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LETTER

In children with eczema, expansion of epitope-specific IgE is associated with peanut allergy at 5 years of age

To the Editor,

A well-known risk factor for food allergies is childhood eczema or atopic dermatitis (AD).[1] Even the non-lesional skin of AD subjects with food allergies has morphologic changes characteristic of a distinct endotype.[2] Allergen exposure from house dust and/or contamination on caregivers hands on inflamed skin may provoke the release of alarmins resulting in inflammatory Th2-skewing.[3]

In a recent study, we followed the evolution of serum epitope-specific (ses-)IgE and ses-IgG$_4$ antibodies in a subset of 341 infants at risk for peanut allergy (LEAP trial). Children in the early peanut consumption group acquired a different ses-IgE repertoire compared with avoiders that developed allergy, suggesting that oral ingestion promotes immunologic tolerance.[4,5] We sought to further evaluate whether antibody profiles could be an early indicator of allergic epicutaneous sensitization to peanut.

Peanut allergy and sensitization status were defined at 5 years of age into the following mutually exclusive groups: Allergic, Sensitized, and Non-allergic. In this sub-cohort, 38/172 (22%) Avoidance Group children developed peanut allergy. Peanut sensitization was observed in 59/172 (34%) Avoiders and 94/169 (56%) Consumers. The remaining 150 (44%) were Non-allergic and equally represented (75/172 and 75/169) in the Avoidance and Consumption Groups, respectively. Detailed antibody profiling was published previously[5] by these outcomes, and this analysis further stratifies by the presence of eczema at 2.5 years of age. Since together with egg allergy, eczema was an inclusion criterion, 335 (98%) participants had eczema at 4–11 months. By 2.5 years, 297 (87%) children still had eczema, defined as the SCORAD>0 (Table E1). Levels of ses-IgE and ses-IgG$_4$ against 64 sequential epitopes from Ara h 1, 2, and 3 allergens were measured at 4–11 months, 1, 2.5, and 5 years of age (see Supplementary Material). Even though sample sizes in the "no eczema" groups were small (Table E2), several interesting observations could be found.

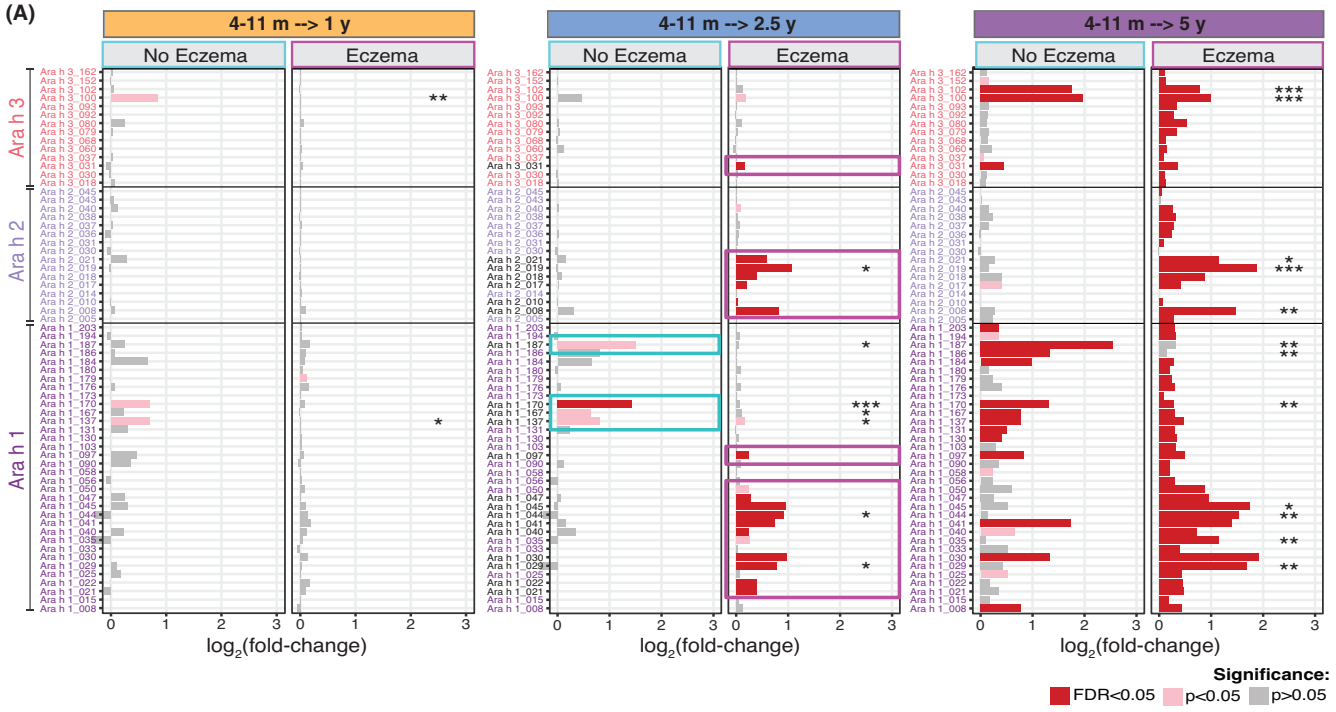
None of the Non-allergic children and Sensitized Avoiders had increases in ses-IgE levels, regardless of their eczema status (Figures E1A and E2). However, the expansion of ses-IgE to a distinct set of epitopes on Ara h 1 and Ara h 2 proteins was observed only among Allergic Avoiders with eczema (magenta rectangles in Figure 1A). Although the sample size was very small, none of the peanut allergic avoiders without eczema ($n = 3$) had ses-IgE to those epitopes at a 2.5-year timepoint but did develop ses-IgE to some of the epitopes of the eczema group by 5 years.

