Oral food challenge - Up to date

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they are time consuming, expensive and may cause severe clinical reactions including life-threatening anaphylactic reactions [8].

However, standardized OFC are laborious, time-consuming, require patient collaboration and safety measures [3].

The double-blind placebo controlled food challenge (DBPCFC) is the gold standard for diagnosis of peanut allergy.[1,10,11] However, it is time-consuming and expensive, and there is a risk of severe reaction.

Food challenges belong to the stone age!

The golden age of allergy: *in vitro* testing!

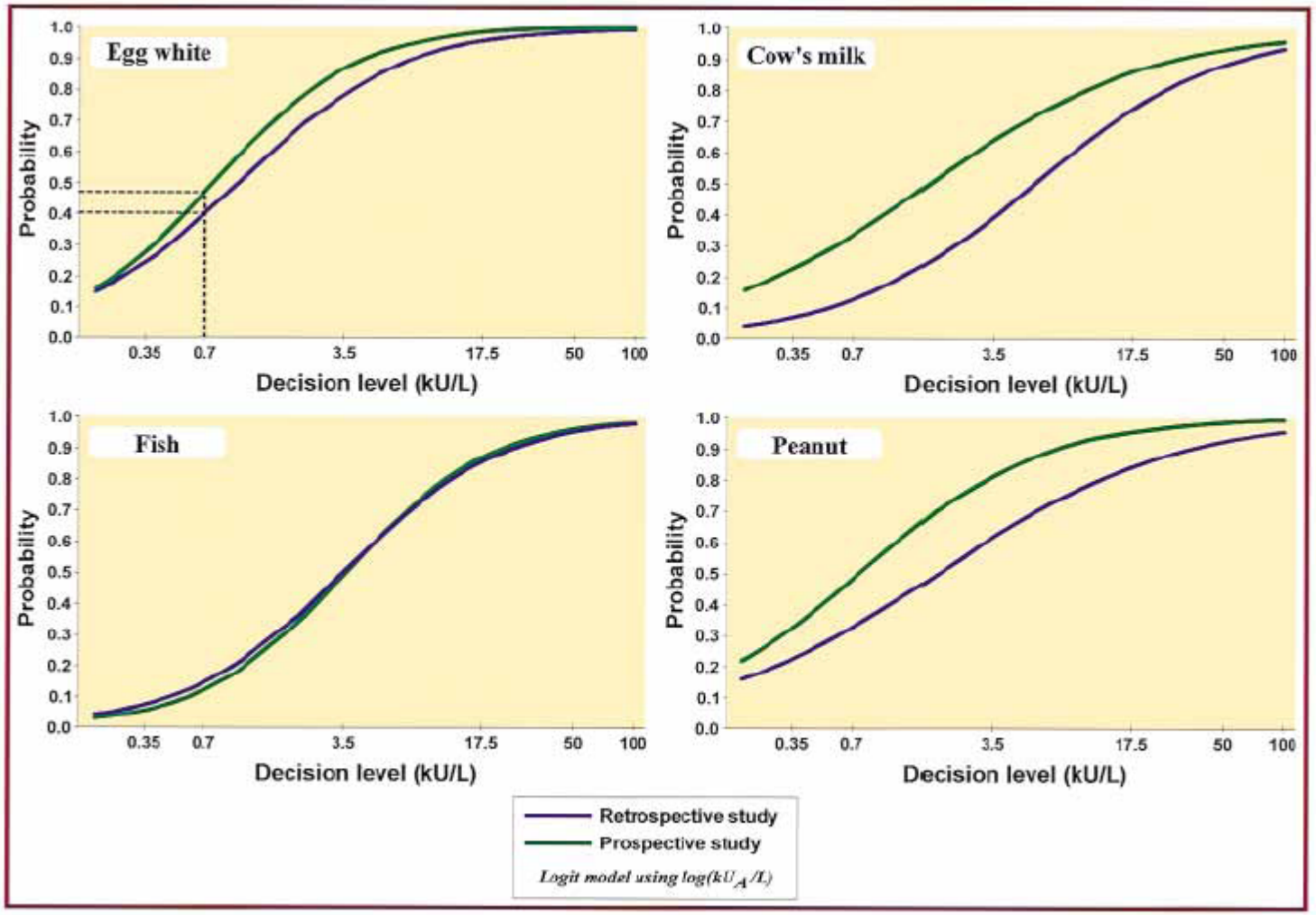


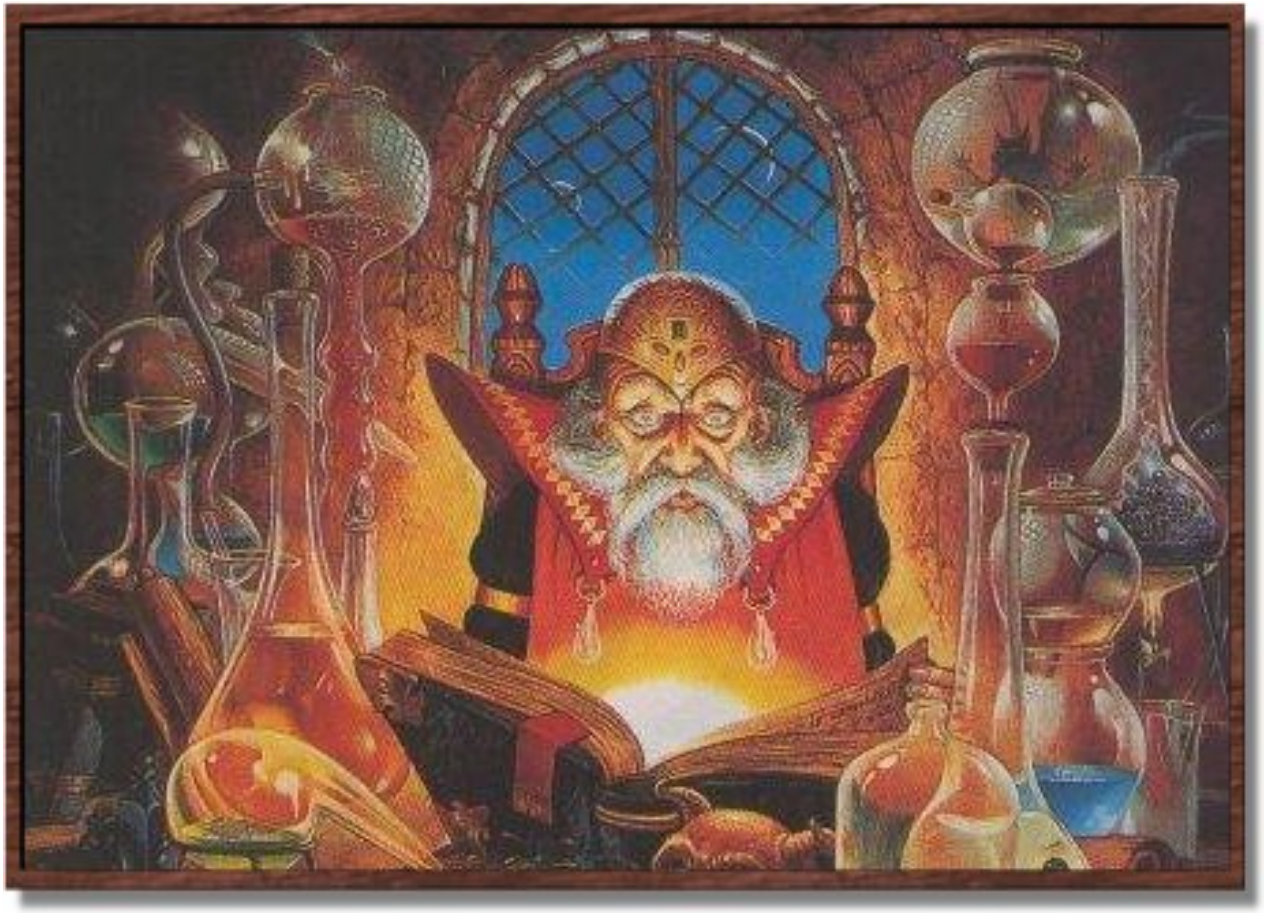
FIG 1. Probability of reacting to a food at a given IgE value.

Sampson HA *et al.* J Allergy Clin Immunol 2001: 107: 891-6

IgE cut-off levels for egg and milk allergy

Authors	Sampson (JACI 2001)	Boyano Martinez *et al.* (CEA 2001)	Osterballe and Bindslev-Jensen (JACI 2003)	Celik-Bilgili *et al.* (CEA 2005)	Benhamou *et al.* (PAI 2008)
Study subject number	100	81	56	501	51
Presence of atopic dermatitis	61%	43%	100%	88%	no
Age of study subjects	Median 3.8 yrs. (range 3 mo. to14 yrs.)	Mean 16 mo. (range 11 to 24 mo.)	Median 2.2 yrs. (range 0.5 to 4.9 yrs.)	Median 13 mo. (range 1 mo. to 16.1 yrs.)	Median 3.9 yrs. (range 16 mo. To 11.9 yrs.)
CAP FEIA™ cut off points for egg allergy (in kU/L)	(95%) 7	(90%) 0.35	(95%) 1.5	(95%) 12.6	(90%) 8.20
CAP FEIA™ cut off points for milk allergy in (kU/L)	(95%) 15	n.a.	n.a.	(95%) 88	n.a.

