

# Weaning: the Optimal Time for Solid Food Introduction for Allergy Prevention

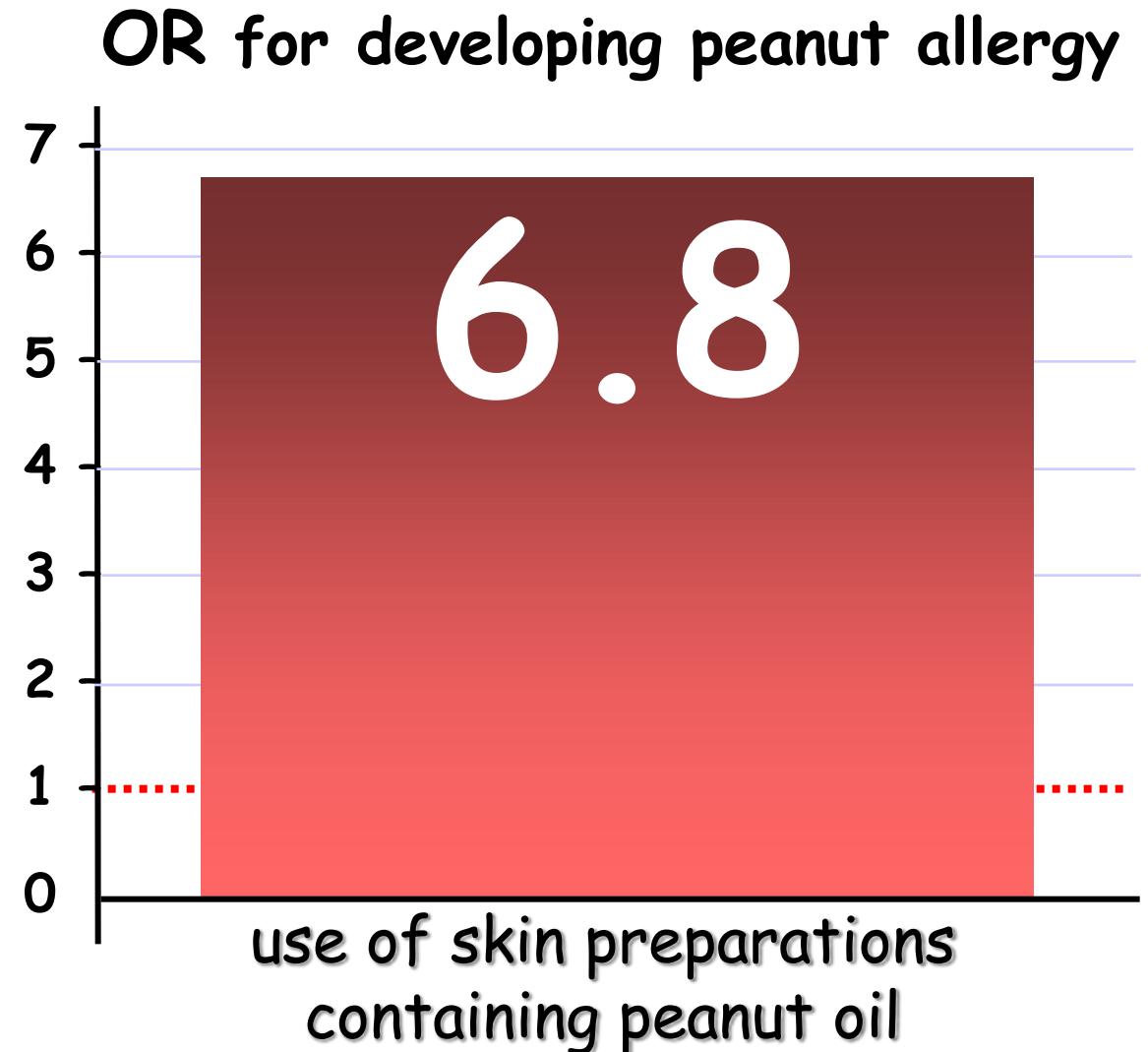
- ✓ introduction
- ✓ starting point
- ✓ old recommendations
- ✓ new findings
- ✓ development of tolerance
- ✓ other possible mistakes
- ✓ not only allergy
- ✓ allergy development?
- ✓ what can be done?
- ✓ conclusions

