The Microbiome and Food Allergies

Presented by
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Today's Presenter

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Disclosures

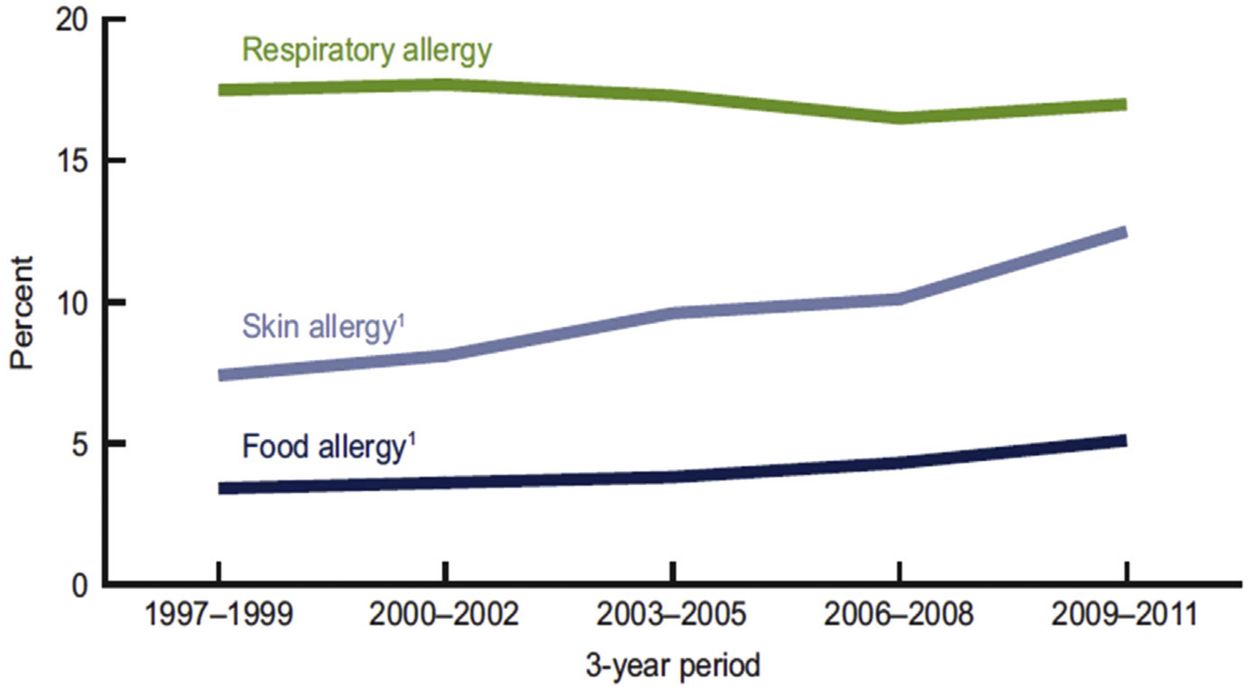
- **Aimmune Therapeutics – Scientific Advisory Board**
- **FARE – Medical Advisory Board**
- Bulmann Laboratories AG – Consulting
- Sanofi USA – Consulting
- **Vedanta Biosciences – Research support**
- **NIAID – Research support**
- Food Allergy Science Initiative / Broad Institute – Research support
- Massachusetts General Hospital -- Employer

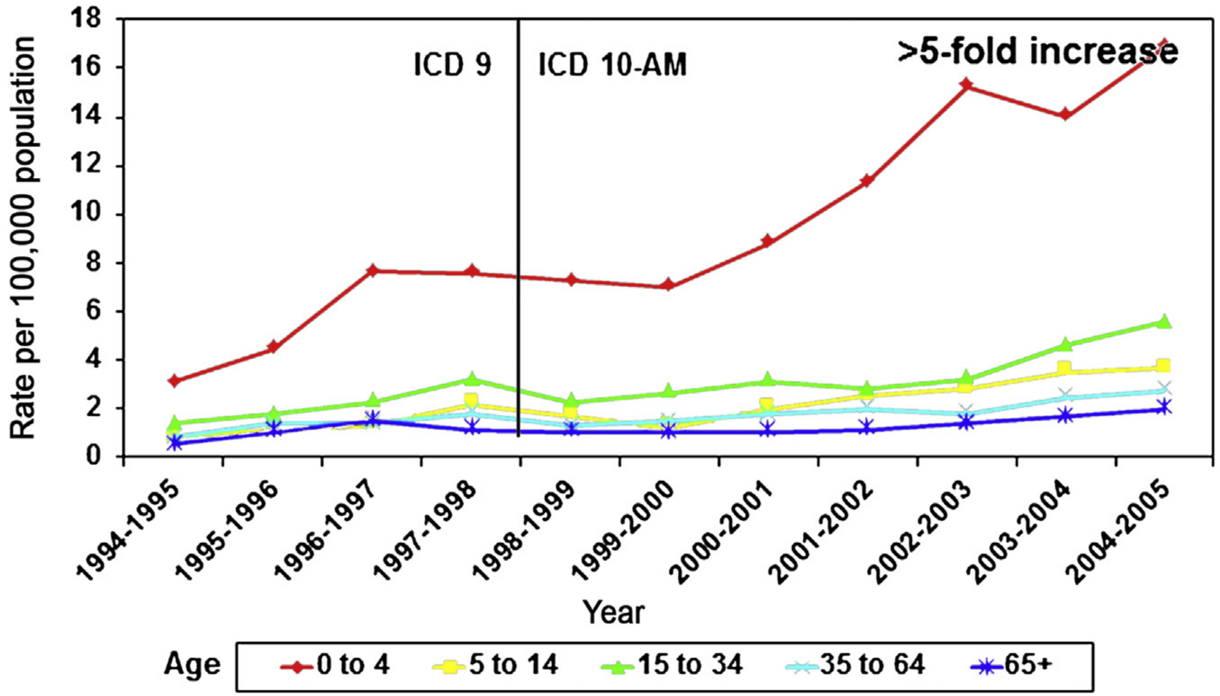
Disclosures

Overview

- Food allergy 101
  - Epidemiology, hygiene and tolerance
- Cohort studies indirectly suggesting a role for the microbiome
- Building the case for the importance of the microbiome
  - Association, Functional, Intervention (in progress)
- Why it matters and what the future may bring
  - 'Sutton's Law', Prevention, Secondary Prevention and Treatment
- Questions

Food allergy 101: Epidemiology



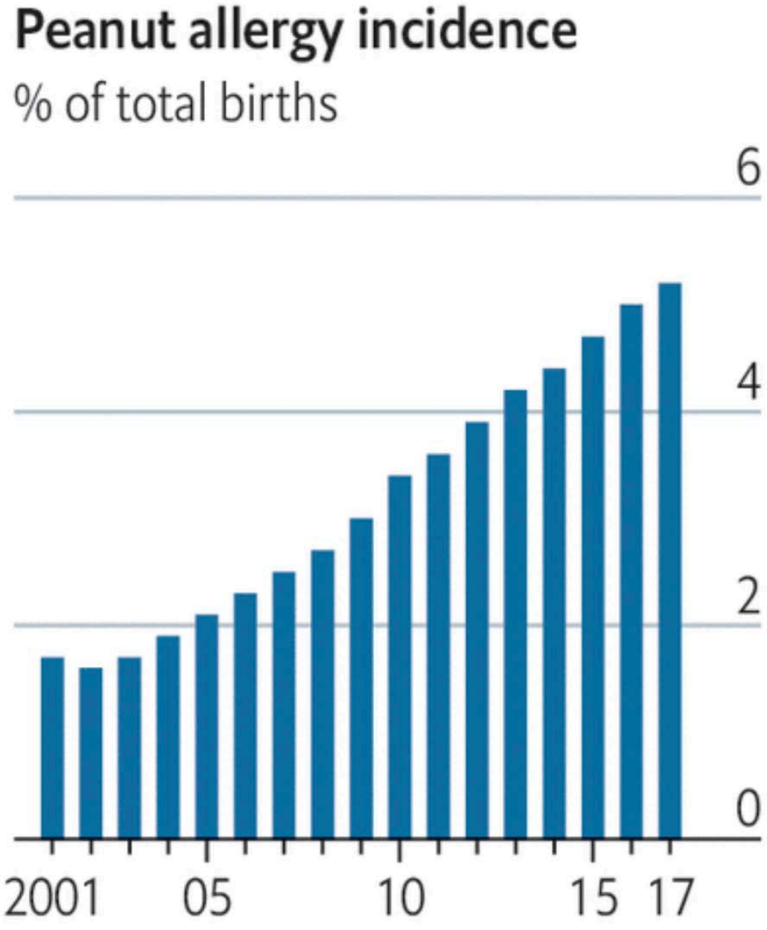


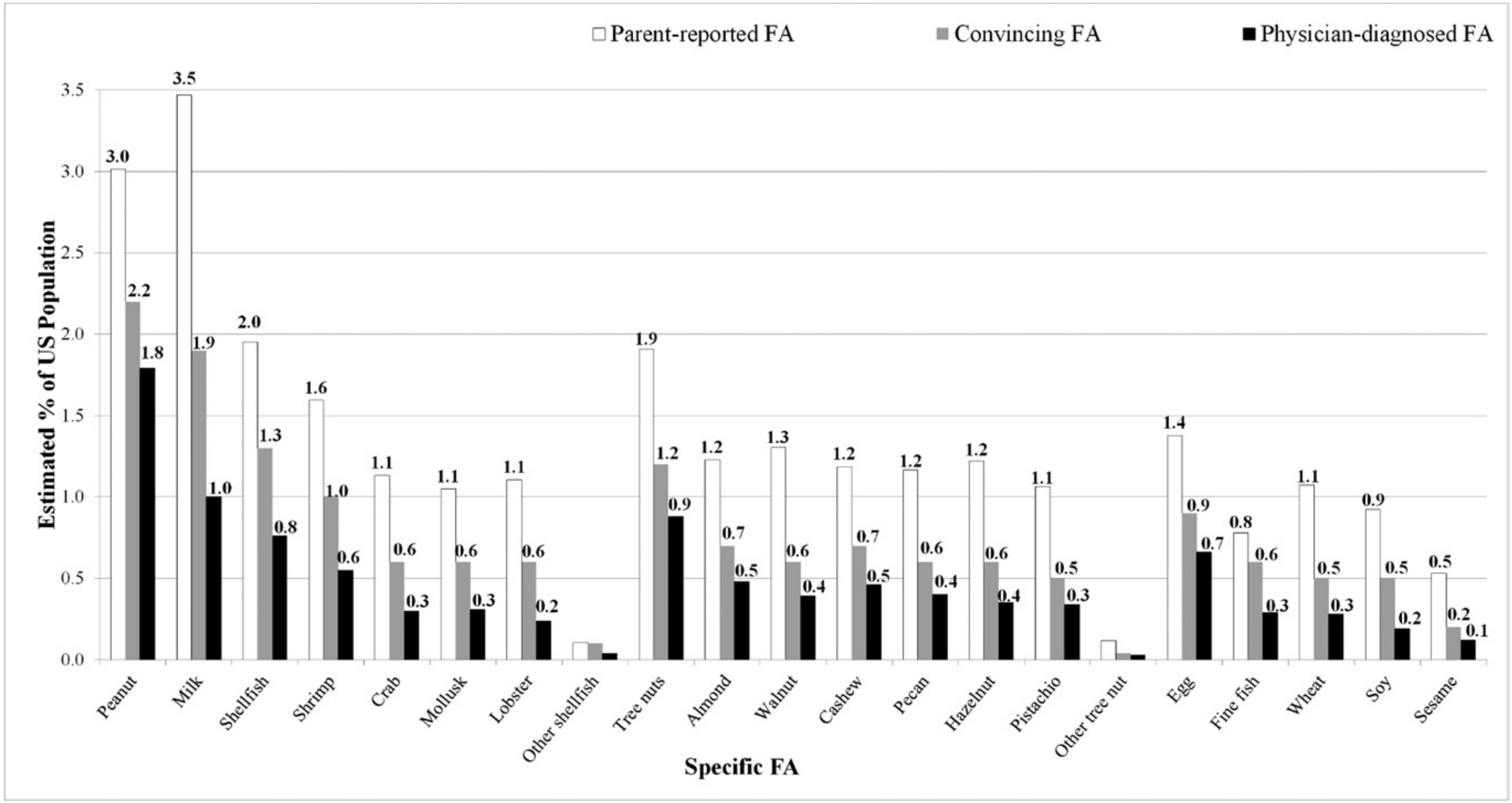
Jackson KD et al. National Child Health Services Data Brief #121; May 2013

Liew WK et al. J Allergy Clin Immunol 2009; 123:434e42

Sampson HA. Allergol Int. 2016 Oct;65(4):363–9.

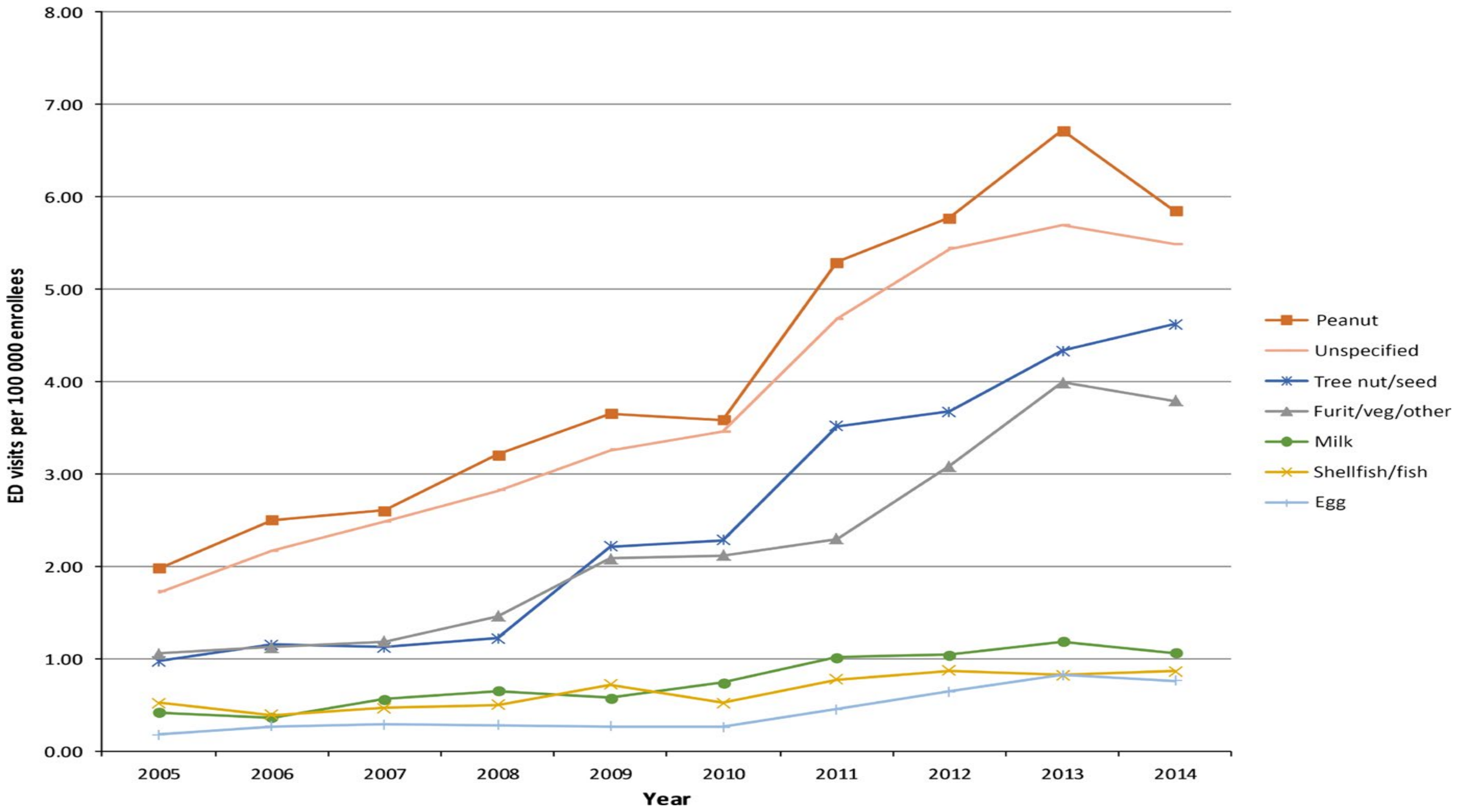
Food allergy 101: Epidemiology





Lieberman J, et al.Ann Asthma All Immunol; 2018121(5):S13.   Gupta RS, et al. Pediatrics. 2018 Dec;142(6):e20181235.

