La dieta del bambino allergico:
dai latti speciali allo svezzamento

Diego Peroni

Università di Pisa

La dimensione del problema

La dieta con latti speciali

Lo svezzamento

Le scelte possibili

Conclusioni

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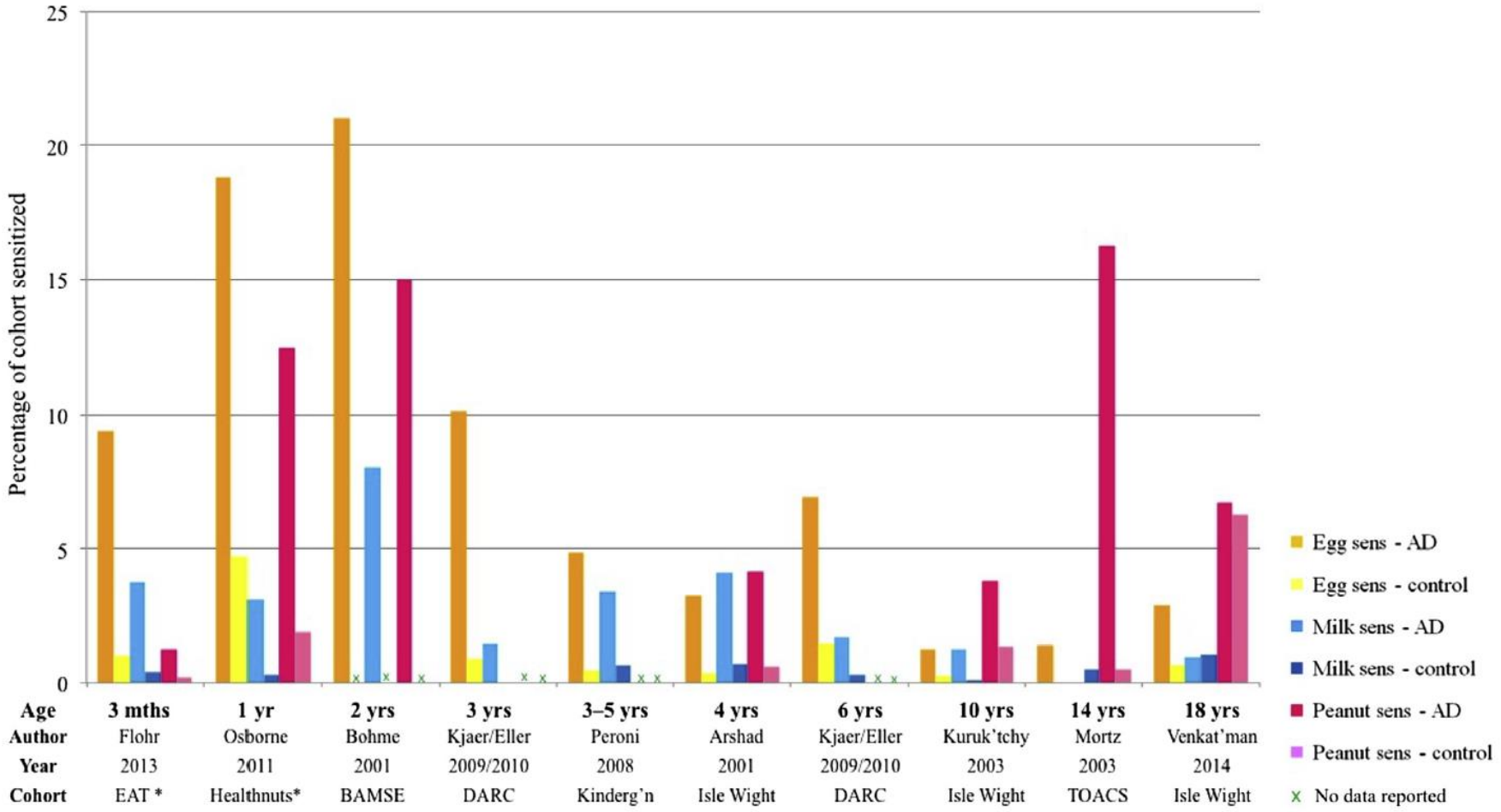
IN SUPREMÆ DIGNITATIS 1343

Does atopic dermatitis cause food allergy? A systematic review.

Tsakok, JACI 2016; 137:1071



In population-based studies, the likelihood of food sensitization was up to 6 times higher in patients with AD versus healthy control subjects at 3 months of age (**odds ratio, 6.18**; 95% CI, 2.94-12.98; P <.001).

Does atopic dermatitis cause food allergy? A systematic review.

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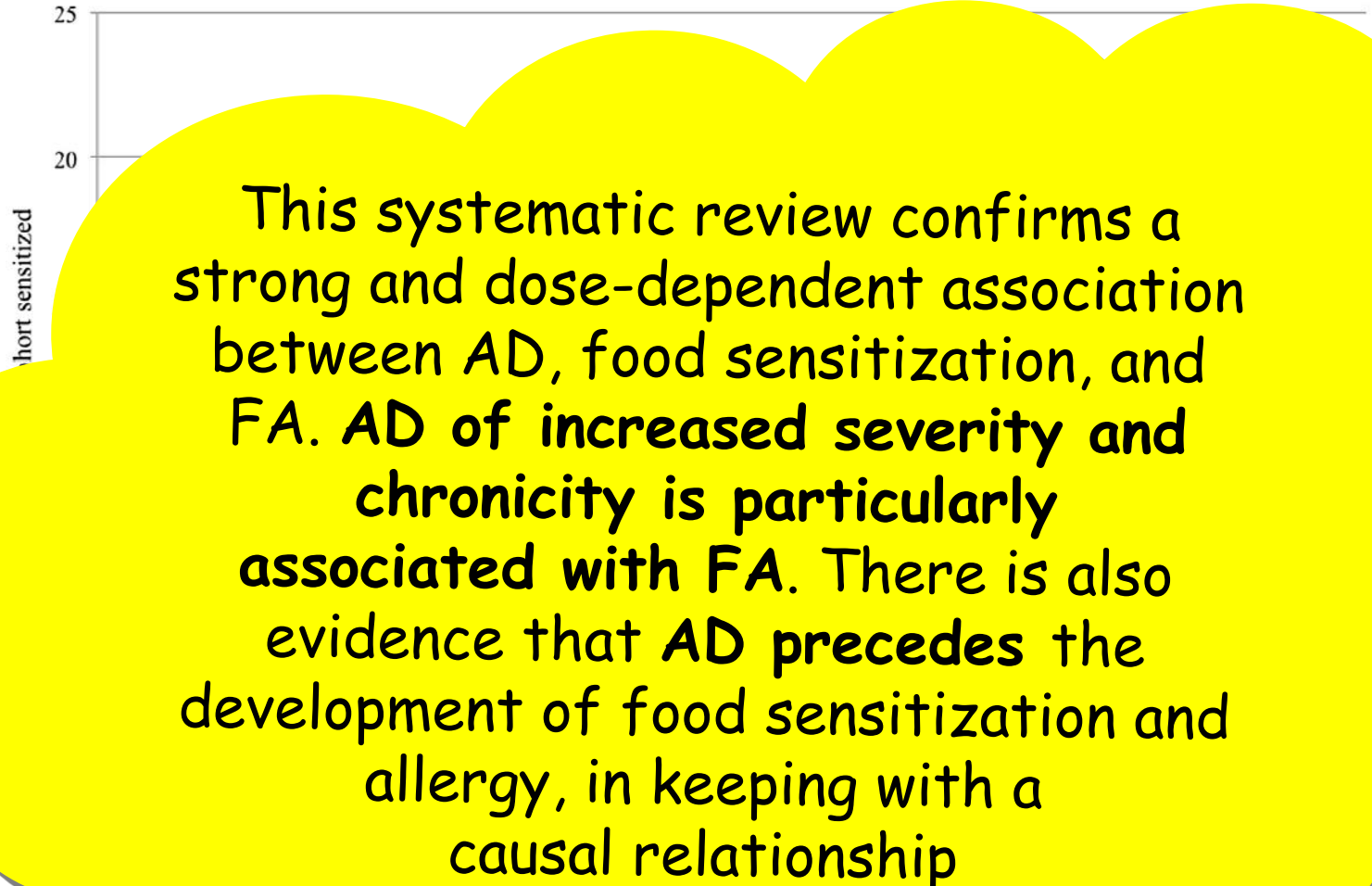


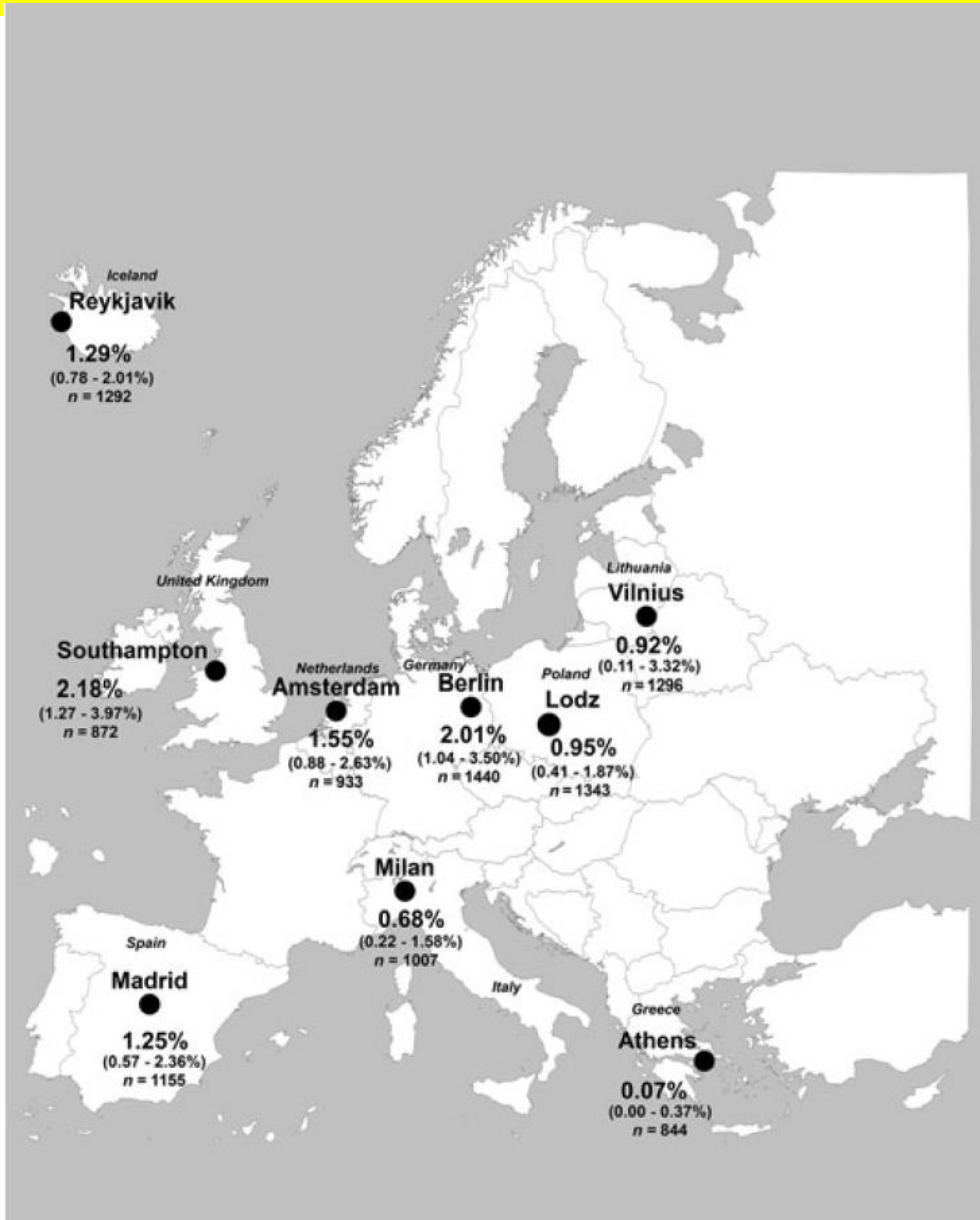
This systematic review confirms a strong and dose-dependent association between AD, food sensitization, and FA. **AD of increased severity and chronicity is particularly associated with FA**. There is also evidence that **AD precedes** the development of food sensitization and allergy, in keeping with a causal relationship

In popula… …on was up to 6 times highe… …y control subjects at 3 months of age (odds ratio, 6.1… …12.98; P <.001).

Incidence and natural history of hen's egg allergy in the first 2 years of life—the EuroPrevall birth cohort study.

Xepapadaki, Allergy 2016; 71:350.

EuroPrevall birth cohort study, children with a suspected HEA and their age-matched controls were evaluated in 9 countries, using a standardized protocol including measurement of
- HE-specific serum IgE,
-SPT, and
-double-blind, placebo-controlled food challenges (DBPCFC)



Incidence and natural history of hen's egg allergy in the first 2 years of life—the EuroPrevall birth cohort study.

Xepapadaki, *Allergy* 2016; 71:350.

EuroPrevall birth cohort
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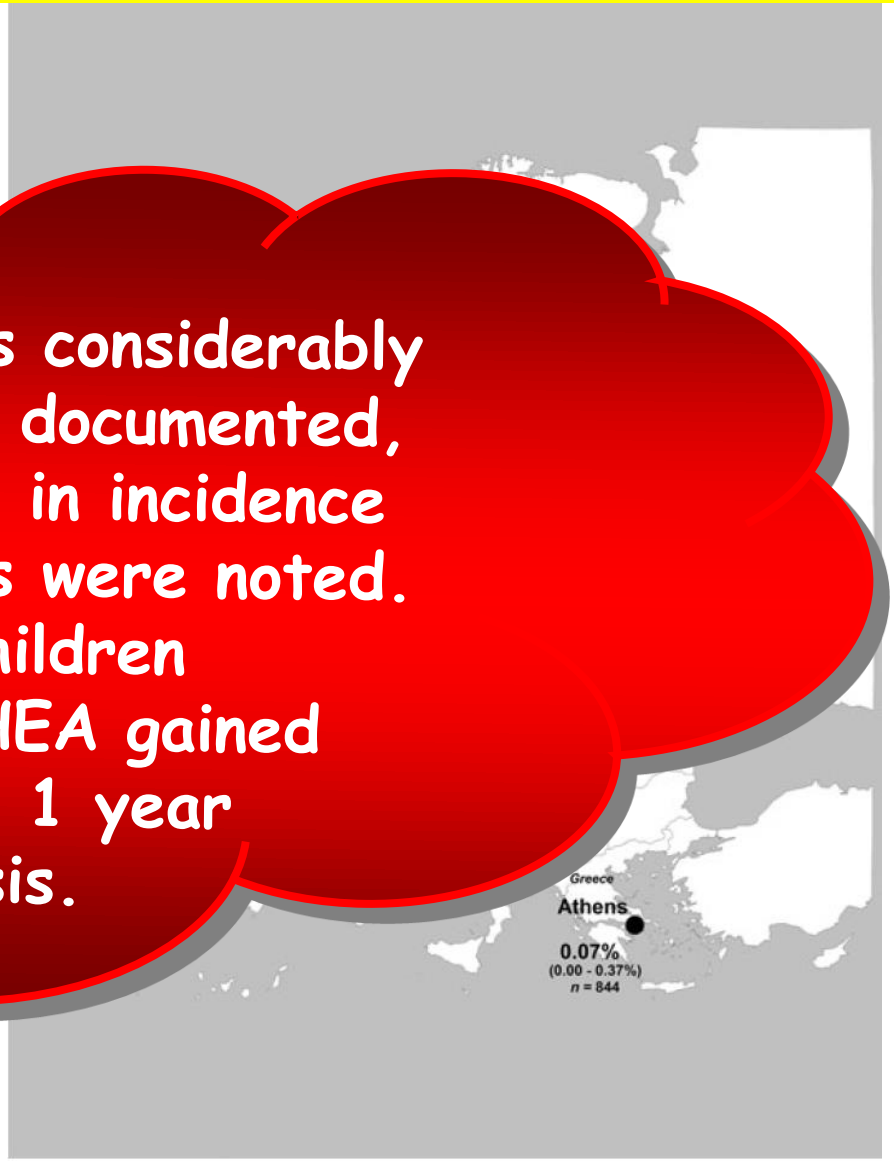
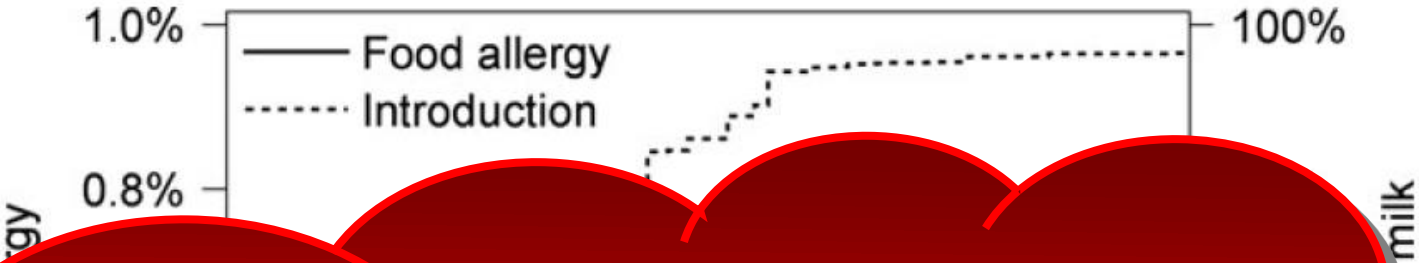
Incidence of HEA was considerably lower than previously documented, although differences in incidence rates among countries were noted. Half of the children with documented HEA gained tolerance within 1 year postdiagnosis.



Incidence and natural history of challenge-proven cow's milk allergy in European children – EuroPrevall birth cohort.

Schoemaker, 2015;70: 963



Confirmed challenge-proven CMA in <1% of children up to age 2. Affected infants without detectable specific antibodies to cow's milk were very likely to tolerate cow's milk one year after diagnosis, whereas only half of those with specific antibodies in serum 'outgrew' their disease so soon.

