated-measures models (1 for peanut and 1 for egg, respectively), which also included a covariate for SCOARD score.

All repeated-measures longitudinal models used an unstructured covariance structure to model the correlation among time points within each subject, treated time as a categorical variable, and also included covariates for time and the interaction between time and *S aureus* colonization status. Bootstrap sampling of 1000 replicates within each time point was used to assess where (or if) a divergence existed in the relative distribution of IgE production to egg, peanut, and milk sIgEs and total IgE comparing those who ever had skin *S aureus* with those who never had skin *S aureus*.

Because peanut and egg allergy (independent variables) were only assessed at 60 and 72 months, 4 (peanut allergy at 60 and 72 months and egg allergy at 60 and 72 months) separate logistic regression models were constructed for each *S aureus* colonization location (skin, nose, and combination of skin or nose [dependent variables]). These logistic regression models included covariates for SCORAD scores (collected at 60 or 72 months, respectively), LEAP study treatment assignment, and interaction between LEAP study treatment assignment and *S aureus* colonization status. Because there were a small number of subjects with peanut allergy and complete separation occurred, the Firth-penalized likelihood method was used only for the peanut allergy models. These were secondary analyses on study outcomes, and no adjustments have been made for multiple comparisons. All

TABLE II. Concurrent skin and nasal *S aureus* colonization and eczema severity

	4-11 mo			12 mo			30 mo			60 mo		
	No *S aureus*	*S aureus*	*P* value	No *S aureus*	*S aureus*	*P* value	No *S aureus*	*S aureus*	*P* value	No *S aureus*	*S aureus*	*P* value
Skin *S aureus*												
SCORAD			<.001			<.001			<.001			<.001
No.	525	115		563	63		576	40		583	45	
Mean (SD)	32.6 (18.5)	42.3 (18.6)		20.5 (14.1)	31.6 (16.5)		15.1 (12.9)	33.1 (16.8)		5.9 (9.9)	22.1 (15.3)	
LS means (SE)	33.1 (0.8)	40.1 (1.6)		21.0 (0.6)	27.5 (1.5)		15.4 (0.5)	28.4 (1.8)		6.3 (0.4)	17.1 (1.3)	
Difference LS means (*S aureus* − no *S aureus*)			6.9 (3.6-10.2)			6.5 (3.3-9.6)			13.0 (9.4-16.6)			10.8 (8.1-13.5)
Nasal *S. aureus*												
SCORAD			.009			.015			.024			.005
No.	544	96		591	35		584	32		534	94	
Mean (SD)	33.5 (18.9)	39.6 (17.8)		21.4 (14.7)	26.5 (14.1)		16.0 (13.6)	21.7 (17.5)		6.5 (10.3)	10.6 (14.6)	
LS means (SE)	33.7 (0.8)	38.5 (1.7)		21.4 (0.6)	26.4 (2.0)		16.0 (0.6)	20.6 (2.0)		6.6 (0.5)	9.5 (1.0)	
Difference LS means (*S aureus* − no *S aureus*)			4.8 (1.2-8.3)			5.0 (1.0-9.1)			4.6 (0.6-8.7)			2.9 (0.9-4.9)

Data are presented for eczema severity defined by SCORAD score for all participants who were in the LEAP study, with available data for each time point divided into groups based on whether a patient had *S aureus* at the concurrent visit or did not have *S aureus* at the concurrent visit. *P* values are from a longitudinal repeated-measures model comparing the difference in least squares means in SCORAD scores between patients without *S aureus* colonization and those with *S aureus* colonization.
LS, Least squares.

analyses were performed at the .05 level of significance by using SAS software, version 9.4, or JMP software, version 12 (SAS, Cary, NC). Data sets for the analyses are available through TrialShare, a public Web site managed by the Immune Tolerance Network (https://www.itntrialshare.org/LEAP_JACI_2019.url).

RESULTS

Participants

The characteristics of participants screened and enrolled in the LEAP and LEAP-On studies have been published previously.[19,20]

Characteristics of *S aureus* colonization in the LEAP study, with no differences noted in *S aureus* colonization between intervention groups

Approximately half (48.8%) of the participants had some form of *S aureus* colonization (32.2% skin and 32.3% nasal) on at least 1 LEAP study visit (Table I), and the majority of these participants had positive test results only once (see Table E1 in this article's Online Repository at www.jacionline.org). The greatest rates of colonization were recorded at 4 to 11 months of age (18% for skin and 15% for nose); these decreased up to 30 months of age, with a small increase observed at 60 months of age (Table I). With the exception of results at 60 months, the skin was more commonly the sole colonized location compared with the nose (Table I). No significant differences in terms of frequency and persistence in all forms of *S aureus* colonization were noted between the LEAP study avoiders and consumers (see Table E1). There was a small but significant association between *S aureus* colonization in the nose and on the skin, but concordance at any particular time was slight (see Table E2 in this article's Online Repository at www.jacionline.org).

Very few of the total *S aureus*–positive swab samples were identified as methicillin resistant (skin, 7/263 [2.7%]; nose, 2/257 [0.8%]).

Additionally, we performed an exploratory analysis to investigate the relationship between skin *S aureus* colonization at baseline and oral or topical antibiotic/steroid medication use at baseline. We did not find a statistically significant difference ($P = .695$) in terms of skin *S aureus* colonization when comparing subjects reported at baseline to have received these medications versus those who had not (data not shown).

