

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



Attilio Boner  
University of  
Verona, Italy

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

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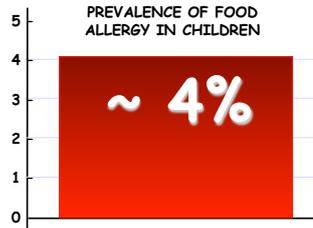
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## Food Allergy Among Children in the United States *Branum Pediatrics 2009;124:1549*

- ✓ A cross-sectional survey of data on food allergy among children <18 yrs
- ✓ in the 1997-2007



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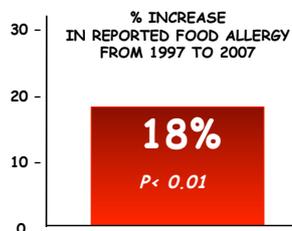
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### Spontaneous development of clinical tolerance to foods

Vickery BP *JACI* 2011;127:576

✓ In general, resolution of allergy to **egg**, **milk**, **wheat**, and **soy** can be expected, although sensitivity can persist into the second decade of life, which is longer than previously appreciated.



✓ In contrast, most patients allergic to **peanut**, **tree nuts**, and **seafood** will not outgrow their disease and must maintain strict elimination diets.



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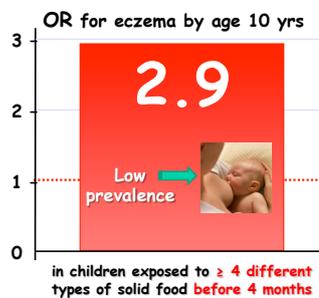
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### Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study.

Fergusson DM, *Pediatrics*. 1990;86:541-6.

- ✓ a birth cohort of New Zealand children
- ✓ early solid feeding practices
- ✓ risks of recurrent or chronic eczema in childhood was examined
- ✓ follow-up to age 10 yrs



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### Recommended Approaches to Allergy Prevention



*Pediatrics* 2000;106:346

- ✓ No maternal dietary restriction during pregnancy, (peanuts?)
- ✓ breastfeeding,
- ✓ dietary restrictions while breastfeeding,
- ✓ the use of hypoallergenic formulas, and
- ✓ delays in the introduction of certain foods into the infant's diet




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## Breast feeding



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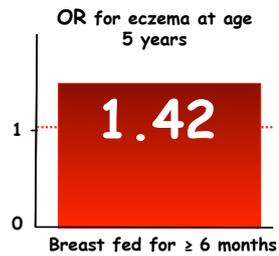
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### The association between infant feeding practices and subsequent atopy among children with a family history of asthma. *Mihrshahi S Clin Exp Allergy. 2007;37:671-9.*

- ✓ A cohort of 516 children with a family history of asthma in Sydney, Australia,
- ✓ followed from birth to age 5 years



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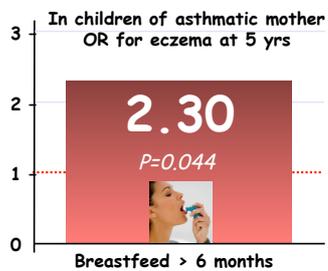
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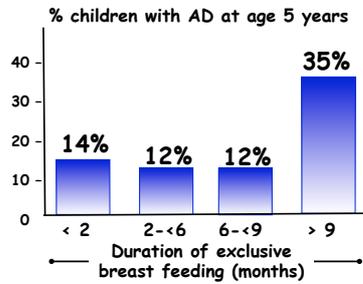
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**Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years.**

*Person ClinExpAll 2006;36:1011*

- ✓ 200 unselected healthy newborns (42% has a family history of allergy)
- ✓ Follow up at ages 5 (n=163), 11 (n=150) and 20 years (n=164) with clinical examination and skin prick testing




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## Solid foods: Milk - Egg




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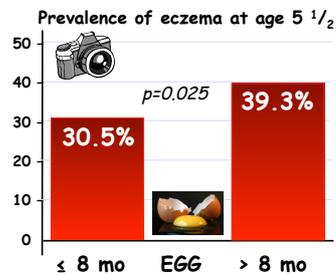
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**The Introduction of Solids in Relation to Asthma and Eczema** *Zutavern Arch Dis Child 2004;89:303*