Food allergy diagnosis: Back to the kitchen



Food challenge, when?

For the diagnosis

- *The diagnosis is uncertain when*:

  ☞ IgE values are in the gray zone

  ☞ IgE values do not correlate with the history

  ☞ history not suggestive of food allergy

TABLE V. Recommended interpretation of food allergen–specific IgE levels (kU_A/L) in the diagnosis of food allergy

	Egg	Milk	Peanut	Fish	Soy	Wheat	
Reactive if ≥ (no challenge necessary)	7	15	14	20	65	80	Probability
Possibly reactive (physician challenge*)					30†	26†	of
Unlikely reactive if < (home challenge*)	0.35	0.35	0.35	0.35	0.35	0.35	reaction

Sampson HA *et al.* J Allergy Clin Immunol 2001: 107: 891-6

For follow-ups

- The probability of outgrowing food allergy:
  - ☞ spIgE modification over time

TABLE III. Probability of developing tolerance for egg and milk allergy based on the decrease in respective food sIgE levels over 12 months

Decrease in sIgE over 12 months (%)	Probability of developing tolerance	
	Egg allergy	Milk allergy
50	.52	.31
75	.65	.45
90	.78	.66
99	.95	.94

sIgE, specific immunoglobulin E.
Data for children diagnosed before age 4 years.

Shek LP *et al.* J Allergy Clin Immunol. 2004;114:387-91

For follow-ups

- Probability of outgrowing:
  - lower spIgE
  - primary avoidance
  - no recent reaction

Food challenge tests
- The gaps -

- Improving protocols
- Defining the risk for severe reactions
- Improving indications

Paediatric oral peanut challenges: a comparison of practice in London and Western Switzerland

S. Ludman[1], J. Wassenberg[1], G. Du Toit[2], A. T. Fox[2], G. Lack[2] & P. A. Eigenmann[3]

[1]Allergy, Immunology and Rheumatology Unit, University Hospital, Lausanne, Switzerland; [2]Children's Allergy Service, St Thomas' Hospital, London, UK; [3]Paediatric Allergy Unit, University Hospitals, Geneva, Switzerland

Allergy 2013; **68**: 539–541.

- Retrospective analysis of 100 most recent peanut challenges done in a clinical setting at St Thomas' (London) and Geneva/Lausanne (CH)

Table 1 Characteristics of all peanut challenges and comparison of key positive data

Patient characteristics of all peanut food challenges

	Total	St Thomas	Switzerland	*P* value
Food challenges	200	100	100	–
Male	121	61	60	1.000
Age (years ± SD)	6.85	5.9 ± 4.2 (0.7 – 16.7)	7.8 ± 3.5 (2.35–16.5)	0.007
Positive FC	73	25	48	0.001
Negative FC	117	69	48	–
Inconclusive	10	6	4	0.748
Positive FC with medication	35	12	23	0.995
Adrenaline	2	1	1	1.000
Other food allergy	139	87	52	0.001
Eczema	94	57	37	0.007
Asthma	54	17	37	0.002

Allergy 2013; **68**: 539–541.

Key values of positive food challenges

	Centre	Number (N)	Mean	Standard deviation	*P* value
Age at challenge (years)	1	25	5.8	4.1	0.006
	2	48	8.4	3.5	
Cumulative peanut protein ingested(g)	1	27	2.3	3.3	0.160
	2	48	1.5	1.8	
Specific IgE (kU/L)	1	17	0.5	0.6	0.022
	2	43	12.3	20.0	

Centre 1 = St Thomas' Hospital; Centre 2 = Combined Swiss hospitals.

Allergy 2013; **68**: 539–541.

Table 2 Summary of protocols for peanut challenges in London and Switzerland

	Peanut product	Cumulative challenge doses in grams (Peanut protein doses in grams)						Cumulative dose (g)	Maximum protein dose(g)
St Thomas	Whole peanut	Buccal smear	0.5 (0.1)	2 (0.5)	4 (1.0)	10 (2.6)	15 (3.9)	31.5	8.19
St Thomas	Peanut butter	Buccal smear	0.6	2.3	4.5	11	17	35.4	9.2
St Thomas	Bamba	Buccal smear	0.85 (0.1)	2.13 (0.3)	4.25 (0.5)	8.5 (1.0)	34 (4.1)	66.73	8.0
Switzerland	Peanut protein	–	0.03	0.1	0.3	1	3	4.43	4.43

- **When you do a food challenge**:
  - Aim for a total dose corresponding to a serving
  - No need for « lip testing »
  - Set your % of positive challenges
  - Exchange your experience with colleagues

AAAAI – EAACI Practall
Standardizing Double-blind Placebo-controlled Oral Food Challenges

Hugh A Sampson, MD; Roy Gerth van Wijk, MD; Carsten Bindslev-Jensen, MD, PhD; Scott Sicherer, MD, Suzanne Teuber; MD and A Wesley Burks, MD; Andre Dubois, MD; Kirsten Beyer, MD; Philippe A. Eigenmann, MD; Jonathan M. Spergel, MD, PhD; Thomas Werfel, MD; and Vernon M. Chinchilli, PhD

J Allergy Clin Immunol, 2012 Dec;130(6):1260-74.

SCORING THE CHALLENGE

Subjective Symptoms

-General non-specific pruritus

-Scratching

-Nasal pruritus

-Ocular pruritus

-Dyspnea (without objective signs)

-Throat “tightness”

-Nausea

-Abdominal pain

-Oral/throat pruritus

-Complaints of weakness, dizziness, not feeling well, etc.

J Allergy Clin Immunol, 2012 Dec;130(6):1260-74.

GREEN:
- Not usually an indication to alter dosing.
-Not generally sufficient to consider a challenge positive.

ORANGE (scores increasing to orange):
- Caution, dosing could proceed, be delayed, have a dose repeated rather than escalated.
- If clinically indicated, dosing is stopped.
- Symptoms that recur on 3 doses, or persist (e.g., 40 minutes) are more likely indicative of a reaction than when such symptoms are transient and not reproducible.
-3 or more scoring areas in yellow more likely represent a true response.

RED:
- Objective symptoms likely to indicate a true reaction
- Usually an indication to stop dosing.

J Allergy Clin Immunol, 2012 Dec;130(6):1260-74.

I. SKIN:

A. Erythematous Rash- % area involved_____

B. Pruritus

0 = Absent

1 = Mild, occasional scratching

2 = Moderate -scratching continuously for > 2 minutes at a time

3 = Severe – hard continuous scratching – excoriations

Message: Use standardized criteria for challenge interpretation

D. Rash

0 = Absent

1 = Mild – few areas of faint erythema

2 = Moderate – areas of erythema

3 = Severe – generalized marked erythema (>50%)

J Allergy Clin Immunol, 2012 Dec;130(6):1260-74.

doi: 10.1111/cea.12284

Clinical & Experimental Allergy, **44**, 572–578

ORIGINAL ARTICLE Clinical Allergy

Positive reactions to placebo in children undergoing double-blind, placebo-controlled food challenge

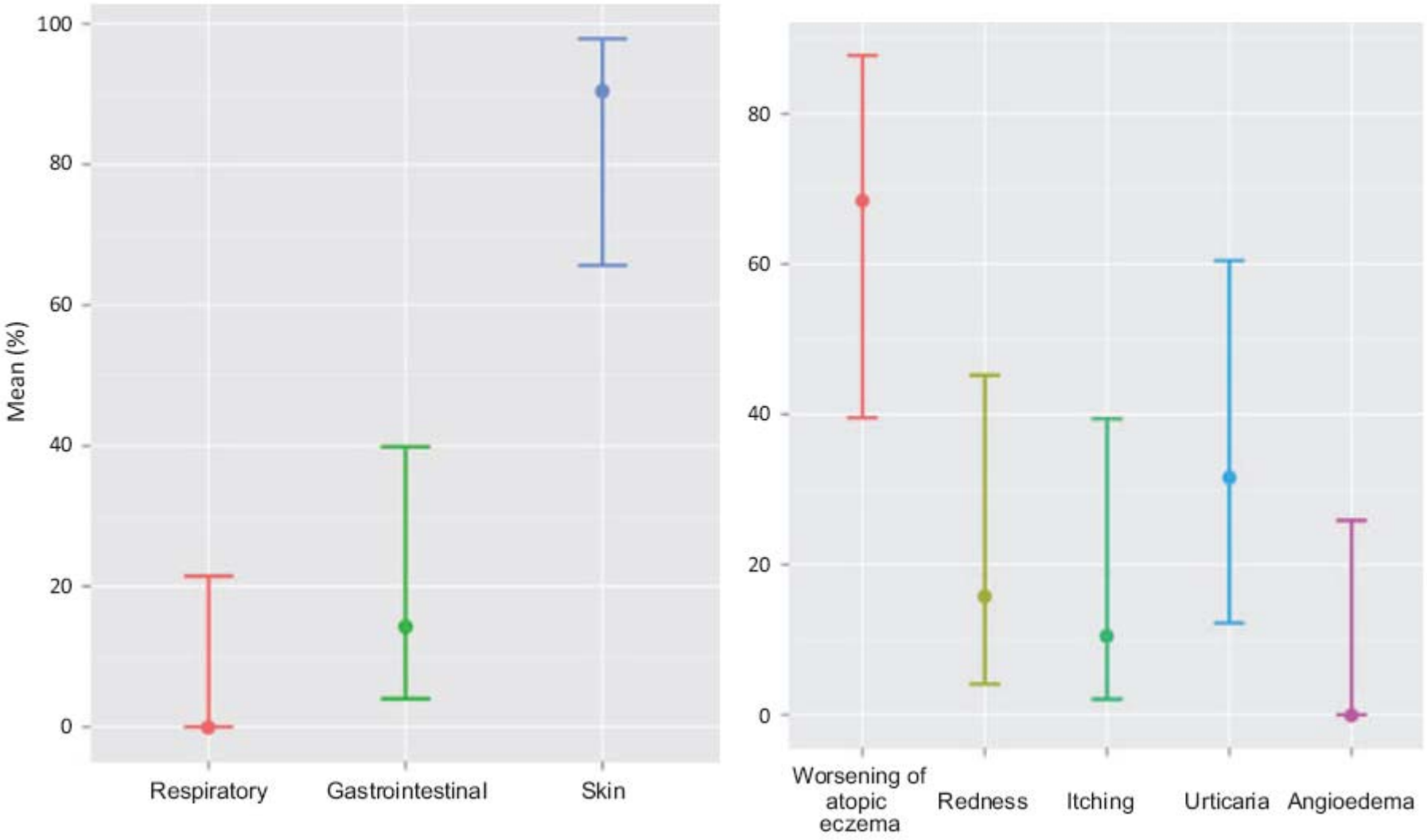
B. Ahrens, B. Niggemann, U. Wahn and K. Beyer

Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany

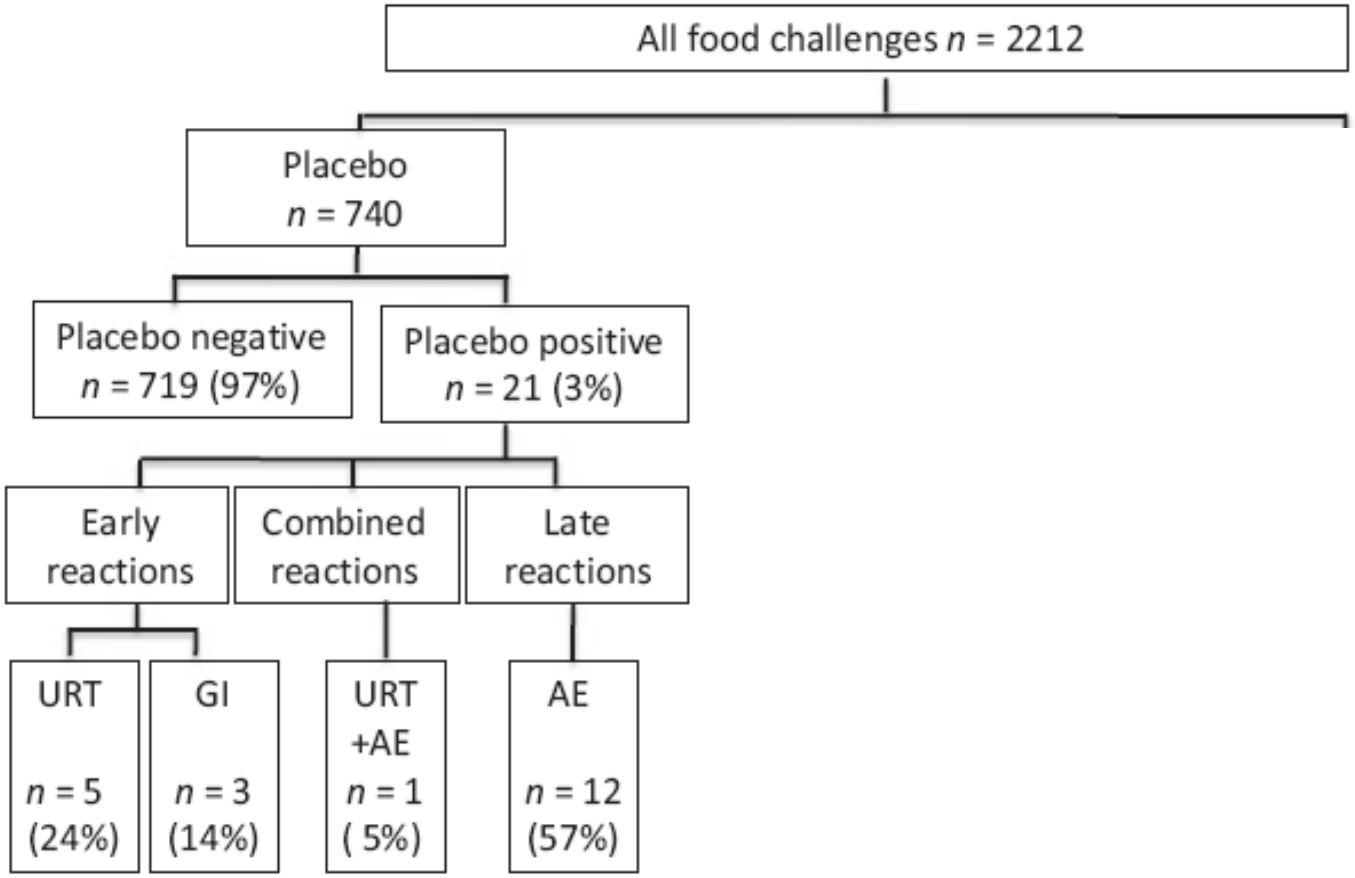
Table 1. Patient history of study participants

n = 740 Placebo challenges from 639 children	n = 719 Negative placebo challenges from 618 children			n = 21 Positive placebo challenges from 21 children		
	Unknown	No	Yes	Unknown	No	Yes
Atopic eczema (ever)	4	56	558	0	0	21
Asthma (ever)	2	506	110	0	16	5
Allergic rhino-conjunctivitis (ever)	2	561	55	0	19	2

Proportion of placebo reactions by organ



Clinical & Experimental Allergy, **44**, 572–578



Message: Consider DBPCFCs in young children with AE

Clinical & Experimental Allergy, **44**, 572–578

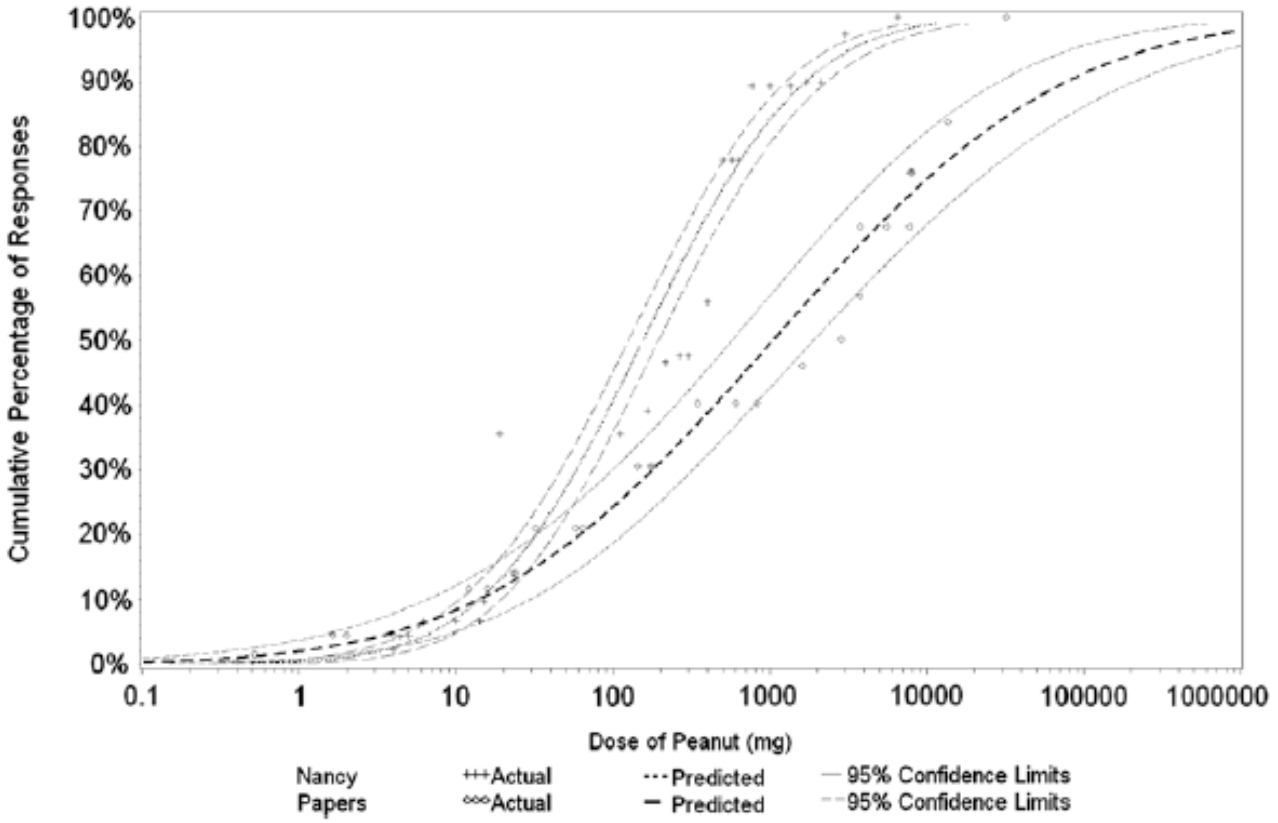
Food challenge tests
- The gaps -

- Improving protocols
- Defining the risk for severe reactions
- Improving indications

Are there threshold doses?

