

Food allergy in children: predictive factors of outgrowth or persistence

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Chair, Food Allergy Committee, World Allergy Organization

Dubai, January 28^o , 2023

Consulting/Advisory Board: Danone, Stallergenes, Abbott, DBV, Novartis

Funded Research (Institution): Danone, Ordesa Spain, Sanofi, Novartis, Ferrero, Hipp GmBDH, Humana SpA

Employee: Ospedale Pediatrico Bambino Gesù, Roma

Upon completion of this activity, participants should be able to know about:

- natural history of CMA
- natural history of egg allergy
- natural history of peanut allergy
- natural history of wheat allergy

- dietary influences on the acquisition of tolerance

- natural history in different food allergy phenotypes

Getting tolerance

Natural history of milk allergy

Natural history of egg allergy

Natural history of peanut allergy

Clinical course of multiple food allergies

Conclusions

Will my child get rid of food allergies?

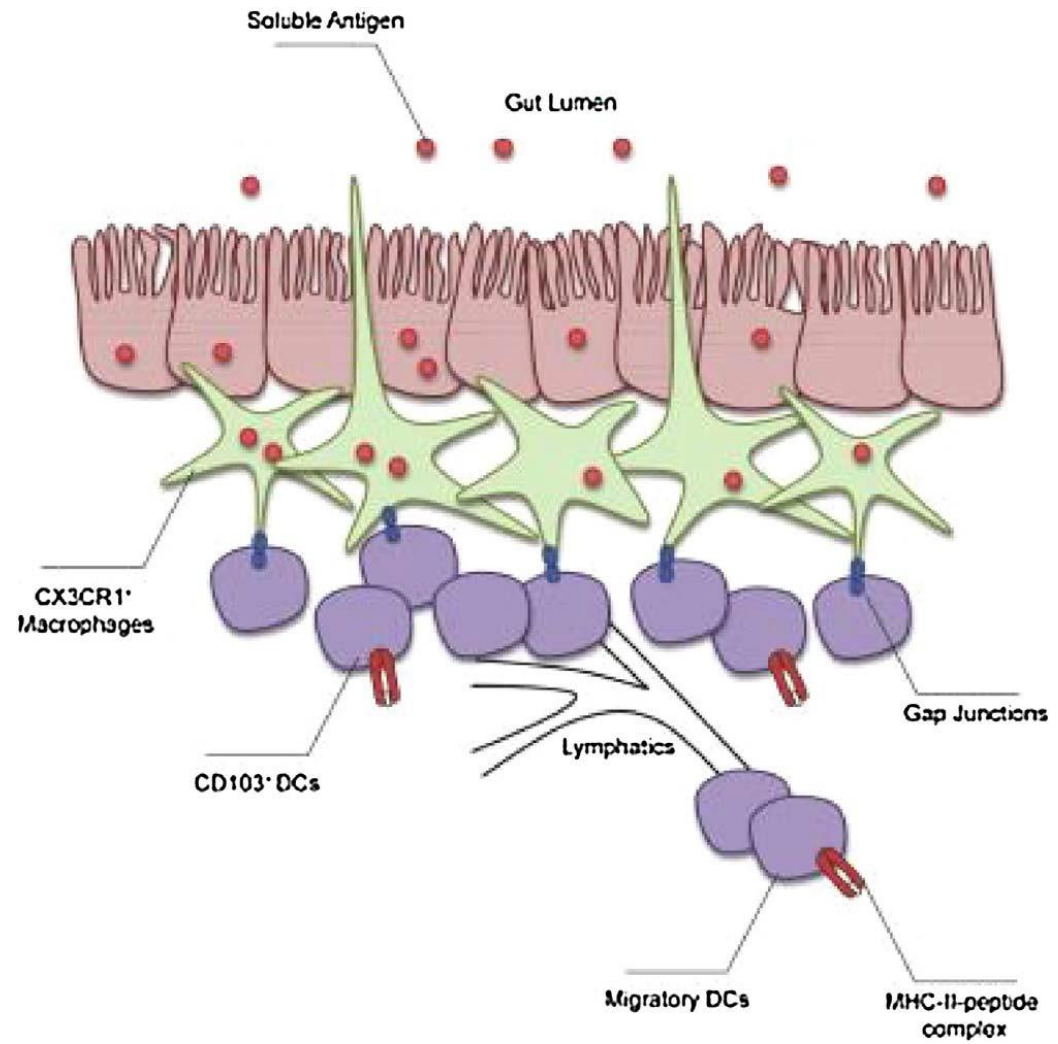


Food allergy is an oral tolerance failure.

What is food tolerance?

The physiologic response to a food

- ✓ Dendritic cells
- ✓ T-cells
- ✓ B - cells
- ✓ S IgE
- ✓ Microbiome
- ✓ Food characteristics
- ✓ Food timing
- ✓ Environmental factors
- ✓ [.....]



Why is it important to predict food tolerance?

To...

... formulate a prognosis

... make decisions about immunomodulatory therapy

... plan durable interventions for the prevention of accidental reactions in the family

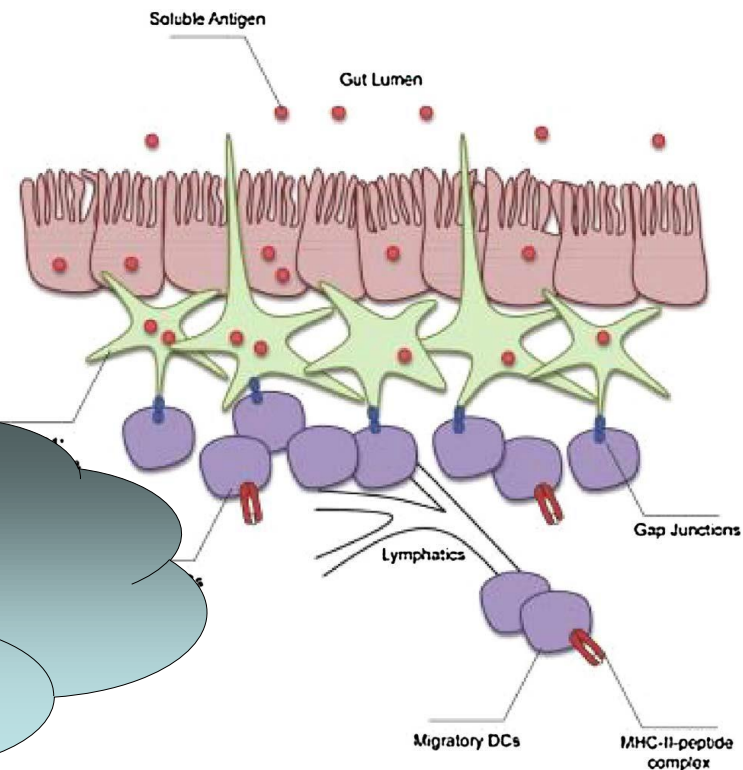
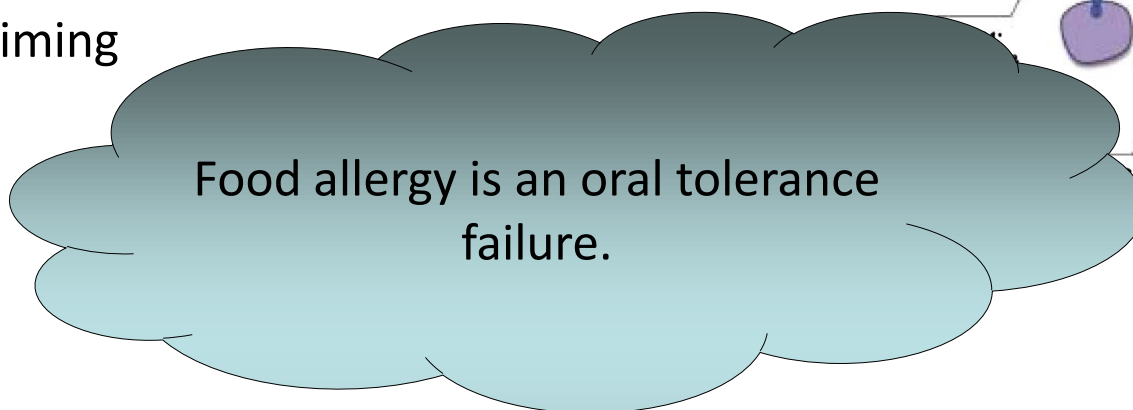
... plan durable interventions for the prevention of accidental reactions in the community

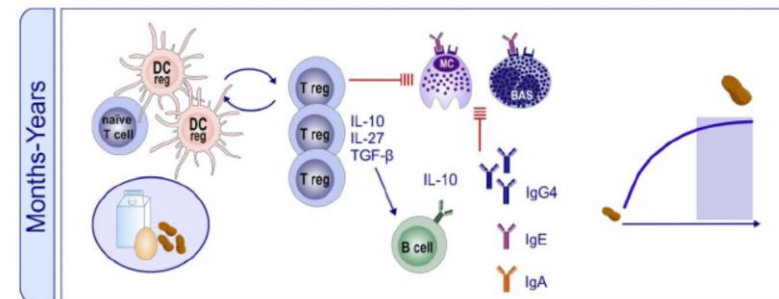
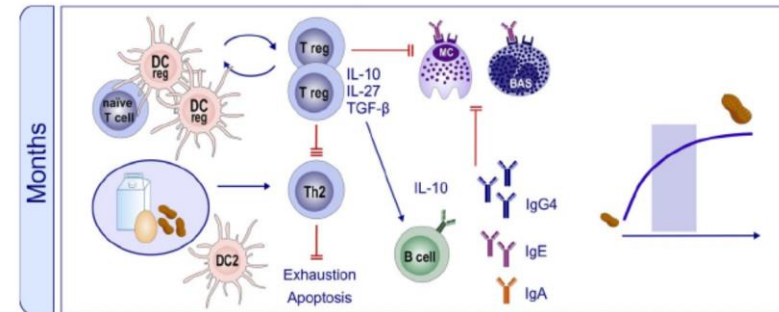
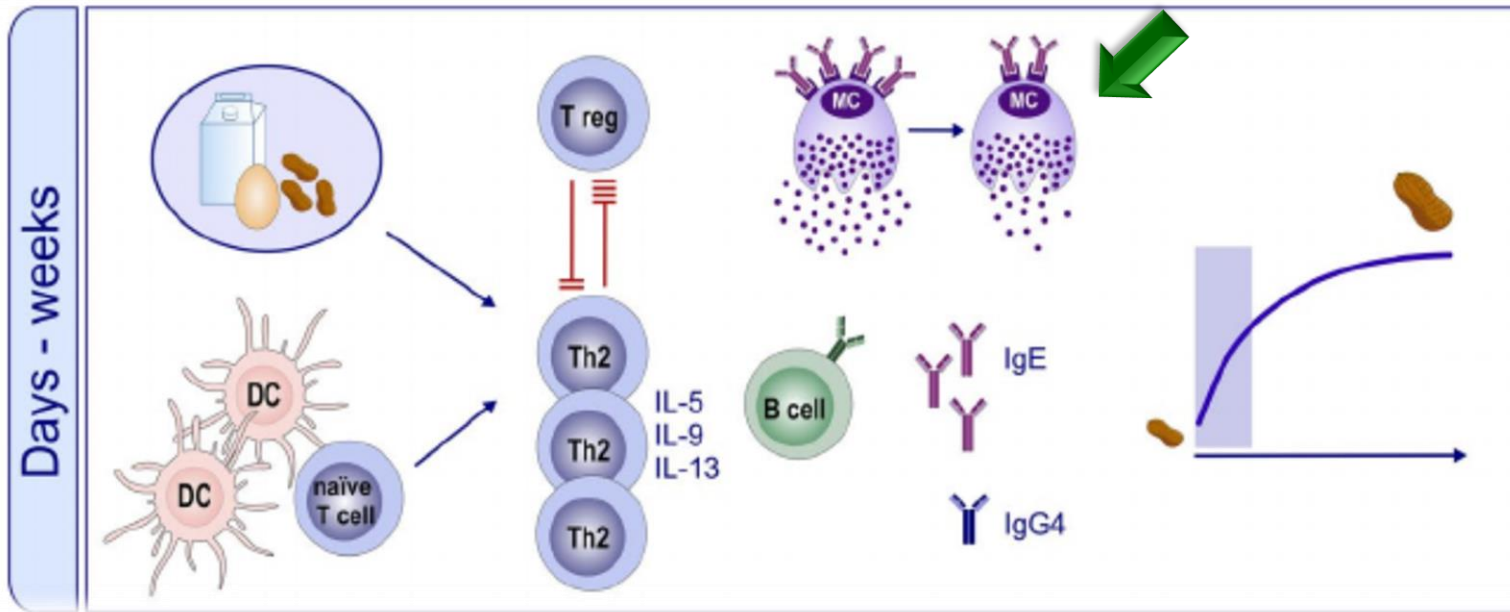
... evaluate the effect of immunomodulation interventions on the natural history.

Will my child get rid of food allergies?

Potential targets to restore the physiologic response to a food:

- Dendritic cells
- T-cells
- Microbiome
- Food characteristics
- Food timing





Eiwegger T. Recent developments and highlights in food allergy. *Allergy* 2019;74:2355-2367



Featured collection: Debates in allergy medicine

In this series we introduce each topic as a dialogue between two different views based on the scientific method. The dialectical method has served scholars for more than 2500 years, and this series takes up the tradition of comparing the different views presented and perhaps even encouraging a change of course, as can often happen in allergy.

Debate

Debates in Allergy Medicine: Does oral immunotherapy shorten the duration of milk and egg allergy? The pro argument

The development of oral tolerance or food allergy is an active process, related to dynamic interactions between host immune cells, microbiome, dietary factors, and food allergens. Oral tolerance is the default...

Valentina Pecora, Rocco Luigi Valluzzi, Maurizio Mennini, Vincenzo Fierro and Lamia Dahdah

World Allergy Organization Journal 2018 11:11

Published on: 15 June 2018

 The [Debate to this article](#) has been published in *World Allergy Organization Journal* 2018 11:12

[> Full Text](#) [> PDF](#)

Debate

Debates in Allergy Medicine: Oral immunotherapy shortens the duration of milk and egg allergy - the con argument

Oral immunotherapy (OIT) has been shown to be effective for inducing desensitization in children with cow's milk and egg allergy. In contrast, there is limited evidence that OIT can induce tolerance or sustain...

Wenyin Loh and Mimi L. K. Tang

World Allergy Organization Journal 2018 11:12

Published on: 15 June 2018

 The [Debate to this article](#) has been published in *World Allergy Organization Journal* 2018 11:11



Citation Impact

5.676 - [2-year Impact Factor](#)

1.567 - [Source Normalized Impact per Paper \(SNIP\)](#)

1.936 - [SCImago Journal Rank \(SJR\)](#)

Five hospital sessions

Variable	Session				
	1 (day 1)	2 (days 14 to 28)	3 (days 28 to 56)	4 (days 42 to 70)	5 (days 56 to 84)
Dose	1 Drop*	1 mL	10 mL	50 mL	100 mL
	2 Drops*	5 mL	10 mL	50 mL	100 mL
	3 Drops*	5 mL	20 mL	(interval 2 hr)	(interval 2 hr)
	4 Drops*	10 mL	20 mL	100 mL	200 mL
	0.1 mL	10 mL	50 mL		
	0.2 mL				
	0.5 mL				
	0.5 mL				
	1 mL				
Interval between doses		20–30 min (*sublingual)		20–120 min	
Maintenance dose (home)	0.5 to 1 mL twice daily	5 to 10 mL twice daily	20 to 50 mL twice daily	100 mL twice daily	200 mL daily (... progressive free diet)

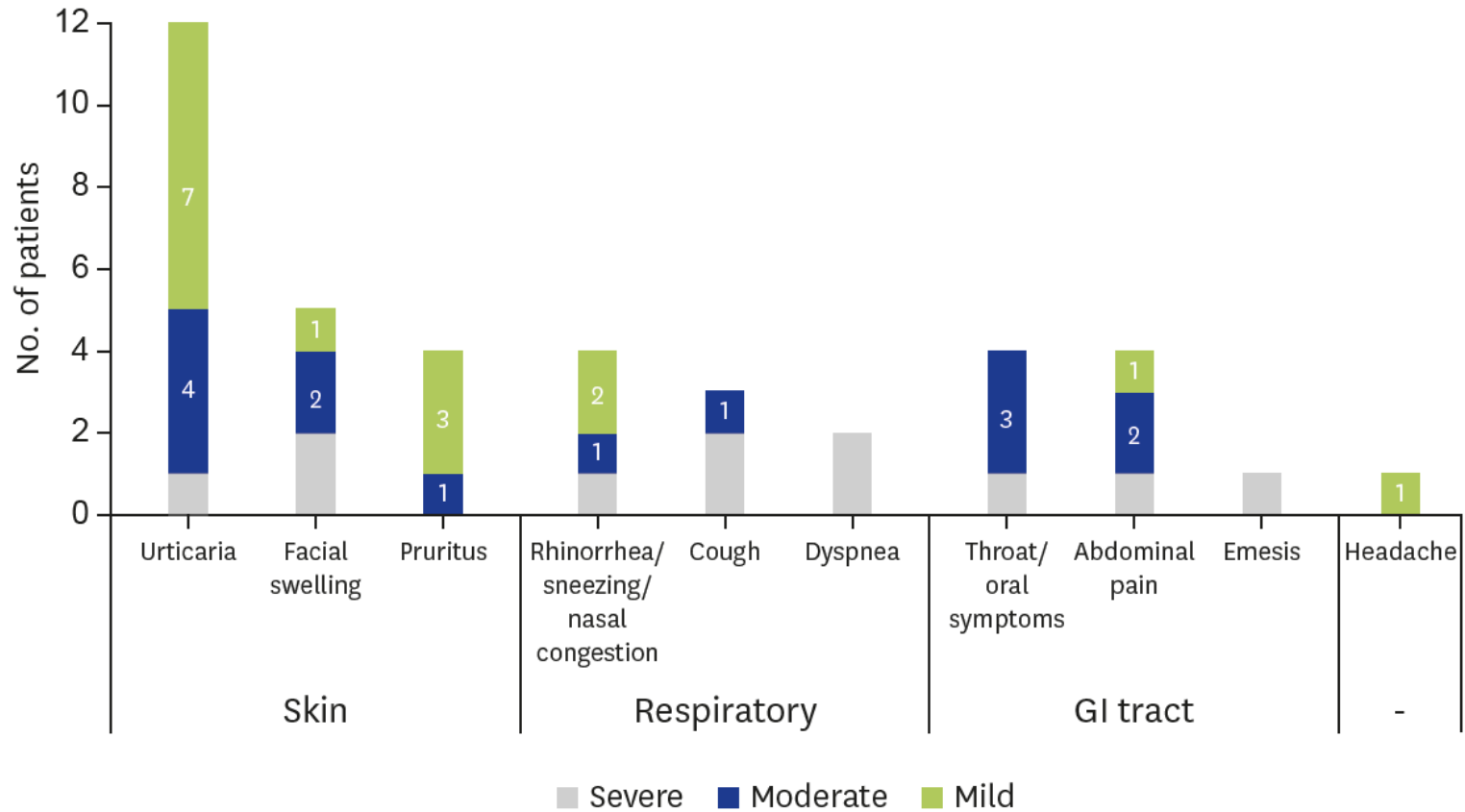


Mota I. Cow's milk oral immunotherapy in real life: 8-year long-term follow-up study. Asia Pac Allergy. 2018;8:e28.

- Empty stomach
- Irregular intake
- Exercise
- Infection
- Medication use
- Menses
- Suboptimal control of asthma or of allergic rhinitis
- Treatment at home
- High sIgE
- Wide skin reactivity

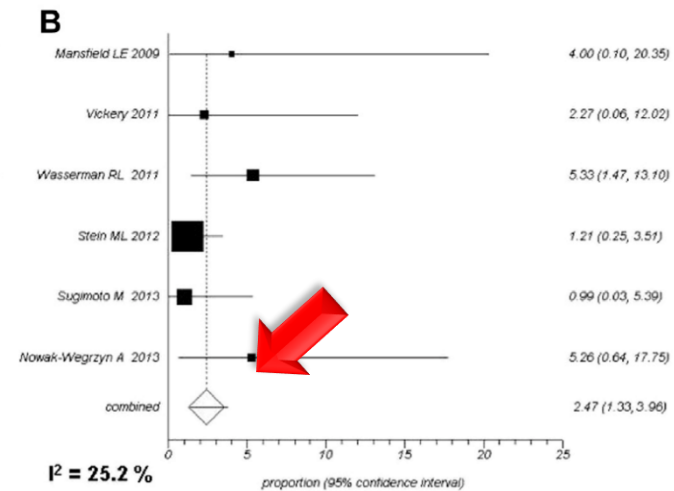
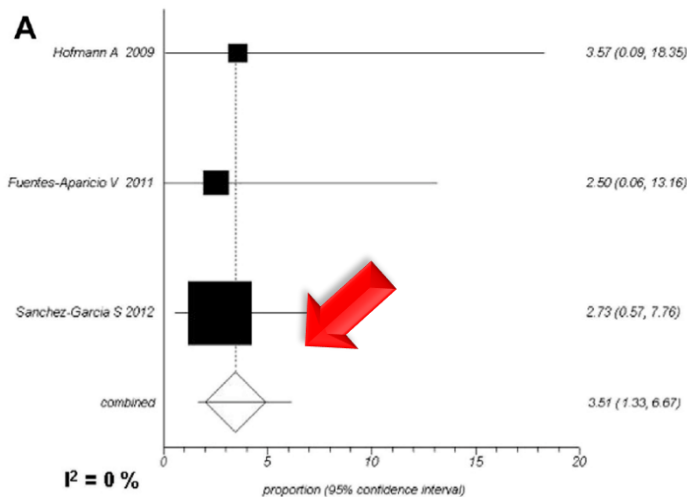


Pajno GB. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73:799-815



Mota I. Cow's milk oral immunotherapy in real life: 8-year long-term follow-up study. Asia Pac Allergy. 2018;8:e28.

