

Pediatric Allergy in Honduras: **The dominant effects of IgE specific for** **cross-reactive carbohydrates**

Charlene M. Dunaway Altamirano, MD PhD
Allergy & Immunology Fellow
University of Virginia

Food Allergy

- An immune-mediated adverse reaction to food
- IgE-mediated hypersensitivity reactions
- Peanut allergy is a leading cause of food-related anaphylaxis
- Diagnostic tools: food challenge, skin-prick testing, serum IgE levels
- Presence of IgE alone not sufficient to diagnose a food allergy

Epidemiology in the U.S.

**33 million Americans
live with a life-
threatening food
allergy**

**8% of American
children have a
reported food allergy**

**Emergency room
visits related to food
allergy every 10
seconds**

Global burden

- Australia: Melbourne HealthNuts and SchoolNuts cohort studies
 - FA rates of 11% in infants and 3.8% in 4-year-old children
- Europe: EuroPrevall multi-center project
 - Geographic variability with reported FA rates ranging from 1.9% in Iceland (Reykjavik) to 5.6% in Poland (Lodz)
- United States: Population-based surveys
 - 7.6% of children and 10.8% of adults have probable FAs
- **In lower- and middle-income countries (LMICs), such as Honduras, FA is thought to be uncommon, but reliable studies are limited**

Hypothesis

Prevalence of sensitization to specific food allergens in LMICs is lower than that reported in similar populations from industrialized countries

Food allergy in Honduras

- International collaboration with a Honduran research team
- Cross-sectional, population-based study in the city of San Pedro Sula
- Unselected pediatric population
- Sample size of 400
- IRB approved by Universidad Católica de Honduras

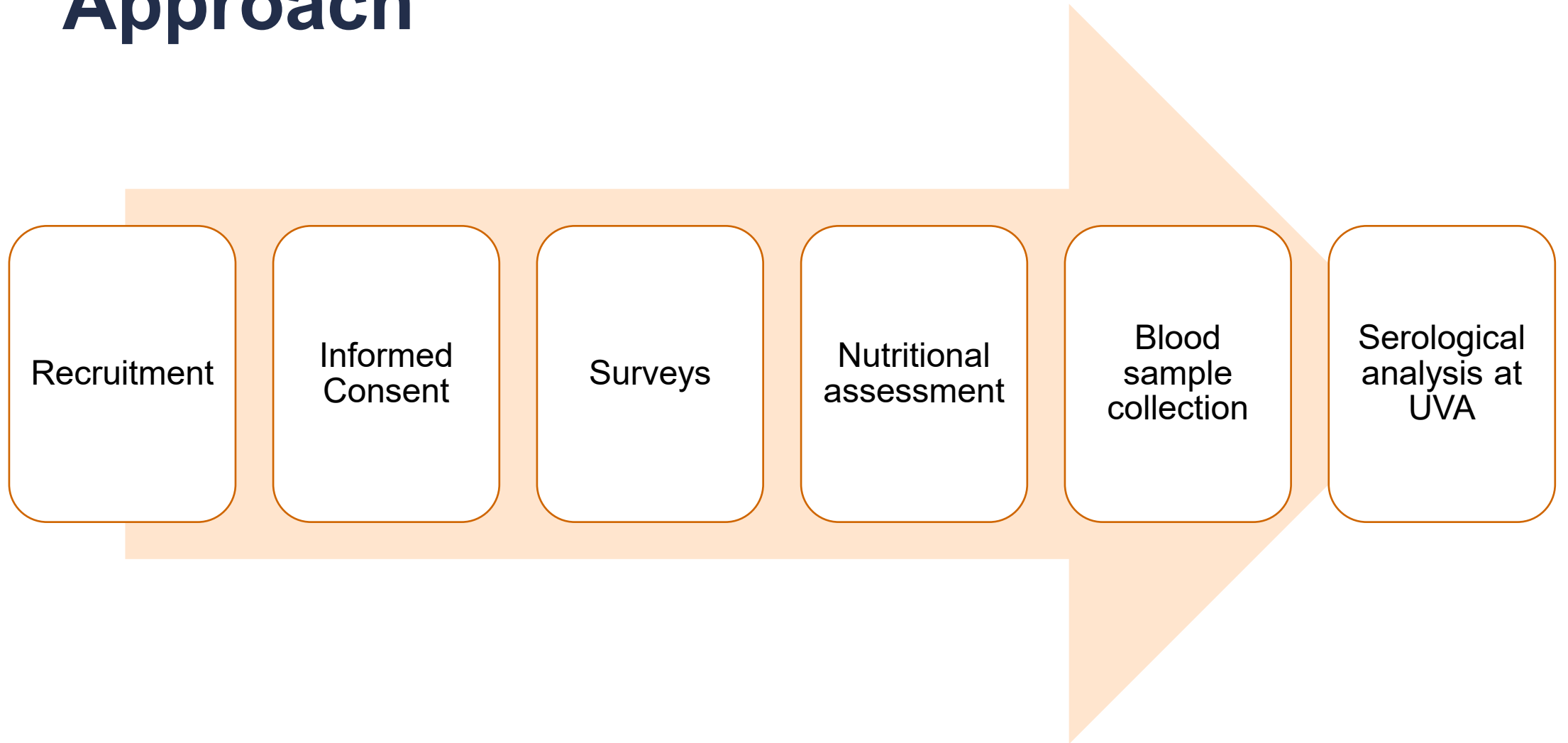


Study design

- **Inclusion criteria:** subjects 5-12 years of age attending local elementary schools or routine pediatric visits at local health centers
- **Exclusion criteria:** subjects outside the target age range, recent venipuncture, history of anemia, acute pathology
- **Recruitment strategy:** subjects invited to participate in a study of nutrition
- Annual per capita income between \$5000-\$9000



Approach



Our study population

Characteristics	N=359
Mean Age, yrs	8.3 (5-12)
Sex, n (%)	
Female	200 (55.7)
Male	159 (44.3)
Recruitment location, n (%)	
Community health center	32 (8.9)
Elementary school	327 (91.1)

Our study population

Characteristics

N=359

Animals in the household, n (%)	277 (77.2)
History of GI parasites, n (%)	73 (20.3)
History of tick bite, n (%)	87 (24.2)
Allergic comorbidities, n (%)	192 (53.5)
Mean AEC (k/μL)	0.412