Food allergy 101: Epidemiology



Motosue MS, et al. Pediatr Allergy Immunol. 2018 Aug;29(5):538–44.

Food allergy 101: The Hygiene Hypothesis

Hay fever, hygiene, and household size

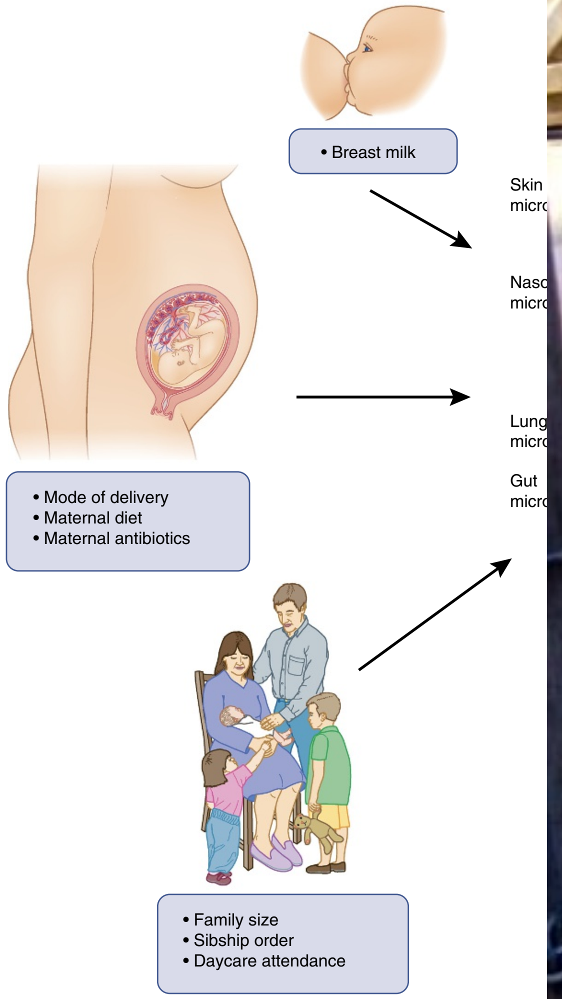
David P Strachan

Hay fever has been described as a "post industrial revolution epidemic,"[1] and successive morbidity surveys from British general practice suggest that its prevalence has continued to increase over the past 30 years.[2] Other evidence suggests a recent increase in the prevalence of asthma[2] and childhood eczema.[3] This paper suggests a possible explanation for these trends over time.

"Over the past century declining family size, improvements in household amenities, and higher standards of personal cleanliness have reduced the opportunity for cross infection in young families."

Strachan DP. BMJ. 1989 Nov 18;299(6710):1259–60.

Food allergy 101: The Hygiene Hypothesis (Plus)



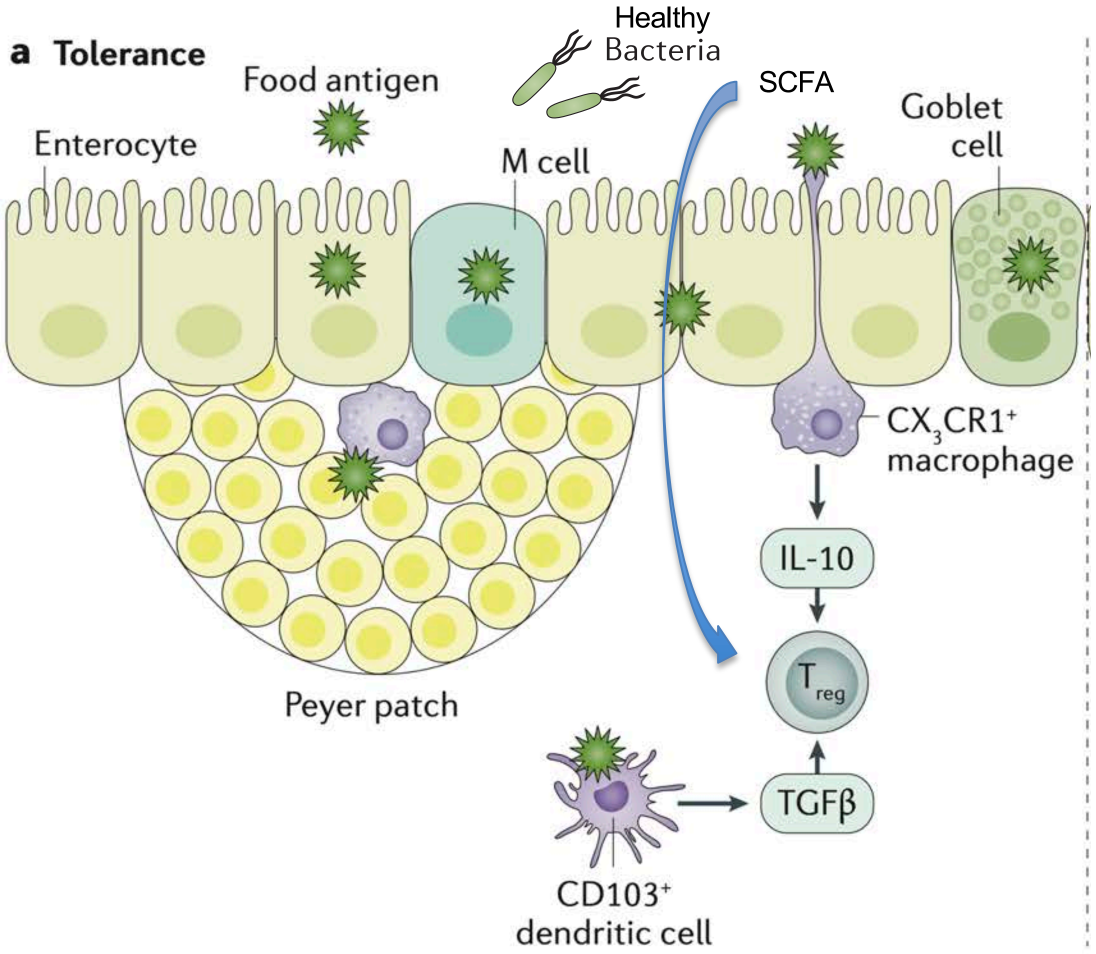
Lambrecht BN, Hammad H. Nat I

Food allergy 101: Glossary

- MICROBIOME: The sum of microbes and their genomic elements in a particular environment.
- SHORT-CHAIN FATTY ACID: Fatty acids with fewer than 6 carbon atoms.
- RORγt+ Treg CELLS: Also referred to as type 3 regulatory T (Treg) cells, these Foxp3+ Treg cells are generated in response to the intestinal microbiota and are essential for suppression of type 2 immunity.
- PROBIOTIC: Live microorganisms with beneficial effects on the host.
- PREBIOTIC: Nondigestible substrates that promote the growth, function, or both of beneficial microorganisms.
- DYSBIOSIS: A state of imbalance in a microbial ecosystem.

Bunyavanich S, Berin MC. J Allergy Clin Immunol. 2019 Dec;144(6):1468–77.

Food allergy 101: The tolerance paradigm



Modified from Renz H, et al. Food allergy. Nat Rev Dis Primers. 2018 Jan 4;4:17098–20.

Overview

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  - Epidemiology, hygiene and tolerance
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Observational cohort studies (allergy generally)

- Prenatal maternal exposure to pets
- Birth by vaginal versus cesarean section delivery
- Growing up in rural environment (close contact with animals)
- Growing up with pets (or older siblings)

Aichbhaumik N, et al. Clin Exp Allergy 2008;38:1787-94.

Bager P, et al. Clin Exp Allergy 2008;38:634-42.

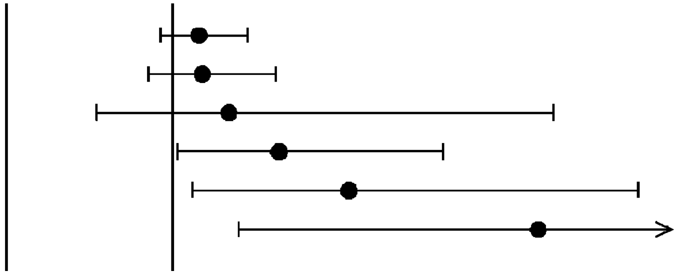
von Mutius E, Radon K. Immunol Allergy Clin North Am 2008;28:631-47

Ownby DR, et al. JAMA 2002;288: 963-72.

Kim H, et al. Curr Allergy Asthma Rep 2019;19:22.

Observational cohort studies specific to food allergy

Ref.	First author	n	CS (%)	Outcome	Ages (years)	Prevalence (%)
				Food allergy (* = food atopy)		
[1]	Liem	13 980	NA	Constructed diagnosis	0–6	4
[2]	Salam	3464	21	Rep, foods/drugs	8–17	13
[3]	Rentz–Polster	8953	16	Phy, foods	3–17	<1
[4]	Negele	2500	17	IgE to food allergens*	2	9
[5]	Laubereau	865	17	IgE to food allergens*	1	11
[6]	Eggesbo	2803	12	Rep, egg/fish/nuts	1–2	1



		Summary ORs		Heterogeneity statistics	
Outcome	*N**	Fixed effects model OR, 95% CI	Random effects model OR, 95% CI	*Q*	*P*-value
Food allergy/food atopy	6	1.32 (1.12–1.55)	1.45 (1.12–1.86)	8.99	0.11
Inhalant atopy	4	1.06 (0.87–1.28)	1.07 (0.82–1.38)	4.14	0.25
Eczema/atopic dermatitis	8	1.03 (0.98–1.09)	1.03 (0.98–1.09)	1.64	0.98
Allergic rhinitis	7	1.23 (1.12–1.35)	1.24 (1.08–1.43)	10.60	0.10
Asthma	13	1.18 (1.11–1.23)	1.18 (1.05–1.32)	31.38	<0.01
Hospitalization for asthma	7	1.23 (1.18–1.27)	1.21 (1.12–1.31)	18.58	<0.01

Bager P, et al. Clin Exp Allergy. 2008 Apr;38(4):634–42.

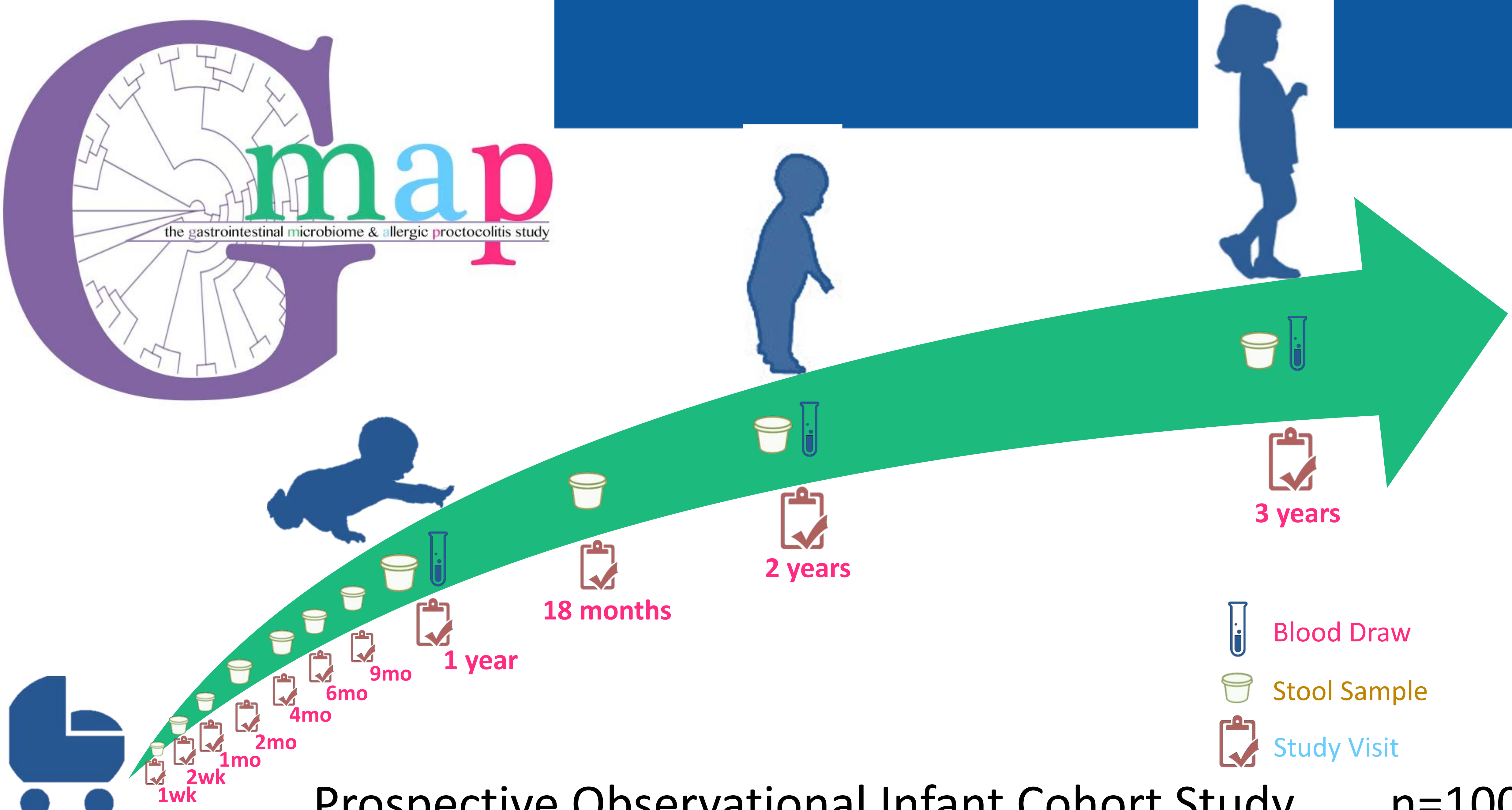
Observational cohort studies specific to food allergy

	Unadjusted		Adjusted[†]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Female gender	0.79 (0.65, 0.96)	0.018	0.81 (0.65, 1.00)	0.052
Preterm delivery	0.54 (0.32, 0.91)	0.021	0.52 (0.30, 0.92)	0.025
Number of siblings				
None	1.0		1.0	
One	0.74 (0.60, 0.93)		0.72 (0.57, 0.92)	
Two	0.62 (0.44, 0.86)		0.56 (0.38, 0.81)	
Three or more	0.32 (0.15, 0.65)	*P* trend:	0.31 (0.14, 0.68)	*P* trend:
Per sibling	0.75 (0.66, 0.85)	*<0.001*	0.72 (0.62, 0.83)	*<0.001*
Cat ownership				
No cat	1.0		1.0	
Cat outside only	0.79 (0.45, 1.41)	0.43	0.93 (0.49, 1.77)	0.83
Cat allowed inside	0.62 (0.45, 0.85)	0.004	0.75 (0.52, 1.09)	0.13
Dog ownership[‡]				
No dog	1.0		1.0	
Dog outside only	0.77 (0.55, 1.08)	0.13	1.09 (0.75, 1.57)	0.66
Dog allowed inside	0.55 (0.41, 0.73)	<0.001	0.72 (0.52, 0.99)	0.043
Age at first introduction of egg				
4–6 months	1.0		1.0	
7–9 months	1.11 (0.84, 1.46)		1.03 (0.77, 1.39)	
10–12 months	1.30 (0.98, 1.73)	*P* trend	1.28 (0.95, 1.74)	*P* trend
>12 months	4.87 (3.30, 7.18)	*<0.001*	4.36 (2.84, 6.67)	*<0.001*
Immediate family (parent/s or	1.58 (1.26, 1.99)	<0.001	1.82 (1.40, 2.36)	<0.001

Koplin JJ, et al. Allergy. 2012 Nov;67(11):1415–22.