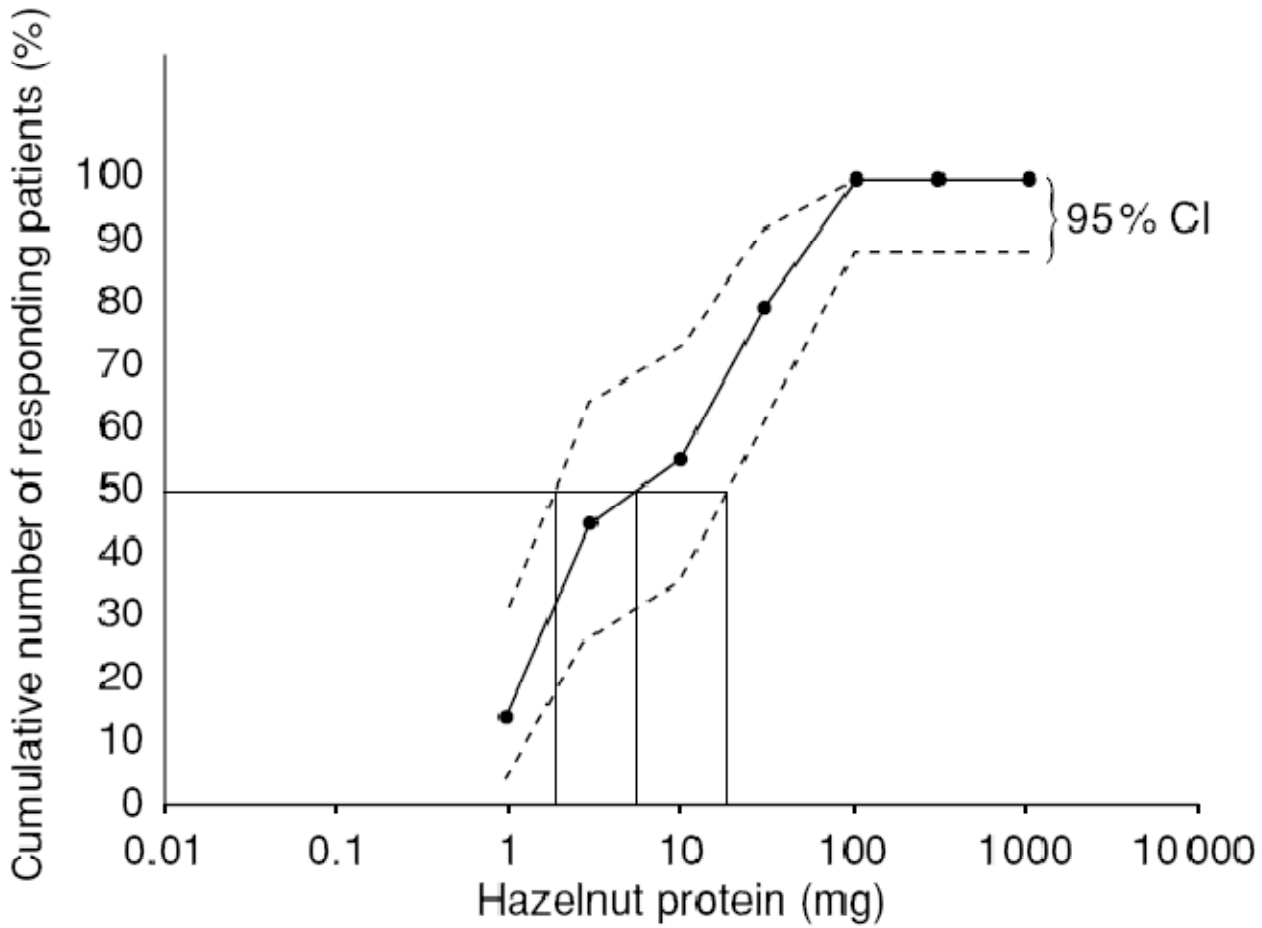
A few examples from the literature

Threshold doses to peanut in 286 French patients



Taylor SL et al Food ChemTox 2010;48:814-9.

Threshold doses for hazelnut



Flinterman et al Clin Exp Allergy 2002;32:157

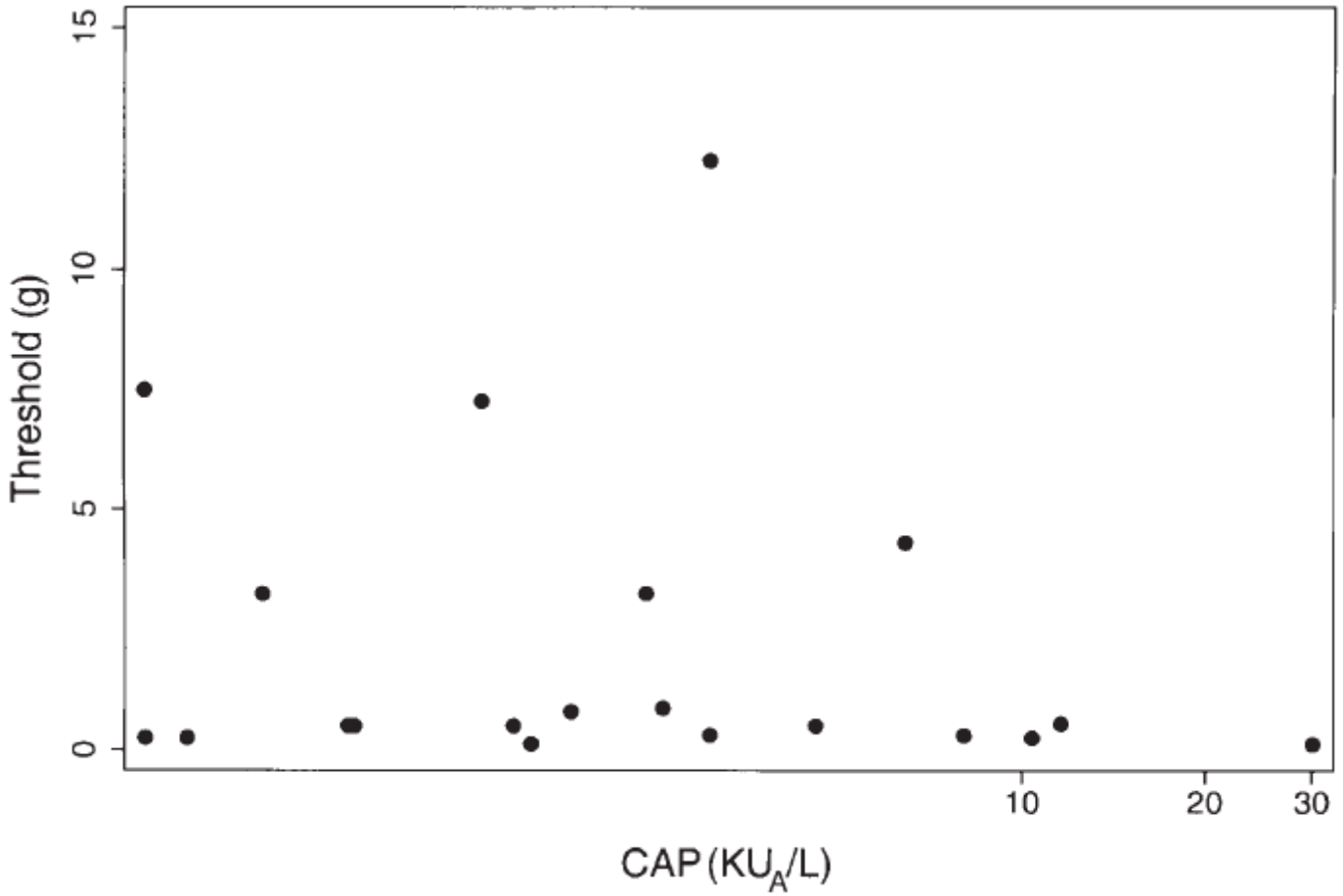
Threshold doses for eggs

TABLE I. Performance characteristics of the NOAEL (in grams of whole egg) in different age groups

Age (y)	Threshold (g)	NOAEL (g)
≤2	1.6	1.0
>2	6.1 (3.4)*	2.2 (2.6)*
0.5 to 4.9†	2.2	1.4
0.5 to 4.9‡	3.7 (2.5)*	1.7 (1.5)*

