

Prevention of Allergic Disease

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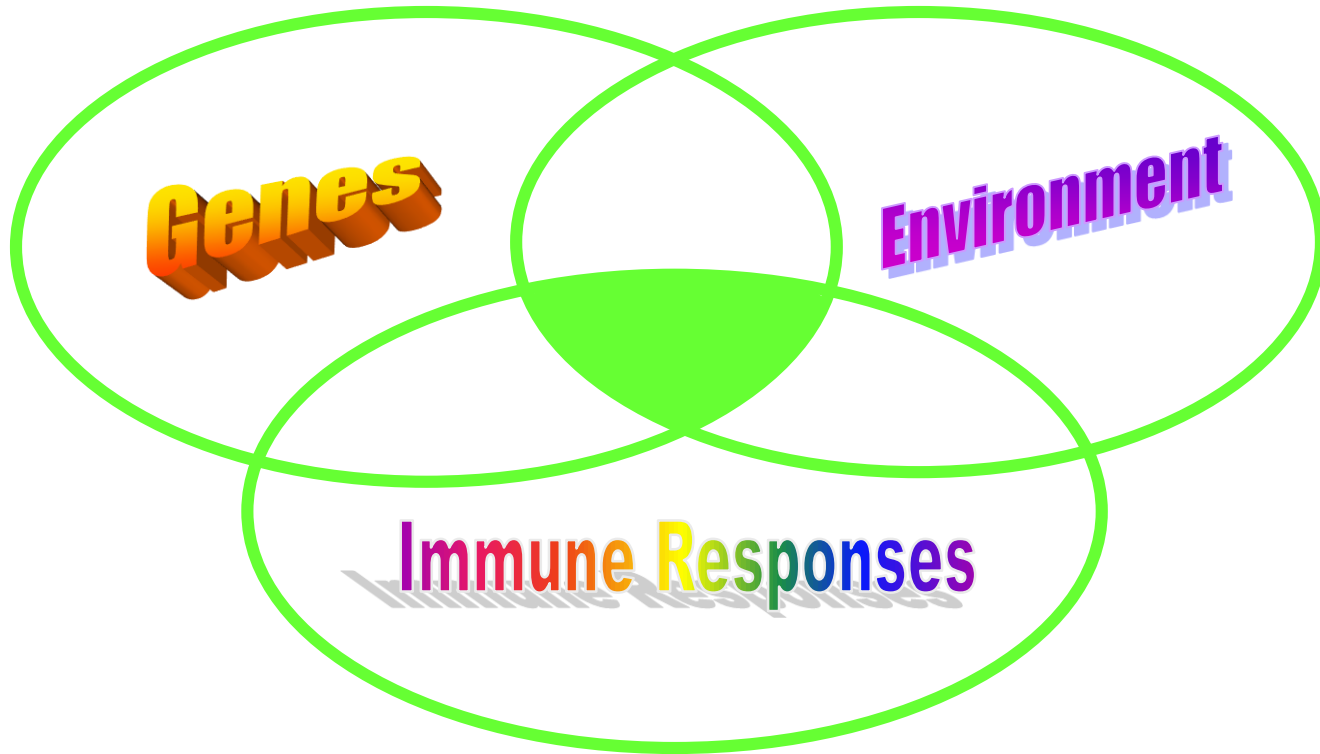
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Determinants of Allergic Disease



- Rapid rise in prevalence must relate to changes in the environment
- Understanding the environmental factors leading to allergic disease can aid the development of prevention and treatment strategies

Environmental Influences

- Microbial exposures in early life
 - Hygiene hypothesis
 - Intestinal microbiota
 - Probiotics and Prebiotics
 - Breastfeeding
 - Timing of exposure to food allergens
-
- Vitamin D / UV exposure
 - Immunomodulatory dietary factors
 - Omega-3 fatty acids
 - Folate?
 - Pollutants

Prevention of Allergic Disease

- Prevention guidelines.... for babies at **INCREASED RISK** of allergic disease (family history of allergic disease)
 - Breastfeed for at least 6 months
 - If unable to breastfeed in first 4-6 months, introduce hydrolysed formula (in Australia, partially hydrolysed HA formulas)
 - Introduce complementary foods from 4-6 months
 - Avoid exposure to cigarette smoke
 - Elimination diets during pregnancy or lactation **not** recommended
- ASCIA infant feeding guidelines.... for **ALL** babies
 - Breastfeed for at least 6 months
 - Introduce foods from 4-6 months
 - This applies to all foods
 - This applies to babies with eczema

Benefits of breastfeeding and breast milk

- Breast feeding helps the **emotional bond** between mother and child and contributes to the emotional development of the infant
- Breast milk is **nutritionally complete** for infants from 0 to 6 months
 - contains all the nutrients a baby needs for growth and development & is easily digested
- Breast milk contains large number of **immune factors** such as immunoglobulins, cytokines, prebiotics etc that assist in gut maturation, physiological development and immunity
 - Breast fed babies have fewer and less severe infections
- Breast feeding may lower risk of developing chronic diseases such as childhood obesity, diabetes, CVD in later life
- Breast milk promotes a healthy gut microbiota
 - Higher numbers of 'good' bacteria, fewer pathogenic bacteria

Breast feeding and Prevention of Allergic Disease

- Systematic Reviews fail to show a protective effect for breastfeeding in prevention of allergic disease ¹
- Studies with longer term follow up show increased risk for food allergy, asthma, rhinitis ²⁻⁵
- Methodological issues with breastfeeding studies
 - Unethical to randomise breastfeeding as an intervention
 - Recall bias and reverse causation
 - Variable definitions of breastfeeding and allergic outcomes
 - Failure to adjust for confounding factors
 - Risk factors for allergic disease
 - Study population – allergic disease risk, breast milk composition

1. Yang YW et al. Br J Dermatol 2009;161: 373
2. Matheson MC et al. J Allergy Clin Immunol 2007;120: 1051-1057
3. Rusconi F et al. Am J Respir Crit Care Med 1999;160: 1617-1622
4. Wright AL et al. Thorax 2001;56: 192-197
5. Sears MR et al. Lancet 2002;360: 901-907

Systematic Reviews show no beneficial effects for breastfeeding in prevention of allergic disease

Table 2. Pooled Odds Ratios (ORs) According to Study Characteristics Yang YW et al. Br J Dermatol 2009;161: 373

Group	Pooled OR (95% CI)	Number of study populations ^a	Between-group heterogeneity, <i>P</i> -value
<i>Categorical variable</i>			
Comparison group			0.15
Partial breastfeeding	0.95 (0.76-1.18)	18	
Conventional formula	0.70 (0.50-0.99)	9	
Adjusted for AD risk factors			0.10
Yes	0.96 (0.78-1.20)	13	
No	0.70 (0.51-0.96)	14	
Presence of family history ^b			0.53
Yes	0.78 (0.58-1.05)	16	
No	0.93 (0.60-1.45)	6	
Outcome assessment			0.17
Self-reported	1.01 (0.76-1.35)	8	
Physician-diagnosed	0.78 (0.61-0.99)	19	
<i>Continuous variable</i>			
Breastfeeding duration, per 1-month increase	0.98 (0.80-1.20)	27	0.82
Follow-up, per 1-year increase	1.08 (0.97-1.21)	27	0.16
Publication year, per 1-year increase	1.02 (1.00-1.04)	27	0.03

CI, confidence interval; AD, atopic dermatitis. ^aTwenty-seven study populations extracted from 21 studies. ^bIncludes only studies with family history-specific ORs.