Gmap

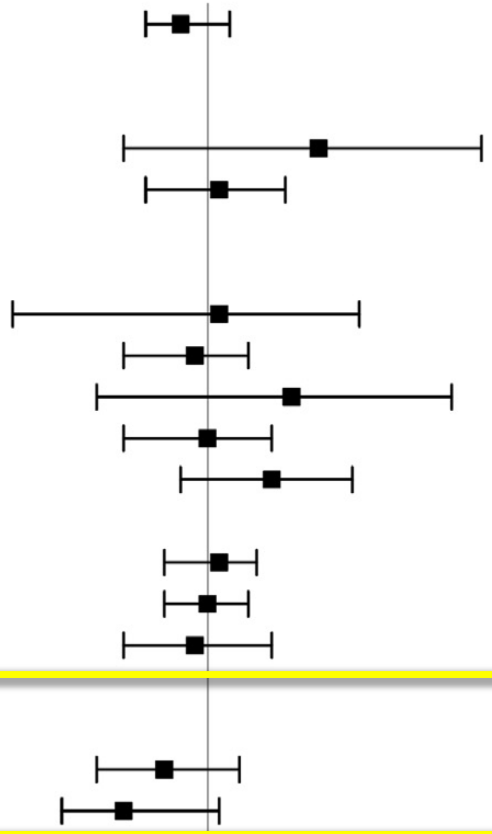
the gastrointestinal microbiome & allergic proctocolitis study



Prospective Observational Infant Cohort Study n=1003

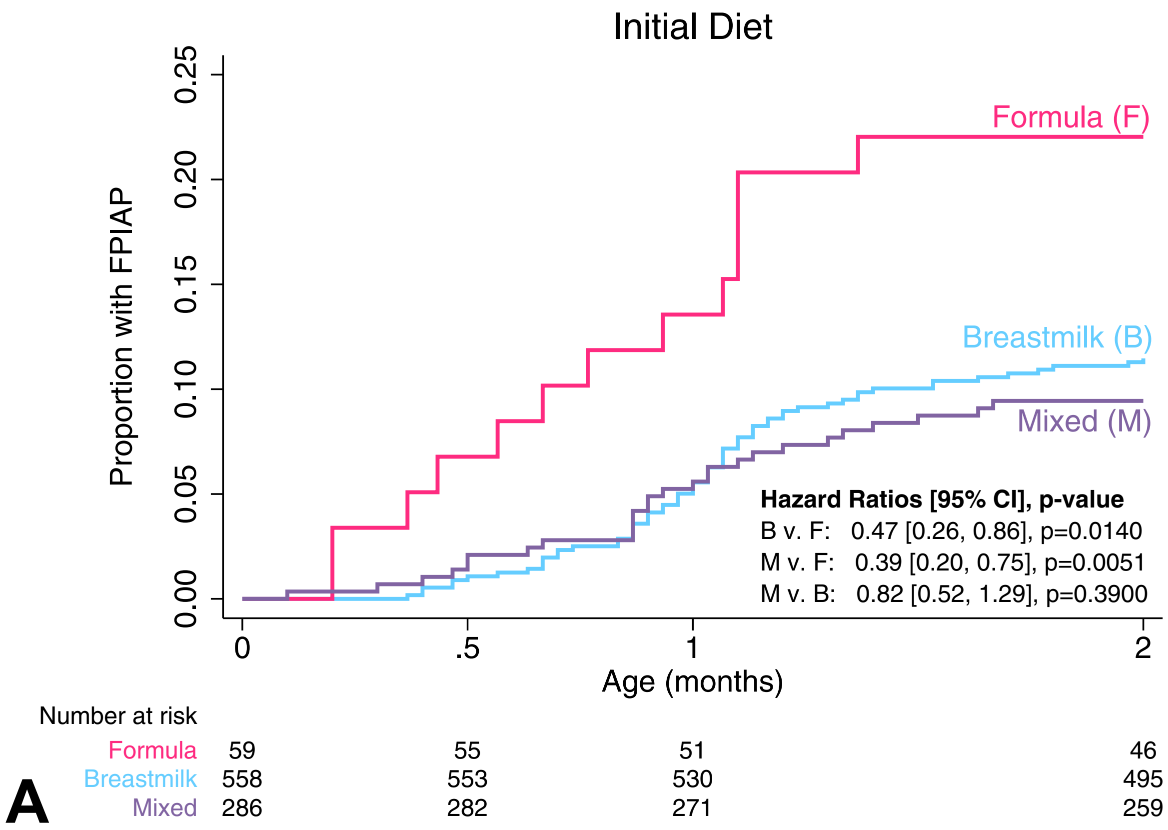
Observational cohort studies: GMAP

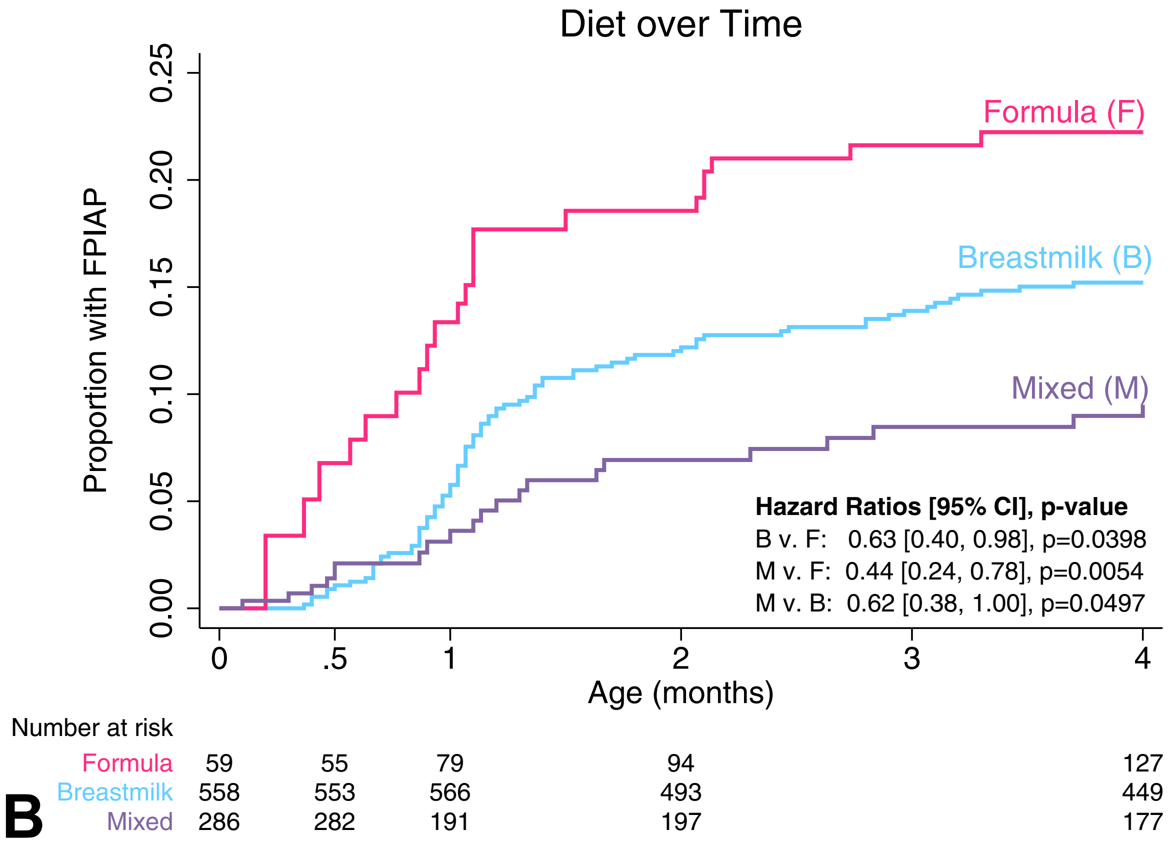
	Cohort: n (%) 903	FPIAP: n (%) 153	Unaffected: n (%) 750	Odds Ratio [95% CI]	p-value
Demographics					
Female	417 (46)	65 (42)	352 (47)	0.8 [0.6, 1.2]	0.315
Gestational Age					
>37 weeks	806 (89)	134 (88)	672 (90)	*	
25-32 weeks	9 (1)	3 (2)	6 (1)	2.5 [0.5, 9.6]	0.198
33-37 weeks	88 (10)	16 (10)	72 (10)	1.1 [0.6, 1.9]	0.711
Race					
White	601 (69)	104 (70)	497 (68)	*	
Black	16 (2)	3 (2)	13 (2)	1.1 [0.2, 3.5]	0.880
Asian	164 (19)	25 (17)	139 (19)	0.9 [0.5, 1.4]	0.532
Other	10 (1)	3 (2)	7 (1)	2 [0.4, 7.5]	0.305
Multiple Race	84 (10)	14 (9)	70 (10)	1 [0.5, 1.7]	0.885
Hispanic or Latino	41 (6)	11 (9)	30 (5)	1.7 [0.8, 3.3]	0.165
Delivery Characteristics					
C-section	286 (32)	50 (33)	236 (31)	1.1 [0.7, 1.5]	0.769
Maternal Antibiotics at Delivery	449 (50)	76 (50)	373 (50)	1 [0.7, 1.4]	0.988
Infant Perinatal Antibiotics	80 (9)	13 (9)	67 (9)	0.9 [0.5, 1.7]	0.862
Initial Diet					
Formula	59 (7)	14 (9)	45 (6)	*	
Breastmilk	558 (62)	98 (64)	460 (61)	0.7 [0.4, 1.3]	0.245
Mixed	286 (32)	41 (27)	245 (33)	0.5 [0.3, 1.1]	0.076



Martin VM, et al. J Allergy Clin Immunol Pract. 2020 May;8(5):1692–1699.e1.

Observational cohort studies: GMAP





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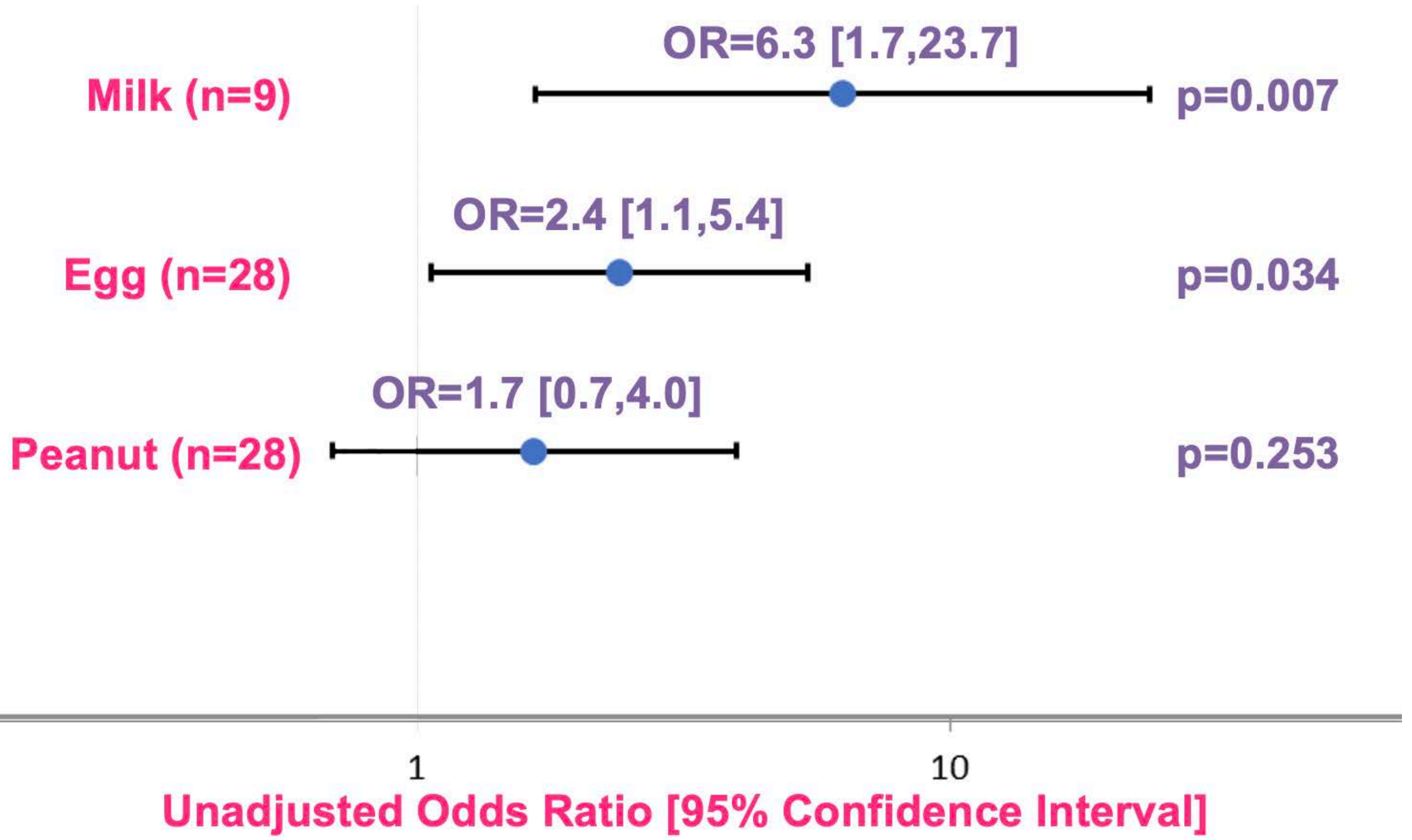
Observational cohort studies: GMAP



