

L'alimentazione nella prevenzione delle allergie: miti o realtà?

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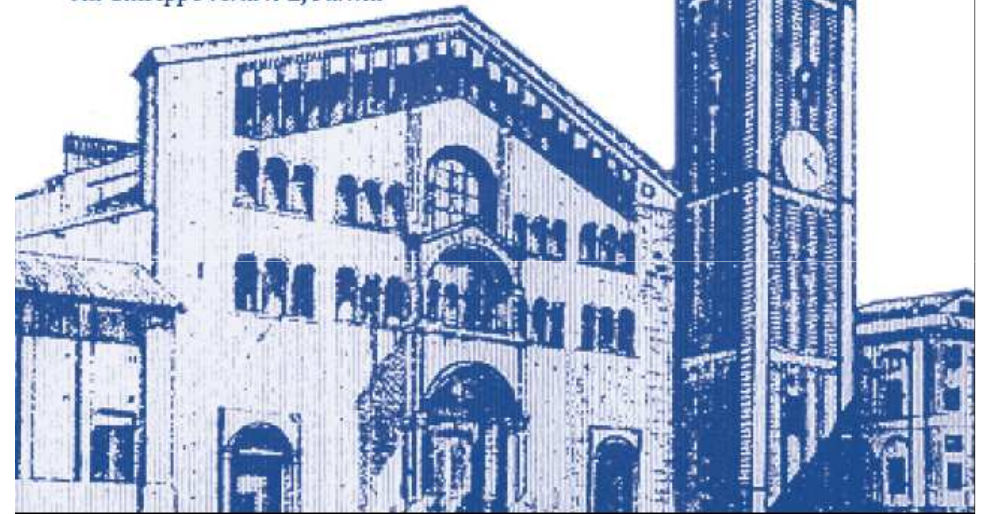


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Gustav Klimt

Alimentazione: quando?



Epidemiological and immunological studies suggest that dietary modification in fetal life could affect the development of allergic diseases. Somewhat conflicting findings imply that there might be critical time windows of exposure to foods and nutrients during pregnancy.





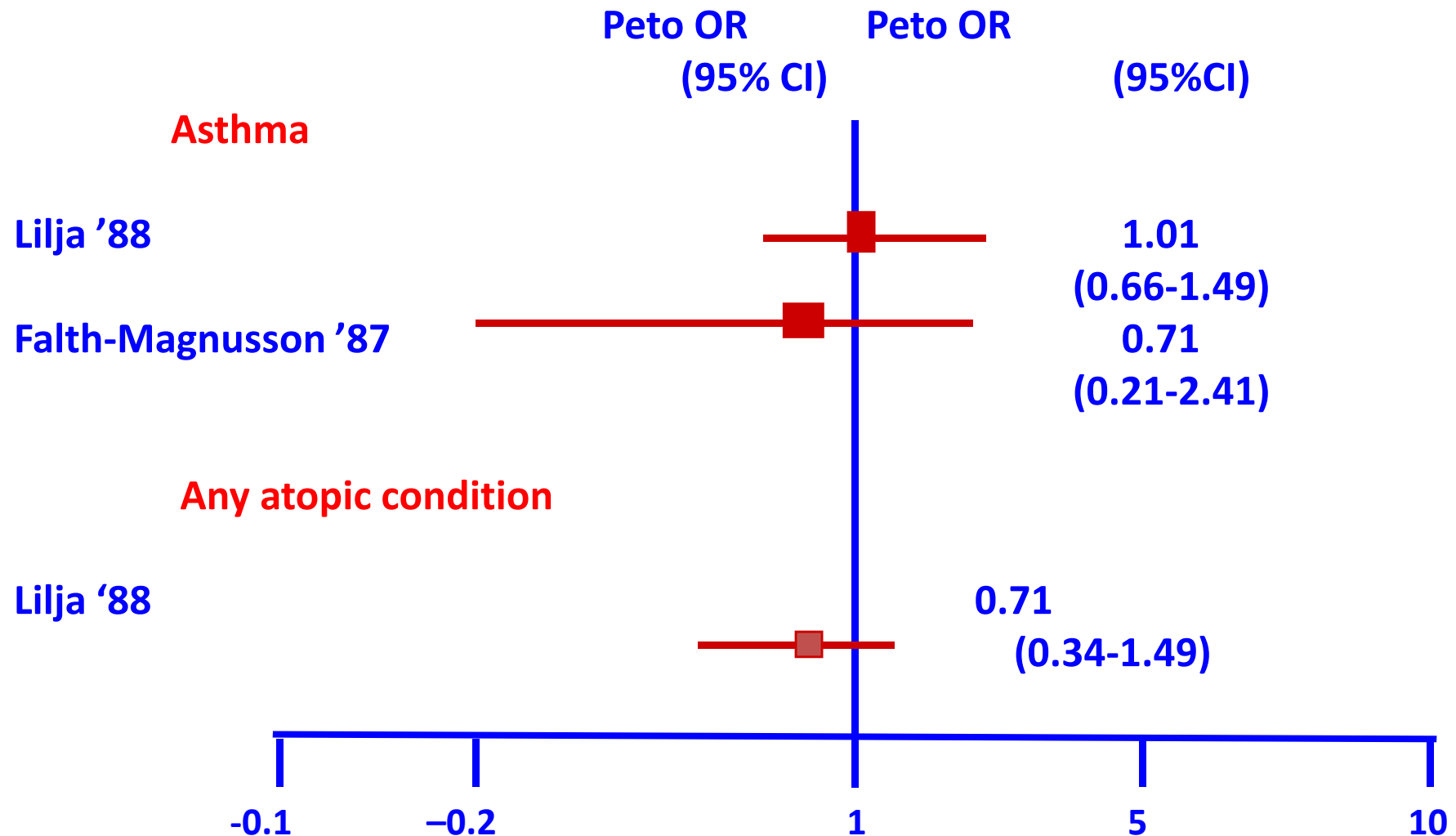
As maternal antigen avoidance,

Kramer review of 504 woman suggests that the avoidance could

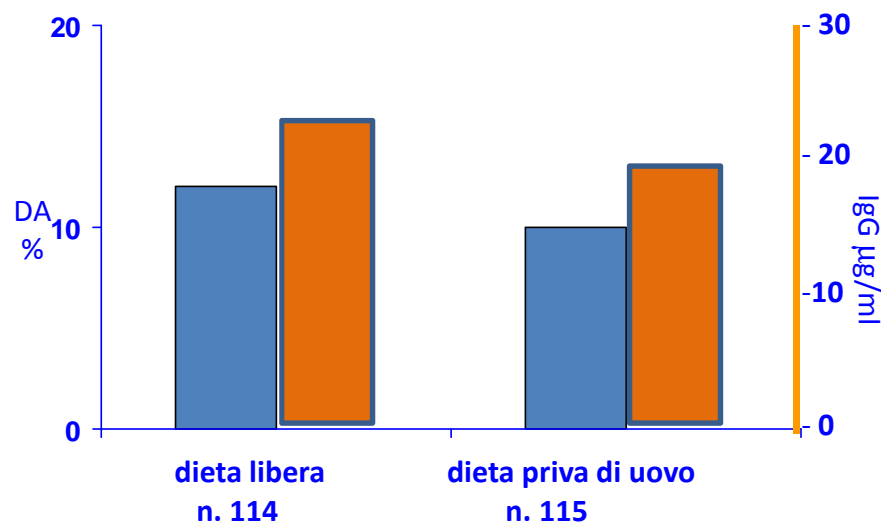
- lead to lower birth weight**
- increase in pre-term birth**

Maternal avoidance during pregnancy: asthma and any atopic condition in first 12-18 mo.

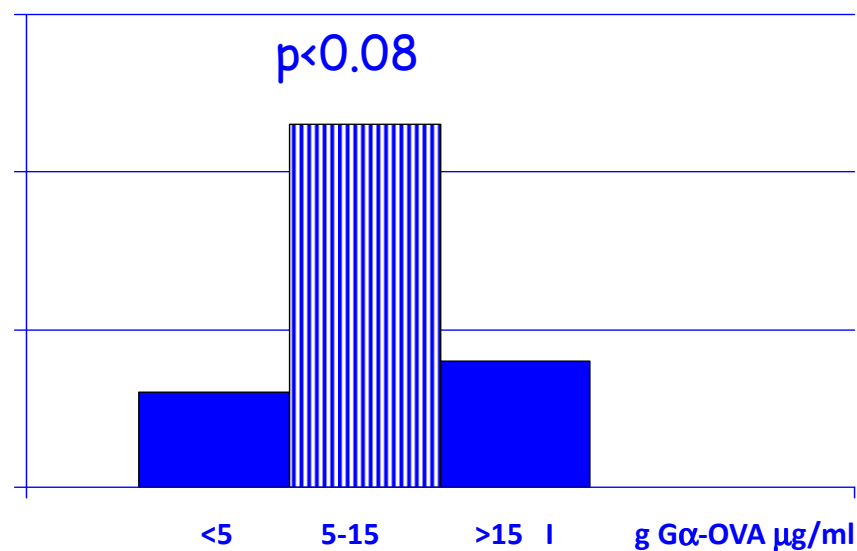
(Kramer 2002)



DA e livelli di IgG a-OVA a 18 mesi in 229 bambini nati da madri a dieta priva di uovo o a dieta libera



%



Vance GH et al, Clin Exp Allergy 2004

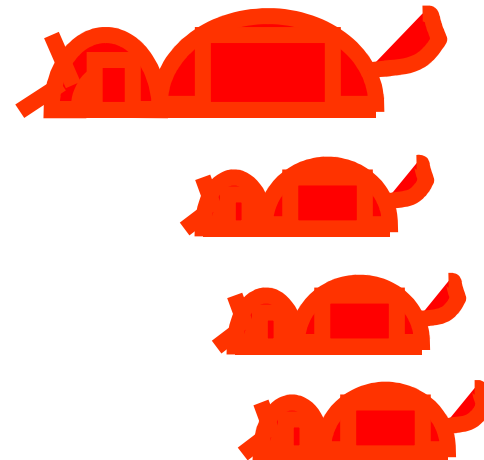
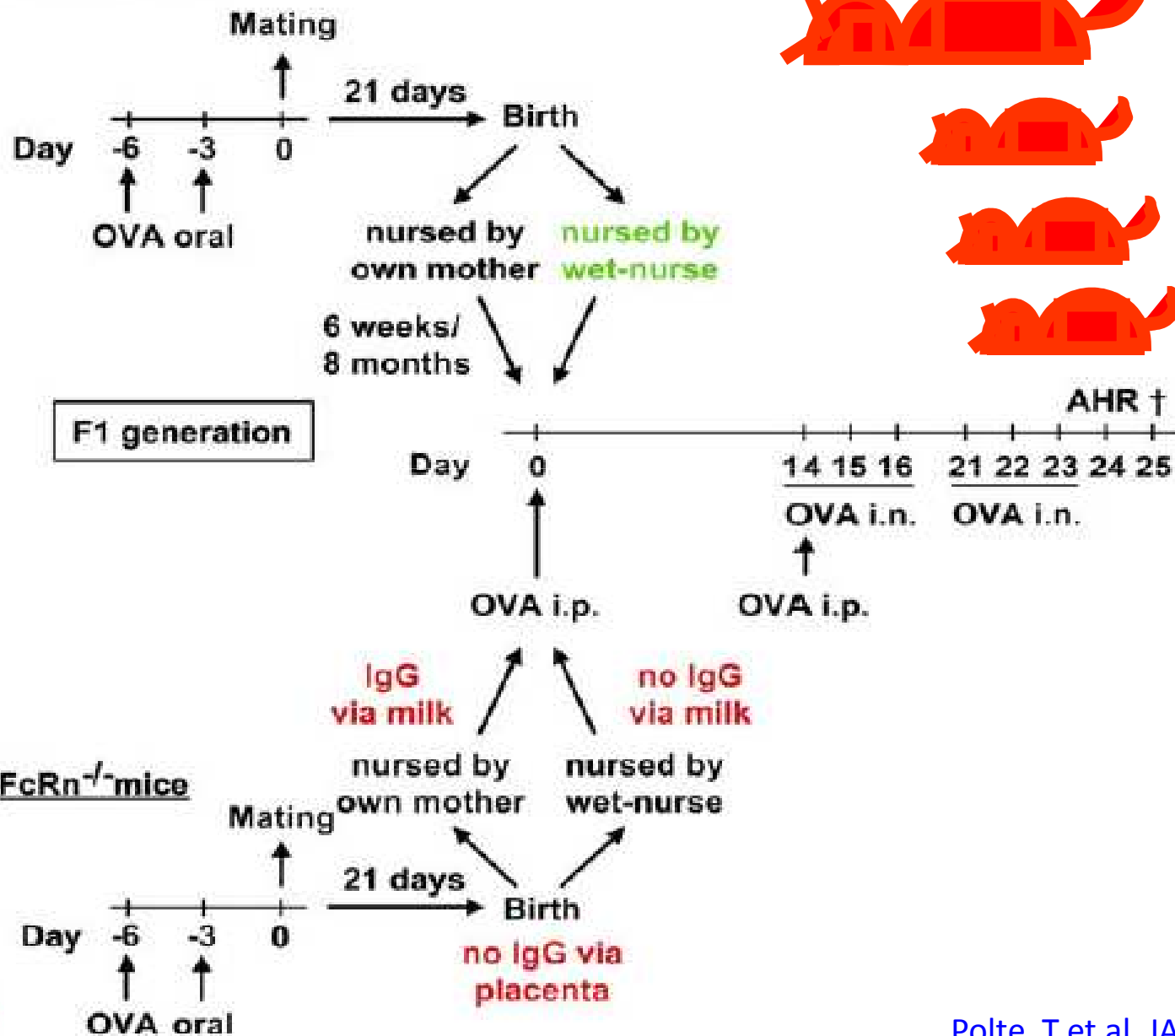
Szajewska H, IMAJ 2012