S aureus colonization affected eczema severity and resolution

Eczema severity. *S aureus* colonization was significantly associated with concurrent eczema severity (measured by mean [SD] SCORAD score and SCORAD severity classification) across all study time points. Participants with skin *S aureus* had higher SCORAD scores compared with those who did not have skin *S aureus* (Table II). The majority of the subjects who were colonized by skin *S aureus* had concurrent moderate and severe eczema at all time points (see Fig E1 in this article's Online Repository at www.jacionline.org). Those with nasal *S aureus* colonization also had greater SCORAD scores compared with those who did not have nasal *S aureus*; however, the association was less strong than that observed between skin *S aureus* and eczema severity (Table II).

Eczema persistence and deterioration. As previously published, eczema severity decreased over time, and there was no significant difference in eczema severity between the 2 LEAP study intervention groups.[21] Although SCORAD scores generally decreased over time, this was not the case for participants whose skin was colonized with *S aureus* at certain visits (Fig 1). Indeed, considering the 12- to 30- and 60- to 72-month time intervals, eczema significantly worsened in participants with immediately preceding skin *S aureus* colonization relative to those without.

Preceding nasal *S aureus* colonization was not associated with eczema persistence or deterioration (see Fig E2 in this article's Online Repository at www.jacionline.org).

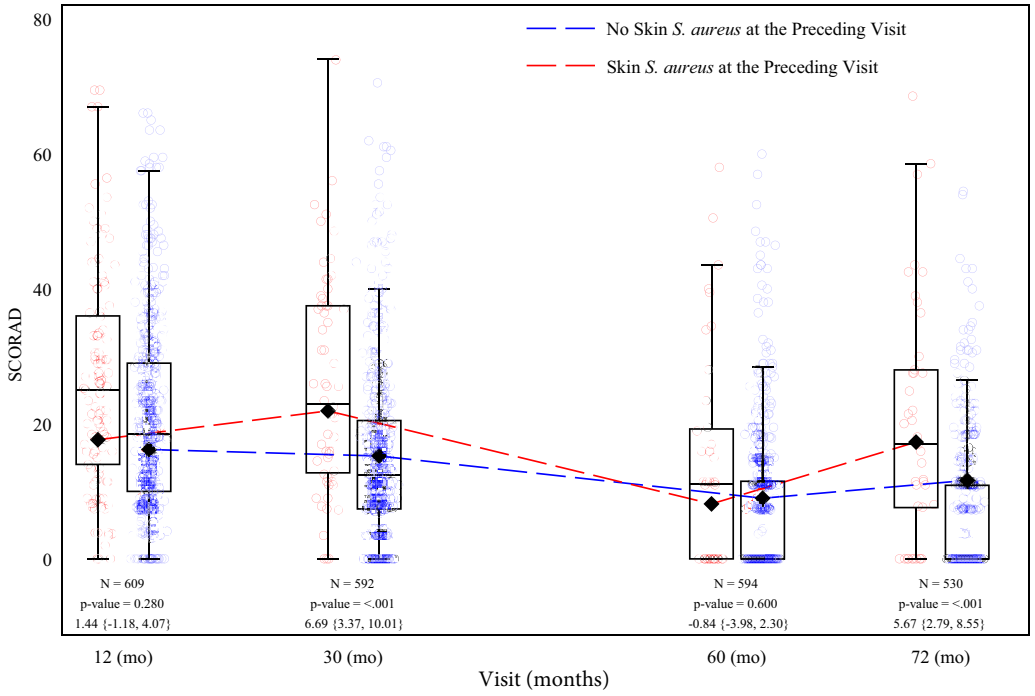

FIG 1. Eczema severity by skin *S aureus* colonization at the preceding visit. Data are presented for all participants who were in the LEAP and LEAP-On studies with available SCORAD data for each study assessment time point divided into groups based on whether subjects had skin *S aureus* at the previous visit (in red) or did not have skin *S aureus* at the previous visit (in blue). *Black diamonds* represent model predicted means, *boxes* represent 25th and 75th percentiles, *error bars* represent 2.5th and 97.5th percentiles, and the *middle line of the box* represents the median. The total number of subjects contributing to the analysis at each time point, *P* values, mean differences, and 95% CIs around that difference directly above each assessment time point refer to the least squares mean difference (*S aureus* − no *S aureus*) and *P* value comparison between those who had skin *S aureus* at the previous visit and those who did not have skin *S aureus* at the previous visit by using a longitudinal repeated-measures model adjusted for SCORAD score at the previous visit, time, *S aureus* status at the previous visit, and the interaction between *S aureus* status at the previous visit and time.

S aureus colonization was associated with food sIgE and total IgE production

Hen's egg white and peanut sIgE production at each LEAP and LEAP-On study visit was significantly associated with skin *S aureus* positivity at any time point in the interval from baseline to 60 months (Fig 2 and see Fig E3 in this article's Online Repository at www.jacionline.org, respectively). Importantly, these associations were corrected for eczema severity at each time point.

Notably, high levels of hen's egg white and peanut sIgE production at each visit were also associated with skin *S aureus* positivity at any time point in the interval from baseline to 60 months ($P < .05$, Fig 3). In Fig 3 the divergence in the distribution at each time point demonstrates that high-level hen's egg white and peanut sIgE levels were disproportionately represented in those participants whose skin was colonized with *S aureus* compared with those whose skin was not. For peanut sIgE, this association was most apparent at 30 months but remained subsequently. In contrast, the association for hen's egg white sIgE became stronger over time, with *S aureus*–positive participants comprising more than half of the upper tail of the relative distribution of sIgE despite only representing a third of the overall sample. Furthermore, we investigated the relationship between skin *S aureus* and high-level sIgE production to cow's milk and found a similar relationship with that observed for egg white and peanut. Indeed, at 30, 60, and 72 months, high levels of cow's milk sIgE were associated with skin *S aureus* colonization at any time point in the interval from baseline to 60 months (see Fig E4 in this article's Online Repository at www.jacionline.org). Finally, high levels of total IgE at all assessments were associated with any skin *S aureus* positivity (see Fig E4).