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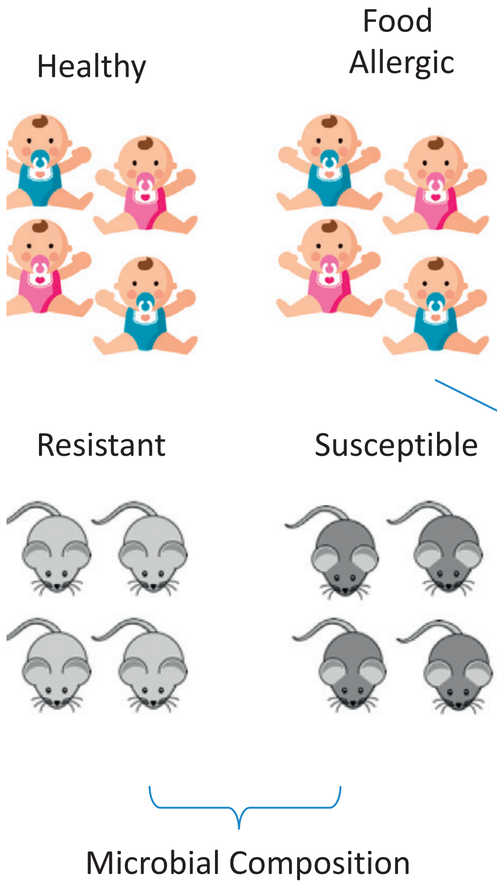
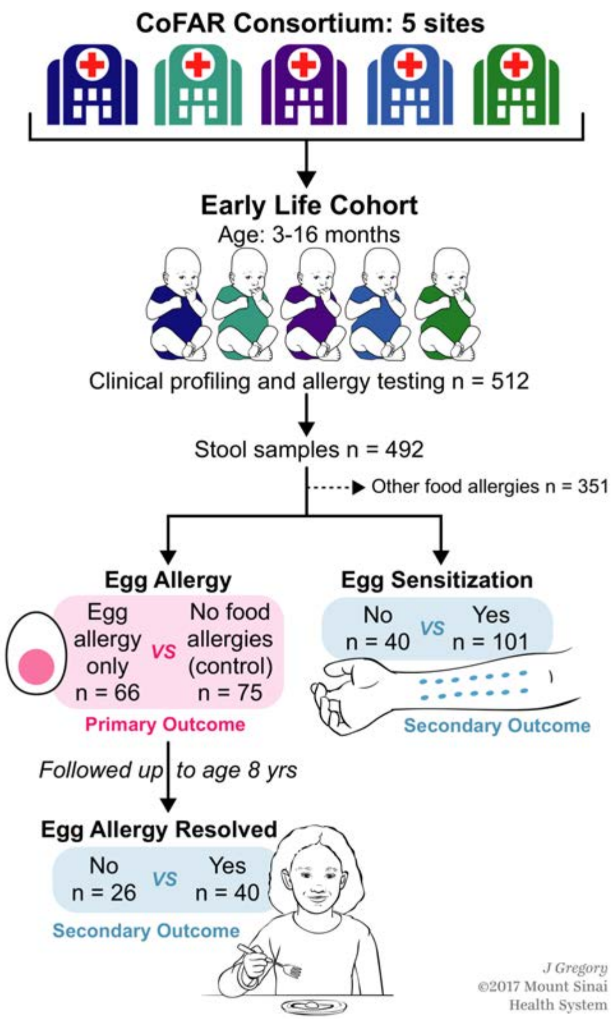
Hierarchy of Evidence

Observational



Bunyavanich S, Berin MC. J Allergy Clin Immunol. 2019 Dec;144(6):1468–77.

Egg allergy and egg sensitization

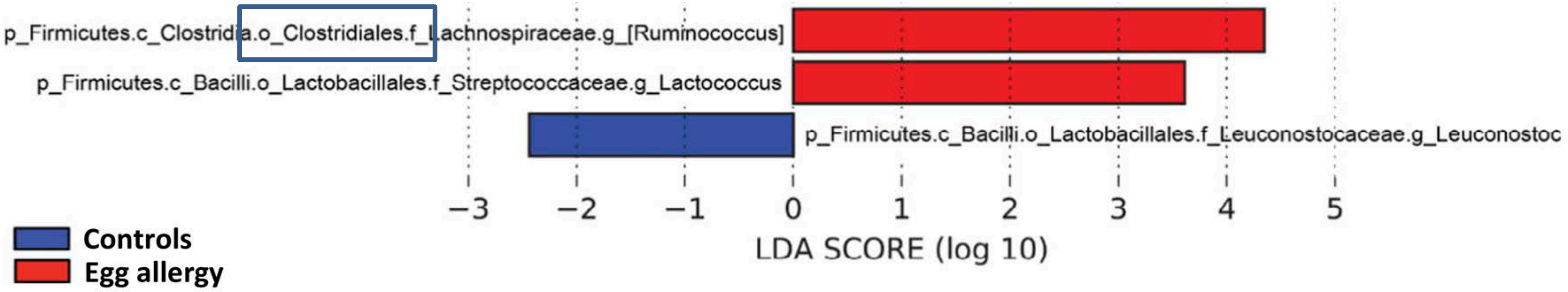


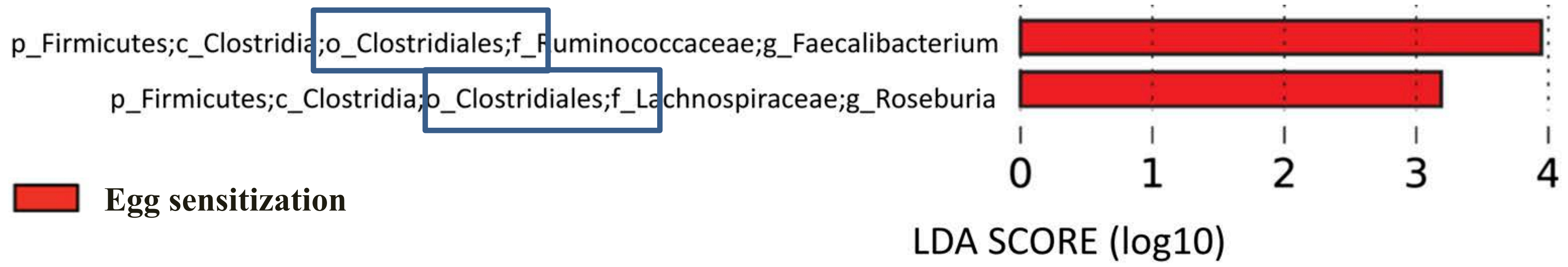
Characteristics	All subjects (n = 141)	Egg allergy (n = 66)	Controls (n = 75)	*P* value*
Sex—female	46 (32.6%)	19 (28.8%)	27 (36.0%)	0.38
Age—Mo	9.7 (3.4)	11.7 (2.8)	7.9 (2.8)	4.5×10^{-13}
Race—Caucasian	103 (73.0%)	47 (71.2%)	56 (74.7%)	0.71
Egg sIgE (kU_A/L)	3.4 (5.9)	5.3 (7.6)	1.7 (3.2)	5.3×10^{-4}
Egg SPT (wheal mm)	7.0 (4.3)	8.4 (4.0)	5.7 (4.2)	1.8×10^{-4}
Atopic dermatitis				0.03
None	7 (5.0%)	6 (9.1%)	1 (1.3%)	
Mild	25 (17.7%)	16 (24.2%)	9 (12.0%)	
Moderate	70 (49.6%)	27 (40.9%)	43 (57.3%)	
Severe	39 (27.7%)	17 (25.8%)	22 (29.3%)	
Currently breastfeeding	55 (39.0%)	16 (24.2%)	39 (52.0%)	9.7×10^{-4}
Mode of delivery—vaginal	96 (68.1%)	44 (66.7%)	52 (69.3%)	0.86
Solid food intake	127 (90.1%)	65 (98.5%)	62 (82.7%)	1.5×10^{-3}
Antibiotics—any during lifetime	88 (62.4%)	50 (75.8%)	38 (50.7%)	2.9×10^{-3}
Resolution of egg allergy by age 8 y	n/a	40 (60.6%)	n/a	n/a

Number (%) or mean (SD) reported.
*Fisher's exact test for categorical variables, *t* test for continuous variables.

Fazlollahi M, et al. Allergy. 2018 Jul;73(7):1515–24.

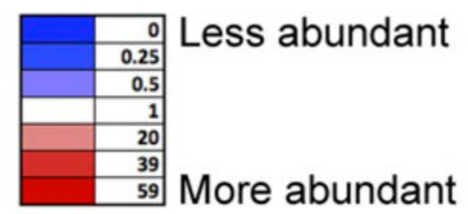
Egg allergy and egg sensitization

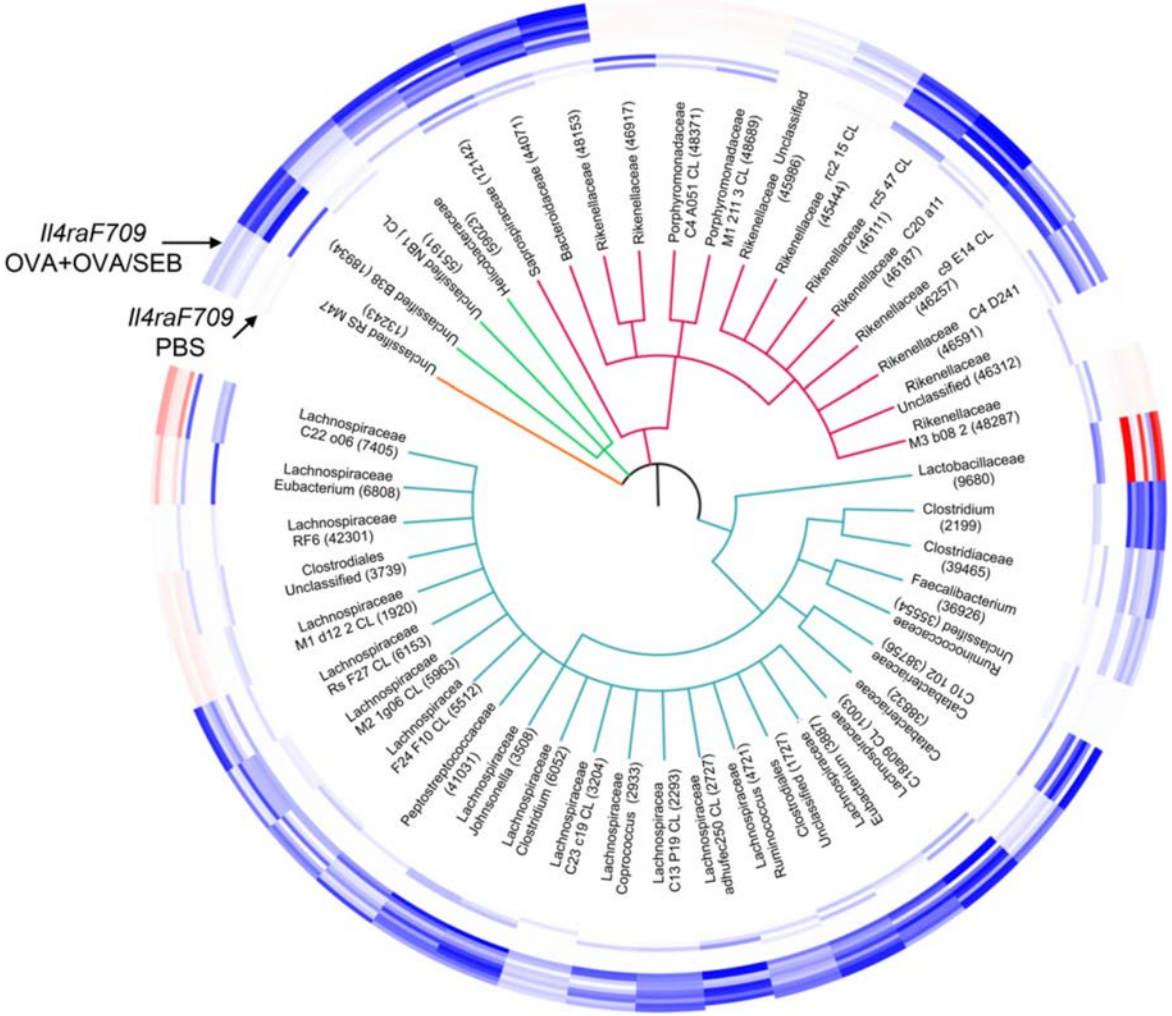




Fazlollahi M, et al. Allergy. 2018 Jul;73(7):1515–24.

The IL4raF709 OVA model





Clostridiales

Noval Rivas M, et al. J Allergy Clin Immunol. 2013 Jan;131(1):201–12.