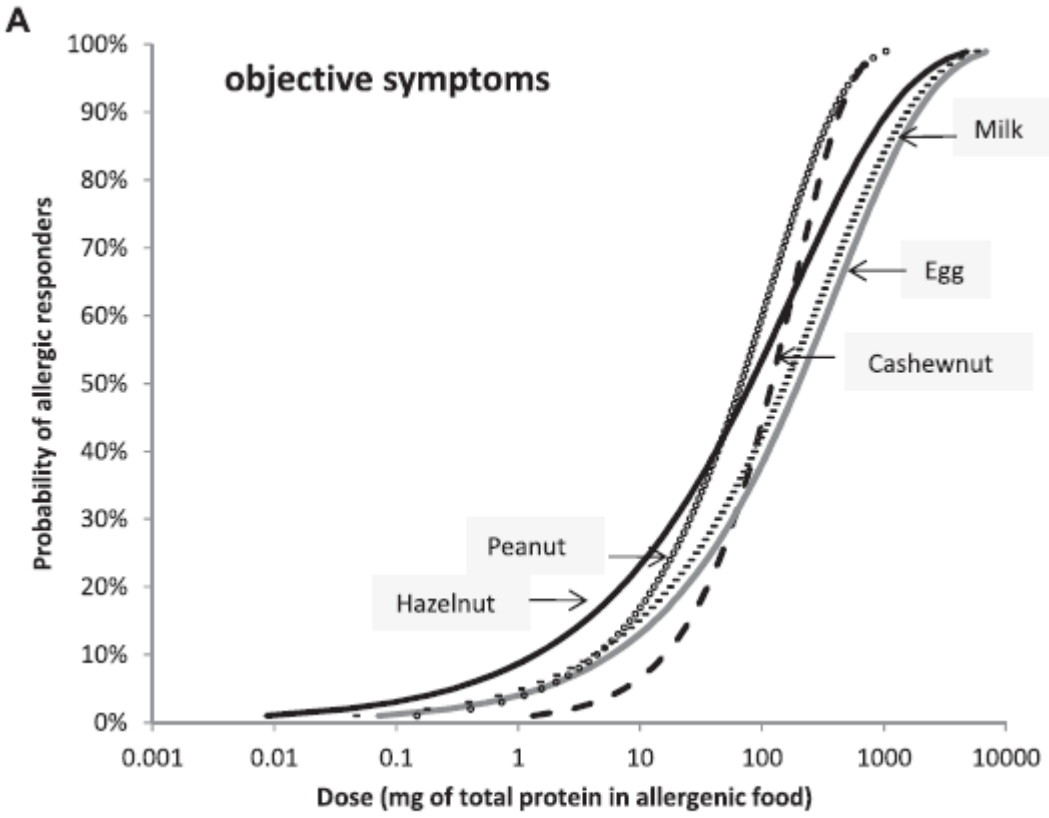
Osterballe et Bindslev-Jensen. J Allergy Clin Immunol 2003;112:196

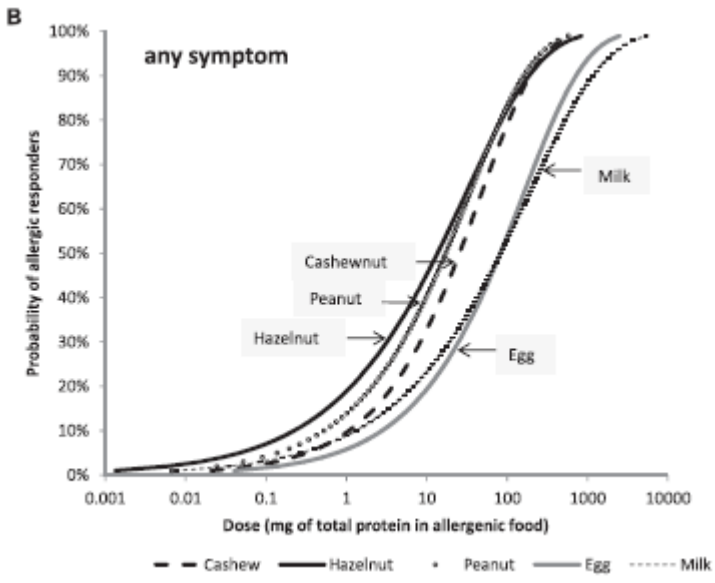
Threshold doses for eggs



Osterballe et Bindslev-Jensen. J Allergy Clin Immunol 2003;112:196

Threshold doses in Dutch children to 5 foods





Bloom MW et al JACI 2013;131:172-9.

Yes, there are threshold doses

but!

they are: **-patient/population-related**

-often with a large variation

between subjective and objective

WHY?

Reaction severity = (Host factors X Event factors) X ?

Host factors	X	**Event factors**	X ?
Age		Allergen dose	
Asthma		Food matrix	
Severity of previous reactions		Food form (raw/cooked egg)	
General health (Pollenosis)		Allergen stability	
Recent infection		Season (pollen)	
Medication		Exercise	
Attitude to risk		Alcohol	
Anxiety/ panic		Use of rescue medication	
		Anxiety/panic	