Reported allergic reactions to food

<ul style="list-style-type: none"><input type="checkbox"/> <u>Skin and/or Oral Mucosa Symptoms</u><ul style="list-style-type: none"><input type="checkbox"/> Hives<input type="checkbox"/> Itching<input type="checkbox"/> Rash<input type="checkbox"/> Swelling (except lip and/or tongue swelling)<input type="checkbox"/> Lip and/or tongue swelling<input type="checkbox"/> Difficulty swallowing<input type="checkbox"/> Hoarse voice<input type="checkbox"/> Itchy mouth<input type="checkbox"/> Throat tightening<input type="checkbox"/> Mouth or throat tingling<input type="checkbox"/> Other: _____<input type="checkbox"/> <u>Respiratory Symptoms</u><ul style="list-style-type: none"><input type="checkbox"/> Chest tightening<input type="checkbox"/> Nasal congestion<input type="checkbox"/> Repetitive cough<input type="checkbox"/> Trouble breathing<input type="checkbox"/> Wheezing<input type="checkbox"/> Other: _____	<ul style="list-style-type: none"><input type="checkbox"/> <u>Gastrointestinal Symptoms</u><ul style="list-style-type: none"><input type="checkbox"/> Belly pain<input type="checkbox"/> Cramps<input type="checkbox"/> Diarrhea<input type="checkbox"/> Nausea<input type="checkbox"/> Vomiting<input type="checkbox"/> Other: _____<input type="checkbox"/> <u>Cardiovascular and/or Heart Symptoms</u><ul style="list-style-type: none"><input type="checkbox"/> Chest pain<input type="checkbox"/> Rapid heart rate<input type="checkbox"/> Fainting, dizziness, or feeling light headed<input type="checkbox"/> Low blood pressure<input type="checkbox"/> Other: _____<input type="checkbox"/> <u>Other Symptoms</u><ul style="list-style-type: none"><input type="checkbox"/> Anxiety<input type="checkbox"/> Feeling of impending doom<input type="checkbox"/> Headache<input type="checkbox"/> Other: _____
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Similar survey used by Gupta et al. in the U.S. population-based studies

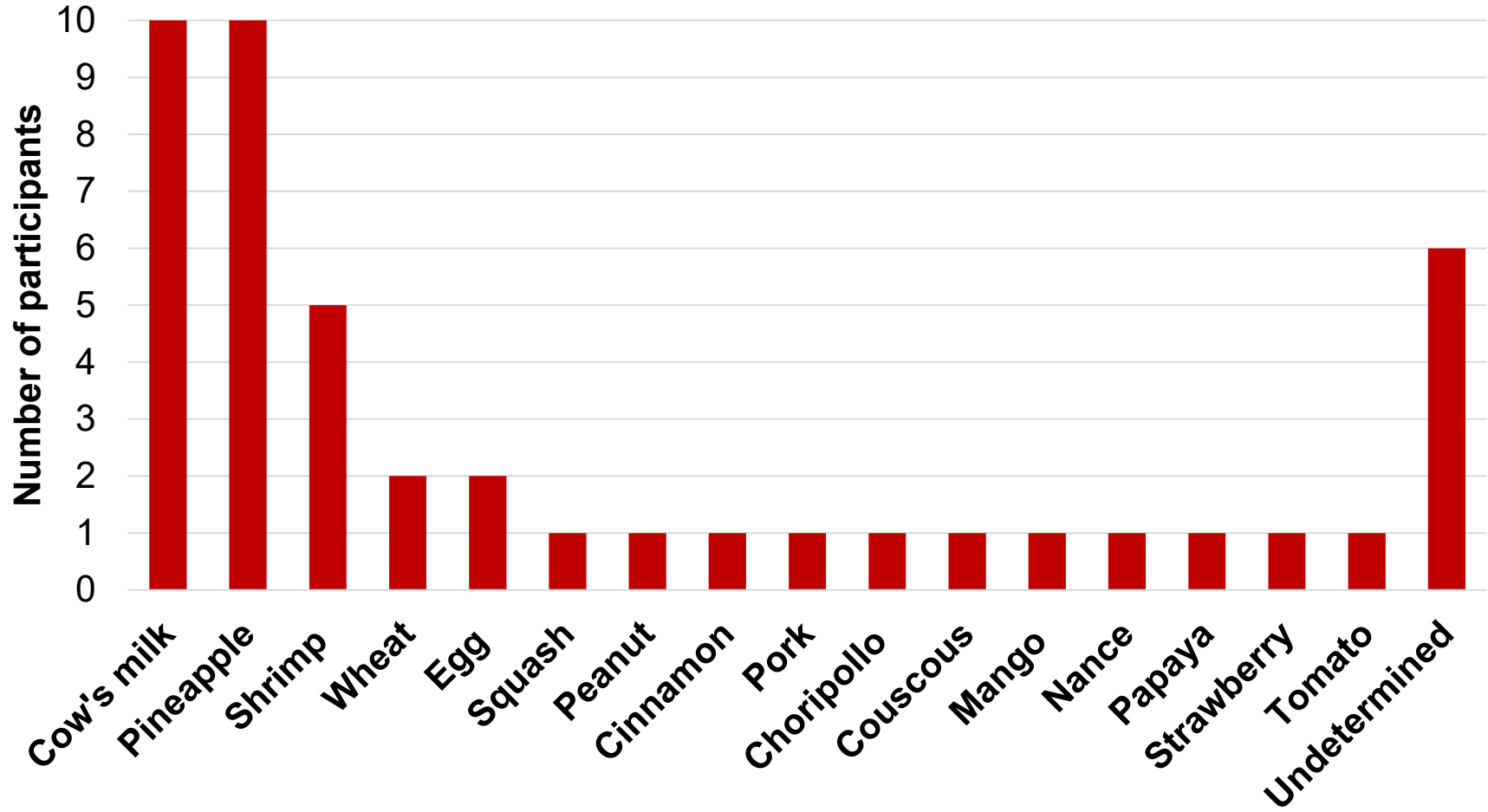
Reported allergic reactions to food

Characteristics	N=359
Prior immediate reaction to foods, n (%)	44 (12.3)
Prior delayed reaction to foods, n (%)	13 (3.6)