To assess whether the observed associations between *S aureus* colonization and high sIgE production to foods were food specific or confounded by total IgE, we examined the correlation between total IgE and each of the 3 food sIgEs (cow's milk, egg white, and peanut). The 3 pairwise correlations between each food and total IgE levels were moderate and consistent over the 4 study visits (see Fig E5 in this article's Online Repository at www.jacionline.org). By using multivariate logistic regression models, egg white and peanut sIgE levels at 60 months were significantly associated with skin *S aureus* positivity after adjusting for total IgE levels at 60 months (see Fig E6 in this article's Online Repository at www.jacionline.org). This association was less strong for cow's milk sIgE. In contrast, after adjustment with each food sIgE, total IgE levels were no longer significantly associated with skin *S aureus* positivity (see Fig E6).

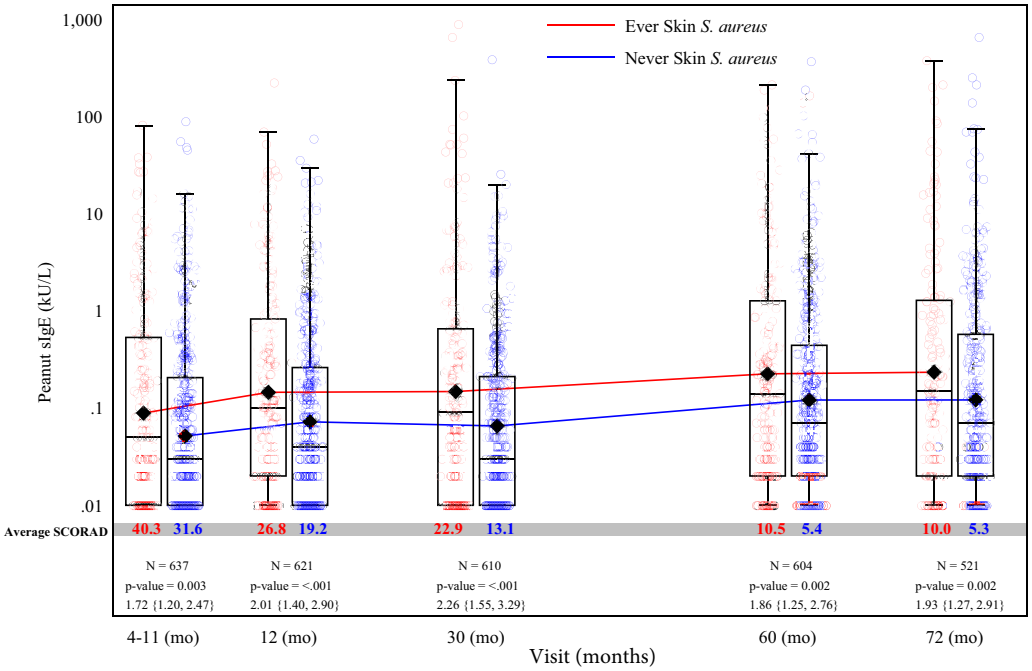

FIG 2. Peanut sIgE over time by skin *S aureus* colonization status. Data are presented for all participants who were in the LEAP and LEAP-On studies with available peanut sIgE data for each study assessment time point divided into groups based on whether subjects ever had skin *S aureus* from baseline to 60 months (in red) or never had skin *S aureus* from baseline to 60 months (in blue). *Black diamonds* represent model predicted means, *boxes* represent 25th and 75th percentiles, *error bars* represent 2.5th and 97.5th percentiles, and the *middle line of the box* represents the median. The total number of subjects contributing to the analysis at each time point, *P* values, mean differences, and 95% CIs around that mean difference directly above each assessment time point refer to the comparison between those who never have *S aureus* and those who ever have *S aureus* groups by using a longitudinal repeated-measures model adjusted for SCORAD, time, *S aureus* status, and the interaction between *S aureus* status and time. Average SCORAD scores at each time point are annotated directly below the box plots for those who ever had skin *S aureus* (red) and those who never had skin *S aureus* (blue).

S aureus colonization was related to persistence and development of food allergy

Persistence of egg allergy. Of the 408 subjects with protocol-defined egg allergy at baseline, 42.7% and 38.1% had persistent egg allergy at 60 and 72 months, respectively.

Overall, participants with skin and/or nasal *S aureus* colonization in the interval from baseline to 60 months were 1.57 (95% CI, 1.02-2.42; $P = .042$) times as likely to have persistent egg allergy at 60 months of age as opposed to those who did not (Table III). This association was slightly stronger for nasal (odds ratio [OR] 1.61; 95% CI, 1.03-2.52; $P = .036$) as opposed to skin (OR 1.39; 95% CI, 0.88-2.19; $P = .160$) *S aureus* colonization. Skin *S aureus* colonization before 72 months of age was the only colonization pattern significantly associated with the likelihood (OR, 1.77; 95% CI, 1.09-2.89; $P = .022$) of egg allergy persisting until that age. There was a nonsignificant trend for preceding nasal (OR, 1.54; 95% CI, 0.95-2.49; $P = .079$) and skin and/or nasal (OR, 1.59; 95% CI, 0.99-2.55; $P = .055$) colonization and egg allergy persisting at 72 months. When comparing the LEAP study intervention groups, no association was noted between persistent egg allergy and *S aureus* colonization. All ORs were corrected for eczema severity at 60 or 72 months accordingly (Table III).