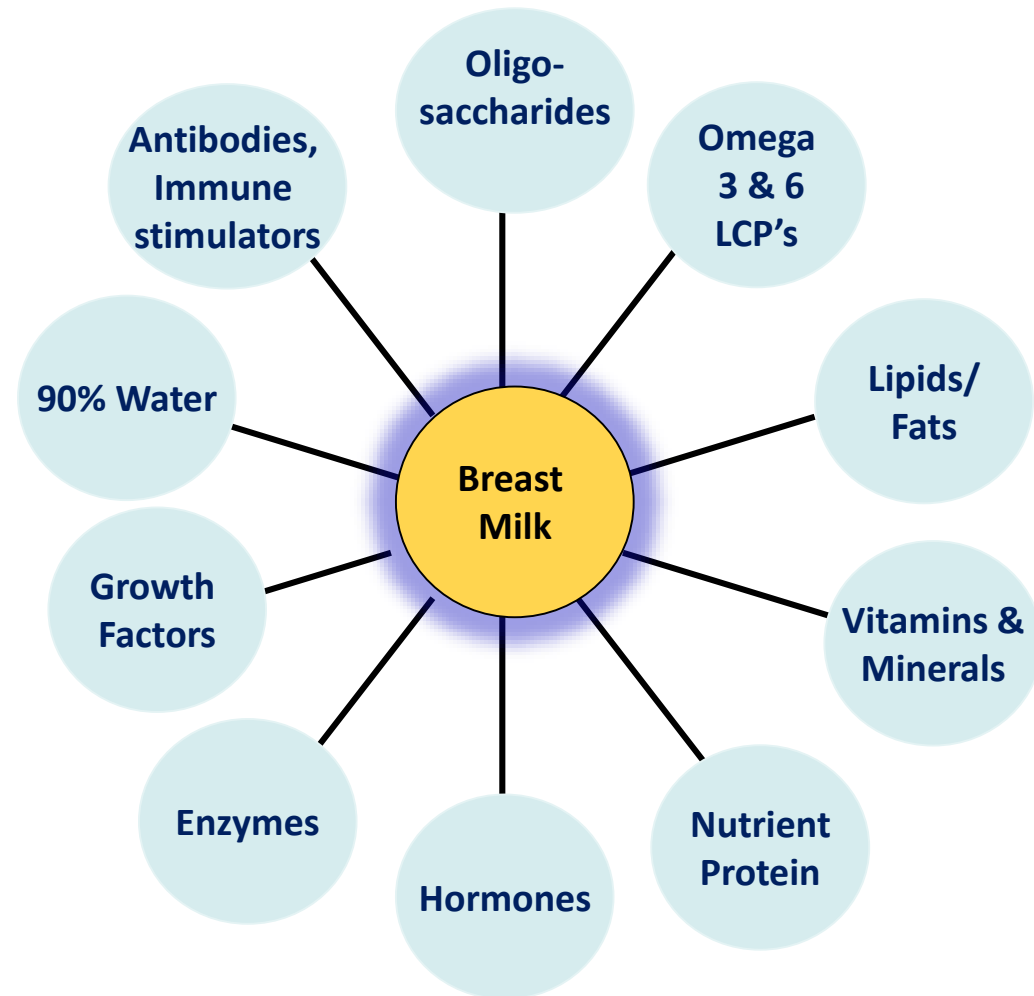
Breast Milk Immune Factors

Anti-microbial compounds
 Immunoglobulins: sIgA, SIgG, SIgM
 Lactoferrin, lactoferrin B and H
 Lysozyme
 Lactoperoxidase
 Nucleotide-hydrolyzing
 Antibodies
 κ-casein and α-lactalbumin
 Haptocorrin
 Mucins
 Lactadherin
 Free secretory component
 Oligosaccharides and pre-biotics
 Fatty acids
 Maternal leukocytes and Cytokines
 sCD14
 Complement and complement receptors
 β-defensin-1
 Toll-like receptors
 Bifidus factor

Tolerance/priming compounds
 Cytokines: IL10 and TGFβ
 Anti-idiotypic antibodies

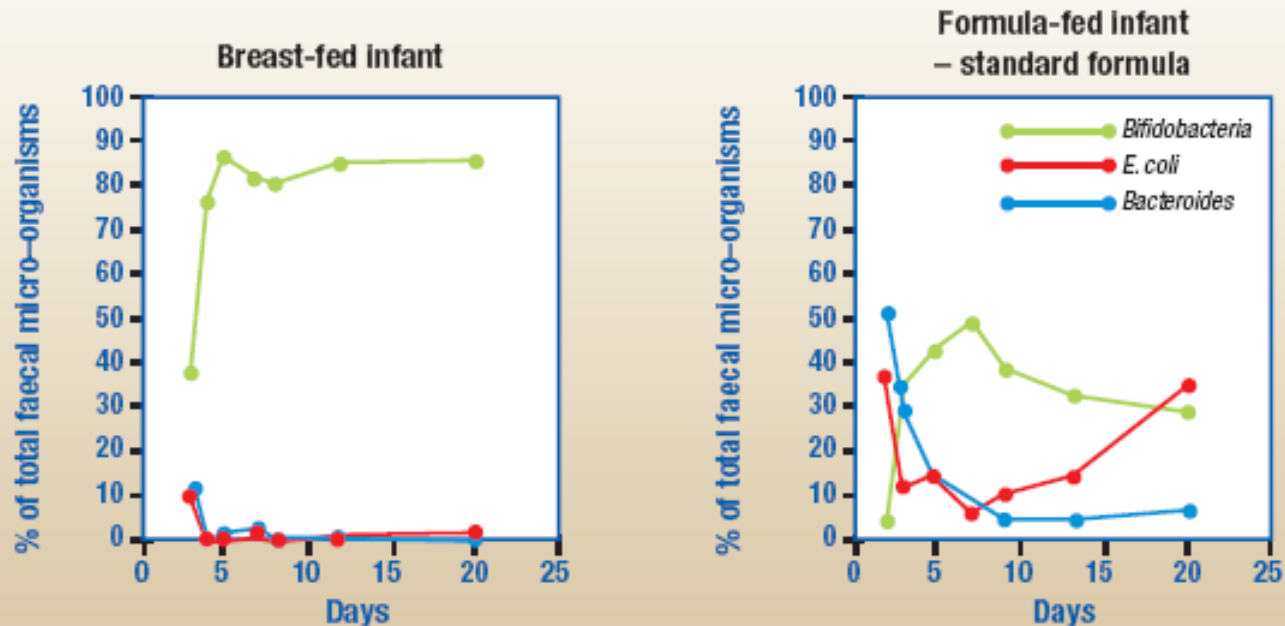
Immune development compounds
 Macrophages
 Neutrophils
 Lymphocytes
 Cytokines
 Growth factors
 Hormones
 Milk peptides
 Long-chain polyunsaturated fatty acids
 Nucleotides
 Adhesion molecules

Anti-inflammatory compounds
 Cytokines: IL-10 and TGFβ
 IL-1 receptor antagonist
 TNFα and IL-6 receptors
 sCD14
 Adhesion molecules
 Long-chain polyunsaturated fatty acids
 Hormones and growth factors
 Osteoprotegerin
 Long-chain polyunsaturated fatty acids
 Hormones and growth factors



Effect of breastfeeding on gut microbiota

Development of intestinal microbiota in a breast-fed and a formula-fed infant in the first 20 days after birth.²¹



Adapted from Harmsen et al, 2000. Study of 6 breast-fed and 6 formula-fed infants, over 21 days after birth.²¹

Breast Milk Immune Factors

- A systematic review showed that TGF β levels in human breast milk correlated with protection against allergic disease in infancy and early childhood ¹
- In mice, presentation of food or inhaled allergen within breast-milk can induce tolerance to that allergen in offspring; and tolerance induction is dependent upon the presence of TGF β and CD4+ T cells within breast milk ^{2,3,4}
- Mother mice previously sensitised to an allergen and re-exposed to that allergen during breastfeeding have allergen-IgG immune complexes within breast milk that induce tolerance in offspring without a requirement for TGF β ⁵
- ***Introducing foods while breastfeeding may promote tolerance***

1. Oddy WH, Rosales F. *Pediatr Allergy Immunol* 2010;21: 47-59.
2. Verhasselt V et al. *J Pediatr* 2010 Feb; 2010 156: S16-20.
3. Verhasselt V et al. *Mucosal Immunol* 2010 3: 326-333.
4. Verhasselt V et al. *Nat Med* 2008;14: 170-175.
5. Mosconi E et al. *Mucosal Immunol* 2010;3: 461-474.

Timing of Introduction of Complementary Foods

- Recent studies suggest a “window of opportunity” for tolerance induction between 4-6 months
- Delayed introduction of egg into the diet (at 7-12m vs 4-6 m) was associated with ~1.5 times increased risk of egg allergy
- Introduction of wheat prior to 3 months or after 6 months is associated with increased risk of islet cell autoantibodies than introduction between 4-6 months
- Exposure to gluten prior to 4 months or after 6 months was associated with increased risk of coeliac disease auto-antibodies and biopsy-diagnosed coeliac disease compared to exposure between 4 to 6 months

Koplin J et al. J Allergy Clin Immunol 2010;126:807-13;

Norris JM et al. JAMA 2003; 290:1713-20;

Norris JM et al. JAMA 2005; 293:2343-51

INFANT FEEDING ADVICE

BREASTFEED FOR AT LEAST 6 MONTHS:

- There are many nutritional and non-nutritional benefits of breastfeeding for both the mother and infant.
- Breastfeeding is recommended for at least 6 months.
- Breastfeeding can continue beyond 12 months, or for as long as mother and infant wish to continue.

BEFORE 4 MONTHS:

- If complementary infant formula is required before solid foods are started, a standard cow's milk infant formula may be used (where there is no history of allergic disease in the infant's parents or siblings).
- Infants with a history of allergic disease in the infant's parents or siblings may be placed on a partially hydrolysed formula (usually labeled "HA" or hypo-allergenic). These formulas are not suitable for children who have already developed cow's milk allergy.
- Soy milk and other mammalian milks such as goat milk are not recommended for allergy prevention.