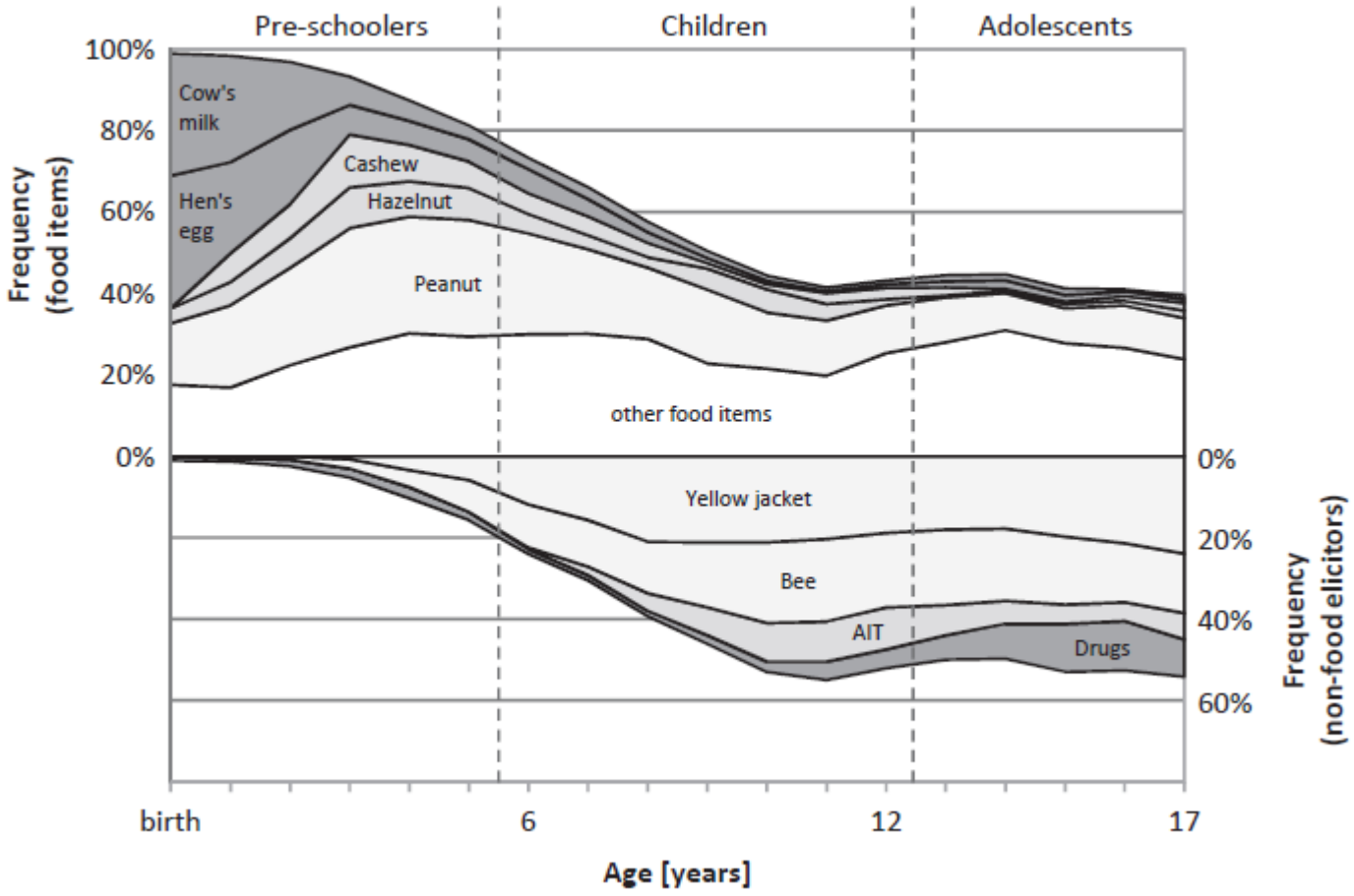
Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. Grabenhenrich JACI 2016; ;137:1128

Recorded details of anaphylaxis in 90 tertiary allergy centers in 10 Europea countries, aiming to oversample the most severe reactions.

Data were retrieved from medical records.

Between July 2007 and March 2015, anaphylaxis was identified in 1970 patients younger than 18 years.

Causes according to age



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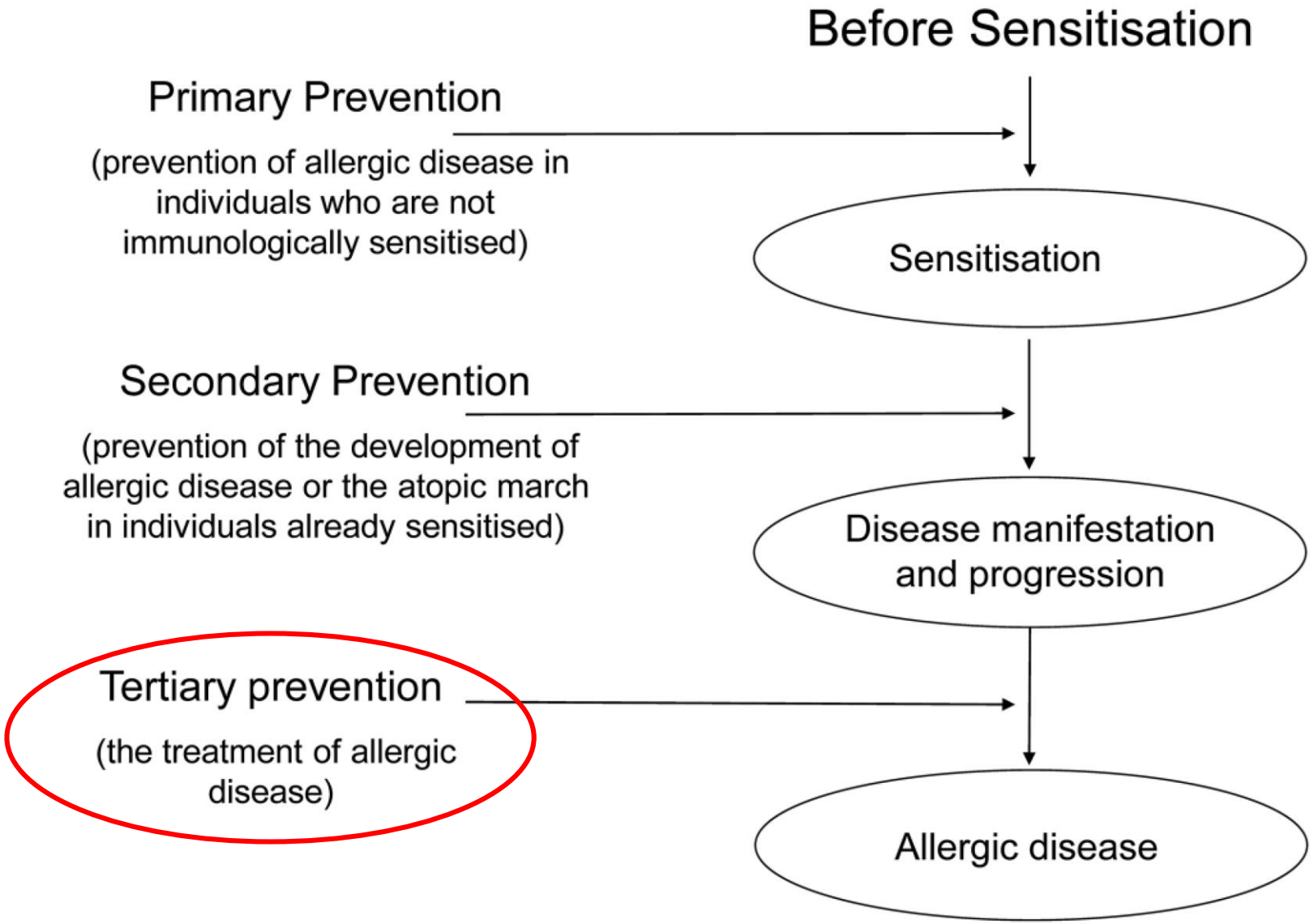
Modifying the infant's diet to prevent food allergy.

Grimshaw K, et al. Arch Dis Child 2017;102:179



Food Allergy. H.Sampson JACI 2003; 111:S540

The success of elimination diet requires that

- the correct allergen is identified
- the patient maintains a diet completely devoid of all forms of the offending allergen
- and other factors not provoke similar symptoms during the period of study

Formule idrolisate
Cosa sono?

Idrolisi = scissione delle proteine in frammenti < 6.000 Dalton: riduzione potere allergico

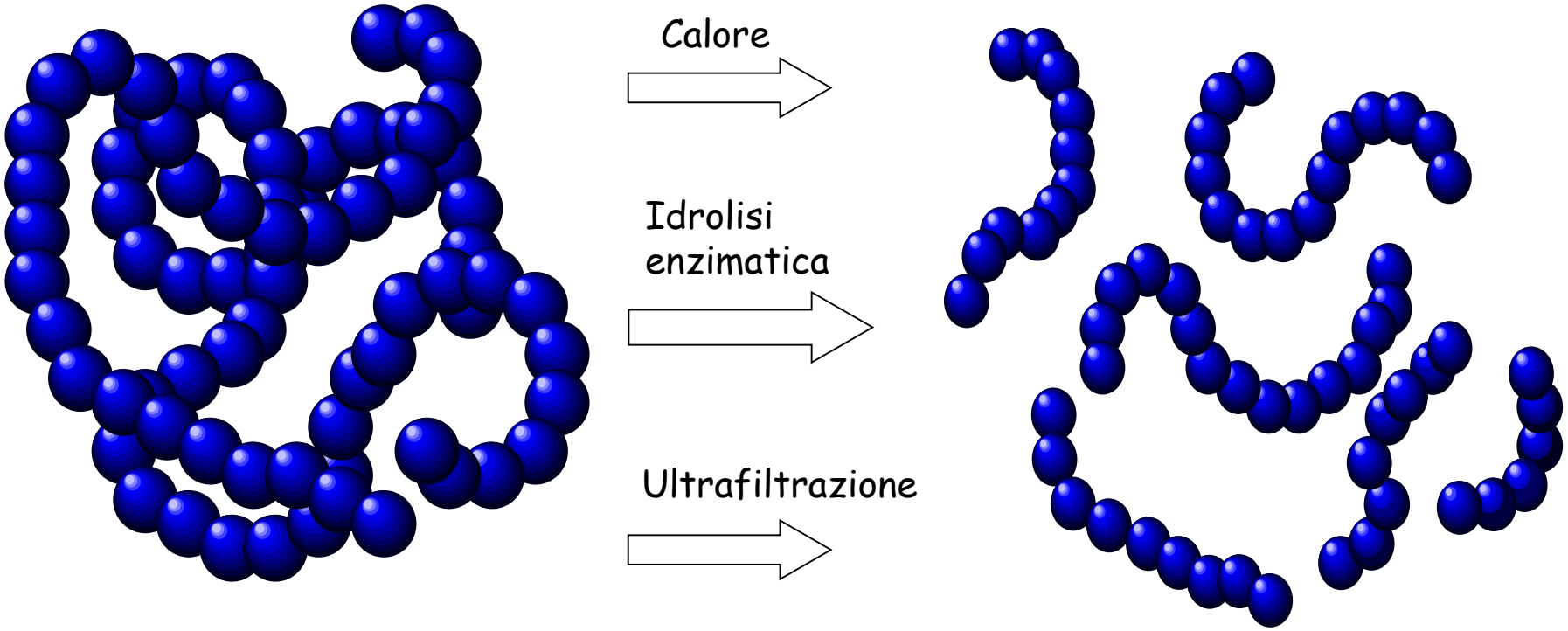
Il trattamento di idrolisi consiste nel sottoporre il latte a tre ordini di manipolazioni:

- trattamento enzimatico (mediante l'utilizzo di vari enzimi: pepsina, tripsina, papaina, proteasi batteriche ecc.)
- trattamento termico
- ultrafiltrazione

Si ottengono così tre tipi di latte:

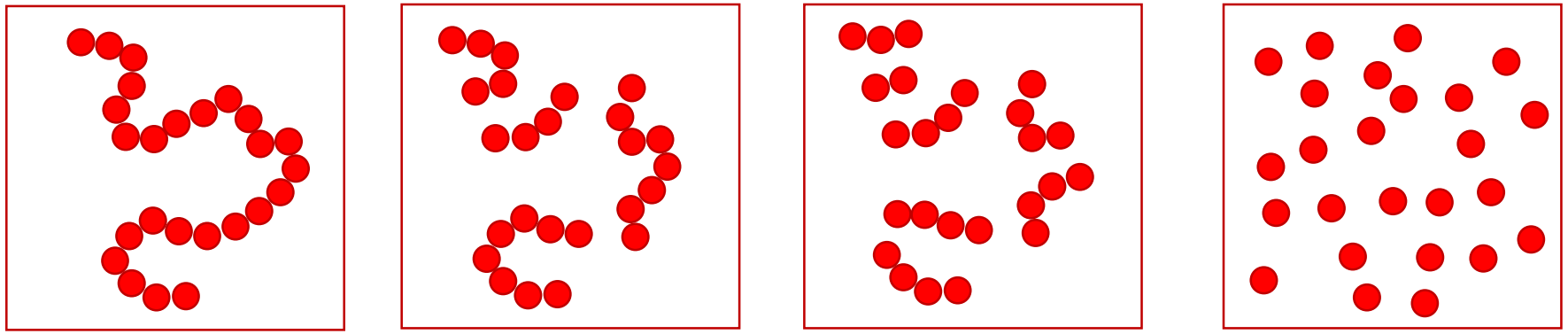
1) Latti parzialmente idrolisati
2) Latti estensivamente idrolisati
3) Formule aminoacidiche

Riduzione della ALLERGENICITA' di una PROTEINA



Minore è la lunghezza dei peptidi e minore è il peso della proteina..... minore è il residuo allergenico del peptide/proteina

Idrolizzati Proteici



Proteina intatta

Idrolizzato Parziale

Idrolizzato Estensivo

Aminoacidi

Allergenicita'

Formule idrolisate

Si differenziano in base alla tipologia di proteine contenute

- Idrolisati parziali
- Idrolisati estensivi

- Idrolisati di caseina
- Idrolisati di sieroproteine

BSACI guideline for the diagnosis and management of cow's milk allergy Luyt D, CEA 2014;44:642

Substitute formulas available in the UK for cow's milk allergic infants

extensively hydrolysed formulas

Type of formula	Example (alphabetical order)	Manufacturer	Composition[1] Protein source	Carbohydrate	Minerals (mg/100 ml)
EHF[2]	Aptamil Pepti 1 and 2 (2 suitable from 6 months)	Milupa	Hydrolysed whey 73% peptides < 1000 Da	Fish oils (omega 3 and 6). Lactose and maltodextrin	Calcium 52 Iron 0.5
	Althéra	Nestlé	Hydrolysed whey 95% peptides < 1000 Da	Palm, coconut, rapeseed and sunflower oil. Maltodextrin, lactose	Calcium 41 Iron 0.73
	Nutramigen 1 and 2 (2 suitable from 6 months)	Mead Johnson	Hydrolysed casein 95% peptides < 1000 Da	Palm, coconut, soya and sunflower oil. Glucose syrup, modified corn starch, fructose. Lactose free	Calcium 77 and 94 Iron 1.22 and 1.2
	MCT Pepdite	Nutricia SHS	Hydrolysed soya and pork collagen 64% peptides < 1000 Da	Coconut, maize, palm kernel and walnut oil. 75% fats MCT. Glucose syrup. Lactose free.	Calcium 49 Iron 1.0
	Pepdite	Nutricia SHS	Hydrolysed soya and pork collagen 64% peptides < 1000 Da	Coconut, soya and sunflower oil. Glucose syrup. Lactose free.	Calcium 45 Iron 1.3
	Pepti Junior	Cow and Gate	Hydrolysed whey 57% peptides < 1000 Da	Coconut, soya and fish oil; 50% MCT. Glucose syrup Lactose content insignificant	Calcium 76 Iron 1.2
	Pregestimil	Mead Johnson	Hydrolysed casein 95% peptides < 1000 Da	Corn, soya and sunflower oil; 55% MCT. Corn syrup and corn starch. Lactose free.	Calcium 94 Iron 1.8
	Similac Alimentum	Abbott	Hydrolysed casein 95% peptides < 1000 Da	Sunflower and soya oil. 33% MCT Sucrose, modified corn starch. Lactose free.	Calcium 71 Iron 1.2

Hypoallergenic formulas: optimal choices for treatment versus prevention

Bahna Ann All AsthImmunol 2008;101:453

Advantages

- ✓ Well tolerated by the vast majority of cow's milk allergic individuals (approximately 95%)
- ✓ For prevention, can be used as a supplement or a substitute to breastfeeding in infants at high risk of allergy
- ✓ Nutritionally adequate

Limitations

- ✓ High cost
- ✓ Unpalatable taste
- ✓ Potential error in reconstitution
- ✓ High osmolality potential
- ✓ Can cause allergy in exquisitely milk allergic individuals (5-10%)

Formula aminoacidica

- Idrolisi totale
- Del tutto priva di potere allergenico
- Piuttosto sgradevole
- Facilmente assorbibile → accrescimento soddisfacente anche con quantità inferiori

BSACI guideline for the diagnosis and management of cow's milk allergy Luyt D, CEA 2014;44:642

Substitute formulas available in the UK for cow's milk allergic infants

Type of formula	Example (alphabetical order)	Manufacturer	Composition[1] Protein source	Carbohydrate	Minerals (mg/100 ml)
AAF[3]	Neocate LCP	Nutricia SHS	Amino acids	Coconut, canola and sunflower oil. Glucose syrup. Lactose free	Calcium 65.6 Iron 1.0
	Neocate Active (suitable from 12 months)	Nutricia SHS	Amino acids	Coconut, canola and sunflower oil. Glucose syrup. Lactose free.	Calcium 95.1 Iron 1.3
	Neocate Advance (suitable from 12 months)	Nutricia SHS	Amino acids	Coconut, canola, and sunflower oil. Glucose syrup. Lactose free.	Calcium 50 Iron 0.62
	Nutramigen AA	Mead Johnson	Amino acids	Palm, coconut, soya and sunflower oil. Glucose syrup and tapioca starch. Lactose free.	Calcium 64 Iron 1.22
Soya[4]	Infasoy	Cow and Gate	Whole soya	Glucose syrup. Suitable for vegans	Calcium 54 Iron 0.8
	Wysoy	SMA Nutrition	Whole soya	Glucose syrup.	Calcium 67 Iron 0.8

amino acid formulas

Hypoallergenic formulas: optimal choices for treatment versus prevention

Bahna Ann All AsthImmunol 2008;101:453

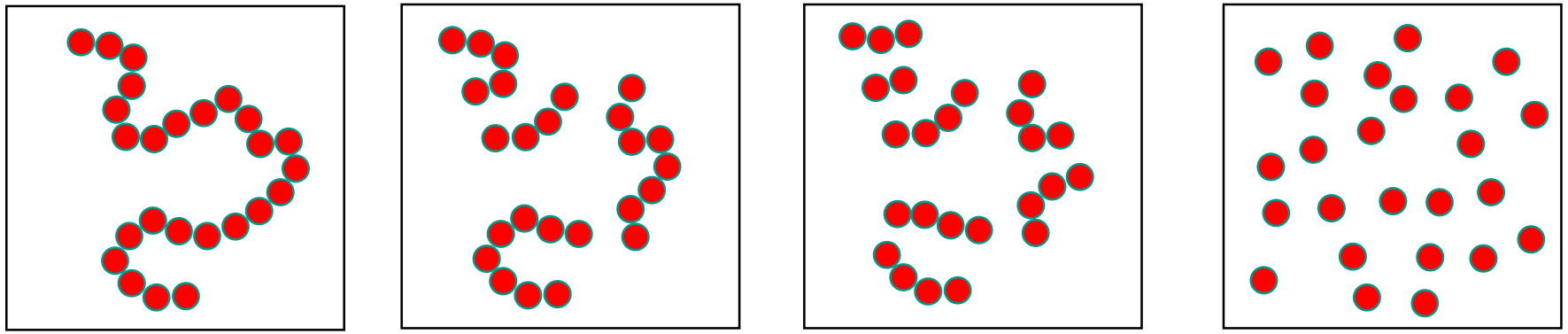
Advantages

- ✓ Well tolerated by almost all children allergic to cow's milk or to multiple foods
- ✓ For prevention, can be used as a supplement or a substitute to breastfeeding in infants at high risk of allergy
- ✓ Nutritionally adequate

Limitations

- ✓ High cost
- ✓ Unpalatable taste
- ✓ Potential errors in reconstitution

Idrolisati



Proteina intatta

Idrolizzato Parziale

Idrolizzato Estensivo

Aminoacidi

Costo

Palatabilità

BSACI guideline for the diagnosis and management of cow's milk allergy Luyt D, CEA 2014;44:642

Food items and ingredients that contain cow's milk protein

Butter, butter fat, butter milk, butter oil
Casein (curds), caseinates, hydrolysed casein, calcium caseinate, sodium caseinate
Cheese, cheese powder, cottage cheese
Cow's milk (fresh, condensed, dried, evaporated, powdered (infant formulas), UHT)
Cream, artificial cream, sour cream
Ghee
Ice cream
Lactalbumin, lactoglobulin
Low-fat milk
Malted milk
Margarine
Milk protein, milk powder, skimmed milk powder, milk solids, non-fat dairy solids, non-fat milk solids, milk sugar
Whey, hydrolysed whey, whey powder, whey syrup sweetener
Yogurt, fromage frais

BSACI guideline for the diagnosis and management of cow's milk allergy Luyt D, CEA 2014;44:642

Recommendations on the use of alternative 'milk' beverages

1. They are not suitable for infants as a main drink under 1 year of age. A nutritionally complete formula should always be chosen, preferably to 2 years of age (although they can be used for cooking).