- ✓ 642 children recruited before birth and followed to the age 5 1/2 years
- ✓ Retrospective evaluation of solid foods introduction performed at age 12 months




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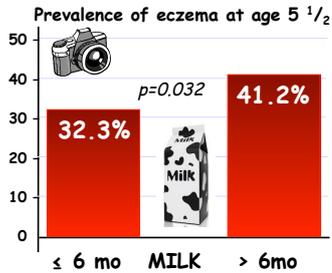
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**Solid Food Introduction in Relation to Eczema; Results from a Four-Year Prospective Birth Cohort Study.** *Filipiak J Pediatr 2007;151:352*



- ✓ Introduction of solid foods in the first 12 months (birth cohort)
- ✓ Occurrence of eczema during the first 4 years of life
- ✓ an intervention group (n=2252) (allergenic food such as cow's milk and dairy products, eggs, fish, tomatoes, nuts, soy products, and citrus fruits were to be avoided entirely during the first year)
- ✓ nonintervention group (n=3739).



In this large population-based prospective birth cohort study, there was **no evidence for a protective effect** in relation to eczema **from delayed introduction of solids beyond the fourth month and of most potentially allergenic solids beyond the sixth month of life.**

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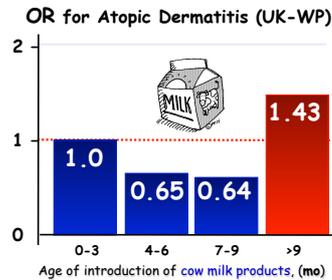
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**Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA Birth Cohort Study.** *Snijders BE, Pediatrics 2008; 122:e115-e122.*

- ✓ 2558 infants in an ongoing prospective birth cohort study in the Netherlands
- ✓ introduction of cow milk products and other food products
- ✓ Follow-up: 2 years




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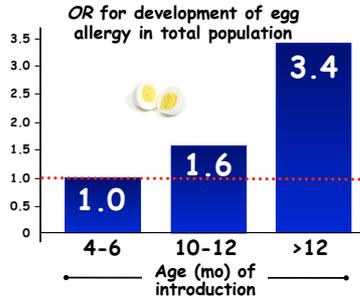
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**Can early introduction of egg prevent egg allergy in infants? A population-based study**

*Koplin JACI 2010;126:807*

- ✓ Population-based cross-sectional study.
- ✓ 2589 infants.
- ✓ To determine whether confirmed egg allergy in 12-month-old infants is associated with:
  - (1) duration of breast-feeding and
  - (2) ages of introducing egg and solids




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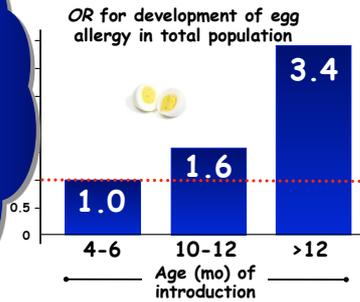
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These findings persisted even in children without risk factors (OR = 3.3; 10-12 mo.)  
to avoid reverse causality




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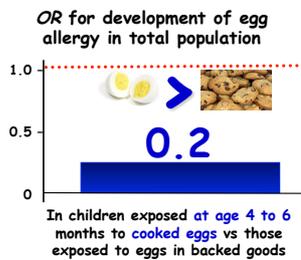
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**Age at the Introduction of Solid Foods During the First Year and Allergic Sensitization at Age 5 Years**

*Nwaru Pediatrics 2010;125:50*

- ✓ 994 children
- ✓ age at the introduction of solid foods
- ✓ adjustment for potential confounders
- ✓ allergen-sIgE at 5 years



**Late introduction of:** -  
 potatoes (>4 months), -  
 oats (>5 months), -  
 rye (>7 months), -  
 wheat (>6 months), -  
 meat (>5.5 months), -  
 fish (>8.2 months), -  
 eggs (>10.5 months) **was**  
 significantly directly  
**associated with**  
**sensitization to food**  
**allergens.**