*Attilio Boner*

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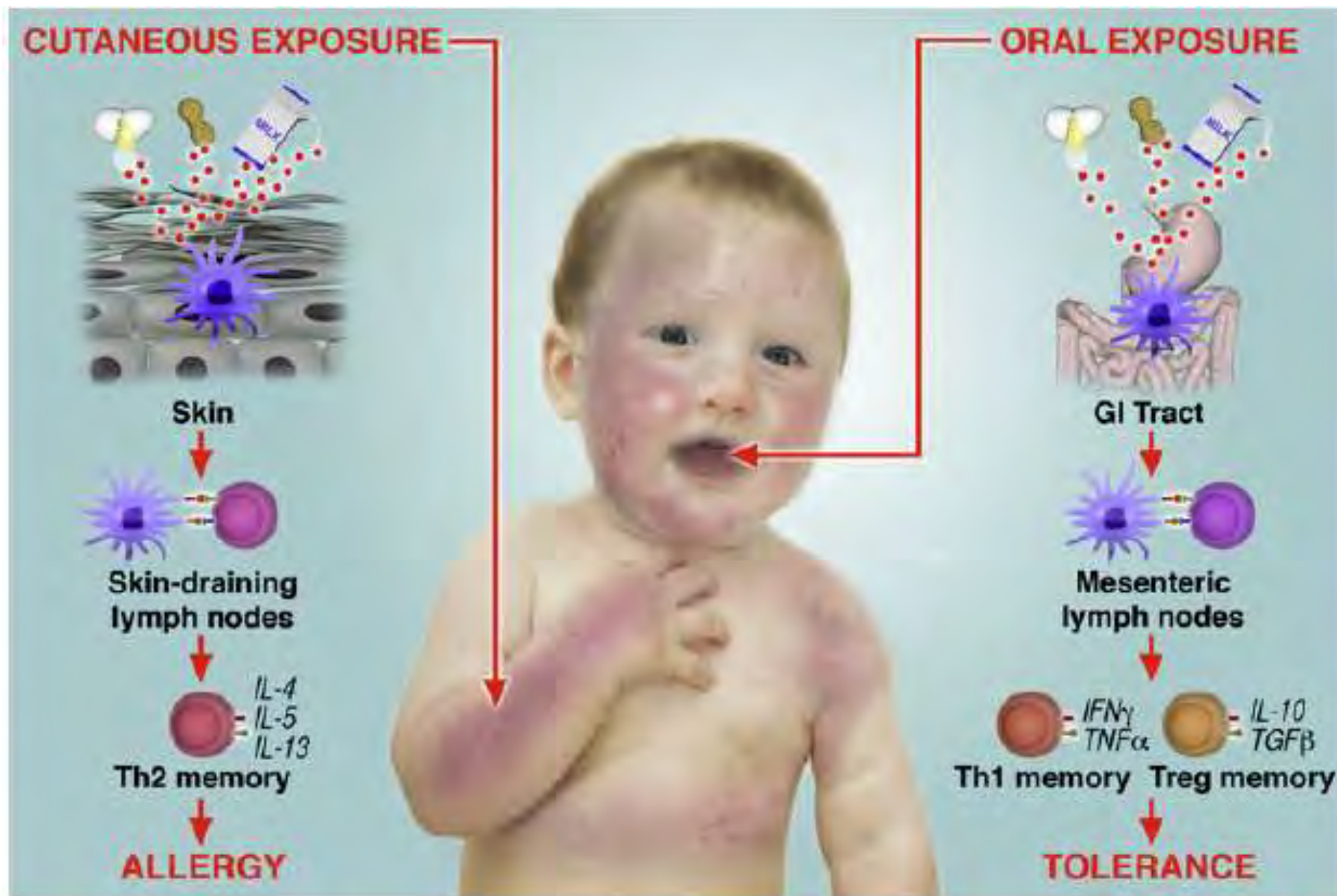
# Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. *Lack G, NEJM 2003;348:977.*

- ✓ 13,971 preschool children,
- ✓ a convincing history of peanut allergy
- ✓ subgroup that reacted to a double-blind peanut challenge.



# Epidemiologic risks for food allergy

*Lack, JACI 2008;121:1331-6*

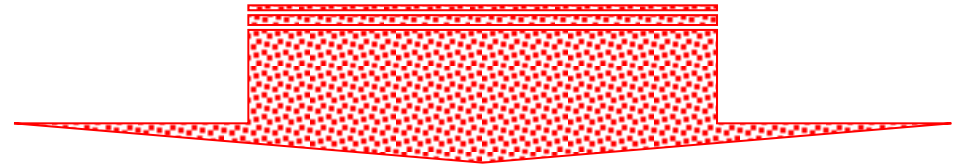


# Atopic dermatitis.

*Bieber T. NEJM 2008;358:1483-94.*



In subjects with early-onset eczema, IgE sensitization often occurs weeks or months after eczematous lesions appear,

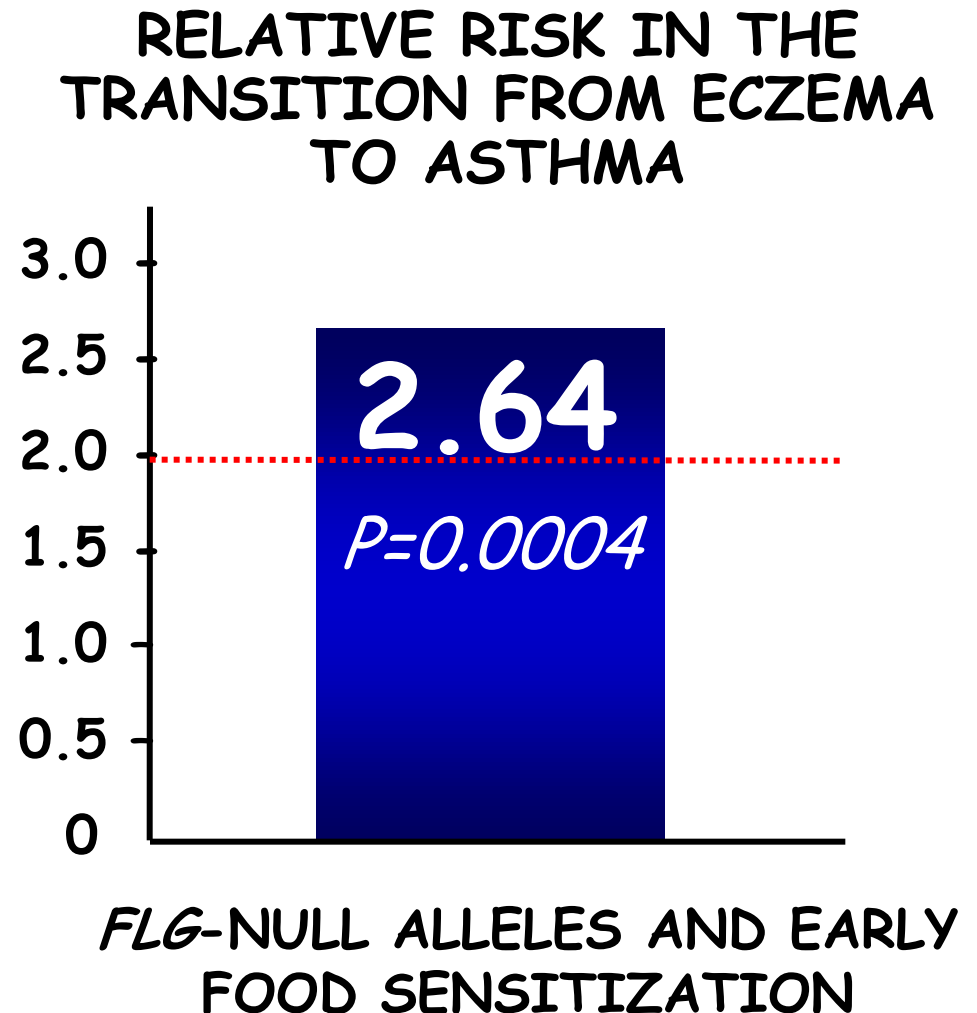


**This suggests the skin as the initial site of allergen introduction.**

# An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma

*Marenholz JACI 2009; 123:911*

- ✓ 871 individuals of the prospective German Multicenter Allergy Study cohort.
- ✓ Genotyped for 3 *FLG* mutations.