2. Their use in children should be under the close guidance of a dietitian as shortfalls in energy, protein, calcium, riboflavin, vitamin A and D, and essential fatty acids are likely without an alternative dietary source. Weight and growth should be regularly monitored.

3. They are not available on prescription and therefore should not be suggested to families with financial constraints where a more suitable complete formula can be prescribed.

BSACI guideline for the diagnosis and management of cow's milk allergy Luyt D, CEA 2014;44:642

Recommendations on the use of alternative 'milk' beverages

4. They are not available on prescription and therefore should not be suggested to families with financial constraints where a more suitable complete formula can be prescribed. Their use in older children and adults should be under the supervision of a dietitian to ensure adequate calcium intake.

5. Care should be taken to ensure that specific ingredients are not allergenic to a particular individual, for example nut milks and nut allergy, soya milks and soya allergy.

6. Rice milk should not be used under age 4.5 years due to its natural inorganic arsenic content.

BSACI guideline for the diagnosis and management of cow's milk allergy Luyt D, CEA 2014;44:642

Recommended calcium intake*

Age	Adequate intake (mg/day)
0–12 months	525
1–3 years	350
4–6 years	450
7–10 years	550
11–14 years (male)	1000
11–14 years (female)	800
15–18 years (male)	1000
15–18 years (female)	800

*UK recommendations differ from those of other countries (e.g. US).

BSACI guideline for the diagnosis and management of cow's milk allergy Luyt D, CEA 2014;44:642

Home reintroduction should not be attempted if any of the following features are present

1) Previous cow's milk allergy symptoms that significantly affected breathing [cough, wheezing, or swelling of the throat, for example cough, stridor, or choking sensation or throat tightness (in older children)], the gut (i.e. severe vomiting or diarrhoea), or the circulation (faintness, floppiness or shock)
2) A less severe reaction with only trace exposure
3) Regular asthma preventative inhaler treatment and/or poorly controlled asthma.
4) Multiple or complex allergy
5) No significant reduction in SPT wheal diameter/sIgE level since diagnosis
6) High sIgE levels without history of any prior milk exposure (e.g. exclusively breastfed or hypoallergenic formula fed infants withsevere eczema)
7) Parents who are unable to comprehend or adhere to the protocol
8) Children with any of these features should undergo a supervised challenge in hospital.
9) In children at highest risk, a supervised baked milk challenge is preferable

Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA): A summary report

Fiocchi JACI 2010;126:1119

➢ Problems:

- **Inadvertent intake** (labeling and level of dietary education);

- **Misconceptions about safety** of partially hydrolyzed formula, heated milk products, or homologous nonbovine milk formula (eg, goat's milk formula);

- **Taste adversion** for treatment formula;

- **Poor intake and feeding difficulties** or refusal to feed;
- Risk of **decreased growth** velocity;
- Other confounding food allergies (eg, egg, soy, or wheat).

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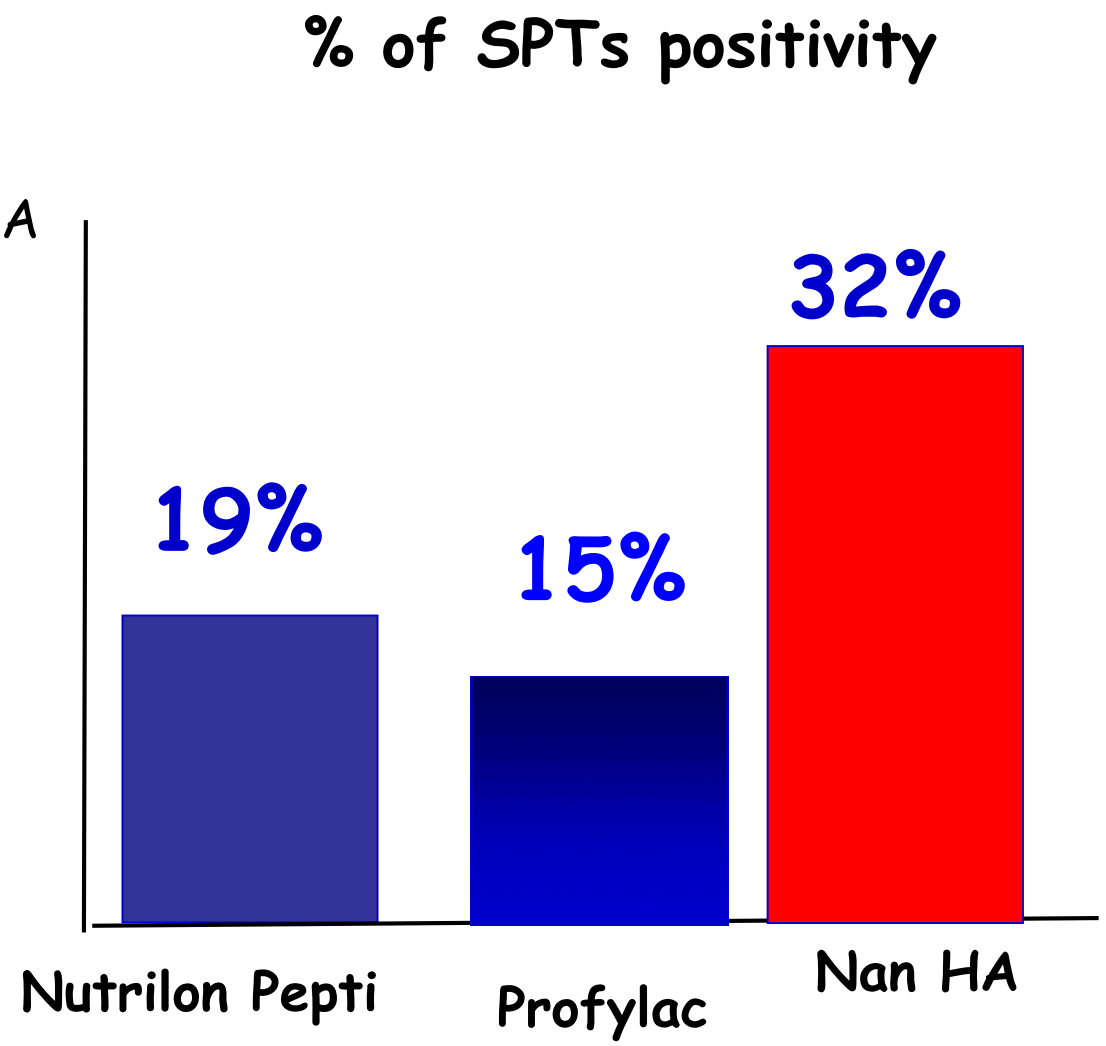
Hypoallergenicity of an extensively hydrolyzed whey formula. Giampietro, PAI 2001

32 children with proven CMA tested with the extensive hydrolysate whey formula Nutrilon Pepti, Profylac extensive) and Nan HA (partial) whey hydrolysate.

Skin-prick tests (SPTs)

Oral challenge



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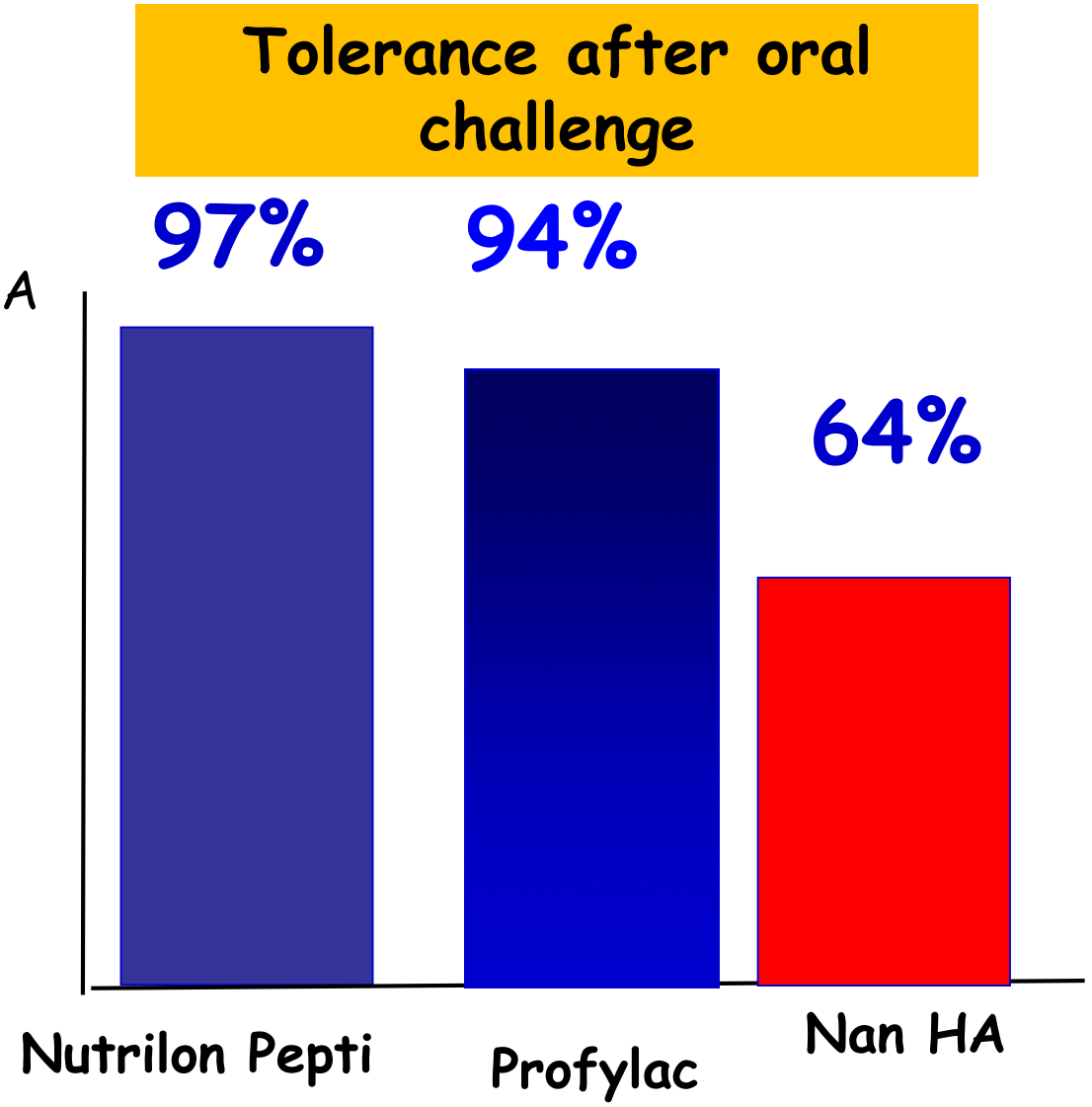
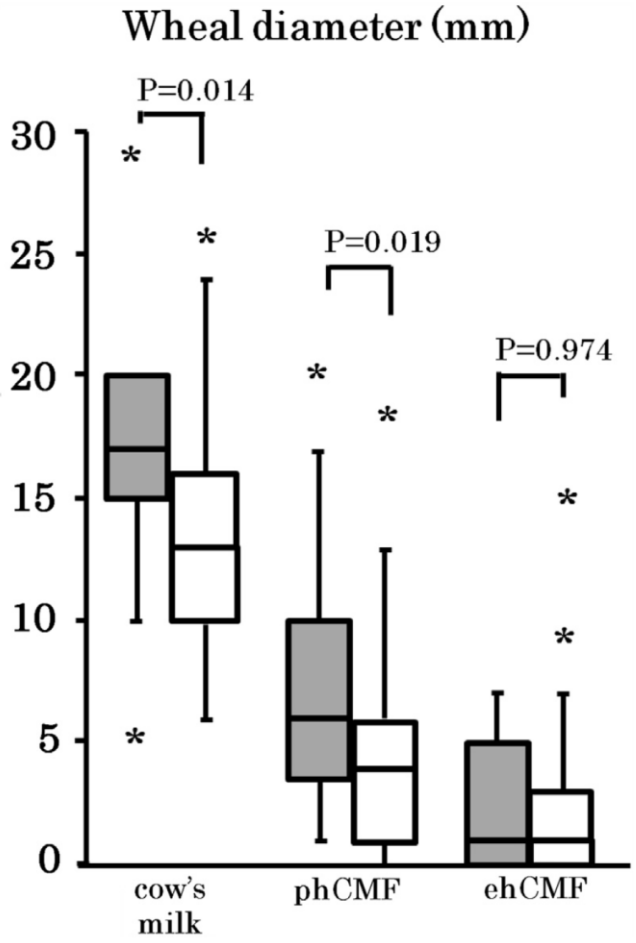


Most cases of cow's milk allergy are able to ingest a partially hydrolyzed formula.

Kido J, 2015 Ann Allergy Asthma Immunol

Wheal diameter after skin prick testing with cow's milk, partially hydrolyzed formula (phCMF), and extensively hydrolyzed formula (ehCMF) in children with cow's milk allergy

who did (n 13, gray bars) or did not develop (n 40, white bars) allergic reactions from the oral provocation test with phCMF



Profile of milk allergic patient tolerating partially hydrolyzed whey formula. T Lee, JACI prat 2015; 3:116

1.

A seven month-old female presented with concern for milk allergy.

She had been breastfed until age ten weeks and then transitioned to a partially hydrolyzed whey formula (pHWF), Gerber Good Start Gentle®, which she was tolerating well. She had also been successfully introduced to fruits (including bananas), vegetables, and grains.

At age six months, she ingested banana yogurt. Within five minutes, she developed a dry cough, vomiting, and hives over 90% of her body.

Her parents immediately brought her to the pediatrician, who administered oral steroids and antihistamines, and her symptoms resolved. No epinephrine was administered.

Profile of milk allergic patient tolerating partially hydrolyzed whey formula. T Lee, JACI prat 2015; 3:116

2.

A local allergist performed skin testing with the following results (wheal mm/flare mm): plain yogurt 14/30, banana yogurt 12/22, CM 4/8, fresh banana 5/14, commercial banana extract 0/0. Serum specific IgE (sIgE) levels sent to an outside commercial laboratory were: milk 8.01 kUA/L, casein 23.4 kUA/L, alpha-lactoglobulin<0.35 kUA/L, beta-lactoglobulin<0.35 kUA/L, banana <0.35 kUA/L.

The allergist switched from pHWF to an amino acid-based formula, Nutricia Neocate®, and to avoid bananas. The patient did not like the taste of the amino acid-based formula, and her parents became concerned

Profile of milk allergic patient tolerating partially hydrolyzed whey formula. T Lee, JACI prat 2015; 3:116

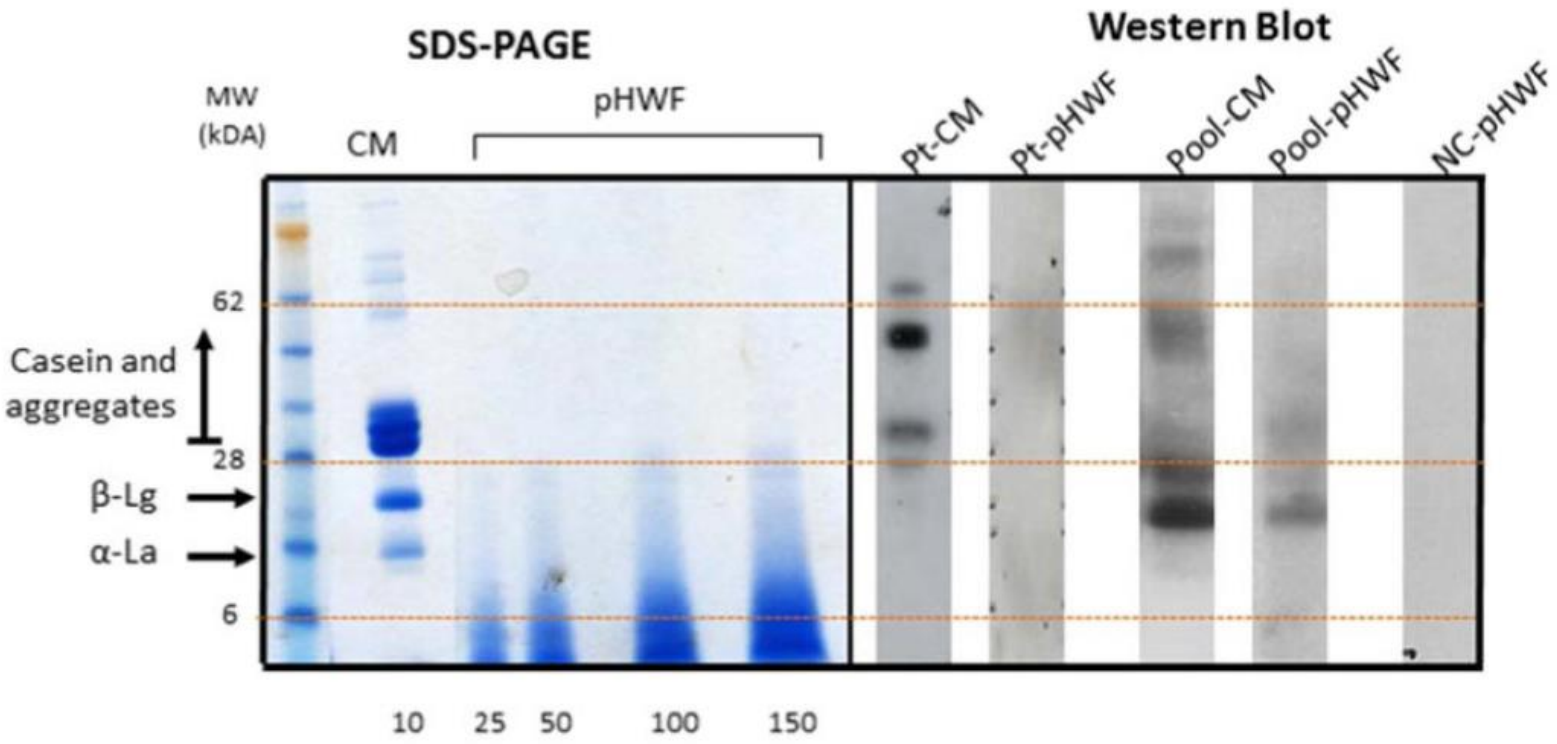
3.