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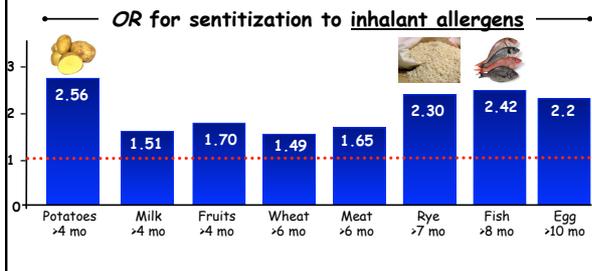
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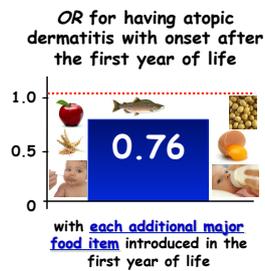
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**Development of atopic dermatitis according to age of onset and association with early-life exposures**

*Roduit JACI 2012;130:130*

- ✓ Introduction to complementary food in the first year of life.
- ✓ Development of atopic dermatitis, taking into account the reverse causality.
- ✓ 1041 children birth cohort study.
- ✓ Feeding practices reported by parents in monthly diaries between the 3rd and 12th months of life.




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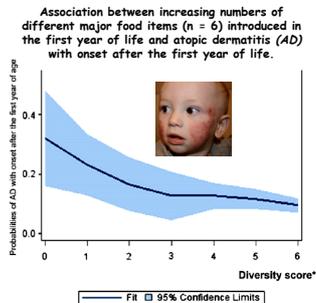
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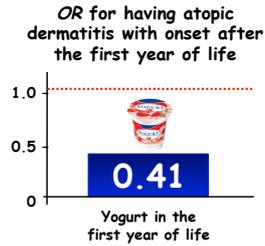
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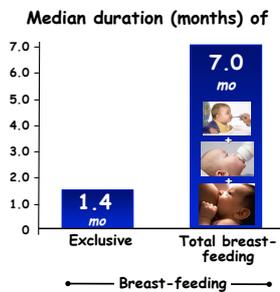
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**Timing of infant feeding in relation to childhood asthma and allergic diseases.**

*Nwaru JACI 2013;131:78*

- ✓ 3781 consecutively born children.
- ✓ Dietary exposures.
- ✓ Asthma, allergic rhinitis, and atopic eczema, IgE antibodies at the age of 5 years.




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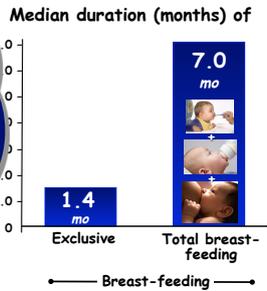
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**Timing of infant feeding in relation to childhood asthma and allergic diseases.** *Nwaru JACI 2013;131:78*

✓ Introduction of wheat, rye, oats, or barley at 5 to 5.5 months was inversely associated with asthma and allergic rhinitis, whereas introduction of other cereals at less than 4.5 months increased the risk of atopic eczema.




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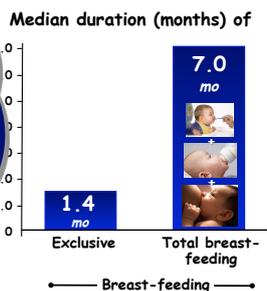
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**Timing of infant feeding in relation to childhood asthma and allergic diseases.** *Nwaru JACI 2013;131:78*

✓ Introduction of egg at 11 months or less was inversely associated with asthma, allergic rhinitis, and atopic sensitization, whereas introduction of fish at 9 months or less was inversely associated with allergic rhinitis and atopic sensitization.




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**gluten**

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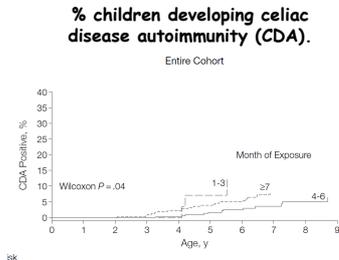
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**Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease.** Norris JM, JAMA. 2005;293:2343-2351

✓ development of celiac disease autoimmunity (CDA)

✓ 1560 children at increased risk for celiac disease or type 1 diabetes, as defined by possession of either HLA-DR3 or DR4 alleles, or having a first-degree relative with type 1 diabetes.