Interventions	Incidence
EoE after immunotherapy (overall)	2.72% (1.7–4)
Subgroups according to quality (type of publication)	
Medium to high (full-length article)	3.51% (1.3–6.7)
Low (abstract)	2.5% (1.3–4)



Lucendo AJ. Relation between EoE and OIT for food allergy: a systemic review and metanalysis. *Ann Allergy Asthma Immunol* 2014;113:624-9

- 23 trials: 18 RCTs, 5 CCTs
- 22 of these trials meta-analyzed
- 982 subjects
- Benefit for children and mixed population on OIT
- CM, HE, and peanut
- Efficacy during treatment: RR 0.14, 95% CI 0.08, 0.24

Nurmatov U.

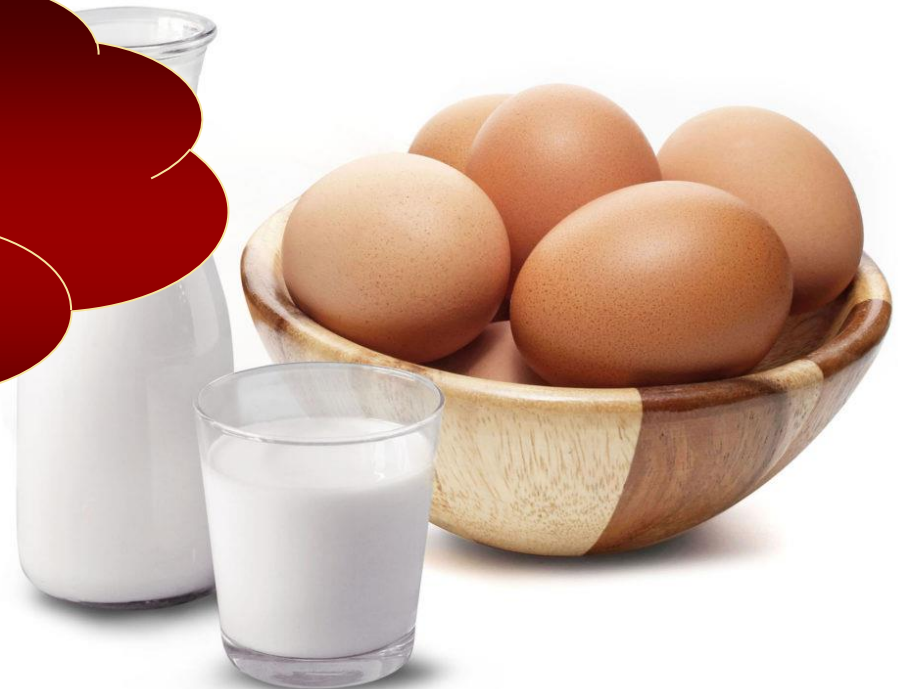
Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017;72:1133-1147.

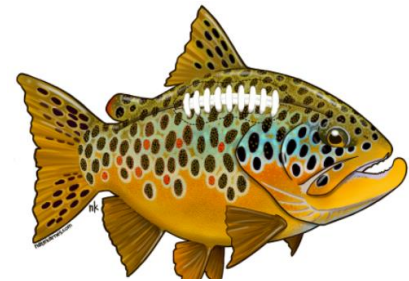


- 7 studies - only 4 included in the meta-analysis
- HE , 169 subjects
- CM, 25 subjects
- effectiveness assessed by OFC after 1 to 3 months of discontinuation of OIT
- Non- significant trend for longer-term benefits of OIT (RR 0.29, 95% CI 0.08, 1.13)

FA-AIT gets desensitization,
but not SU

Nurmatov U. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017;72:1133-1147.















Recommendations ^a	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations
A recommendation cannot currently be made for OIT as a treatment option to increase the threshold of reaction while on treatment in children allergic to other foods (e.g. fish, wheat, peach)	II	B	Weak recommendation based on a few cases reported in one RCT at high risk of bias ⁴⁸ and two CCTs at moderate risk of bias ^{49,50}	Risk of adverse reactions to be considered


^a OIT for food allergy should only be undertaken in highly specialized clinical centers with expertise and facilities to safely deliver this therapy.


- 36 trials of immunotherapy
- 2,126 subjects

de Silva D; GA2LEN Food Allergy Guidelines Group. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. *Allergy*. 2022;77:1852-1862

Allergen immunotherapy

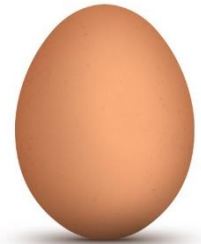
Oral immunotherapy			<div style="display: flex; align-items: center; justify-content: center;">  <div style="text-align: left;">Oral immunotherapy</div> </div> <div style="text-align: center; margin: 10px 0;">  <p>NNT 2</p> </div> <p style="text-align: center; margin-top: 10px;">to increase tolerance to single dose of 300 mg or 1000 mg peanut protein</p>
Epicutaneous immunotherapy			
Sublingual immunotherapy			
Subcutaneous immunotherapy			

 = Unknown safety and effectiveness

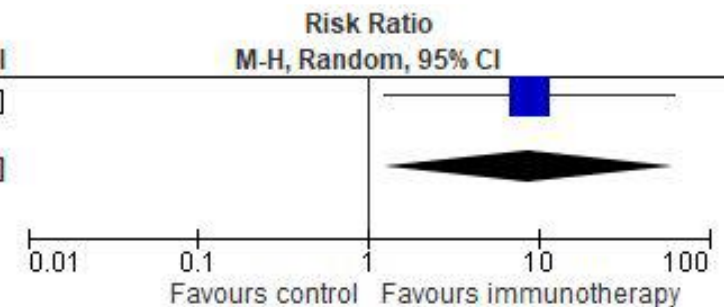
 = Probably good safety and effectiveness

OIT: effectiveness in desensitization & SH

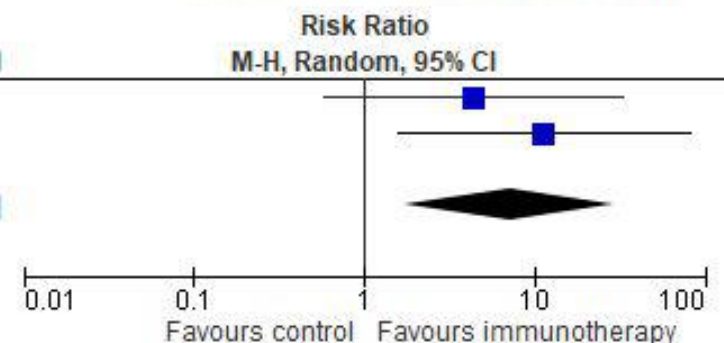
- Benefit for desensitization in patients on OIT :
 - peanut, RR 9.9, CI 4.5–21.4
 - cow's milk, RR 5.7, CI 1.9–16.7
 - hen's egg , RR 8.9, CI 4.4–18
- Benefit for sustained hyporesponsiveness in patients on OIT :
 - peanut, RR 8.75, CI 1.2.–61.6
 - cow's milk, no data
 - hen's egg , RR 7.12, CI 1.5.–82.7



Study or Subgroup	Immunotherapy		Control		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Chinthrajah 2019	21	60	1	25	100.0%	8.75 [1.24, 61.57]
Total (95% CI)		60		25	100.0%	8.75 [1.24, 61.57]
Total events	21		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.18 (P = 0.03)						

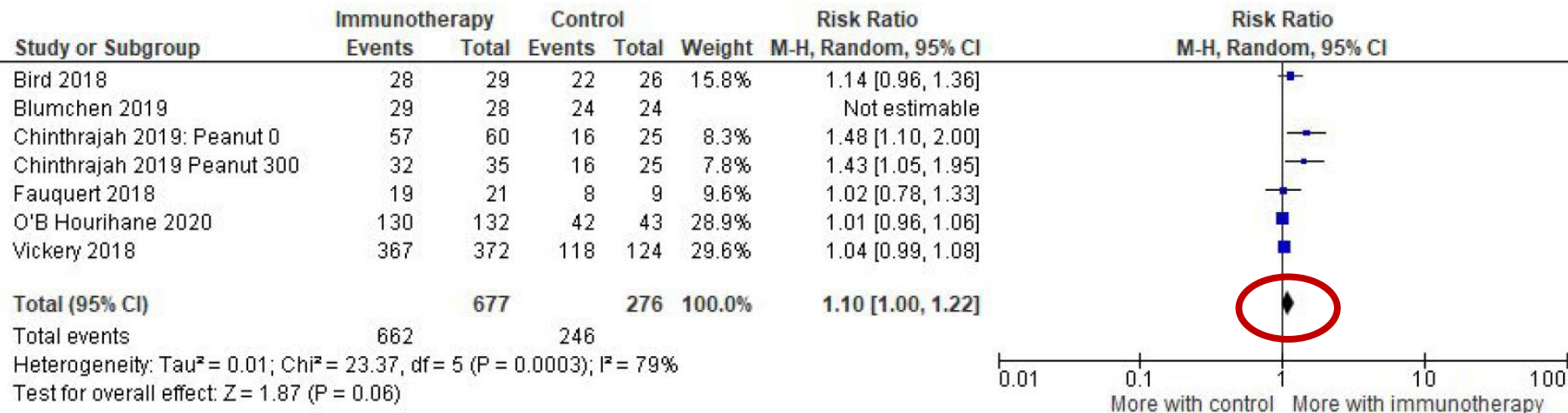


Study or Subgroup	Immunotherapy		Control		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Caminiti 2015	5	16	1	14	49.0%	4.38 [0.58, 33.10]
Escudero 2015	11	30	1	31	51.0%	11.37 [1.56, 82.71]
Total (95% CI)		46		45	100.0%	7.12 [1.73, 29.36]
Total events	16		2			
Heterogeneity: Tau ² = 0.00; Chi ² = 0.45, df = 1 (P = 0.50); I ² = 0%						
Test for overall effect: Z = 2.71 (P = 0.007)						



OIT: adverse reactions

- 7 comparisons examined the number of people experiencing adverse events
- OIT not associated with an increased number of AE
- data heterogeneous
- trend was also borderline, with $P=0.06$.



de Silva D; GA2LEN Food Allergy Guidelines Group. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. *Allergy*. 2022;77:1852-1862

OIT: adverse reactions

- 3 comparisons examined the number of people experiencing anaphylaxis



5 comparisons examined the number of people given intravenous adrenaline for anaphylaxis during the study period.



de Silva D; GA2LEN Food Allergy Guidelines Group. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. *Allergy*. 2022;77:1852-1862

Safety of FA-AIT

Recommendations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations
It is recommended to carefully monitor patients for local and systemic allergic reactions in FA-AIT particularly during the up-dosing phase of FA-OIT	I	A	Strong recommendation based on SR and meta-analysis ¹⁸ including RCTs at low risk of bias ^{9,42}	
It is recommended to monitor patients for symptoms of new-onset eosinophilic esophagitis which may appear in the course of FA-OIT	I	B	Moderate recommendation based on SR ³³ including one RCT and case reports	



Pajno GB. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73:799-815

The ideal study on natural history of food allergy

1. A standardized phenotype
2. A precise population
3. Prospective design
4. Repeated oral food challenges
5. OFCs tests must be at predetermined intervals.



Getting tolerance

Natural history of milk allergy

Natural history of egg allergy

Natural history of peanut allergy

Effect of milk exposure on the natural course of CMA

Clinical course of multiple food allergens simultaneously

Conclusions

Natural history of immediate-onset CMA: early studies

Study	Population	Tolerance	Time after diagnosis
Host	Birth cohort	50%	1 year
Garcia-Ara	Referrals	68%	2 years 4 mo
Vanto	Referrals	31%	2
		53%	3
		63%	4

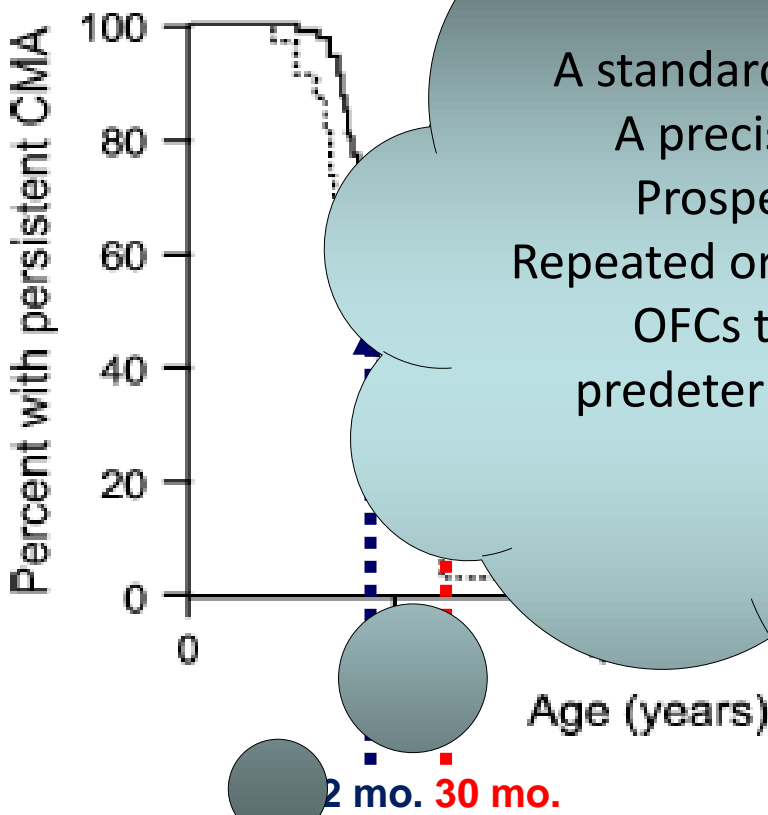
Mean duration of disease:
1-3 years

and intolerance in infancy. *Pediatric Allergy and Immunology* 2003; 13 (s15), 23-8

Immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. *Clin Exp Allergy* 2004;34:866-70

Vanto T. Prediction of the development of tolerance to milk in children with cow's milk hypersensitivity. *J Pediatr.* 2004;144:218-22

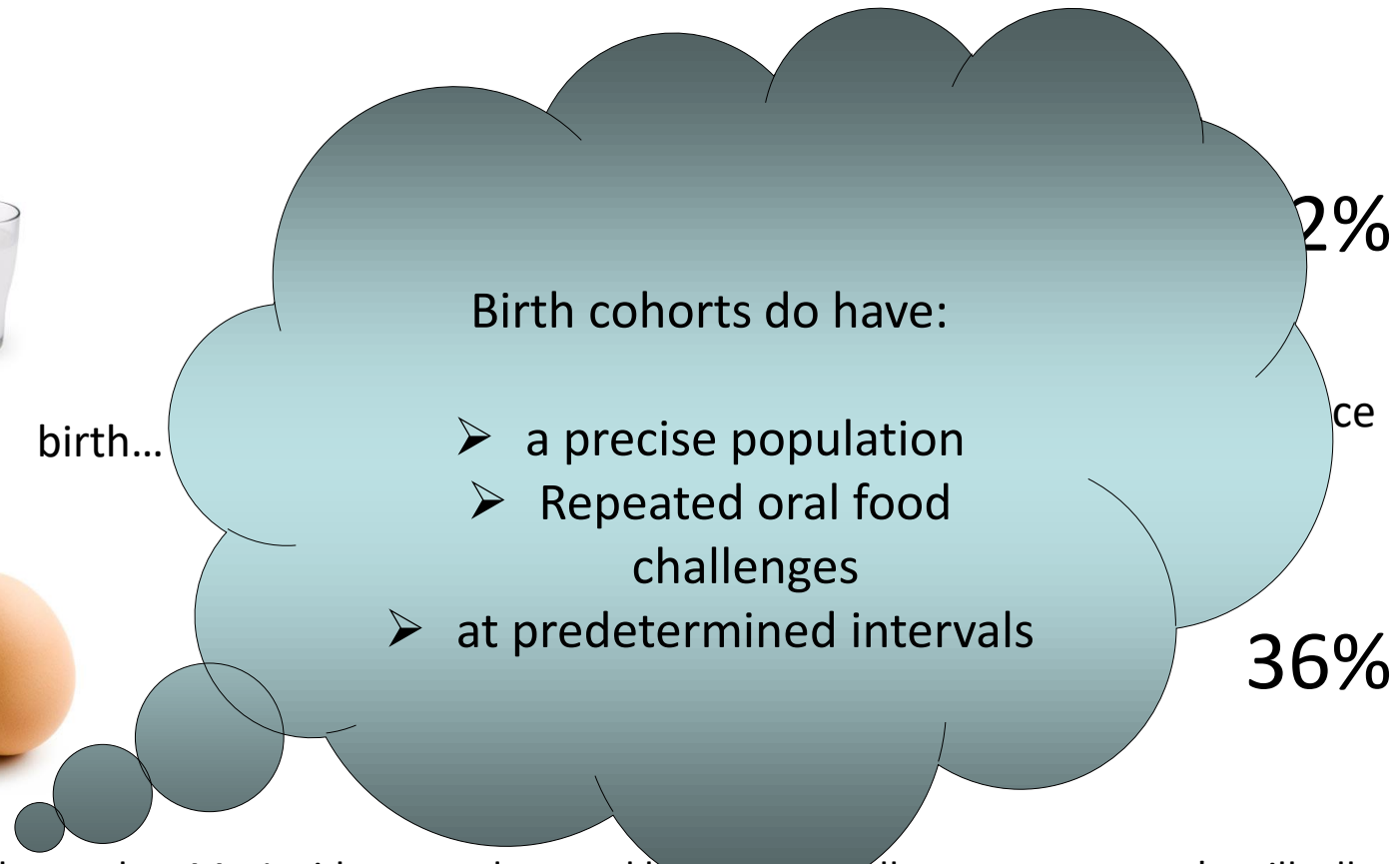
Natural history of immediate-onset CMA: IgE-positive vs. IgE-negative



A standardized phenotype 😊
A precise population 😊
Prospective design 😊
Repeated oral food challenges 😞
OFCs tests must be at predetermined intervals 😞



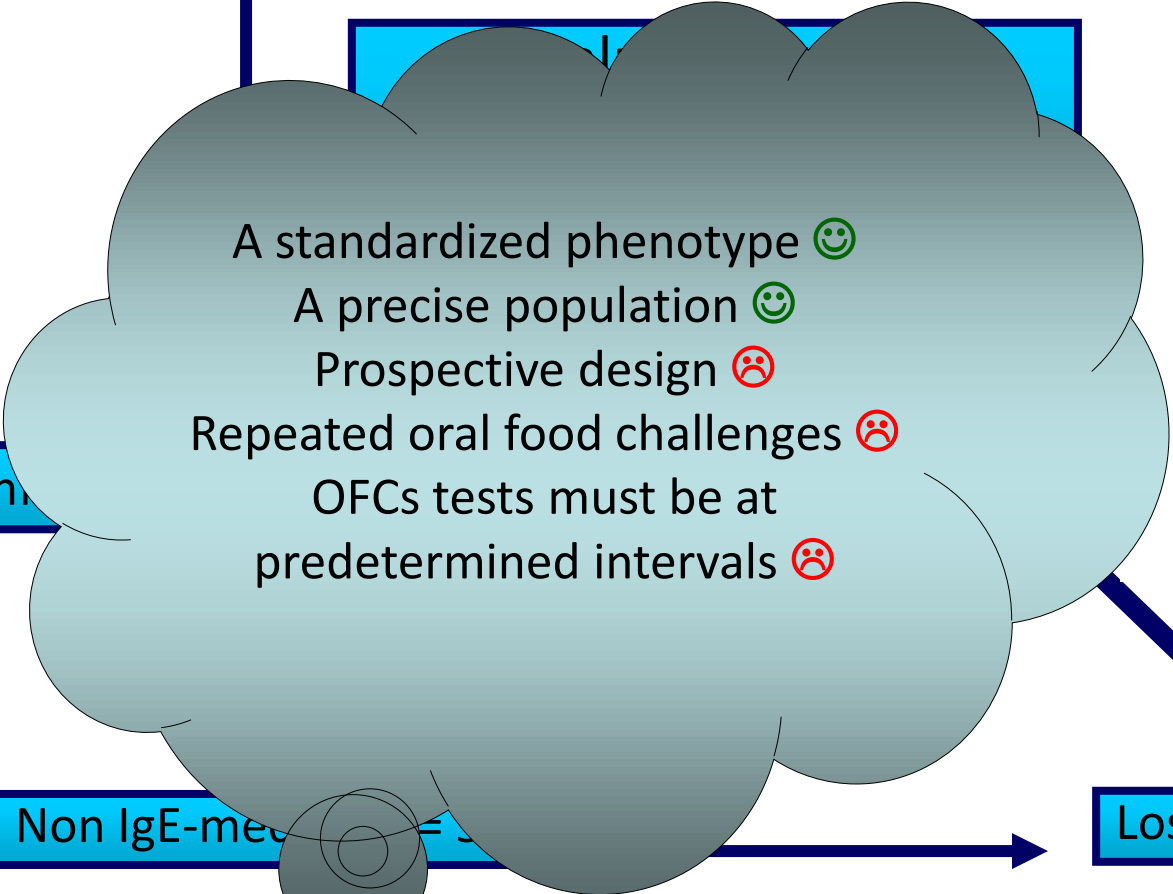
birth...



Schoemaker AA. Incidence and natural history of challenge-proven cow's milk allergy in European children - EuroPrevall birth cohort. *Allergy*. 2015;70:963-72

Xepapadaki P. 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

Presented with suspicion of food allergy = 4117



Con...