# Epidemiologic risks for food allergy

*Lack, JACI 2008;121:1331-6*

There are several **PREDICTIONS** that can be made on the basis of this hypothesis, which can in turn be tested.

One prediction is that **prompt intensive treatment of eczema in early infancy will decrease inflammation in the skin, reduce skin permeability, and prevent allergic sensitization to foods.**

The second prediction is that **reduction of food allergens in the child's environment will lead to a reduction in sensitization.**

However, there is doubt as to whether it is practical and feasible to reduce levels of exposure to proteins in home environments, such as kitchens, and this approach could be extremely difficult to test.

The third prediction is that **early introduction of allergenic foods to the infant's diet (in the first 6 months of life) can reduce the development of food allergies through oral tolerance induction.**

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**Breastfeeding**

**Formula feeding**

**Effects of different formula**



# Breast-feeding and Allergy

## two meta-analyses

*Gdalevich M, J Pediatr 2001;  
139:261-266.*

*van Odiijk OJ, Allergy 2003;  
58:833-843.*

protective effect of exclusive breast-feeding for 4-6 months on the risk of allergic disease (eczema and asthma) in early childhood, particularly in high-risk infants (positive family history).

However, there is no evidence that exclusive breast-feeding for **more than 6 months** prevented asthma, eczema or atopy at 5 years of age, and **with prolonged breast-feeding,**

the risk of atopic dermatitis and atopy, and particularly the risk of asthma in later life, may even increase.

*Kramer MS, BMJ 2007; 335:815.*

*Matheson MC, JACI 2007;120:1051.*

# Breastfeeding and allergies: time for a change in paradigm?

*Duncan Curr Opin Allergy Clin Immunology 2008, 8:398-405*

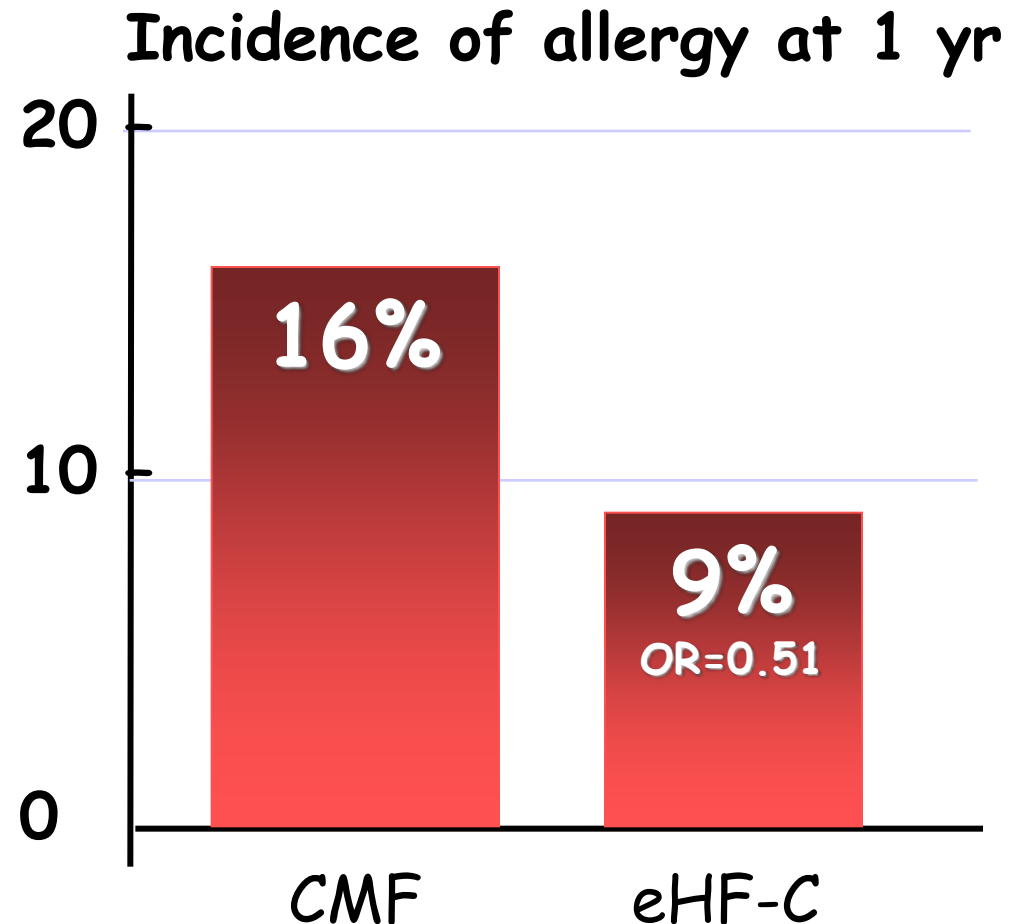
✓ Although breastfeeding is strongly recommended for its **multiple benefits** on child health, most recent studies do not confirm the 'conventional wisdom' that breastfeeding is protective against allergy and asthma.

✓ Early reduction in childhood wheezing may reflect protection from viral infections, but **allergies and asthma at later ages may be increased.**