✓ follow-up: 4.8 years.




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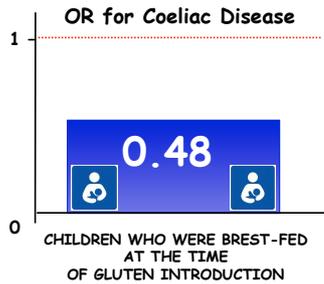
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**EFFECT OF BREAST FEEDING ON RISK OF COELIAC DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES** Akobeng Arch Dis Child 2006; 91: 39

✓ Meta-analysis observational studies published between 1966 and June 2004;  
 ✓ 6 case-control studies




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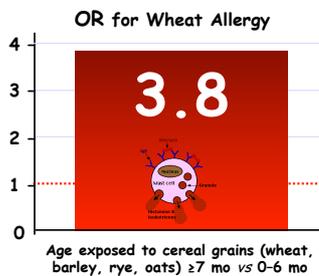
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**Timing of initial exposure to cereal grains and the risk of wheat allergy.** Poole JA, Pediatrics 2006; 117:2175-2182.

✓ 1612 children enrolled at birth

✓ followed to the mean age of 4.7 years.

✓ Questionnaire data and dietary exposures were obtained at 3, 6, 9, 15, and 24 months and annually thereafter.




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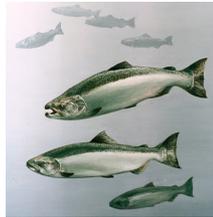
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fish



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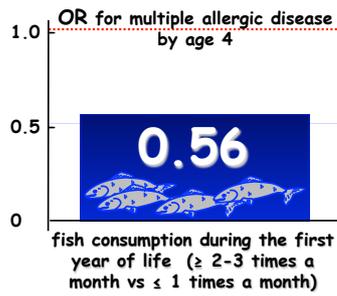
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**Fish consumption during the first year of life and development of allergic diseases during childhood.**

*Kull I. Allergy. 2006;61:1009-15*



- ✓ birth cohort of 4089 new-born infants in Sweden
- ✓ follow-up: 4 years
- ✓ Parental questionnaires at ages 2 months, 1, 2 and 4 years



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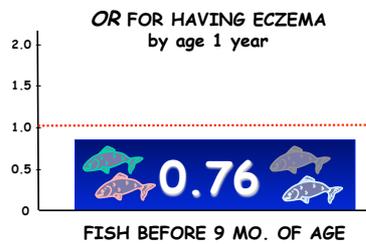
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**Early introduction of fish decreases the risk of eczema in infants**

*Alm Arch Dis Child 2009;94:11*



- ✓ Infants born in Sweden in 2003.
- ✓ 8176 families.



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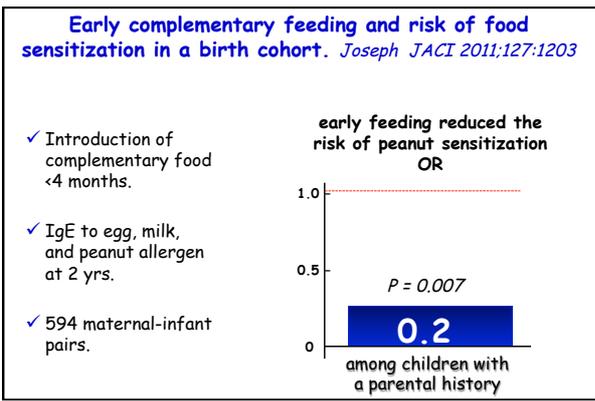
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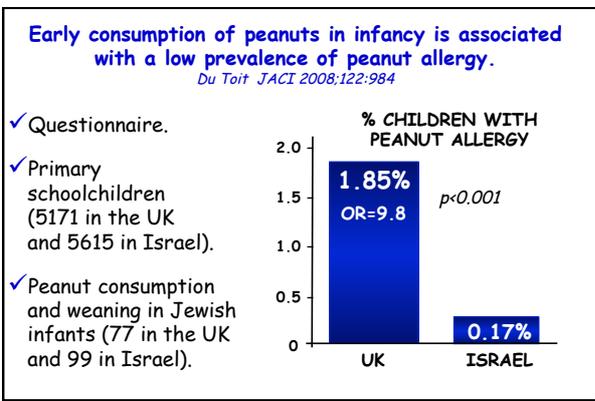
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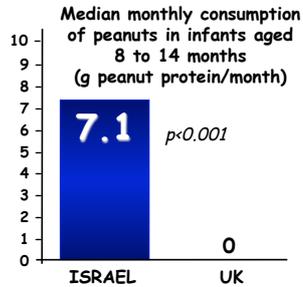
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**Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy.**