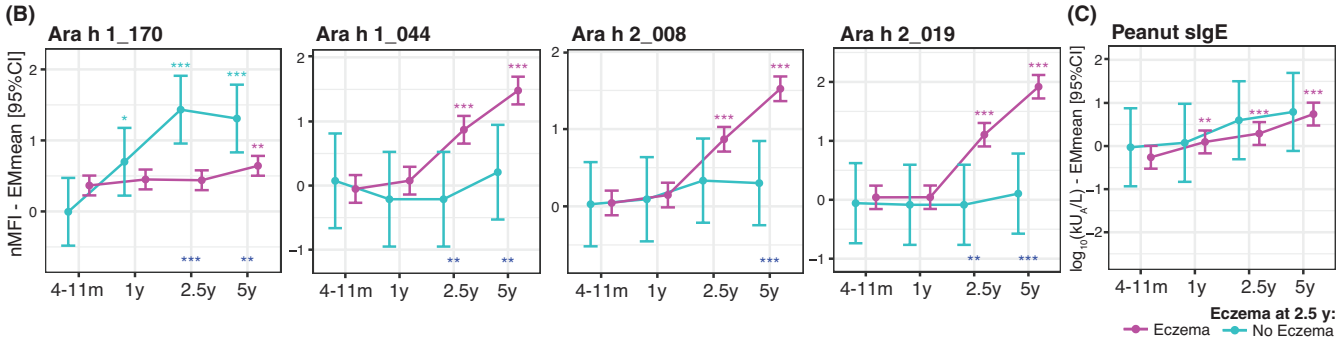
Instead, Allergic Avoiders without eczema developed increases in ses-IgE to a different set of Ara h 1 epitopes (cyan rectangles, Figure 1A,B). Since eczema severity can change over time, we confirmed observed trends by modeling SCORAD with selected ses-IgEs (Figure E3). These differences were only observed in IgE to specific epitopes and not to peanut extract or component proteins (Figure 1C, Figure E1).

Interestingly, IgE epitopes in the eczema group had distinct protein folding structures and biochemical characteristics, that is, less thermal stability, higher potential for creating bonds with other proteins, and position preference in alpha-helix bends (Figure 1D,E, Table E3).

As for the ses-IgG$_4$, Allergic Avoiders with and without eczema had similar profiles (Figure 2). Non-allergic Avoiders without eczema had higher ses-IgG$_4$ levels at 5 years in the majority (92%) of ses-IgG$_4$s. Among Sensitized Avoiders and all Consumers, the presence of eczema was associated with more rapid increases in ses-IgG4 levels at 5 years. These differences were not observed in peanut-specific IgG$_4$.