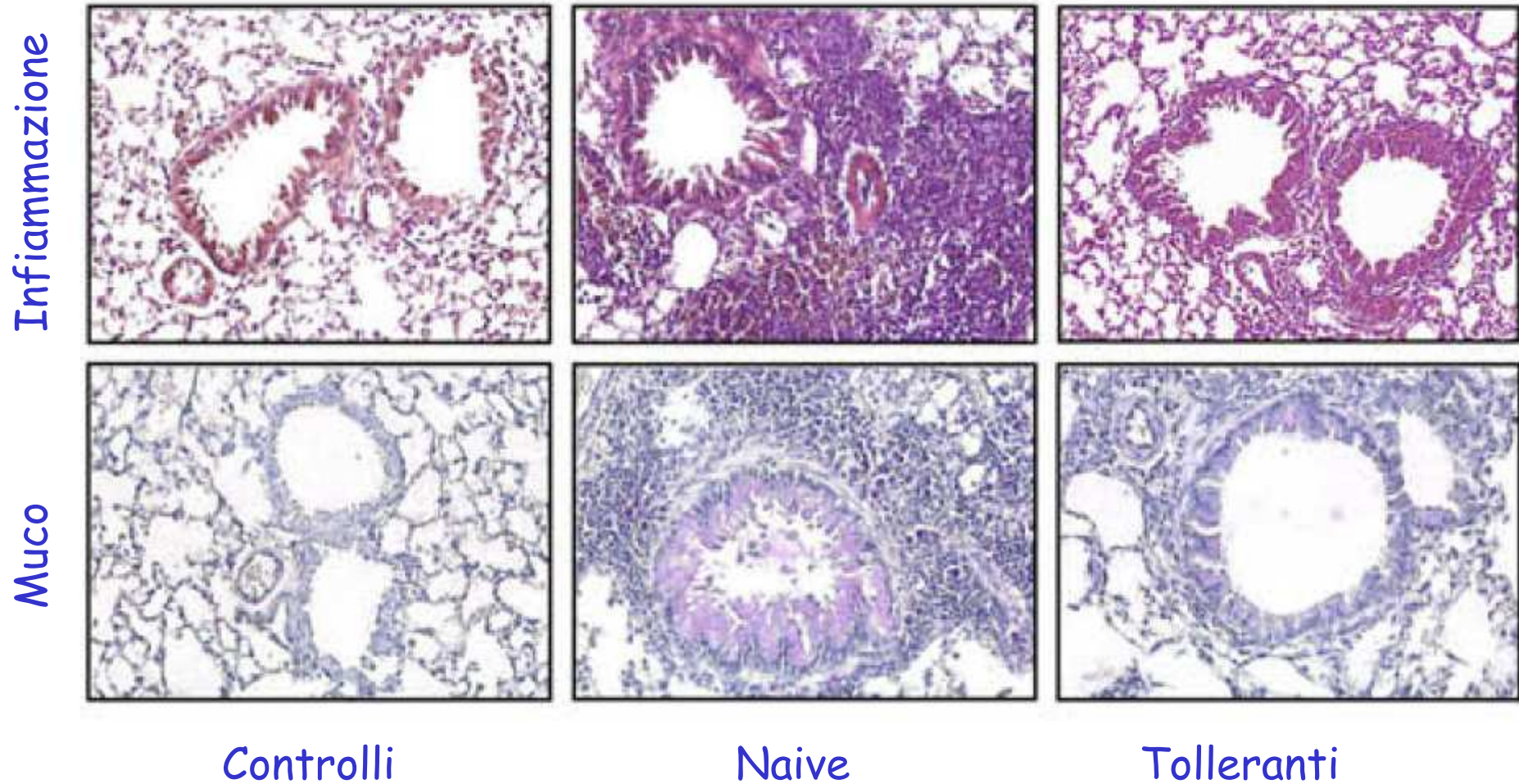
Prescribing an antigen-avoidance diet to a high risk woman during pregnancy or lactation

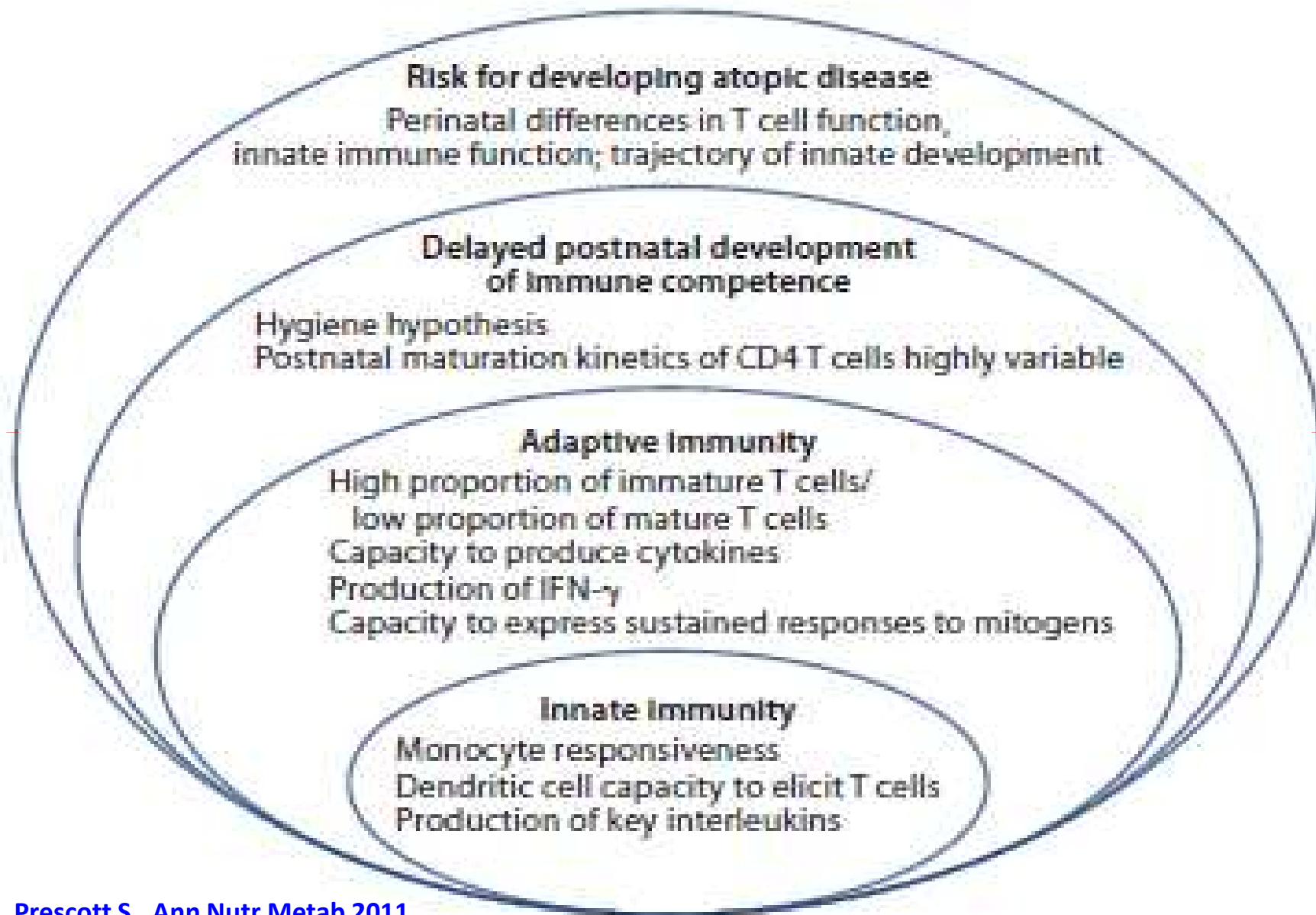
did not reduce her child's risk of atopic diseases such as eczema and asthma.

Balb/c or
C57Bl/6J mice



Trasferimento della tolleranza





Risk factors

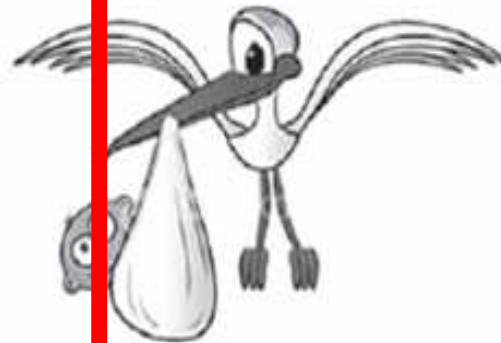
- Tobacco smoke^A
- Environmental pollutants^A
- Abnormal intestinal flora colonisation^A
- Decreased exposure to sunlight^B



Before conception



Pregnancy



Perinatal



1st year of life



Older than 1 year

- Early introduction of solid foods before 3–4 months of age^B
- Formula feeding?^B
- Diet low in n–3 PUFA, antioxidants and soluble fibre^B
- Delayed introduction of solid foods^B
- Vitamin D deficiency^C

Interventions

?

- Healthy, balanced diet^C
- Pro- and prebiotics^B
- n–3 PUFA^B
- Vitamin D^A

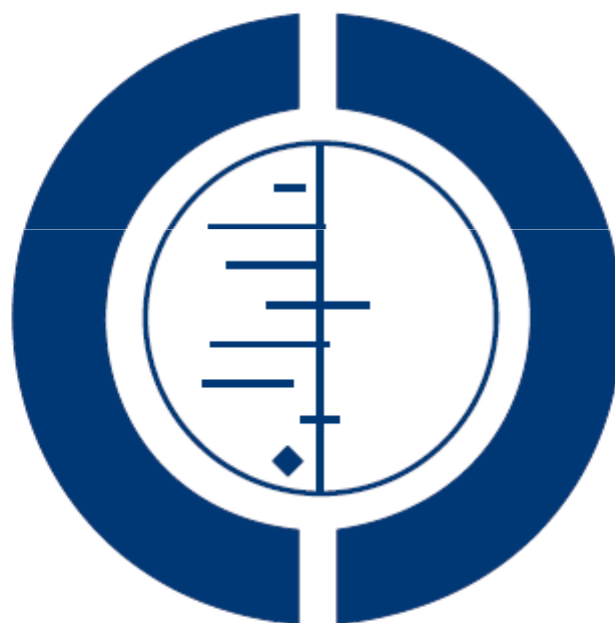
- Breastfeeding for ≥6 months^C
- Hypoallergenic infant formula in the first 6 months if breastfeeding is not possible^C
- Introduction of solid foods at 4–6 months^C
- Pro- and prebiotics^B
- n–3 PUFA^A

- Healthy and balanced diet^A
- Pro- and prebiotics^B
- n–3 PUFA^C



Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants (Review)