*Du Toit JACI 2008;122:984*

- ✓ Questionnaire.
- ✓ Primary schoolchildren (5171 in the UK and 5615 in Israel).
- ✓ Peanut consumption and weaning in Jewish infants (77 in the UK and 99 in Israel).




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**Household peanut consumption as a risk factor for the development of peanut allergy**

*Fox JACI 2009; 123:417*

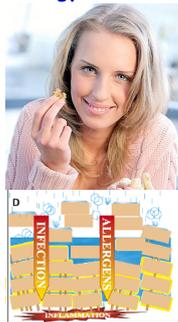
**Background:**

Most children with peanut allergy (PA) react on first known oral exposure to peanut.

Recent data suggest cutaneous exposure as a route of sensitization.

**Objectives:**

This study aimed to establish the relevant route of peanut exposure in the development of allergy.




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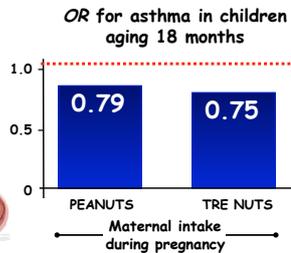
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**Peanut and tree nut consumption during pregnancy and allergic disease in children—should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort.**

*Maslova JACI 2012;130:724*

- ✓ Danish National Birth Cohort (n=61,908).
- ✓ Maternal peanut and tree nut intake during pregnancy and allergic outcomes in children at 18 months and 7 years of age.




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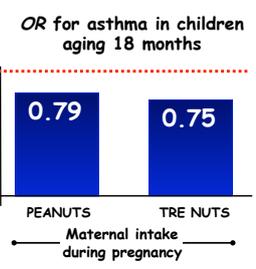
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**Peanut and tree nut consumption during pregnancy and allergic disease in children—should mothers decrease their intake? Final evidence from the Danish N**  
*Maslova JACI 2012;130:724*

Higher tree nut intake was inversely associated with a medication-related asthma diagnosis (OR, 0.81) and self-reported allergic rhinitis (OR, 0.80).




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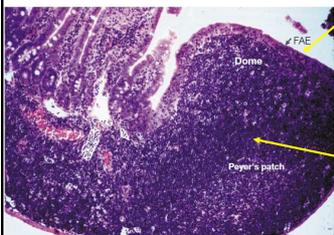
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**Schematic representation of the lymphoid elements of the intestinal immune system. Mowatt Nat Rev Immunol. 2003;3:331**

**inductive sites**



- a) The follicle-associated epithelium (FAE), which is comprised of columnar epithelial cells and also contains microfold (M) cells, dendritic cells (DCs), T cells, B cells and macrophages, separates the intestinal lumen from Peyer's patches.
- b) Peyer's patches are aggregates of secondary lymphoid tissue present in the submucosa of the small intestine. The area immediately beneath the FAE ('dome') is rich in DCs.