Food allergic subjects vs. not allergic

	No reactions n = 315	Self-reported immediate reactions n = 44
Mean Age, yrs	8.2	8.6
Sex, n (%)		
Female	170 (54.0)	30 (68.2)
Male	145 (46.0)	14 (31.8)
Recruitment location, n (%)		
Community health center	24 (7.6)	8 (18.2)
Elementary school	291 (92.4)	36 (81.8)
Animals in the household, n (%)	243 (77.1)	33 (75.0)
History of GI parasites, n (%)	63 (20.0)	10 (22.7)
History of tick bite, n (%)	79 (25.0)	8 (18.2)
Allergic comorbidities, n (%)	158 (50.2)	34 (77.3)
Mean AEC (k/μL)	0.426	0.313

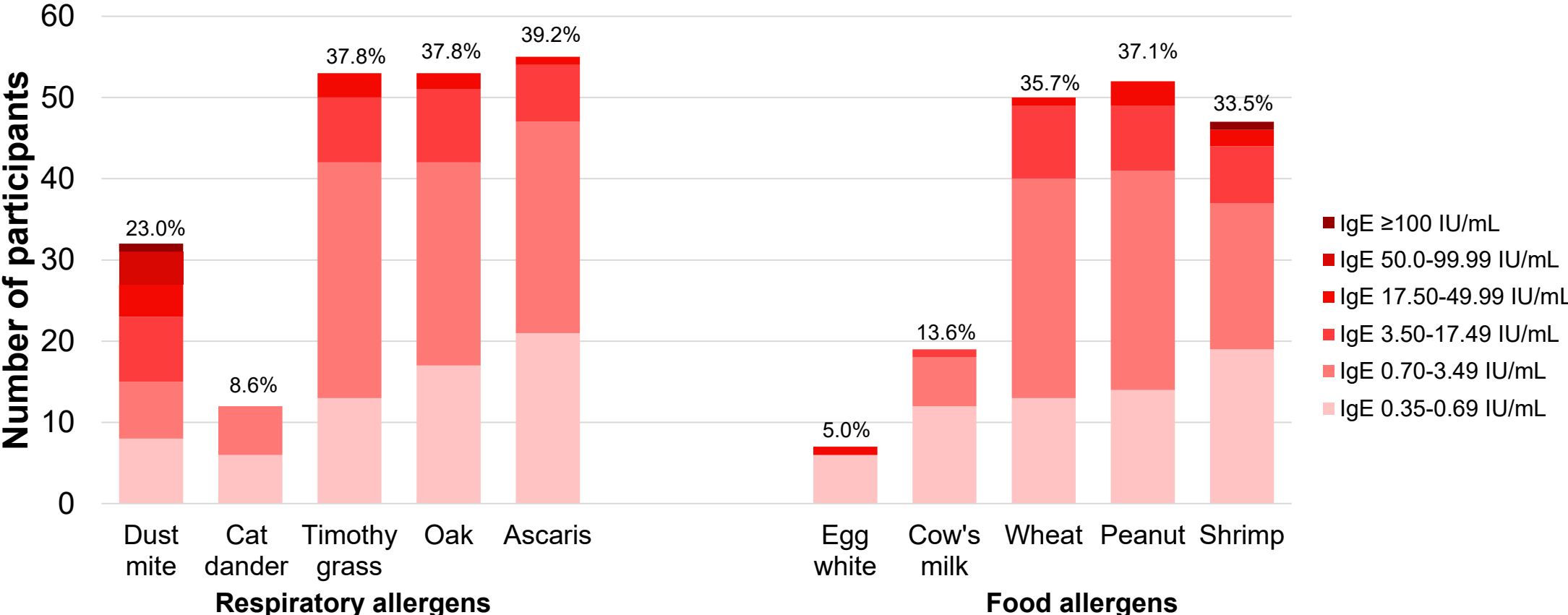
Most reported allergenic foods



N = 44

Patterns of sensitization

Serum IgE levels to food and respiratory allergens in sensitized participants N=140



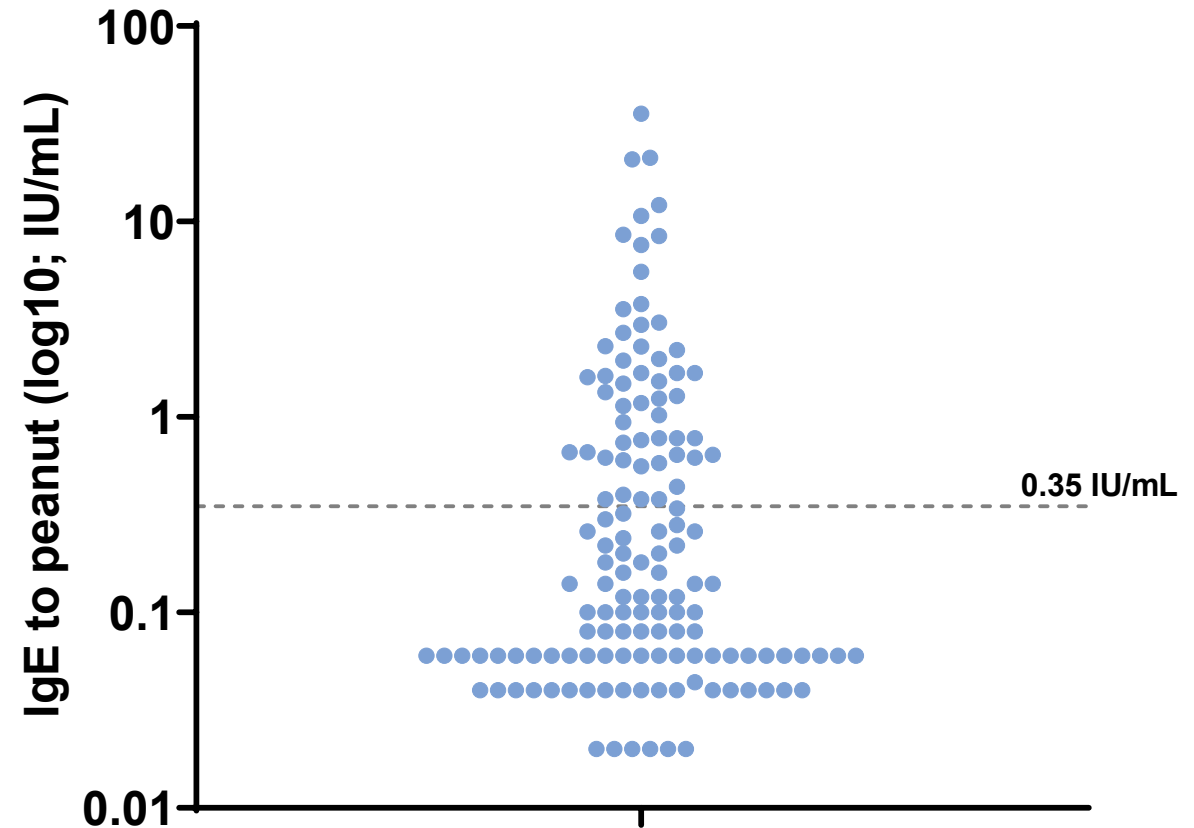
Median total IgE (IU/mL): 186 (5-4122)