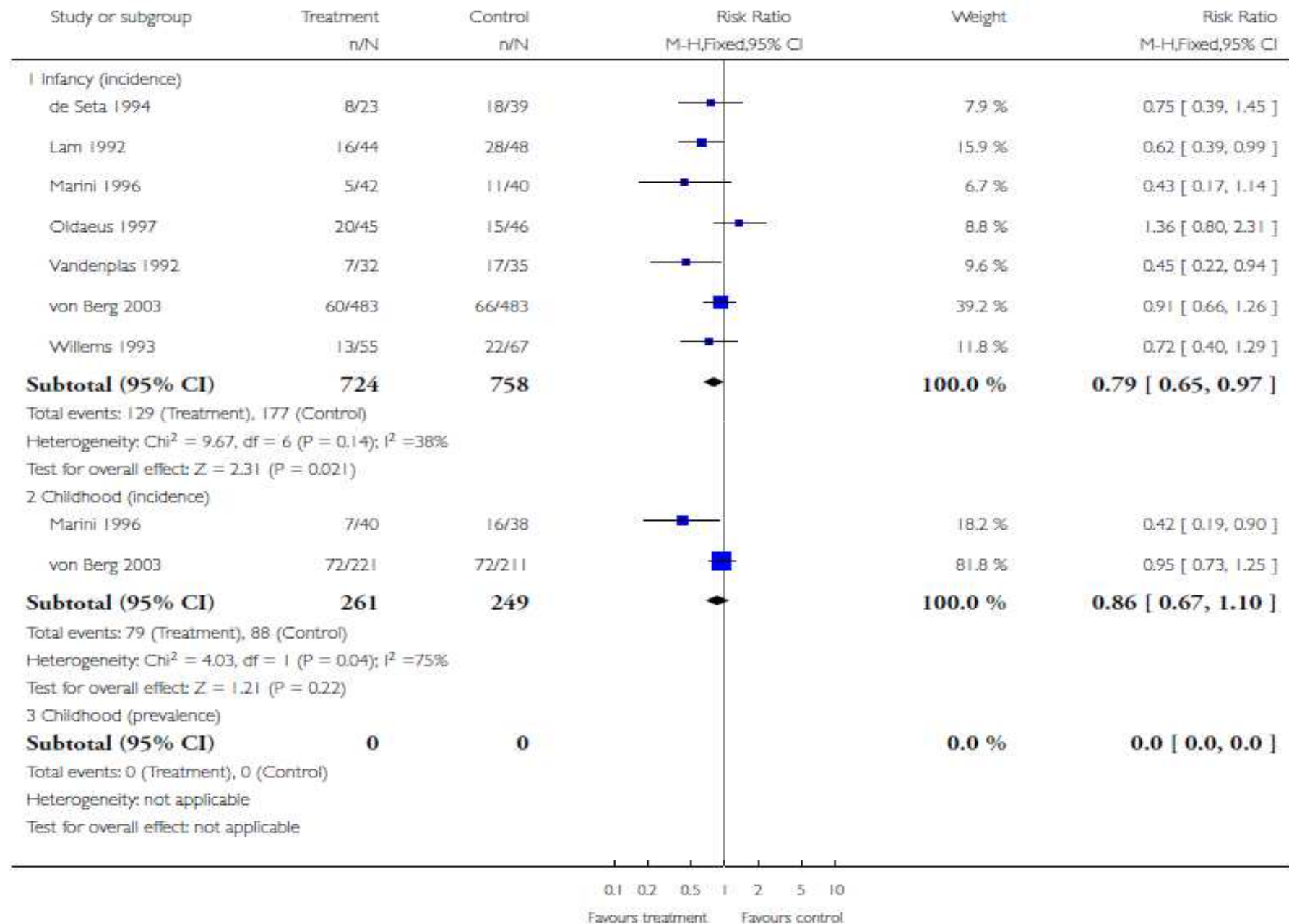
Osborn DA, Sinn JKH



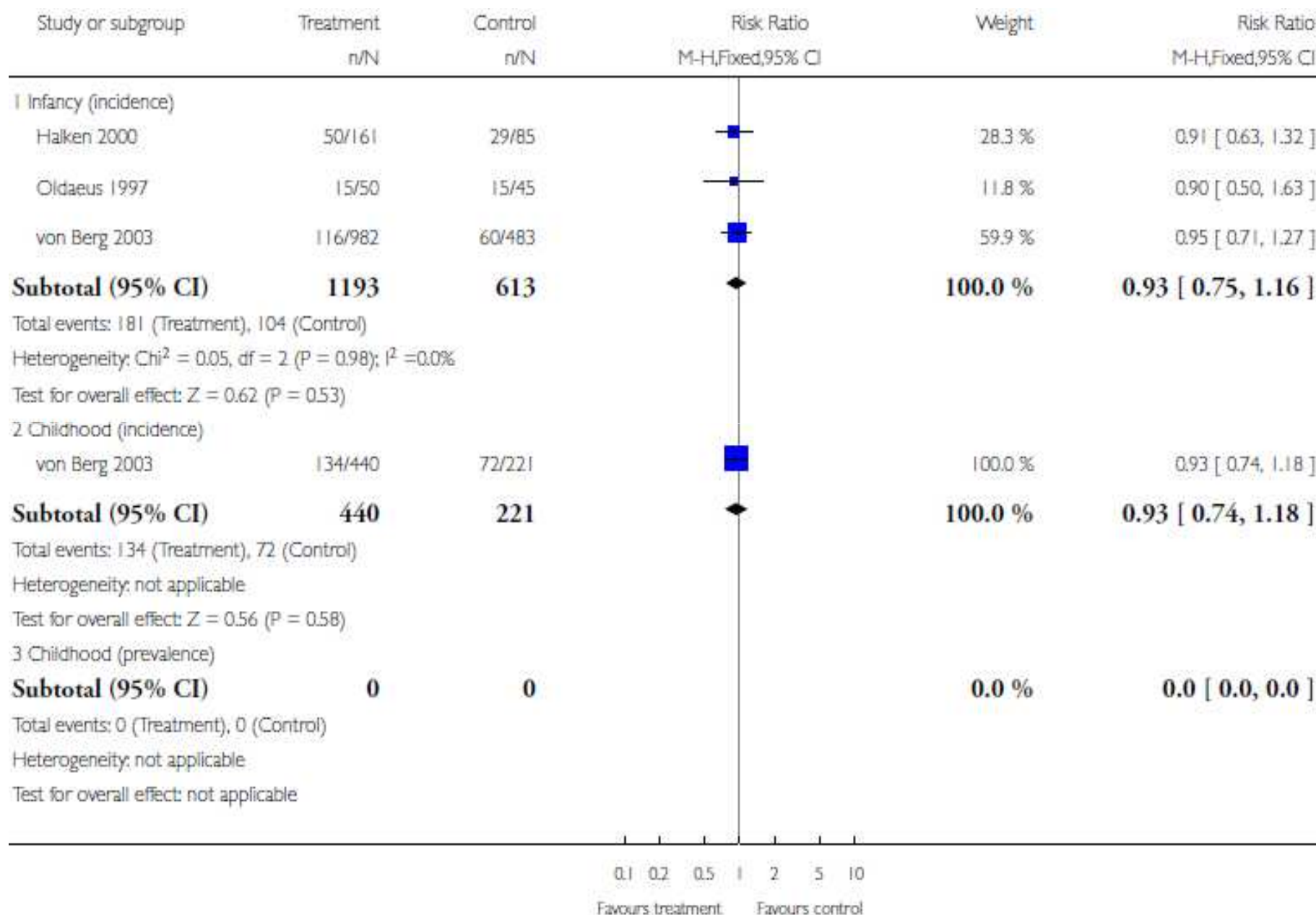
**THE COCHRANE
COLLABORATION®**

The Cochrane Library 2009, Issue 1, last up-to-date 26 July 2006

Prolonged feeding: pHF vs cow's milk formula, Any allergy



Prolonged feeding: eHF vs pHF, Any allergy



AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support feeding with a hydrolysed formula compared to exclusive breast feeding for the prevention of allergy or food intolerance. Until high quality trials are performed that compare prolonged hydrolysed formula feeding to breast or expressed human milk feeding, hydrolysed formula should not be routinely offered to infants for the prevention of allergy or food intolerance in preference to breast milk. There is no evidence of benefit from the use of a hydrolysed formula in preference to human milk for early, short term feeding in low risk infants. In infants at high risk of allergy who cannot be exclusively breast fed, there is limited evidence that prolonged supplementation with hydrolysed formula as opposed to cow's milk formula reduces the risk of allergy. However, there was no significant difference in rates of asthma, eczema or rhinitis. Effects on allergy did not persist

Clinical & Experimental Allergy

Primary prevention with hydrolysed formula: does it change natural onset of allergic disease?

This editorial discusses the findings of the paper by Berg et al. [10] pp. 627–636.

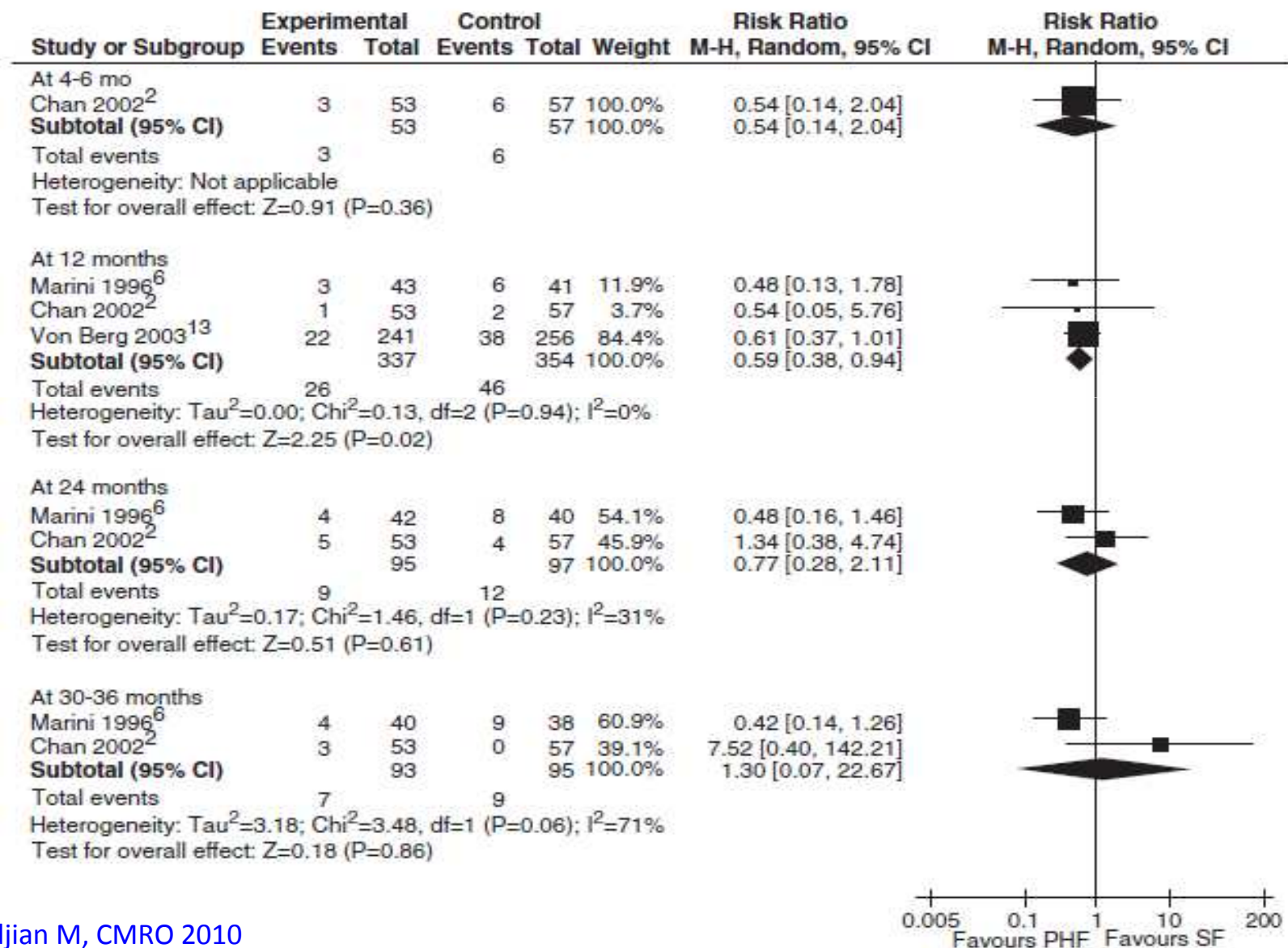
J. Sinn^{1,2} and D. A. Osborn^{1,2}

¹Royal North Shore Hospital, St Leonards, Sydney, NSW, Australia and ²Royal Prince Alfred Hospital, Camperdown, Sydney, NSW, Australia

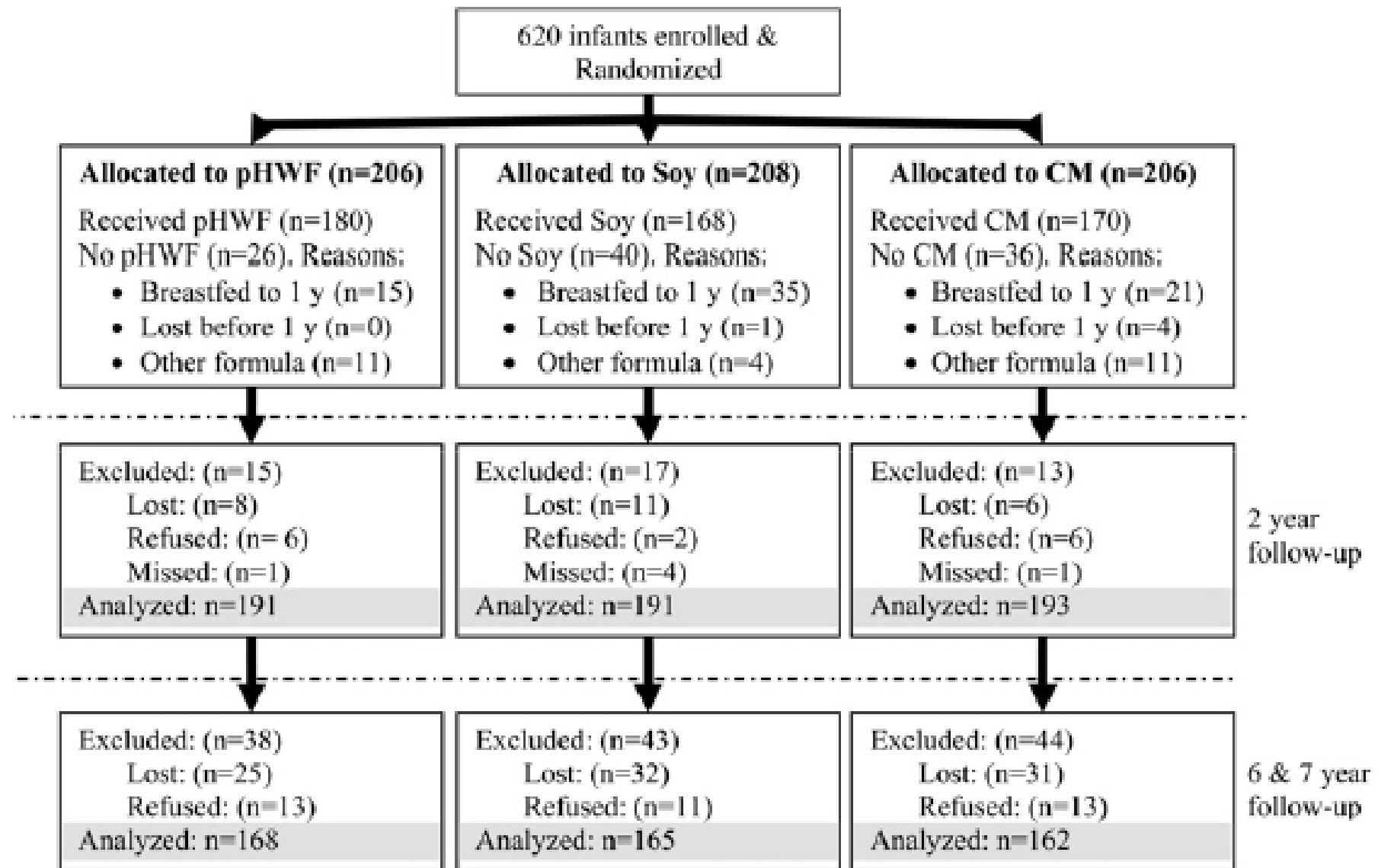
There is some evidence to support the use of infant dietary interventions for prevention of allergy, particularly eczema in infants. Several Cochrane Systematic Reviews [1–4] have examined evidence for use of various interventions and reported that use of a partially hydrolysed or extensively hydrolysed infant formula may prevent allergy in infancy. There is no evidence of benefit from use of a soy formula [1] and inadequate evidence to date to determine the allergy preventing effects of probiotics and prebiotics [3, 4] added to infant feeds. Evidence of benefit from use

infants fed an extensively hydrolysed casein but not the other types of hydrolysed formula compared with use of a cow's milk formula. However, these results should be viewed in the context of all the evidence. The Cochrane review [2] reported methodological concerns with almost all studies, with the GINI study reporting between 10% and 20% losses to follow-up at various time-points. The overall meta-analyses found a significant reduction in infant allergy from use of a hydrolysed formula, with some evidence of benefit from both an extensively hydro-

Incidence rates of AD obtained from studies comparing PHF-W to SF limited to articles published after 1995.