Persistent vs transient milk allergy

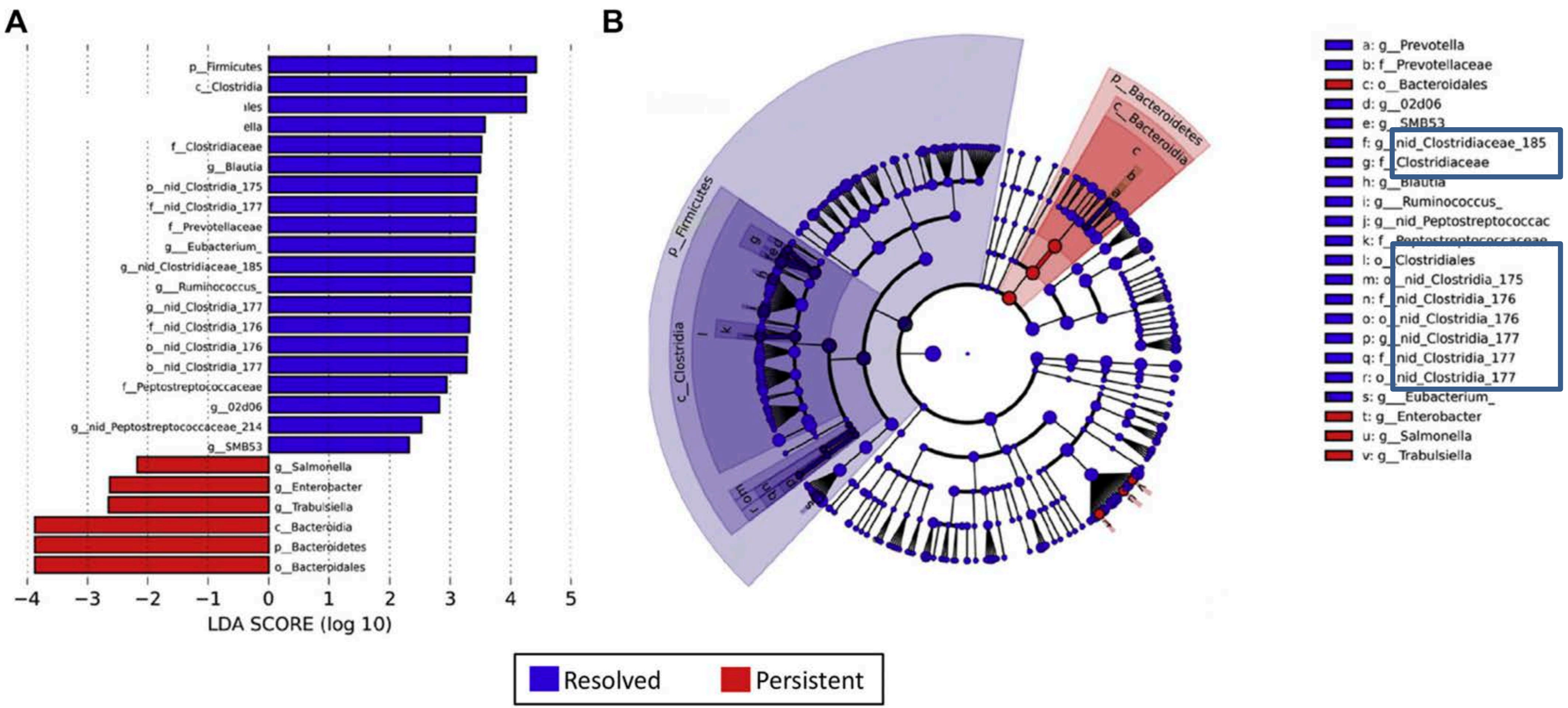
TABLE I. Baseline characteristics of the participating subjects with milk allergy

Characteristics	All subjects with milk allergy included in the analysis	Milk allergy persistent at age 8 y	Milk allergy resolved by age 8 y	*P* value*
Subjects, n (%)	226	98 (43.4)	128 (56.6)	
Age at stool collection (mo), n (%)				.83
3-6	29	11 (37.9)	18 (62.1)	
7-12	144	64 (44.4)	80 (55.6)	
13-16	53	23 (43.4)	30 (56.6)	

No associations with mode of delivery, antibiotics, breast-feeding, AD

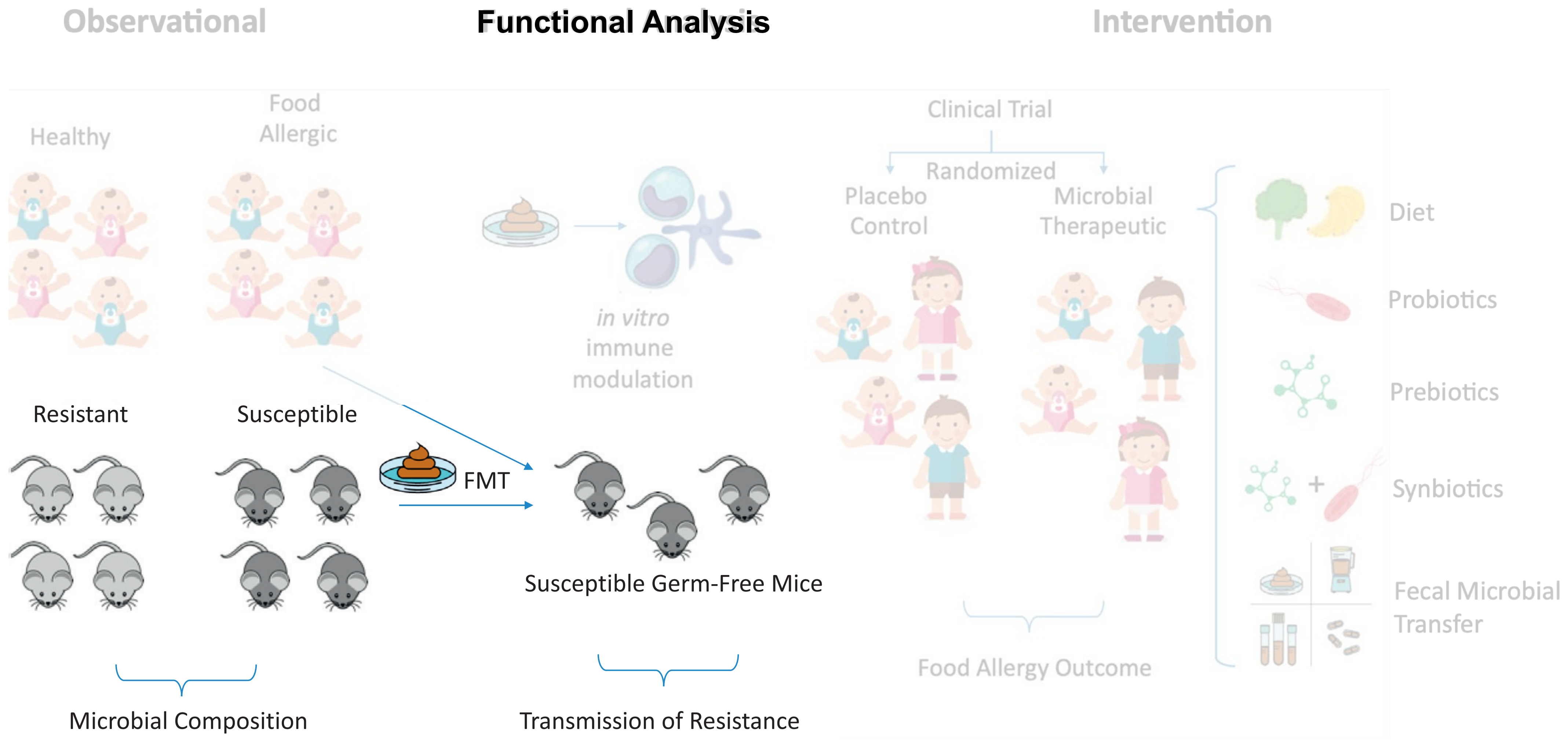
Bunyavanich S, et al. J Allergy Clin Immunol. 2016 Oct;138(4):1122–30.

Persistent vs transient milk allergy



Bunyavanich S, et al. J Allergy Clin Immunol. 2016 Oct;138(4):1122–30.

Hierarchy of Evidence

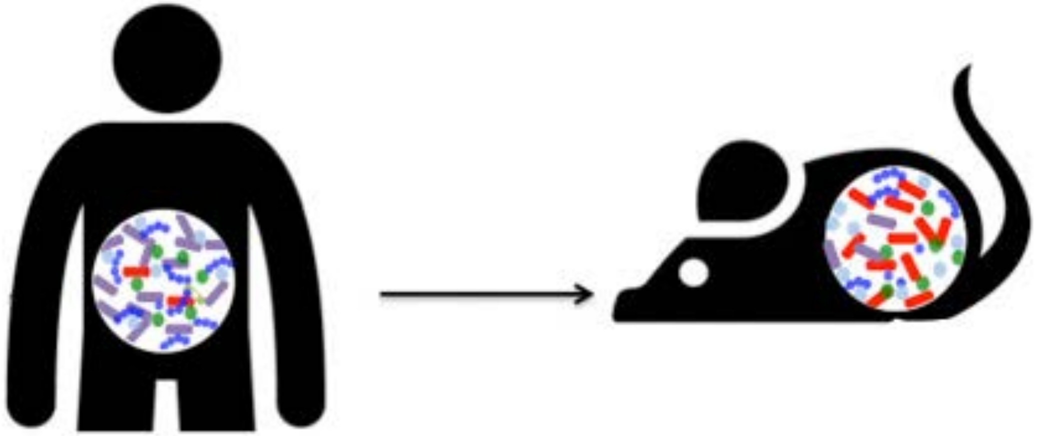


Bunyavanich S, Berin MC. J Allergy Clin Immunol. 2019 Dec;144(6):1468–77.

Food allergic infants: human to murine model

- 56 infants with food allergy*
- 98 age-matched non-allergic controls
- Sampled at multiple timepoints from 1 to 30 months

- 16S but with higher resolution OTU picking
- Functional studies by fecal transplantation

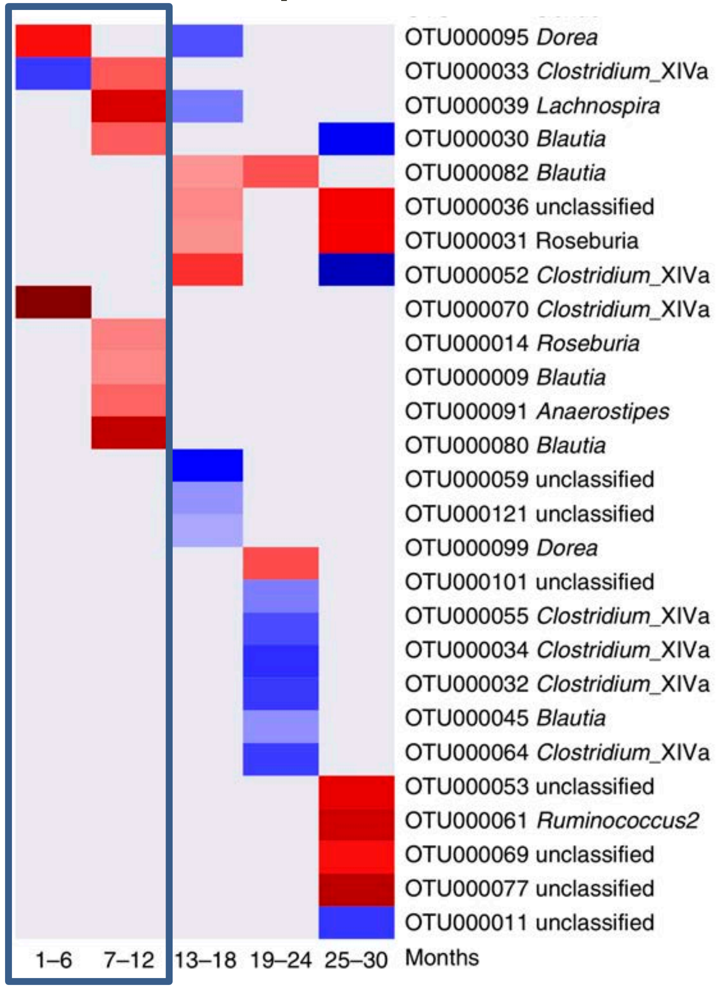


* 'to at least one of the major food allergens including milk, soy, egg, tree nuts, fish, shellfish, wheat, or peanuts'

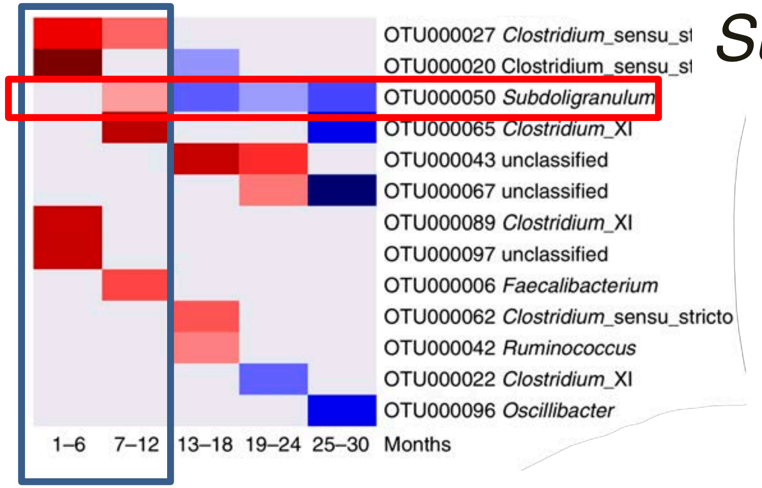
Abdel-Gadir A, et al. Nat Med. 2019 Jul;25(7):1164–74.

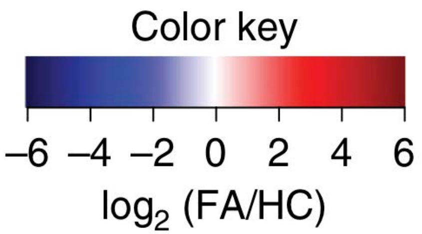
Food allergic infants: human to murine model

Lachnospiraceae

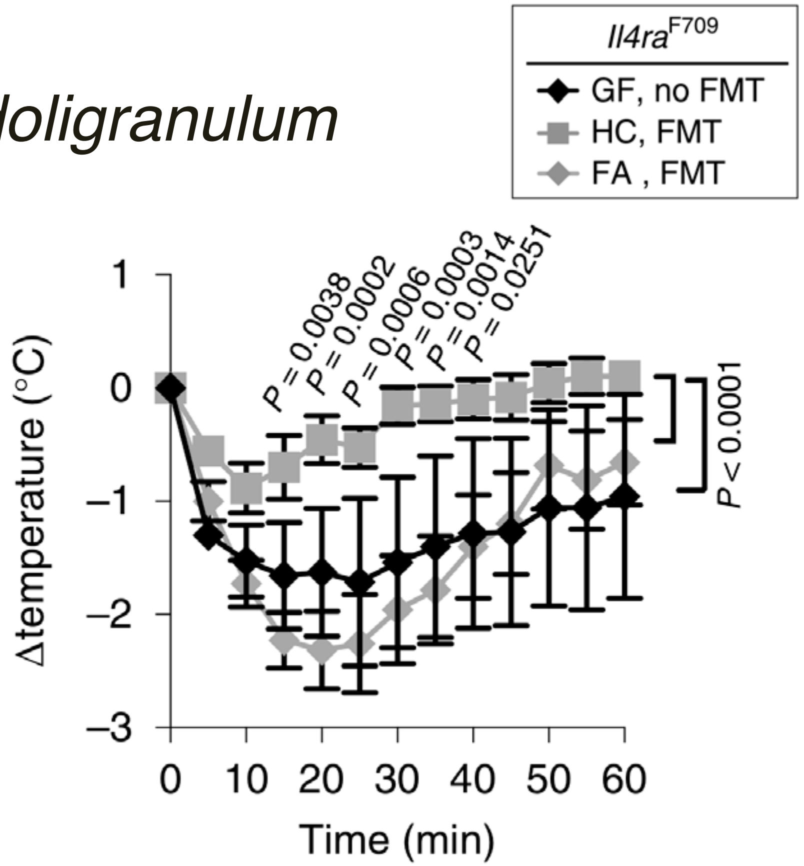


Other Clostridales





Subdoligranulum

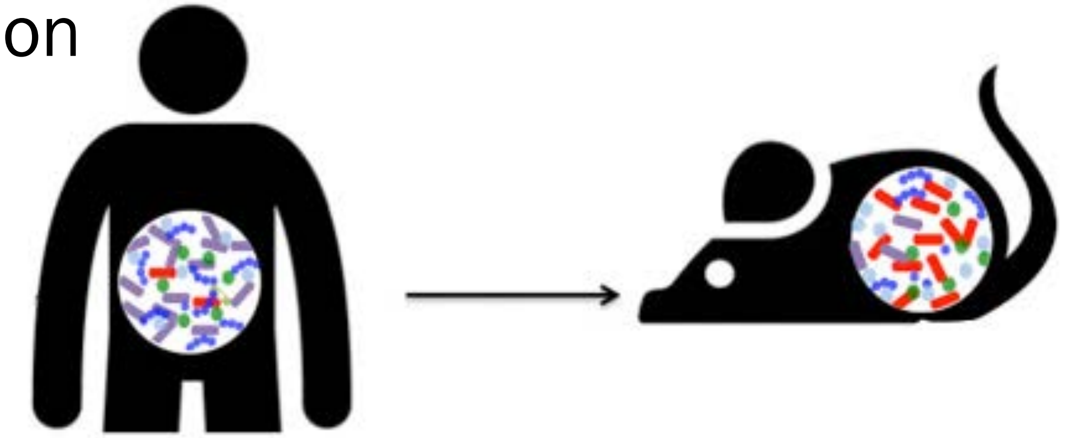


Abdel-Gadir A, et al. Nat Med. 2019 Jul;25(7):1164–74.