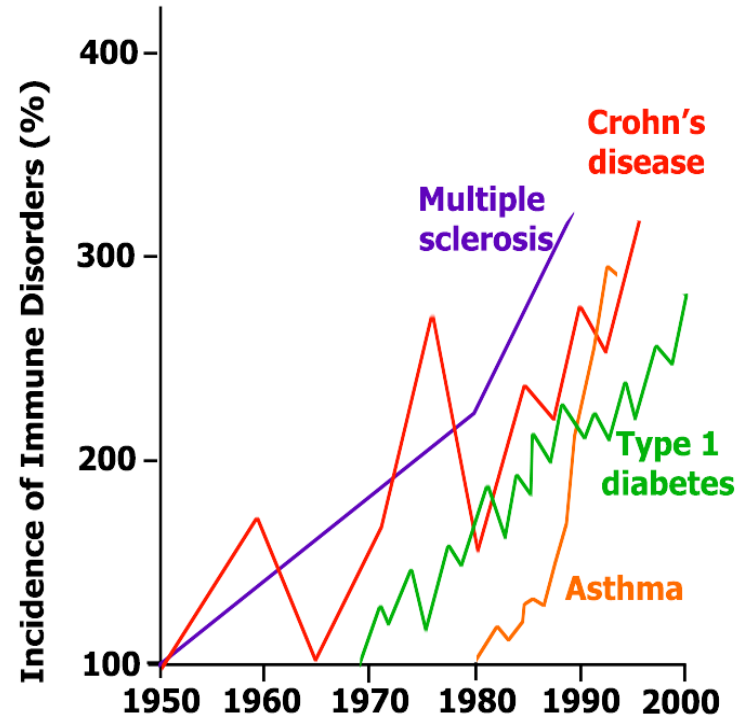
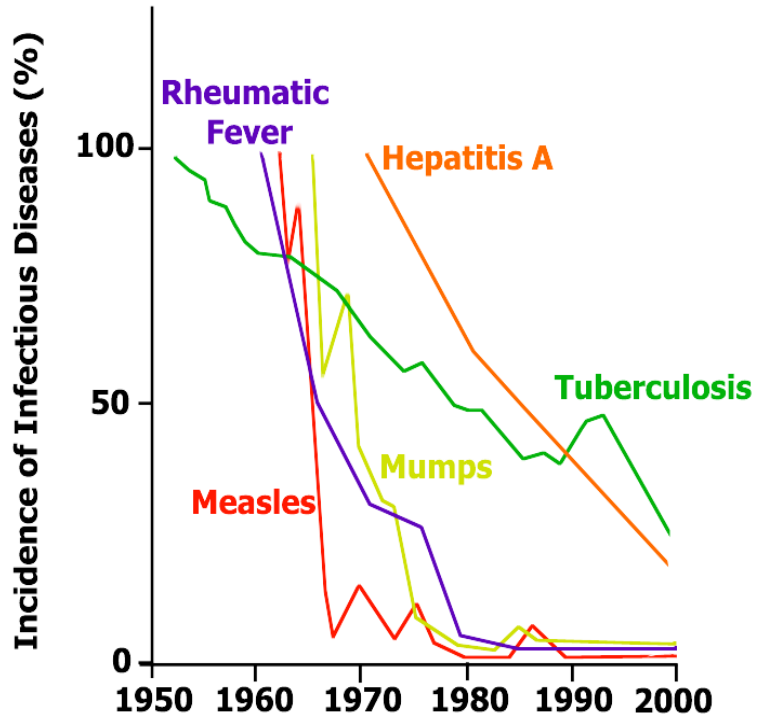
FROM 4-6 MONTHS:

- When your child is ready, 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).
- Give one new food at a time so that reactions can be more clearly identified. If a food is tolerated, continue to give this as a part of a varied diet (see Table for examples).
- 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.

NOTE:

- **There are no particular allergenic foods that need to be avoided**
- Some children will develop allergies. If there is any reaction to any food, you should seek medical advice and that food should be avoided until your child is reviewed by a medical practitioner with experience in food allergy.
- Infants who already have eczema are at higher risk of allergies. In general this advice applies to these children, however if your child develops a reaction to a food this should be discussed with your doctor (as above).
- If you are uncertain about this advice you should discuss this with your doctor.

The Hygiene Hypothesis



Gut Microbiota and Immune Development

The most abundant microbial exposure during life is establishment of the gut microbiota ... major impact on immune responses

**100 trillion bacteria
“ Gut Microbiota ”**

60 -70% of immune cells



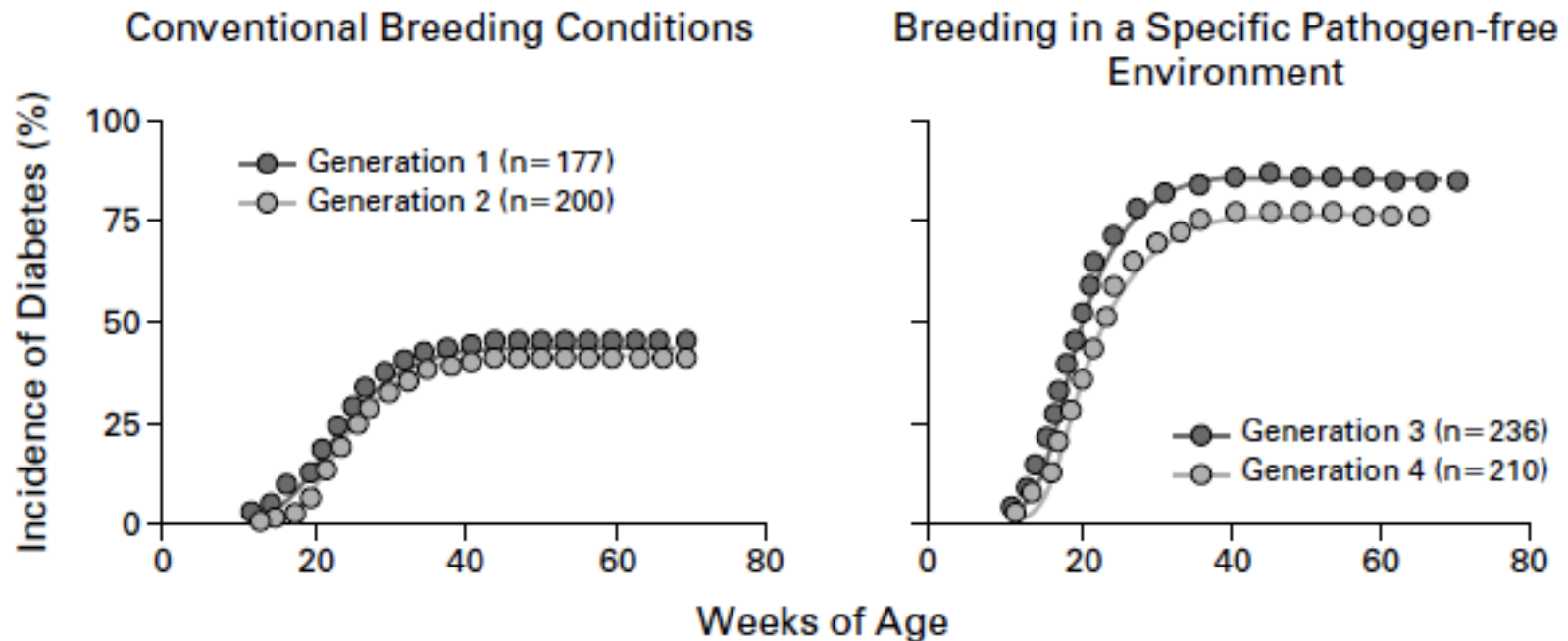
**Surface of approximately
300m²**

100 million neurons

Intestinal Microbiota and Immune Regulation

- Mice bred in germ free conditions have abnormal Gut Associated Lymphoid Tissues (GALT)
 - Small underdeveloped Peyer' s Patches that lack germinal centres
 - Fewer IgA plasma cells and CD4+ T cells in the lamina propria
 - Fewer IEL with reduced cytolytic activity
 - These abnormalities can be corrected by seeding the intestine with *Bacteroides fragilis*
- Mice bred in germ free conditions have failure of oral tolerance induction and persistent Th2 responses
 - This can be corrected if reconstitute microbiota with *B fragilis*
 - But... ONLY if this occurs in the neonatal period

Gut Microbiota and Immune Disorders



The incidence of diabetes, which is normally stable in successive generations bred in a conventional environment (generation 1 and generation 2), increases immediately after breeding conditions are changed to a specific pathogen-free environment through the use of cesarean delivery and isolated living conditions (generation 3 and generation 4).