Overall, peanut allergic avoiders with eczema had distinct ses-IgE profiles, potentially suggesting a different route of allergic sensitization. The trends observed should be interpreted with caution. Eczema was a key LEAP inclusion criterion, thus limiting the number of non-eczema subjects and potentially influencing the results.





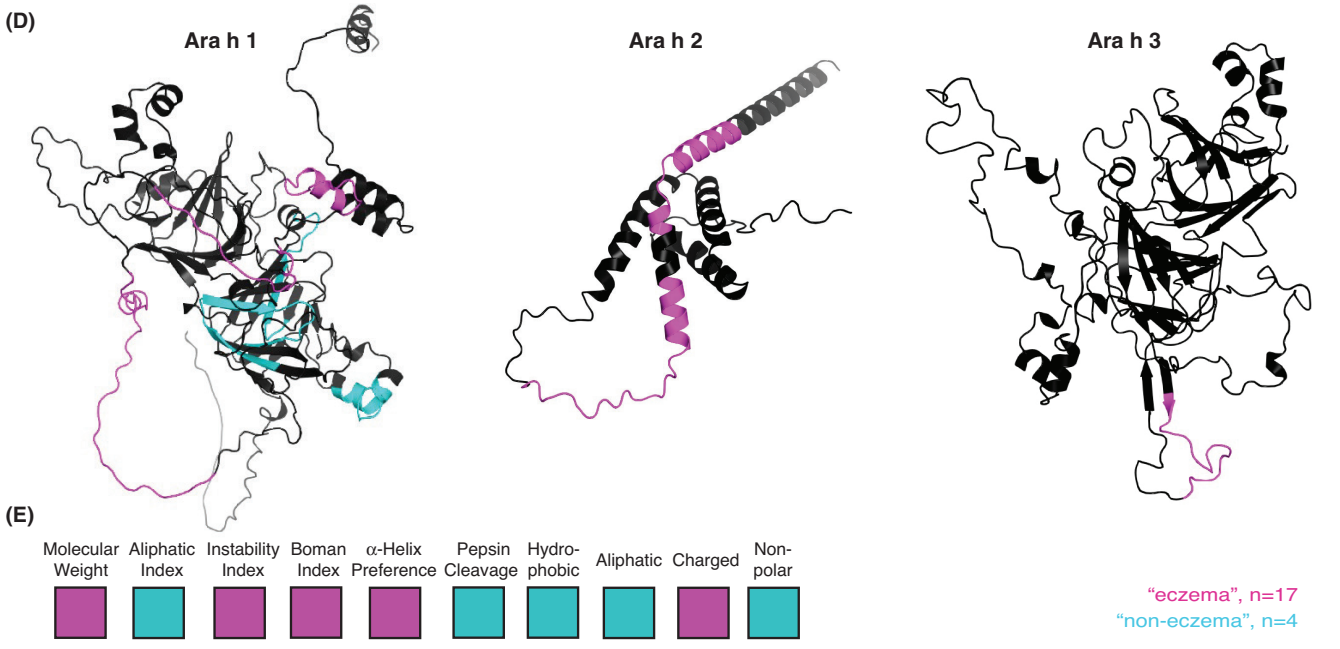


FIGURE 1 Ses-IgE association with eczema status in Allergic Avoiders. (A) Barplots representing changes in ses-IgE from 4–11 m to 1, 2.5, and 5 years (grey if not significant), stars show significance by eczema status. Magenta boxes—"eczema," cyan—"no eczema" group epitopes. (B) Lineplots showing estimated marginal means of epitopes with the largest $\log_2$ fold-changes and peanut-specific IgE (C). Colored stars represent change from 4–11 m and dark blue stars—significance by eczema status ($p < .05$*, <.01**, <.001***). (D) Epitopes position on the crystal structures of respective proteins. (E) Significantly different biochemical properties, colored if higher in either "eczema" or "non-eczema" groups.