MACS study

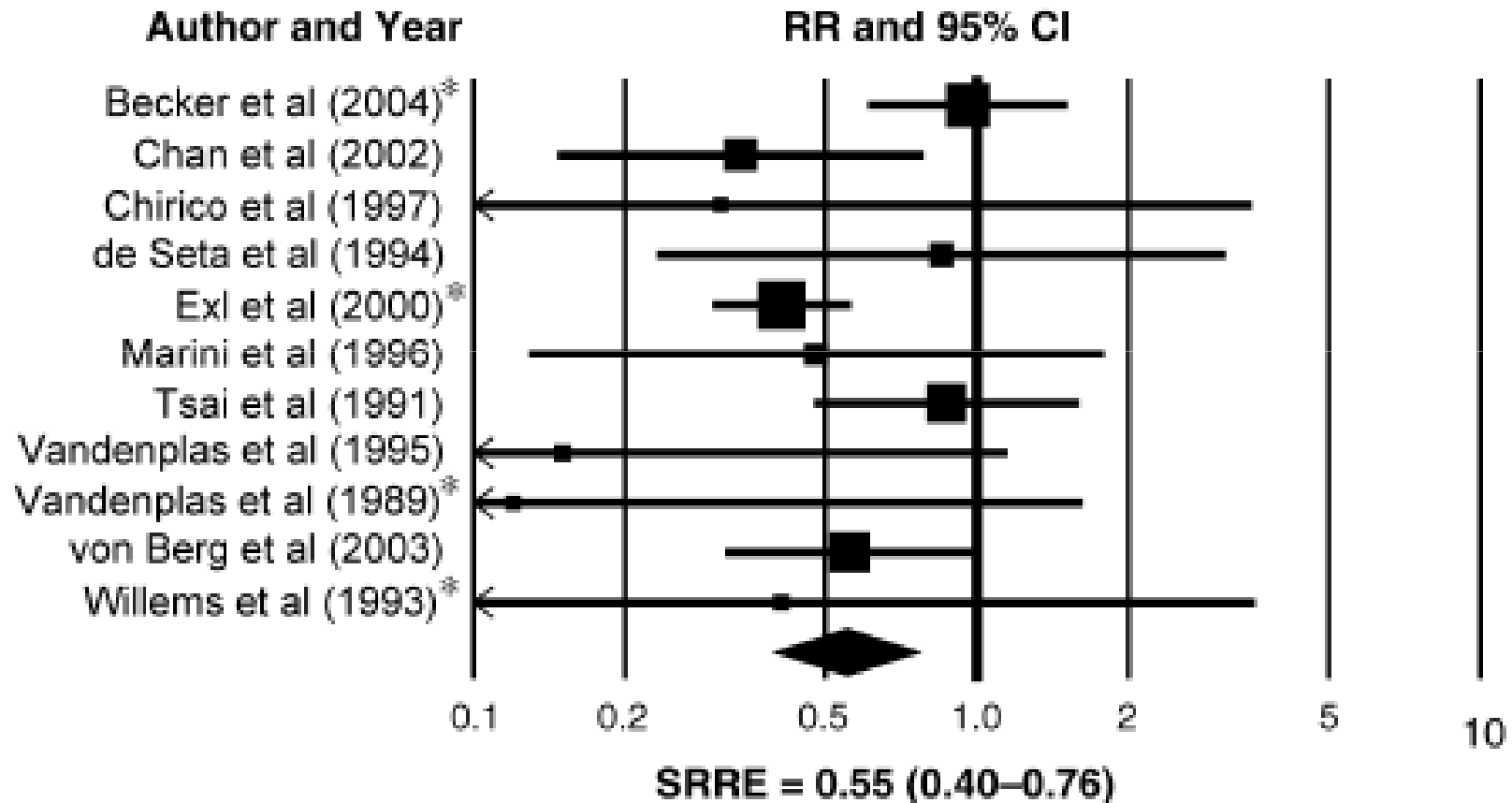


Unadjusted associations between allocated formula and risk of allergic disease

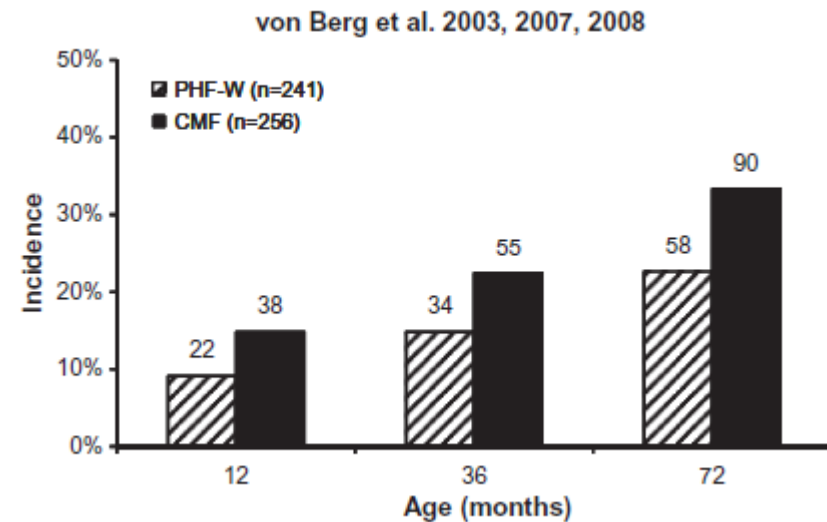
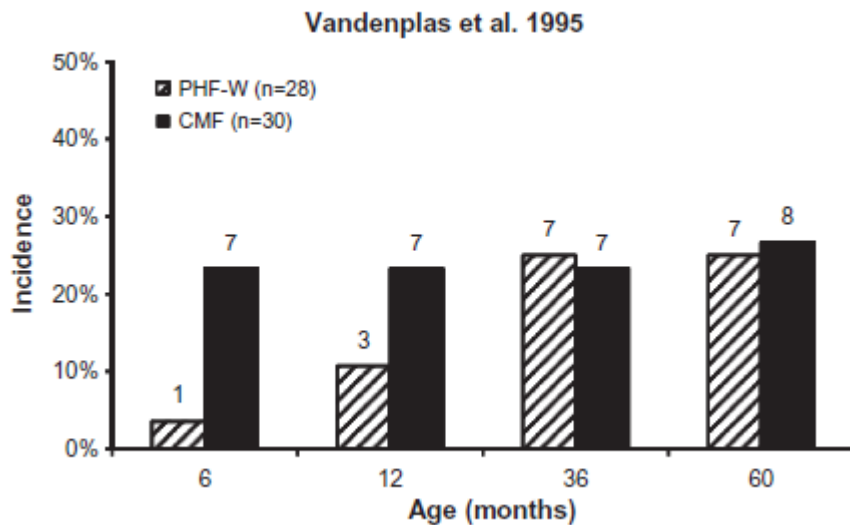
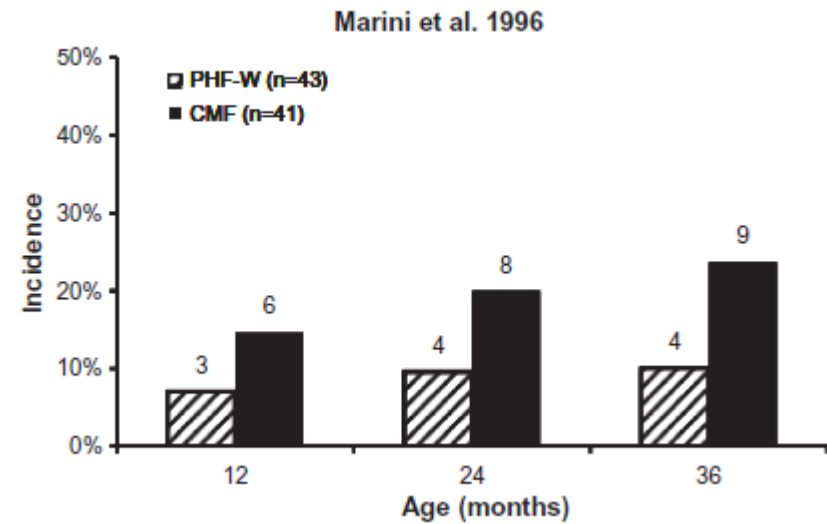
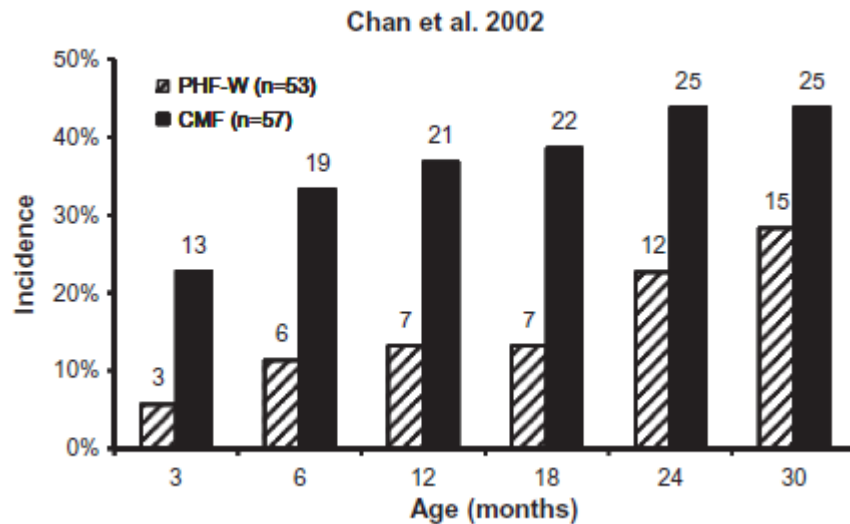
Outcome	Conventional formula (CMF)	Hydrolyzed formula (pHWF)		Soy formula	
	% (n/N)	% (n/N)	Crude OR (95% CI)	% (n/N)	Crude OR (95% CI)
Any allergic manifestation: 0-1 y (228/575)	37.3 (72/193)		1.02 (0.67-1.54)	44.0	1.32 (0.88-1.98)
Any allergic manifestation: 0-2 y (300/575)	48.7 (94/193)			54.5	
Secondary outcomes			1.21 (0.81-1.80)		1.26 (0.84-1.88)
Eczema within first 2 y	43.0 (83/193)			46.1	
Food reactions within first 2 y					
Any food (92/575)	13.5 (26/193)	15.2 (29/191)	1.15 (0.65-2.04)	19.4 (37/191)	1.54 (0.89-2.67)
Cow's milk protein (17/575)	3.1 (6/193)	1.6 (3/191)	0.50 (0.12-2.02)	4.2 (8/191)	1.36 (0.46-4.00)
Cow's milk with + SPT to cow's milk (3/575)	0 (0/193)	0.5 (1/191)	NE	1 (2/191)	NE
Peanut with + SPT to peanut (1/575)	0.5 (1/193)	0 (0/191)	NE	0 (0/191)	NE
Egg with + SPT to egg (8/575)	1.0 (2/193)	0.5 (1/191)	0.50 (0.04-5.59)	2.6 (5/191)	2.57 (0.49-13.40)
Childhood outcomes (period prevalence at 6-7 y)			1.08 (0.69-1.68)		0.95 (0.60-1.48)
Eczema (157/493)	31.5 (51/162)	33.5 (56/162)		30.5	
Asthma (148/495)	32.1 (52/162)	28.0 (47/162)	0.91 (0.57-1.45)	29.7	0.97 (0.61-1.54)
Rhinitis (117/495)	22.2 (36/162)	22.0 (37/162)		26.7	
Persistent asthma (120/494)	25.5 (41/161)	24.2 (40/162)	0.94 (0.56-1.58)	24.2	1.27 (0.77-2.10)

NE, OR not estimable.