Rate of peanut sensitization

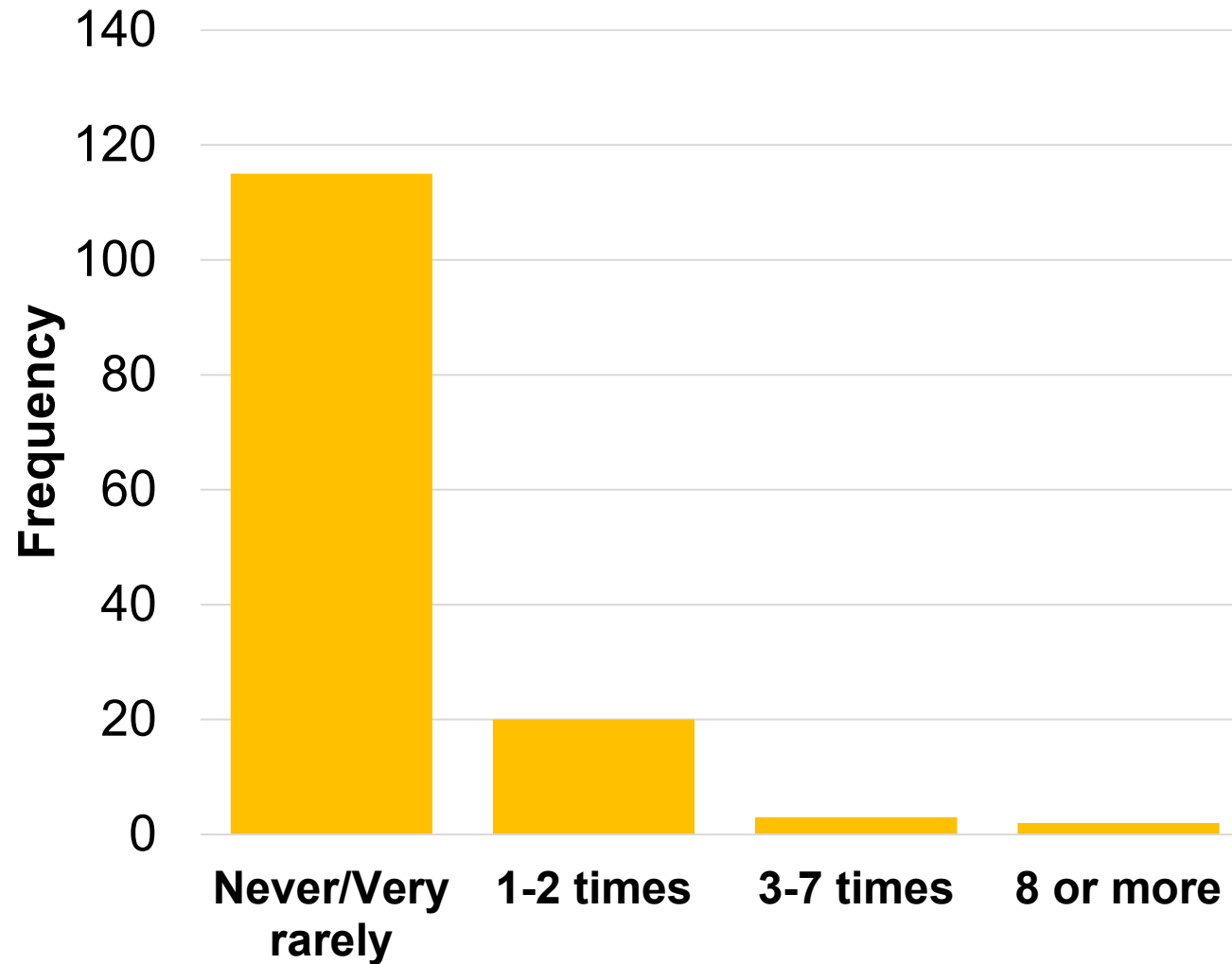
No sensitization, n (%)	88 (62.9%)
Sensitization* , n (%)	52 (37.1%)