The patient was then evaluated in our clinic. Skin testing at our practice showed (wheal mm/flare mm): histamine 6/12, saline 0/0, commercial banana extract 4/0, pHWF 2/0. Based on her history, sIgE and skin test results, we diagnosed her with casein-specific CM allergy.

We advised that the patient resume pHWF but to avoid all other CM.

At follow-up several weeks later, she was back on pHWF and eating bananas with appropriate growth.

Profile of milk allergic patient tolerating partially hydrolyzed whey formula. T Lee, JACI prat 2015; 3:116



Casein and whey (α-lactalbumin and β-lactoglobulin) are the main proteins in CM (column CM). pHWF has no casein proteins (column pHWF).The case patient's serum showed binding to only casein proteins in CM (column Pt-pHWF), and no binding to any proteins in pHWF(column Pt-pHWF).

Profile of milk allergic patient tolerating partially hydrolyzed whey formula. T Lee, JACI prat 2015; 3:116

4.

Some patients may be sensitized to individual milk proteins only. In this case, the patient had a casein-specific allergy and was able to tolerate pHWF, which was a more palatable and economical choice. As she had been tolerating pHWF for many months, the initial allergist's advice to switch her to an amino-acid based formula was not necessary and she could have continued on pHWF.

A specific teaching point from this case is that patients should continue tolerated dietary exposures, and test results need to be appropriately interpreted.

Immunomodulating properties of protein hydrolysates for application in cow's milk allergy. Kiewiet M.B. Pediatr Allergy Immunol 2015: 26: 206

erview recent studies investigating immunomodulating effects of hydrolysates

Author(s)	Year of publication	Described effects	Type of studies	Species *in vivo* studies
Iskander et al.	2013	Decline in the LPS-induced IL-8 production in respiratory epithelial cells after the administration of whey protein hydrolysates	*In vitro*	–
Nielsen et al.	2012	Decrease in expression of inflammation markers in casein hydrolysate treated epithelial cells	*In vitro*	–
Swiatecka et al.	2012	Hydrolyzed pea protein decreased IL-8 production in CaCo2 cells	*In vitro*	–
Oseguera-Toledo et al.	2011	LPS-activated macrophages showed a decrease of inflammation markers after administration of hydrolyzed common bean protein	*In vitro*	–
de Mejia	2009	Lunasin inhibited inflammatory markers and reduced the production of IL-6 and IL1β in macrophages	*In vitro*	–
Wong et al.	1989	Whey hydrolysates enhanced proliferation in murine spleen lymphocytes	*In vitro*	–
Knipping et al.	2012	Whey hydrolysates did not show individual effects on specific cytokines	*In vitro*	–
Mao et al.	2007	Yak milk hydrolysate increased Th1 cytokine expression, but did not affect Th2 cytokines	*In vitro*	–
Cian et al.	2012	A seaweed hydrolysate increased IL-10 production in splenocytes, macrophages and T cells.	*In vitro*	–
Lahart et al.	2011	A casein hydrolysate increased IL-10 production in T cells.	*In vitro*	–
Duan et al.	2012	β-lactoglobulin trypsin hydrolysates increased IL-10 production in splenocytes from sensitized mice	*In vitro*	–
Ndiaye et al.	2012	Increased amount of IL-10+ cells in the small intestine lamina propria after oral administration of yellow pea protein hydrolysate	*In vivo*	Mice
Visser et al.	2012	Decreased in lactulose:mannitol ratio (also compared to AA diet) after casein hydrolysate diet	*In vivo*	Rats
Visser et al.	2010	After casein hydrolysate diet • decreased lactulose:mannitol ratio • increased transepithelial electrical resistance in an ileum sample (*ex vivo*) • mRNA expression tight junction genes were normalized • IL-10 upregulation	*In vivo*	Rats
Tavares et al.	2013	Anti-inflammatory effects from a whey hydrolysate were observed using a paw edema test	*In vivo*	Mice
Wu et al.	2006	IFN-γ/IL-4 ratio increased in spleen T cells from mice fed with chitosan	*In vivo*	Mice

Immunomodulating peptides for food allergy prevention and treatment

Lozano-Ojalvo, Critical Reviews in Food Science and Nutrition

Peptide IT
contain T
IgE on b

Pepti
pro

T c
pepti
diffe
many
HLA
recog

There is a minimum core sequence of 9 to 15 amino acids required for recognition by reactive T cells. Consequently, even if linear, soluble, 15-mer IgE-binding peptides are unlikely to act as full epitopes and cause allergic reactions

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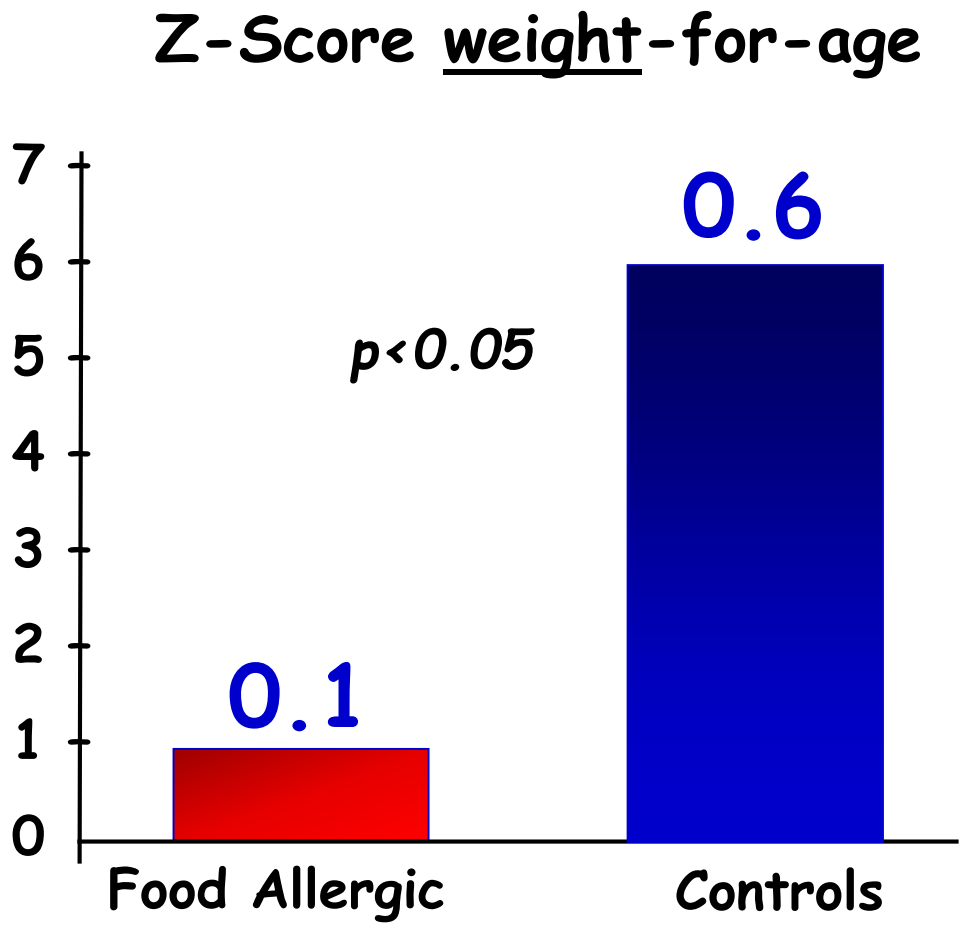
Diet and nutritional status of children with food allergies

Flammarion Pediatr Allergy Immunol 2011;22:161

96 children
(mean age 4.7) with food allergies.

95 paired controls.

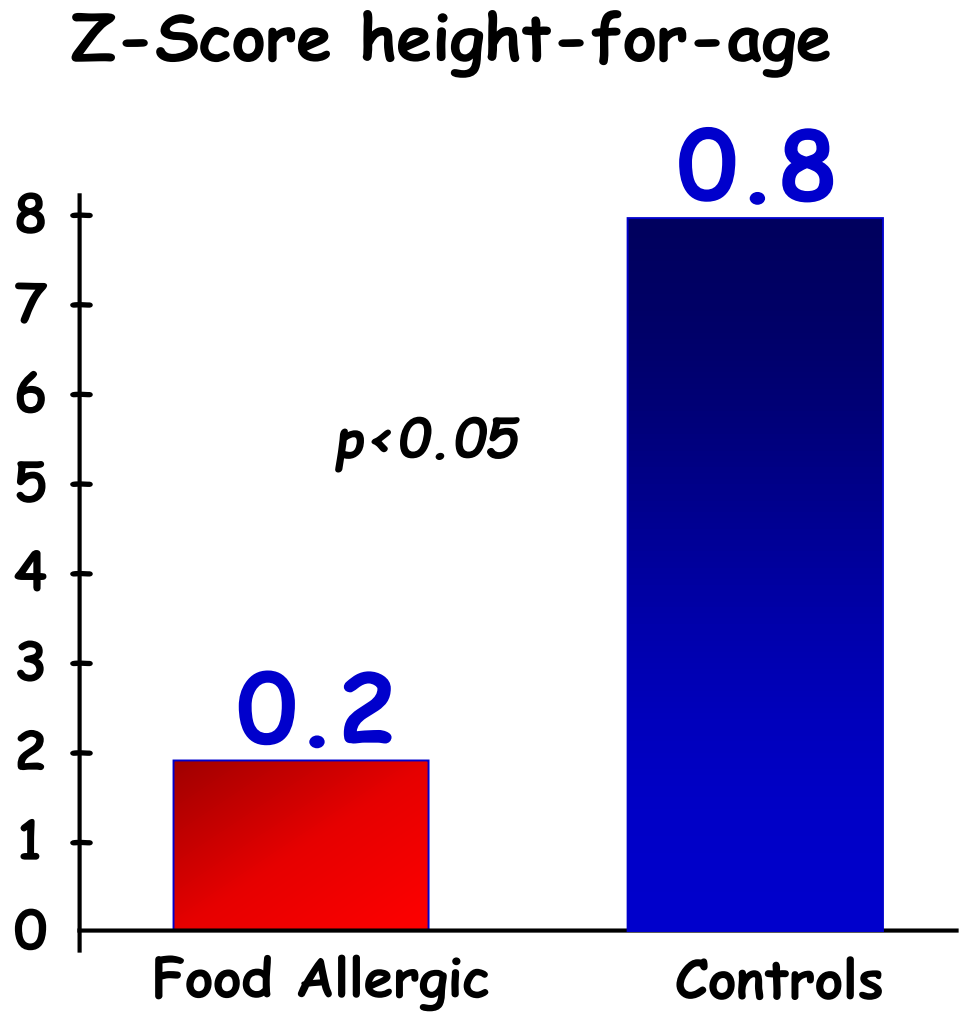
Z scores for weight-for-age, height-for-age and weight-for-height.



Diet and nutritional status of children with food allergies

Flammarion Pediatr Allergy Immunol 2011;22:161

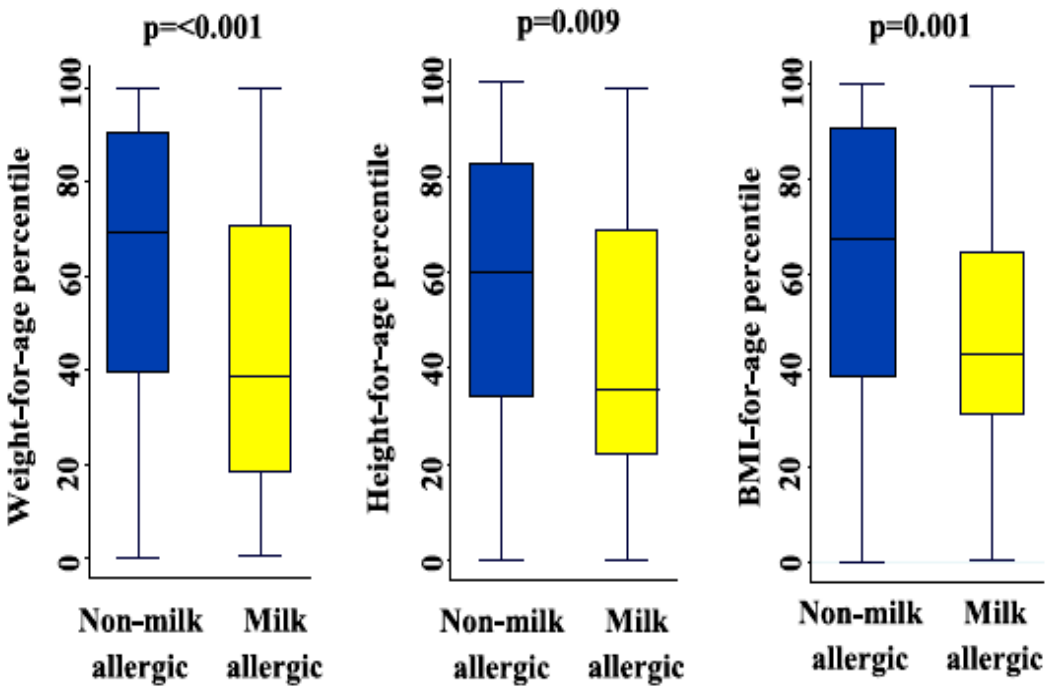
Children with 3 or more food allergies were smaller than those with 2 or less food allergies ($p = 0.04$).



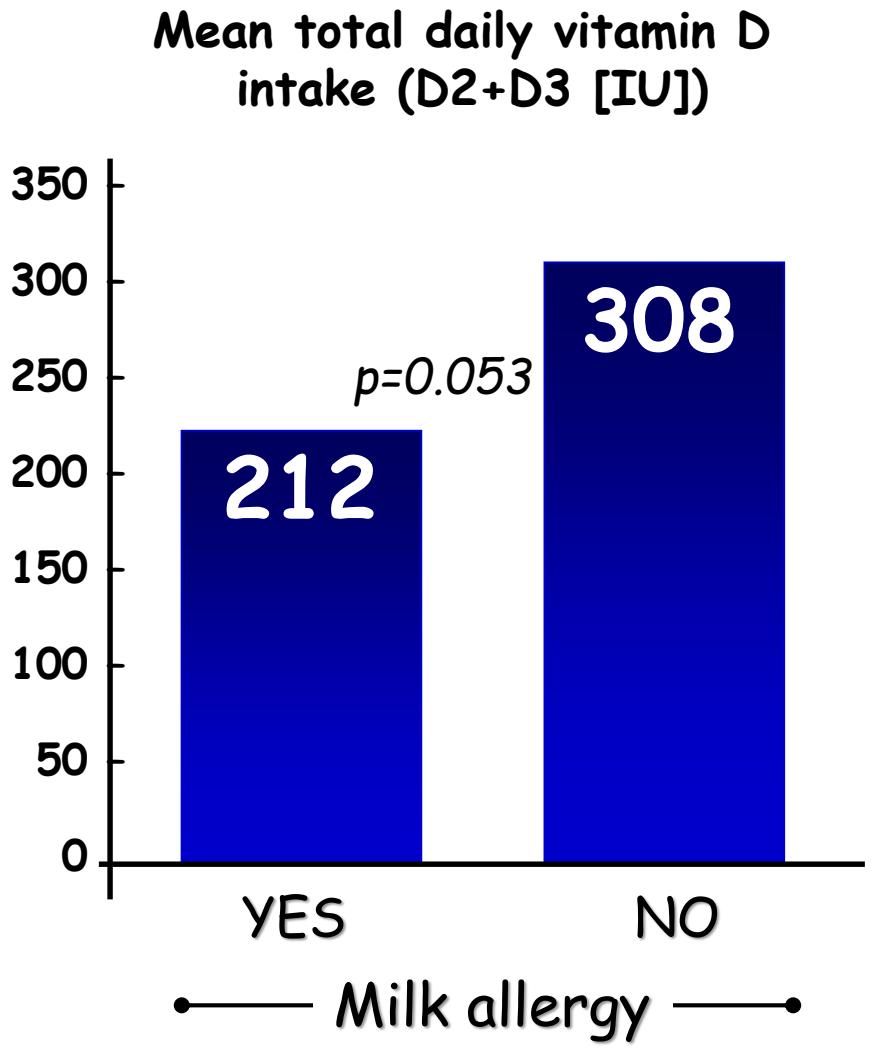
Milk allergy is associated with decreased growth in US children. Robbins KA, JACI 2014;134:1466

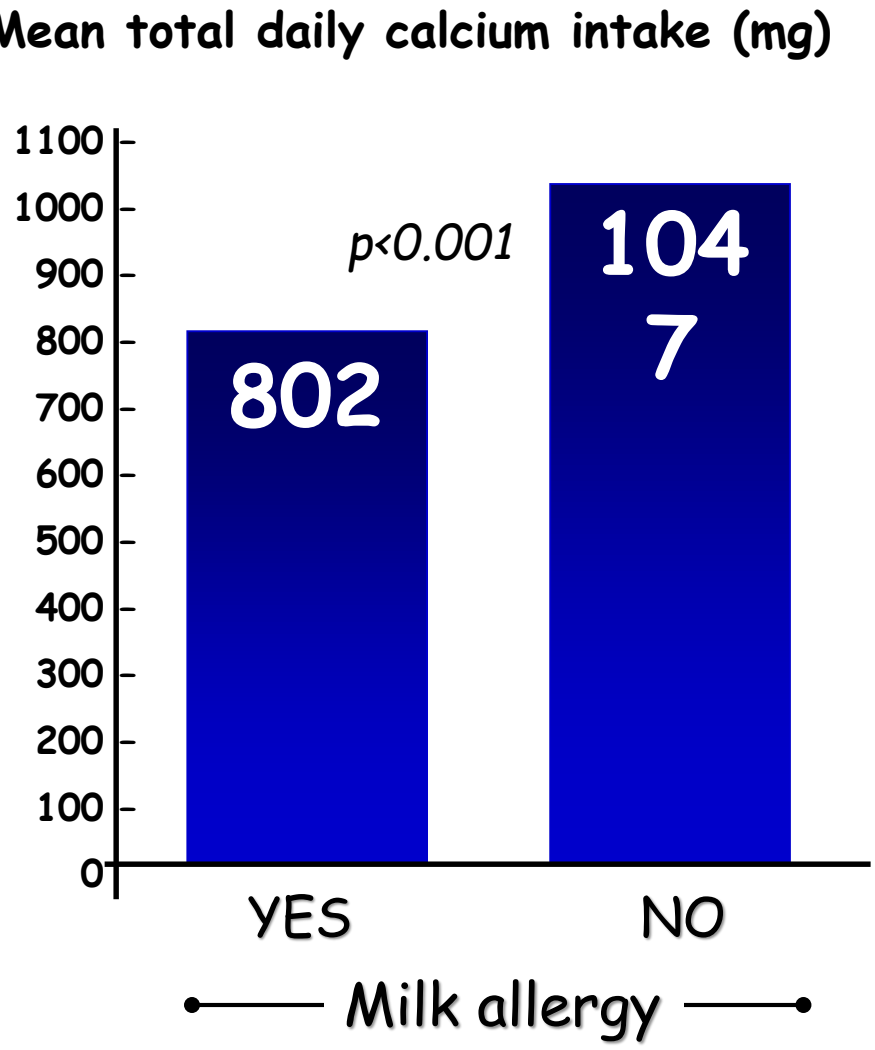
- ✓ Anthropometric measurements and dietary intake of calcium, vitamin D, total calories, protein, and fat between children with and without reported food allergy by using National Health and Nutrition Examination Survey (NHANES).
- ✓ 6189 children aged 2 to 17 years.