Non IgE-med... = ...

Lost to follow-up = 213

The

Three different curves:

Stringent
Less stringent
Least stringent

persistent CMA (%)

60
40

Underestimation of resolution?

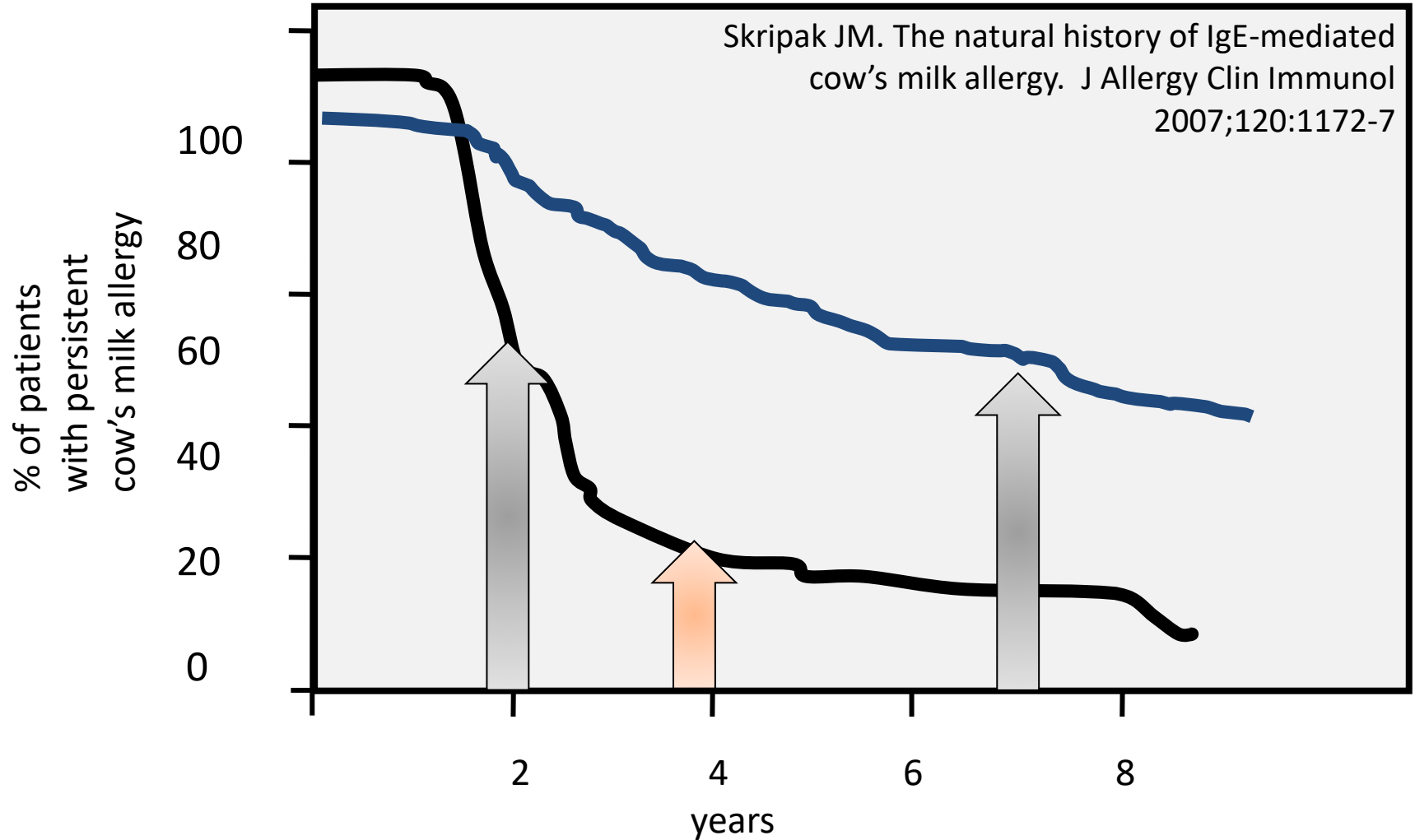
lost to follow-up
challenged
bias

Clinical tolerance definition

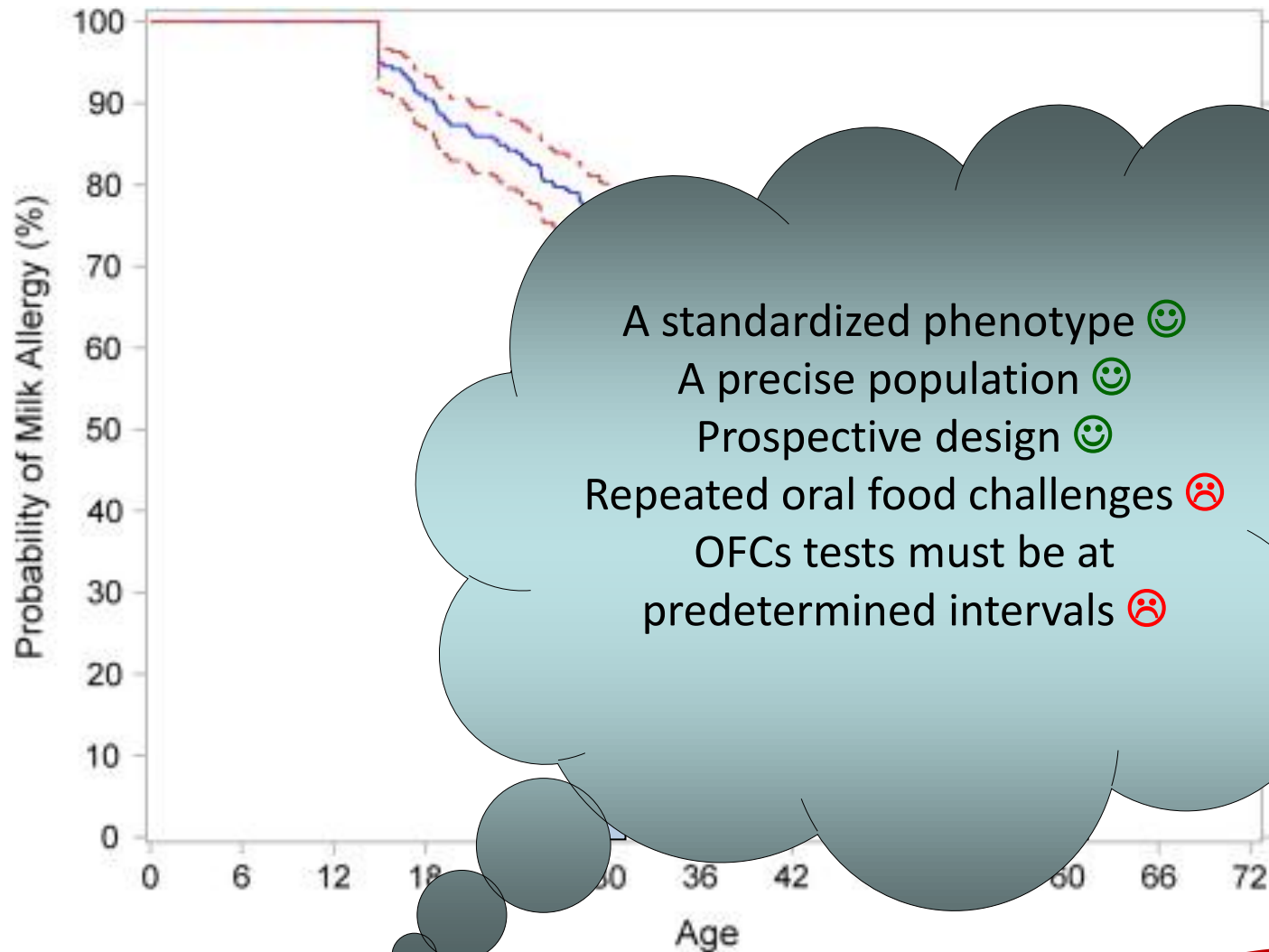
Criteria

1	Pass office challenge or home introduction
2*	Pass office challenge or home introduction OR cm-IgE <3 kU/L and no history of clinical reactivity in previous 12 mo
3	Pass office challenge or home introduction OR cm-IgE <15 kU/L and no history of clinical reactivity in previous 12 mo

atural history of IgE-mediated cow's milk allergy.



Saarinen KM. Clinical course and prognosis of CMA are dependent on milk-specific IgE status. *J Allergy Clin Immunol*. 2005; 116:869-75

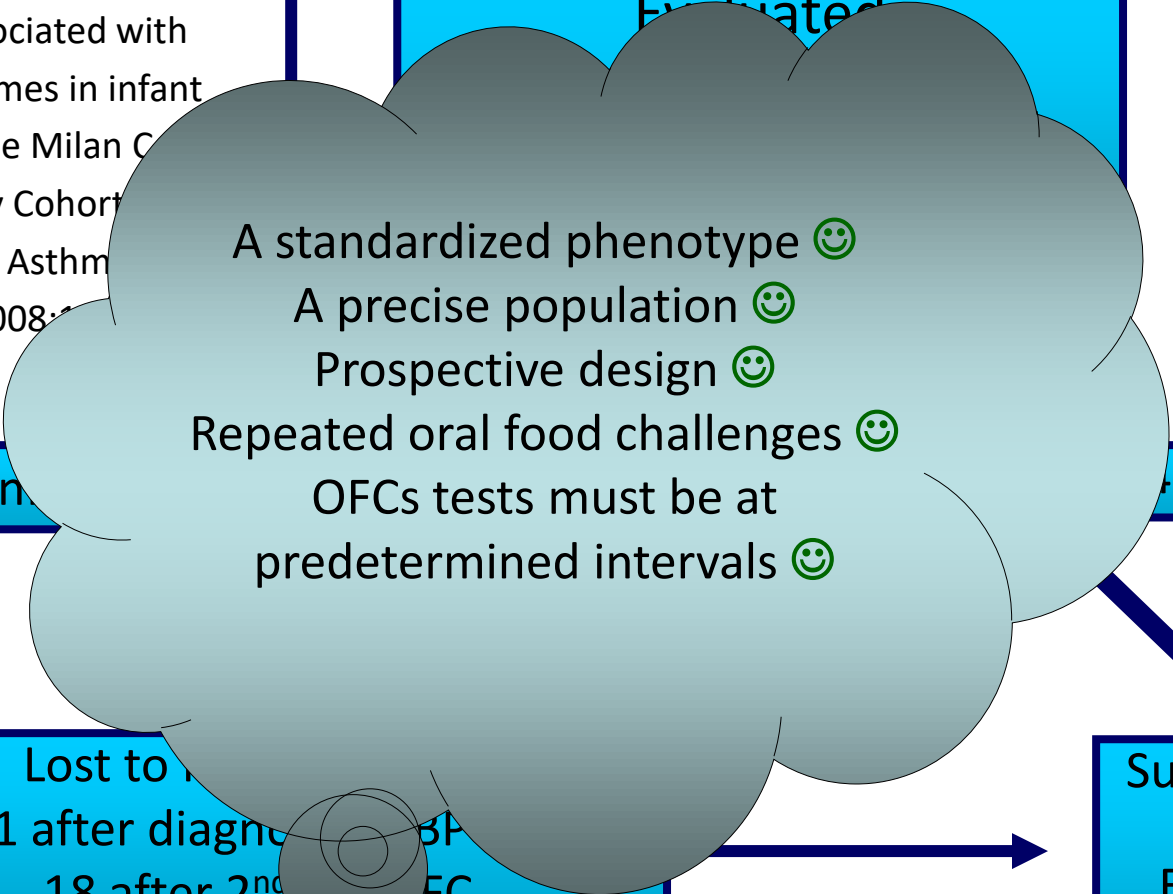


Sicherer SH. The natural history of milk allergy in an observational cohort. J Allergy Clin Immunol. 2013;131:805-12

Presented with suspicion of immediate-onset CMA = 339

Fiocchi A.
 Factors associated with
 CMA outcomes in infant
 referrals: the Milan C
 Milk Allergy Cohort
 Ann Allergy Asthma
 Immunol 2008;1

Evaluated



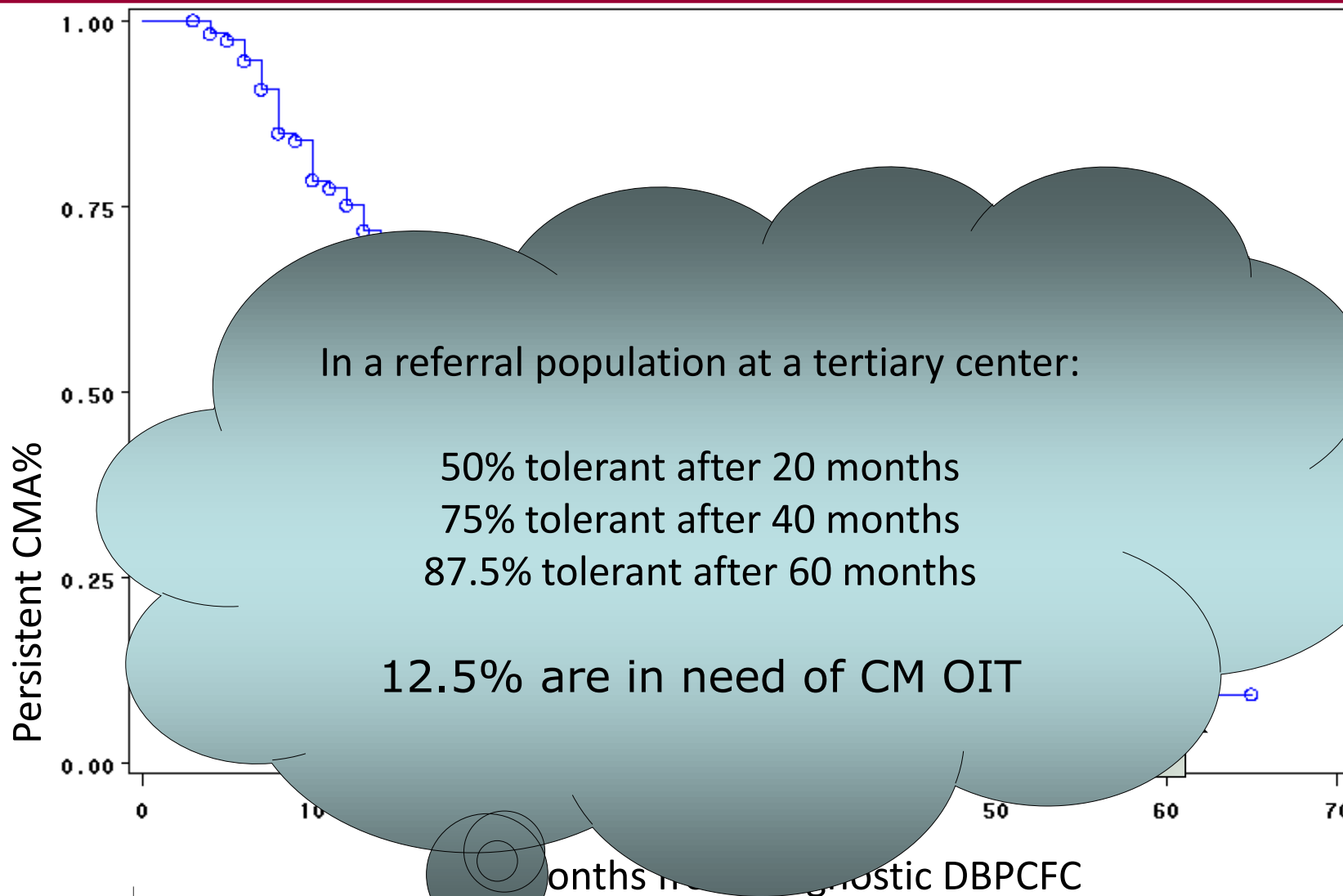
Con

7 (exited the study)

Lost to follow-up:
 21 after diagnosis
 18 after 2nd OFC

Suitable for evaluation =
 153
 Excluded for protocol
 violation: 41

MiCMAC cohort: survival curve



CMA has a good prognosis regarding recovery rate. However, CMA, especially IgE-mediated, in early childhood predicts a high prevalence of atopic diseases into adulthood.



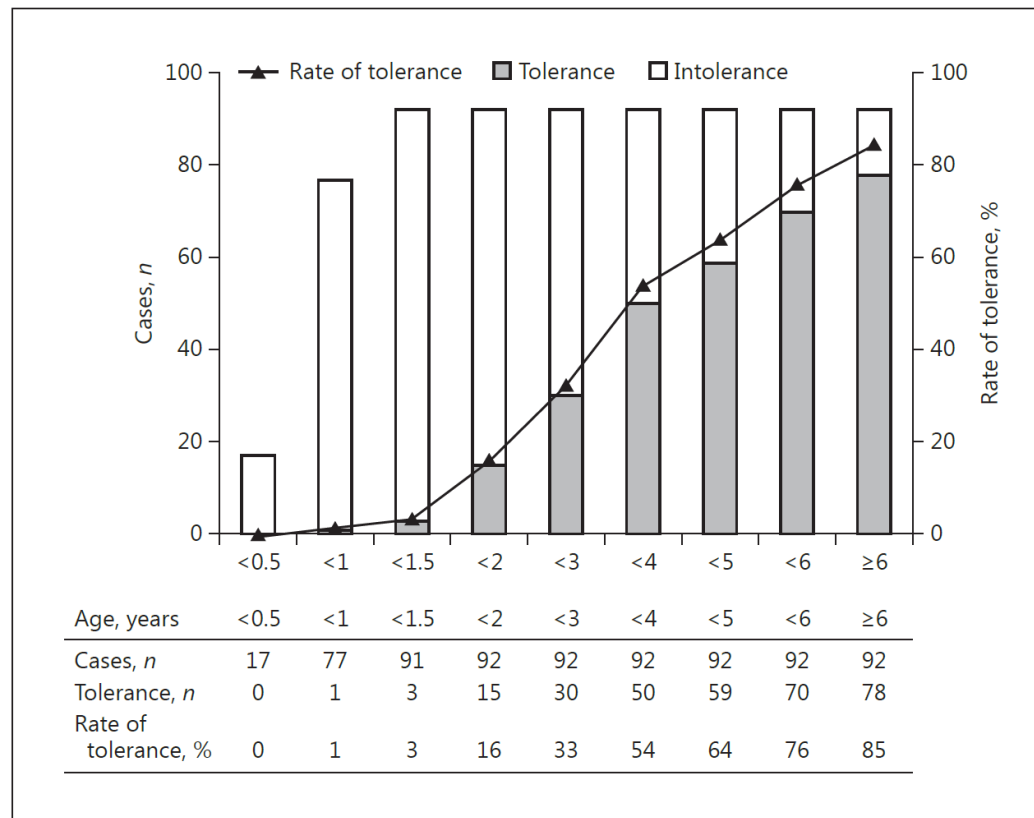
	Years
	3
92%	5
97%	26

Risk of asthma and rhinoconjunctivitis at 15 years of age,
 Risk of asthma and atopic dermatitis at 36 years of age

Hansen MM. The natural course of cow's milk allergy and the development of atopic diseases into adulthood. *Pediatr Allergy Immunol.* 2021;32:727-733

92 children with CMA at a tertiary center

39 (2.2%) diagnosed with CMA.



92 children with CMA in tertiary center

The history of anaphylaxis and high milk-specific IgE levels are associated with persistent CMA.

A.

Years	Percentage
3	55%
5	
7	



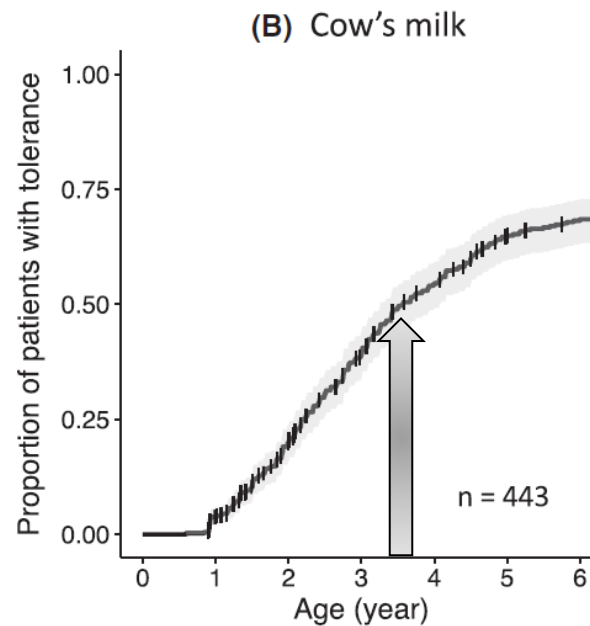
- Persistence associated with:
 - High age at 1st visit
 - Anaphylaxis to CM at history
 - Anaphylaxis to other foods
 - - Sensitization to casein

Kaplan–Meier curve for tolerance acquisition for infantile-onset, immediate-type milk allergy

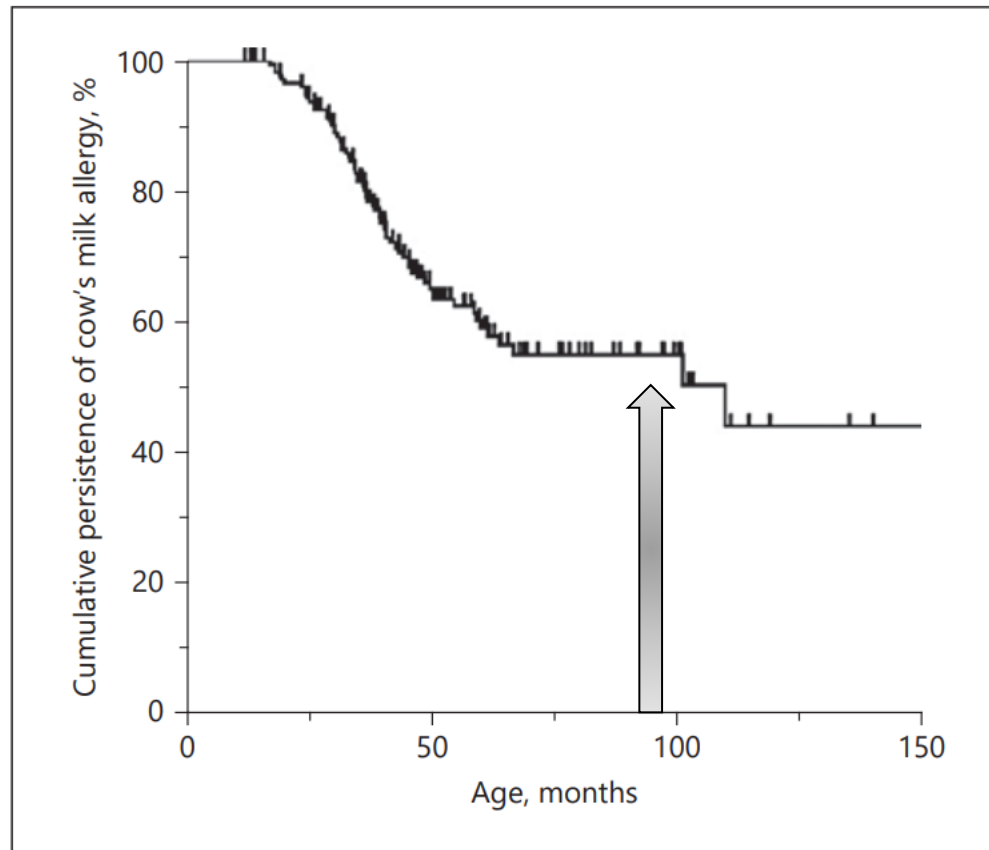
915 patients with immediate-type food allergy symptoms – observed up to 10 years.