* ≥ 0.35 IU/mL

- **None of the subjects reported symptoms associated with peanut consumption**

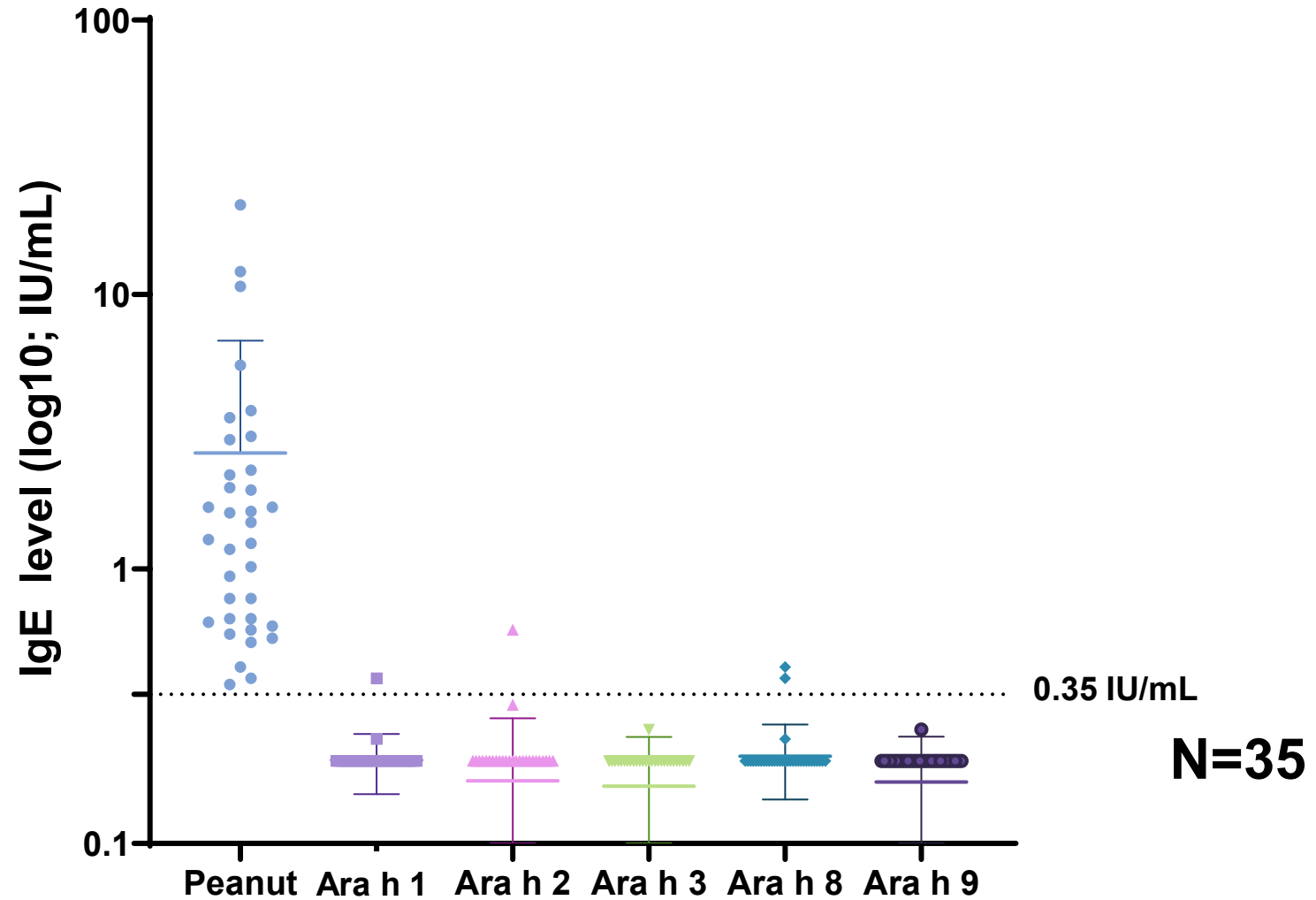


Weekly peanut consumption



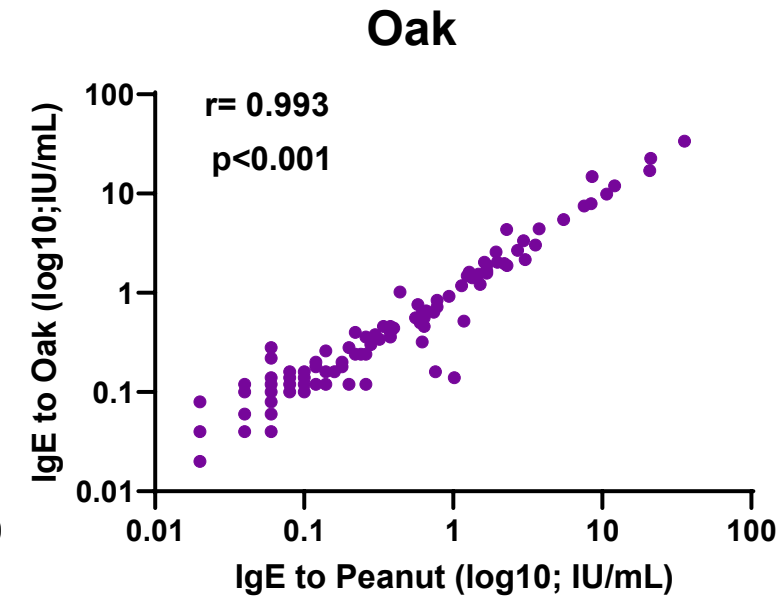
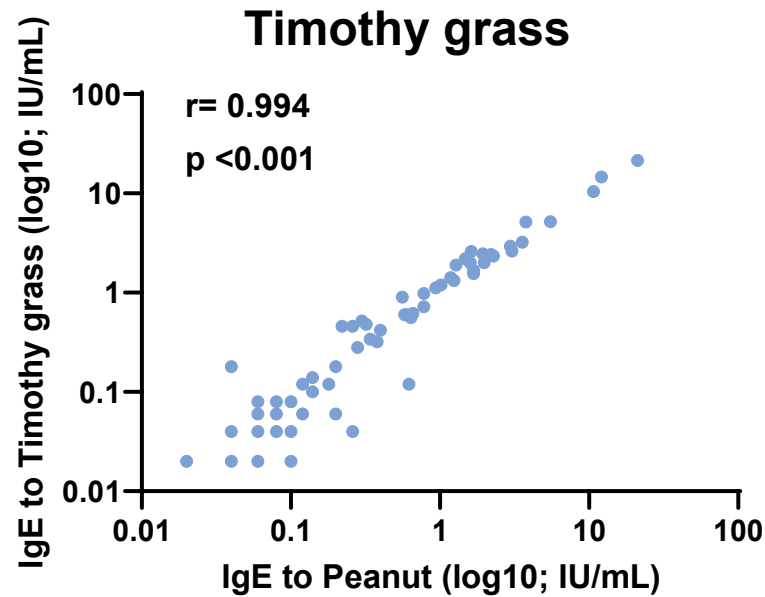
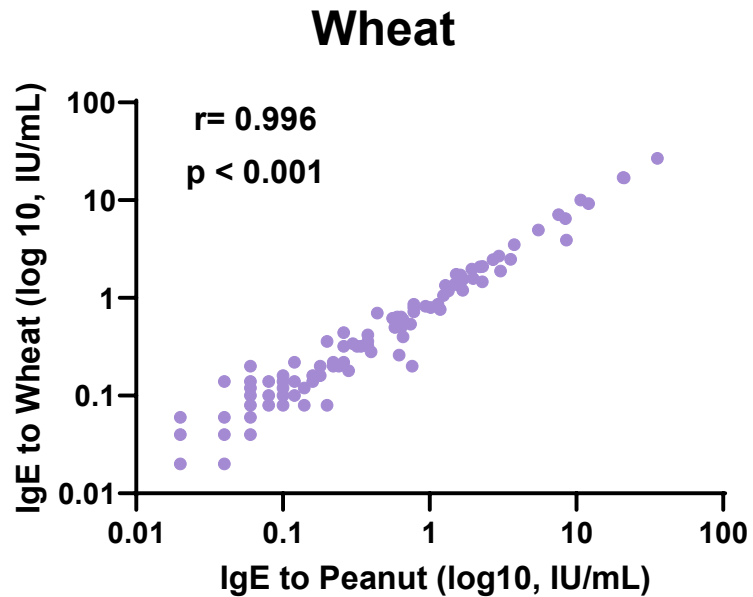
N=140