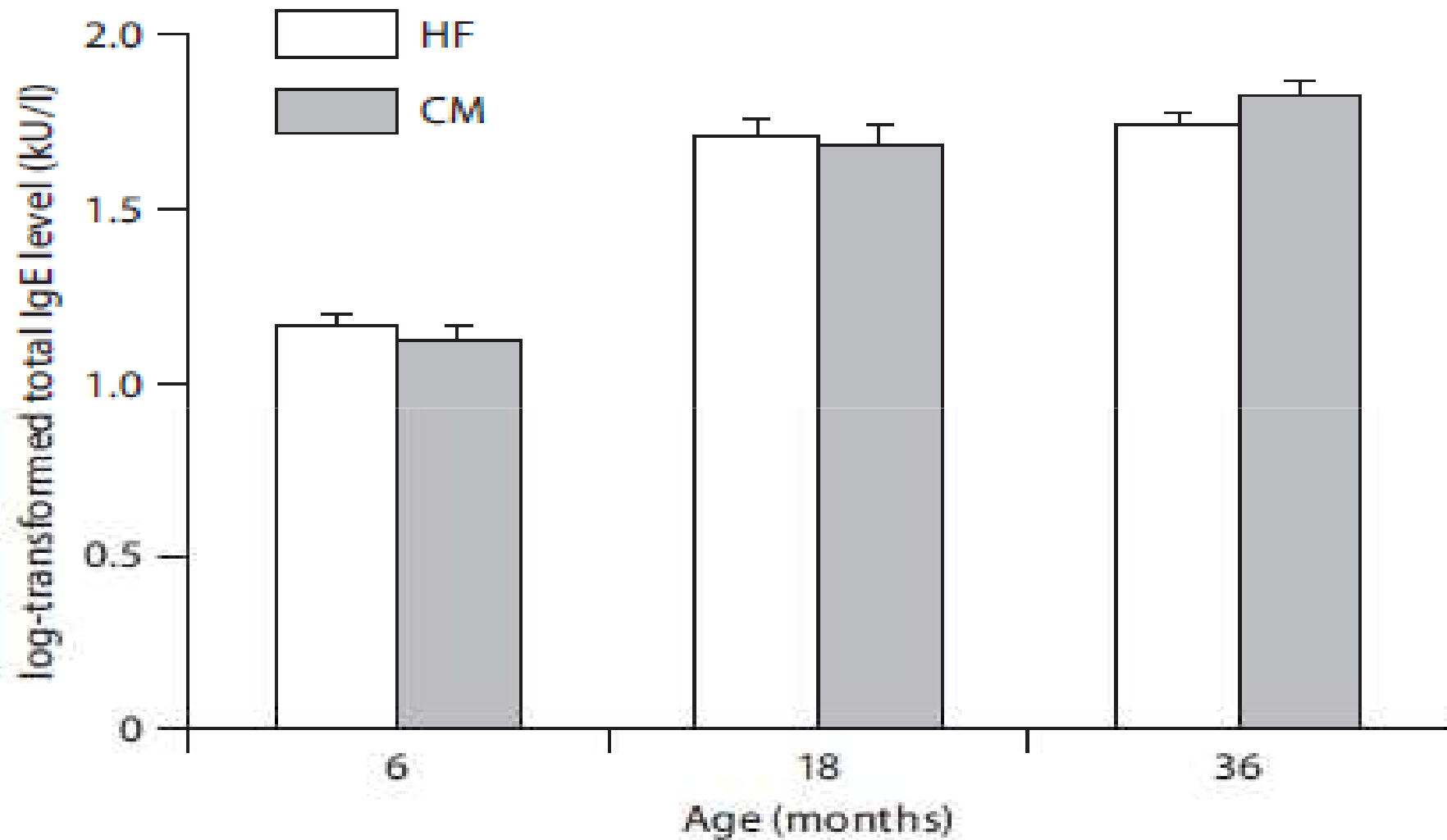
Meta-analysis results of all reviewed/top tier studies: risk of AD (PHF-W vs CMF)



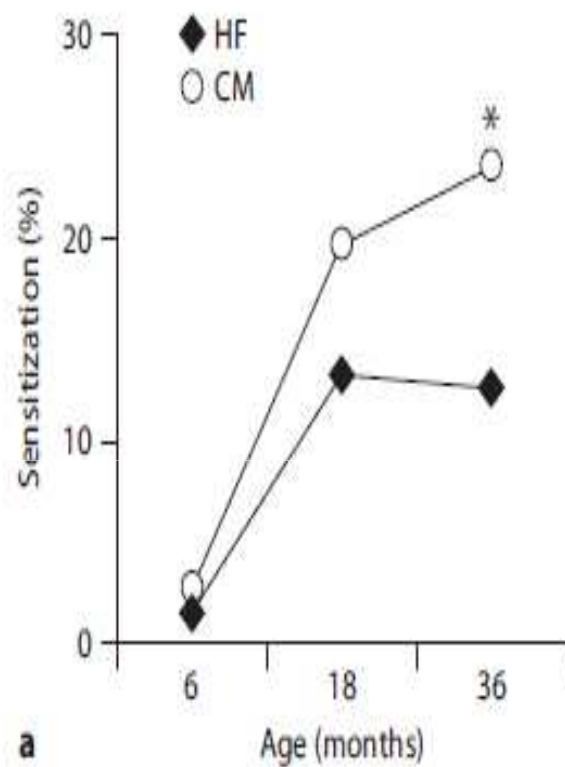
Study-Specific-Cumulative incidence of AD



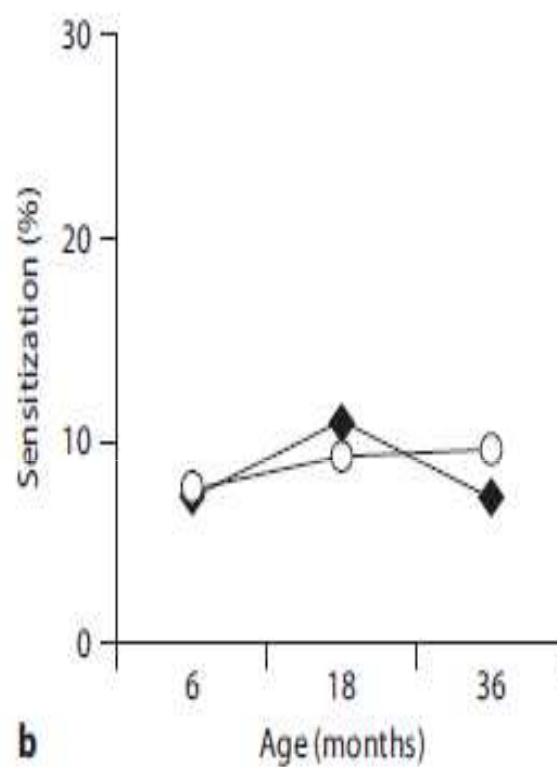
Allergic sensitization of infants fed with HF and CM