Development of peanut allergy. Overall, participants with skin and those with nasal *S aureus* colonization in the interval from baseline to 60 months were 2.94 (95% CI, 1.11-7.76; $P = .029$) and 2.41 (95% CI, 1.04-5.59; $P = .04$) times as likely to have a diagnosis of peanut allergy at 60 months, respectively, as opposed to those who were not colonized. In addition, any preceding form of *S aureus* colonization was significantly associated with peanut allergy at 72 months of age. All ORs were corrected for eczema severity at 60 or 72 months accordingly (Table IV).

Within the peanut consumption group, subjects whose skin was *S aureus* colonized at any study point through the LEAP study were 7.13 (95% CI, 1.14-44.47; $P = .035$) and 3.87 (95% CI, 1.02-14.65; $P = .047$) times as likely to receive a diagnosis of peanut allergy at 60 and 72 months of age, respectively, compared with participants who were never skin *S aureus* colonized (Fig 4 and Table IV). With regard to nasal or skin and/or nasal colonization at both time points, this association was statistically significant only when it concerned nasal *S aureus* and peanut allergy at 60 months of age (Table IV and see Figs E7 and E8 in this article's Online Repository at www.jacionline.org). These ORs are based on a small number of subjects with peanut allergy within the LEAP study consumers group. Specifically, there were only 9 (6 by 60 months and an additional 3 by 72 months) LEAP study consumers who did not have peanut allergy at baseline and received a diagnosis of peanut allergy at 60 months, 72 months, or both. All but 1 of these 9 LEAP study consumers (9/312) had *S aureus* colonization at 1 or more time points (see Fig E9 in this article's Online Repository at www.jacionline.org). The 6 LEAP study consumers who received a diagnosis of peanut allergy at both 60 and 72 months had all stopped consumption

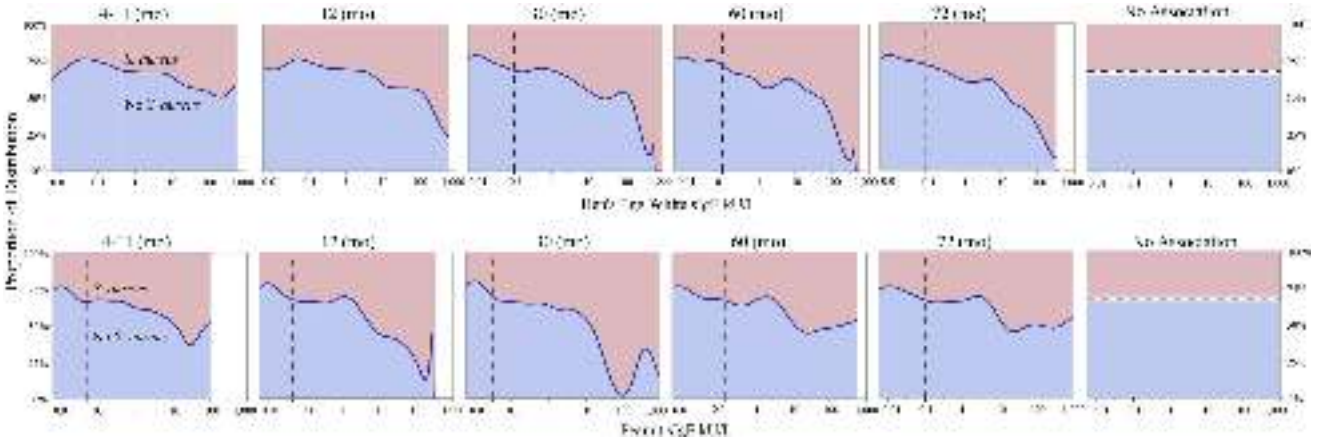

FIG 3. Relative distribution of hen's egg white and peanut sIgE over time by skin *S aureus* colonization status. These figures show the relative distribution of hen's egg white sIgE and peanut sIgE levels between those who ever have skin *S aureus* (shown in red) from 4 to 11 months to 60 months and those who never have skin *S aureus* (shown in blue). *Vertical reference lines* indicate where the distribution begins to significantly differ ($P < .05$) between the 2 groups by using bootstrap sampling of 1000 replicates of the upper percentiles, indicating that those with *S aureus* colonization are overrepresented at the higher end of the sIgE distribution (which is more indicative of allergy). A reference panel is included to illustrate the 67.8% of the trial participants who never had skin *S aureus* and the 32.2% who ever had skin *S aureus* and what a pattern with no association of skin *S aureus* with sIgE levels would look like.

TABLE III. Persistent egg allergy in relation to *S aureus* colonization and treatment assignment

	LEAP study (n = 363)			LEAP-On study (n = 318)		
***S aureus* colonization (baseline to 60 mo)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Overall (*S aureus* vs no *S aureus*)						
Skin *S aureus*	1.39	0.88-2.19	.160	1.77	1.09-2.89	.022
Nasal *S aureus*	1.61	1.03-2.52	.036	1.54	0.95-2.49	.079
Skin and/or nasal *S aureus*	1.57	1.02-2.42	.042	1.59	0.99-2.55	.055
Within peanut consumption group (*S aureus* vs no *S aureus*)						
Skin *S aureus*	1.37	0.73-2.58	.326	1.68	0.85-3.35	.139
Nasal *S aureus*	1.42	0.76-2.67	.276	1.65	0.83-3.26	.154
Skin and/or nasal *S aureus*	1.65	0.89-3.03	.108	1.88	0.96-3.70	.066
Within peanut avoidance group (*S aureus* vs no *S aureus*)						
Skin *S aureus*	1.39	0.74-2.64	.300	1.86	0.95-3.67	.072
Nasal *S aureus*	1.83	0.98-3.43	.059	1.44	0.73-2.86	.295
Skin and/or nasal *S aureus*	1.49	0.81-2.73	.196	1.34	0.69-2.58	.385
Within those with *S aureus* (avoidance vs consumption)						
Skin *S aureus*	0.88	0.44-1.77	.717	0.94	0.44-1.99	.869
Nasal *S aureus*	1.02	0.49-2.09	.955	0.81	0.37-1.77	.600
Skin and/or nasal *S aureus*	0.85	0.47-1.52	.573	0.78	0.41-1.47	.440
Within those without *S aureus* (avoidance vs consumption)						
No skin *S aureus*	0.86	0.51-1.47	.583	0.85	0.47-1.54	.587
No nasal *S aureus*	0.79	0.47-1.34	.386	0.93	0.52-1.66	.799
No skin and/or nasal *S aureus*	0.93	0.50-1.74	.829	1.09	0.55-2.18	.797