Food allergic infants: human to murine model 2

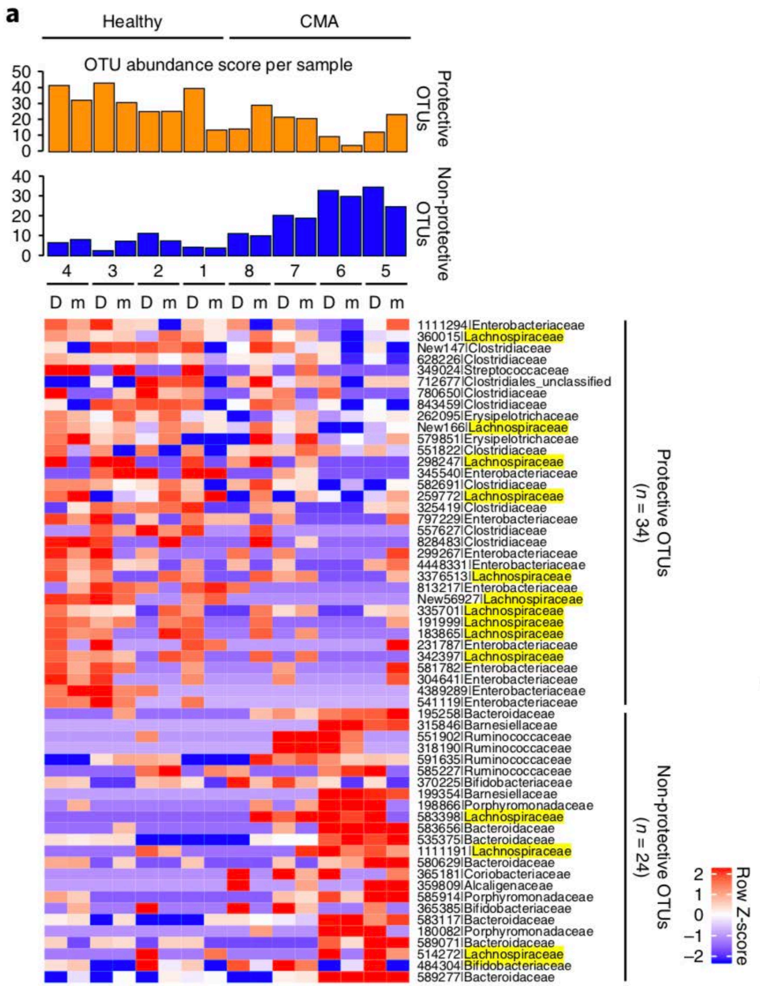
- 4 infants with milk allergy
- 4 age-matched non-allergic controls
- Sampled once during infancy

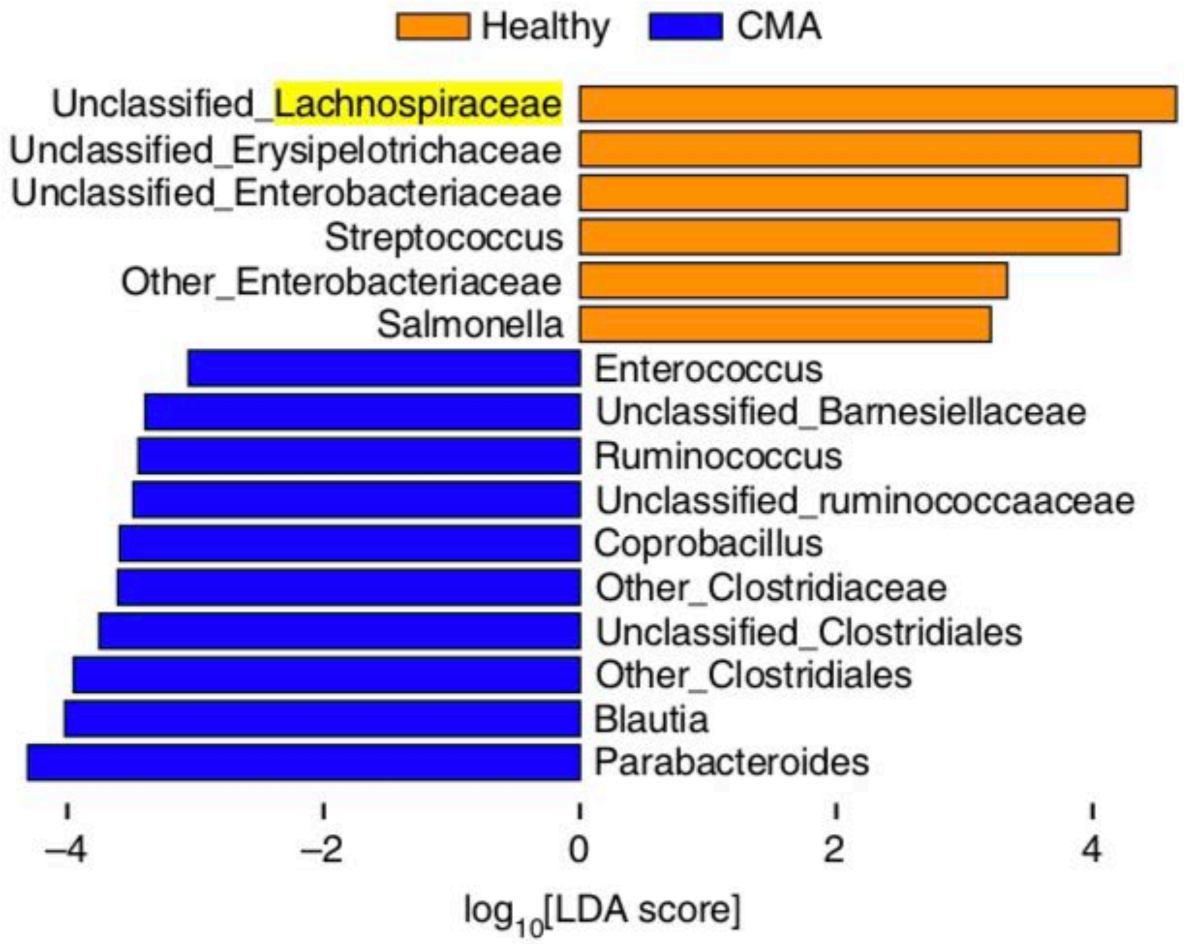
- 16S but with high resolution OTU picking
- Functional studies by fecal transplantation



Feehley T, et al. Nat Med. 2019 Mar;25(3):448–53.

Food allergic infants: human to murine model number 2





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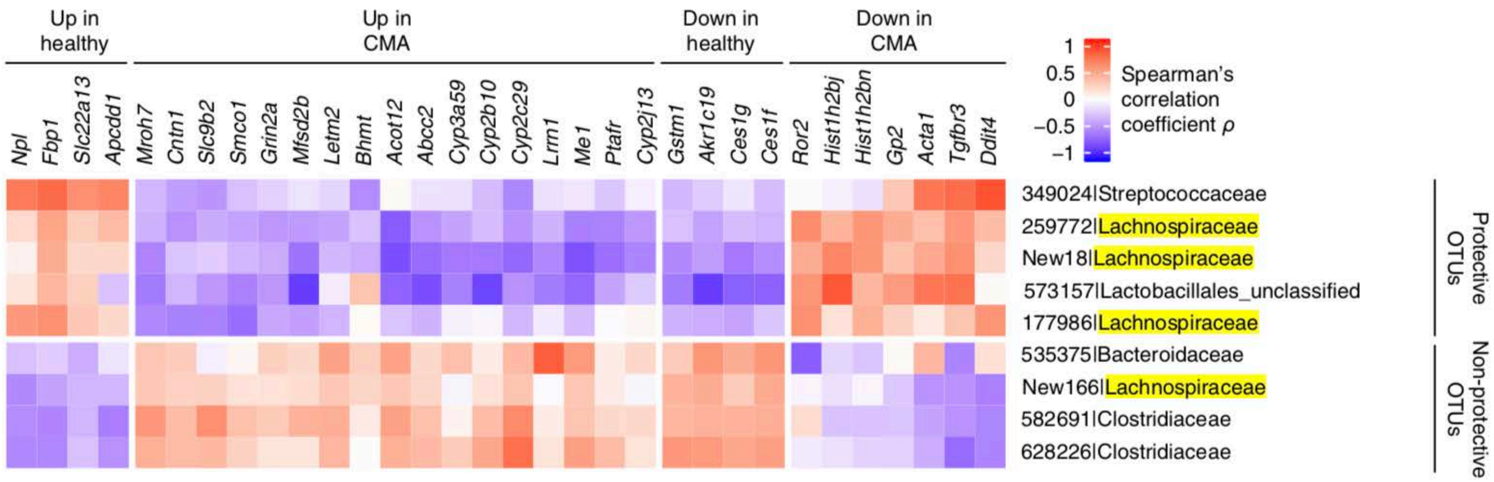
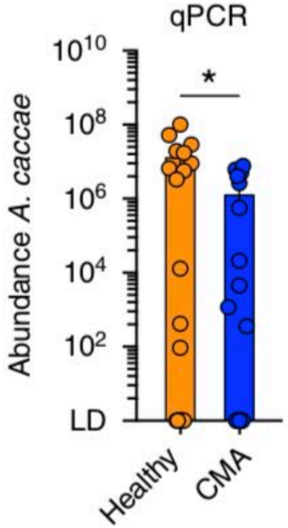
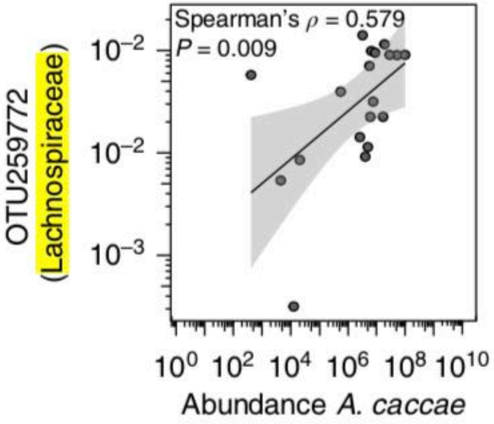
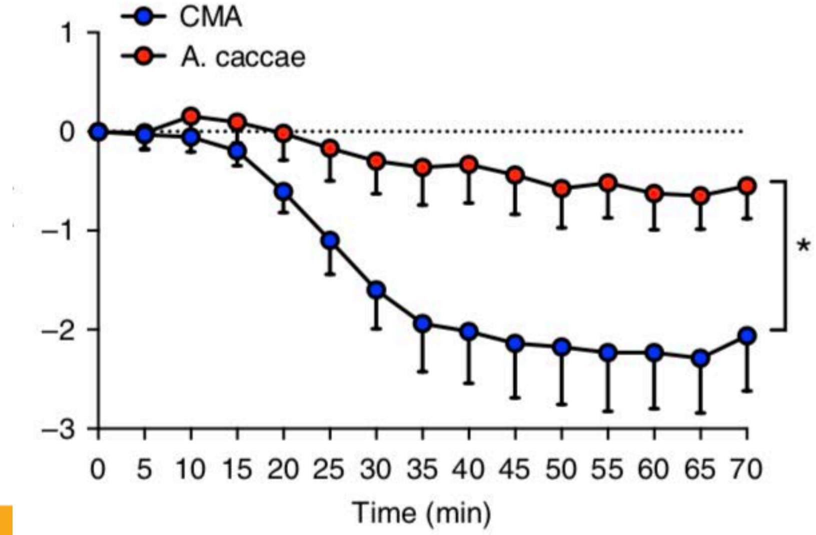


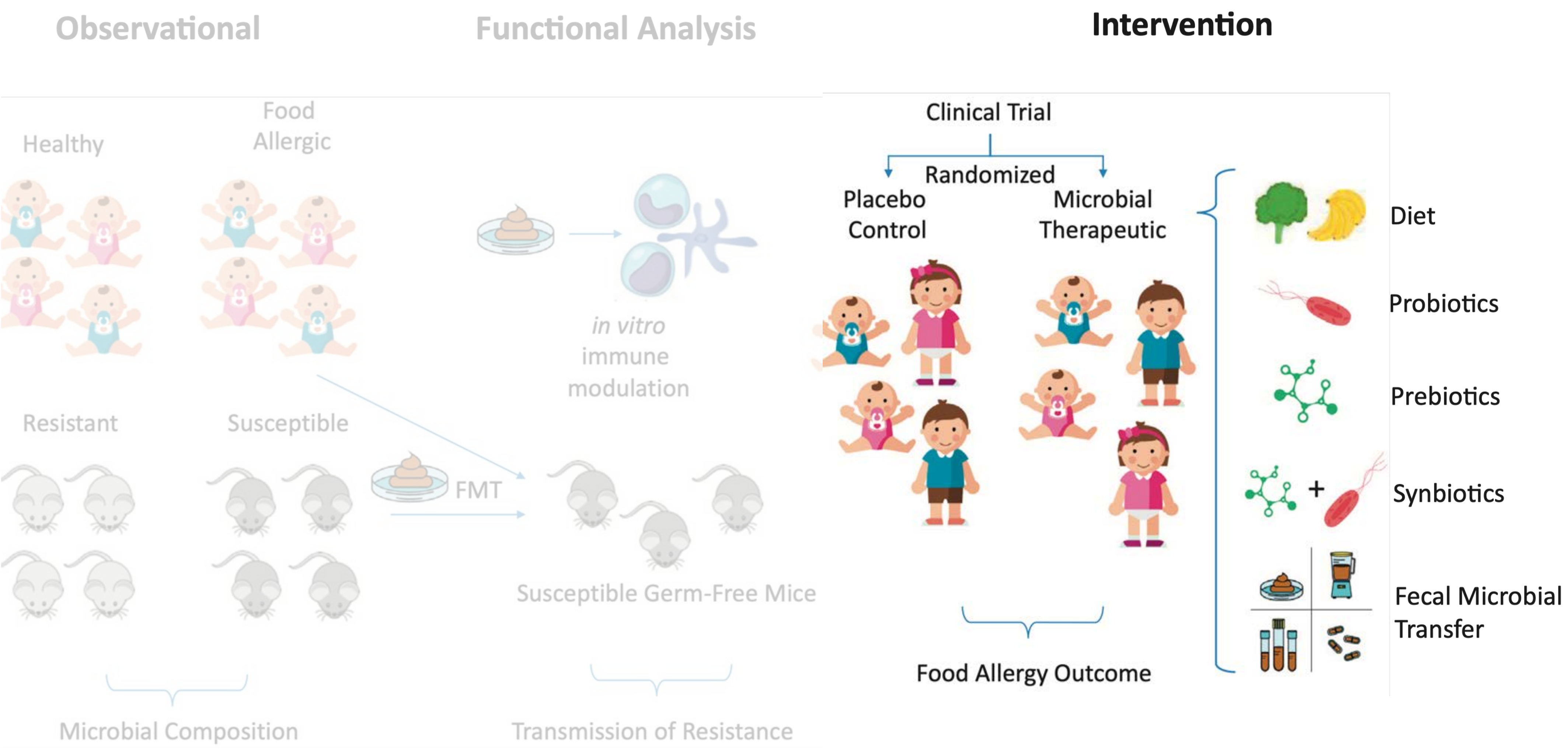






Feehley T, et al. Nat Med. 2019 Mar;25(3):448–53.