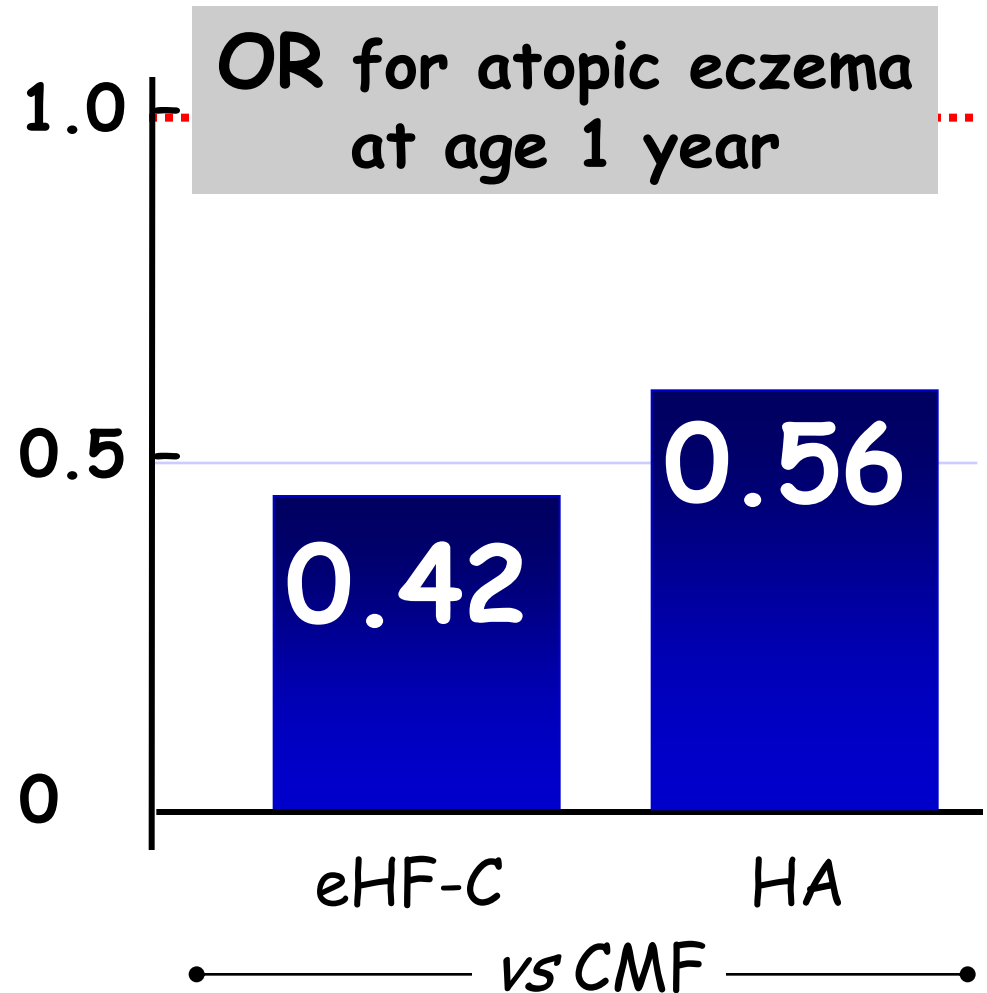
# The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *von Berg A, JACI 2003; 111:533-540.*

- ✓ 2252 infants with a **hereditary risk for atopy**
- ✓ randomly assigned at birth to one of 4 blinded formulas:
  - CMF,
  - partially hydrolyzed whey formula (HA),
  - extensively hydrolyzed whey formula
  - extensively hydrolyzed casein formula (eHF-C).
- ✓ The primary end point at 1 year of age was the presence of allergic manifestation,



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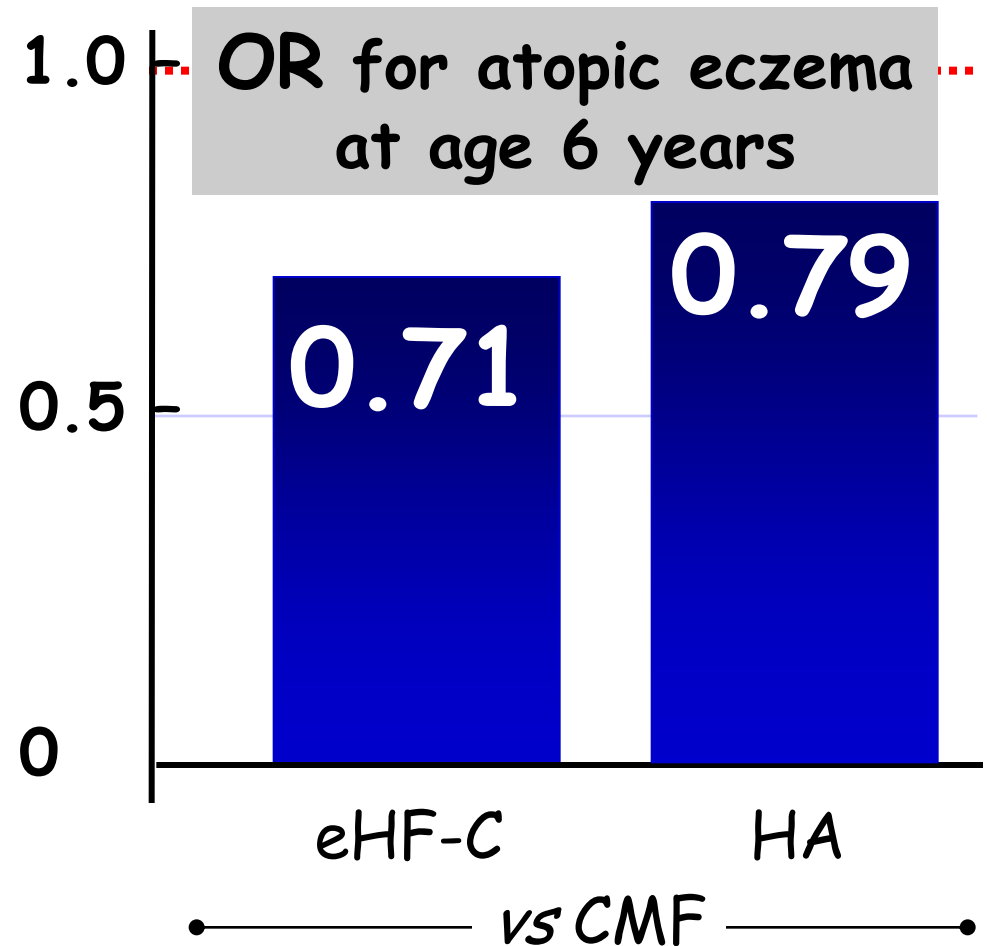
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# Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI).