Hourihane et Knulst Toxicol Applied Pharmacol 2005;207:S152

COOL HEADS
How the ice age boosted our brainpower

SEISMIC BOOM
Breaking the quake barrier

SPACE-TIME CRUSHED
Flat universe bent out of shape

NewScientist

WEEKLY 1 August 2009

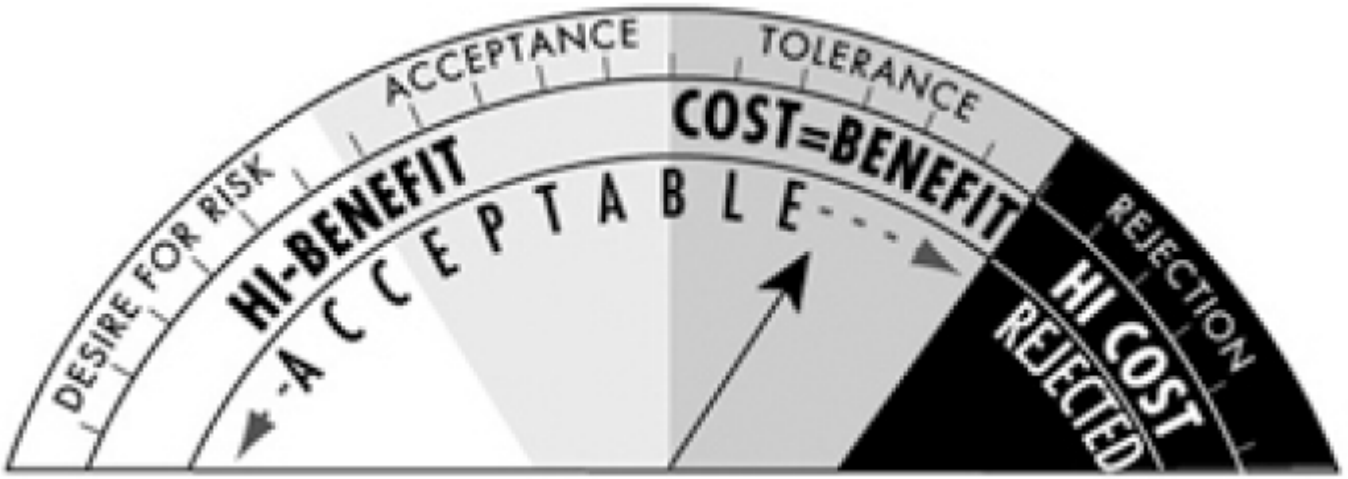
Why this

WARNING! MAY ~~CONTAIN~~ be NUTS

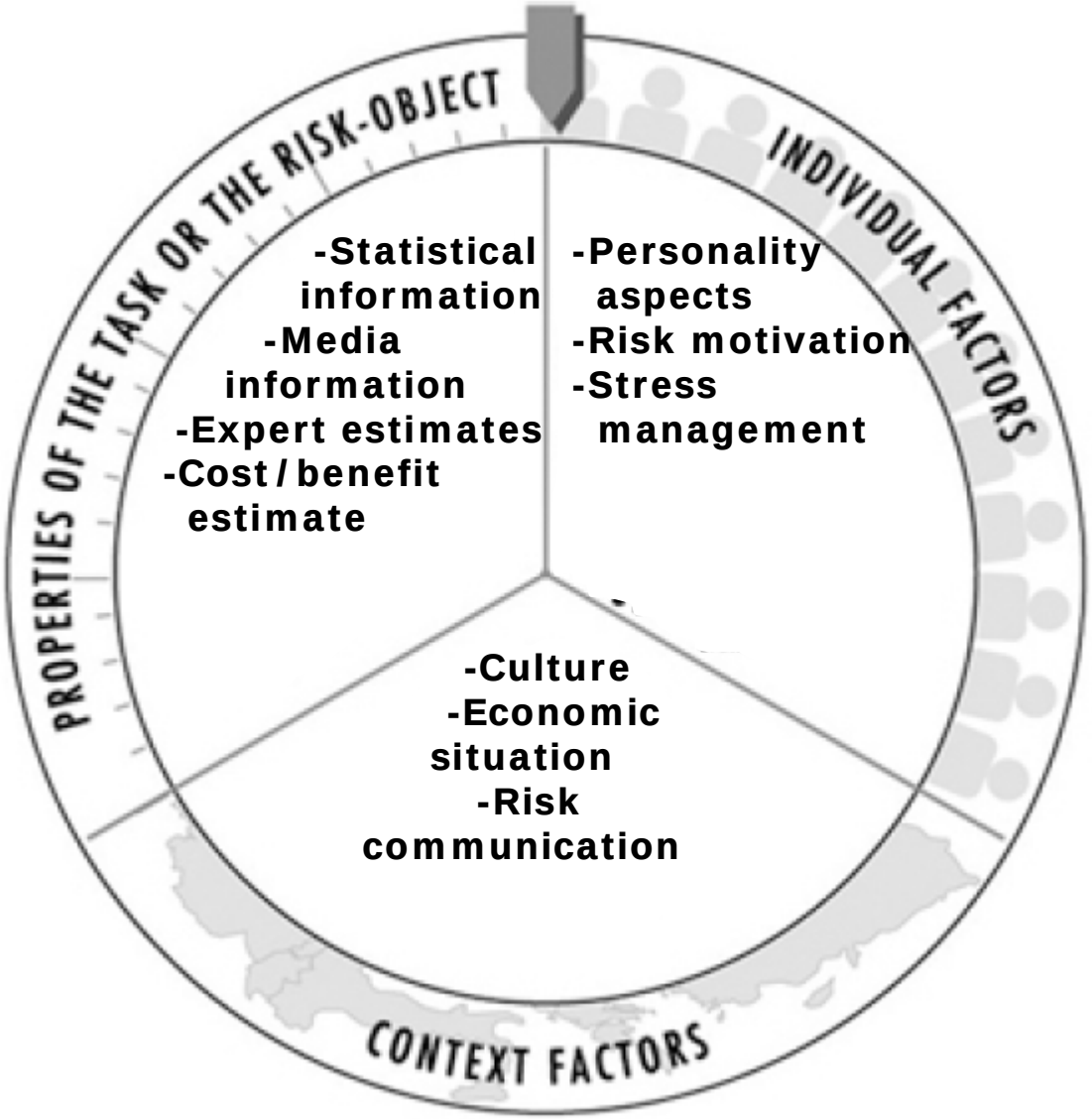
Cutting through the food allergy confusion

£3.25 US$5.95 No2719

Facets of risk acceptance and risk rejection



Google: ILO risk acceptance
http://www.ilo.org/oshenc/part-viii/safety-policy-and-leadership/item/987-risk-acceptace



Google: ILO risk acceptance
http://www.ilo.org/oshenc/part-viii/safety-policy-and-leadership/item/987-risk-acceptace

Indications to determine a thershold level

-patient related-

- Persisting food alergies (peanuts, nuts, fish...).
- Patient/Family anxiety.
- To demonstrate that first symptoms are not always life-threatening (e.g. oral prurit).

Indications to determine a thershold level

-industry related-

- Cost-risk analysis
- Better labelling
- For improvement of "patient/industry " relationship.

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PLOS | ONE

Oral Peanut Challenge Identifies an Allergy but the Peanut Allergen Threshold Sensitivity Is Not Reproducible

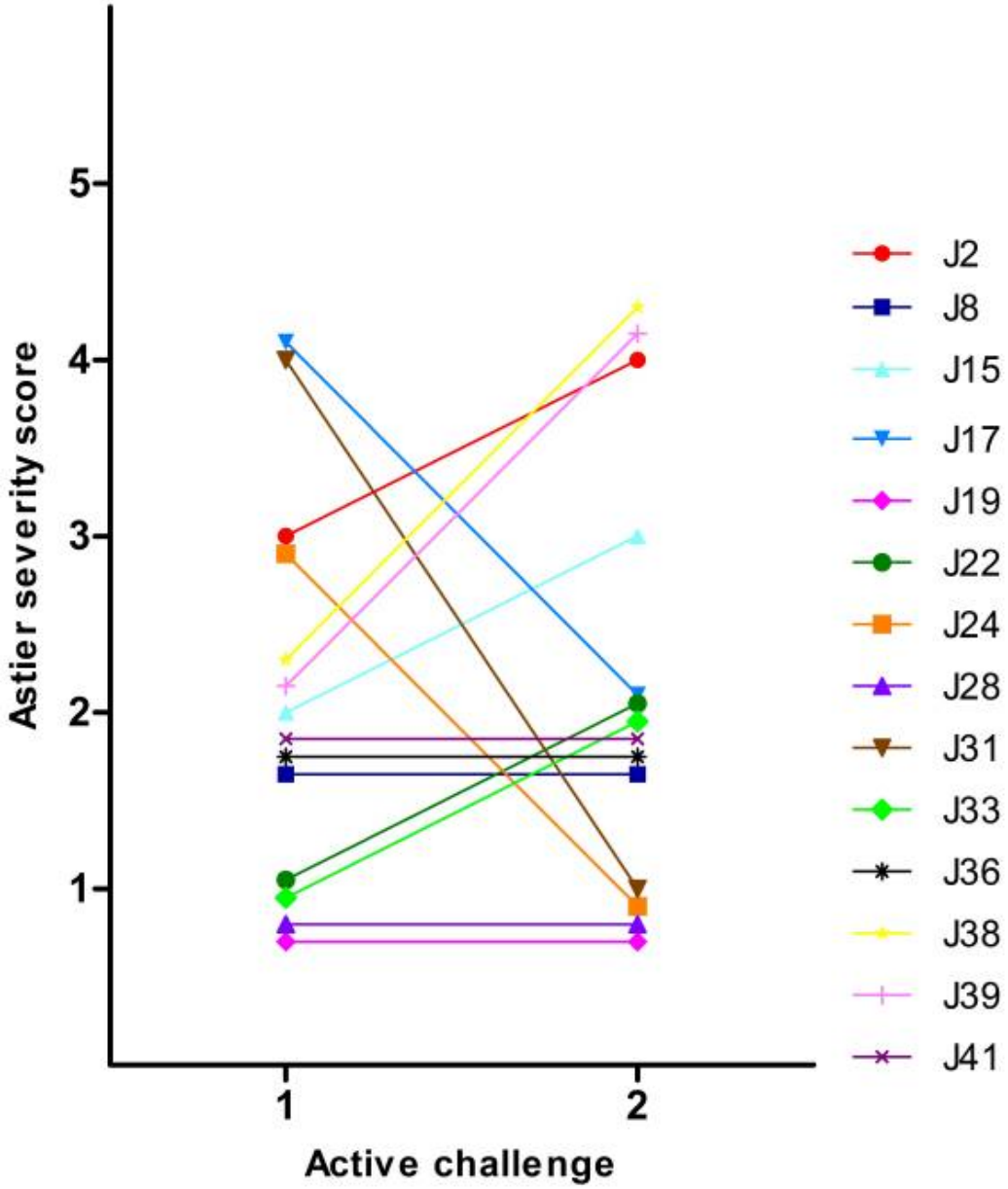
Susanne Glaumann[1,2]*, Anna Nopp[3], S. G. O. Johansson[3], Magnus P. Borres[4,5], Caroline Nilsson[1,2]

PLoS ONE 8(1): e53465. doi:10.1371/journal.pone.0053465

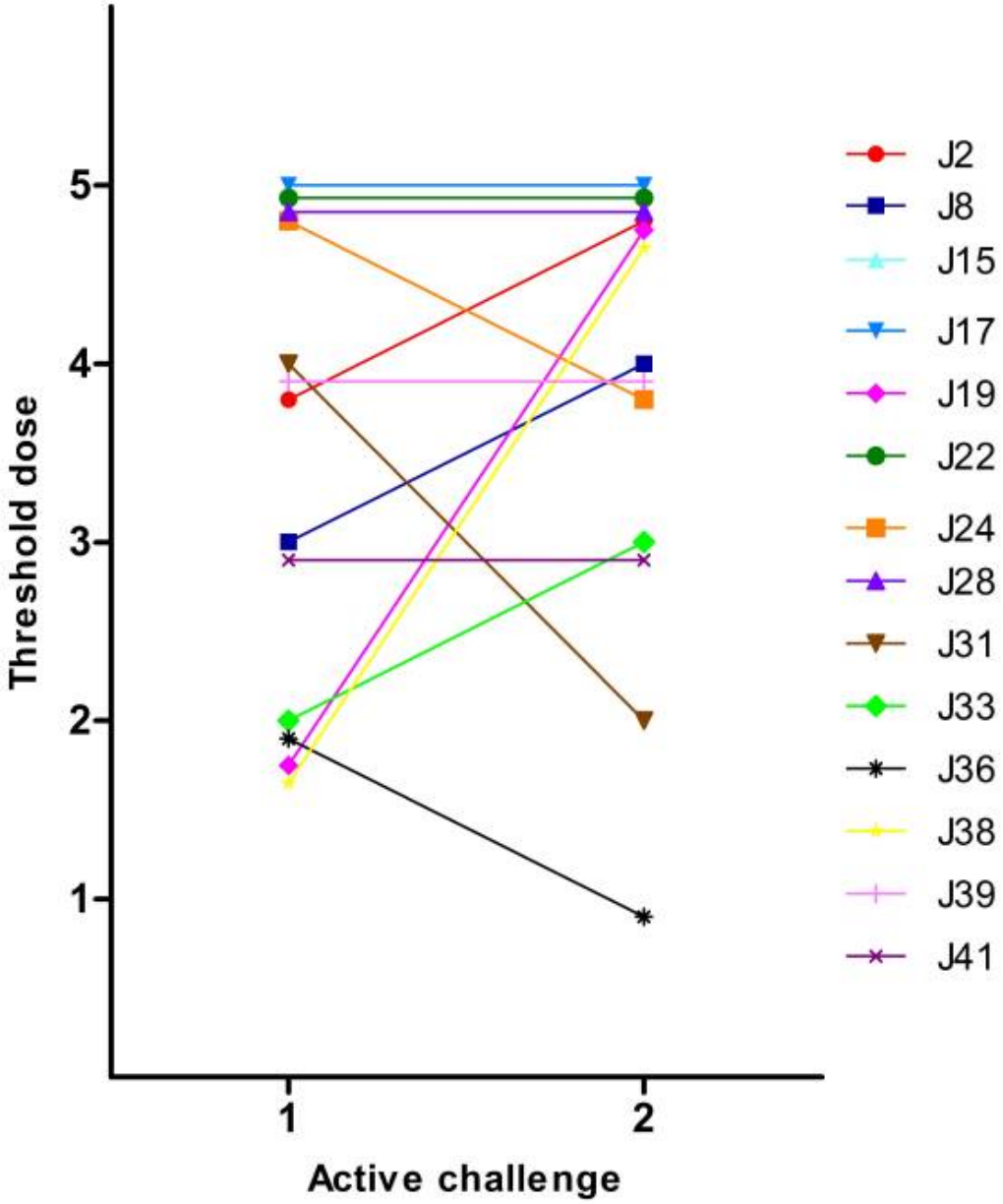
Method:

- Repeated DBPCFC peanut challenge, med interval 14 days (7 – 126)

- 5 doses (0.001-0.01-0.1-1.0-5.0 g)



PLoS ONE 8(1): e53465. doi:10.1371/journal.pone.0053465



PLoS ONE 8(1): e53465. doi:10.1371/journal.pone.0053465

			1st peanut challenge			2nd peanut challenge		
Patient	sex	Age (years)	Symptoms	Severity score	peanut (g)	Symptoms	Severity score	Peanut (g)
J2	female	12.7	urticaria, stomach-ache mouth-itch	3	1.1	asthma, skin-itch, rhinitis, urticaria, stomach-ache	4	6.1
J8	male	15.4	stomach-ache mouth-itch	2	0.1	conjunctivitis, rhinitis, stomach-ache	2	1.1
J15	female	17.4	stomach-ache, mouth-itch	2	0.1	mouth-itch, stomach-ache, urticaria, rhinitis	3	1.1
J17	female	14.0	tiredness, mild asthma, mouth-itch	4	6.1	tiredness, stomach-ache, vomiting, conjunctivitis	2	6.1
J19	male	9.8	mouth-itch	1	0.01	mouth-itch, stomach-ache	1	3.6

Message: Be careful by determining threshold doses for reactions, they might not be definite.

PLoS ONE 8(1): e53465. doi:10.1371/journal.pone.0053465

- **Key messages**

- **The majority of our food allergic patients do not react to traces.**
- **We do not do routine threshold studies.**
- **Consider determining thresholds in severe allergics or chronic patients.**
- **Threshold determination should be done in well trained centers.**

Safety first!

1. Key point for safety

- Your Staff
- The location
- Emergency meds
- IV line?

Risk of oral food challenges

Tamara T. Perry, MD, Elizabeth C. Matsui, MD, Mary K. Conover-Walker, CRNP, and Robert A. Wood, MD *Baltimore, Md*

J Allergy Clin Immunol 2004;114:1164-8

TABLE II. System involvement during failed challenges

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
Skin	68 (75%)	43 (77%)	55 (77%)	16 (76%)	15 (100%)*	197 (78%)
Oral	23 (26%)	12 (21%)	27 (38%)†	3 (14%)	1 (7%)	66 (26%)
Upper respiratory	16 (18%)	15 (27%)	25 (35%)†	4 (19%)	2 (13%)	62 (25%)
Lower respiratory	24 (27%)	19 (34%)	15 (21%)	4 (19%)	5 (33%)	67 (26%)
Gastrointestinal	37 (41%)	31 (55%)	28 (39%)	9 (43%)	3 (20%)	108 (43%)
Cardiovascular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

TABLE III. Severity of reactions during failed food challenges

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
Mild	33 (37%)	18 (32%)	28 (39%)	9 (43%)	10 (67%)	98 (39%)
Moderate	33 (37%)	17 (30%)	25 (35%)	8 (38%)	0 (0%)	83 (33%)
Severe	24 (27%)	21 (38%)	18 (25%)	4 (19%)	5 (33%)	72 (28%)

TABLE IV. Median food-specific IgE (kU_A/L) level and reaction severity

	Milk N = 90	Egg N = 56	Peanut* N = 71	Soy N = 21	Wheat N = 15
Mild	1.9	0.84	1.3	10.1	15.8
Moderate	1.6	1.3	2.1	4.9	—
Severe	2.2	1.3	2.2	24	30.2

*$P < .05$ for trend.

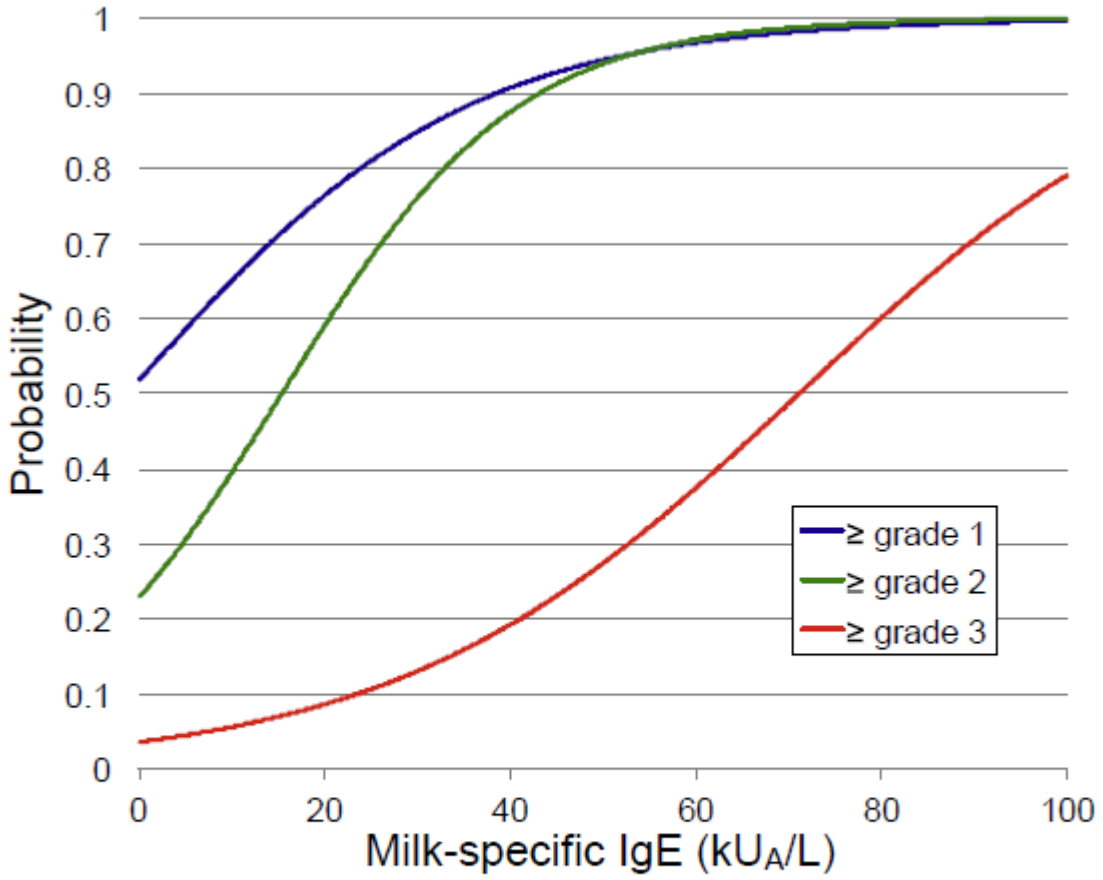


Figure 1. Probability curves for milk-specific IgE levels in patients 0 to 2 years old (n = 153). Fitted predictive probability curves predicting the outcomes after an oral food challenge with cow's milk are shown.