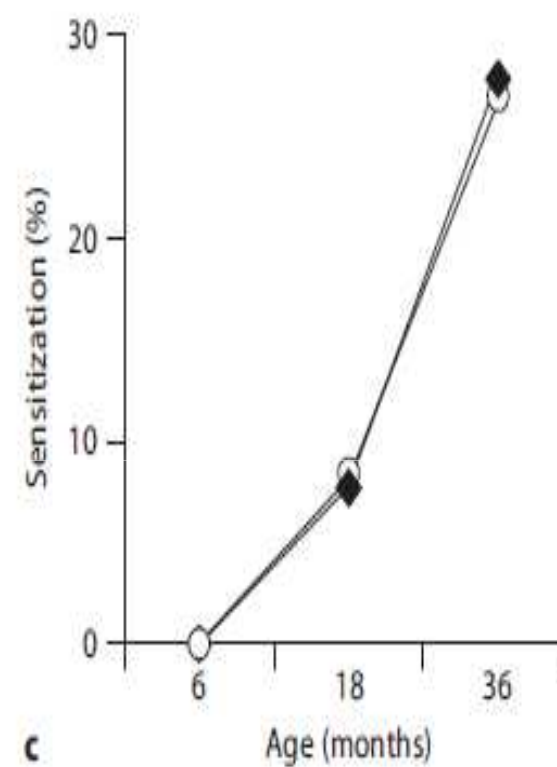
MILK



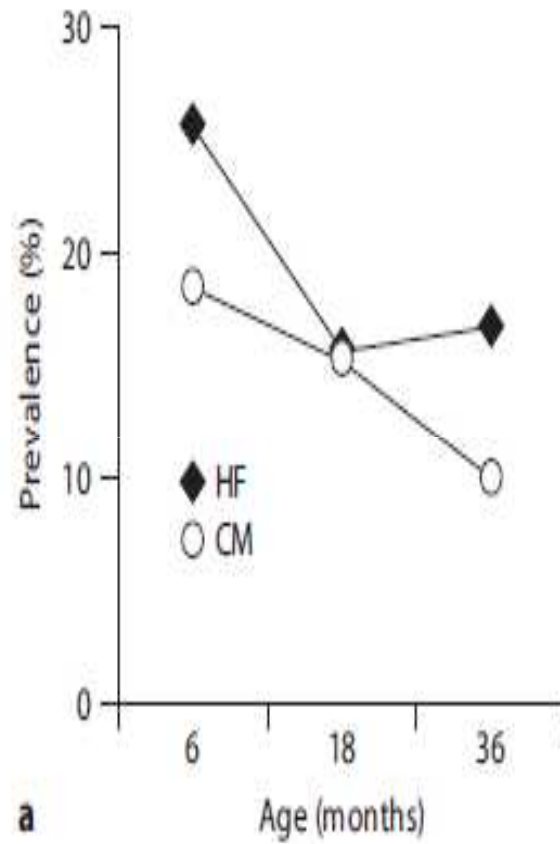
EGG



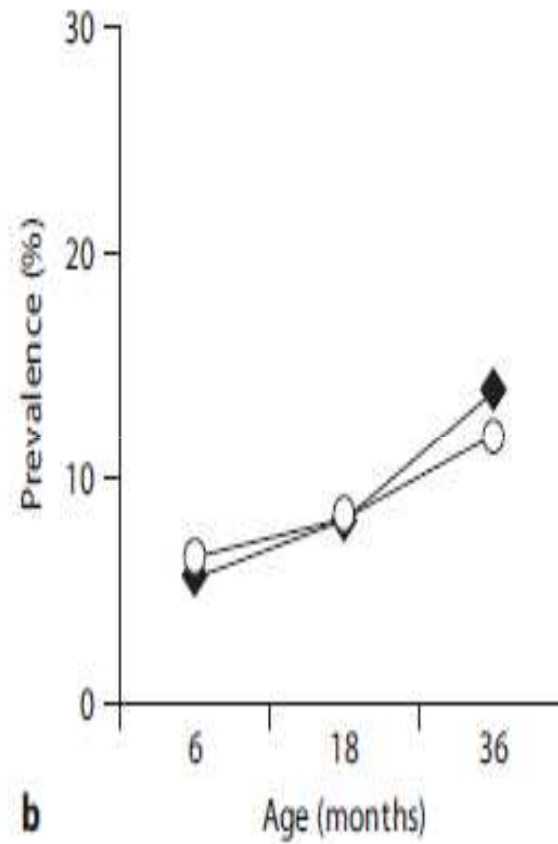
DPT



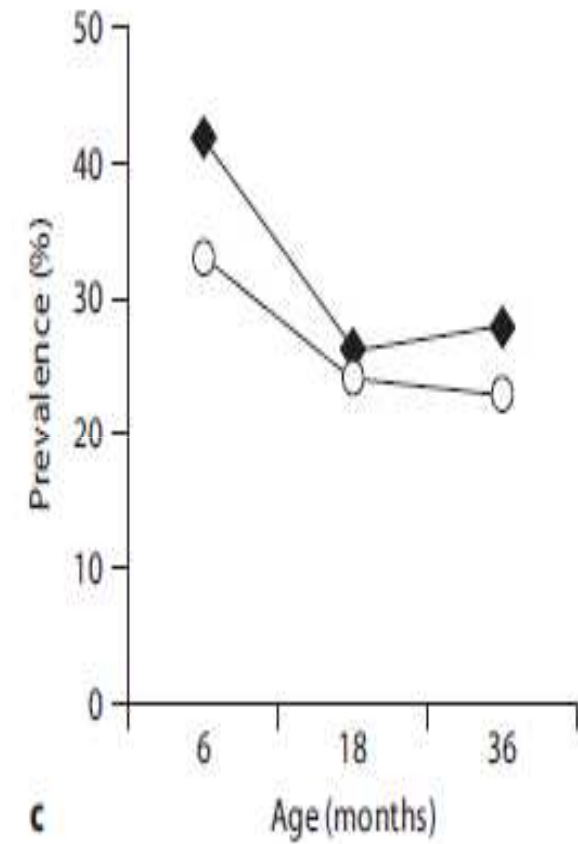
Eczema

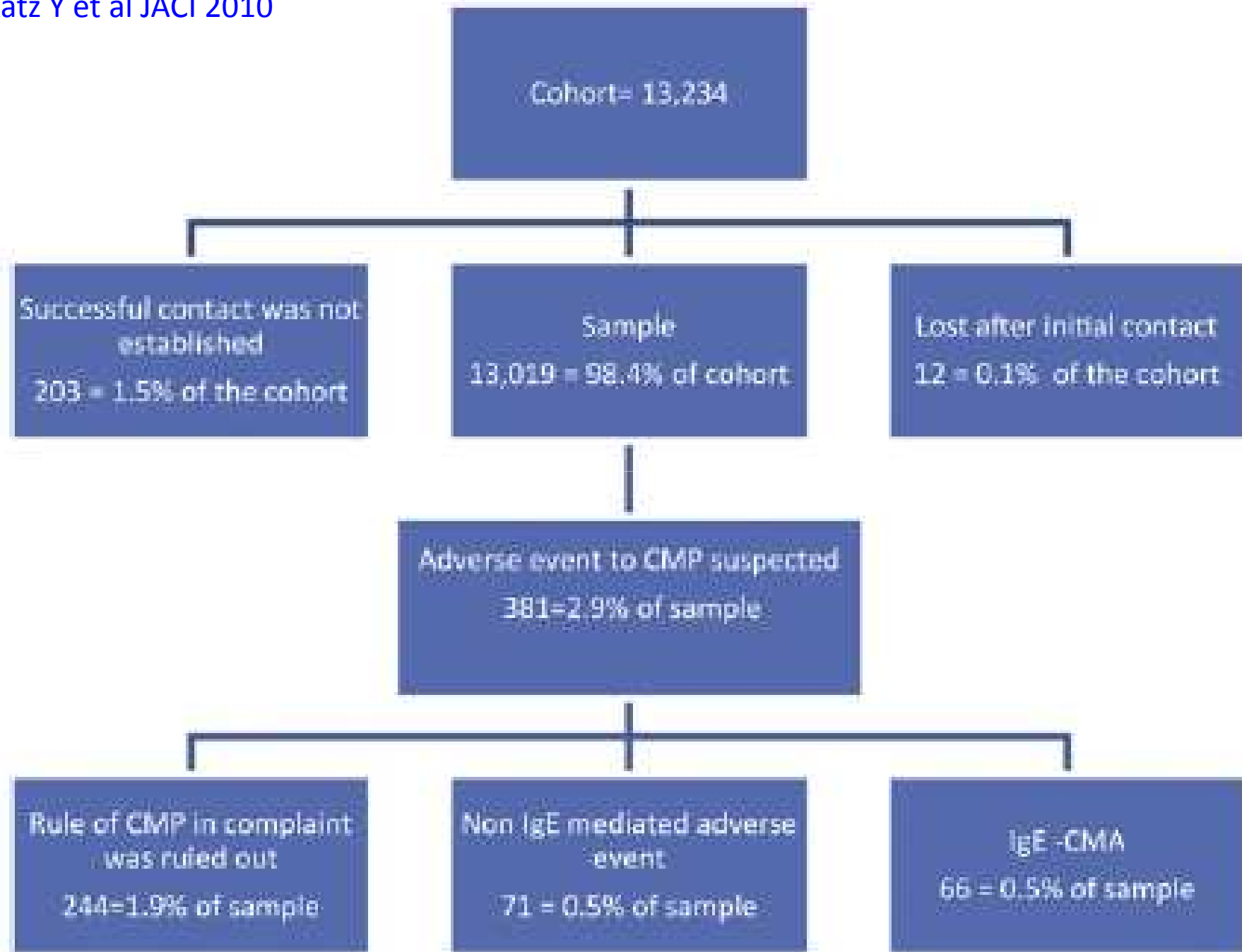


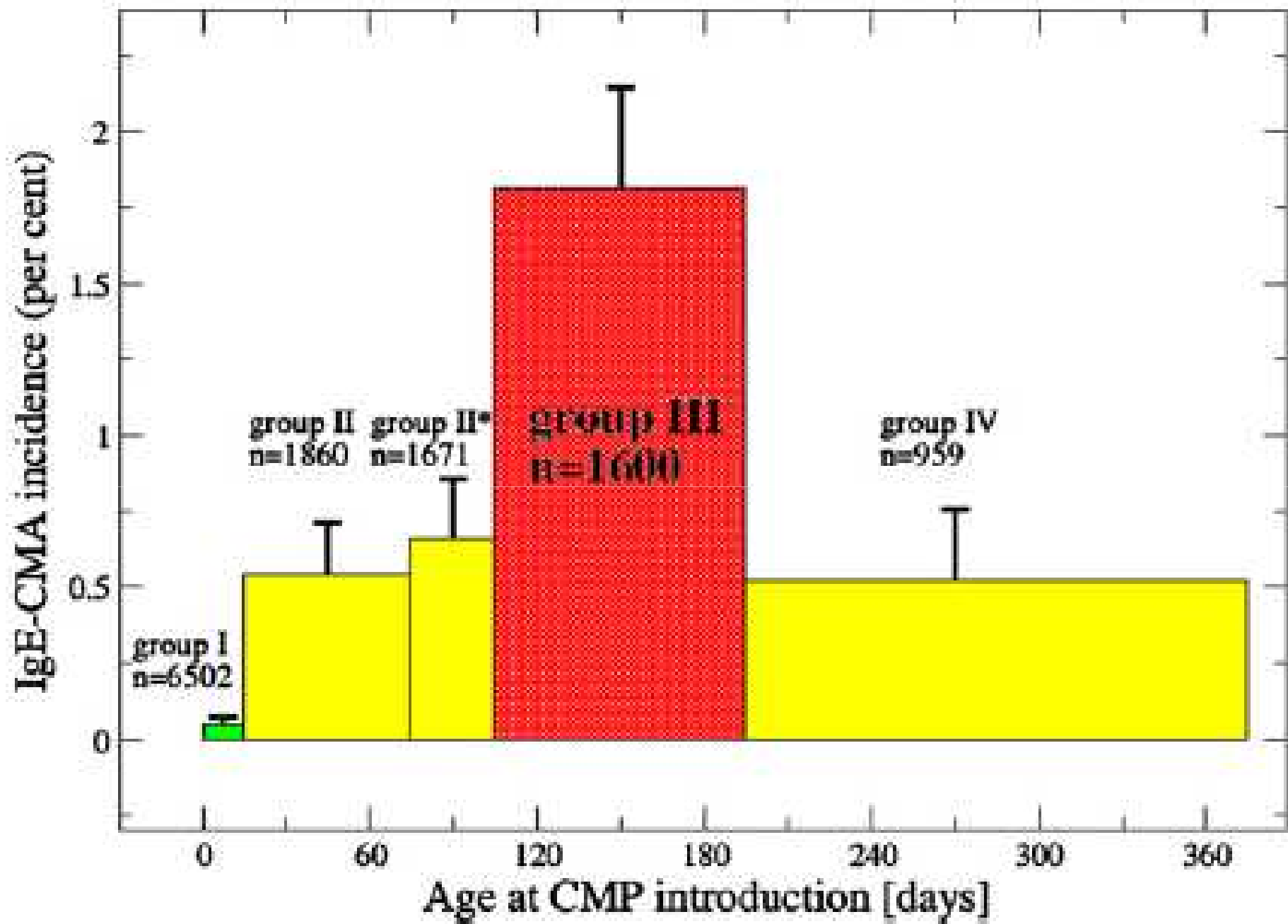
rhinitis/asthma



any allergy

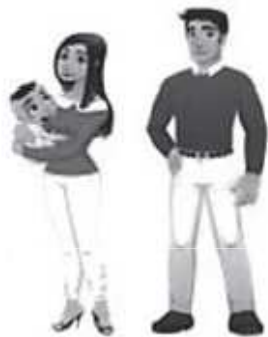






Risk factors

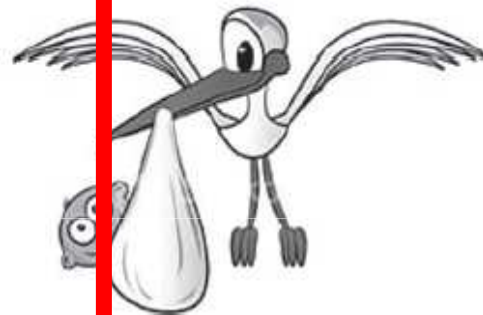
- Tobacco smoke^A
- Environmental pollutants^A
- Abnormal intestinal flora colonisation^A
- Decreased exposure to sunlight^B



Before conception



Pregnancy



Perinatal



1st year of life



Older than 1 year

- Early introduction of solid foods before 3–4 months of age^B
- Formula feeding?^B
- Diet low in n–3 PUFA, antioxidants and soluble fibre^B
- Delayed introduction of solid foods^B
- Vitamin D deficiency^C

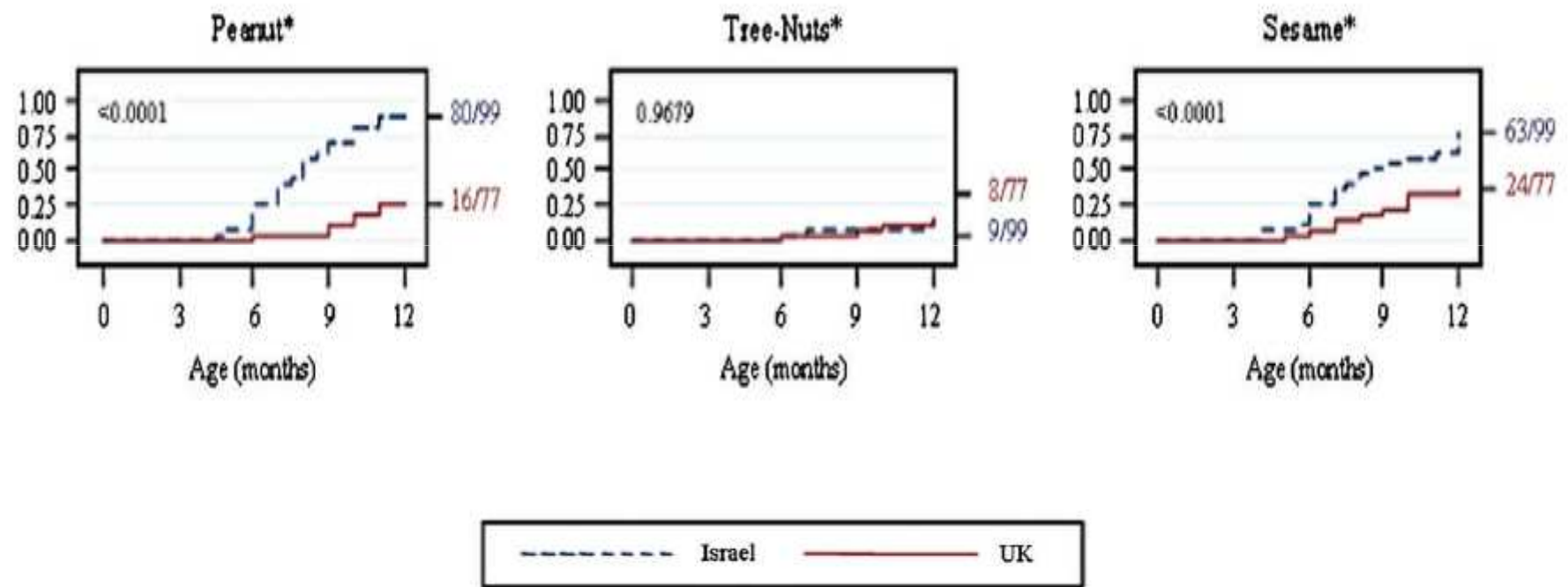
Interventions

?

- Healthy, balanced diet^C
- Pro- and prebiotics^B
- n–3 PUFA^B
- Vitamin D^A

- Breastfeeding for ≥6 months^C
- Hypoallergenic infant formula in the first 6 months if breastfeeding is not possible^C
- Introduction of solid foods at 4–6 months^C
- Pro- and prebiotics^B
- n–3 PUFA^A

- Healthy and balanced diet^A
- Pro- and prebiotics^B
- n–3 PUFA^C



Du Toit G, et al. JACI 2008

The ratio of the risk of food allergies in the UK compared with Israel

Prevalence: 1.85 vs 0.17

	Peanut		Sesame		Tree nuts		Egg		Milk	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
All individuals										
Unadjusted	10.8 (5.2-22.3)	<.001	6.1 (2.5-14.6)	<.001	15.2 (6.6-34.7)	<.001	3.4 (2.1-5.7)	<.001	1.9 (1.4-2.7)	<.001
Adjusted for age group* and sex§	10.4 (4.8-22.2)	<.001	5.3 (2.2-13.0)	<.001	14.0 (6.0-32.5)	<.001	3.1 (1.8-5.2)	<.001	1.7 (1.2-2.4)	.008
Adjusted for age group,* sex,§ food allergy,† and atopy‡	5.8 (2.8-11.8)	<.001	2.7 (1.1-7.0)	.057	8.4 (3.6-19.5)	<.001	1.8 (1.0-3.1)	.054	1.3 (0.9-1.9)	.33
Primary school										
Unadjusted	17.4 (5.5-55.6)	<.001	6.3 (2.2-18.0)	<.001	17.4 (5.5-55.6)	<.001	4.8 (2.4-9.4)	<.001	1.7 (1.1-2.5)	.012
Adjusted for sex§	16.9 (5.3-53.5)	<.001	6.1 (2.2-17.6)	<.001	16.5 (5.3-51.8)	<.001	4.6 (2.3-9.0)	<.001	1.6 (1.1-2.4)	.046
Adjusted for sex,§ food allergy,† and atopy‡	9.8 (3.1-30.5)	<.001	3.6 (1.1-12.1)	.045	9.5 (3.0-29.5)	<.001	2.5 (1.3-4.9)	.011	1.2 (0.8-1.9)	.47

2664 children had completed 2-year questionnaires and 2094 (68%) had specific IgE results at 2 years of age. Information on solid food, AD, and early skin or allergic symptoms was available for 2612 (84%) children