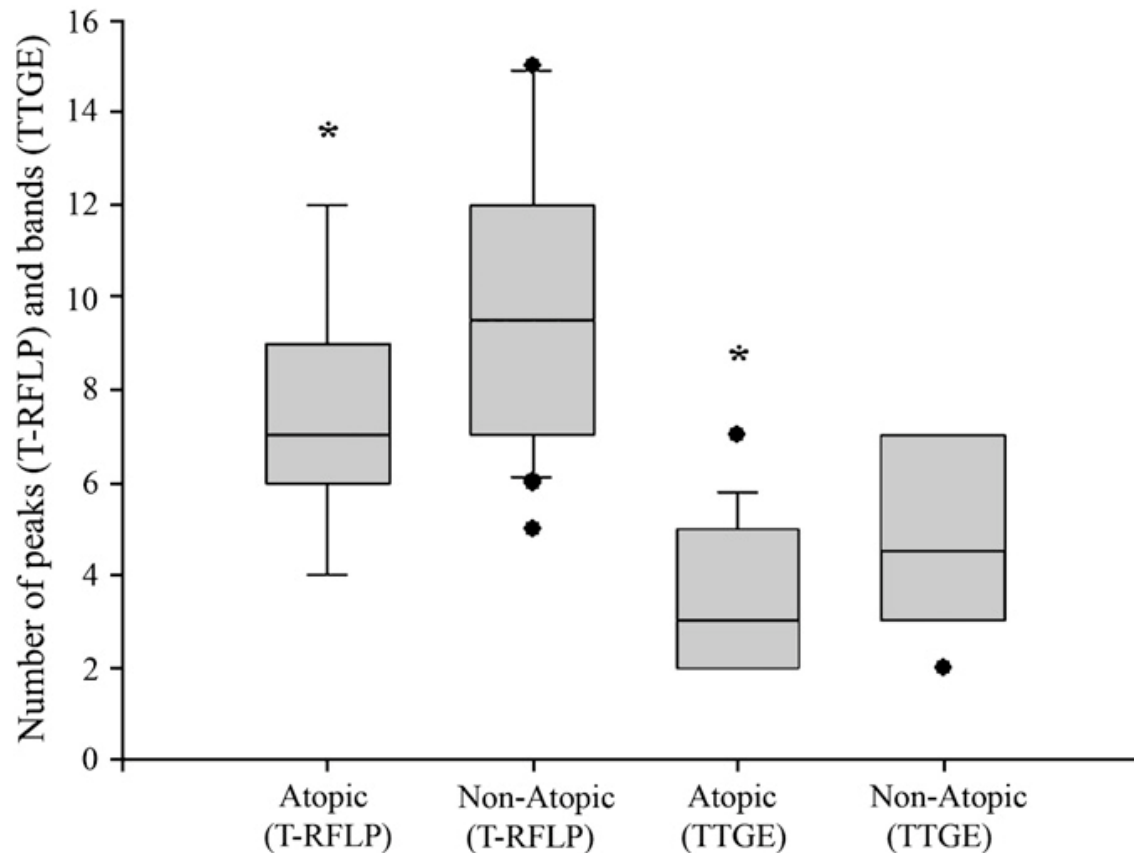
Intestinal Microbiota in Allergic and Non-allergic Children

- Allergic children have altered microbiota ^{1,2,3}
 - lower counts of lactobacilli and bifidobacteria
 - higher levels of *Staphylococcus aureus* and *Clostridium difficile*
- Differences *precede* onset of allergic disease ^{4,5}
 - lower counts bifidobacteria and enterococci at 1 mos
 - lower counts of bifidobacteria and bacteroides at 12 mos
 - higher counts of clostridia in first weeks and at 3 months
 - more often colonised with staphylococcus at 6 mos

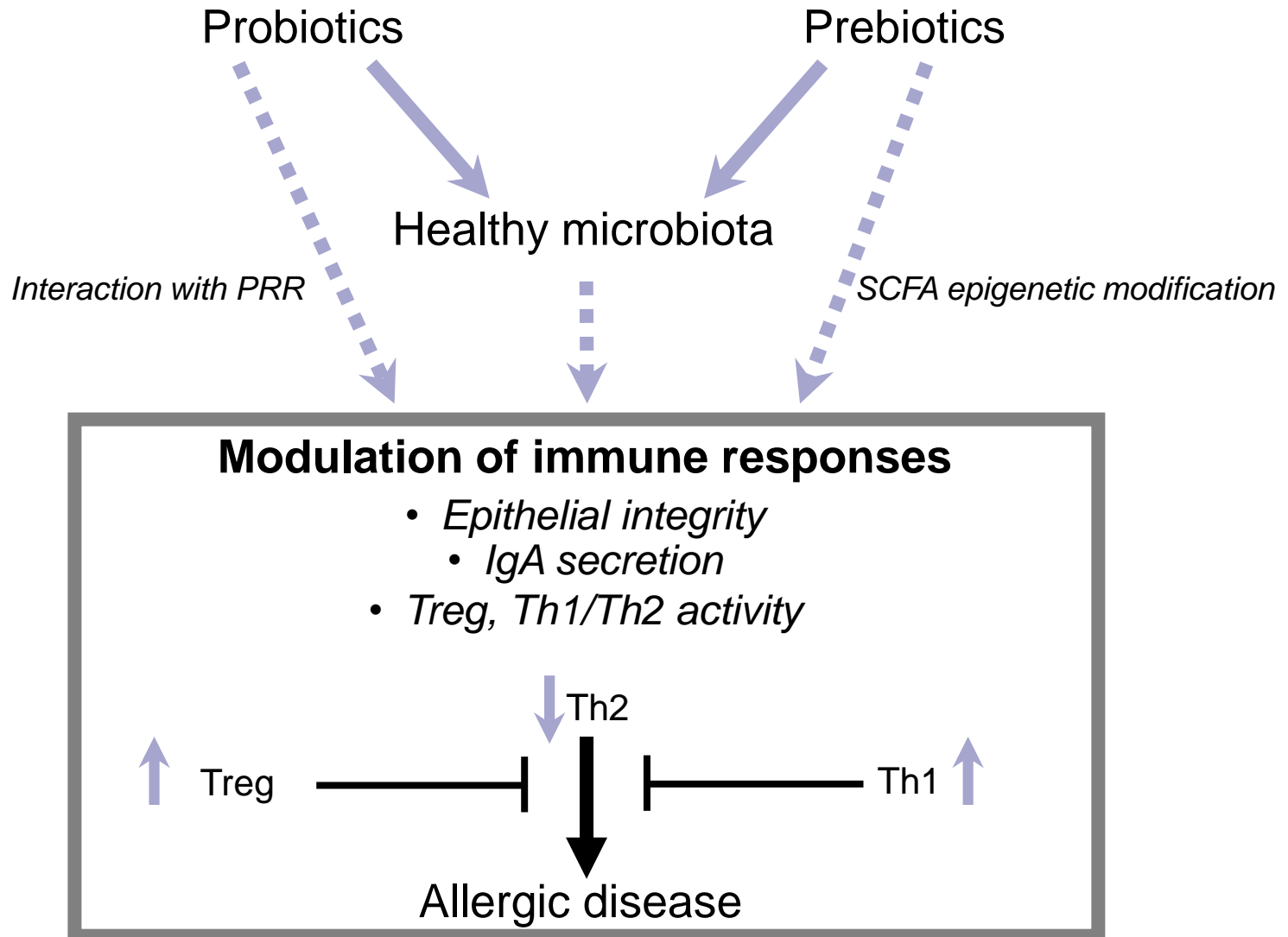
1. Bjorksten B et al. *Clin Exp Allergy* 1999;29:342-6.
2. Kalliomaki M et al. *J Allergy Clin Immunol* 2001;107:129-34.
3. Sepp E et al. *Clin Exp Allergy* 2005;35:1141-6
4. Kalliomaki M et al. *J Allergy Clin Immunol* 2001;107:129-34
5. Bjorksten B et al. *J Allergy Clin Immunol* 2001;108:516-20.