IgE – mediated allergy to milk: 443.

Resolution at 6 yrs: 69%



Probability of developing tolerance:

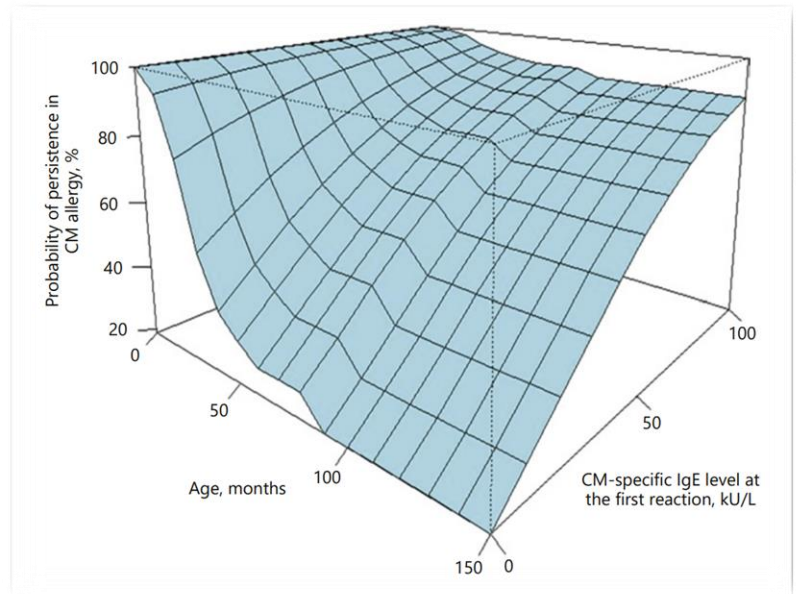


Kim M. The Natural Course of Immediate-Type Cow's Milk and Egg Allergies in Children. *Int Arch Allergy Immunol.* 2020;181:103-110



Probability of developing tolerance:

Initial sIgE level	Tolerance at 24 months	Tolerance at 48 months	Tolerance at 96 months
2 kUI/L			80%
5 kUI/L	30%		
19 kUI/L		50%	
35 kUI/L			50%
44 kUI/L		30%	
52 kUI/L	10%		
60 kUI/L			30%
91 kUI/L		10%	



Profile of the child with long-term CMA

1. Presenting with asthma and/or anaphylaxis
2. Also allergic to baked milk
3. ↑ specific IgE level at ImmunoCAP®
4. Sensitization to casein
5. Co-sensitisation to foods at SPT
6. Co-sensitisation to beef
7. Co-sensitisation to grass and dog dander
8. Co-sensitisation to less prevalent allergens

Skripak JM. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007;120:1172-7

Fiocchi A. Factors associated with cow's milk allergy outcomes in infant referrals: the Milan Cow's Milk Allergy Cohort study. *Ann Allergy Asthma Immunol* 2008;101:166-73

Koike Y. Predictors of Persistent Milk Allergy in Children: A Retrospective Cohort Study. *Int Arch Allergy Immunol.* 2018;175:177-180

Getting tolerance

Natural history of milk allergy

Natural history of egg allergy

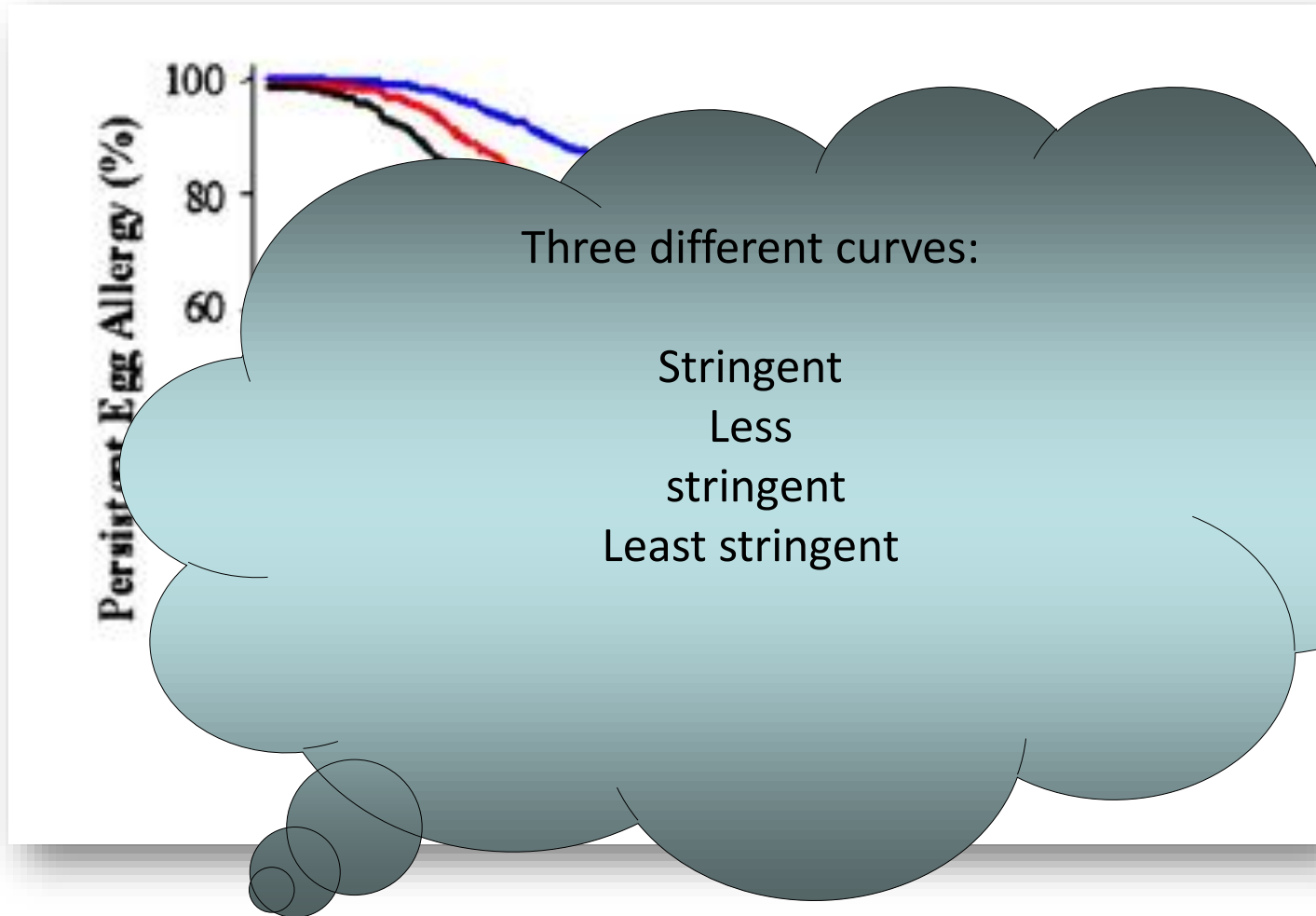
Natural history of peanut allergy

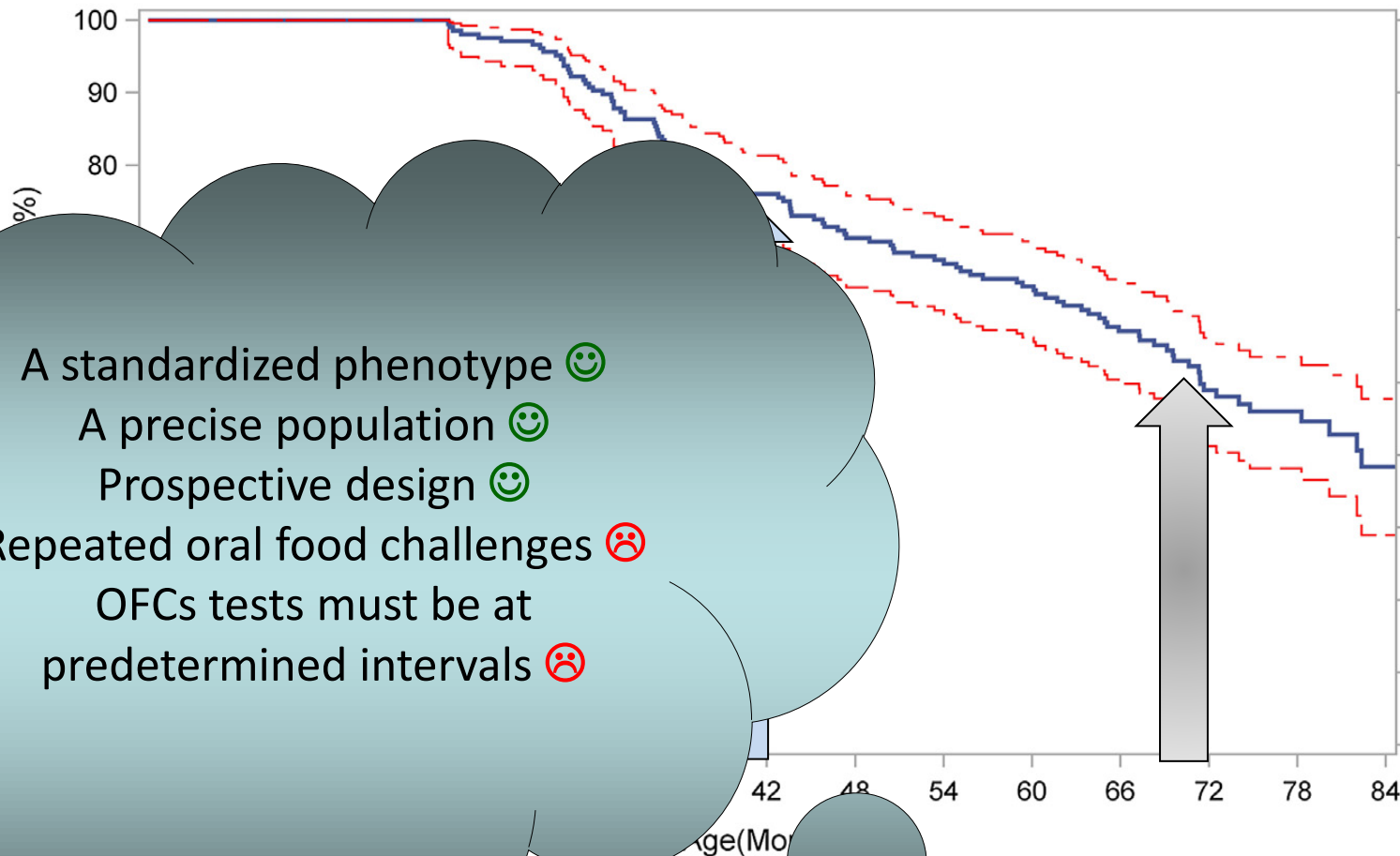
Effect of milk exposure on the natural course of CMA

Clinical course of multiple food allergens simultaneously

Conclusions

A significant proportion of egg allergy persists to adolescence





A standardized phenotype 😊

A precise population 😊

Prospective design 😊

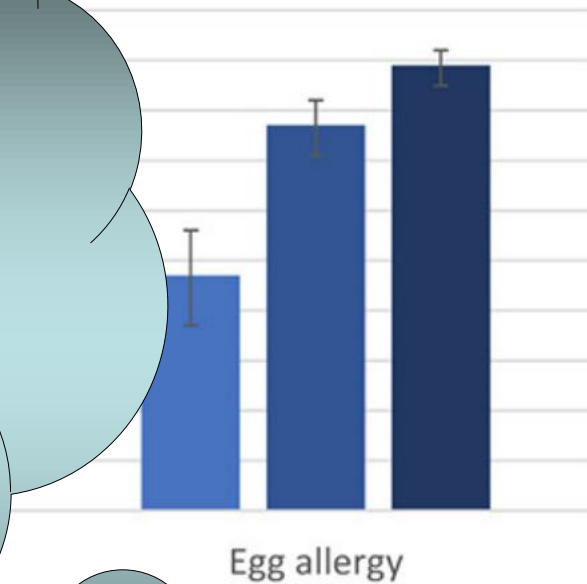
Repeated oral food challenges ☹️

OFCs tests must be at
predetermined intervals ☹️

Natural history of peanut and egg allergy in an Australian birth cohort

By 6 years of age, egg allergy had resolved in 90% of cases

A standardized phenotype 😊
A precise population 😊
Prospective design 😊
Repeated oral food challenges 😊
OFCs tests must be at predetermined intervals 😊



Peters RL. The natural history of peanut and egg allergy in children up to age 6 years in the HealthNuts population-based longitudinal study. *J Allergy Clin Immunol.* 2022;150:657-665

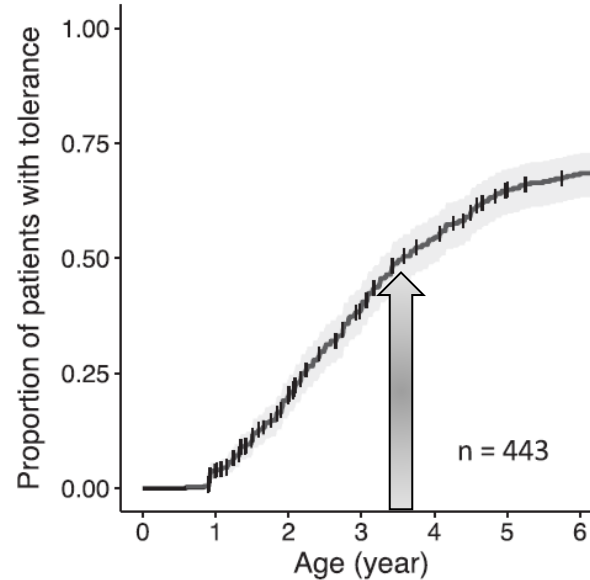
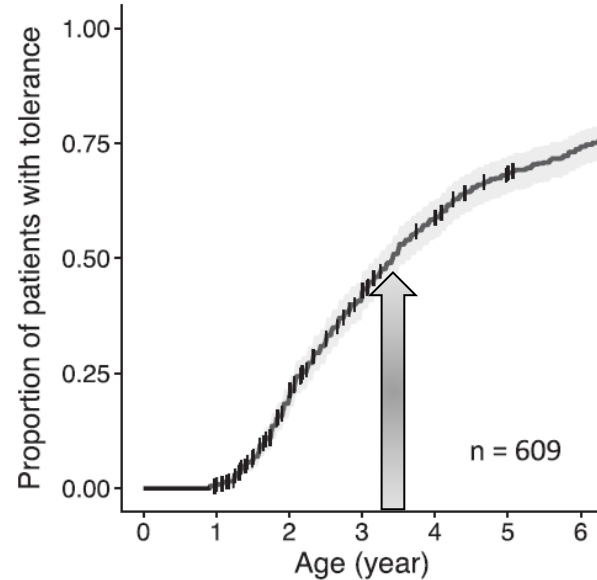
Kaplan–Meier curve for tolerance acquisition for infantile-onset, immediate-type egg allergy

915 patients with immediate-type food allergy symptoms – observed up to 10 years.
IgE – mediated allergy to egg: 609. Resolution at 6 yrs: 74%
IgE – mediated allergy to wheat: 235. Resolution at 6 yrs: 75%

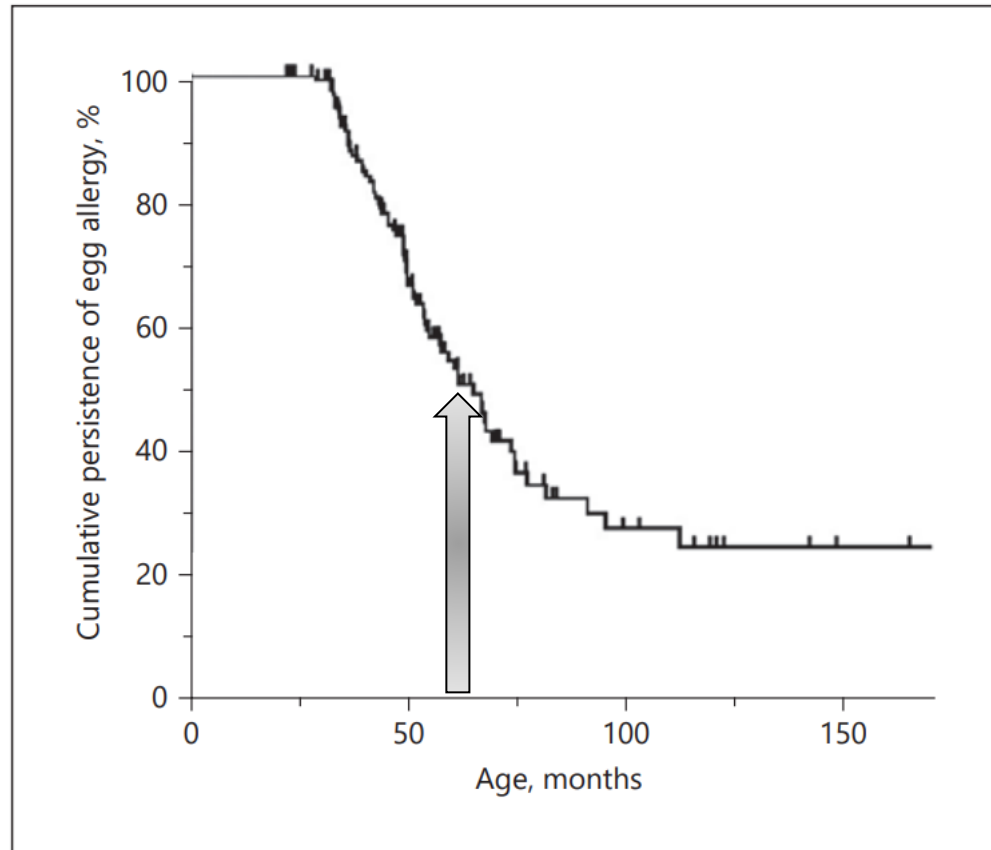


(A) Hen's egg

(B) Cow's milk



Probability of developing tolerance:

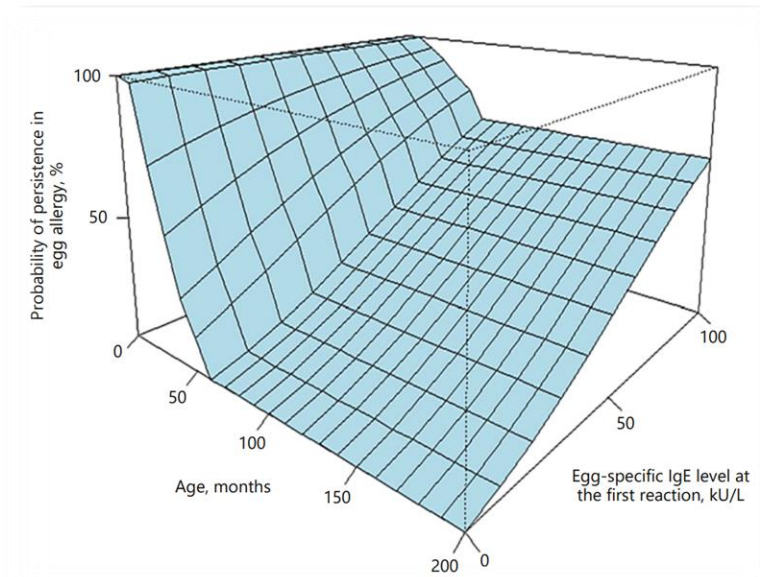


Kim M. The Natural Course of Immediate-Type Cow's Milk and Egg Allergies in Children. *Int Arch Allergy Immunol.* 2020;181:103-110



Probability of developing tolerance:

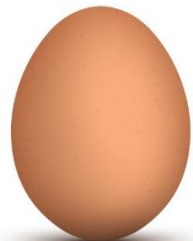
Initial sIgE level	Tolerance at 24 months	Tolerance at 48 months	Tolerance at 72 months
5 kUI/L		80%	
10 kUI/L	13%		
32 kUI/L			80%
48 kUI/L		50%	
75 kUI/L			50%
76 kUI/L	10%		
82 kUI/L		30%	



Recommendations on efficacy of OIT in children with hen's egg allergy

Recommendations ^a	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations
OIT can be recommended as a treatment option to increase the threshold of reaction while on OIT in children with persistent hen's egg allergy, from around 4 - 5 years of age	I	B	Moderate recommendation based on evidence for effect from SR and meta-analysis ¹⁸ including low risk of bias RCTs. ^{8,42} Studies are all small with some heterogeneity in results	Risk of adverse reactions needs to be considered. Age recommendation is based on expert opinion. Additional large studies required
A recommendation cannot currently be made for OIT as a treatment option to achieve post-discontinuation effectiveness in children with persistent hen's egg allergy	I	B	Strong recommendation based on only one RCT with low risk of bias ⁴³	After 4 years of OIT 50% of subjects achieved sustained unresponsiveness 4-6 weeks after stopping OIT. ⁴³ Further studies needed

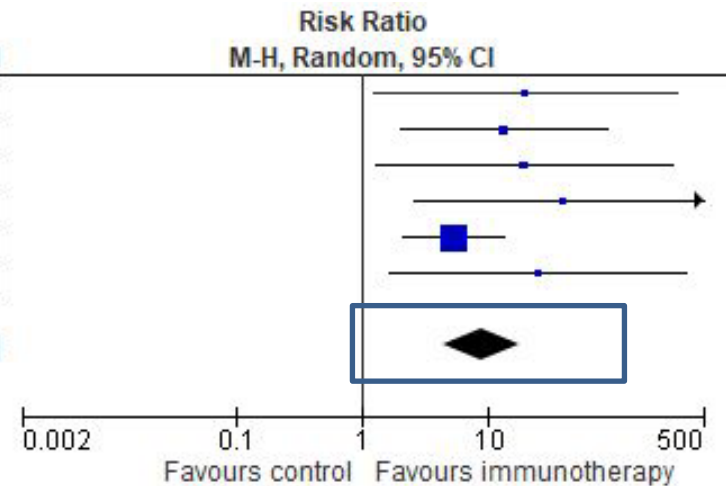
^a OIT for food allergy should only be undertaken in highly specialized clinical centers with expertise and facilities to safely deliver this therapy.