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**Schematic representation of the lymphoid elements of the intestinal immune system.** *Mowatt Nat Rev Immunol. 2003;3:331*



**effector sites: villi**

a) Normal small intestine showing the characteristic architecture of finger-like villi that are covered by a single layer of columnar epithelial cells, which encloses the **central lamina propria (LP)** (effector sites)

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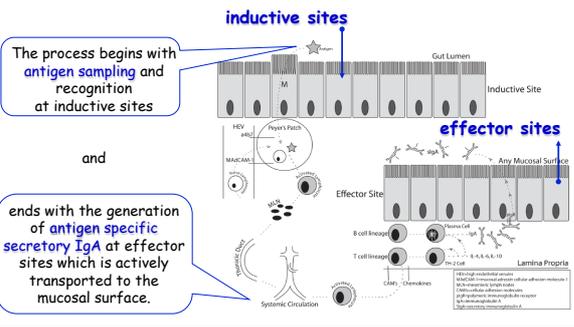
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**Schematic representation of a typical mucosal immune response.** *Hermensen Langenbecks Arch Surg. 2009;394:17-30*




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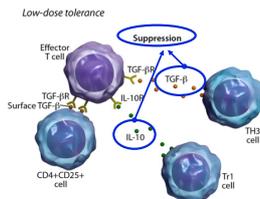
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**MECHANISMS OF TOLERANCE**  
*Burks JACI 2008;121:1344*

There are 2 primary effector mechanisms for inducing oral tolerance:

- 1) **Active Suppression by regulatory T cells**
- or
- 2) **Deletion or Anergy**

1) **Low doses of antigen** favor tolerance driven by **regulatory cells**, which suppress immune responses through soluble or cell surface-associated downregulatory cytokines, such as **IL-10**, and **TGF-β** (**active suppression**).




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**2) High-dose tolerance** is mediated by lymphocyte **anergy** or clonal deletion.

**Anergy can occur through T-cell receptor ligation in the absence of costimulatory signals.**

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**2) Deletion or Anergy**

**2) High-dose tolerance** is mediated by lymphocyte **anergy** or clonal deletion.

**Clonal deletion occurs by means of FAS-mediated apoptosis (CD95).**

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**MECHANISMS OF TOLERANCE**  
*Burks JACI 2008;121:1344*

**Apoptotic T cells release TGF- $\beta$**  in both latent and bioactive forms, and macrophages produce TGF- $\beta$  on ingesting apoptotic cells. The secretion of TGF- $\beta$  through the various mechanisms of clonal anergy and deletion can contribute to an immunosuppressive environment in the gut.

**Active Suppression by regulatory T cells**  
or  
**Deletion or Anergy**

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



Attilio Boner  
University of  
Verona, Italy

- ✓ introduction
- ✓ starting point
- ✓ old recommendations
- ✓ new findings
- ✓ dietary antigens properties
- ✓ development of tolerance
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- ✓ allergy development?
- ✓ what can be done?
- ✓ conclusions

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## Iron Deficiency Anemia and Cognitive Function in Infancy

*Carter Pediatrics 2010;126:e427*

- ✓ Effects of iron deficiency anemia (IDA) on specific domains of infant cognitive function
- ✓ IDA was defined as hemoglobin level < 110 g/L with ≥ 2 abnormal iron deficiency indicators (mean corpuscular volume, red cell distribution width, zinc protoporphyrin, transferrin saturation, and ferritin)
- ✓ At 9 and 12 months, the Fagan Test of Infant Intelligence (FTII); A-not-B task; Emotionality, Activity, and Sociability Temperament Survey; and Behavior Rating Scale



- Infants with IDA showed **poorer recognition memory**
- The Behavior Rating Scale orientation/engagement measure partially mediated these effects

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## Iron-Deficiency Anemia in Infancy and Social Emotional Development in Preschool-Aged Chinese Children

*Chang Pediatrics 2011;127:e927*



- ✓ Children with iron-deficiency anemia (IDA) in infancy whose anemia was **not corrected before 24 months (chronic IDA)** (n=27).
- ✓ Children with IDA in infancy whose anemia was **corrected before 24 months (corrected IDA)** (n=70).
- ✓ Children who were **non-anemic** in infancy and at 24 months (n=64).



Children who had **chronic IDA** in infancy displayed:

1. less positive affect and frustration tolerance;
2. more passive behavior and physical self-soothing in the stranger approach;
3. delay of gratification.