Weighted box plots of anthropometric features for children aged 2 to 17 years comparing children with milk allergy versus those without milk allergy



Milk allergy is associated with decreased growth in US children. Robbins KA, JACI 2014;134:1466





Practical dietary management of protein energy malnutrition in young children with cow's milk protein allergy.

Meyer PAI 2012

Calcium a… D …
suitab…

As children with malnutrition are normally consuming a diet deficient in macro- and micronutrients, multiple deficiencies are common.
It would therefore be inappropriate to give only energy and protein supplementation without adequate micronutrients in an attempt to reverse wasting or stunting.

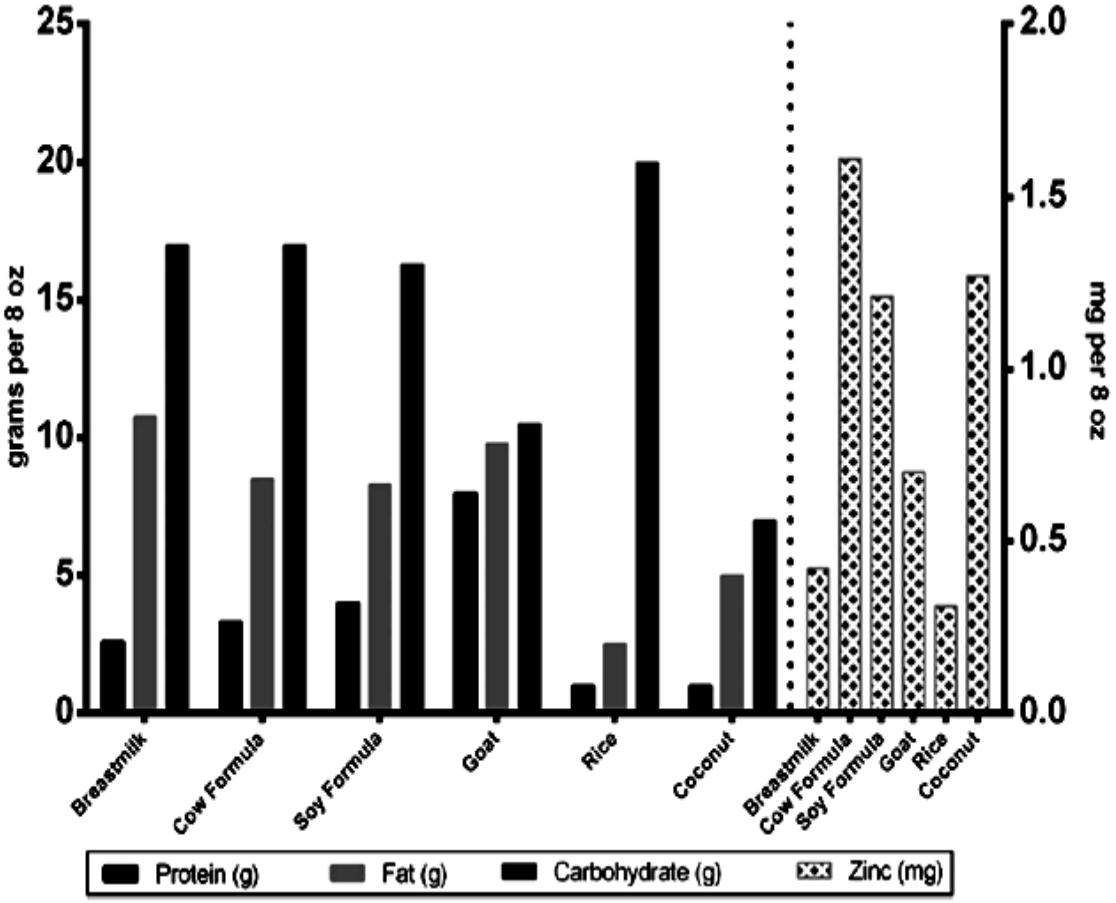
1.2
0.85

Misdiagnosed Food Allergy Resulting in Severe Malnutrition in an Infant

Alvares M, Pediatrics 2013;132:e229

Comparison of nutritional content among breast milk, infant formulas, and milk substitutes occasionally given to toddlers

8 oz = 236 mL



La dieta del bambino allergico:
dai latti speciali allo svezzamento

Diego Peroni

Università di Pisa

La dimensione del problema

La dieta con latti speciali

Lo svezzamento

Le scelte possibili

Conclusioni

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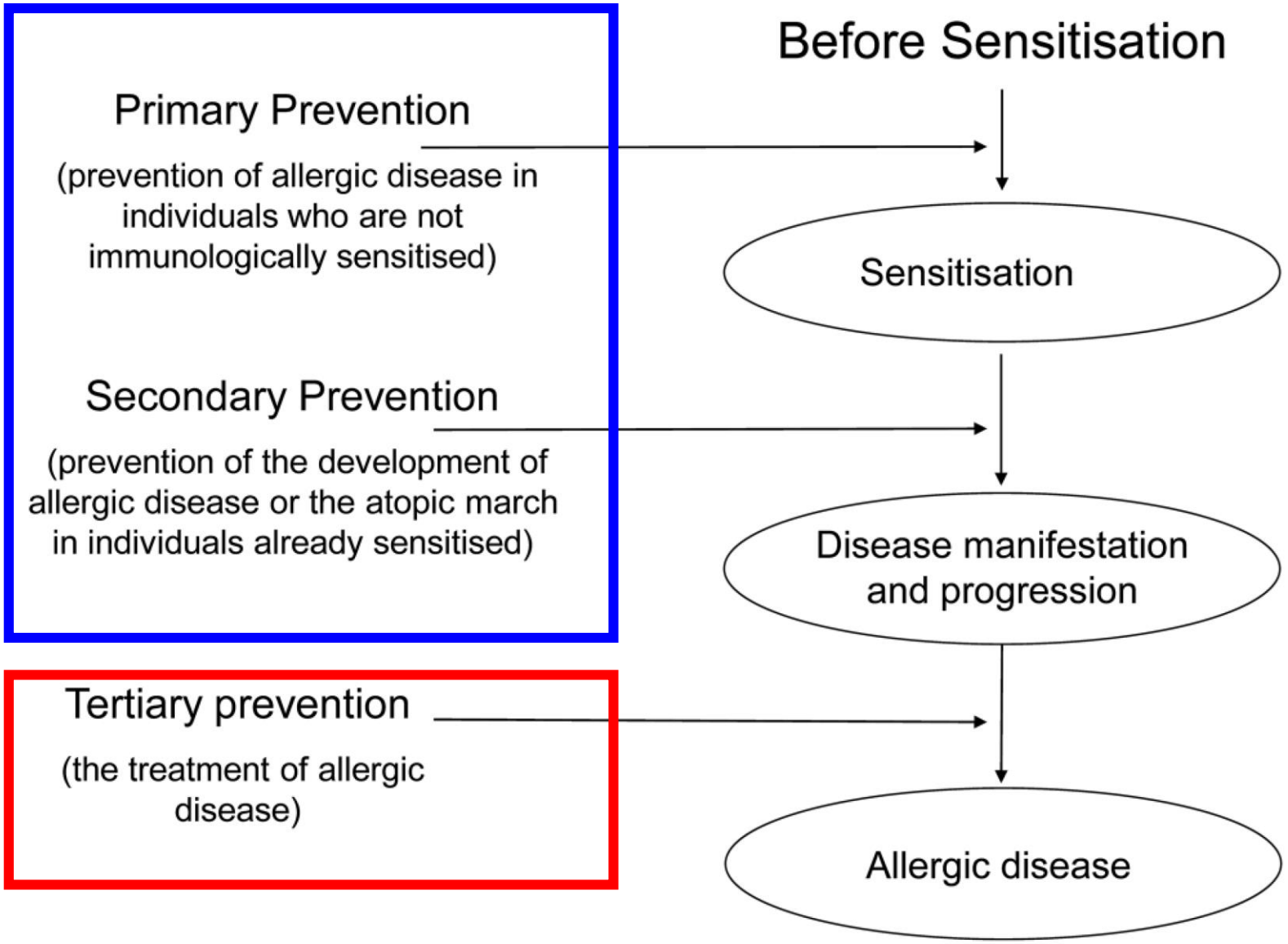
IN SUPREMÆ DIGNITATIS 1343

Modifying the infant's diet to prevent food allergy.

Grimshaw K, et al. Arch Dis Child 2017;102:179



Modifying the infant's diet to prevent food allergy.

Grimshaw K, et al. Arch Dis Child 2017;102:179

Table 1 International reported practices of food introduction in infants

Country	Year data collected	Reference	Proportion of infants introduced to solids before 4 months	Proportion of infants introduced to solids after 6 months	Proportion of infants introduced to allergenic foods before 6 months	Proportion of infa introduced to alle foods by 8–10 mo
Australia	2008–2010	Koplin *et al*[34]	4%	5%		
France	2003–2006	de Lauzon-Guillain *et al*[35]	~30%	~30%		
Germany	2002–2006	Tromp *et al*[36]		55%	69% cow's milk; 21% hen's egg; 15% peanuts; 13% tree nuts; 29% soy	
Greece	2005–2007	de Lauzon-Guillain *et al*[35]	~4%	~10%		
Ireland	2008–2012	O'Donovan *et al*[37]	18% (<17 weeks)	3% (>26 weeks)	57% cow's milk; 57% gluten (wheat (39%), barley (13%), rye (16%)); 40% soy; 8% egg; 6% fish; 6% kiwi	n/a
Portugal	2005–2006	de Lauzon-Guillain *et al*[35]	~5%	~20%		
UK	2010* 2006–2008‡	Lennox *et al*;[38] †McAndrew *et al*;[39] Grimshaw and Roberts[40]	43% 36.6%‡	 1.7%	54% cow's milk; 42% wheat; 10% hen's egg; 19% fish; 6% kiwi; 0.5% peanuts‡	8% (peanuts)
USA	2005–2007	Luccioli *et al*[41]	34%		70% cow's milk; 0.9% hen's egg; 0.5% peanuts; 0.7% soy; 0.2% fish	

Modifying the infant's diet to prevent food allergy.

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Germany	2002–2006	Tro			21% hen's egg; e nuts;	
Greece	2005–2007					
Ireland	2008–2012				en), gg;	n/a
Portugal	2					
UK	2					8% (peanuts)
	20				kiwi;	
USA	2005				n's egg; y; 0.2% fish	

Even well designed observational birth cohort studies cannot determine causality, only associations.
Nevertheless, anecdotal or observational evidence points to lower allergy rates in countries where consumption of dietary allergens as complementary foods starts at an earlier age.

Modifying the infant's diet to prevent food allergy.

Grimshaw K, et al. Arch Dis Child 2017;102:179

The question

Is there a causal relationship between early consumption and reduced risk of food allergy?

3 RCTs have reported fully:

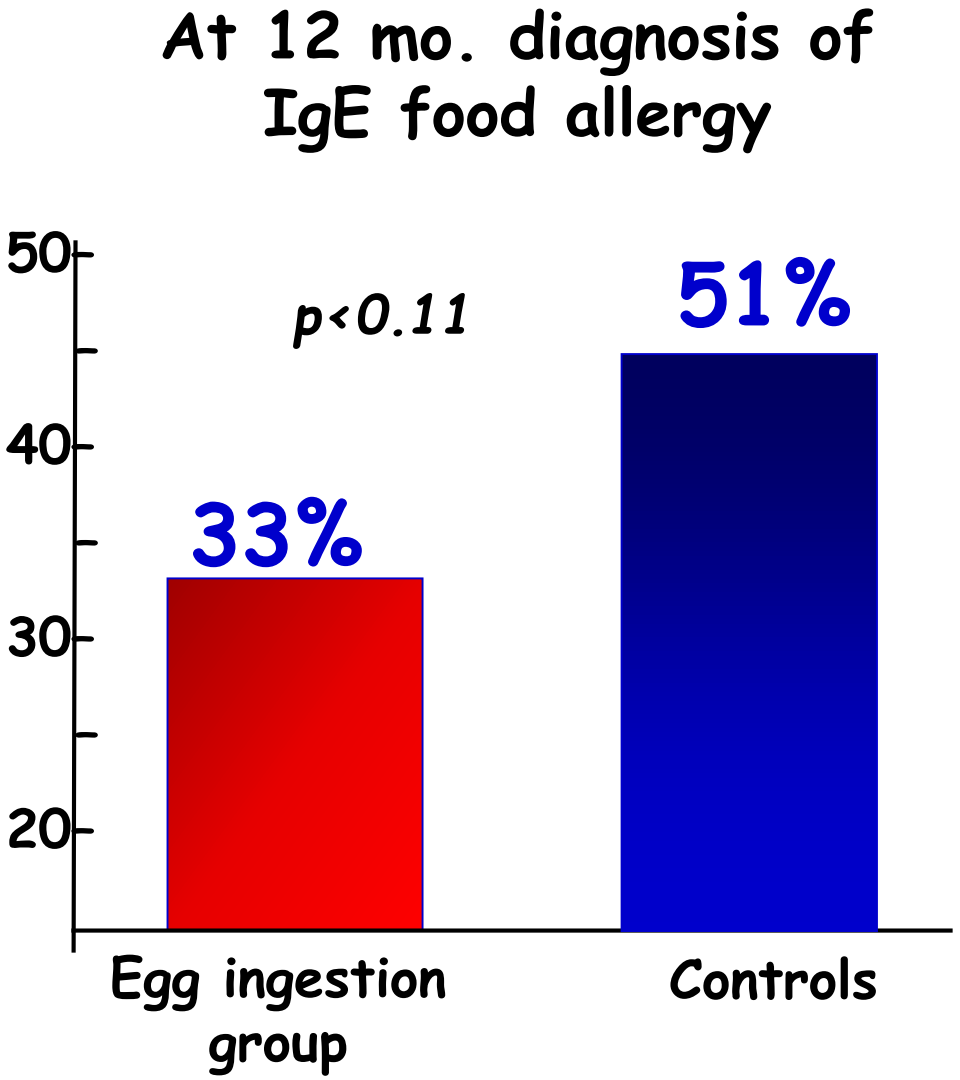
- Solids Timing for Allergy Research (**STAR**),
- Learning Early About Peanut (**LEAP**)
- Enquiring About Tolerance (**EAT**).

Palmer DJ, Early regular egg exposure in infants with eczema: a randomized controlled trial.

J Allergy Clin Immunol 2013;132:387

The Solids Timing for Allergy Research STAR Study enrolled 86 high risk infants aged 4-6 months with moderate/severe eczema.

Infants received egg powder



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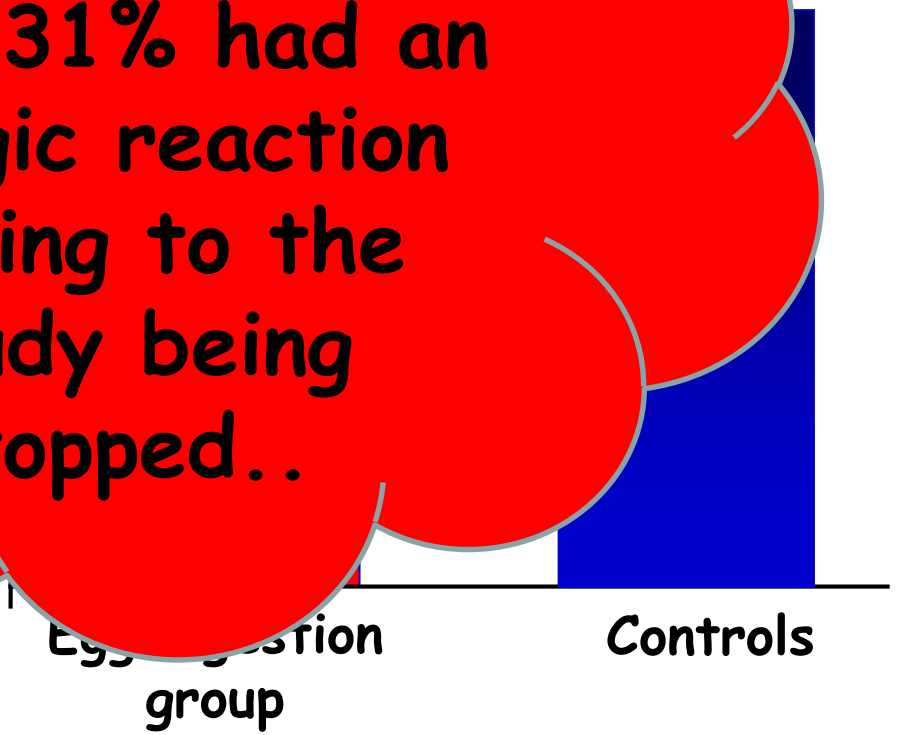
The Solids Timing for Allergy Research STAR Study enrolled 86 high risk infants aged 4-6 months with moderate/severe eczema.

Infants received egg powder

At 12 mo. diagnosis of IgE food allergy

But in the active group 31% had an allergic reaction leading to the study being stopped..



Randomized trial of peanut consumption in infants at risk for peanut allergy. Du Toit G, N Engl J Med 2015;372:803

The LEAP Study (Learning early about Peanut)

530 high risk infants

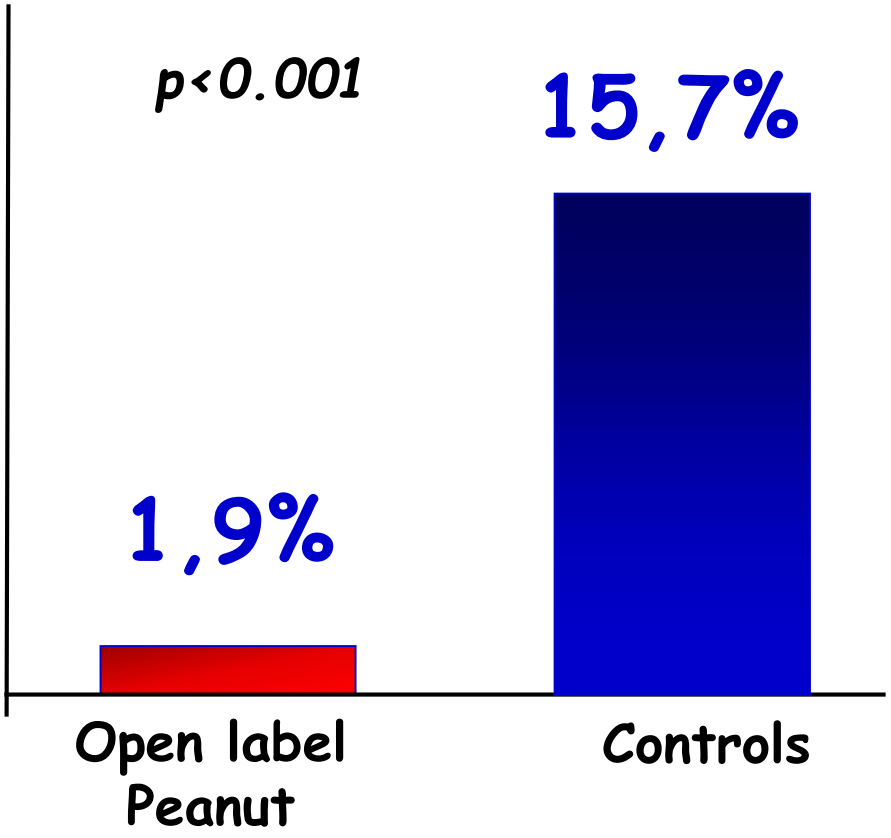
moderate/severe eczema and/or egg allergy

Aged 4-11 mo.