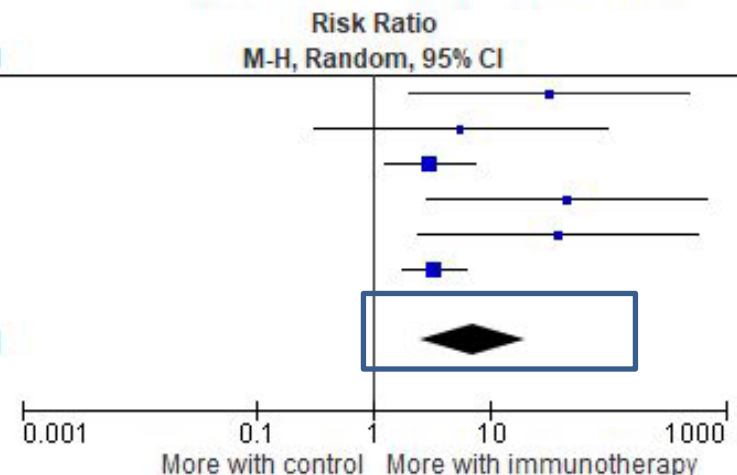
Pajno GB. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2018;73:799-815

- Pooled data from 6 studies of oral immunotherapy in hen's egg found increased likelihood of desensitisation; egg OIT was associated with increased adverse reactions.

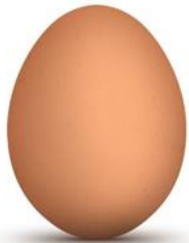
Study or Subgroup	Immunotherapy		Control		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Akashi 2017	8	14	0	16	6.4%	19.27 [1.21, 306.35]
Caminiti 2015	16	17	1	14	13.7%	13.18 [1.99, 87.43]
Dello Iacono 2013	9	10	0	10	6.6%	19.00 [1.25, 287.92]
Itoh-Nagato 2018	20	23	0	22	6.5%	39.29 [2.52, 612.47]
Martín-Muñoz 2019	64	76	4	25	60.1%	5.26 [2.13, 12.99]
Pérez-Rangel 2017	17	19	0	13	6.6%	24.50 [1.60, 374.49]
Total (95% CI)		159		100	100.0%	8.91 [4.42, 17.95]
Total events	134		5			
Heterogeneity: Tau ² = 0.00; Chi ² = 4.00, df = 5 (P = 0.55); I ² = 0%						
Test for overall effect: Z = 6.12 (P < 0.00001)						



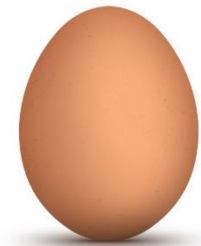
Study or Subgroup	Immunotherapy		Control		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Akashi 2017	17	18	0	16	10.2%	31.32 [2.03, 482.04]
Caminiti 2015	3	17	0	13	9.5%	5.44 [0.31, 96.96]
Dello Iacono 2013	10	10	3	10	28.5%	3.00 [1.25, 7.19]
Escudero 2015	21	30	0	31	10.1%	44.39 [2.81, 701.31]
Itoh-Nagato 2018	19	23	0	22	10.2%	37.38 [2.39, 583.62]
Martín-Muñoz 2019	69	76	7	25	31.5%	3.24 [1.72, 6.10]
Total (95% CI)		174		117	100.0%	7.01 [2.49, 19.75]
Total events	139		10			
Heterogeneity: Tau ² = 0.78; Chi ² = 12.40, df = 5 (P = 0.03); I ² = 60%						
Test for overall effect: Z = 3.69 (P = 0.0002)						



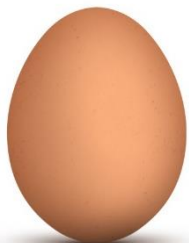
Allergen immunotherapy



The GA²LEN Task Force **suggests** offering **oral immunotherapy** under specialist supervision with standardized evidence-based protocols using food products to selected children (aged 4+ years) with clinically diagnosed persistent severe IgE-mediated **hen's egg or cow's milk allergy** to increase the amount of allergen tolerated while on therapy.



Moderate



Getting tolerance

Natural history of milk allergy

Natural history of egg allergy

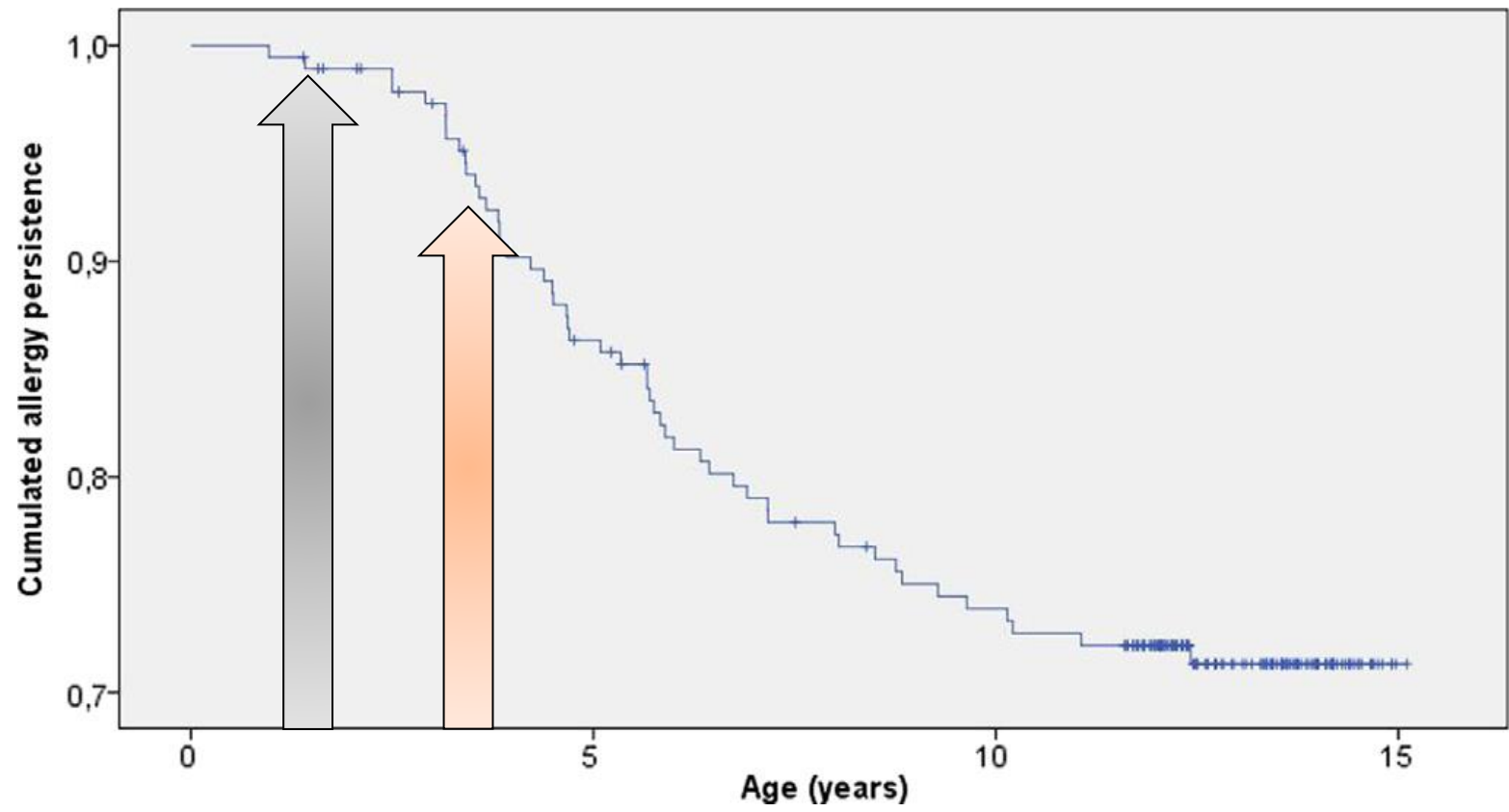
Natural history of peanut allergy

Effect of milk exposure on the natural course of CMA

Clinical course of multiple food allergens simultaneously

Conclusions

Peanut Allergy Natural history

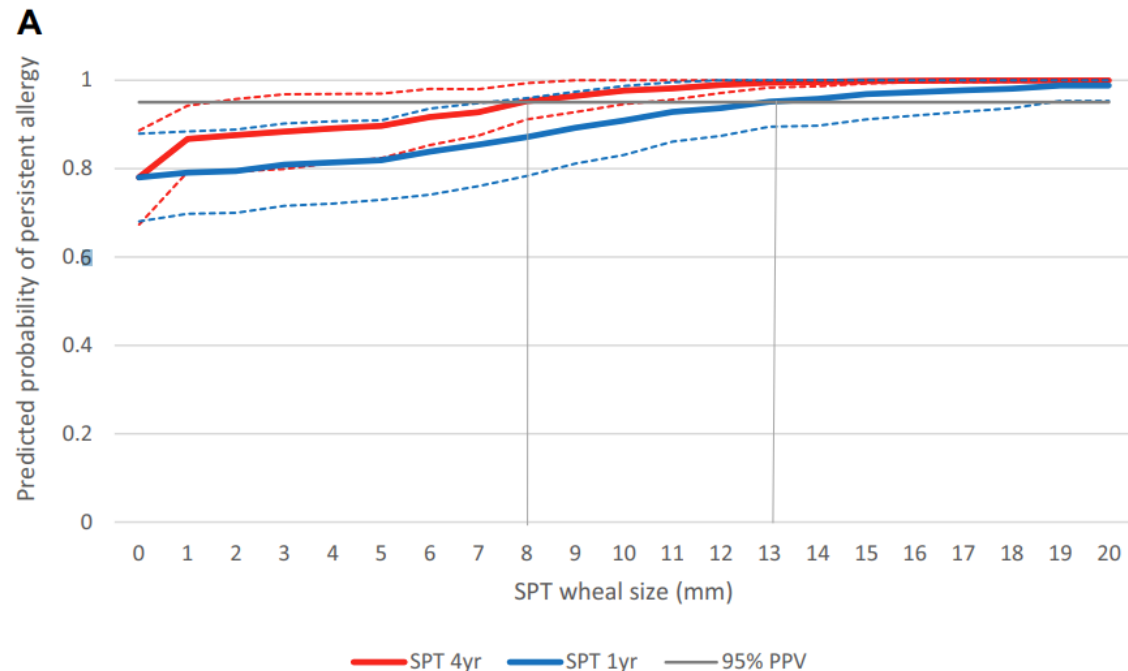


Bégin P. Natural resolution of peanut allergy: a 12-year longitudinal follow-up study.
J Allergy Clin Immunol Pract. 2013;1:528-30

Natural history of peanut allergy in an Australian birth cohort

By 4 years of age, peanut allergy had resolved in 22% of cases.

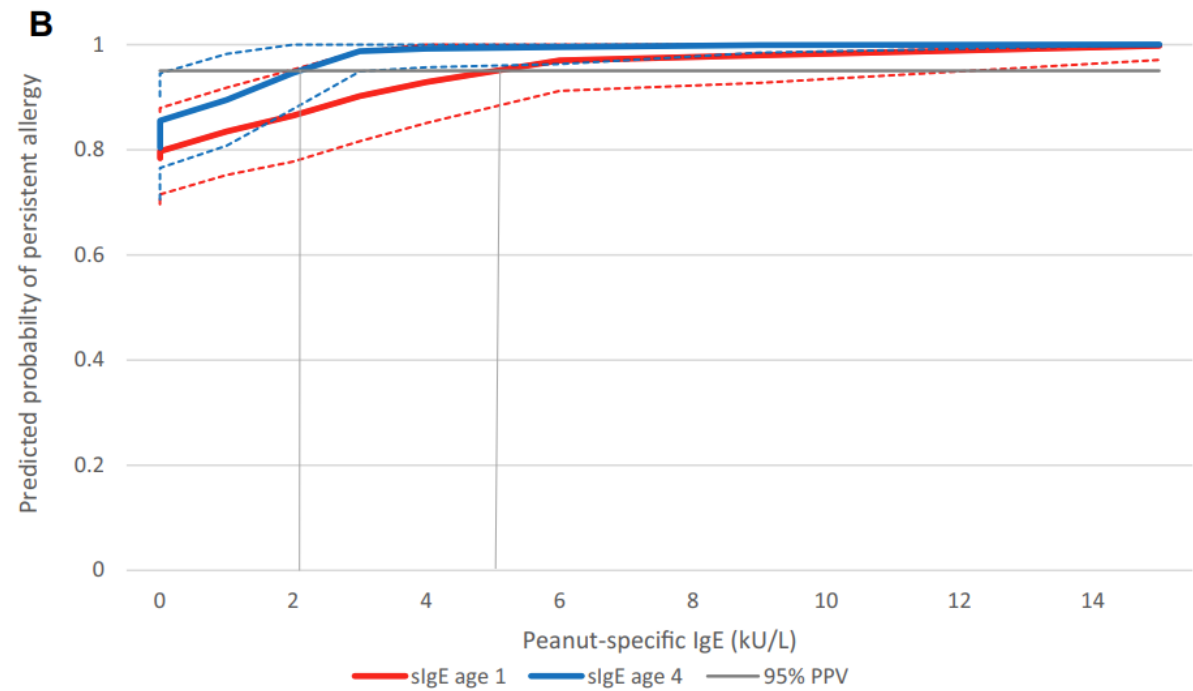
The probability of persistent peanut allergy is higher for children with SPT wheal size equal to or greater than the stated threshold.



Natural history of peanut allergy in an Australian birth cohort

By 4 years of age, peanut allergy had resolved in 22% of cases.

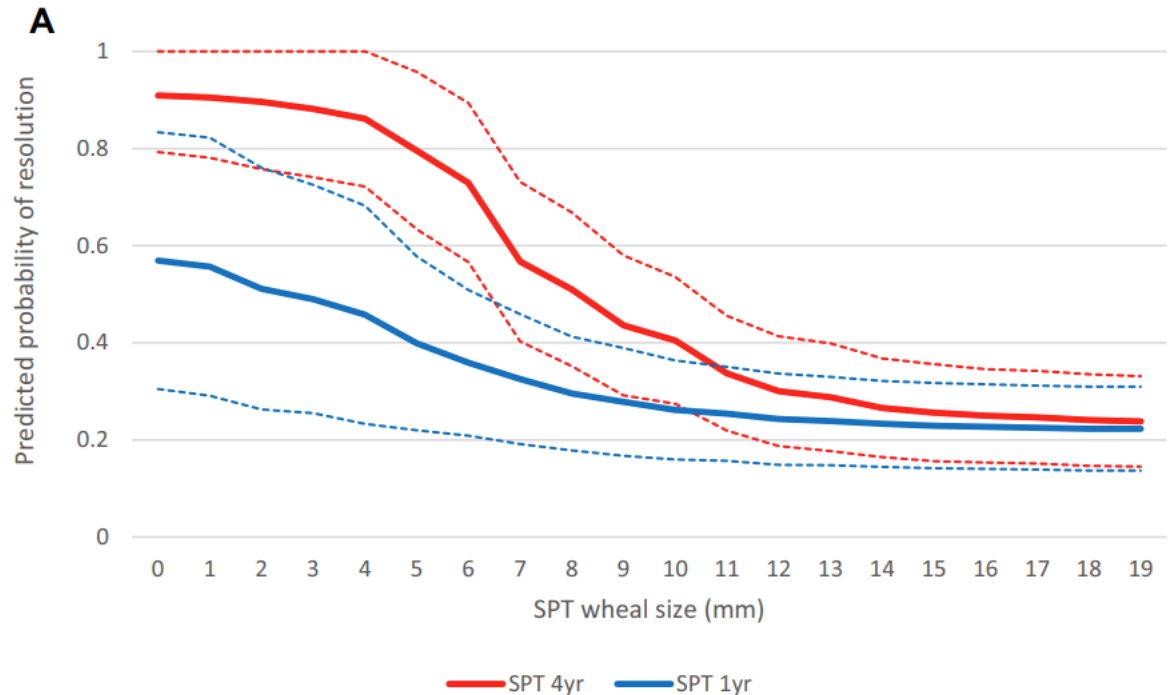
The probability of persistent peanut allergy is higher for children with sIgE levels equal to or greater than the stated threshold.



Natural history of peanut allergy in an Australian birth cohort

By 4 years of age, peanut allergy had resolved in 22% of cases.

The probability of resolved peanut allergy is higher for children with SPT \leq equal to or less than the stated threshold.

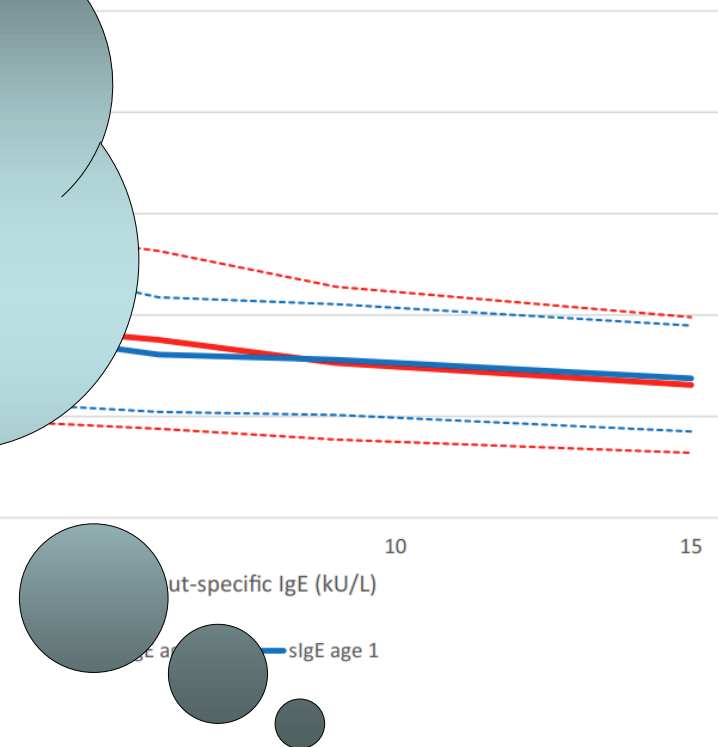


Natural history of peanut allergy in an Australian birth cohort

By 4 years of age, peanut allergy had resolved in 22% of cases.

The probability of resolution of peanut allergy is higher for children with sIgE levels below a stated threshold.