*von Berg A, J Allergy Clin Immunol 2008;121: 1442-1447.*

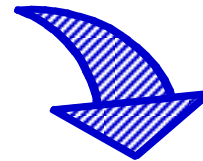
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  - extensively hydrolyzed casein formula (eHF-C).
- ✓ The cohort was followed from birth until 6 years of age with yearly questionnaires



# Infant feeding and allergy prevention: a review of current knowledge and recommendations. A EuroPrevall state of the art paper. *Grimshaw Allergy 2009;64:1407*

## Evidence related to infant cow's milk based formulas

- ✓ Due to inconsistency of findings, there is no clear-cut evidence that the early use of cow's milk hydrolysate exerts a preventive effect on allergic diseases generally or cow's milk allergy in particular.

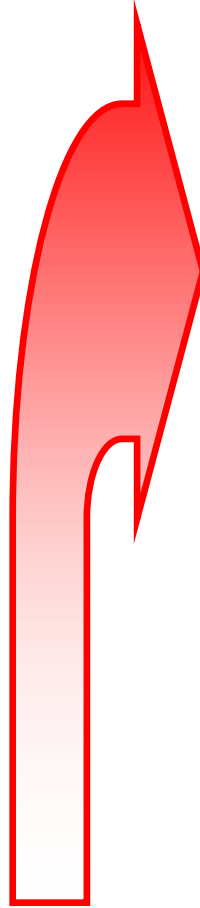


Further carefully designed and correctly powered randomized double-blind placebo-controlled studies are needed before clear recommendations can be made.

# Effect of a partially hydrolyzed whey infant formula at weaning risk of allergic disease in high-risk children: a randomized controlled trial

*Lowe JACI 2011;128:360*

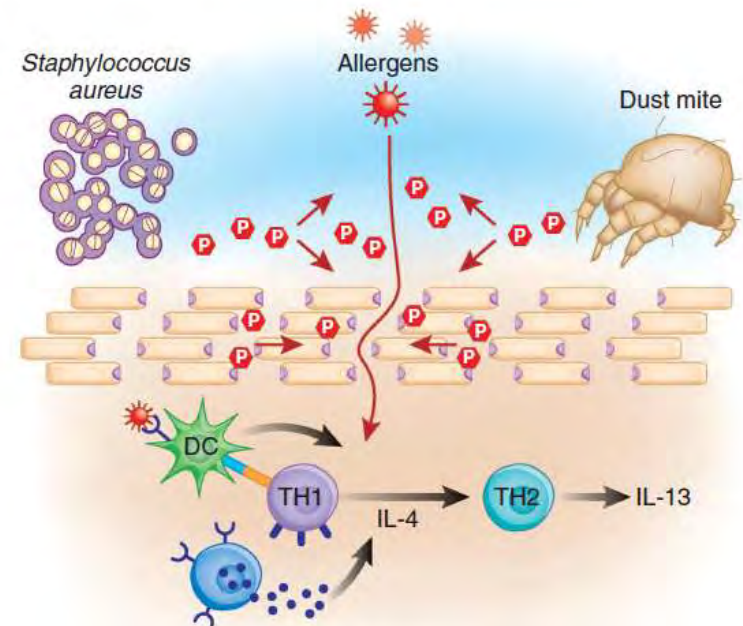
- ✓ To compare a conventional cow's milk formula, a pHWF, or a soy formula.
- ✓ 620 infants with a family history of allergic disease were recruited and randomized to receive the allocated formula at cessation of breast-feeding.
- ✓ Follow-up at 2 yrs, at 6 or 7 yrs.



There was **no evidence** that infants allocated to the **pHWF** or the **soy formula** were at **lower risk** of allergic manifestations in infancy compared with conventional formula.