The Importance of Microbial Diversity

Infants with eczema at 18mos have reduced diversity of fecal microbiota at 1mos

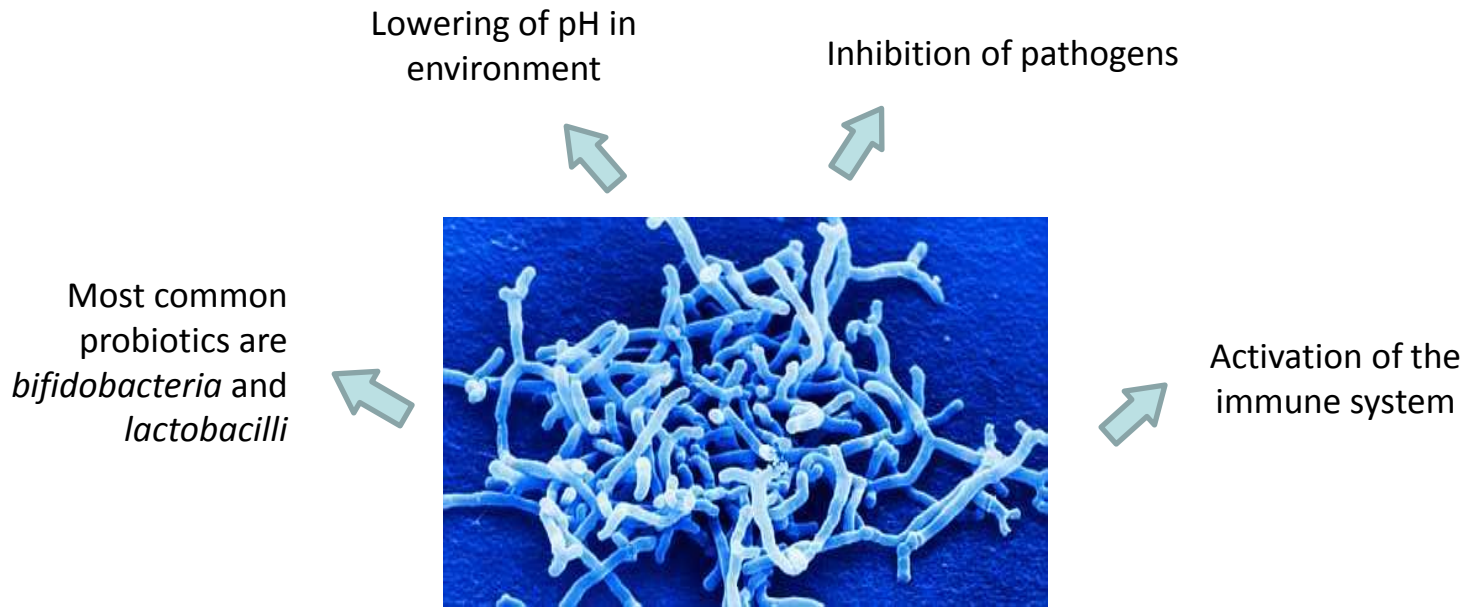


Probiotics and Prebiotics Modulate the Intestinal Microbiota and Immune Responses



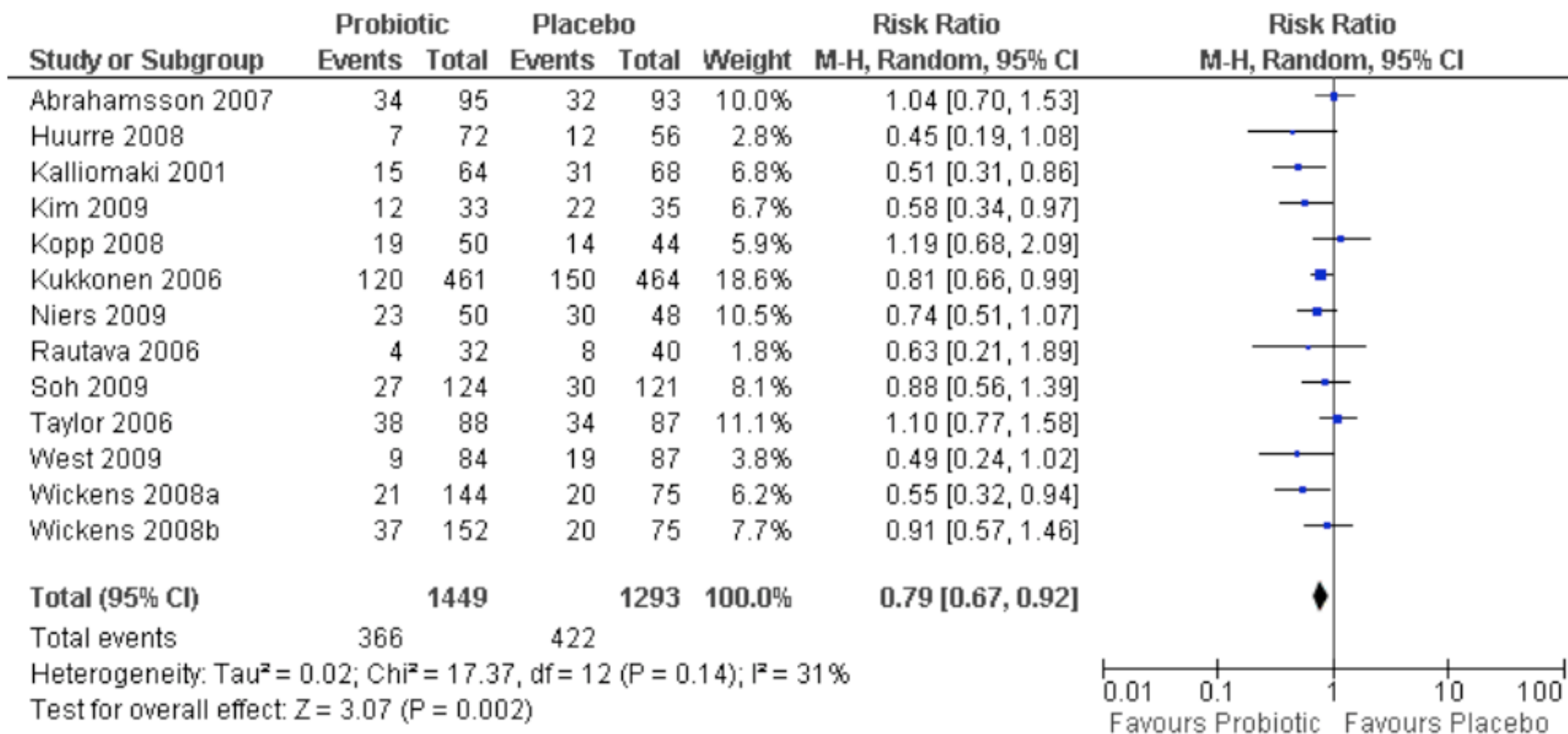
Probiotics

“ Live bacteria when administered in adequate amounts confer health benefits on the host” ¹