OR, 95% CIs, and *P* values from multiple multivariate logistic regression models are shown. One set of models was fit for the 60-month data (outcome of interest being persistent egg allergy, as assessed by raw and pasteurized egg SPT wheal cutoffs at 60 months), and another set of models was fit for the 72-month data (outcome of interest being persistent egg allergy as assessed by raw and pasteurized egg SPT wheal cutoffs at 72 months), with *S aureus* colonization status (1 model each for skin, nasal, and skin and/or nasal *S aureus*) adjusted for SCORAD scores (at 60 and 72 months, respectively), LEAP study treatment assignment, and interaction between *S aureus* status and treatment assignment. Those who do not have protocol-defined egg allergy at baseline are not included in this analysis.

well before 60 months of age because of suspected allergic reactions after peanut consumption. In addition, there were 7 subjects in the consumption group who were allergic at baseline. Of these, 6 had some form of *S aureus* colonization at some point during the study (data not shown). Within the avoidance group, there was no greater risk for peanut allergy at 60 or at 72 months in the subjects with any *S aureus* colonization (Table IV).

The increased risk of peanut allergy at 60 or 72 months of age among the peanut avoiders compared with the peanut consumers was less marked in those who had any *S aureus* compared with those without *S aureus* (Fig 4, *B*; Table IV, and see Figs E7 and E8).

DISCUSSION

Previous findings that *S aureus* colonization in patients with eczema is associated with food sensitization and allergy[17,18] might be confounded by eczema severity. In the LEAP and LEAP-On studies we aimed to elucidate the relationship between

TABLE IV. Peanut allergy in relation to *S aureus* colonization and treatment assignment

	LEAP study (n = 619)			LEAP-On study (n = 538)		
***S aureus* colonization (baseline to 60 mo)**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Overall (*S aureus* vs no *S aureus*)						
Skin *S aureus*	2.94	1.11-7.76	.029	2.19	1.04-4.61	.039
Nasal *S aureus*	2.41	1.04-5.59	.040	2.18	1.05-4.56	.037
Skin and/or nasal *S aureus*	4.24	0.97-18.59	.055	2.78	1.09-7.07	.031
Within peanut consumption group (*S aureus* vs no *S aureus*)						
Skin *S aureus*	7.13	1.14-44.47	.035	3.87	1.02-14.65	.047
Nasal *S aureus*	3.78	0.79-18.11	.096	3.88	1.03-14.61	.045
Skin and/or nasal *S aureus*	12.26	0.68-220.56	.089	5.57	0.96-32.26	.055
Within peanut avoidance group (*S aureus* vs no *S aureus*)						
Skin *S aureus*	1.21	0.65-2.25	.545	1.24	0.65-2.37	.508
Nasal *S aureus*	1.54	0.84-2.82	.162	1.23	0.65-2.32	.519
Skin and/or nasal *S aureus*	1.47	0.81-2.67	.208	1.39	0.75-2.58	.293
Within those with *S aureus* (avoidance vs consumption)						
Skin *S aureus*	4.29	1.60-11.51	.004	3.27	1.27-8.43	.014
Nasal *S aureus*	5.78	2.01-16.65	.001	3.23	1.25-8.34	.015
Skin and/or nasal *S aureus*	5.86	2.43-14.14	<.001	3.97	1.77-8.95	.001
Within those without *S aureus* (avoidance vs consumption)						
No skin *S aureus*	25.26	4.86-131.35	<.001	10.18	3.31-31.35	<.001
No nasal *S aureus*	14.19	3.86-52.21	<.001	10.19	3.31-31.33	<.001
No skin and/or nasal *S aureus*	48.89	2.93-815.20	.007	15.90	2.98-84.66	.001

ORs, 95% CIs, and *P* values from multiple multivariate logistic regression models using the Firth penalized likelihood method are shown. One set of models was fit for the 60-month data (outcome of interest being peanut allergy as assessed by oral food challenge at 60 months), and another set of models was fit for the 72-month data (outcome of interest being peanut allergy as assessed by oral food challenge at 72 months). Predictors of interest included *S aureus* colonization status (one model each for skin, nasal, and skin and/or nasal) adjusted for SCORAD score (at 60 and 72 months, respectively), LEAP study treatment assignment, and interaction between *S aureus* status and treatment assignment. Infants randomly assigned to consumption underwent a baseline open-label food challenge; the 7 subjects who reacted to that challenge are not included in this analysis. Interpret results with caution because a small number of subjects with peanut allergy (especially in the peanut consumption arm) contribute to these analyses.

S aureus and food sensitization/allergy by correcting our analyses for eczema severity.

In the LEAP study cohort approximately half of the participants were found to be colonized by *S aureus* (Table I and see the Methods section in this article's Online Repository at www.jacionline.org). We demonstrate that skin colonization with *S aureus* was related to eczema severity, persistence, and deterioration (Fig 2, Table II, and see the Methods section in this article's Online Repository).