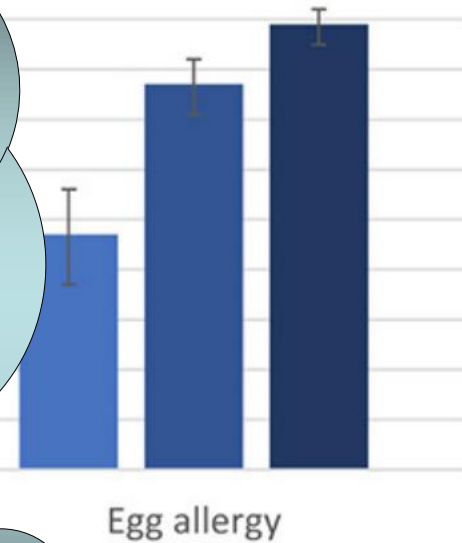
- A standardized phenotype 😊
- A precise population 😊
- Prospective design 😊
- Repeated oral food challenges 😊
- OFCs tests must be at predetermined intervals 😊



Natural history of peanut and egg allergy in an Australian birth cohort

By 6 years of age, peanut allergy had resolved in 29% of cases

A standardized phenotype 😊
A precise population 😊
Prospective design 😊
Repeated oral food challenges 😊
OFCs tests must be at predetermined intervals 😊



Peters RL. The natural history of peanut and egg allergy in children up to age 6 years in the HealthNuts population-based longitudinal study. *J Allergy Clin Immunol.* 2022;150:657-665

Peanut Oral Immunotherapy study: Safety, Efficacy and Discovery (POISED)



4000 mg for 104 weeks → 0



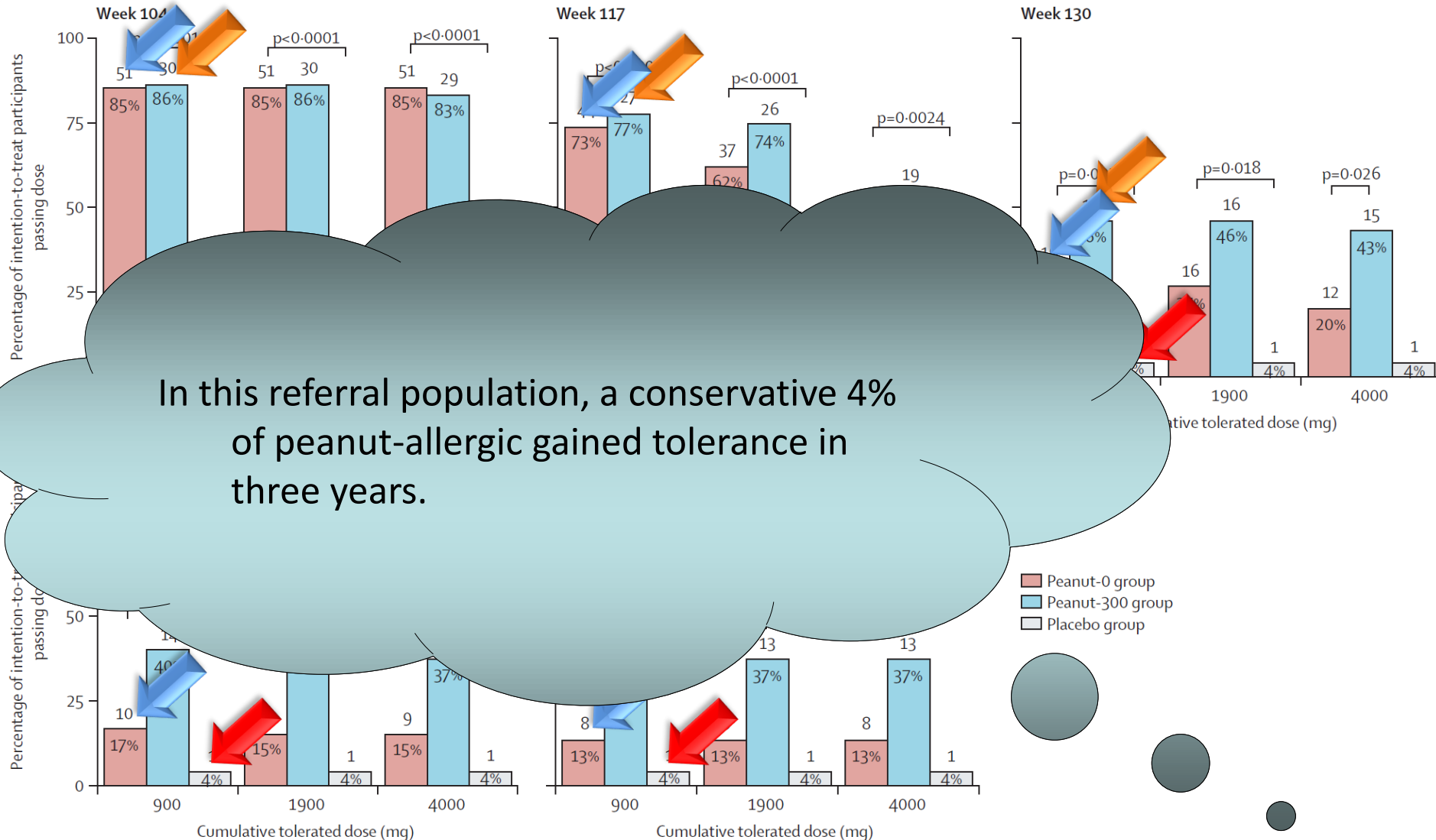
4000 mg for 104 weeks → 300 mg



Placebo for 104 weeks → 0



OIT for peanut: sustained hyporesponsiveness (POISED study)



Can OIT get Sustained Unresponsiveness? the IMPACT trial

Population and design:

A randomised, double-blind, placebo-controlled study in US

Children aged 12 - 48 months

Allergic to peanut, eliciting dose 500 mg or less of peanut protein at DBPCFC

Peanut oral immunotherapy or placebo for 134 weeks (2000 mg peanut protein per day)

26 weeks of avoidance

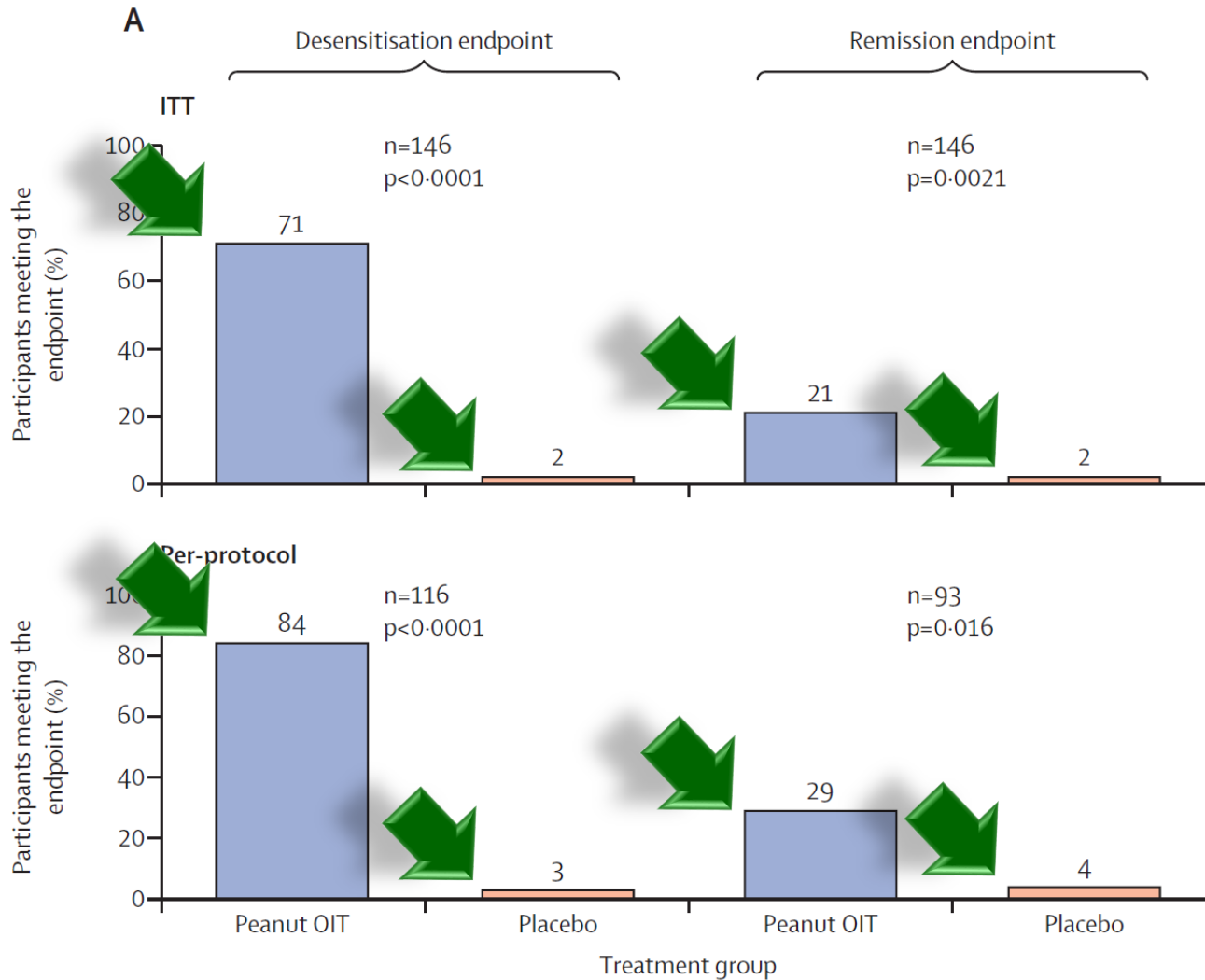
Outcomes:

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Secondary, remission after avoidance (week 160)

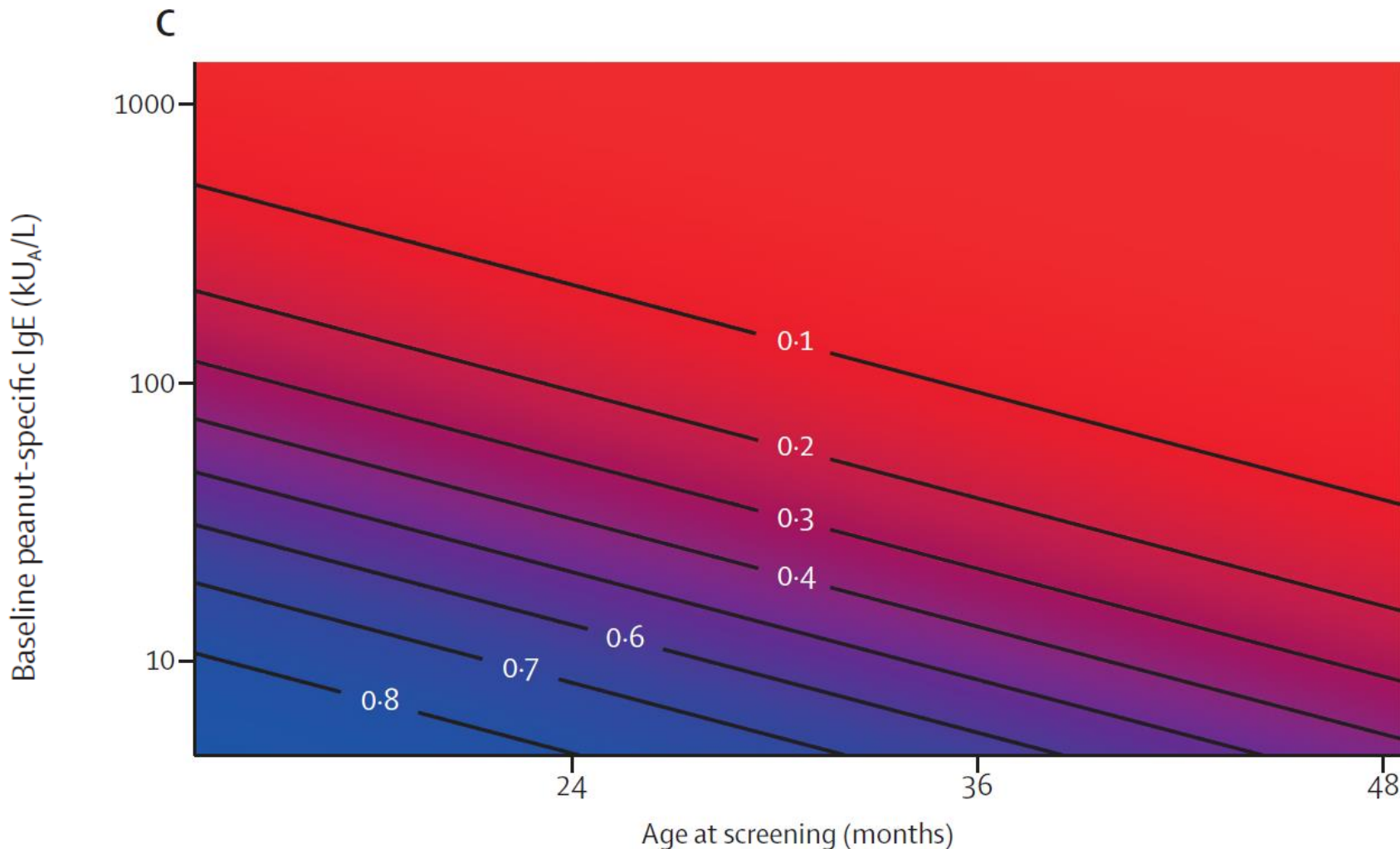
Jones SM. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. *Lancet*. 2022 Jan 22;399(10322):359-371

Can OIT get Sustained Unresponsiveness? the IMPACT trial



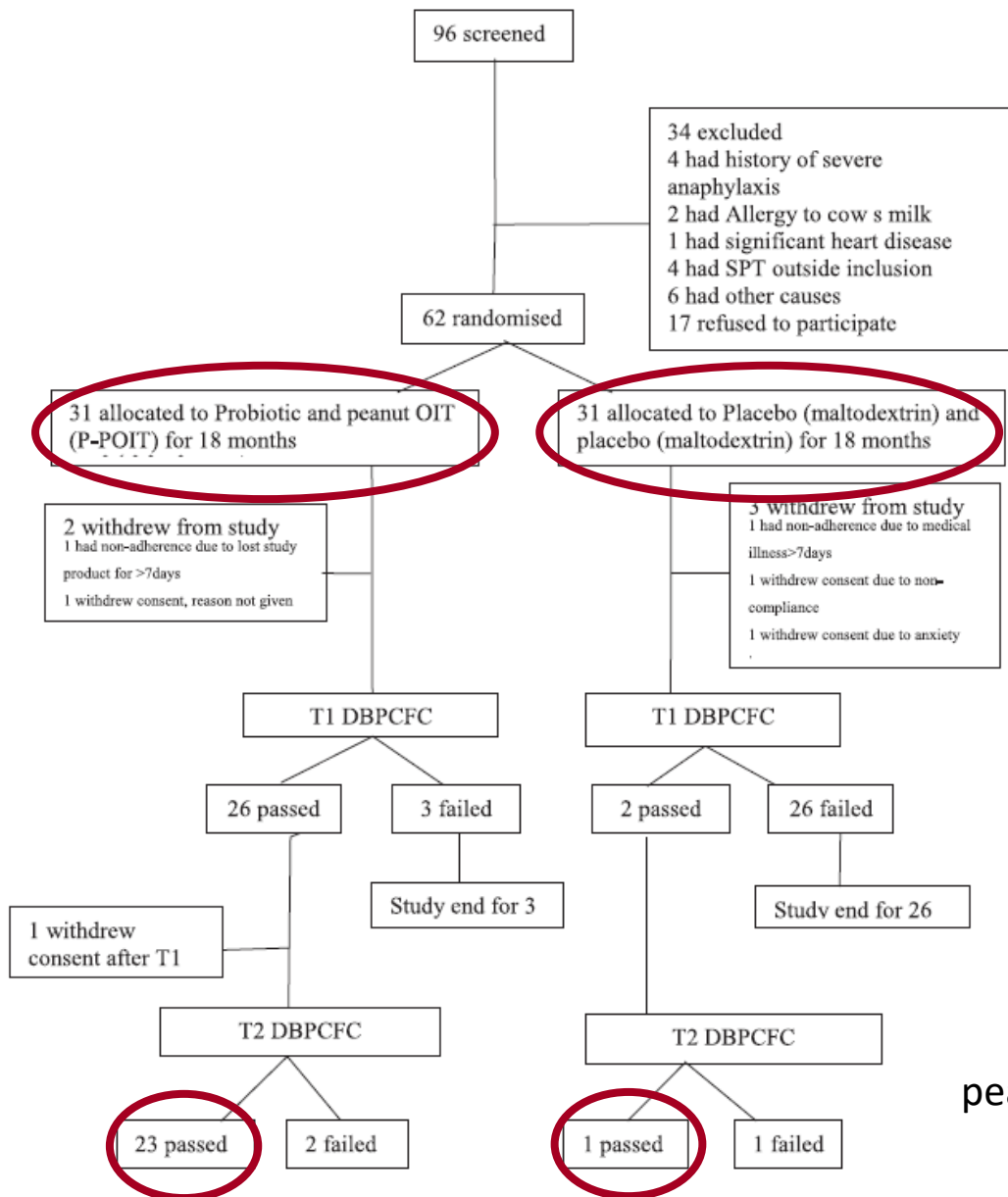
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Predicted probability of remission from the logistic regression model plotted against baseline peanut/specific IgE and age at screening



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Can OIT get Sustained Unresponsiveness?



Tang ML. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol 2015;135:737-44

Does OIT get Sustained Unresponsiveness? the Australian PPOIT-003 trial.

Evidence before this study

- Before Jan 1, 2016, peanut oral immunotherapy (OIT) was highly effective at inducing desensitisation (a temporary increase in reaction threshold while on therapy) but only induced clinical remission (sustained unresponsiveness) in a subset of patients (up to 30% of treated patients in randomised controlled trials).
- The combination therapy, probiotic *Lactobacillus rhamnosus* and peanut OIT (PPOIT) induced high rates of 2–6-week sustained unresponsiveness.
- However, the absence of a peanut OIT group prevented evaluation of the added benefit from a probiotic.

Does OIT get Sustained Unresponsiveness in younger children? the Australian PPOIT-003 trial.

Results

201 participants.

SU eight weeks after treatment:

46% in the PPOIT group

51% in the OIT group

5% in the placebo group

Risk difference 40.44% [95% CI 27.46 to 53.42] for PPOIT vs placebo, $p < 0.0001$,

No difference between PPOIT and OIT (-5.03% [-20.40 to 10.34], $p = 0.52$)

All age groups

Sustained unresponsiveness	36 (46%)	42 (51%)	2 (5%)
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Desensitisation	61 (77%)	61 (73%)	2 (5%)
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Age 1-5 years

Sustained unresponsiveness	25/41 (61%)	24/43 (56%)	2/20 (10%)
----------------------------	-------------	-------------	------------

Desensitisation	36/41 (88%)	34/43 (79%)	2/20 (10%)
-----------------	-------------	-------------	------------

Age 6-10 years

Sustained unresponsiveness	11/38 (29%)	18/40 (45%)	0/19
----------------------------	-------------	-------------	------

Desensitisation	25/38 (66%)	27/40 (68%)	0/19
-----------------	-------------	-------------	------

Does OIT get Sustained Unresponsiveness? the Australian PPOIT-003 trial.

SU over 12 months

85% in the PPOIT group
86% in the OIT group
18% in the placebo group



achieved sustained unresponsiveness

Rescue epinephrine

3% in the PPOIT group
6% in the OIT group
none in the placebo group

	PPOIT group	OIT group	Placebo group
Participants	71	70	34
Eating peanuts	60/71 (85%)	60/70 (86%)	6/34 (18%)
Reactions to peanuts*	22/71 (31%)	24/70 (34%)	4/34 (12%)

Loke P. Probiotic peanut oral immunotherapy versus oral immunotherapy and placebo in children with peanut allergy in Australia (PPOIT-003): a multicentre, randomised, phase 2b trial. *Lancet Child Adolesc Health.* 2022;6(3):171-184

Allergen immunotherapy

The GA²LEN Task Force **recommends** offering **peanut oral immunotherapy** under specialist supervision with standardized evidence-based protocols using peanut products (or licensed pharmaceutical products, where appropriate), to selected children (aged 4+ years) with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.

High

The GA²LEN Task Force **suggests** offering **peanut epicutaneous immunotherapy** under specialist supervision using licensed pharmaceutical products if they become available to selected children aged 4-11 years with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.

Moderate





Mark Schneider, Nestlé CEO (AP Images)

November 29, 2022 12:48 PM EST Updated 05:09 PM | Pharma

[🔗](#) [in](#) [🐦](#)

Nestlé reconsiders peanut allergy program two years after \$2.6B buyout



Nicole DeFeudis
Editor

It seems Nestlé is experiencing some buyer's remorse two years after throwing down \$2.6 billion for Aimmune Therapeutics and its peanut allergy pill Palforzia.