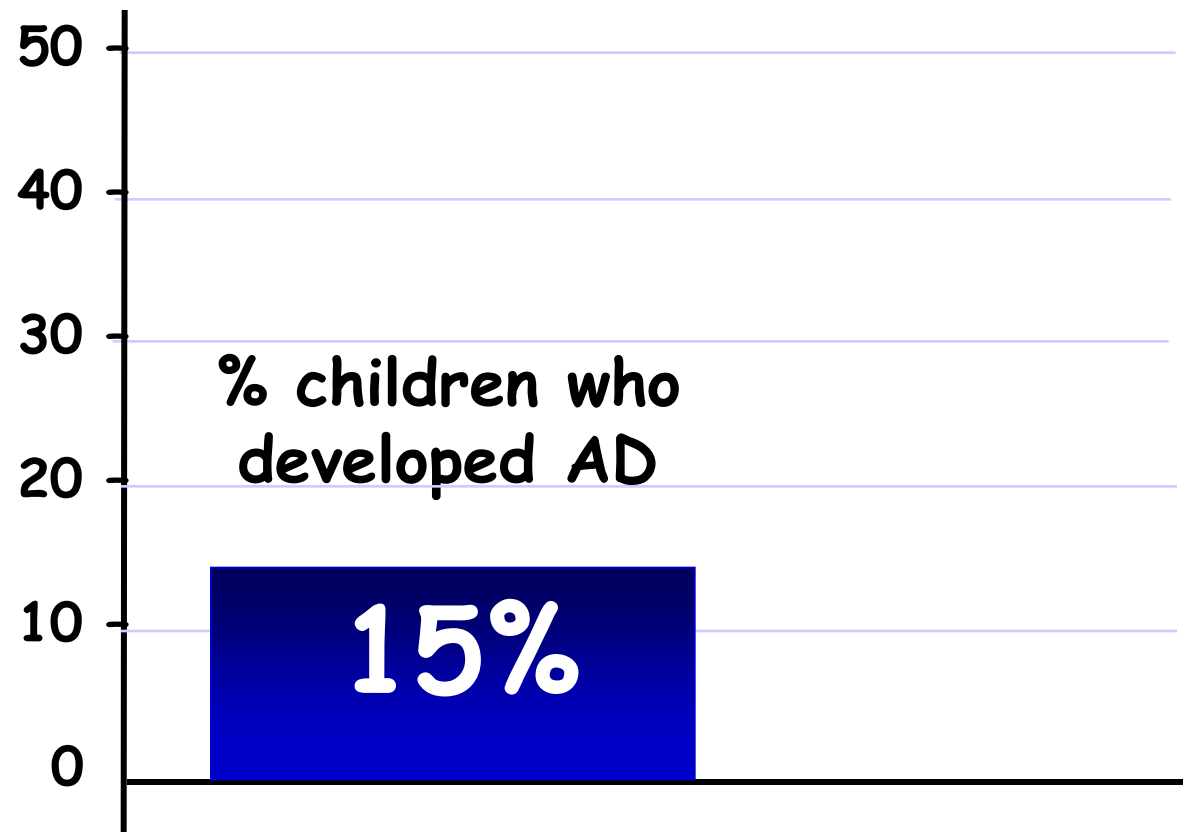
# Good care of the skin



# A pilot study of emollient therapy for the primary prevention of atopic dermatitis.

*Simpson EL, J Am Acad Dermatol. 2010;63:587-93.*

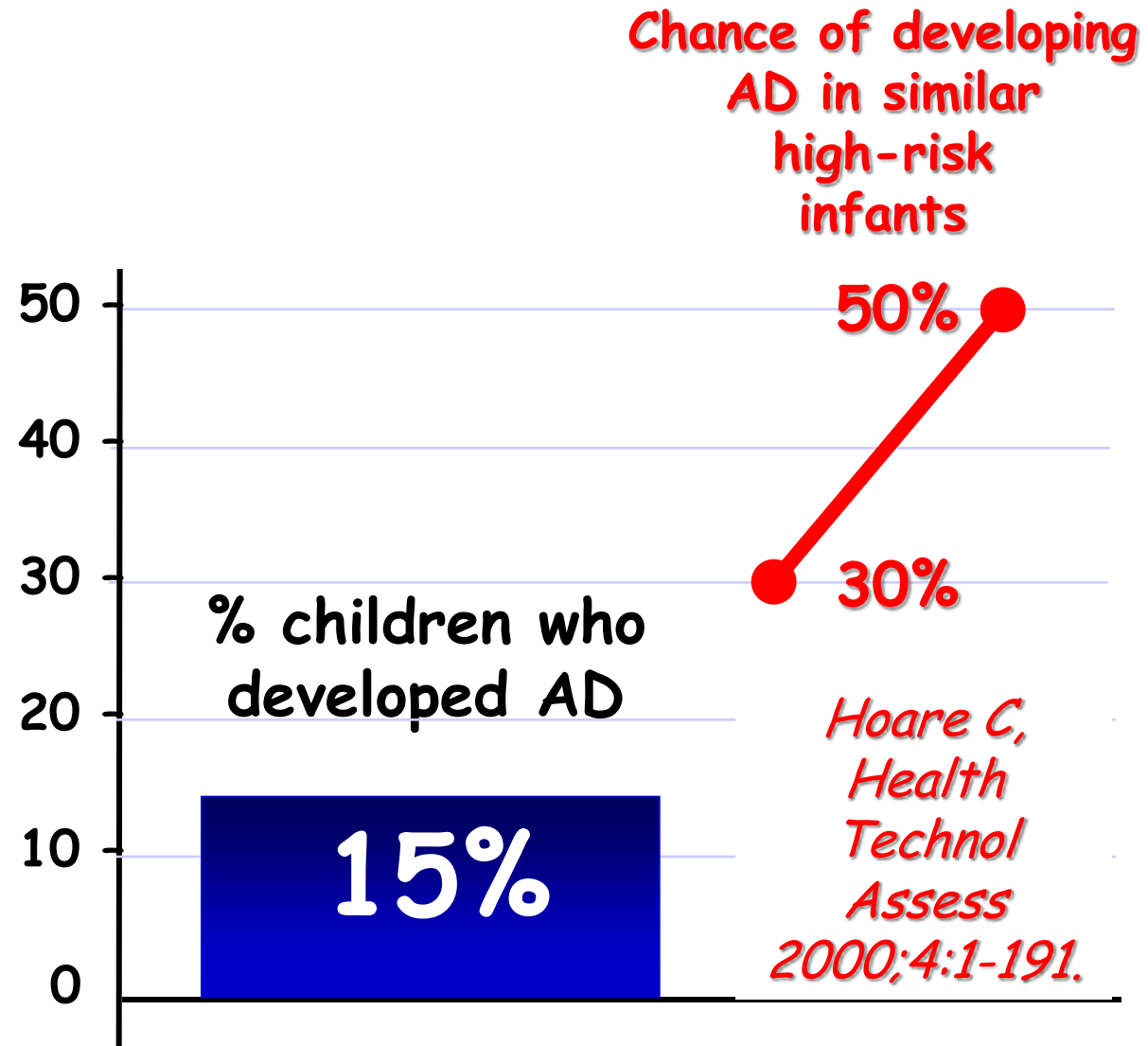
- ✓ 22 neonates at high risk for developing AD
- ✓ emollient therapy from birth.
- ✓ followed up mean time of 547 days



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# Timing of solid foods introduction

# THE IMPORTANCE OF EARLY COMPLEMENTARY FEEDING IN THE DEVELOPMENT OF ORAL TOLERANCE: CONCERNS AND CONTROVERSIES. *Prescott Pediatr Allergy Immunol 2008;19:375*

- ✓ There is mounting concern that the current recommended practice of delaying complementary foods until 6 months of age may increase, rather than decrease, the risk of immune disorders.
- ✓ **Tolerance** to food allergens appears to be driven by regular, early exposure to these proteins during a "**critical early window**" of development (most likely to be between **4 and 6 months of life**).
- ✓ Delayed exposure beyond this period may increase the risk of food allergy, coeliac disease and autoimmunity.

# THE IMPORTANCE OF EARLY COMPLEMENTARY FEEDING IN THE DEVELOPMENT OF ORAL TOLERANCE: CONCERNS AND CONTROVERSIES. *Prescott Pediatr Allergy Immunol 2008;19:375*

There is also evidence that other factors such as **favourable colonization** and **continued breastfeeding** promote tolerance and have **protective effects** during this period when complementary feeding is initiated.

# Immune-modulating micronutrients antioxidants

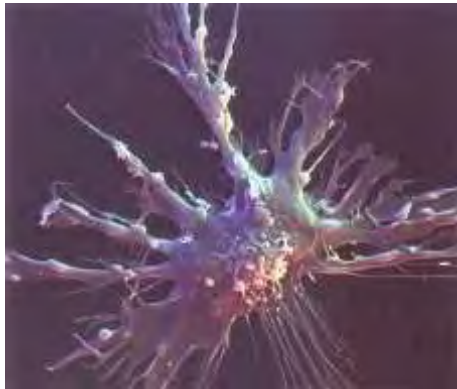




# Inhibition of NF-kappa B and oxidative pathways in human dendritic cells by antioxidative vitamins generates regulatory T cells.