Open label peanut consumption or placebo

At 5 yrs DBPCC

Peanut allergy at DBPCC at 5 yrs



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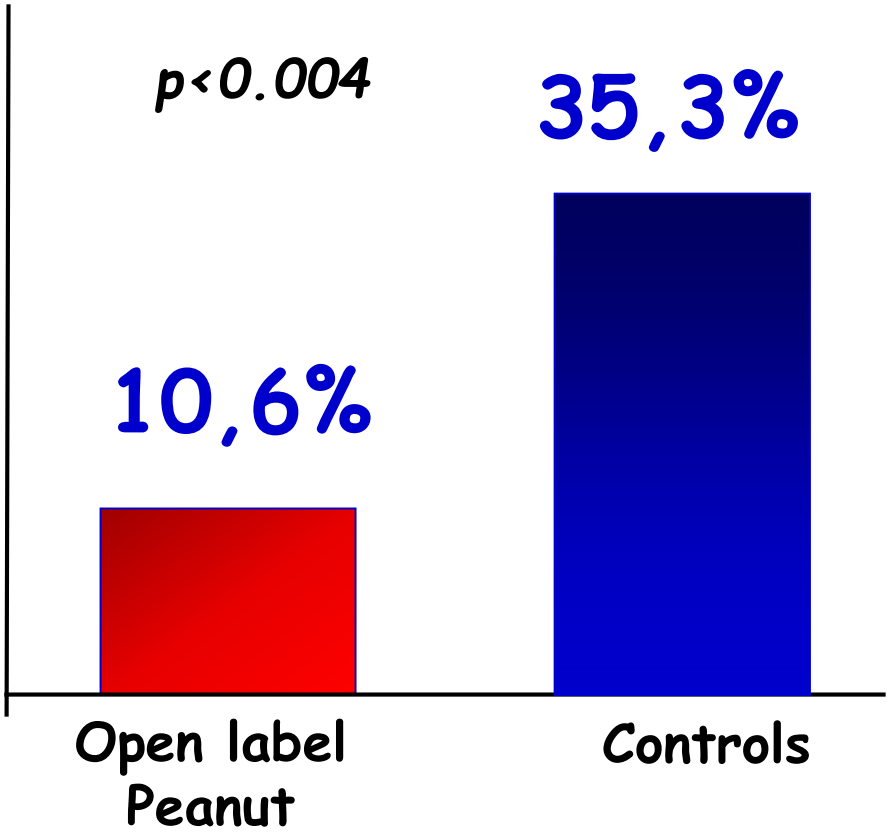
Peanut allergy in 98 with SPT peanut positivity



Randomized trial of peanut consumption in infants at risk for peanut allergy. Du Toit G, N Engl J Med 2015;372:803

Peanut allergy in 98 with SPT peanut positivity

The LEAP Study (Learning early about Peanut)

530 high risk

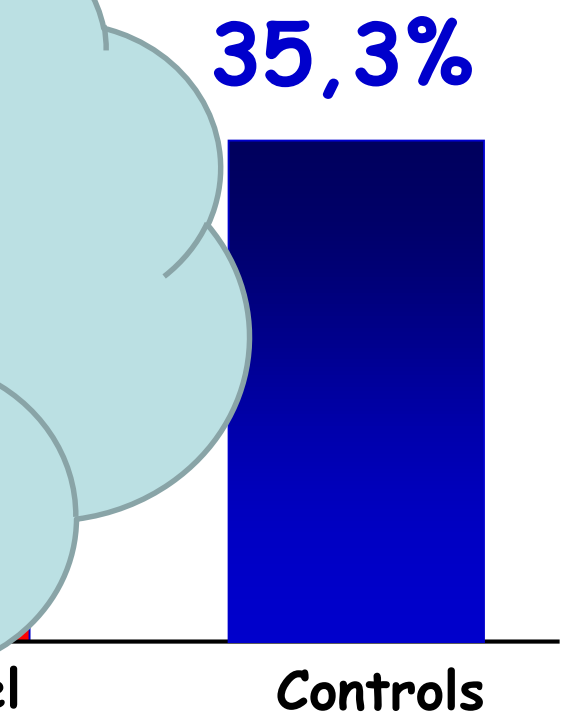
moderate
and/or e

Aged 4-1

Open label
consumption or

At 5 yrs DBPCC

Findings led to a consensus communication, providing interim guidance on early peanut introduction and the prevention of peanut allergy in high risk

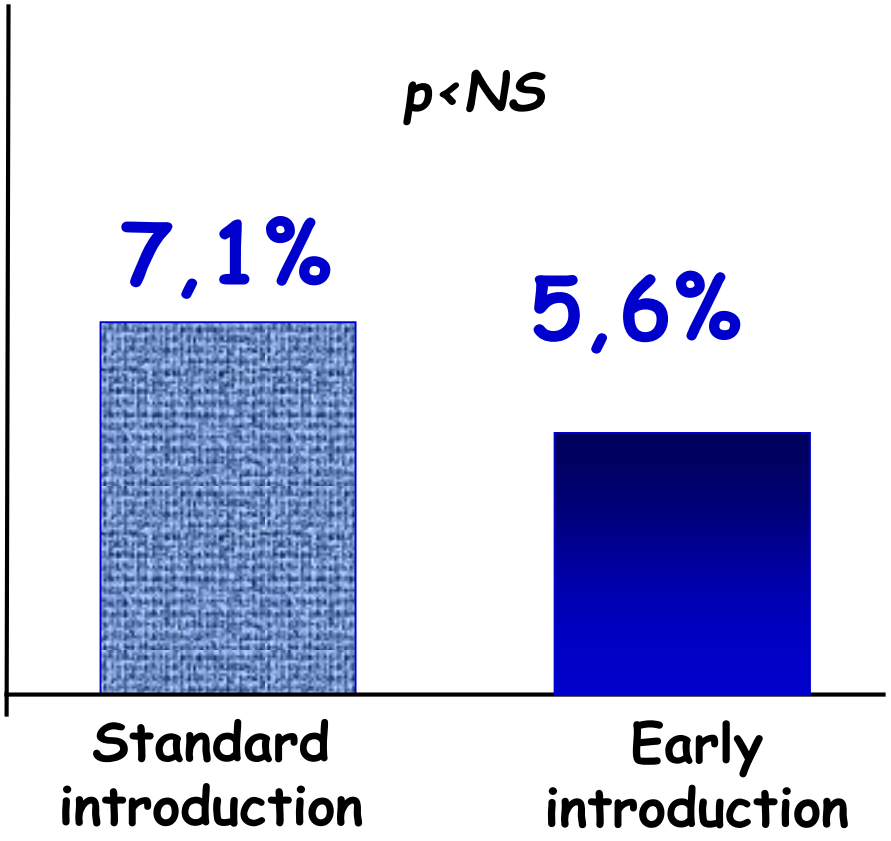


Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. Perkin, N Engl J Med 2016;374:1733

Enquiring about Tolerance (EAT) Study.

1303 exclusively breast-fed infants who were **3 months of age** and randomly assigned them to the **early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat**; early-introduction group) or to the current practice recommended in the United Kingdom of exclusive breast-feeding to approximately 6 months of age (standard introduction group).

Food allergy at 1 of the 6 foods between 1-3 yrs



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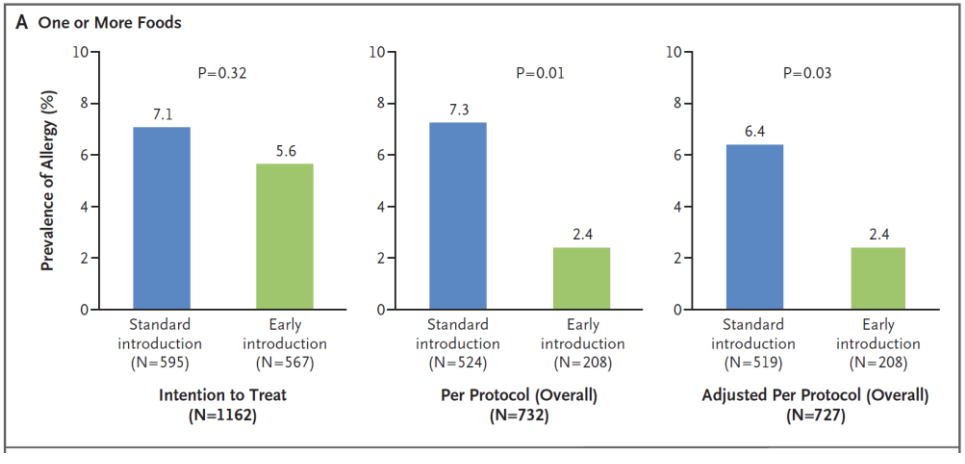
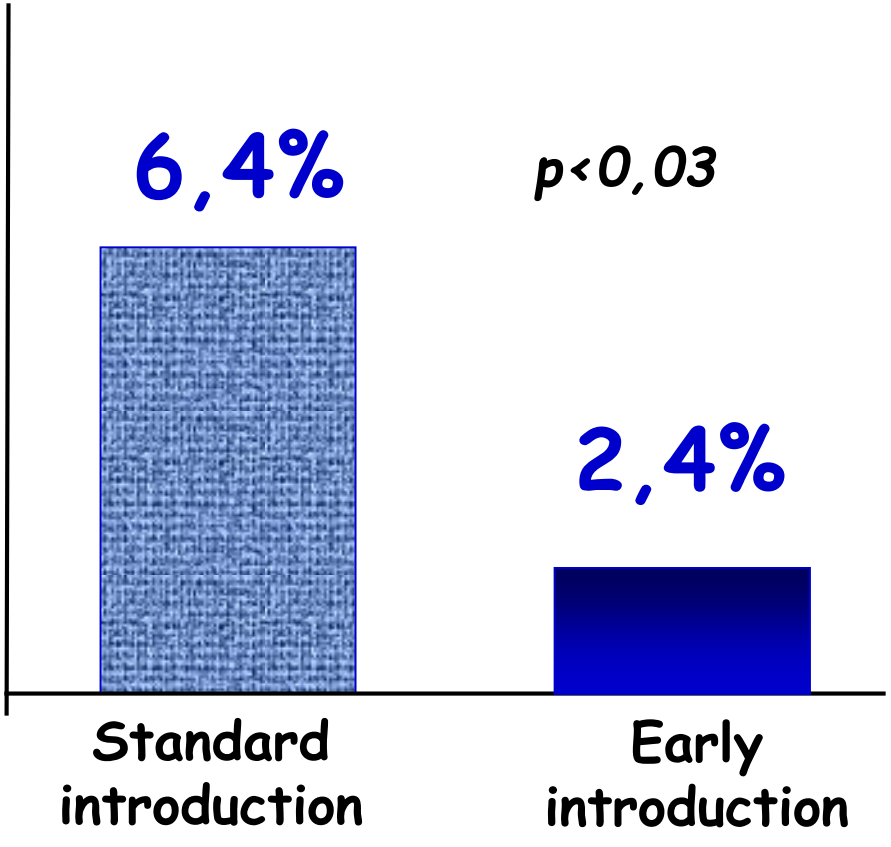
Enquiring about Tolerance (EAT) Study.

However, when the analysis was adjusted for <u>adherence to early introduction</u> ..

Food allergy at 1 of the 6 foods between 1-3 yrs

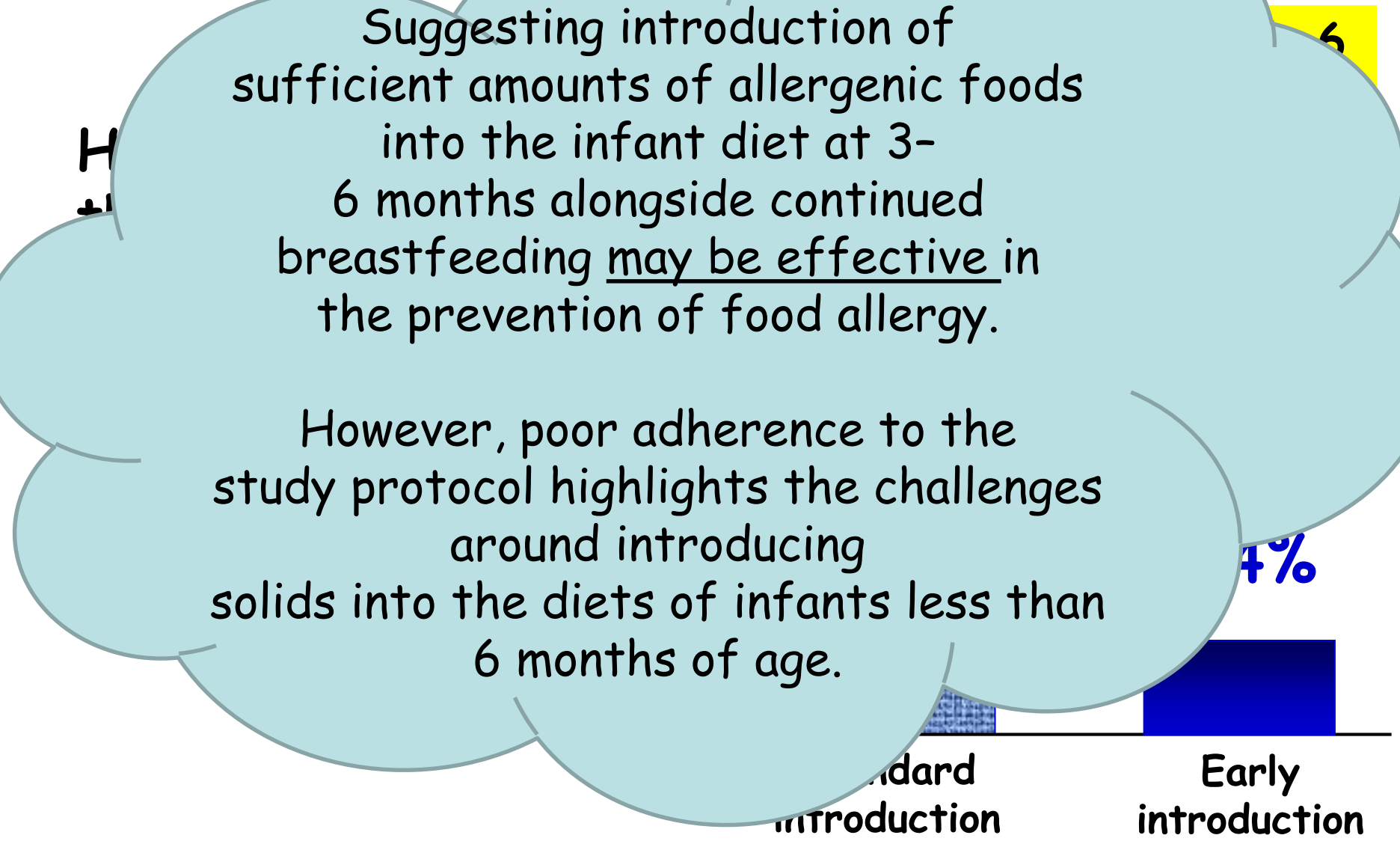




Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. Perkin, N Engl [illegible] 2016 [illegible]733

Suggesting introduction of sufficient amounts of allergenic foods into the infant diet at 3-6 months alongside continued breastfeeding may be effective in the prevention of food allergy.

However, poor adherence to the study protocol highlights the challenges around introducing solids into the diets of infants less than 6 months of age.



Randomized controlled trial of early regular egg intake to prevent egg allergy.

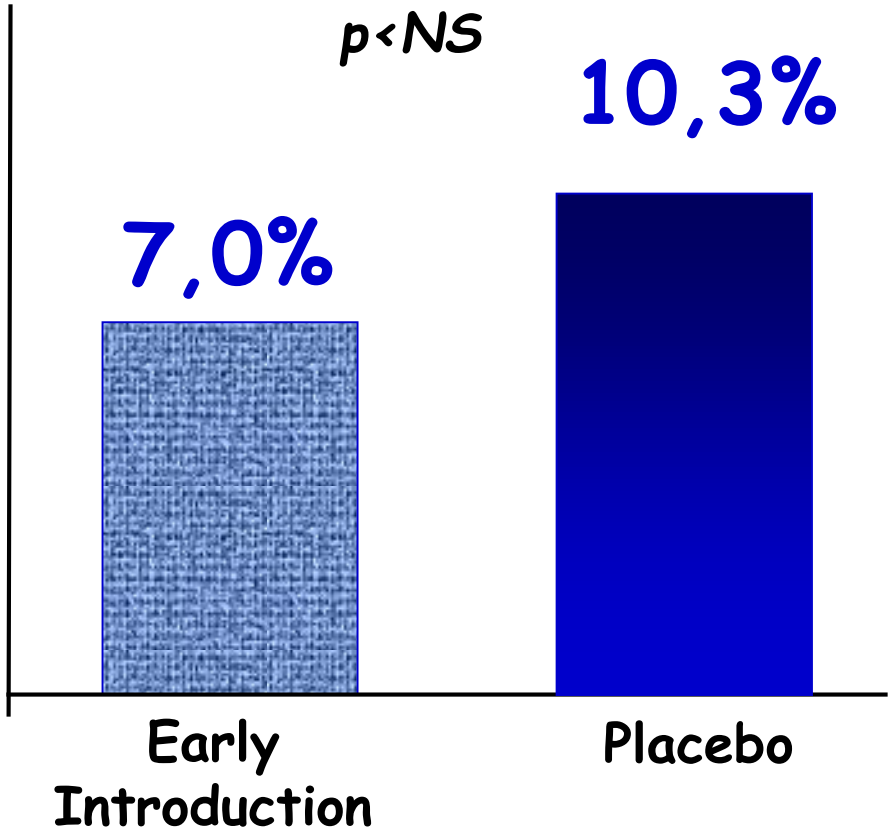
D Palmer JACI 2017

The Starting Time of Egg Protein (STEP) trial.

Infants aged 4 to 6 months were randomly allocated to receive daily pasteurized raw whole egg powder (n 407) or a color-matched rice powder (n 513) to age 10 months

The primary outcome was **IgE-mediated egg allergy** defined by a positive pasteurized raw egg challenge and egg sensitization at age 12 months

Infants with IgE-mediated egg allergy



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Infants aged
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The p
IgE-m
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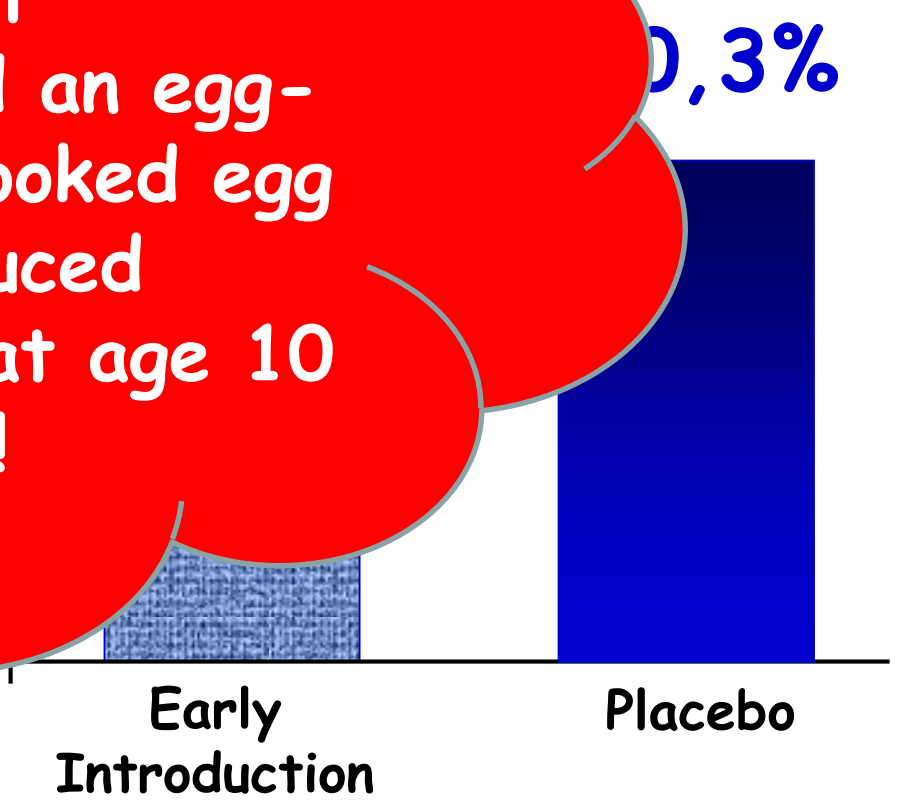
pasteurized raw
egg challenge and egg
sensitization at age 12 months

Infants with IgE-mediated egg allergy

..but all infants followed an egg-free diet and cooked egg was introduced to both groups at age 10 months!