Can OIT get Sustained Unresponsiveness? the IMPACT trial

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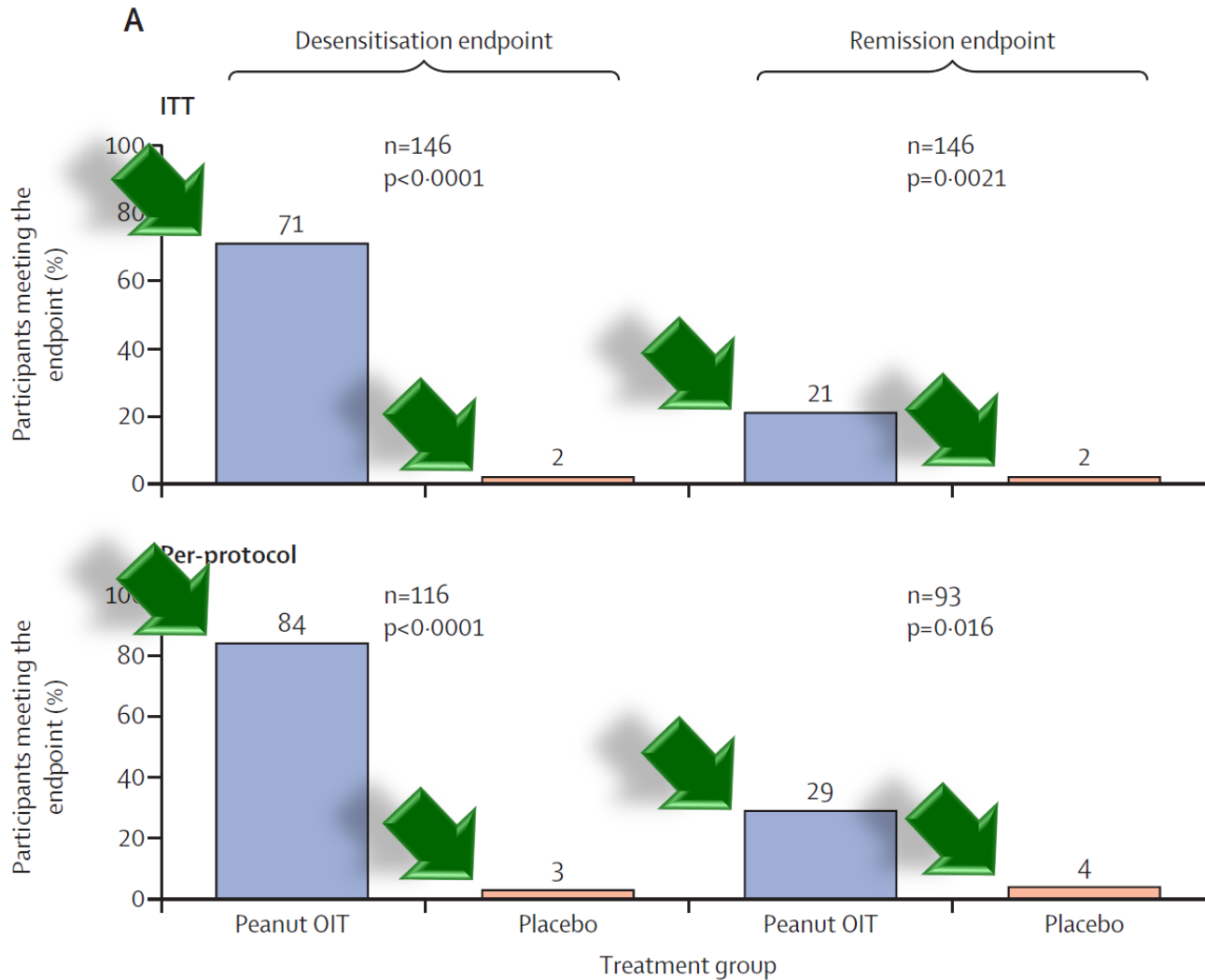
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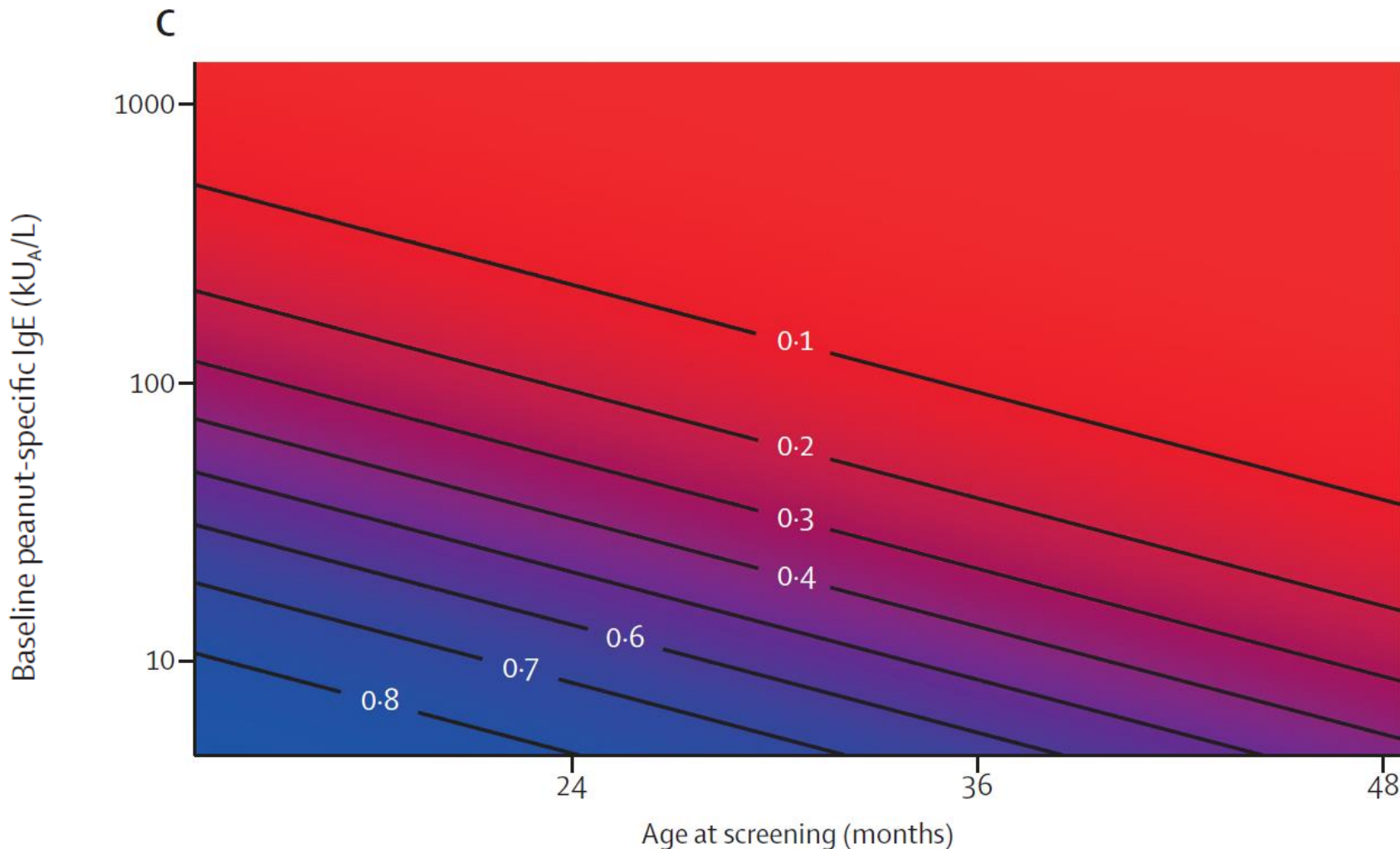
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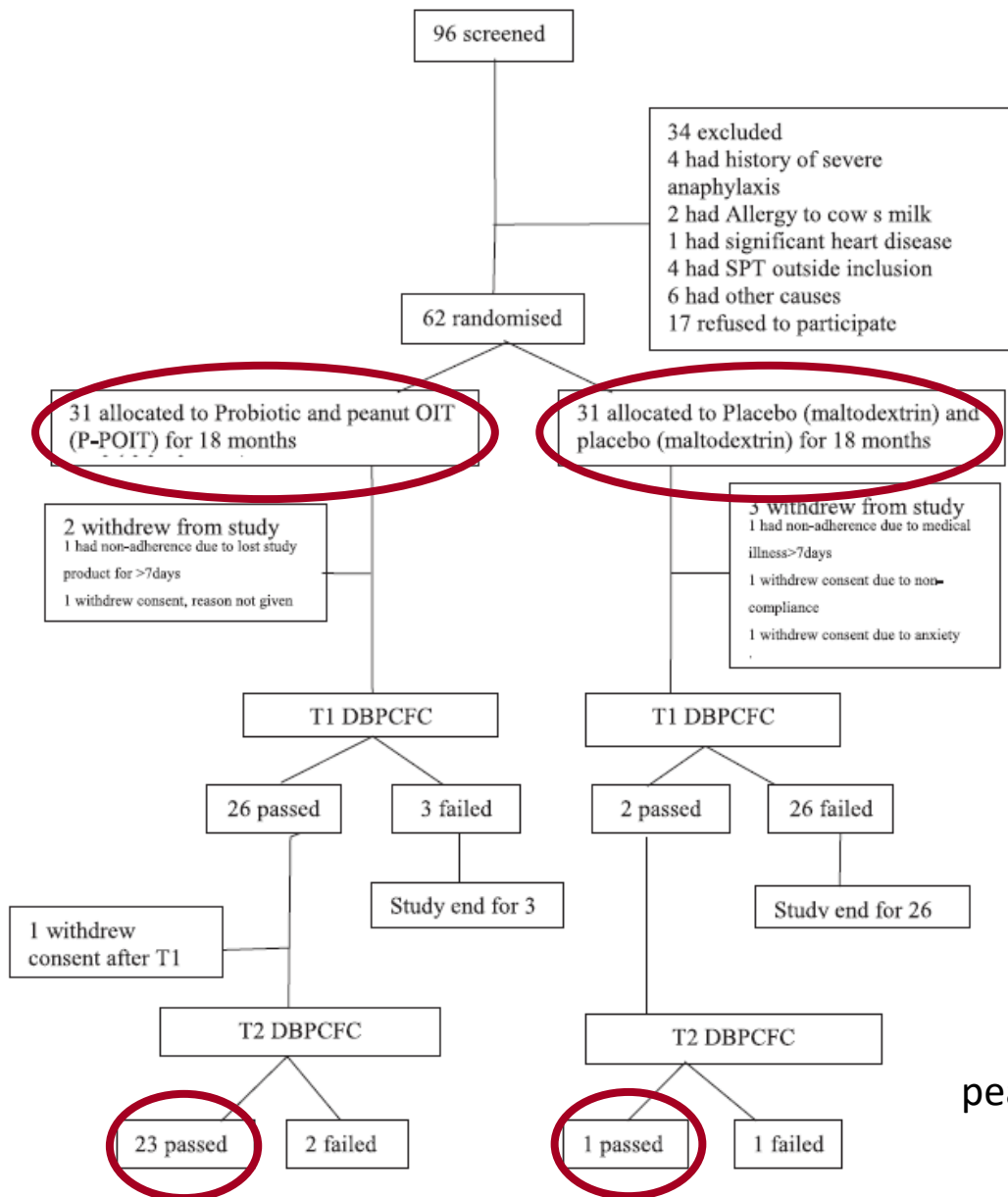
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Getting tolerance

Natural history of milk allergy

Natural history of egg allergy

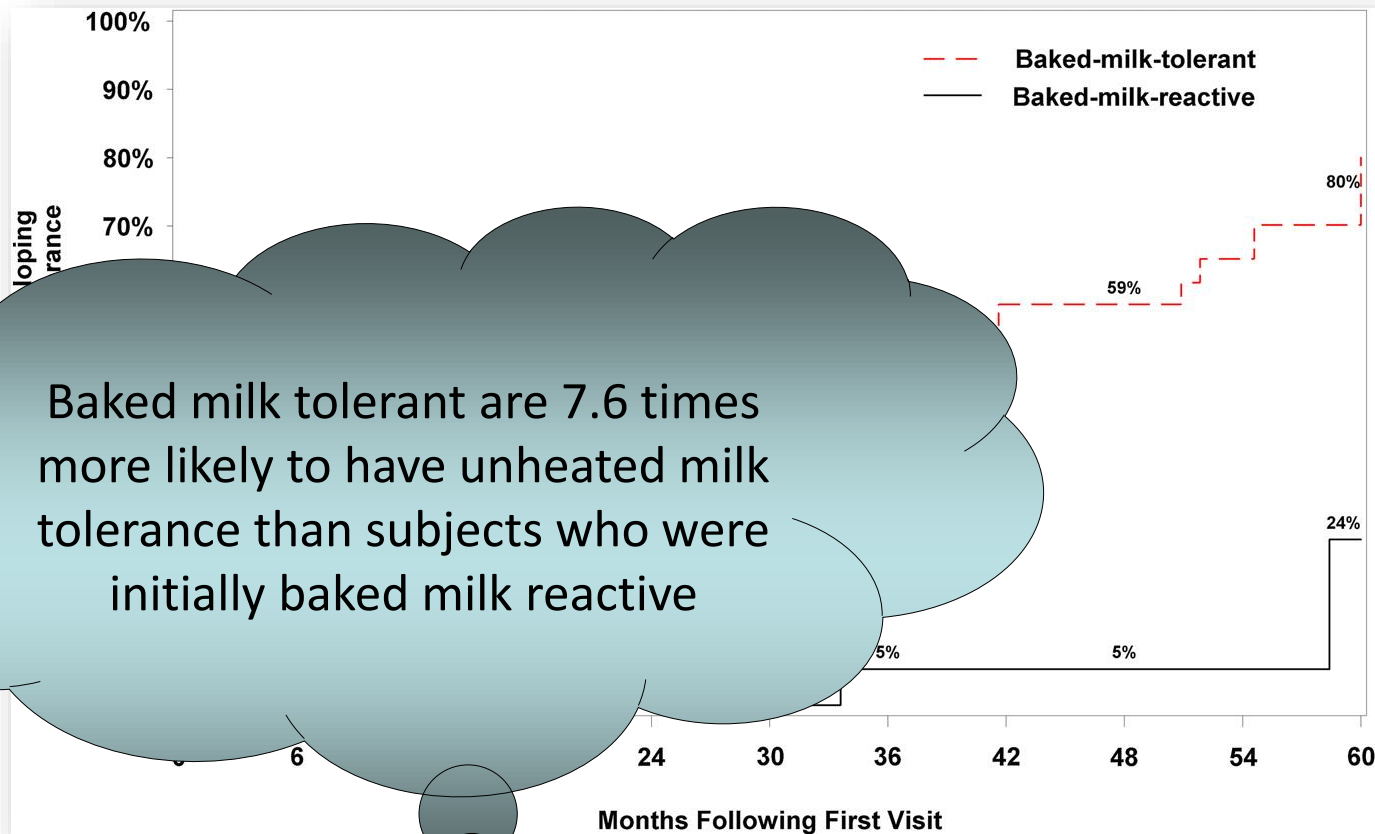
Natural history of peanut allergy

Effect of milk exposure on the natural course of CMA

Clinical course of multiple food allergens simultaneously

Conclusions

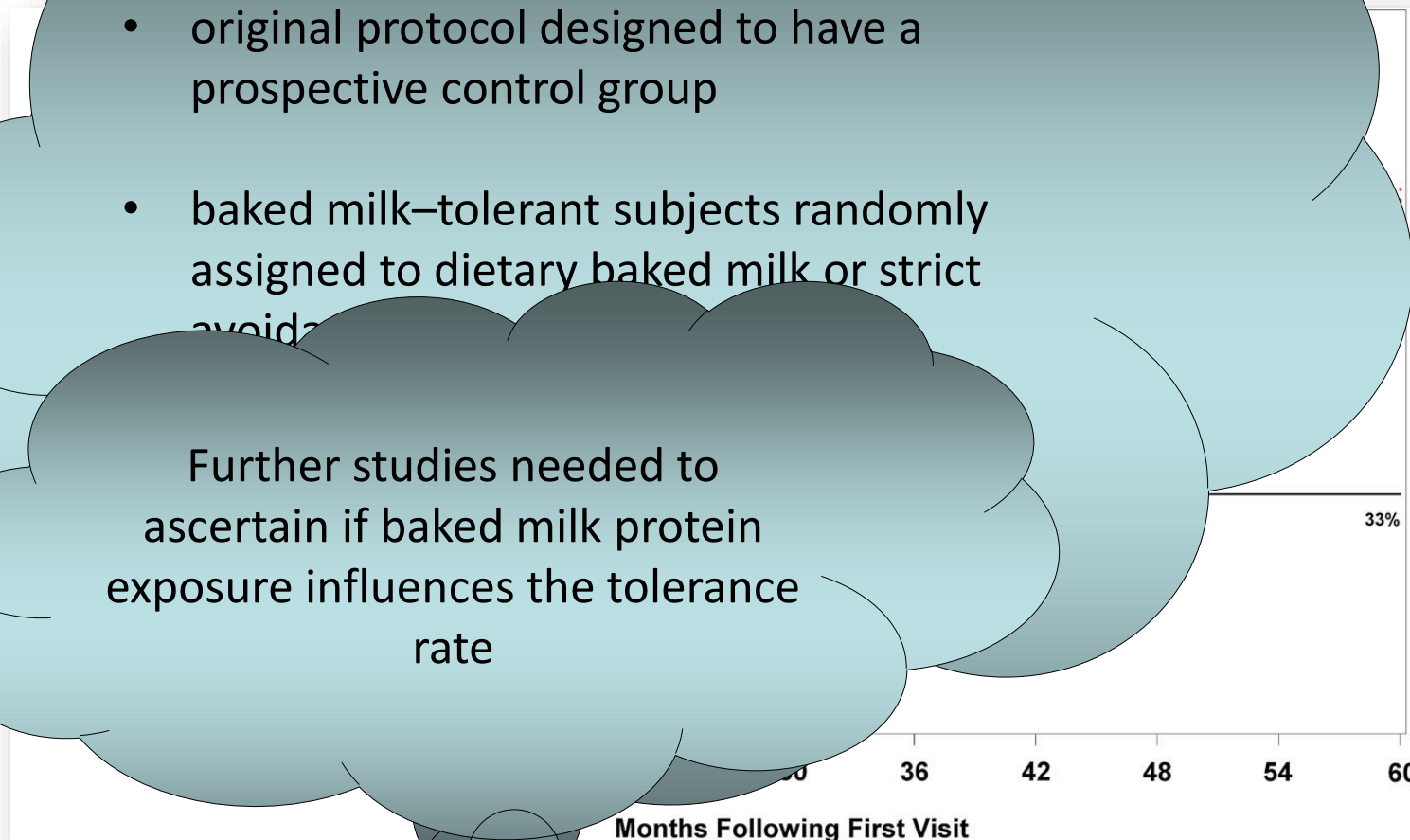
Baked milk accelerates the resolution of cow's milk allergy



Baked milk tolerant are 7.6 times more likely to have unheated milk tolerance than subjects who were initially baked milk reactive

- original protocol designed to have a prospective control group
- baked milk-tolerant subjects randomly assigned to dietary baked milk or strict avoidance

Further studies needed to ascertain if baked milk protein exposure influences the tolerance rate



Should oral immunotherapy with baked cow's milk be used for persons with IgE-mediated CMA who do not tolerate baked cow's milk?



Do vegetable formulae accelerate the resolution of CMA?

Children breastfed, or symptomatic despite current dietary prescription
were switched to a different regimen.

Jan – Apr: SF



May – Aug: eHF

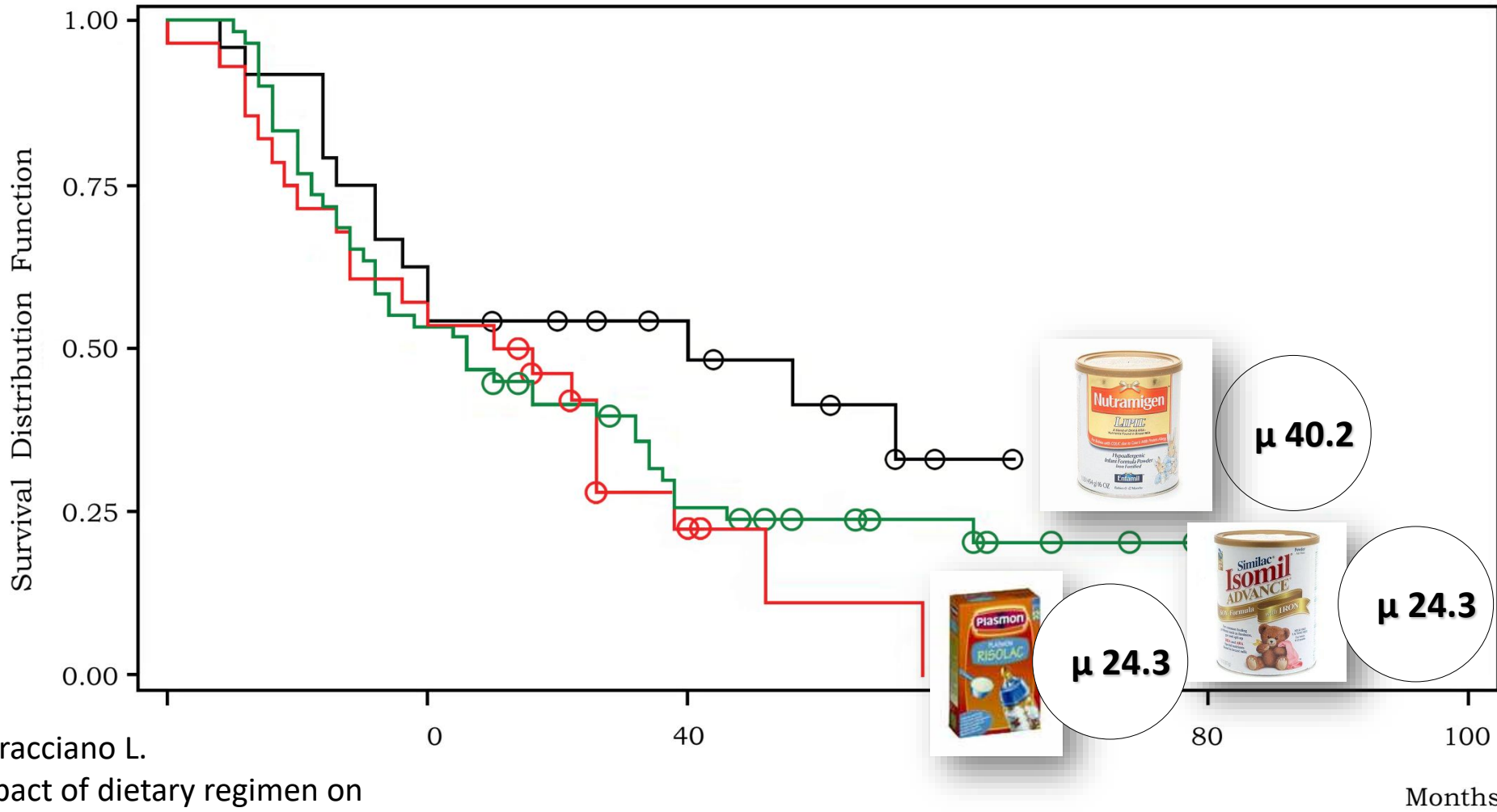


Sept – Dec: HRF



Terracciano L.
Impact of dietary regimen on
the duration of cow's milk
allergy. Clin Experim Allergy
2010, 40:125-9

Shorter duration of CMA in those fed soy or rice



Terracciano L.
Impact of dietary regimen on
the duration of cow's milk
allergy. *Clin Experim Allergy*
2010, 40:125-9

— eHF
— RHF
— SF

P = 0.018; log-rank test

Do casein hydrolyzed formulae accelerate the resolution of CMA?