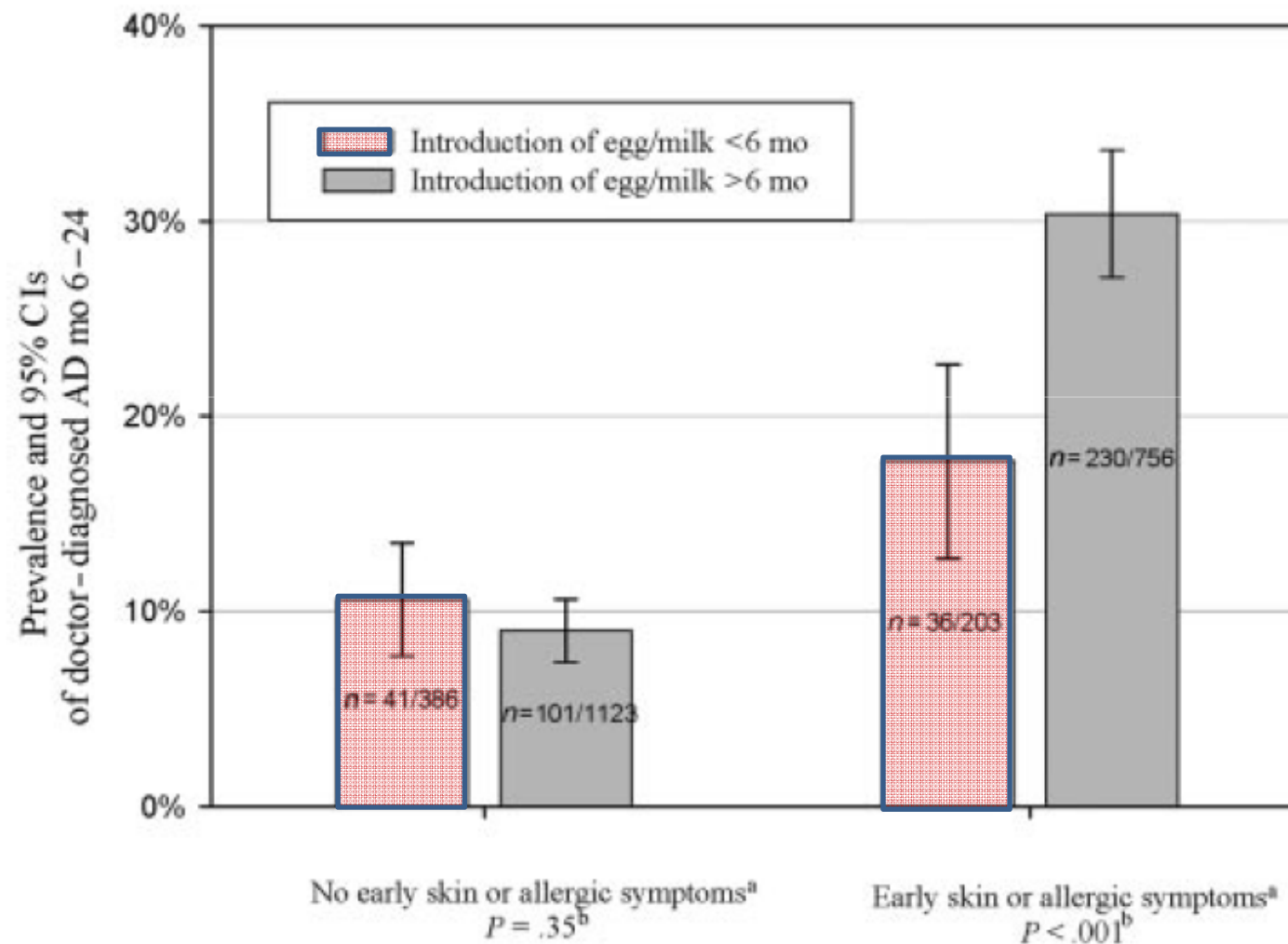




Table 1

Summary of effects of nutritional interventions during pregnancy, lactation, and infancy on the development of atopy

Intervention	Evidence
Restriction diet during pregnancy	No evidence in prevention of atopic diseases
Restriction diet during lactation	No evidence in prevention of atopic diseases with the possible exception of atopic eczema
Length of exclusive breastfeeding	Exclusive breastfeeding for at least 4 months decreases the cumulative incidence of atopic dermatitis and cow's milk allergy in the first 2 years of life in infants at high risk of developing atopic disease Exclusive breastfeeding for at least 3 months protects against wheezing in early life
Use of hydrolyzed formulas	Modest evidence that atopic dermatitis may be delayed or prevented by the use of hydrolyzed formulas in early childhood in infants at high risk of developing atopic disease. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed formulas in the prevention of atopic disease
Use of soy-based formulas	No evidence in allergy prevention
Timing of introduction of solid foods	No current convincing evidence that delaying introduction of solid food, including highly allergic foods such as fish, eggs, and foods containing peanut protein, beyond 4–6 months has a significant protective effect on the development of atopic disease. In infants after 4–6 months of age, there are insufficient data to support a protective effect of any dietary intervention for the development of atopic disease



Food allergy is defined as an adverse health effect arising from a specific immune response that is reproducible on exposure to a given food, and thus is an example of a defect in the development or a breakdown in the maintenance of oral tolerance.

Jarvinen et al. Immunol Allergy Clin N Am 32 (2012) 51-65

Table 2

Recommended practical advice for feeding infants at high risk for allergy (ie, those with at least one first-degree relative with a documented allergic condition, especially moderate to severe atopic dermatitis, food allergy, or asthma)

Breastfeeding	For the minimum first 4–6 months
Supplementation	With partially ^a or extensively ^b hydrolyzed formula for the first 6 months if unable to exclusively breastfeed
Solid food introduction	At 4–6 months starting with yellow/orange vegetables, fruits, and baby cereals; then advance to meats and different-stage foods as appropriate for feeding skills
Highly allergenic foods	Egg, dairy products other than cow's milk per se, peanut, tree nuts, fish, and shellfish can be gradually introduced to infants who have already tolerated the introduction of less allergenic foods (although cow's milk should be avoided until 1 year of age for reasons unrelated to allergy). If, however, an infant has an allergic reaction to a food, or develops moderate to severe atopic dermatitis, or has a sibling with peanut allergy, then evaluation by an allergist is suggested to determine a personalized plan for food introduction

Table 4. The role of infant feeding practices and allergy prevention

Practice	Comments
Breastfeeding and infant formula (role of hydrolysed formulas)	<ul style="list-style-type: none"> – Breast milk contains many immunomodulatory factors with tolerogenic properties [104, 105]; although the allergy-protective effects of breast milk have been inconsistent the evidence is limited to observational studies for ethical reasons; breastfeeding has many benefits for mother and child – Early studies suggested that hydrolysed formulas have an allergy-preventive effect in randomised prospective studies of high-risk infants [61, 134–136] – More recently, a much larger RCT (GINI, n = 2,252 infants) [112, 114, 115] confirmed the allergy-protective effects of hydrolysed formulas; long-term follow-up at 6 years showed a reduced risk of allergic manifestations with both partially and extensively hydrolysed formulas [112] <p><i>Summary:</i> Breastfeeding is recommended whenever possible for the many benefits for mother and child. If breastfeeding is not possible, a hydrolysed formula (usually a partially hydrolysed formula) is recommended for infants at high risk of allergic disease (i.e. infants with parents or siblings who have a history of allergic disease)</p>
Complementary feeding practices (and allergen avoidance)	<ul style="list-style-type: none"> – Early observational studies noted an association between early introduction of solid food (<3–4 months) and early eczema [137, 138] – This prompted combined dietary strategies in high-risk infants (maternal allergen avoidance in pregnancy and lactation, hydrolysed formula, delayed complementary feeding, prolonged avoidance of allergenic foods); initial reports suggested less food-associated atopic dermatitis, urticaria and/or gastrointestinal disease by 12 months [139]; some of these effects may have been due to hydrolysed formula rather than allergenic food avoidance; many of these restrictive practices were incorporated into recommendations for allergy prevention, although subsequent follow-up showed no long-term benefits [140] – Many subsequent studies have failed to show any consistent evidence that delaying the introduction of complementary solid foods beyond 6 months reduces the risk of allergy [reviewed in ref. 7, 91–94] – There have been some suggestions that delaying introduction of foods may actually increase (rather than decrease) allergy; however, at this stage, this is not proven <p><i>Summary:</i> Based on the currently available evidence, many experts across Europe, Australia and North America recommend introducing complementary solid foods from around 4–6 months, with no specific avoidance of allergenic foods [7, 91–94]. More research is needed to determine the optimal time to start complementary solid foods and a number of RCT are exploring the role of earlier introduction of allergenic foods to induce tolerance</p>

Table 2. The role of probiotic and prebiotics supplements in allergy prevention

Supplement	Comments
Probiotics	<ul style="list-style-type: none">– In initial studies using <i>Lactobacillus</i> GG in a randomised human trial (159 mothers supplemented before delivery and infants supplemented for 6 months), analysis showed a 50% reduction in eczema at age 2 years; the protective effect persisted up to 7 years of age [117, 118]; the prevalent eczema was very low and not different from the probiotic-treated group– While there are a number of recognised effects of gut microflora on immune development, the mechanism of the clinical effect seen in this study is not clear; there was no effect on allergic sensitisation, or other allergic outcomes– Subsequent studies of the same strain in other populations have shown no effect [45]– The effects of probiotics are variable and appear to depend on the strain, the timing, method of administration, host and other environmental factors [reviewed in ref. 42] <p><i>Summary:</i> The revised Cochrane meta-analysis concludes that there is some evidence that a probiotic or a synbiotic containing <i>L. rhamnosus</i> may reduce the incidence of eczema in infants at high risk of allergic disease, but that there are no reproducible data for other probiotics; there is no evidence that any probiotic prevents other allergic conditions or sensitisation; they also advised caution based on methodological concerns with some of the included studies</p>
Prebiotics	<ul style="list-style-type: none">– Initial studies using prebiotics in cow-milk-based formula showed reduced cumulative incidence of allergic outcomes in high-risk children including atopic dermatitis, recurrent wheezing and allergic urticaria in the treatment group compared with the placebo at 2 years; there were also reduced respiratory tract infections, fever episodes and antibiotic prescriptions reported [48]– Subsequent studies have also found a reduced risk of atopic dermatitis in children at low risk of allergic disease [50]– Mechanisms of effect are likely to include effects in promoting favourable colonisation with healthy commensal bacteria, as well as direct effects on the immune system [63, 64] <p><i>Summary:</i> There is encouraging evidence that prebiotics have a number of health-promoting effects, including immune effects, which may reduce the risk of allergic and infectious outcomes; the results of several large multicentre studies are awaited with interest as there are still relatively few studies to report on allergy outcomes</p>

Table 3. The role of other specific nutritional supplements in allergy prevention

Supplement	Comments
n-3 PUFA (fish oil)	<ul style="list-style-type: none">– Epidemiological studies suggest dietary n-3 PUFA exposure in pregnancy [119, 120] and early childhood [54, 121] may protect against asthma and allergic disease– There are well-described immune effects of n-3 PUFA, including a range of anti-inflammatory properties [122]– RCT using fish oil in pregnancy demonstrate immunological effects [22] and some evidence of reduced allergic outcomes [61, 62, 123]– Postnatal interventions with fish oil have not shown consistent or long-term benefits [56, 57] <p><i>Summary:</i> The current findings suggest that any allergy-protective effects of increasing n-3 PUFA status are more likely to be greatest in pregnancy (i.e. earlier in development); the largest, most definitive RCT (n = 706 mothers of high-allergy-risk infants) recently found that fish oil in pregnancy was associated with a reduced risk of both eczema and egg sensitisation [123]; because of the differential effects of n-3 PUFA in the antenatal versus the postnatal period, future systematic reviews should examine these interventions separately</p>
Vitamin D	<ul style="list-style-type: none">– Based on recognized immunoregulatory effects and declining levels with more sedentary lifestyles, vitamin D has been proposed as a candidate factor in the rise in both ‘autoimmune’ and ‘allergic’ diseases [124]– Several authors have demonstrated a protective relationship between maternal vitamin D intake or status and asthma, wheezing or allergic rhinoconjunctivitis in children [125–127]; this is supported by studies showing a protective association between decreasing latitude (and by extension, likely higher vitamin D status through sunlight exposure) and allergic disease in both Australia and the US [73, 128, 129]– On the other hand, highlighting the conflicting literature, a contrary argument that relative vitamin D excess may increase the risk of allergic disease has also been proposed based on other observational [130–132] and immunological [133] studies <p><i>Summary:</i> There is a sound basis for further investigating the role of changing vitamin D status in the rising rates of immune disease; to address this more definitively, RCT are needed: several pregnancy trials are underway and the findings of these are awaited with great interest</p>

Breastfeeding

Many studies have shown that breastfeeding may have the protective effect against future atopic dermatitis and early childhood wheezing. ESPGHAN and the European Society for Paediatric Allergology and Clinical Immunology jointly recommend exclusive breast-feeding for 4-6 months for allergy prevention, while the WHO recommends exclusive breastfeeding for 6 months.

Dietary products with reduced allergenicity

For clinical practice, based on the current evidence, currently recommendations state that infants with a documented hereditary risk of allergy (i.e., an affected parent and/or sibling) who cannot be breastfed exclusively should receive a formula with confirmed reduced allergenicity, i.e., a partially or extensively hydrolyzed formula, as a means of preventing allergic reactions

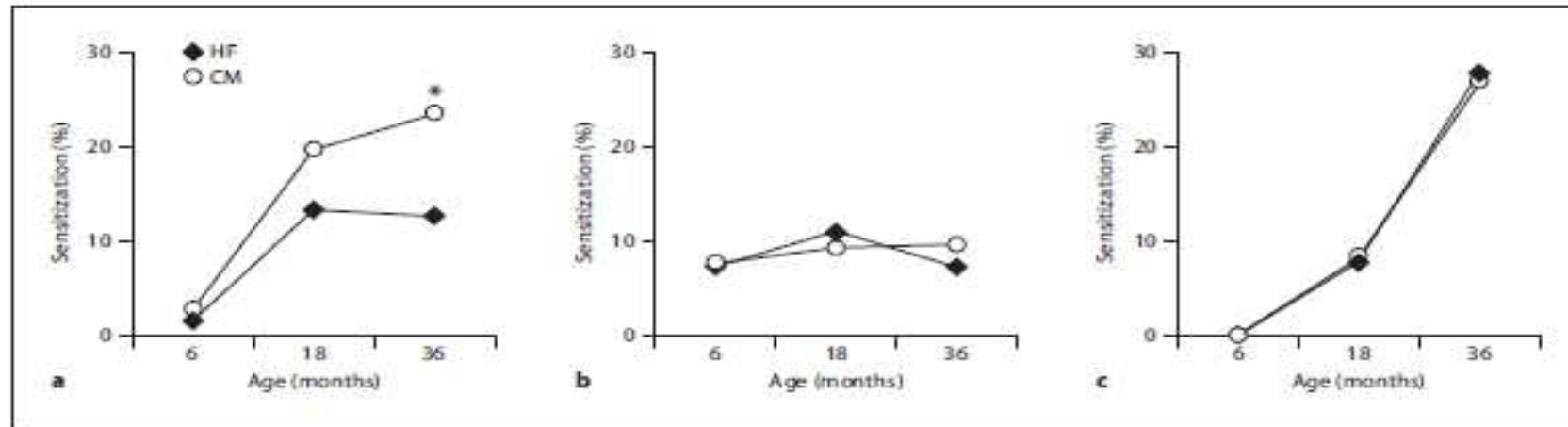


Fig. 3. Percentages of infants sensitized to different allergens at 6, 18 and 36 months of age. **a** Milk protein sensitization. The asterisk indicates a significant difference between the two study groups as determined by Pearson's χ^2 test. **b** Egg white sensitization. **c** *D. pteronyssinus* sensitization.