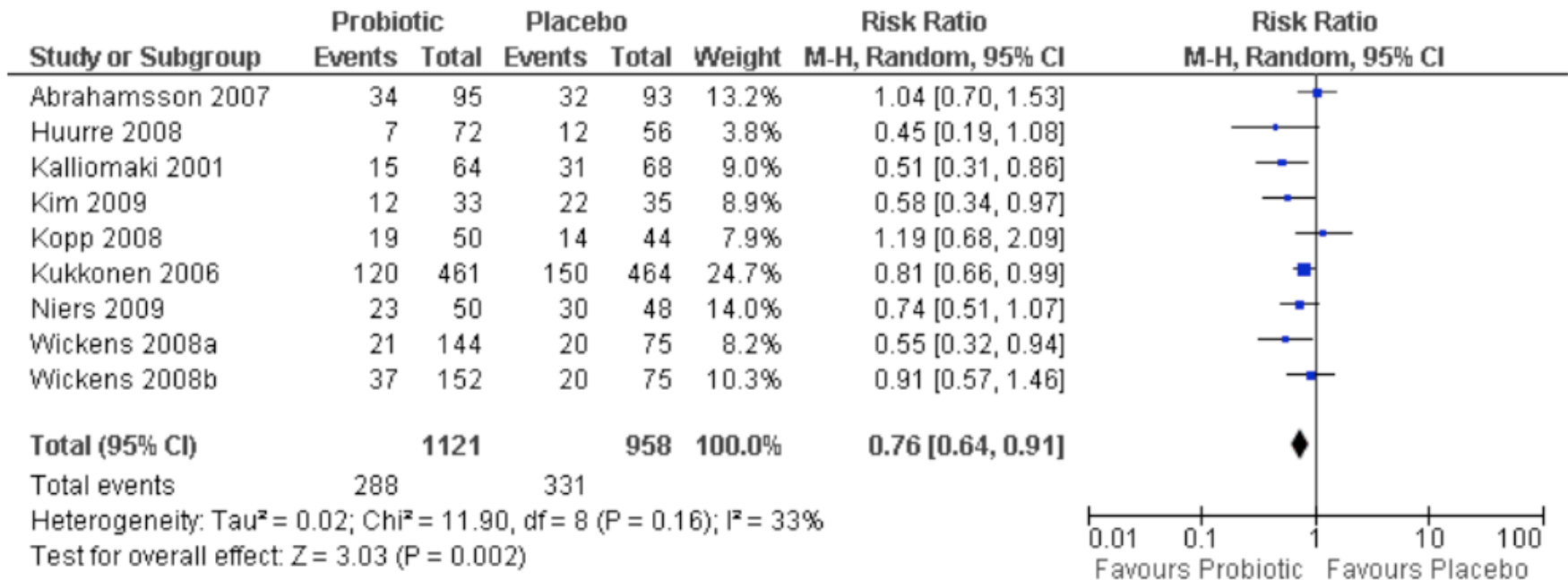


1. FAO & WHO Working Group, 2002

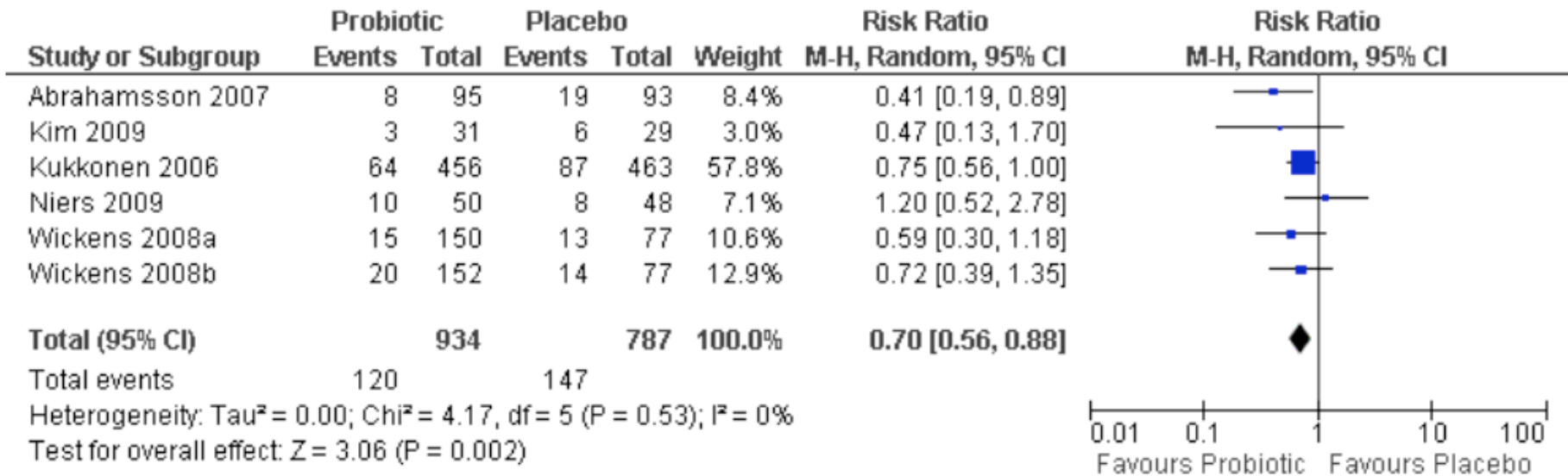
Probiotics for Prevention of Eczema



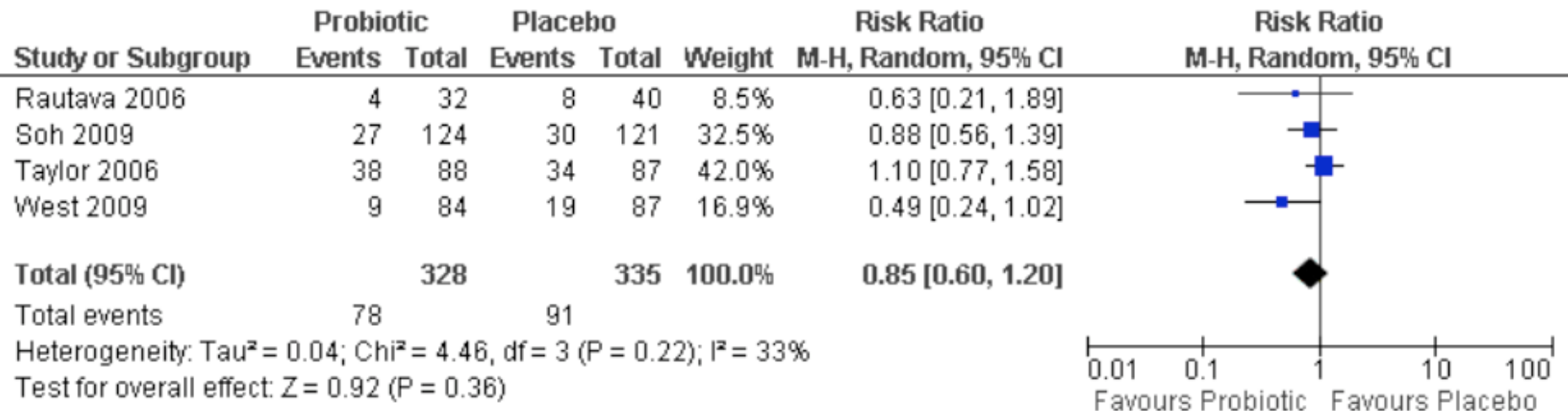
Probiotics Commenced Prenatally: Eczema



Probiotics Commenced Prenatally: IgE-associated Eczema

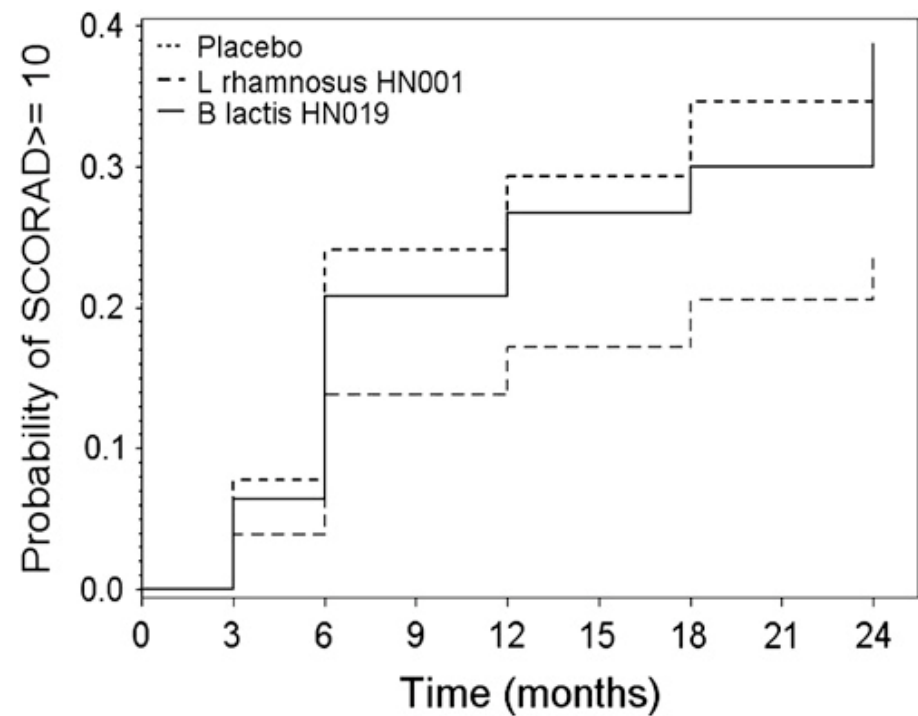
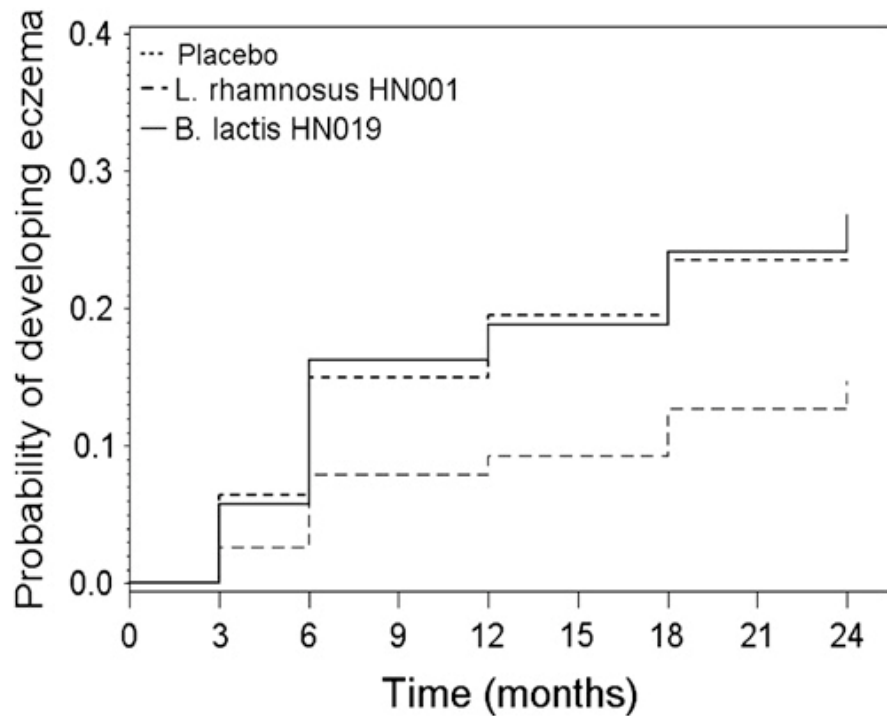


Probiotics Commenced Postnatally: Eczema



Species Specificity of Probiotic Effects

- Probiotic bacteria have common effects on innate immune responses but species specific effects on adaptive immune responses



Effects on Other Allergic Conditions: Increased Asthma?