Hierarchy of Evidence



Bunyavanich S, Berin MC. J Allergy Clin Immunol. 2019 Dec;144(6):1468–77.

Clinical trials

- Probiotics for Cow's Milk Allergy
  - 119 infants with CMA, *L. casei* and *B. lactis* did not accelerate tolerance
  - 55 infants with EHCF and *L rhamnosus* GG (LGG) did resolve sooner
  - 220 infants with EHCF and LGG resolved CMA at higher rates during follow up to 3 years
  - Response associated with changes in frequency of butyrate producing organisms
- LGG as adjuvant to peanut OIT (Tang et al): at 4 years follow up, 67% v 4% actively consuming peanut
  - Larger follow up study with OIT alone arm in progress

Fazlollahi M, et al. Allergy. 2018 Jul;73(7):1515–24.

Clinical trials

- NCT02960074 Boston Children’s Hospital, Rima Rachid
- NCT03936998 MGH-Vedanta Biosciences, Wayne Shreffler

Discovery Centers

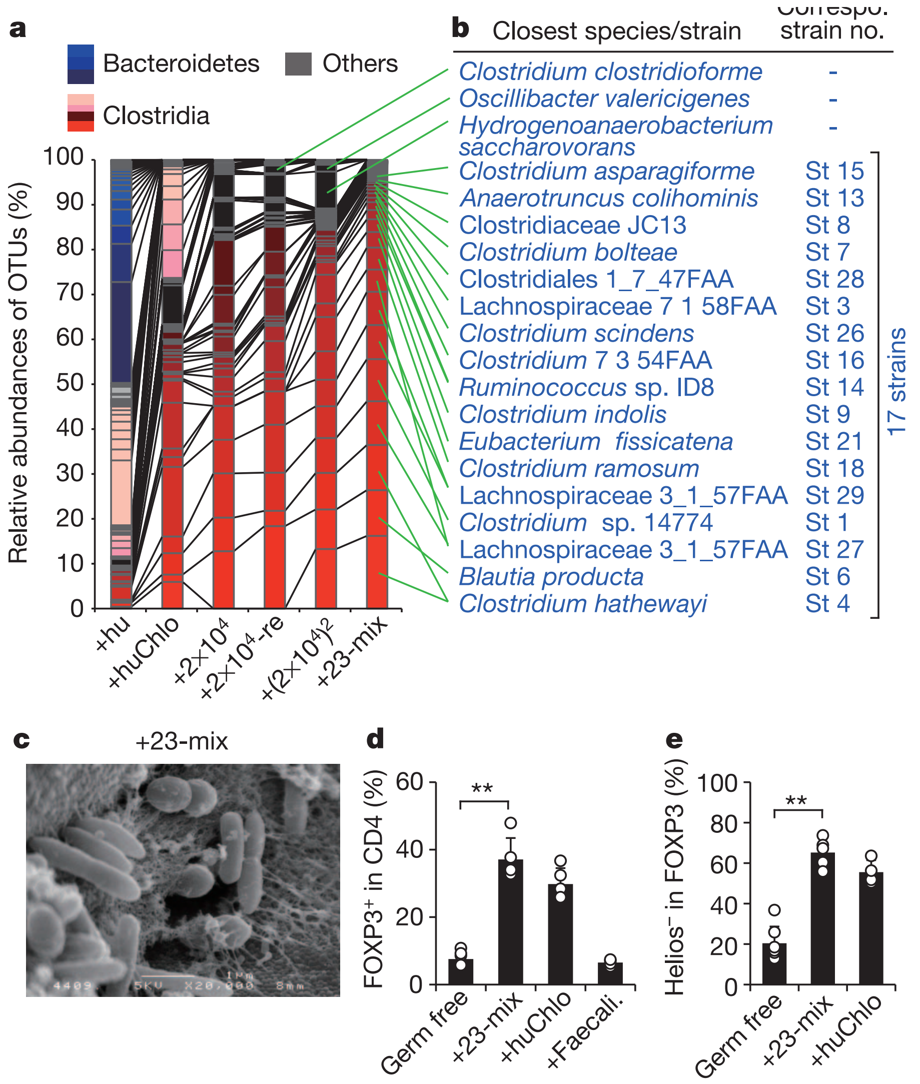
Conduct novel research on treatments, diagnostics, prevention and improvements to care

- Boston FARE Clinical Network Discovery Center
  - MGH Brigham
  - Boston Children’s Hospital

https://www.foodallergy.org/resources/fare-clinical-network-centers-distinction

T_{reg} induction by a rationally selected mixture of Clostridia strains from the human microbiota

Koji Atarashi[1,2,3]*, Takeshi Tanoue[1,2]*, Kenshiro Oshima[4,5]*, Wataru Suda[5], Yuji Nagano[1,2], Hiroyoshi Nishikawa[6], Shinji Fukuda[1,7], Takuro Saito[6], Seiko Narushima[1], Koji Hase[1,3], Sangwan Kim[5], Joëlle V. Fritz[8], Paul Wilmes[8], Satoshi Ueha[9], Kouji Matsushima[9], Hiroshi Ohno[1], Bernat Olle[10], Shimon Sakaguchi[6], Tadatsugu Taniguchi[2], Hidetoshi Morita[4,11], Masahira Hattori[5] & Kenya Honda[1,2,4]



Atarashi K, et al. Nature; 2013 Jul 30;500(7461):232–6.

Clinical trials: NCT03936998

VE416 Phase Ib/II in Peanut Allergy- **Plan Final**

Phase Ib | Phase II | Post-Phase II Maintenance

55 weeks

Age 12-55*

--- 7 weeks --- | 1 wk | (10 / group) Age 12-55 | --- 6 -10 w build up ---- | -------- 10 w maint ------ | 1 wk | ------ 24 weeks -------- | 1 wk

Active (10) | Vanc x5d | VE416 x 6 wks

Placebo (10) | PBO | PBO x 6 wks

(30)

Entry DBPCFC (143 mg) Phase II Inclusion: <100 mg

Cohort 1 (10) | PBO | PBO + PNOIT | PNOIT maintenance (40 mg) + PBO

Cohort 2 (10) | Vanc x5d | VE416 + PNOIT | PNOIT maintenance (40 mg) + VE416

Cohort 3 (10) | PBO | VE416 + PNOIT | PNOIT maintenance (40 mg) + VE416

Cohort 4 (10) | PBO | PBO + PNOIT | PNOIT maintenance (40 mg) + PBO

DBPCFC1 (5030 mg)

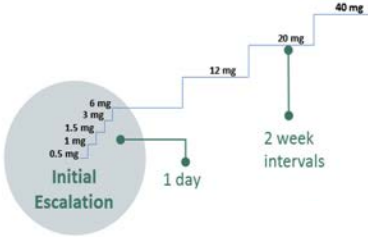
Inclusion: tolerates at least 300 mg (430 mg cumulative) (→ randomized 1:1)

PNOIT: 300 mg daily

Ad lib: 1 peanut at least three times a week

DBPCFC2 (5030 mg)

Step	Dose (mg)	Sum Dose (mg)
1	3	
2	10	13
3	30	43
4	100	143



Step	Dose (mg)	Sum Dose (mg)
1	30	30
2	100	130
3	300	430
4	600	1030
5	1000	2030
6	3000	5030

Step	Dose (mg)	Sum Dose (mg)
1	30	30
2	100	130
3	300	430
4	600	1030
5	1000	2030
6	3000	5030

* Extension of inclusion down to age 12 after interim safety review

Wait! What about the skin??

#1412 - Longitudinal trajectories of eczema severity, duration, and affected body-region predict risk of food allergy in combination with filaggrin gene mutations

Ylescupidez, Alyssa / Du Toit, George / Salavoura, Katerina / Brough, Helen / Radulovic, Suzana / Bahnson, Henry T / Lack, Gideon

Staph, Staph, Staph (?)

Other research

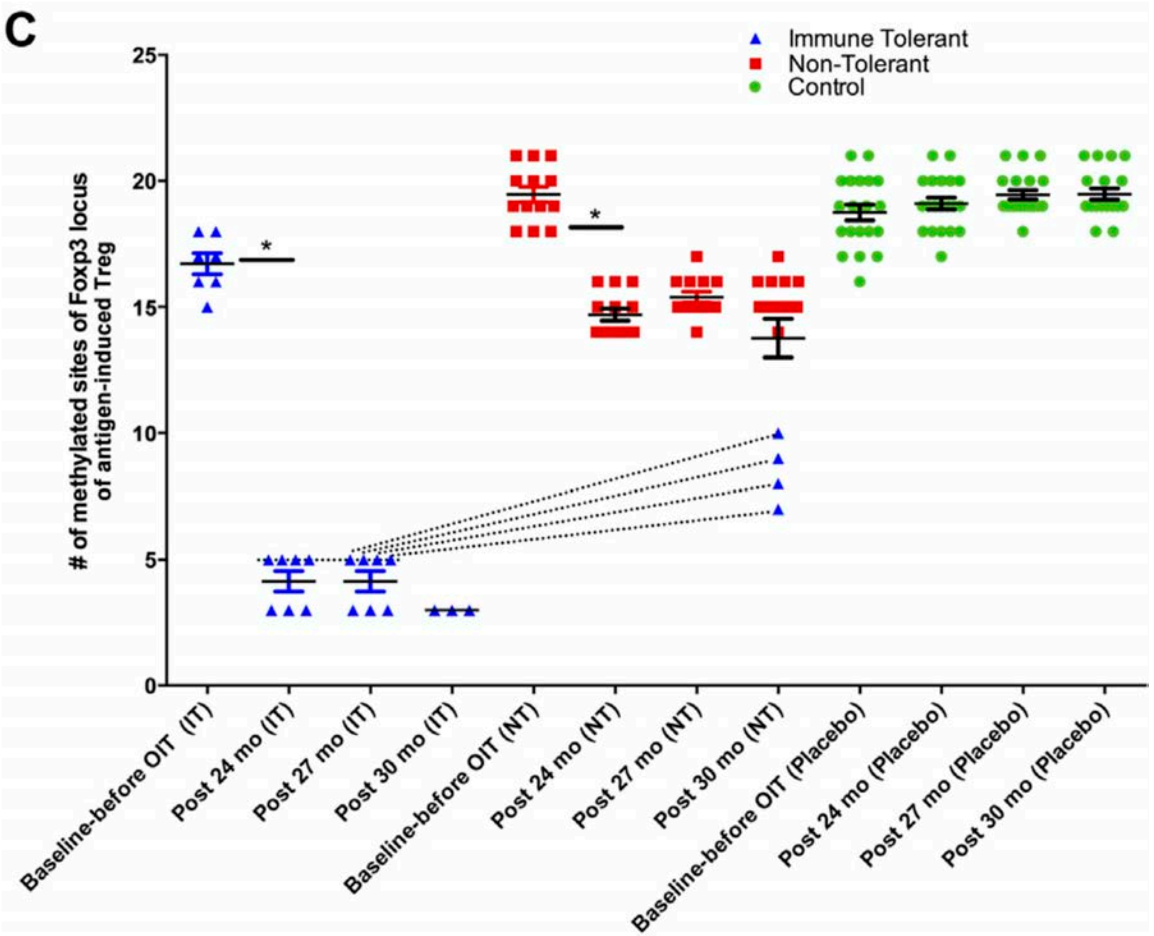
- Basic mucosal immunology and food science
  - The mechanisms of sensing the diet are complex and poorly understood with myriad sensors utilized by specialized epithelial cells, immune cells and neuronal cells all likely sensing both bioactive components of food and metabolites of the microbiome
- Non-IgE-mediated food allergies, such as FPIES, EoE and FPIAP
- Role of microbiome in shaping the immune repertoire and metabolizing food proteins
- Impact of OIT on microbiome and relationship to outcomes
- Much more to come!!

Potential impact: does the Willie Sutton rule apply?

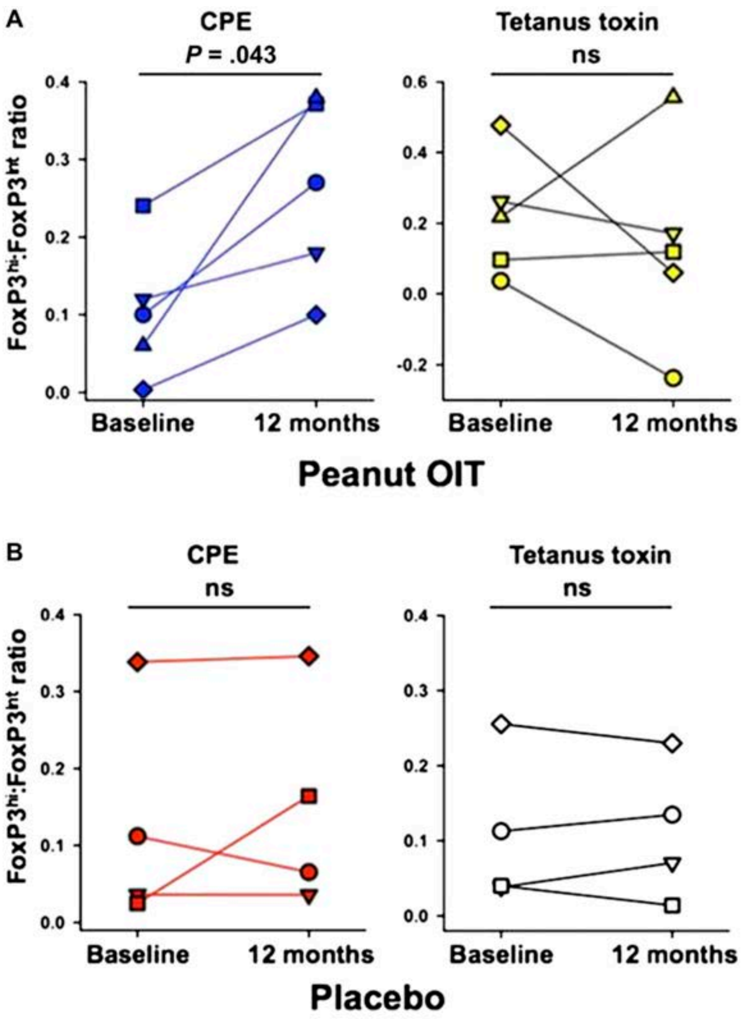
- The most obvious intervention would seem to be the one that is most likely to address the tolerance paradigm

- Prevention, Secondary Prevention and Treatment

Evidence of Treg induction by OIT to food Ag



Syed A, et al. J Allergy Clin Immunol. 2014;133(2):500–10.