In addition, we demonstrate that, even after correcting for eczema severity, hen's egg white and peanut sIgE levels at each visit in the LEAP and LEAP-On studies were significantly associated with skin *S aureus* positivity at any LEAP study time point (Fig 2 and see Fig E3). This relationship was even stronger when we looked into high-level hen's egg white and peanut sIgE production (Fig 3). Similar findings were noted for cow's milk, where high-level sIgE production to milk at 30, 60, and 72 months of age was related to any skin *S aureus* colonization (see Fig E4). Together, these data suggest that *S aureus* is associated with hen's egg, peanut, and cow's milk allergy.

Moreover, high levels of total IgE production were significantly associated with any skin *S aureus* colonization (see Fig E4), which is consistent with literature reporting that *S aureus* can promote a polyclonal IgE response.[12] To investigate whether sIgE to foods in patients with *S aureus* colonization is explained by total IgE production, we explored the relationship between total IgE levels and food sIgE levels to cow's milk, hen's egg white, and peanut and found a significant but moderate correlation (see Fig E5). Furthermore, we found that the association between egg white or peanut sIgE levels at 60 months and *S aureus* colonization was not explained by total IgE levels (see Fig E6). However, the association between total IgE levels and skin *S aureus* was not significant when we adjusted our analysis for each food sIgE (milk, egg white, and peanut; see Fig E6). Overall, these results indicate that in our study population high polyclonal IgE production in patients with *S aureus* colonization could only partly account for the association between skin *S aureus* colonization and high levels of egg white and peanut sIgE.

Allergy to hen's egg typically resolves during early childhood.[22] However, in the LEAP and LEAP-On studies, 42.7% and 38.1% of baseline participants with egg allergy had persistent egg allergy at 60 and 72 months of age, respectively. Our results demonstrate that any *S aureus* positivity increased the odds of hen's egg allergy persisting at 60 (OR, 1.57; $P = .042$) or 72 (OR, 1.59; $P = .055$) months of age independent of eczema severity (Table III), suggesting that *S aureus* can prevent the acquisition of natural tolerance to hen's egg.

In the LEAP study peanut consumption was successful in preventing peanut allergy at 60 months of age. Interestingly, LEAP study consumers with *S aureus* skin colonization were 7.13 ($P = .035$) and 3.87 ($P = .047$) times more likely to have peanut allergy primarily confirmed by peanut challenge at 60 or 72 months of age, respectively (Fig 4 and Table IV). Although these associations are based on only 9 (6 by 60 months and an additional 3 by 72 months) LEAP study consumers who did not have peanut allergy at baseline and received a diagnosis of peanut allergy at 60 and/or 72 months, it is worth noting that all but 1 of these participants were colonized with *S aureus* at 1 or more LEAP study visits (see Fig E9). The 6 subjects with peanut allergy by 60 months of age had all stopped consuming peanut well before 60 months of age. Therefore it could be argued that the reason for failing to acquire oral tolerance was

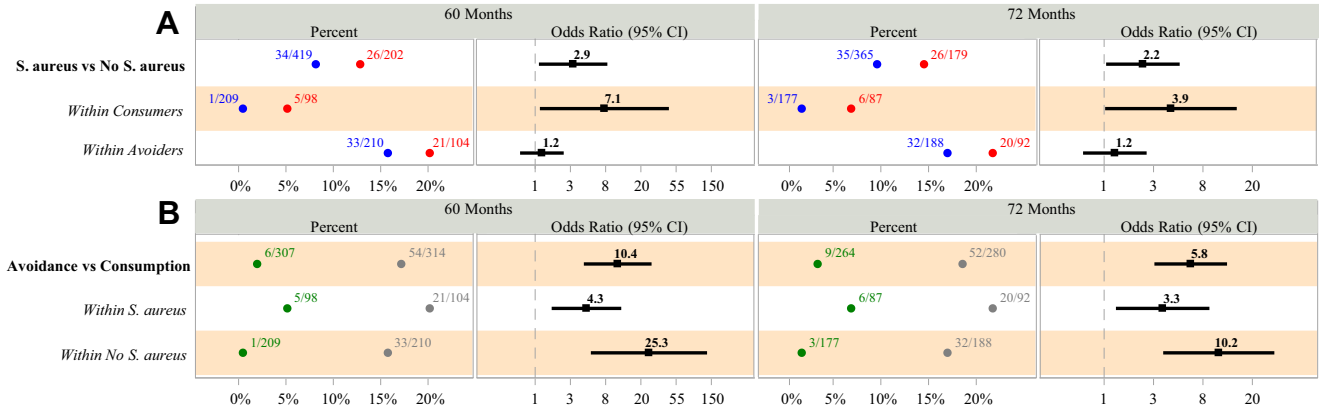

FIG 4. Peanut allergy in relation to skin *S aureus* colonization and treatment assignment percentages (from raw data), ORs, and 95% CIs from multiple multivariate logistic regression models by using the Firth penalized likelihood method are displayed. One model was fit for the 60-month data (outcome of interest being peanut allergy, as assessed by means of oral food challenge at 60 months), and another model was fit for the 72-month data (outcome of interest being peanut allergy as assessed by means of oral food challenge or the relevant diagnostic algorithm at 72 months). Predictors of interest included skin *S aureus* colonization status adjusted for SCORAD scores (at 60 and 72 months, respectively), LEAP study treatment assignment, and interaction between skin *S aureus* status and treatment assignment. **A,** For the plot, summary of the relationship between peanut allergy and skin *S aureus* colonization status (overall, within consumers, and within avoiders). In the *Percent* panel numerators refer to the number of subjects with peanut allergy, whereas the denominator refers to the number of subjects with skin *S aureus* (in red) and those without skin *S aureus* (blue). **B,** For the plot, summary of the relationship between peanut allergy and peanut consumption (overall, within those with skin *S aureus*, and within those without skin *S aureus*). In the *Percent* panel numerators refer to the number of subjects with peanut allergy, whereas the denominator refers to the number of subjects in the avoidance group (in gray) and those in the consumption group (green). Interpret results with caution because a small number of patients with peanut allergy (especially in the peanut consumption arm) contribute to these analyses.