- Effect on asthma and wheezing
 - 3 fold increase in recurrent (≥ 5 episodes) wheeze at 2 years (LGG) ¹
 - Trend to increased wheeze or asthma at 7 years (LGG) ²
 - Trend to increased wheeze with OR 1.92 (L acidophilus LAVRI A1) ³
 - No difference in cumulative incidence of ‘any allergic disease’ (eczema, food allergy, asthma, allergic rhinitis) at 2 years or FE(NO) at 5 years with probiotic mix/prebiotic ^{4,5}
 - No effect on asthma or rhinitis at 2 years ⁶

1. Kopp MV et al. *Pediatrics* 2008;121:e850

2. Kalliomaki et al. *JACI* 2007;119:1019

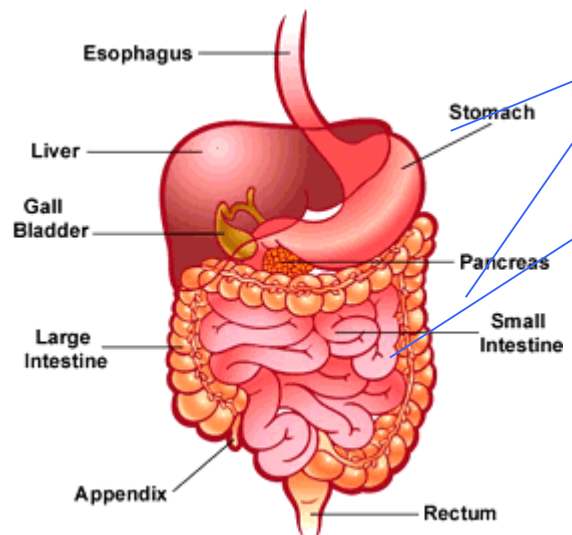
3. Prescott et al. *Allergy* 2008;63:1481-90

4. Kukkonen et al. *JACI* 2007;119:192-8; 5. Kukkonen et al. *PAI* 2011;22:249-51

6. Dotterud et al. *Allergy* 2009; 64:64

Prebiotics

"non-digestible oligosaccharides that selectively stimulate the growth of non-pathogenic bacteria in the large intestine"

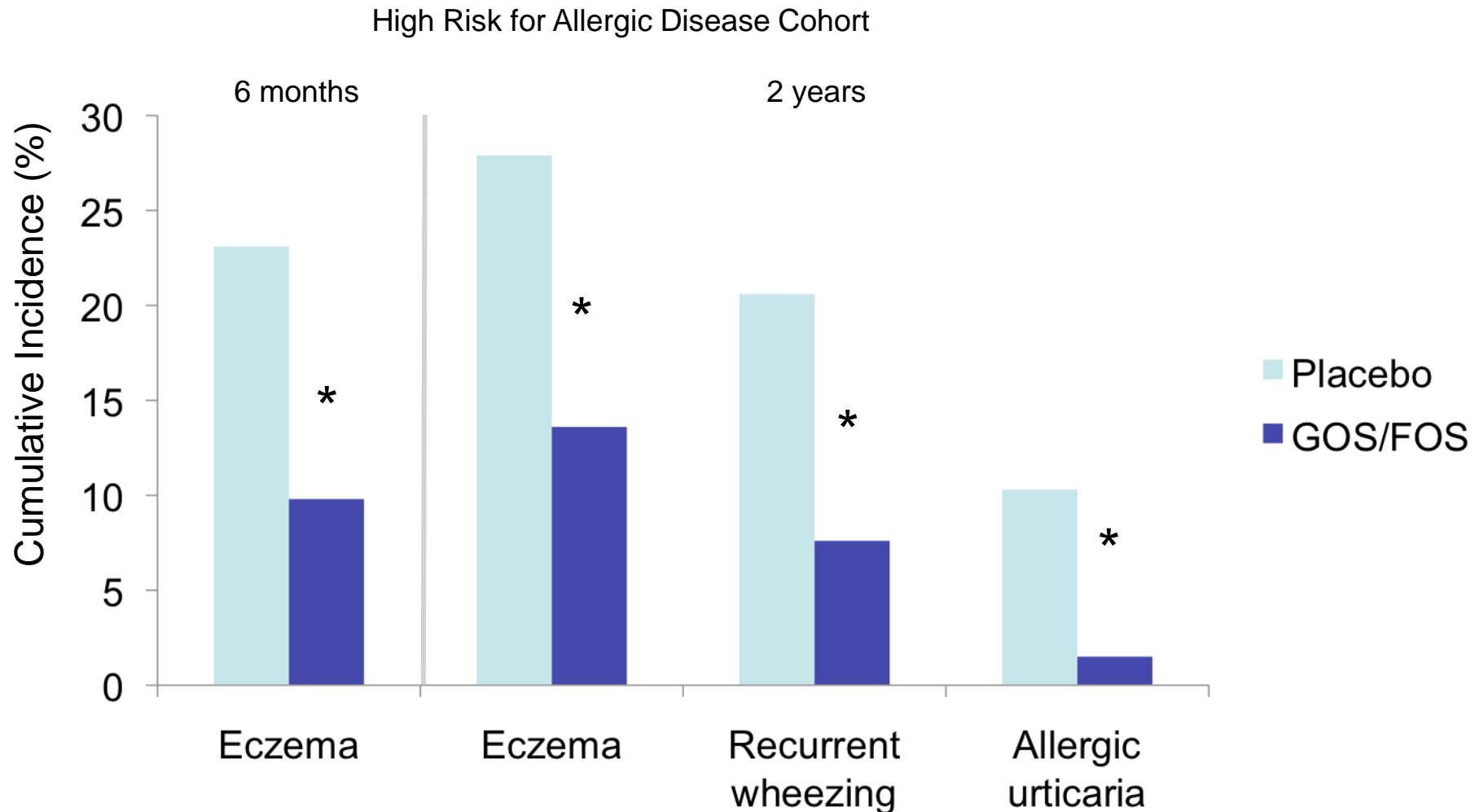


• resist digestion and absorption

reach the large bowel unmodified and can selectively feed friendly bacteria.

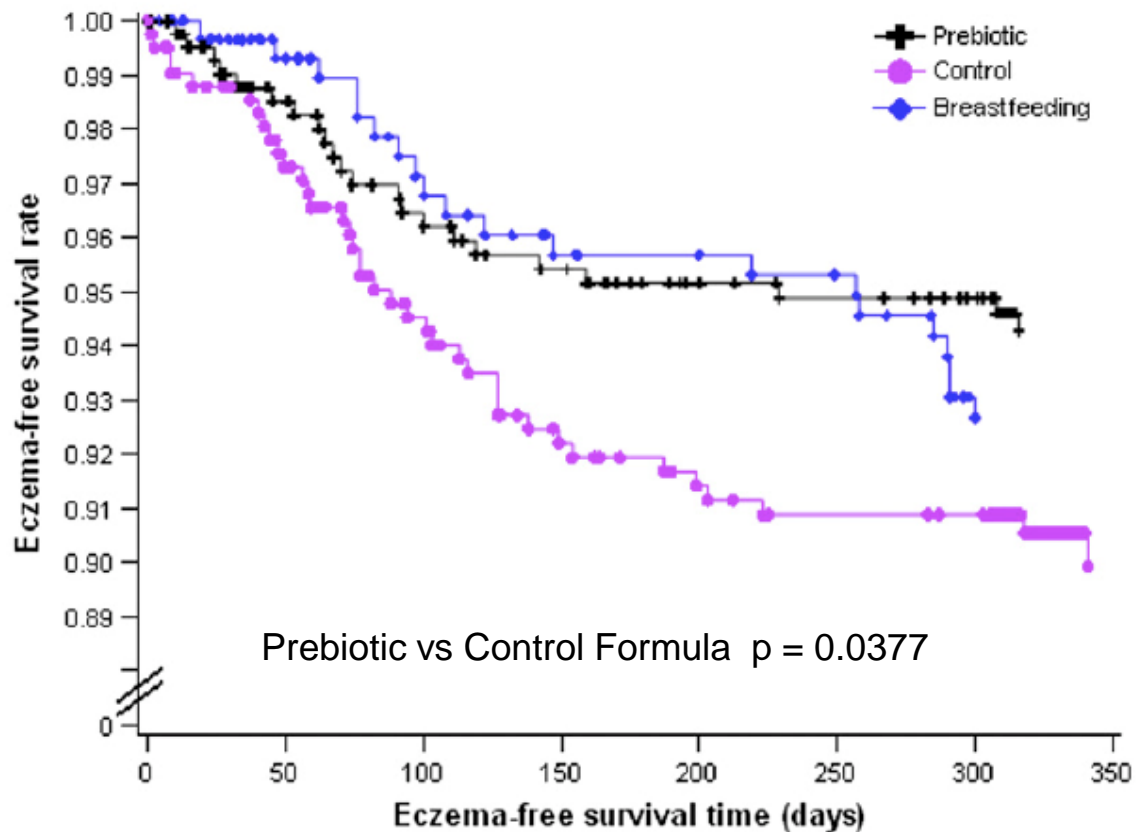
- increase in beneficial bacteria (bifidobacteria)
- increase metabolic mediators: SCFA, ↓ pH
- direct effects on gut immune system