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### Iron-Deficiency Anemia in Infancy and Social Emotional Development in Preschool-Aged Chinese Children

Chang *Pediatrics* 2011;127:e927



- ✓ Children with iron-deficiency anemia (IDA) in infancy whose **anemia was not corrected before 24 months (chronic IDA)** (n=27).
- ✓ Children with IDA in infancy whose **anemia was corrected before 24 months** (corrected IDA) (n=70).
- ✓ Children who were **non-anemic** in infancy and at 24 months (n =64).



In contrast, the behavior and affect of children whose **anemia was corrected before 24 mo of age** were comparable to those of children who were non-anemic throughout infancy.




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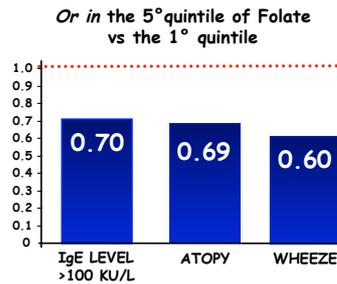
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### Higher serum folate levels are associated with a lower risk of atopy and wheeze

Matsui *JACI* 2009;123:1253

- ✓ Serum folate and total IgE levels.
- ✓ 8083 subjects 2 years of age and older.




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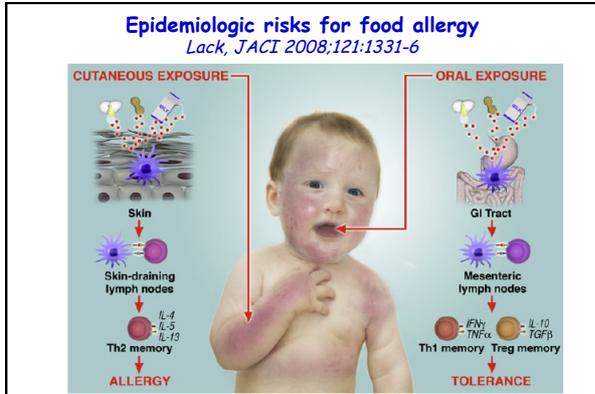
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**Breastfeeding**



**Formula feeding**



**Effects of different formula**




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## Breast-feeding and Allergy

### two meta-analyses

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

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### 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 most recent studies do not confirm 'conventional wisdom' that breastfeeding is against allergy and asthma.



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

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## Timing of solid foods introduction



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**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.**

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**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.
- 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.
- ✓ **Delayed exposure beyond this period may increase the risk of food allergy, coeliac disease and autoimmunity.**

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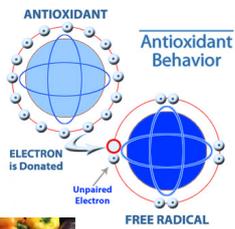
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**Immune-modulating micronutrients antioxidants**




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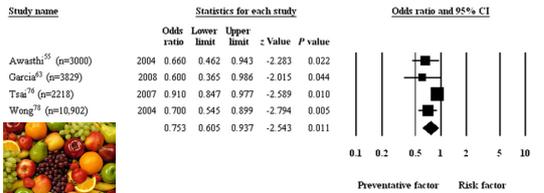
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**Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis.** Nurmatov U, *JACI*. 2011;127:724

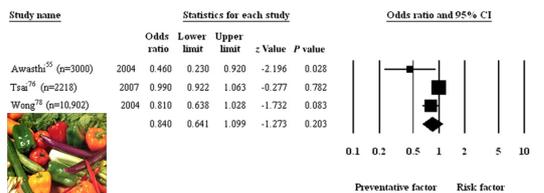
**Association between fruit intake (highest vs lowest) and wheeze in children 10 to 14 years old**



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

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**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.

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**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.

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**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.

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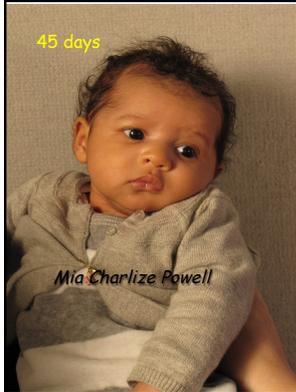
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