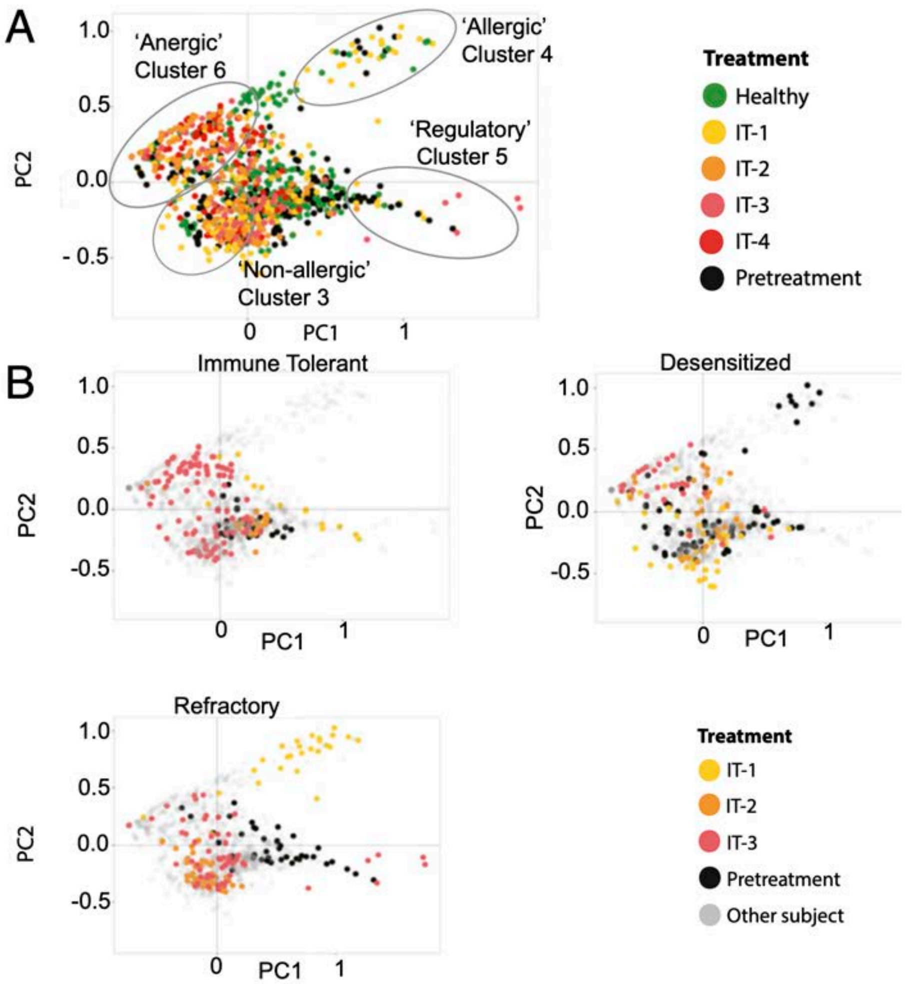


Varshney P, et al. J Allergy Clin Immunol. 2011;127(3):654–60.

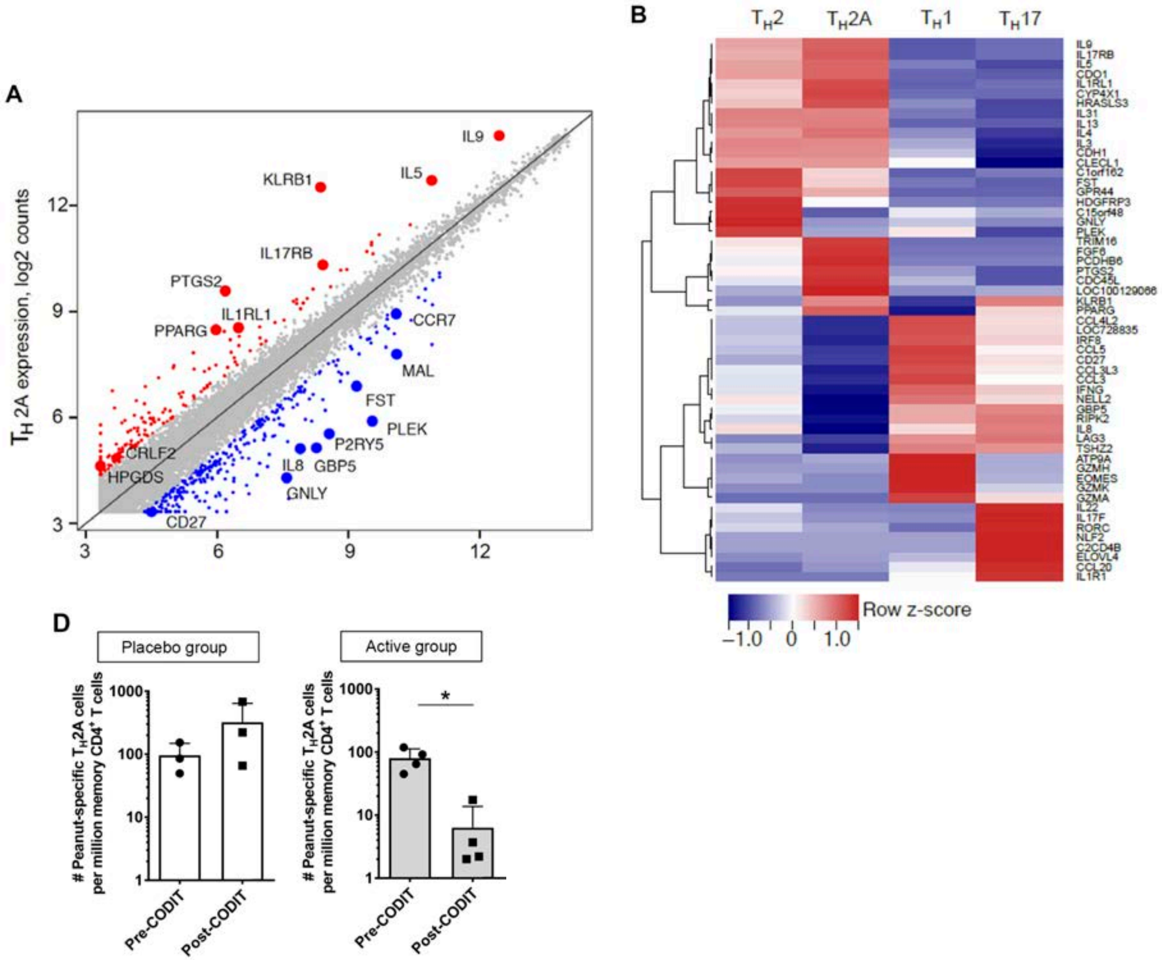
Overview

- Food allergy 101
  - Epidemiology, hygiene and tolerance
- Cohort studies indirectly suggesting a role for the microbiome
- Building the case for the importance of the microbiome
  - Association, Functional, Intervention (in progress)
- Why it matters and what the future may bring
  - ‘Sutton’s Law’, Prevention, Secondary Prevention and Treatment
- Questions

Evidence of Treg induction by OIT to food Ag – or not?



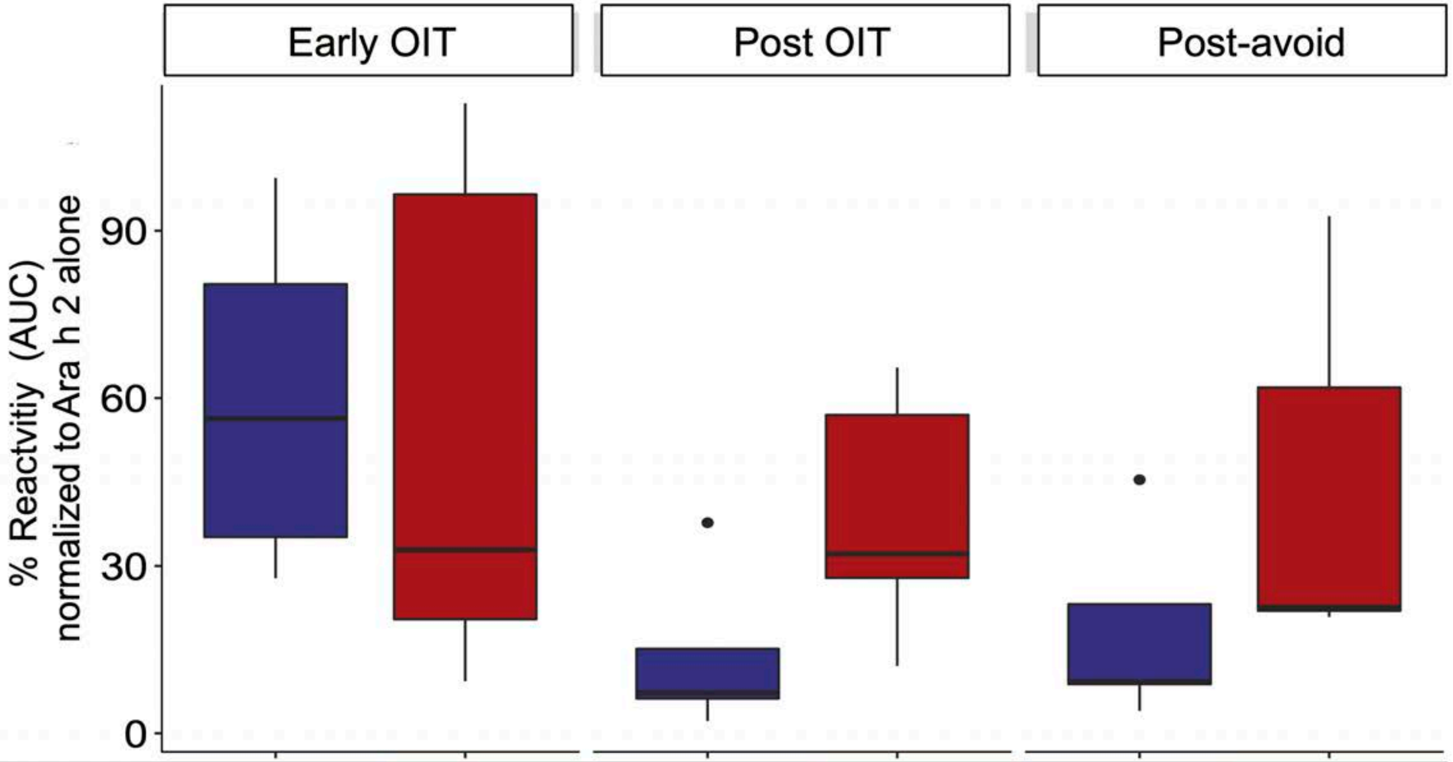
Ryan JF, et al. PNAS USA. 2016 Mar 1;113(9):E1286–95.



Wambre E, et al. Sci Transl Med. 2017 2;9(401):eaam9171.

Frischmeyer-Guerrerio PA, et al. J Allergy Clin Immunol. 2017

A key role for neutralizing antibodies



Sensitization serum	SU	TD	SU	TD	SU	TD
Suppressive serum	SU	TD	SU	TD	SU	TD

Patil SU, et al. J Allergy Clin Immunol. 2019 Aug 1.

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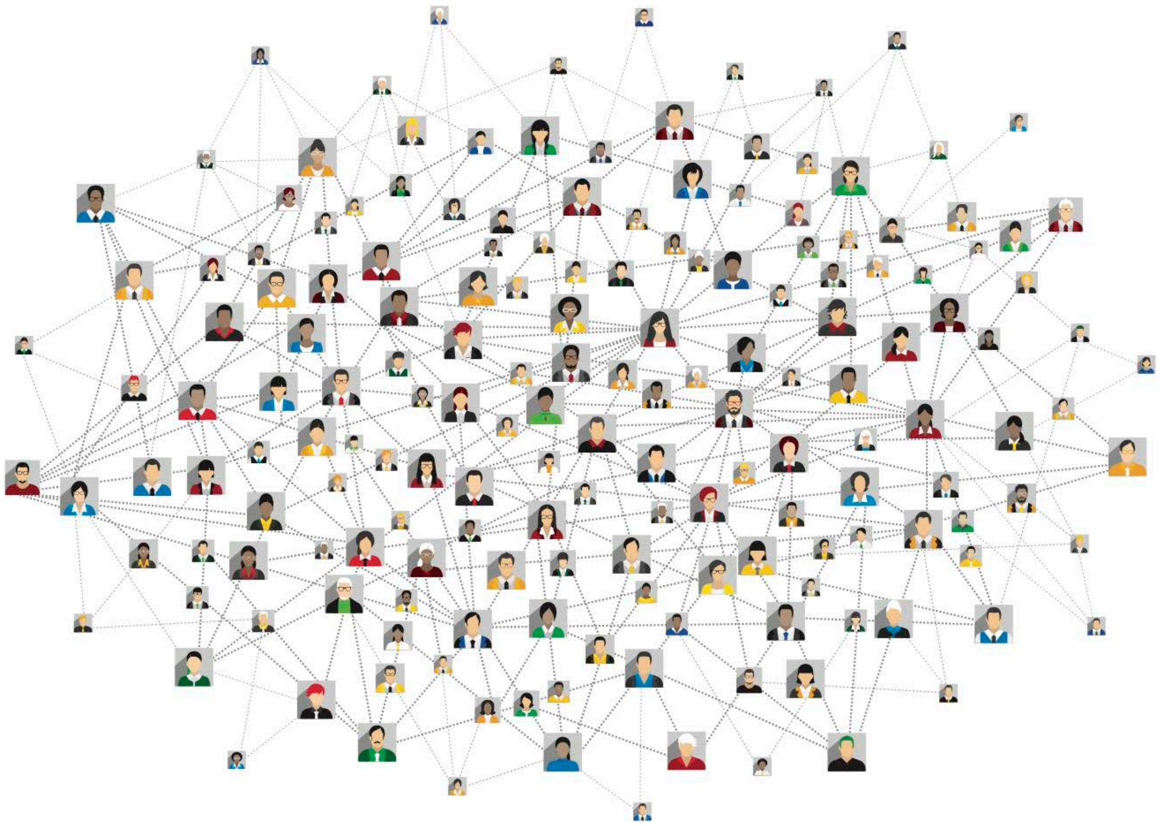
- Key collaborators:
  - MIT/FASI: Chris Love
  - MGH: Sarita Patil, Qian Yuan, Tori Martin, Yamini Virkud, Robert Anthony
  - FARE Discovery Center: Rima Rachid, Chen Rosenberg, Joyce Hsu

Question & Answer

YOUR Food Allergy Story Drives Research Forward

FARE Patient Registry®



The FARE Patient Registry connects people living with food allergies to researchers seeking answers.

Join in 3 easy steps:

1. Enroll for free
2. Create your confidential patient profile
3. Take our surveys

JOIN TODAY at FAREregistry.org

Thank you!