inadequate consumption rather than the immunologic effect of *S aureus*. However, these 6 subjects stopped eating peanut during the course of the study because of symptoms during consumption that strongly suggested peanut allergy. This indicates that the reduced duration of peanut consumption was the consequence of an accelerated development of peanut allergy. More specifically, there are 2 possible explanations for the development of peanut allergy despite previous peanut consumption in these subjects: (1) they had an accelerated form of peanut allergy potentiated by *S aureus* and/or (2) *S aureus* might have inhibited tolerance mechanisms related to peanut consumption. The fact that *S aureus* was associated with a greater risk of peanut allergy among peanut consumers but not peanut avoiders (Fig 4, *B*; Table IV, and see Figs E7 and E8) further suggests that peanut consumption was less effective in the prevention of peanut allergy among participants with *S aureus* compared with those with no *S aureus*.

S aureus has been implicated in the development and severity of atopic diseases, such as eczema, allergic rhinitis, and asthma. With regard to food allergy, an epidemiologic clinical study indicates an association between skin *S aureus* and milk, egg, or peanut allergy in children with eczema.[16] There are murine studies that support a biological explanation between *S aureus* and food allergy. Indeed, SEB coapplied on the skin with ovalbumin or peanut extract increases the systemic production of ovalbumin sIgE[23] and enhances peanut-specific $CD4^+$ T_H2 responses on subsequent exposure to peanut extract alone,[24] respectively. Additionally, SEB administered orally with antigen (ovalbumin or peanut) results in highly T_H2-polarized immune responses to the antigen, whereas subsequent oral challenge with the respective antigen triggers anaphylaxis.[25] In all 3 studies antigen-specific immune responses were not observed with SEB or the antigen alone, suggesting that *S aureus* might be acting as adjuvant.

Our results show an association between skin *S aureus* and high sIgE production to hen's egg white, peanut, and cow's milk, as well as to high total IgE levels. However, we demonstrated that the relationship between *S aureus* and sIgE production to egg white and peanut was primarily explained by the corresponding food allergen sIgE and not total IgE levels. *S aureus* has been associated with more severe forms of atopic diseases, and our data extend these observations in patients with food allergy.

Study strengths include the longitudinal design of the LEAP study, with detailed clinical assessments and colonization results obtained at 4 scheduled study intervals. Because our results are corrected for eczema severity, we are able to confirm that the association between *S aureus* carriage and egg/peanut sIgE production or allergy occurred independently of eczema severity.

There are limitations to the colonization results reported because use was made of less sensitive bacteriological culture techniques and not DNA-based testing. Nevertheless, cultures allow for the detection of live microorganisms and not remnant nonviable genetic material from prior infection. Because we did not genotype the isolated strains, it is not possible to match organisms over time and between skin and nasal swabs. Swabs were collected on only 4 occasions in the LEAP study and were not collected in the LEAP-On study. Diagnostic food challenges

were undertaken to peanut but not hen's egg. A major limitation is related to interpretation of the association between *S aureus* and peanut allergy in the consumers, which, although significant, is based on the very small numbers of LEAP study consumers with peanut allergy as it is reflected in the wide CIs around the ORs. Larger numbers of participants who become peanut allergic, despite being fed peanut in infancy/early childhood, would be required to assess whether these findings demonstrate that *S aureus* colonization interferes with oral tolerance induction. Finally, even after adjusting for eczema severity, we cannot rule out that the observed association between colonization and food allergy could be due to other confounding factors.

S aureus has been implicated in the development and severity of atopic diseases, namely eczema, allergic rhinitis and asthma; our findings extend these observations to the development of food allergy independent of eczema severity. The role of *S aureus* as a potential environmental factor should be considered in future interventions aimed at inducing and maintaining tolerance to food allergens in eczematous infants. Further prospective longitudinal studies measuring *S aureus* with more advanced techniques and interventional studies eradicating *S aureus* in early infancy will help elucidate its role in the development of eczema or food allergy.

We thank the many nurses, dietitians, doctors, and administrative staff of the Guy's and St Thomas' NHS Foundation Trust Children's Allergy Service for clinical and logistical assistance over the period of the study and Poling Lau for administrative support in the preparation of this manuscript. Above all, we are indebted to all of the children and their families who generously took part in this study.

LEAP and LEAP-On Study Team

Clinical support: Susan Chan, Adam Fox

Nursing staff: Helen Fisher, Mable Abraham, Muhsinah Adam, Louise Coverdale, Claire Duncan, Amy Nixon, Una O'Dwyer-Leeson, Victoria Offord, Aine Sheridan, Fiona Watson, Natalie Witham

Dietitians: Kathryn Cockerell, Mary Feeney, Gail Harland, Tiffany Miller, Charlotte Stedman

Study management and administration: Catherine Clarke, Richard Cleaver, Gemma Deutsch, Alicia Parr

Laboratory projects: Natalia Becares, Matthew Crossley, Natalia do Couto Francisco, Kerry Richards, Ewa Pietraszewicz, Alick Stephens, Asha Sudra, Rianne Wester, Alastair Wilson, Celine Wu

Play specialists: Jenna Heath, Kathryn Hersee

Phlebotomist: Devi Patkunam

ITN staff: Adam Asare, Eduard Chani, Judith Evind, Noha Lim, Audrey Plough, Judith Evind, Don Whitehouse

National Institute of Allergy and Infectious Diseases staff: Margarita Gomez Lorenzo, Joy Laurienzo Panza

Rho Federal Systems Staff: Stephanie Lussier, Jack Hu, Travis Mason

Clinical implications: There might be a role for *S aureus* eradication in interventions aimed at inducing and maintaining tolerance to foods in eczematous infants.