Yoneyama et al. Ann Allergy Asthma Immunol 115 (2015) 244e255

TABLE VI. Treatment administered during failed challenges

	Milk N = 90	Egg N = 56	Peanut N = 71	Soy N = 21	Wheat N = 15	Total N = 253
None	22 (24%)	11 (20%)	9 (13%)	7 (33%)	3 (20%)	52 (21%)
Antihistamine	68 (76%)	44 (79%)	62 (87%)	13 (62%)	12 (80%)	199 (77%)
Epinephrine	5 (6%)	10 (18%)	7 (10%)	3 (14%)	3 (20%)	28 (11%)
Steroids	2 (2%)	6 (11%)	4 (6%)	1 (5%)	1 (7%)	14 (6%)
Albuterol	2 (2%)	2 (3.4%)	5 (7%)	0 (0%)	2 (13%)	11 (4%)

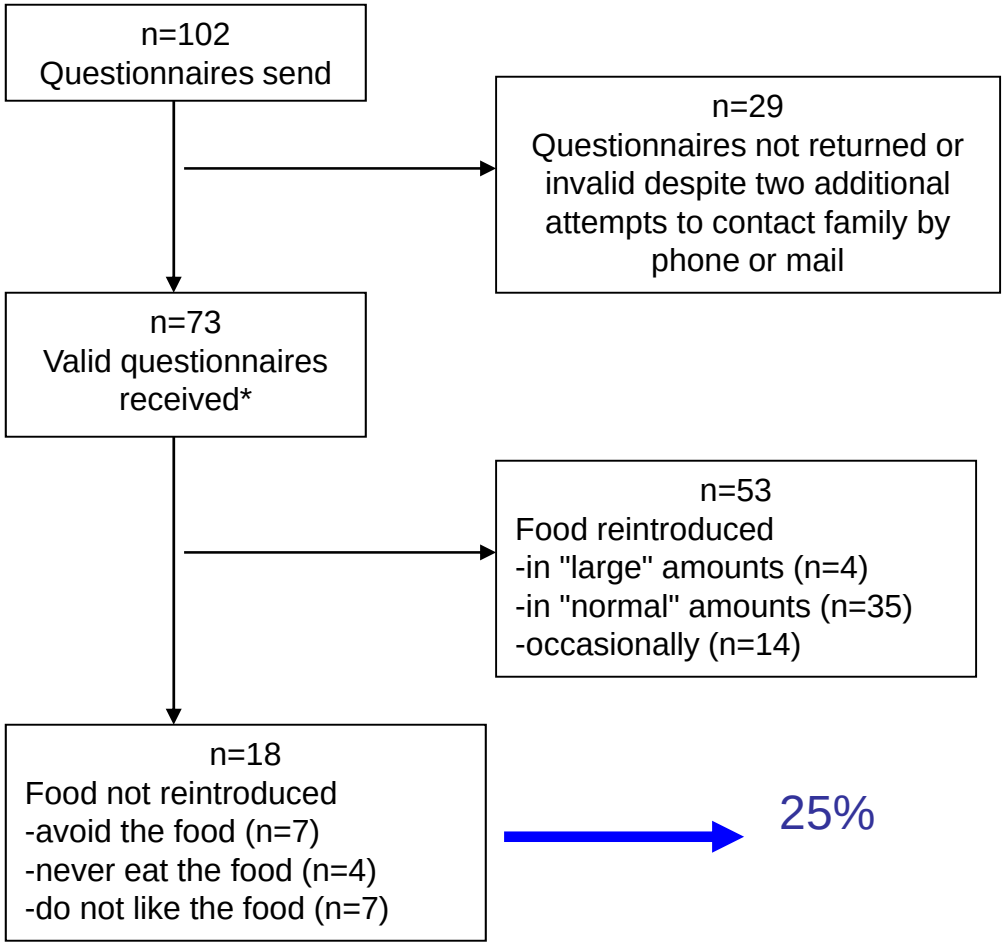
Food challenge tests
- The gaps -

- Improving protocols
- Defining the risk for severe reactions
- Improving indications

What happens at home?

Continuing food-avoidance diets after negative food challenges

Pediatr Allergy Immunol 2006: 17: 601–605

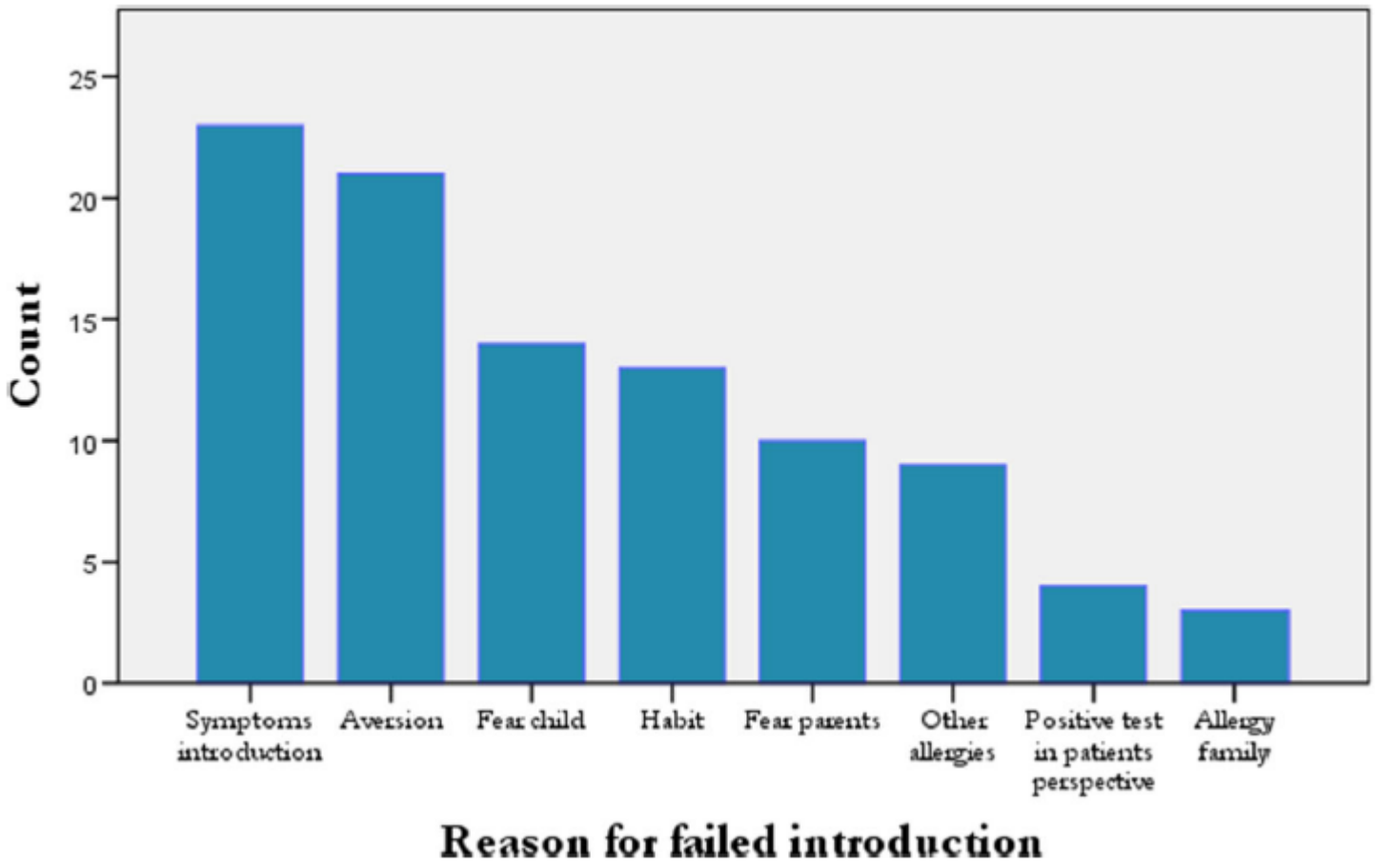


Why is the food not introcused?

Table 1. Factors potentially influencing the pattern of food consumption after a negative challenge

	Eats food after negative challenge	Does not eat food after negative challenge	Statistical significance (p-value)
Gender			
Female	16	11	0.026
Male	37	7	
Food tested			
Egg	15	6	0.134
Milk	18	2	
Peanut	7	6	
Others	13	4	
Severity of reaction at diagnosis			
Severe (respiratory or cardio-vascular)	23	4	0.16
Less severe or positive tests without any reaction	30	14	
Anxiety of a reaction during the diet			
High ($\geqslant$5/10)	32	10	0.78
Low (<5/10)	20	8	
Duration of diet (diagnosis to challenge)			
Prolonged ($\geqslant$24 months)	25	6	0.37
Short (<24 months)	19	9	

Patient number	Food	Amount of food given at challenge	Symptoms reported after challenge
6	Fish	40 g of trout	Oral itching with salt water fish
12	E110/E124	100 mg E110 & 100 mg E124	Urticaria with larger amounts
16	Egg	One hard boiled egg	AD flares with raw egg
23	Milk	100 ml of milk. Peri-oral rash at beginning of challenge fading away during challenge	Peri-oral skin rashes, oral pruritus, sneezing attacks
27	Egg	One hard boiled egg	Skin rash with not completely cooked eggs
31	Soy	DBPCFC (15 g soy milk powder corresponding to 1.7 g of proteins)	Still believes he is allergic, no clear symptoms
42	Peanuts	28 g peanut butter, peri oral rash at the beg of the challenge, fading away after	Doubts on tolerance, no clear symptoms
68	Milk	155 ml milk	Itching with specific cheeses
71	Milk	DBPCFC (6 g of proteins)	AD flares



Van der Valk JPM et al. Eur J Pediatr (2015) 174:1093–1099

Enjoy your food challenges!