Peanut components were mostly undetectable



*Peanut components are all recombinant allergens

Peanut sensitization correlates with IgE to other plant-derived allergens

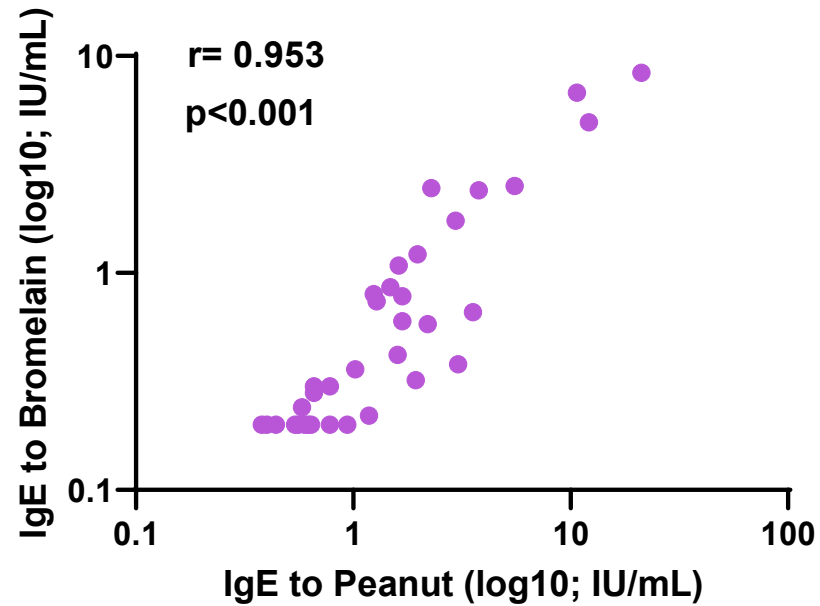


N=52

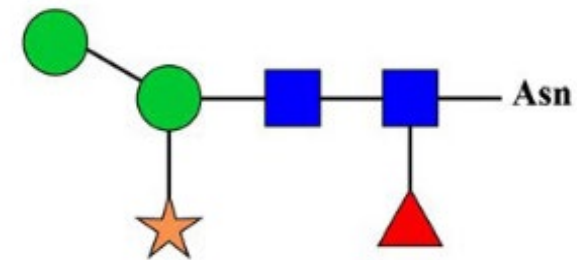
Cross-reactive carbohydrates

- Cross-reactive carbohydrate determinants (CCDs) are oligosaccharides epitopes found on glycoproteins derived from plants, insects and parasites
- Can be recognized by IgE with limited clinical relevance
- A study by Amoah *et al.* among Ghanaian schoolchildren demonstrated high prevalence of peanut-sensitization associated with anti-CCD IgE and *Schistosoma haematobium* infection
 - Peanut-specific IgE (0.35kU/L) prevalence was 17.5%

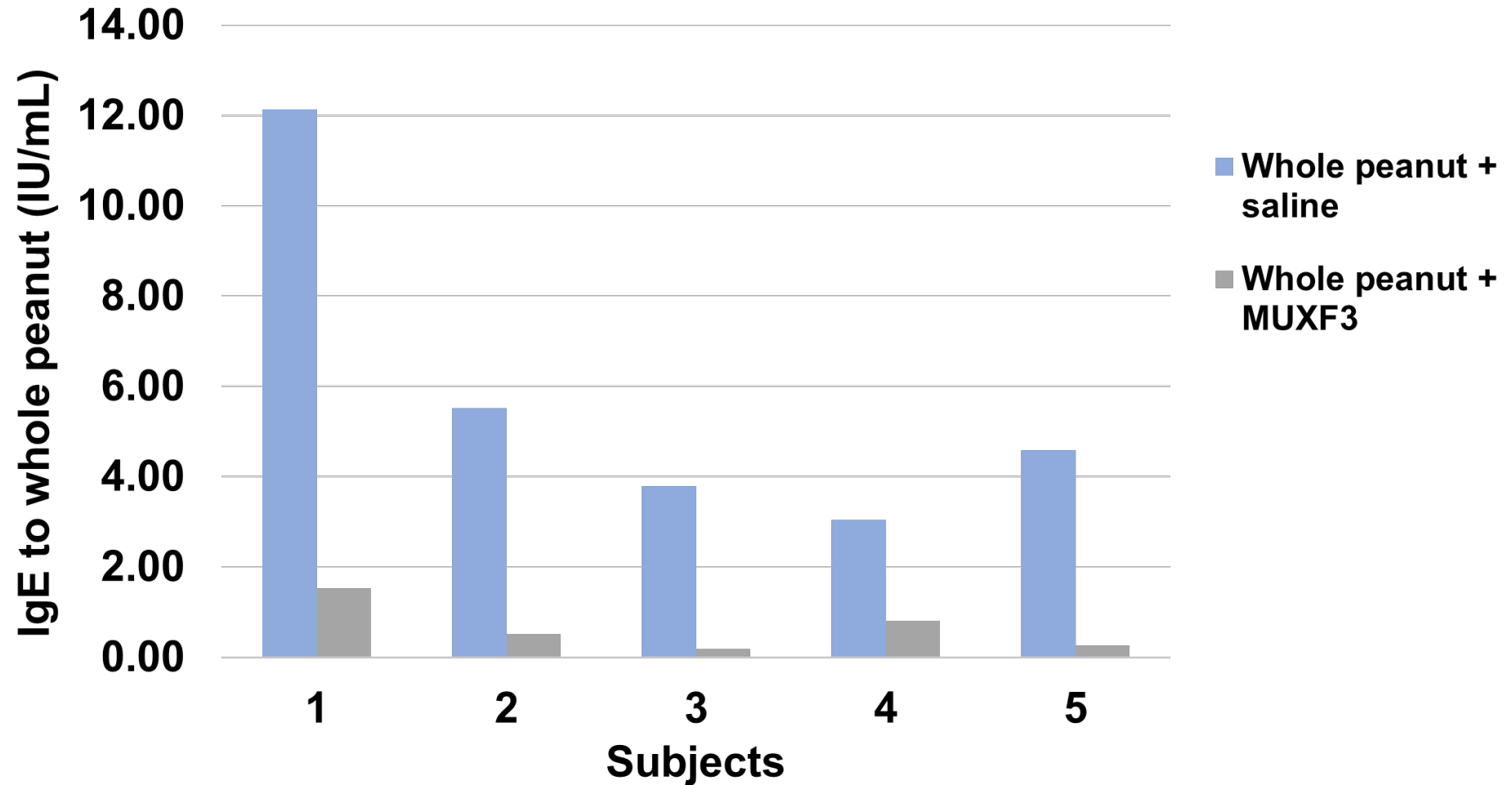
Peanut sensitization strongly correlates with IgE to bromelain (MUXF3)