*Tan PH, J Immunol. 2005;174:7633-44.*

human dendritic cell



stimulation with  
proinflammatory cytokines

Activation of NF-kappaB, protein kinase C,  
and p38 MAPK pathways

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antioxidants ascorbate (vitamin C),  
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Activation of NF-kappaB, protein kinase C,  
and p38 MAPK pathways

Inhibition of activation and cells become resistant to  
phenotypic and functional changes following stimulation

# Inhibition of NF-kappa B and oxidative pathways in human dendritic cells by antioxidative vitamins generates regulatory T cells.

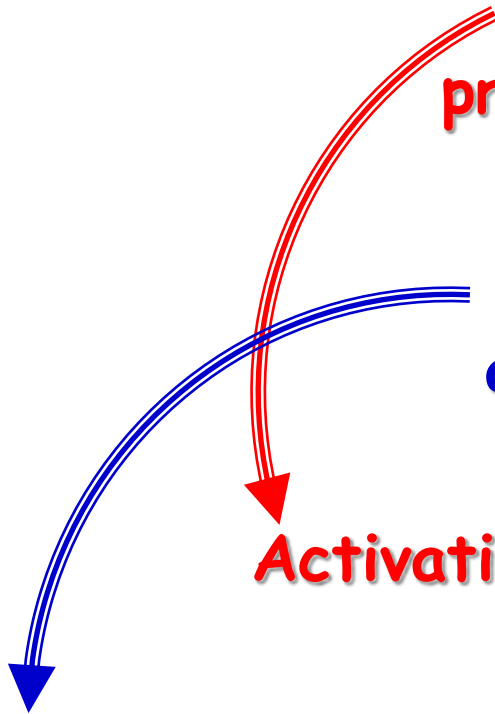
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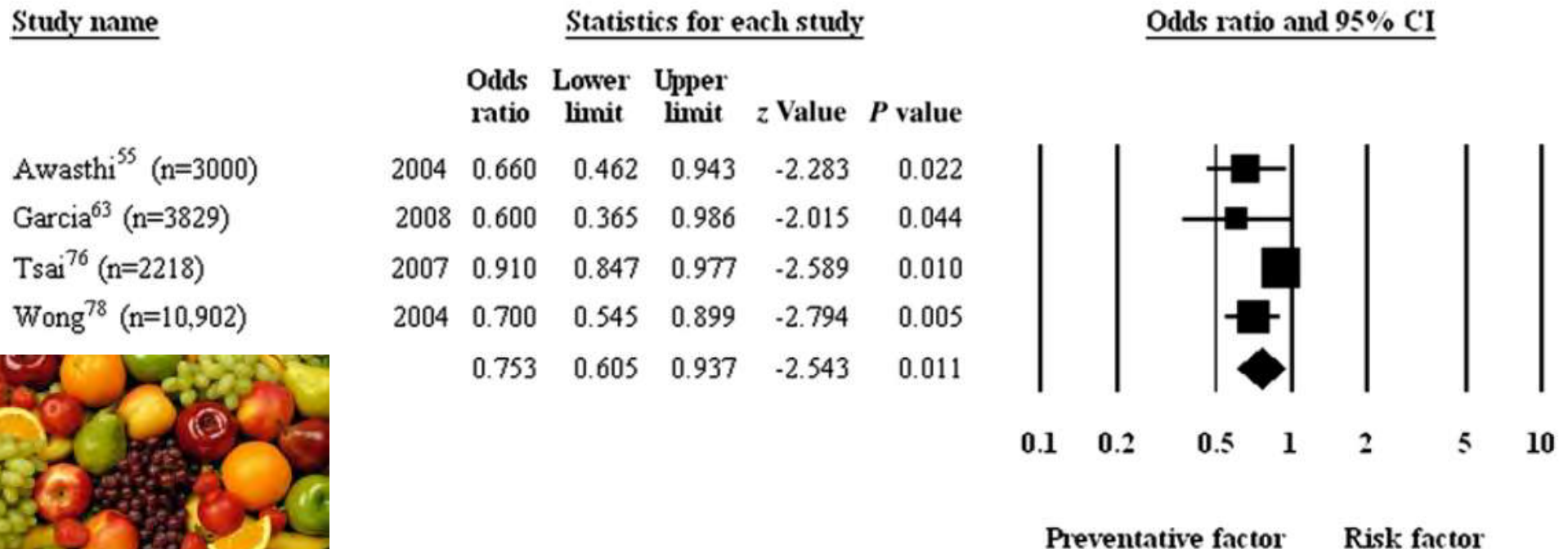
Activation of NF-kappaB, protein kinase C,  
and p38 MAPK pathways



T cells (including CD4(+)CD45RO, CD4(+)CD45RA, and CD4(+)CD25(-) subsets) were anergized and behave as regulatory T cells

# Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis. *Nurmatov U, JACI. 2011;127:724*