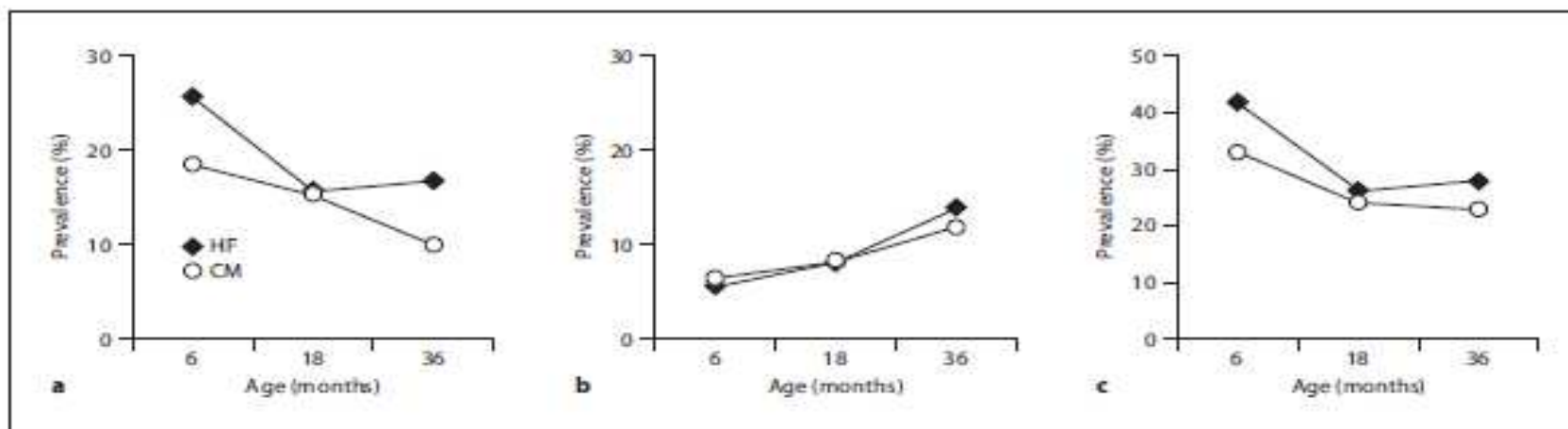


Fig. 4. Prevalence of allergic diseases in infants at 6, 18 and 36 months of age. **a** Prevalence of eczema/atopic dermatitis. **b** Prevalence of allergic rhinitis/asthma. **c** Prevalence of any allergic diseases.

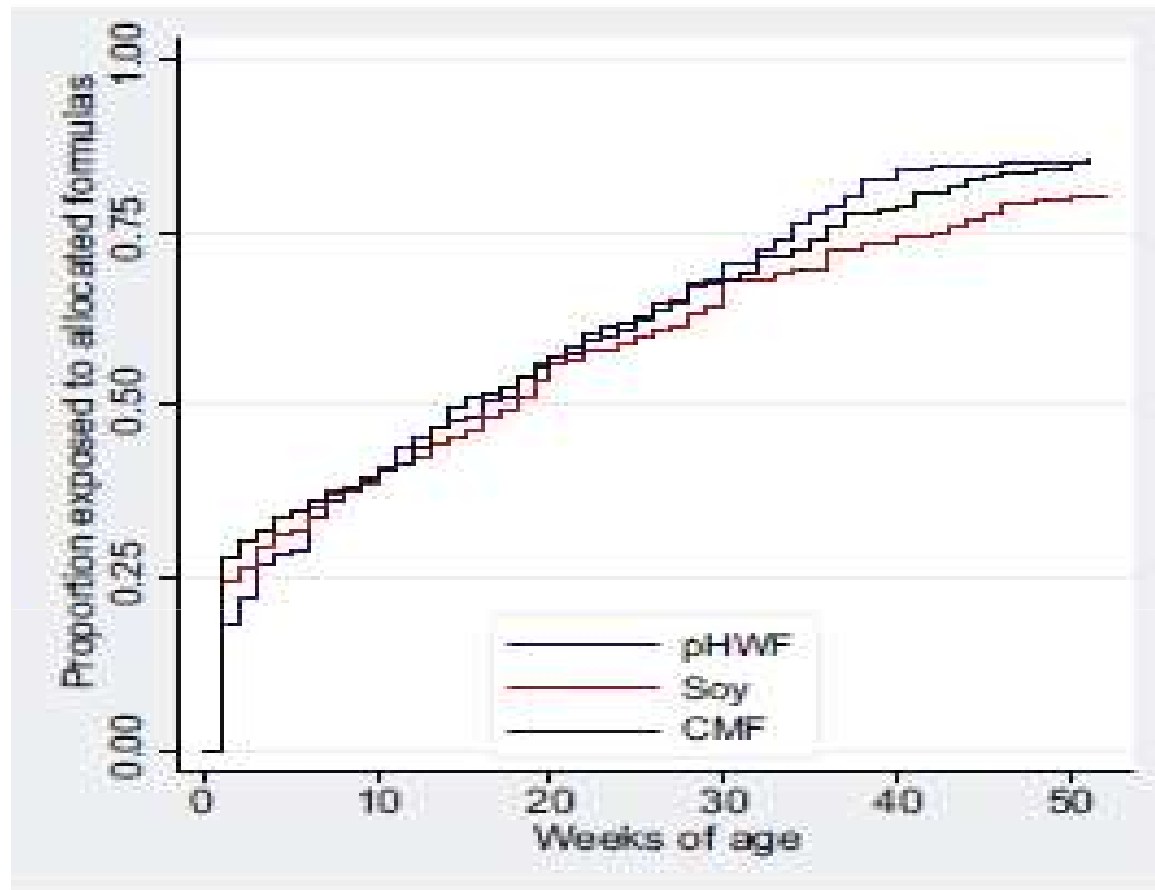


FIG 2. Proportion of infants exposed to the allocated formula from the time of birth (0 weeks) until 52 weeks of age.

Lowe et al. J Allergy Clin Immunol 2011;128:360-5

Complementary food

Previously, for complementary feeding, early exposure to solid foods during infancy was associated with the development of allergic diseases, particularly eczema. Currently, the guidelines downplay the role of solid foods in the development of allergies, stating that there is no convincing scientific evidence that the avoidance or delayed introduction of potentially allergenic foods (e.g., cow's milk, egg, peanut, tree nut, fish and seafood) beyond 4-6 months reduces allergies in infants considered to be at increased risk for the development of allergic diseases or in those not considered to be at increased risk.

Probiotics and/or prebiotics

- Negli ultimi anni è stata posta particolare attenzione al ruolo che la flora batterica dell'intestino può svolgere nel promuovere la maturazione del sistema immunitario fin dai primi giorni di vita. Nel neonato un appropriato stimolo microbico è di estrema importanza per equilibrare il rapporto Th1/Th2, che alla nascita è sbilanciato verso la risposta Th2.
- Numerosi studi clinici hanno dimostrato che la selezione di ceppi batterici come *Lactobacilli* e *Bifidobacteri*, attraverso l'integrazione nella dieta di probiotici, può facilitare lo sviluppo della tolleranza e, ritardare o evitare la sensibilizzazione agli allergeni.
- Le più recenti metaanalisi traggono la conclusione che **non ci sono sufficienti evidenze per consigliare l'uso dei probiotici nella prevenzione dell'allergia.**

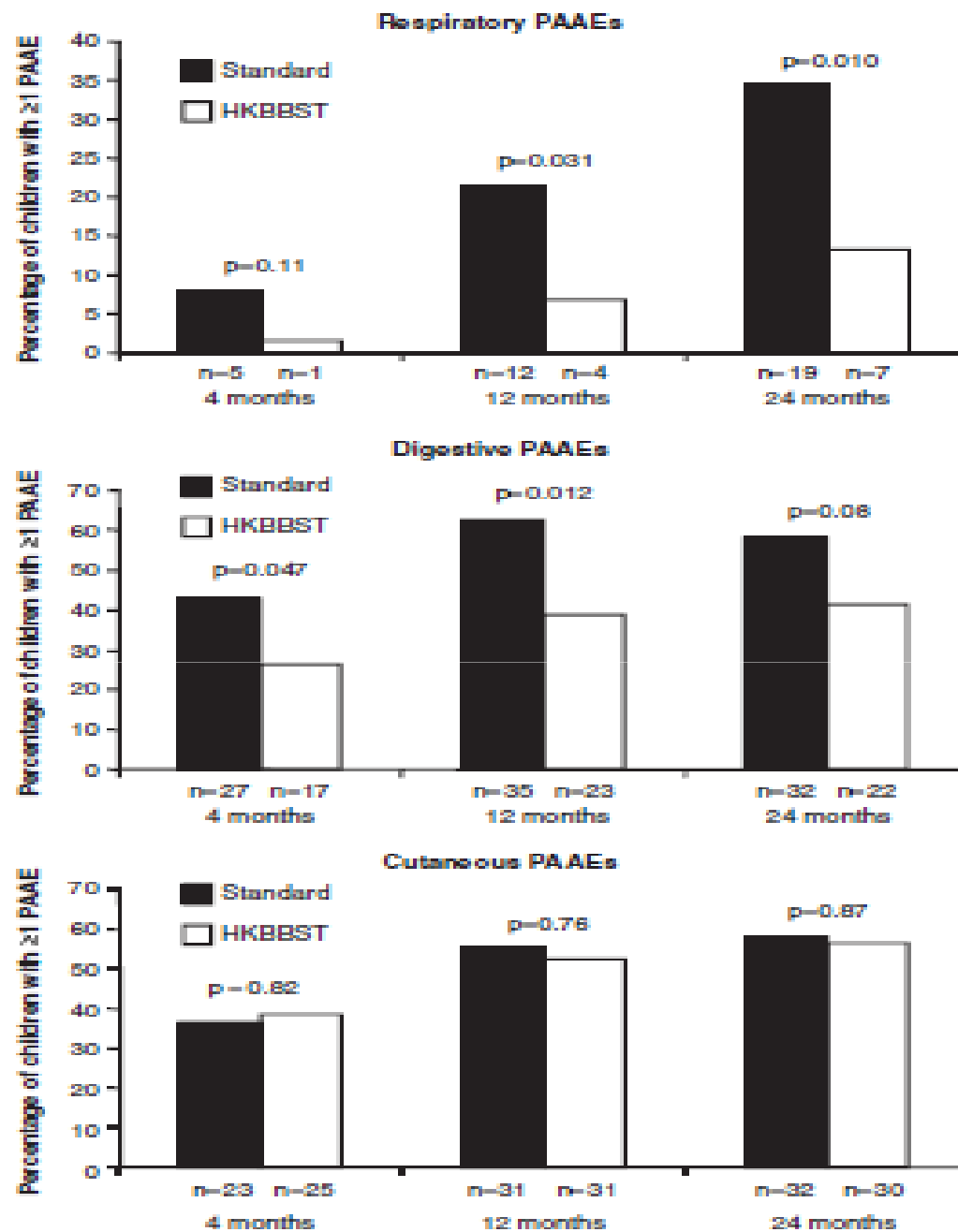


Figure 3 Percentage of children with respiratory, digestive or cutaneous PAAEs in standard and HKBBST groups at 4, 12 and 24 months.

**Morisset et al. European
Journal of Clinical Nutrition
(2011) 65, 175-183**

Other nutritional interventions

Neither can specific recommendations be made for the use of long-chain polyunsaturated fatty acids, antioxidants (e.g., vitamin C, vitamin E, beta-carotene, zinc), folate, and vitamin D.

Dieta di eliminazione

- Nelle fasce d'età successive, la rigorosa **dieta di eliminazione** della durata di un paio di settimane circa rimane l'approccio terapeutico tuttora maggiormente consolidato. Prevede l'allontanamento dell'agente causale per un periodo di tempo variabile, finalizzato alla naturale acquisizione della tolleranza, che in oltre l'80% dei casi si verifica entro i primi 3 anni di vita. Se la dieta di eliminazione comporta un netto miglioramento dei sintomi senza ricorrere a farmaci, supporta la diagnosi fino alla conferma che è ottenuta con il **test di scatenamento**.
- Sebbene accettata universalmente come trattamento sintomatico e preventivo nei confronti delle reazioni avverse, la dieta di eliminazione rimane lontana dall'essere considerata risolutiva. Comporta piuttosto il costante pericolo di esposizione accidentale all'alimento, con manifestazioni cliniche anche letali.

Test di Provocazione Orale

Il test alimentare orale (OFC) è considerato il test standard di riferimento per la diagnosi di allergia alimentare, essenziale per la pianificazione dei regimi di eliminazione, per ridurre il rischio di esposizione accidentale.

Conclusioni

- There were no data suggesting that diet modification changed sensitization of other food allergens or aeroallergens.
- Early nutrition may have profound implications for long-term health and atopy later in life, it presents an opportunity to prevent or delay the onset of atopic diseases.
- There have been attempts to reduce the risk of the development of allergy using dietary modifications, from promoting longer breast-feeding and delayed introduction of potentially allergenic foods to active prevention of atopy using specific dietary components.
- Still, there are many open questions and additional studies are needed to document the long term effect of dietary interventions in infancy to prevent atopic disease.