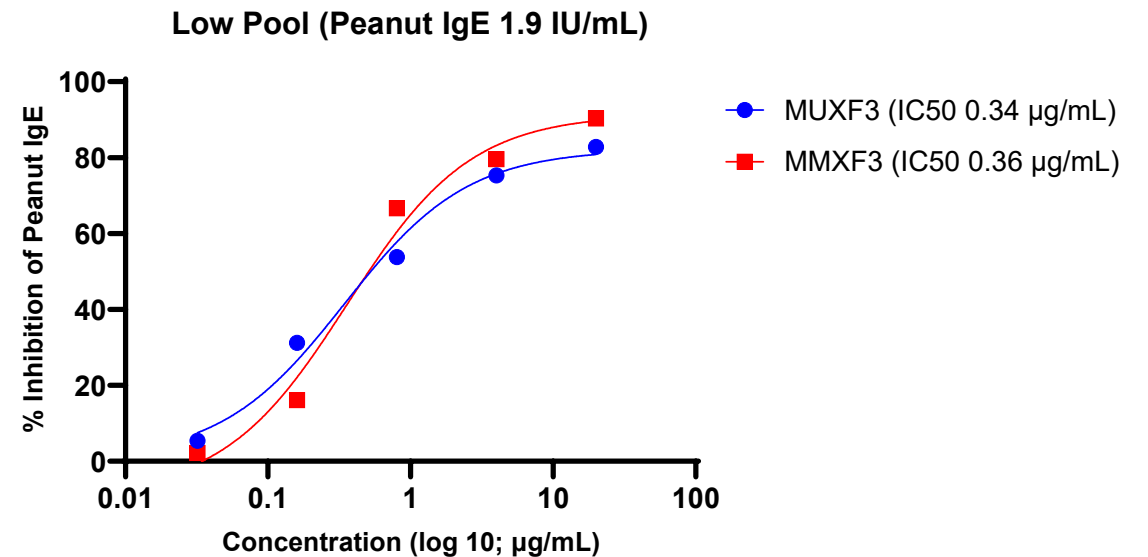
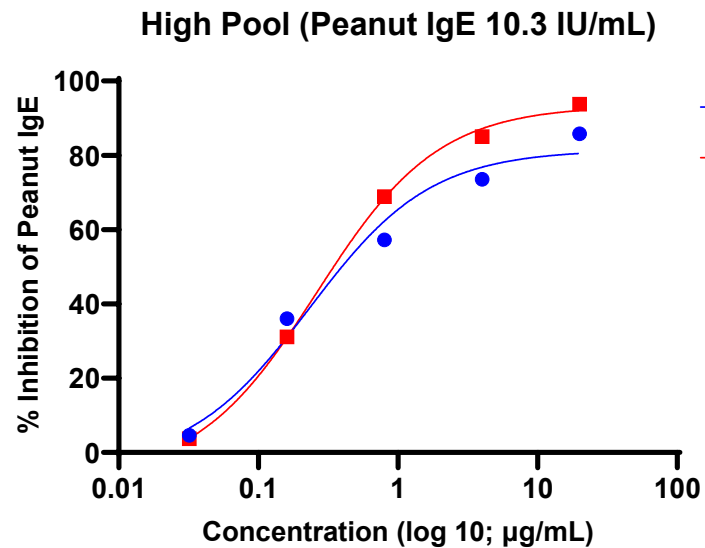
MUXF3 structure