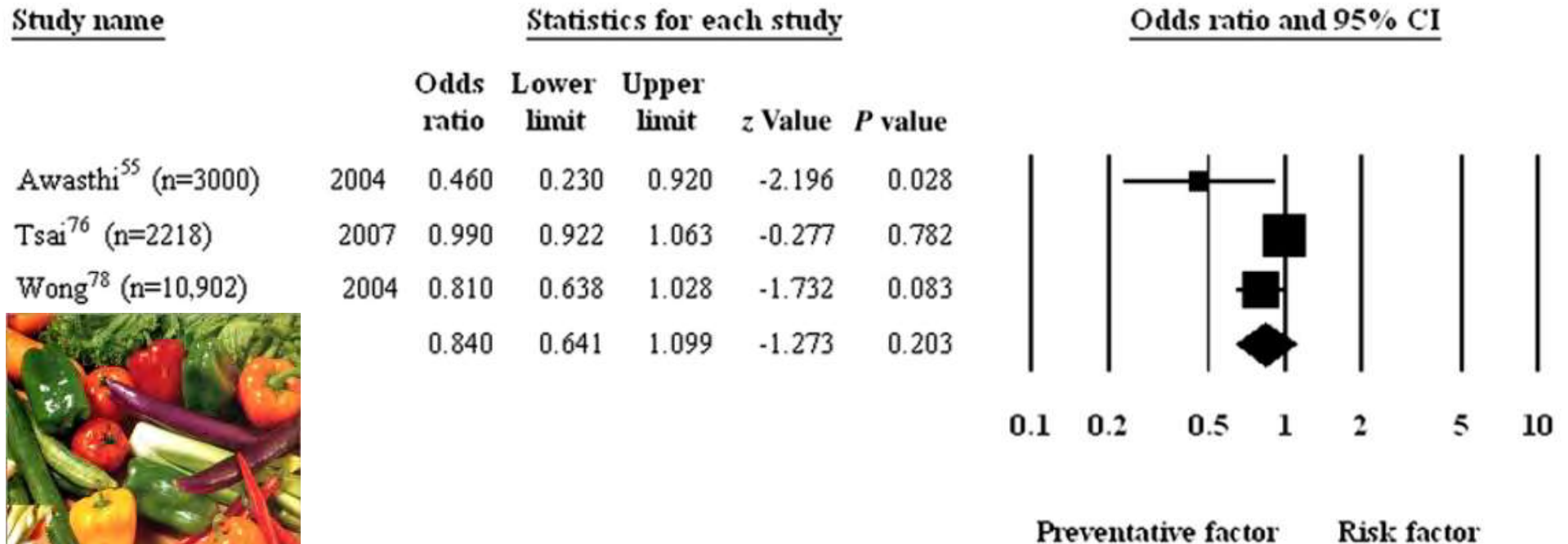
## Association between fruit intake (highest vs lowest) and wheeze in children 10 to 14 years old



Test for heterogeneity:  $df(Q)$  3,  $P = .032$ ,  $I^2 = 66\%$  Random effects model

# Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis. *Nurmatov U, JACI. 2011;127:724*

## Association between vegetable intake (highest vs lowest) and wheeze in children 10 to 14 years old



Test for heterogeneity:  $df(Q)$  3,  $P = .031$ ,  $I^2 = 71.2\%$  Random effects model



# Vitamin A: The Key to A Tolerant Immune System?

Ash M [www.nutricology.com](http://www.nutricology.com)



- ✓ Carotenoids have been called the colors of nature.
- ✓ Over 600 have been identified, and they give vegetables their gorgeous rainbow of hues, from green to orange to red to purple. About fifty can be converted into vitamin A.
- ✓ The major carotenoids in humans are beta-carotene, alpha-carotene, lycopene, lutein, and beta-cryptoxanthin.
- ✓ The conversion of carotenoids to vitamin A is not as efficient or perfect as we've been led to believe.
- ✓ In addition, up to 50% of beta-carotene is highly dependent on fat consumption at the same time, and cooked carotenoids are better absorbed than raw.
- ✓ Poor protein status or zinc deficiency also affects beta-carotene uptake, and its conversion to retinol (vitamin A).



**Retinoic acid can enhance conversion of naive into regulatory T cells independently of secreted cytokines.**

*Nolting J, J Exp Med. 2009;206:2131-9.*





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# Risk factors for the development of food allergy

- (1) genetic predisposition to atopy,
- (2) immature mucosal immune system,
- (3) inadequate normal gut flora,
- (4) increase in mucosal permeability,
- (5) decrease in skin barrier function
- (6) IgA deficiency or other immunologic defects,
- (7) gastrointestinal infections,
- (8) formula feeding,
- (9) early introduction of solid foods before 4 months of age,
- (10) delayed introduction of solid foods after 6 months of age.

# Key points underlying changes in complementary feeding practices. *Jennings & Prescott Postgrad Med J 2010;86:94*

- ✓ There is little evidence that delaying the introduction of complementary solid foods beyond 6 months reduces the risk of allergy, and there have been some suggestions that delaying introduction of foods may actually increase (rather than decrease) allergy.
- ✓ There is insufficient evidence to support previous advice to specifically delay or avoid potentially allergenic foods (such as egg, peanuts, nuts, wheat, cow's milk and fish) for the prevention of food allergy or eczema.
- ✓ This also applies to infants with siblings who already have allergies to these foods.

# Feeding advice based on current evidence

*Jennings & Prescott Postgrad Med J 2010;86:94*

## Infant formulas before 4 months:

If complementary formula is required before solid foods are started, recommendations vary:

- Where there is **no family history** of allergic disease in the infant's parents or siblings, **a standard cow's milk formula** may be used.
- Infants with a **family history of allergy** (parents or siblings) should be started on **a partially hydrolysed cow's milk formula** (usually labelled "**HA**" or hypo-allergenic). For known cow's milk allergy, these formulas are not suitable; elemental formulas are used instead.
- **Soy milk and other mammalian milks (eg, goat's milk) are not recommended for allergy prevention** or for infants with known cow's milk allergy.

# Feeding advice based on current evidence

*Jennings & Prescott Postgrad Med J 2010;86:94*

## Starting complementary foods:

- From **4-6 months** onwards when a child is ready, parents should consider introducing a **new food every 2-3 days**, according to what the family usually eats (**regardless of whether the food is thought to be highly allergenic**).
- In this way, reactions can be more clearly identified and the food excluded (or continued) as a part of a varied diet.
- Infants are **unlikely to develop a new allergy to any food that is already tolerated, if it is given regularly**.
- Breast milk or an appropriate infant formula should remain the main source of milk until 12 months of age, although cow's milk can be used in cooking or with other foods.



# Food allergy: separating the science from the mythology

*Brandtzaeg, P. Nat. Rev. Gastroenterol. Hepatol. 2010;7:380-400.*

Any event causing epithelial barrier defects may underlie food allergen sensitization, not only in the gut but also elsewhere in the body, such as the skin and airways.

Good care of the skin in early life might be a preventive strategy





"Grazie per i minuti  
della vostra vita che avete  
regalato al mio nonno con la  
vostra attenzione".

*Mia Charlize Powell*

Mi dispiace.  
Ti prego perdonami.  
Grazie.  
Ti amo.

*Hew Len*