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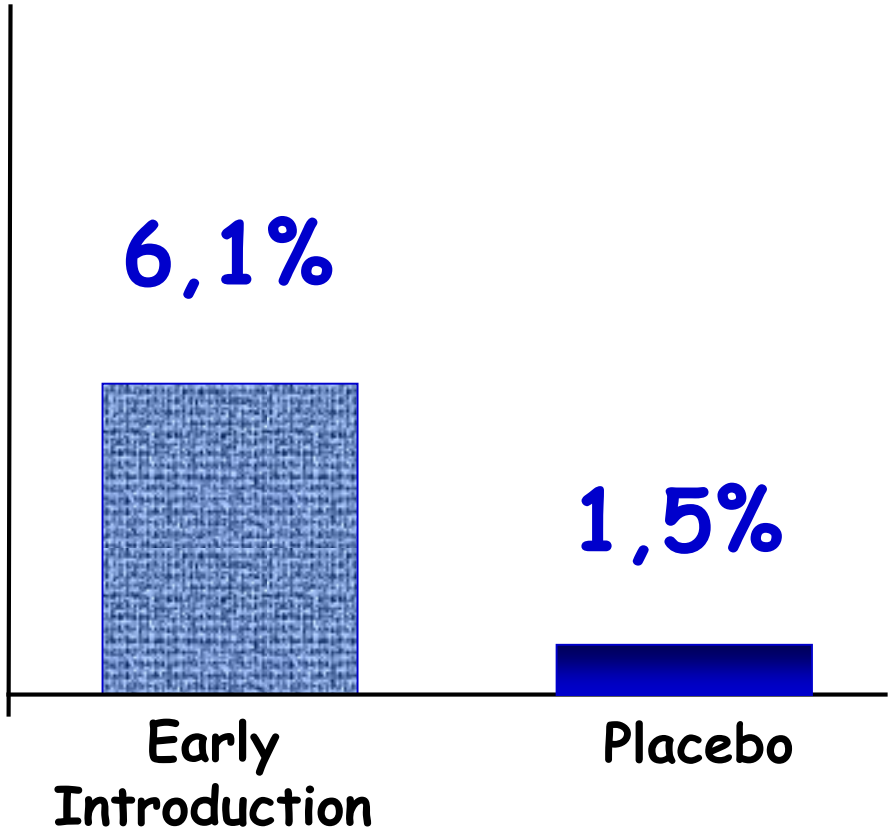

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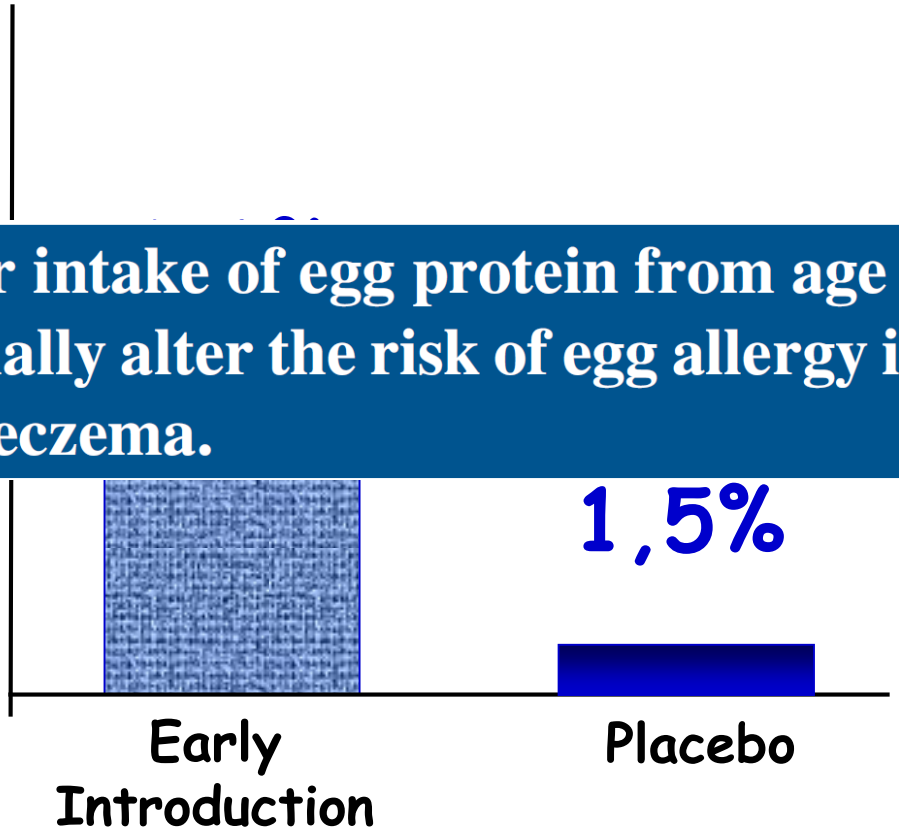
(n 5

The
IgE-mediated egg allergy defined by a positive pasteurized raw egg challenge and egg sensitization at age 12 months

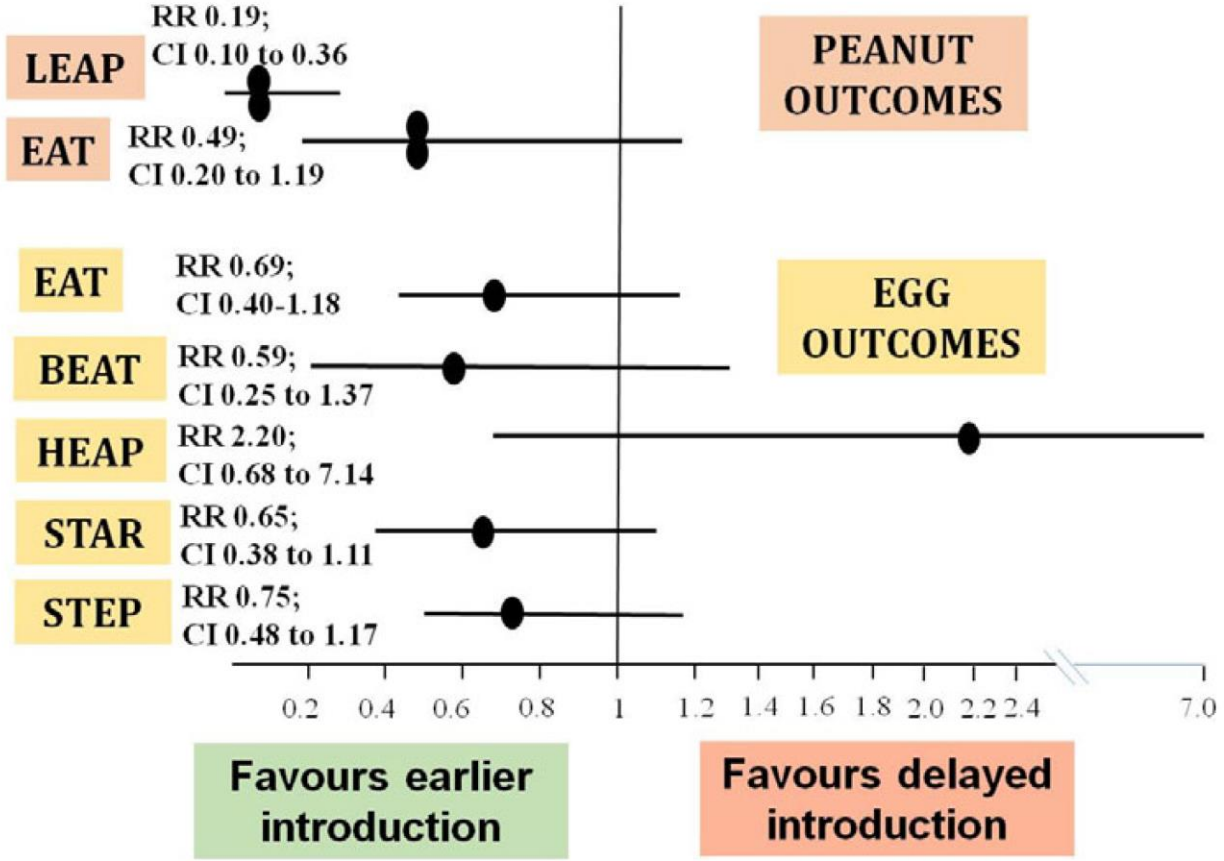
Clinical implications: Regular intake of egg protein from age 4 to 6 months does not substantially alter the risk of egg allergy in infants without symptoms of eczema.



Early introduction of food reduces food allergy – Pro. Palmer PAI 2017

Findings from randomised controlled trials investigating the timing of commencement of regular inclusion of peanut and/or egg in infant diets on food allergy outcomes:

Enquiring About Tolerance (EAT), Learning Early About Peanut Allergy (LEAP), Beating Egg Allergy Trial (BEAT), Hen's Egg Allergy Prevention(HEAP), Solids Timing for Allergy Reduction (STAR), and Starting Time of Egg Protein (STEP) trials.



Preventing Food Allergy in Infancy — Early Consumption or Avoidance?

Gary W.K. Wong, M.D.

In the EAT trial, the rate of adherence was the highest for dairy products in the form of yogurt, as opposed to textural food such as egg. This difference may well be due to the rather immature oral motor skills of young infants at 3 to 4 months of age and also to concerns of the parents about choking.

If feeding these foods is safe,

-What is the minimal amount needed for inducing tolerance to these foods?

-Will the regimen be as effective if we introduce these foods at a later age but early enough before sensitization may occur?

-How can we improve the preparation of foods to make them easier for parents to administer?

Preventing Food Allergy in Infancy — Early Consumption

Evidence is building that early consumption rather than delayed introduction of foods is likely to be more beneficial as a strategy for the primary prevention of food allergy. **So feed your children and hope that they will EAT.**

In the EAT st for dairy product food such as egg. Th ature oral motor s d also to concerns

If feed

-What is t g tolerance to these foods?

-Will the regimen be as ef e introduce these foods at a later age but early enough before sensitization may occur?

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IN SUPREMÆ DIGNITATIS 1343

Frequency, severity and causes of unexpected allergic reactions to food: a systematic literature review

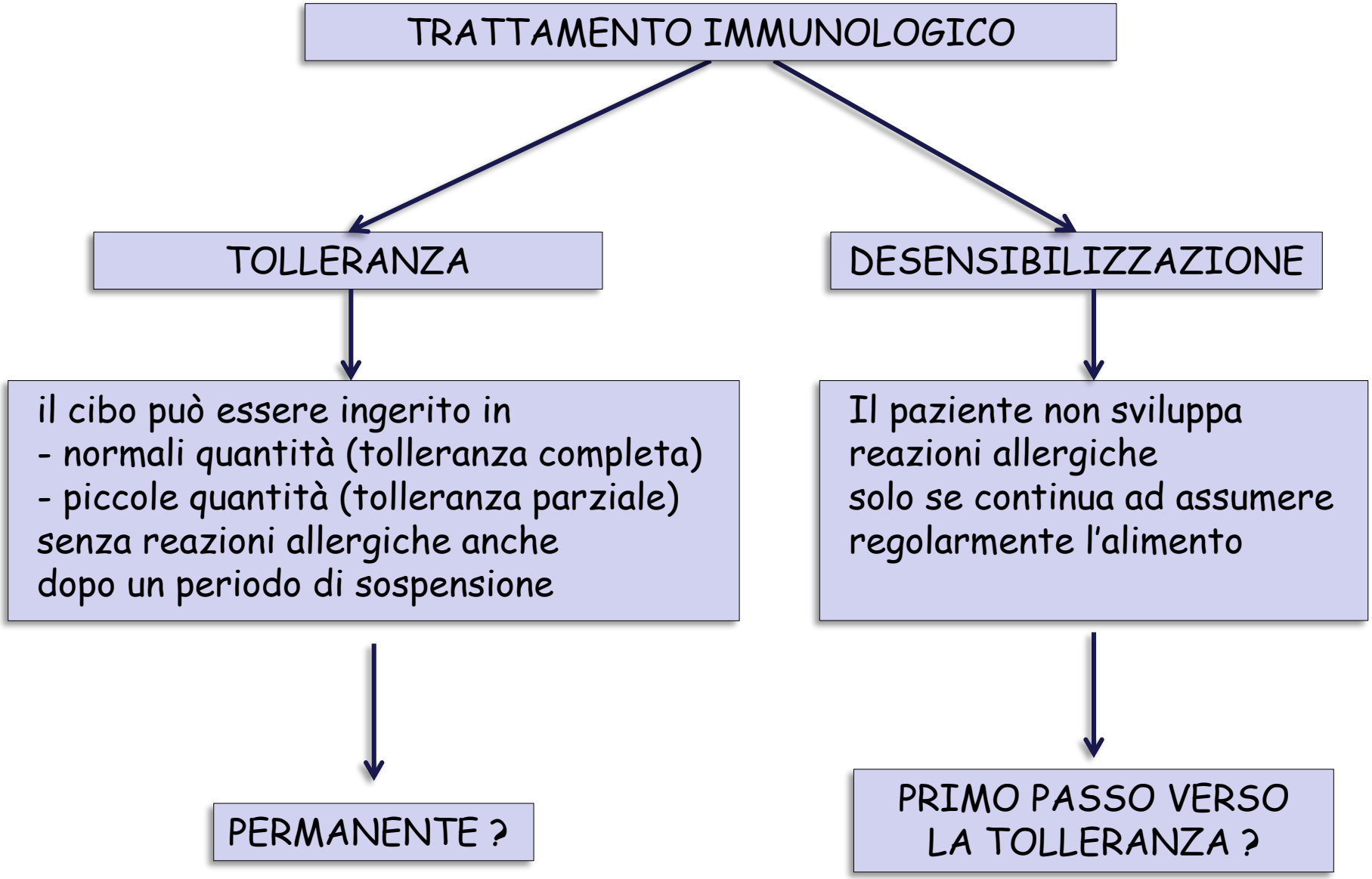
Versluis A, CEA 2015;45:347-367

- ✓ 24 studies (18 observational, 6 qualitative)
- ✓ food allergic patients aged > 12 years
- ✓ frequency, severity and causes of unexpected allergic reactions to food

1. the main causal foods: peanut, nuts, egg, fruit/vegetables, milk

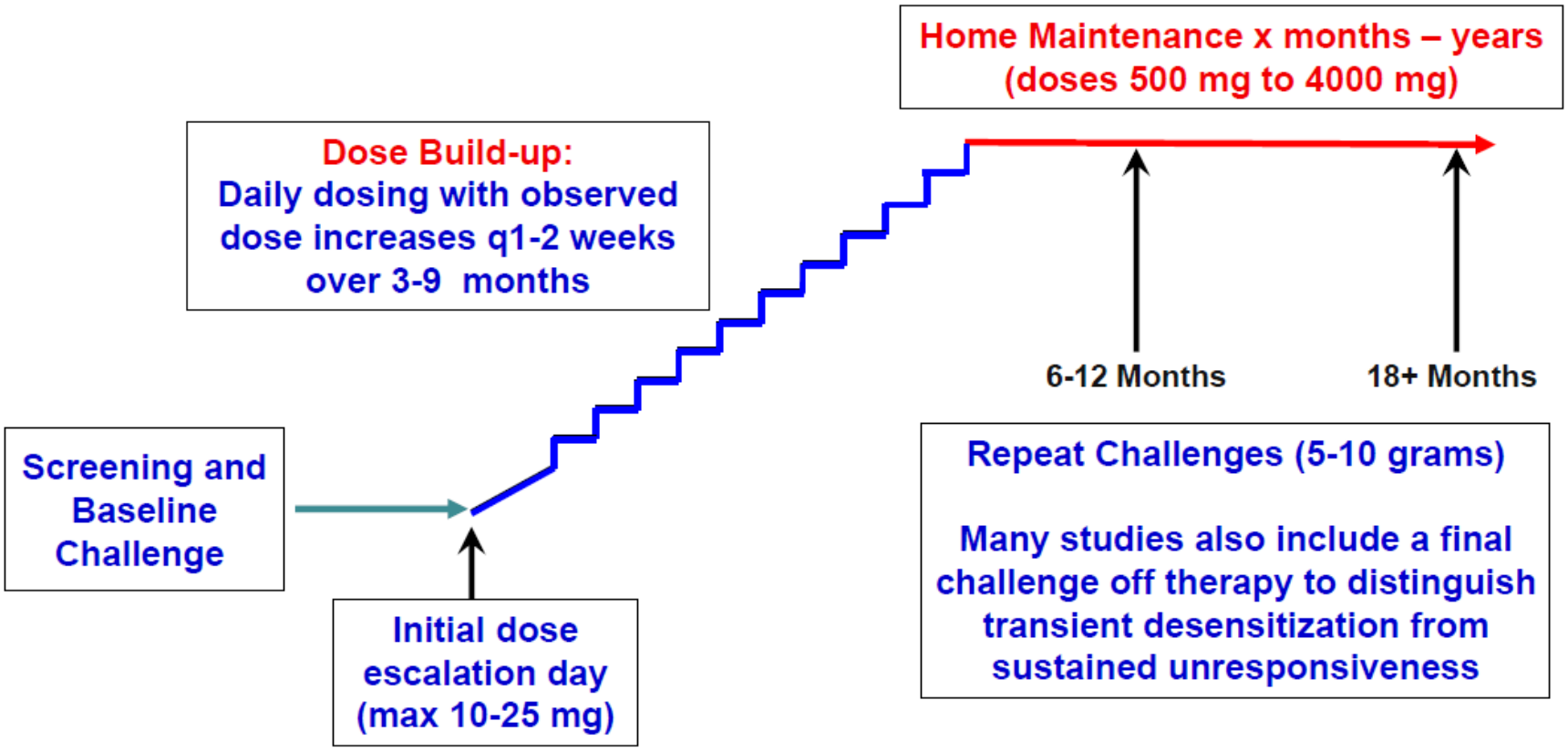
2. severe reactions and fatalities occur
3. most reactions place at home, but a significant number also place when eating at friends' houses or in restaurants
4. labelling issues, but also attitude and risky behaviour of patients can attribute to unexpected reactions

IMMUNOTERAPIA ORALE



Food allergen immunotherapy: Current status and prospects for the future. R Wood JACI 2016; 137: 973.