MUXF3 inhibits IgE binding to whole peanut

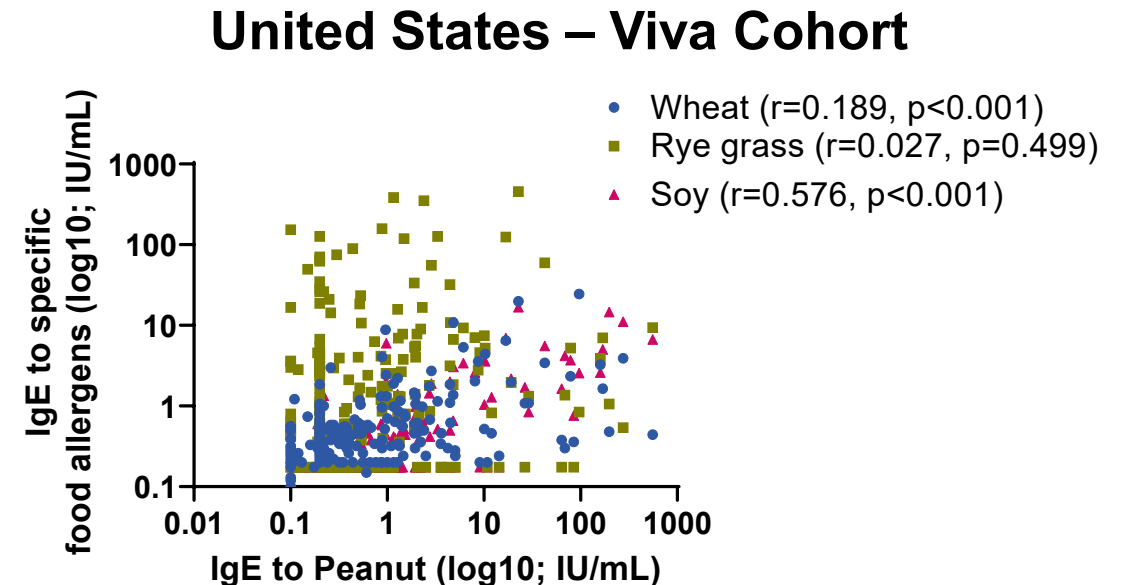
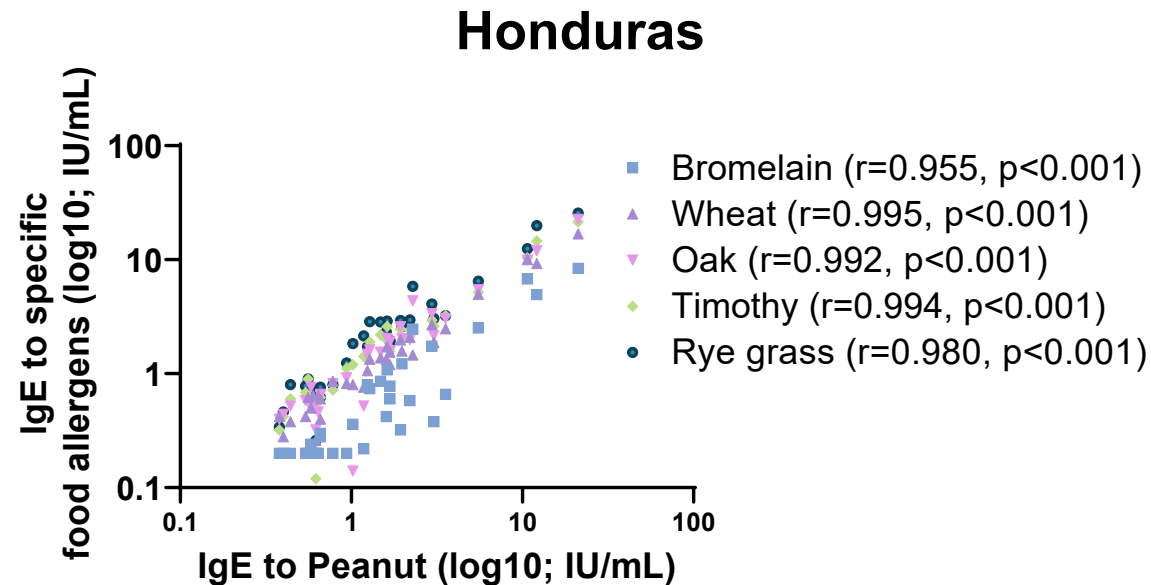


MUXF3 and MMXF3 dose-dependent inhibition of IgE binding to peanut



*MUXF3 and MMXF3 inhibitors were kindly provided by Dr. Friedrich Altman

Patterns of sensitization in US children compared to Honduran children



*Samples from Project Viva provided by Dr. Emily Oken and Dr. Diane Gold

Summary

- Food sensitization is common among Honduran children despite low rates of reported clinical symptoms
- There is a strong correlation between IgE to peanut and IgE to other plant-derived allergens, in particular to wheat, oak, and grass pollen
- This pattern of sensitization seems to be driven by IgE recognition of cross-reactive carbohydrate determinants, such as MUXF3, and is strikingly different from that observed in other similar populations
- This cross-reactivity could be a major confounder for interpretation of serum IgE results for food allergens in Central America
- This CCD sensitization pattern raises the possibility that IgE to CCDs could confer protection against symptomatic food allergy

Next steps

- Continue component analysis for additional foods
- Glycan microarray analysis to potentially identify specific CCD structure preferentially recognized by IgE in this population
- Indirect basophil activation assays
- Comparison of IgE sensitization patterns in pediatric subjects from Honduras with confirmed food allergies

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References

- Sicherer, Scott H., and Hugh A. Sampson. "Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management." *Journal of Allergy and Clinical Immunology* 141.1 (2018): 41-58.
- Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, Nadeau KC. The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States. *Pediatrics*. 2018
- Warren, C.M., Sehgal, S., Sicherer, S.H. et al. Epidemiology and the Growing Epidemic of Food Allergy in Children and Adults Across the Globe. *Curr Allergy Asthma Rep* 24, 95–106 (2024)
- Akdis, Cezmi A. "Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?." *Nature Reviews Immunology* 21.11 (2021): 739-751.
- Lieberman JA, Gupta RS, Knibb RC, Haselkorn T, Tilles S, Mack DP, Pouessel G. The global burden of illness of peanut allergy: A comprehensive literature review. *Allergy*. 2021 May;76(5):1367-1384.
- McGowan EC, Peng RD, Salo PM, Zeldin DC, Keet CA. Changes in Food-Specific IgE Over Time in the National Health and Nutrition Examination Survey (NHANES). *J Allergy Clin Immunol Pract*. 2016 Jul-Aug;4(4):713-20. doi: 10.1016/j.jaip.2016.01.017. Epub 2016 Apr 25. PMID: 27133095; PMCID: PMC4939113.
- Greenhawt M, Shaker M, Wang J, Oppenheimer JJ, Sicherer S, Keet C, Swaggart K, Rank M, Portnoy JM, Bernstein J, Chu DK, Dinakar C, Golden D, Horner C, Lang DM, Lang ES, Khan DA, Lieberman J, Stukus D, Wallace D. Peanut allergy diagnosis: A 2020 practice parameter update, systematic review, and GRADE analysis. *J Allergy Clin Immunol*. 2020 Dec;146(6):1302-1334.
- Amoah AS, Obeng BB, Larbi IA, Versteeg SA, Aryeetey Y, Akkerdaas JH, Zuidmeer L, Lidholm J, Fernández-Rivas M, Hartgers FC, Boakye DA. Peanut-specific IgE antibodies in asymptomatic Ghanaian children possibly caused by carbohydrate determinant cross-reactivity. *J Allergy Clin Immunol*. 2013 Sep 1;132(3):639-47.
- Platts-Mills TA, Hilger C, Jappe U, van Hage M, Gadermaier G, Spillner E, Lidholm J, Keshavarz B, Aalberse RC, van Ree R, Goodman RE. Carbohydrate epitopes currently recognized as targets for IgE antibodies. *Allergy*. 2021 Aug;76(8):2383-94.
- Wilson JM, Workman L, Schuyler AJ, Rifas-Shiman SL, McGowan EC, Oken E, Gold DR, Hamilton RG, Platts-Mills TA. Allergen sensitization in a birth cohort at midchildhood: Focus on food component IgE and IgG4 responses. *Journal of Allergy and Clinical Immunology*. 2018 Jan 1;141(1):419-23.