Otherwise healthy children (aged 1-12 months) with CMA

Already treated for a period of 15-30 days prior to recruitment with a formula that was selected and prescribed by a family pediatrician or physician when the symptoms appeared.

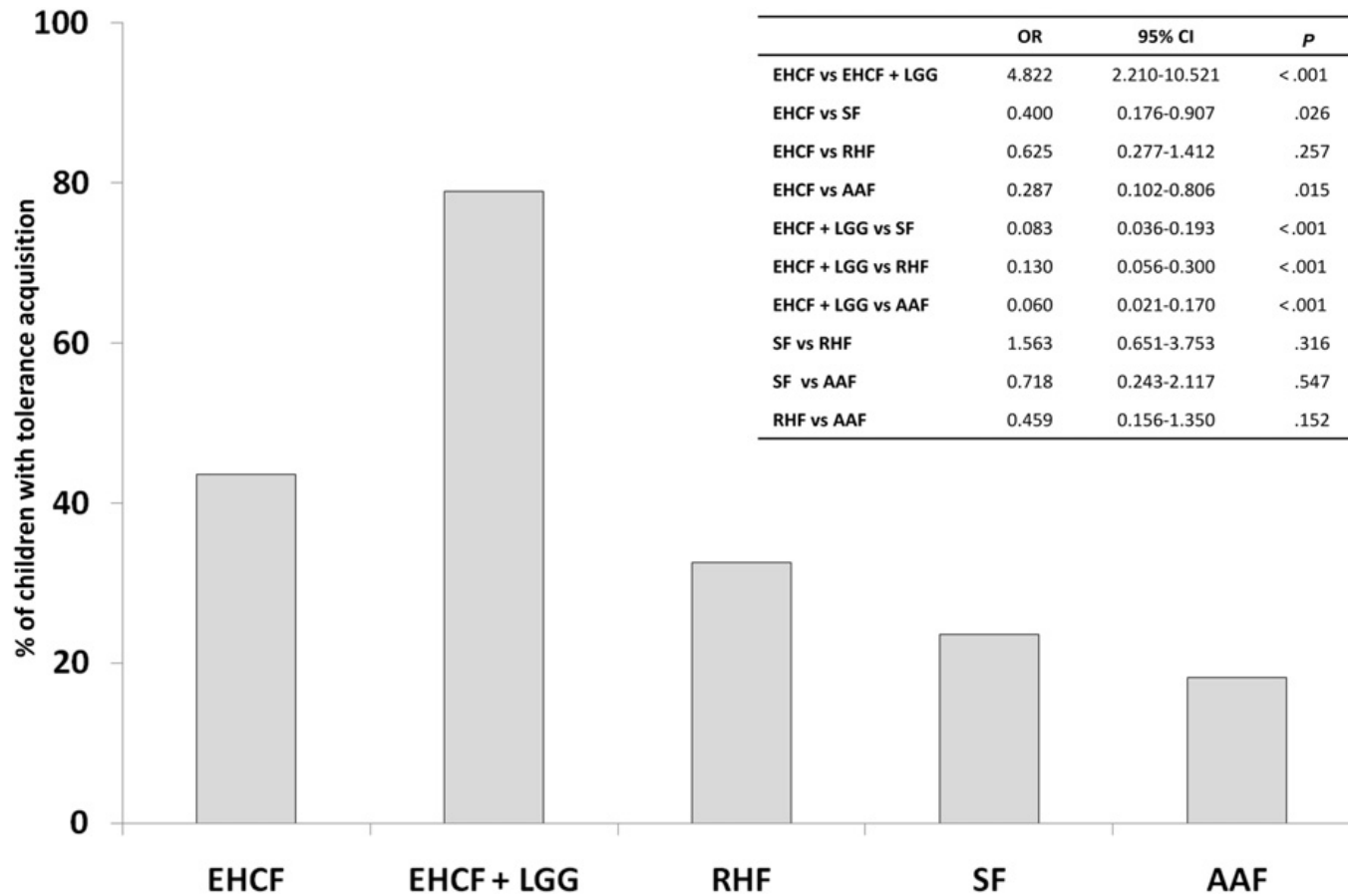
Prospectively evaluated in an open nonrandomized design

- (1) Extensively hydrolyzed casein formula ([EHCF], n = 55);
- (2) EHCF + Lactobacillus rhamnosus GG [LGG], n = 71);
- (3) Hydrolyzed rice formula (RHF, n = 46);
- (4) soy formula (n = 55);
- (5) amino acid based formula (n = 33).

Food challenge after 12 months for acquisition of tolerance.

Berni Canani R. **Formula selection** for management of children with cow's milk allergy **influences the rate of acquisition of tolerance**: a prospective multicenter study. J Pediatr. 2013;163:771-7

Do casein hydrolyzed formulae accelerate the resolution of CMA?



	OR	95% CI	P
EHCF vs EHCF + LGG	4.822	2.210-10.521	< .001
EHCF vs SF	0.400	0.176-0.907	.026
EHCF vs RHF	0.625	0.277-1.412	.257
EHCF vs AAF	0.287	0.102-0.806	.015
EHCF + LGG vs SF	0.083	0.036-0.193	< .001
EHCF + LGG vs RHF	0.130	0.056-0.300	< .001
EHCF + LGG vs AAF	0.060	0.021-0.170	< .001
SF vs RHF	1.563	0.651-3.753	.316
SF vs AAF	0.718	0.243-2.117	.547
RHF vs AAF	0.459	0.156-1.350	.152

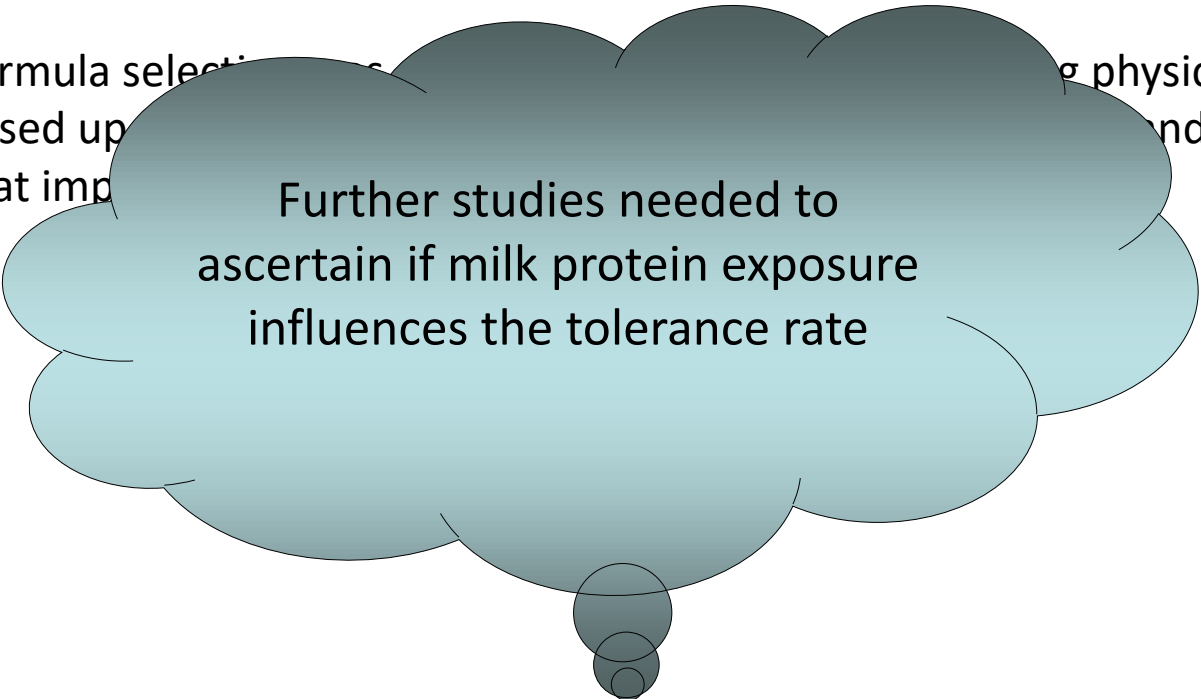
Berni Canani R. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. *J Pediatr.* 2013;163:771-7

Do vegetable formulae accelerate the resolution of CMA?

The main limitations of our study are related to the lack of randomization

This was necessary because of the difficulties in recruitment of patients with CMA prior to treatment initiated by the primary care physician.

Formula selection was based on the physician and was presumably based upon local and specific practice patterns that impacted the study.



Further studies needed to ascertain if milk protein exposure influences the tolerance rate

Getting tolerance

Natural history of milk allergy

Natural history of egg allergy

Natural history of peanut allergy

Effect of milk exposure on the natural course of CMA

Clinical course of multiple food allergens simultaneously

Conclusions

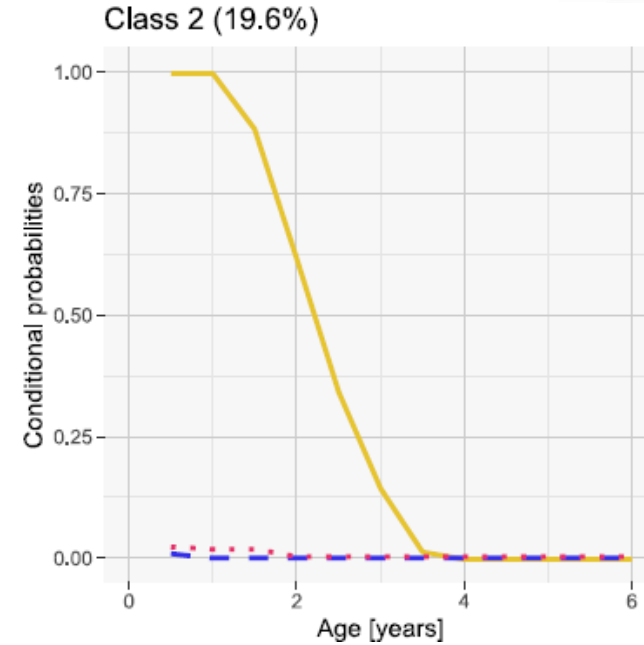
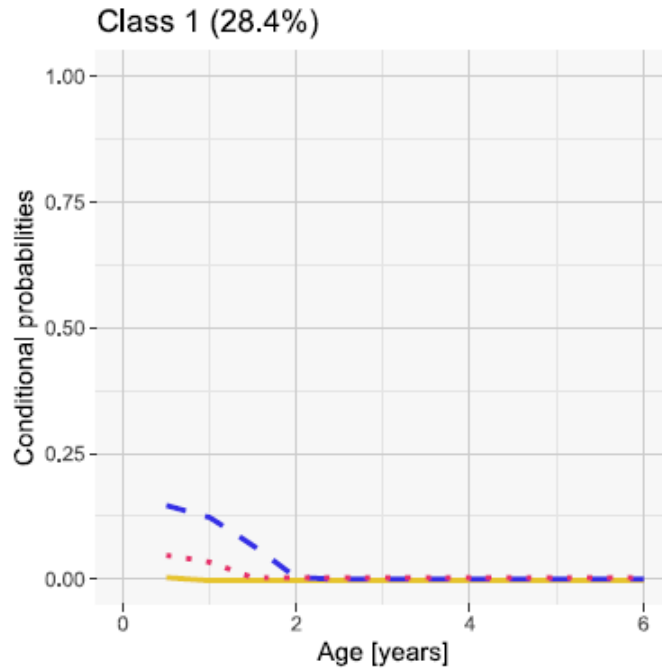
HealthNuts cohort: 5 phenotypes of allergic disease in infancy

- no allergic disease (70%)
- non-food-sensitized eczema (16%)
- single egg allergy (9%)
- multiple food allergies (predominantly peanut, 28%)
- and multiple sensitizations

Shared a... were identified, suggesting
diff... Data on natural history in the
different phenotypes still not
available

1. sensitization only (28.4%) - sensitized to foods but tolerate them
2. Transient egg allergy (19.6%) - outgrew egg allergy by 3 years [less likely AD]

- Hen's egg
- - - Cow's milk
- Wheat



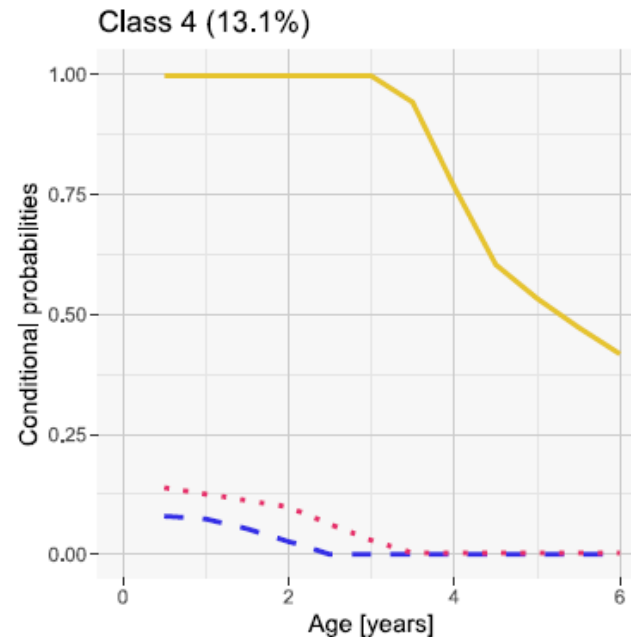
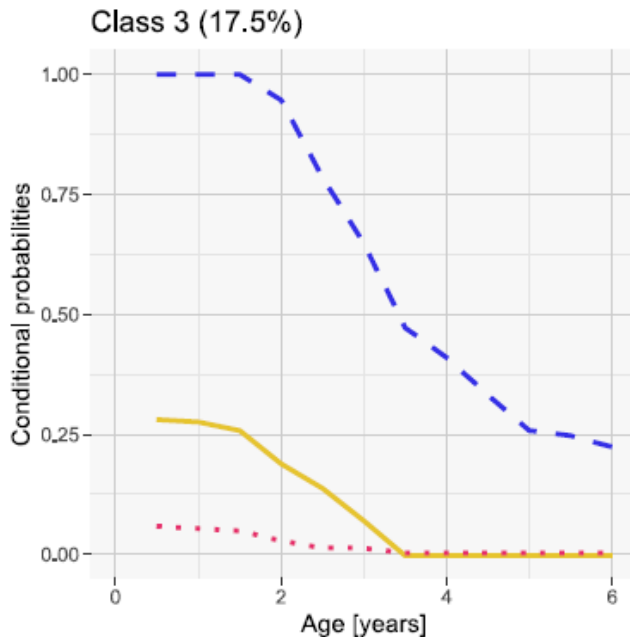
3. Milk ± transient egg allergy (17.5%)

- CMA : 50% tolerant by 4 years
- 25% also had transient egg allergies

- Hen's egg
- - - Cow's milk
- Wheat



4. Prolonged egg allergy (13.1%) persistent egg allergy at age 6 years [likely AD]

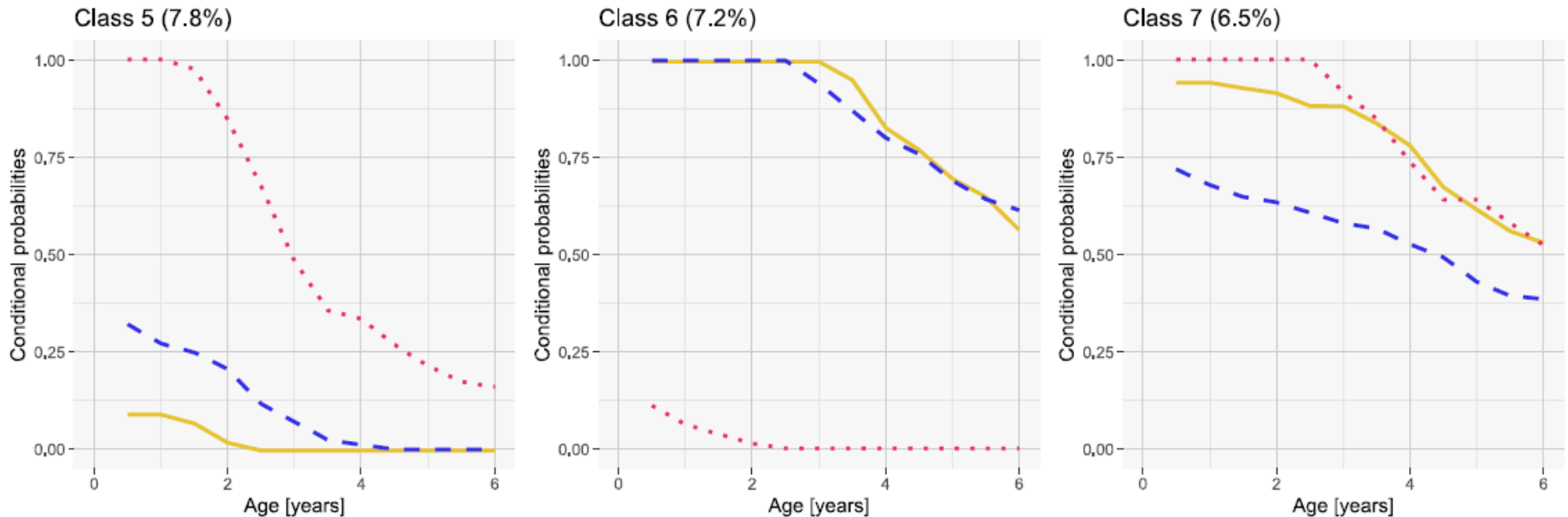


5. Wheat ± transient milk allergy (7.8%) class
around a quarter had transient milk allergies

6. Persistent egg and milk allergy phenotype (7.2%)
higher egg white and milk-sIgE levels

6. Multiple food allergy phenotype (6.5%)
allergic to eggs, milk, and wheat -- likely to persist.

- Hen's egg
- - - Cow's milk
- Wheat



Desensitization vs. tolerance

Natural history of milk allergy

Natural history of egg allergy

Natural history of peanut allergy

Effect of milk exposure on the natural course of CMA

Clinical course of multiple food allergens simultaneously

Conclusions

Natural history differs in different settings (open population vs. referrals)

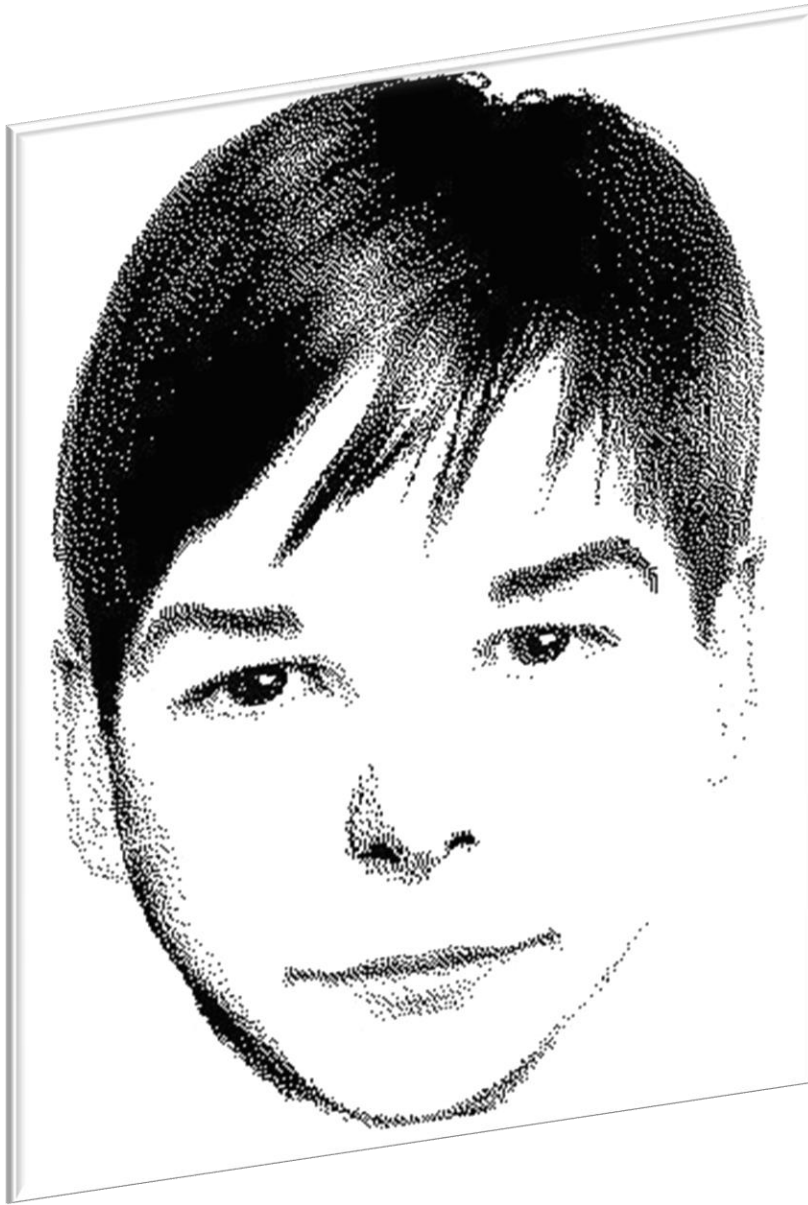
Food allergy phenotype linked to natural history

OFC in natural history:

- every 20- 24 months for milk
- every 30 – 36 months for egg
- Anticipate if natural exposure w/o consequences
 - Delay if natural exposure with symptoms

OFC during OIT: every day!.....

OFC during EPIT: tbd.



Identikit of the ideal candidate to OIT Biologics