Schematic representation of the typical approach to OIT. For SLIT, the overall scheme is similar, with far lower goal doses and a somewhat more rapid dose build-up.



Food allergen immunotherapy: Current status and prospects for the future. R Wood JACI 2016; 137: 973.

TABLE III. Milk OIT studies

Reference	Year	Design	Samples size	Subject age (y)	Maintenance dose	Duration	Primary outcome
Meglio et al[36]	2004	Open label	21	6-10	200 mL	6 mo	72% Desensitization to 200 mL of cow's milk daily
Longo et al[37]	2008	Randomized, open label	30	5-17	150 mL	10-d Rush escalation, 1 y of maintenance	36% Tolerant (≥150 mL) and 54% partially tolerant (5-150 mL)
Skripak et al[38]	2008	Randomized, placebo controlled	13	6-17	500 mg	23 wk	Median OFC threshold increased from 40 to 5,140 mg after OIT
Narisety et al[31]	2009	Open label (follow-up)	13	6-16	500-4,000 mg	3-17 mo	Median OFC threshold of 7,000 mg (with 33% tolerating 16,000 mg)
Pajno et al[40]	2010	Randomized, placebo controlled	15	4-10	200 mL	18 wk	67% Tolerant to 200 mL of cow's milk
Martorell et al[39]	2011	Randomized, placebo controlled	30	2-3	200 mL	1 y	90% Showing complete desensitization
Keet et al[25]	2012	Randomized, placebo controlled	20 for OIT	6-17	1,000-2,000 mg	60 wk	70% Desensitized to 8-g OFC, SU in 40% after 6 wk
Wood et al[41]	2015	Omalizumab DBPC, open-label OIT	57	7-32	3,300 mg	24 mo	80% Desensitized to 10-g OFC, SU in 42% after 8 wk

Food allergen immunotherapy: Current status and prospects for the future.

R Wood JACI 2016; 137: 973.

TABLE IV. SLIT studies

Reference	Year	Food	Design	Sample size	Subject age (y)	Maintenance dose (mg)	Duration	Primary outcome
Enrique et al[21]	2005	Hazelnut	Randomized, placebo controlled	23	19-53	13.25	8-12 wk	Significant increase in OFC threshold with active SLIT
Kim et al[71]	2011	Peanut	Randomized, placebo controlled	18	2-10	2.5	12 mo	OFC threshold 20 times greater SLIT vs placebo (median, 1710 vs 85 mg)
Fleischer et al[72]	2013	Peanut	Randomized, placebo controlled	37	12-36	1.4-3.7	44 wk	70% Receiving peanut SLIT were responders vs 15% receiving placebo
Keet et al[25]	2012	Milk	Randomized, SLIT vs OIT	10 for SLIT	6-17	7	60 wk	Median OFC threshold increased 40-fold (2458 mg) from baseline
Narisety et al[31]	2015	Peanut	DBPC SLIT vs OIT	20	7-13	3.7	12 mo	Median OFC threshold increased from 21 to 496 mg
Burks et al[73]	2105	Peanut	Open label (follow-up)	37	12-36	1.4-3.7	36 mo	Four (10.8%) of 37 desensitized to 10 g of peanut powder, all 4 with SU

Specific oral tolerance induction in children with very severe cow's milk-induced reactions (Longo: JACI 2008; 121: 343-7)

PROTOCOLLO

RASH PHASE: in ospedale

- Durante il primo giorno: intervalli di un'ora tra le dosi
- Successivamente: intervalli di due ore
- Oxatomide 1 mg/Kg/die durante tutto il trattamento

4 reazioni gravi con necessità di adrenalina im

TABLE III. In-hospital treatment schedule: Rush phase

Day	Dilution	Doses
1	1 drop of CM in 10 mL of water	5 drops, 10 drops, 1 mL, 2 mL, 5 mL, 10 mL
2	5 drops of CM in 20 mL of water	2 mL, 4 mL, 8 mL, 16 mL
3	1 mL of CM in 20 mL of water	2 mL, 4 mL, 8 mL, 12 mL
4	3 mL of CM in 20 mL of water	3 mL, 6 mL, 9 mL, 10 mL
5	10 mL of CM in 20 mL of water (1:3)	3 mL, 6 mL, 9 mL
6	10 mL of CM in 10 mL of water (1:2)	3 mL, 6 mL, 9 mL
7	No dilution: pure CM (1:1)	2 mL, 4 mL, 6 mL
8	No dilution: pure CM (1:1)	4 mL, 7 mL, 10 mL
9	No dilution: pure CM (1:1)	8 mL, 12 mL, 15 mL
10	No dilution: pure CM (1:1)	13 mL, 16 mL, 20 mL

Doses were administered at 1-hour intervals on the first day and at 2-hour intervals on subsequent days (from the second to the 10th day).
CM, Cow's milk.

Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy (Martorell: CEA 2011; 41: 1297)

PROTOCOLLO

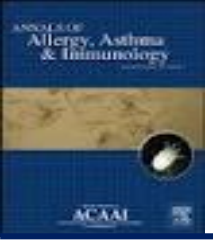
- Aumento delle dosi in ospedale
- Mantenimento a domicilio
- Totale: 16 settimane
- Monitoraggio stretto

	Milk (dilution)	Dose (mL)
Day 1	1/100	1
In hospital		2
Doses hourly		4
		8
	1/10	1.6
Day 2	1/10	1.6
In hospital		3.2
Doses		6
hourly		12
	Pure	2.5
Dose maintained at home, with elevation	Pure	4
once a week in hospital		6
Total 16 weeks		8
		10
		12
		15
		20
		25
		30
		40
		50
		75
		100
		125
		150
		200

tolleranza completa: >200 ml di latte

tolleranza parziale: 20-200 ml di latte

non tolleranza: <20 ml di latte



Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study Pajno 2010; Ann Allergy and Clin Immunol:105: 376-381

PROTOCOLLO

- 18 settimane di trattamento
- dose raddoppiate

  ogni settimana in ospedale

Table 1. Oral Immunotherapy Protocol

Day/week	Dose No.	Volume
1/1	1	1 drop[a]
7/2	2	2 drops[a]
14/3	3	4 drops[a]
21/4	4	8 drops[a]
28/5	5	16 drops[a]
35/6	6	32 drops[a]
42/7	7	64 drops[a]
49/8	8	5 drops[b]
56/9	9	10 drops[b]
63/10	10	20 drops[b]
70/11	11	2 mL[b]
77/12	12	4 mL[b]
84/13	13	8 mL[b]
91/14	14	16 mL[b]
98/15	15	32 mL[b]
105/16	16	64 mL[b]
112/17	17	128 mL[b]
119/18	18	200 mL[b]

[a] Cow's milk diluted 1:25.
[b] Undiluted CM.

DESENSIBILIZZAZIONE FRUTTA A GUSCIO (es. nocciola):

T0: **giorno 1:** prick test, prick by prick, somministrazione per os da 1-2 mg fino a circa 10 mg (ogni 30 min),
giorno 2: somministrazione per os da 10 fino a circa 25 mg (ogni 30 minuti)

T1: dopo 2-3 mesi:
giorno 1: dalla dose "casalinga" fino a 40 mg (ogni 30 min)
giorno 2: da 40 mg fino a 50 mg (ogni 30 min)

T2: dopo 4-5 mesi:
giorno 1: dalla dose "casalinga" fino a 100-120 mg (ogni 30 min)
giorno 2: da 100-120 fino a 180-200 (ogni 30 min)

T3: dopo 6-7 mesi:
giorno 1: dalla dose "casalinga" fino a 300 mg (ogni 30 min)
giorno 2: da 300 fino a 400 (ogni 30 min)

T4: dopo 8-10 mesi:
giorno 1: dalla dose "casalinga" fino a 500 mg (ogni 30 min)
giorno 2: da 500 fino a 600 (ogni 30 min)

T5: dopo 12 mesi:
giorno 1: dalla dose "casalinga" fino a 900 mg (ogni 30 min)
giorno 2: da 900 fino a 1200 mg (ogni 30 min)

NB: a casa i genitori devono continuare a fare ingerire gli alimenti meglio se tutti i giorni, ma comunque almeno 2-3 volte la settimana. Devono iniziare per le prime 3 volte con la terzultima dose, poi 3 volte con la penultima e poi con l'ultima dose raggiunta in ambulatorio per i 2-3 mesi successivi.

Arrivati ad una dose accettabile per cui anche la contaminazione non sarebbe un problema ci si può fermare

La dieta del bambino allergico:
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Diego Peroni

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La dimensione del problema

La dieta con latti speciali

Lo svezzamento

Le scelte possibili

Conclusioni

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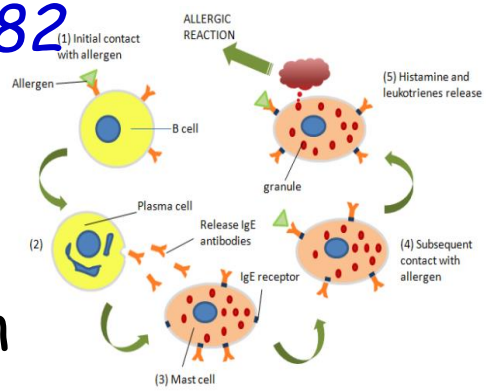
Factors augmenting allergic reactions

Niggemann B, Allergy 2014;69:1582



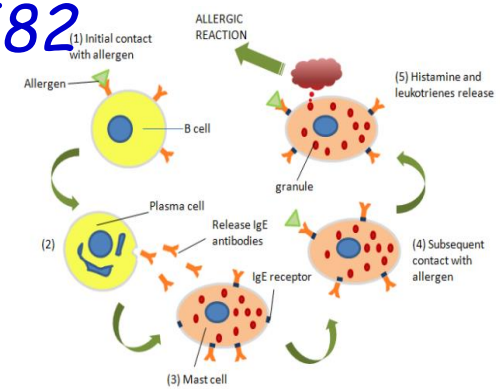
- Augmenting factors may explain why certain conditions lead to anaphylaxis.

- Augmenting factors may exhibit 3 effects:
  1) lowering the threshold,
  2) increasing the severity, and
  3) reversing acquired clinical tolerance.

- Common augmenting factors are
  - physical exercise,
  - menstruation,
  - NSAIDs,
  - alcohol,
  - body temperature,
  - acute infections,
  - antacids.

Factors augmenting allergic reactions

Niggemann B, Allergy 2014;69:1582



Therapeutic options may address causative, preventive, pragmatic, or symptomatic considerations:

- avoid the eliciting food
- take an antihistamine before any situation with a possible risk of augmentation
- separate food and sport (at least for 2 h)
- carry an adrenaline autoinjector at all times

Modifying the infant's diet to prevent food allergy.

Grimshaw K, et al. Arch Dis Child 2017;102:179

Table 3 Intervention trials with food allergy as a primary or secondary outcome

Nutrient	Study name	Location	Recruitment status	Identifier
Vitamin D	The VITALITY trial	Australia	Recruiting	NCT02112734
Vitamin A	Vitamin A supplementation at birth and atopy in childhood	Guinea Bissau	Active	NCT01779180
PUFAs	DHA to Optimise Mother Infant Outcomes (DOMInO) trial	Australia	Completed	ACTRN12605000569606
PUFAs	The Infant Fish Oil Supplementation (IFOS) trial	Australia	Active	ACTRN12606000281594
PUFAs	Can supplementation with *Lactobacillus reuteri* and omega-3 fatty acids during pregnancy and lactation reduce the risk of allergic disease in infancy? (PROOM-3)*	Sweden	Recruiting	NCT01542970
Probiotics	Primary prevention of atopic disease by perinatal administration of probiotics	The Netherlands	Completed	NCT00200954
Probiotics	Influence of probiotics on atopy, immunological responses and gut microflora, follow-up to 5 years	Singapore	Completed	NCT00365469
Probiotics	Microbiota as a potential target for food allergy	Italy	Recruiting	NCT02087930
Probiotics	Effect of lactobacillus GG on atopic march	Italy	Recruiting	NCT01891916
Prebiotic	Prebiotics in the Prevention of Atopy (PIPA)	Italy	Completed	NCT02116452

†Atopic sensitisation.
PUFA, polyunsaturated fatty acid.

Diet and asthma: vitamins and methyl donors.

Han Y, Lancet Respir Med 2013; 1:813.

	Potential mechanisms of action	Observational studies	RCTs
Vitamin A	Downregulation of oxidative stress and Th2 (allergic) immune responses	Findings from >20 studies (including three birth cohorts) provide weak evidence for an inverse association between dietary intake and asthma (but not wheeze). Prenatal or postnatal vitamin A supplementation was not significantly associated with asthma, wheeze, or FEV_1/FVC in children. Intake of vitamin A and D (as cod liver oil) was associated with incident asthma in a study of adults	No primary RCT of vitamin A to prevent or treat asthma in children or adults has been done
Vitamin C	Downregulation of oxidative stress and Th2 (allergic) immune responses	Findings from more than 30 studies of postnatal dietary intake suggest an inverse association between vitamin C intake and asthma in children and adults, with generally consistent results for wheeze and airway responsiveness but not asthma severity. When studies of prenatal dietary intake are reviewed along with those of postnatal intake, weak and inconsistent evidence exists of an association between vitamin C intake and asthma or atopy in children	No primary RCT of vitamin C supplementation during pregnancy to prevent asthma has been done. Although nine RCTs have shown no significant evidence for an effect of vitamin C supplementation on indicators of asthma severity or control, none has had adequate statistical power to detect weak to moderate effects of vitamin C on asthma morbidity
Vitamin D	Enhanced steroid responsiveness, antiviral properties, upregulation of T-regulatory cells, prevention of gains in adiposity, effects on lung development or function	Results from six of seven birth cohort studies with sample size >750 mother–child pairs support an inverse association between maternal vitamin D status during pregnancy and asthma or wheeze in childhood. Longer follow-up is necessary to properly assess an association with asthma in all six positive studies. Findings from three studies (one longitudinal) suggest that vitamin D insufficiency or deficiency is associated with increased risk of severe asthma exacerbations	RCTs of vitamin D supplementation during pregnancy to prevent asthma have not been done. Similarly, results of RCTs of vitamin D supplementation to reduce asthma morbidity in children or adults have not been published
Vitamin E	Downregulation of oxidative stress, airway inflammation, and Th2 (allergic) immune responses	Findings from >20 studies of postnatal dietary intake suggest an inverse association between vitamin E intake and physician-diagnosed asthma in children and adults, with inconsistent results for wheeze, self-reported asthma, and airway responsiveness. When studies of prenatal dietary intake are reviewed along with those of postnatal intake, weak evidence exists of an inverse association between vitamin E intake and asthma or atopy in children	No primary RCT of vitamin E supplementation during pregnancy to prevent asthma has been done. Although two RCTs showed no significant effects of vitamin E supplementation on airway responsiveness or inflammatory and immune markers in adults with asthma, other findings support a protective effect of vitamin E supplementation against ozone-induced bronchoconstriction

RCTs=randomised controlled trials. FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. Th2=type 2 helper T cell.

Food allergen immunotherapy: Current status and prospects for the future.

R Wood JACI 2016; 137: 973.


TABLE IV. SI

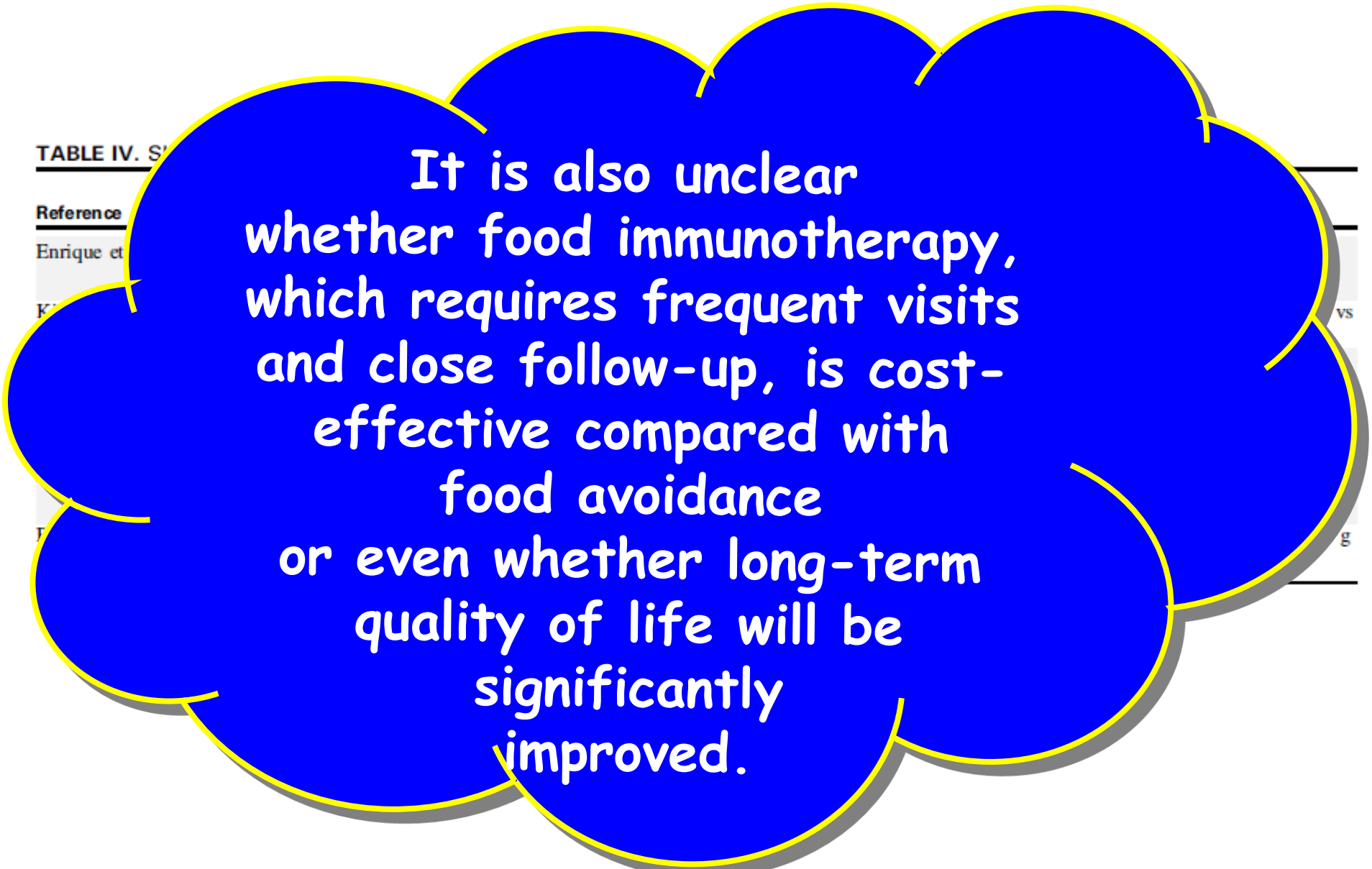
Reference

Enrique et

Personally, I firmly believe
that **many issues need to be addressed before food immunotherapy**
should be used in clinical practice.
Systemic reactions
occur unpredictably during and after
treatment, and at present,
it appears that **OIT actually increases the risk of systemic reactions**
compared with practicing avoidance.

Food allergen immunotherapy: Current status and prospects for the future.

R Wood JACI 2016; 137: 973.



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