Prebiotics and Prevention of Allergic Disease

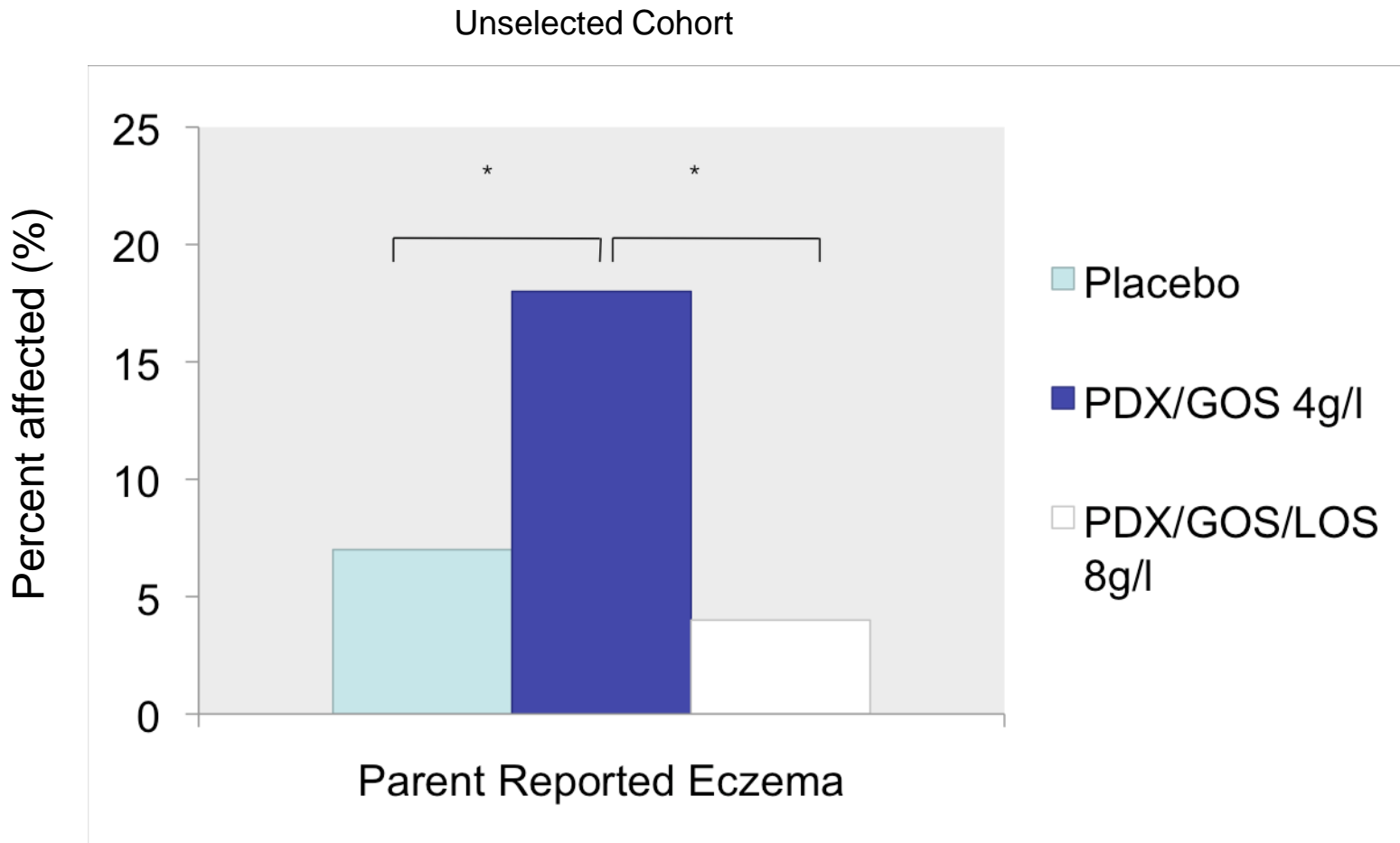


Prebiotics for Prevention of Allergic Disease

Low Risk for Allergic Disease Cohort

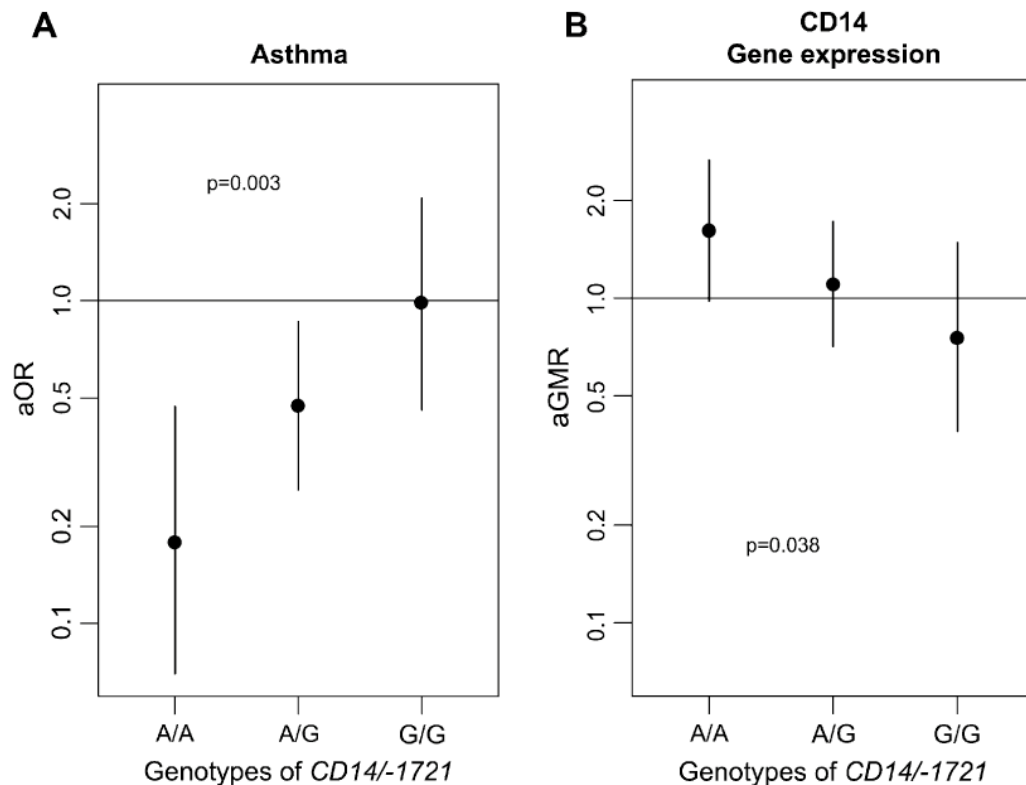


Prebiotics and Prevention of Allergic Disease



Gene-Environment Interactions

- Genetic polymorphisms can modify the impact of environmental exposures
 - Eg: CD14 polymorphisms modify beneficial effects of farm milk



Summary

- Limited prevention strategies available at present and aimed at high risk infants
- Current guidelines
 - Breastfeeding for at least 6 months
 - Introduce foods (including common allergenic foods)
 - For high risk infants - hydrolysed formula if unable to breastfeed in first 4-6 months of life
- Probiotics and prebiotics may offer additional avenues for prevention of allergic disease
 - Further clinical studies required to clarify specific agents, timing (probiotics), dose
 - Additional investigation of mechanisms of action