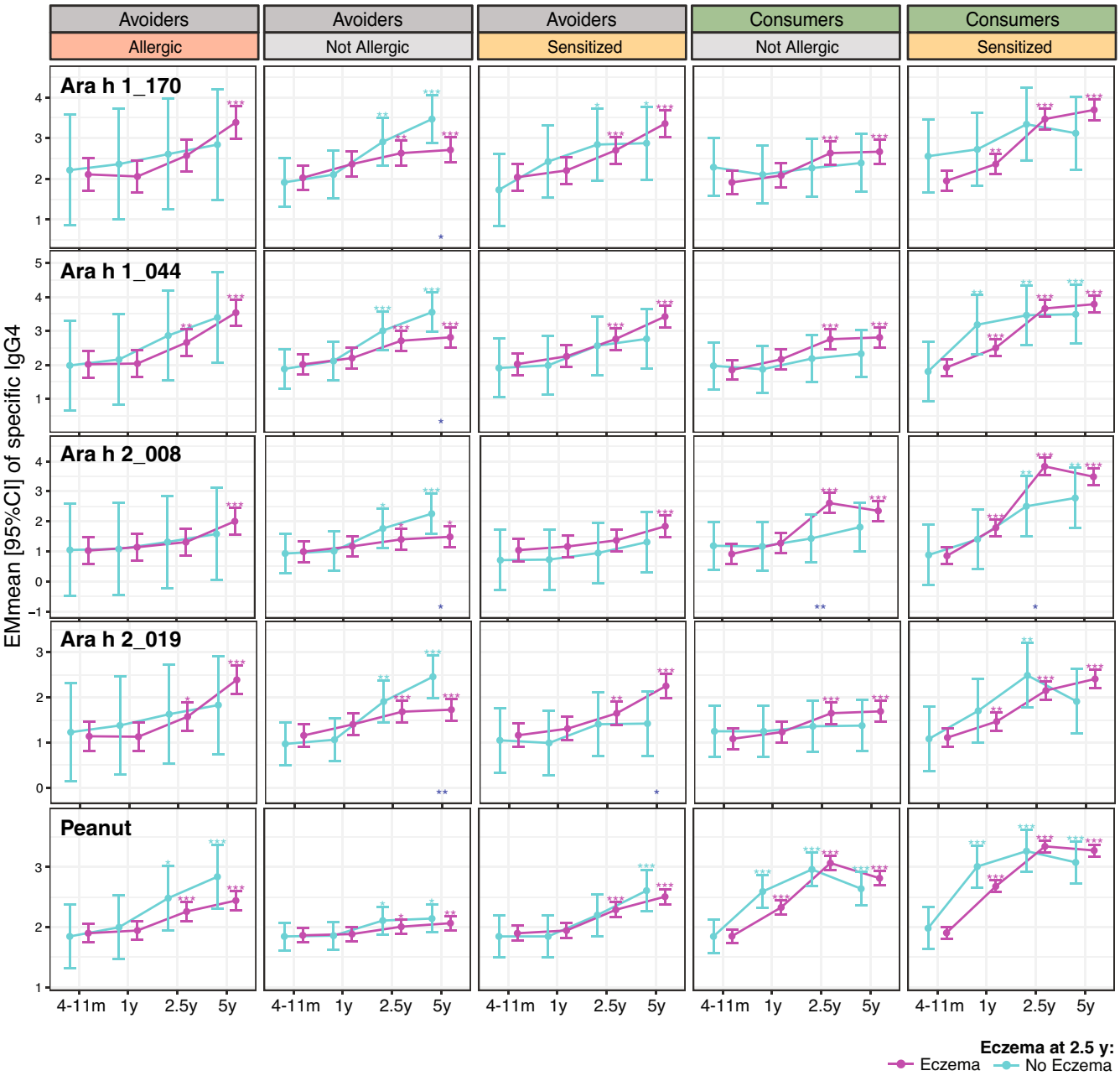


FIGURE 2 Ses-IgG4 association with eczema. Lineplots showing estimated marginal means and 95% confidence intervals (CI) of IgG4 specific to selected epitopes (normalized MFI) and peanut extract ($\log_{10}$ of mg/ml) by early peanut exposure and 5-year allergy status at all timepoints. Colored stars represent change from 4–11 m and dark blue stars—significance by eczema status ($p < .05$*, <.01**, <.001***).

AUTHOR CONTRIBUTIONS

The study was conceptualized by G.L., G.T., M.S.F., and H.A.S. Sample acquisition, data curation, analysis and visualization were carried out by M.S., H.T.B., and M.S.F. Original draft was written by M.S., M.S.F, and H.S. All authors reviewed, edited, and approved the manuscript.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.