REFERENCES

1. Laouini D, Kawamoto S, Yalcindag A, Bryce P, Mizoguchi E, Oettgen H, et al. Epicutaneous sensitization with superantigen induces allergic skin inflammation. J Allergy Clin Immunol 2003;112:981-7.
2. Skov L, Olsen JV, Giorno R, Schlievert PM, Baadsgaard O, Leung DY. Application of Staphylococcal enterotoxin B on normal and atopic skin induces up-regulation of T cells by a superantigen-mediated mechanism. J Allergy Clin Immunol 2000; 105:820-6.
3. Meylan P, Lang C, Mermoud S, Johannsen A, Norrenberg S, Hohl D, et al. Skin colonization by Staphylococcus aureus precedes the clinical diagnosis of atopic dermatitis in infancy. J Invest Dermatol 2017;137:2497-504.
4. Lebon A, Labout JA, Verbrugh HA, Jaddoe VW, Hofman A, van Wamel WJ, et al. Role of Staphylococcus aureus nasal colonization in atopic dermatitis in infants: the Generation R Study. Arch Pediatr Adolesc Med 2009;163:745-9.
5. Totte JE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SG. Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. Br J Dermatol 2016;175:687-95.
6. Riechelmann H, Essig A, Deutschle T, Rau A, Rothermel B, Weschta M. Nasal carriage of Staphylococcus aureus in house dust mite allergic patients and healthy controls. Allergy 2005;60:1418-23.
7. Shiomori T, Yoshida S, Miyamoto H, Makishima K. Relationship of nasal carriage of Staphylococcus aureus to pathogenesis of perennial allergic rhinitis. J Allergy Clin Immunol 2000;105:449-54.
8. Okano M, Takishita T, Yamamoto T, Hattori H, Yamashita Y, Nishioka S, et al. Presence and characterization of sensitization to staphylococcal enterotoxins in patients with allergic rhinitis. Am J Rhinol 2001;15:417-21.
9. Herz U, Ruckert R, Wollenhaupt K, Tschernig T, Neuhaus-Steinmetz U, Pabst R, et al. Airway exposure to bacterial superantigen (SEB) induces lymphocyte-dependent airway inflammation associated with increased airway responsiveness —a model for non-allergic asthma. Eur J Immunol 1999;29:1021-31.
10. Huvenne W, Callebaut I, Plantinga M, Vanoirbeek JA, Krysko O, Bullens DM, et al. Staphylococcus aureus enterotoxin B facilitates allergic sensitization in experimental asthma. Clin Exp Allergy 2010;40:1079-90.
11. Davis MF, Peng RD, McCormack MC, Matsui EC. Staphylococcus aureus colonization is associated with wheeze and asthma among US children and young adults. J Allergy Clin Immunol 2015;135:811-3.e5.
12. Bachert C, van Steen K, Zhang N, Holtappels G, Cattaert T, Maus B, et al. Specific IgE against Staphylococcus aureus enterotoxins: an independent risk factor for asthma. J Allergy Clin Immunol 2012;130:376-81.e8.
13. Semic-Jusufagic A, Bachert C, Gevaert P, Holtappels G, Lowe L, Woodcock A, et al. Staphylococcus aureus sensitization and allergic disease in early childhood: population-based birth cohort study. J Allergy Clin Immunol 2007;119:930-6.
14. Uong P, Curran-Everett D, Leung DYM. Staphylococcus aureus colonization is associated with increased inhaled corticosteroid requirements in patients with atopic dermatitis and asthma. J Allergy Clin Immunol Pract 2017;5:1782-3.
15. Tanaka A, Suzuki S, Ohta S, Manabe R, Furukawa H, Kuwahara N, et al. Association between specific IgE to Staphylococcus aureus enterotoxins A and B and asthma control. Ann Allergy Asthma Immunol 2015;115:191-7.e2.
16. Jones AL, Curran-Everett D, Leung DYM. Food allergy is associated with Staphylococcus aureus colonization in children with atopic dermatitis. J Allergy Clin Immunol 2016;137:1247-8.e3.
17. Flohr C, Perkin M, Logan K, Marrs T, Radulovic S, Campbell LE, et al. Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. J Invest Dermatol 2014;134:345-50.
18. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol 2016;137:1071-8.
19. 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.
20. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of avoidance on peanut allergy after early peanut consumption. N Engl J Med 2016;374:1435-43.
21. du Toit G, Sayre PH, Roberts G, Lawson K, Sever ML, Bahnson HT, et al. Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early About Peanut Allergy study cohort. J Allergy Clin Immunol 2018;141:1343-53.
22. Xepapadaki P, Fiocchi A, Grabenhenrich L, Roberts G, Grimshaw KE, Fiandor A, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life-the EuroPrevall birth cohort study. Allergy 2016;71:350-7.
23. 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.
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. Ganeshan K, Neilsen CV, Hadsaitong A, Schleimer RP, Luo X, Bryce PJ. Impairing oral tolerance promotes allergy and anaphylaxis: a new murine food allergy model. J Allergy Clin Immunol 2009;123:231-8.e4.