

GP CME - Workshop

Early childhood nutrition and preventing allergy – the evidence

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Primary allergy prevention

Definition

Promotion of immunological tolerance and prevention of the development of IgE-mediated responses, i.e.

sensitisation or **allergic disease**.

Immediate-type food allergy



Urticaria



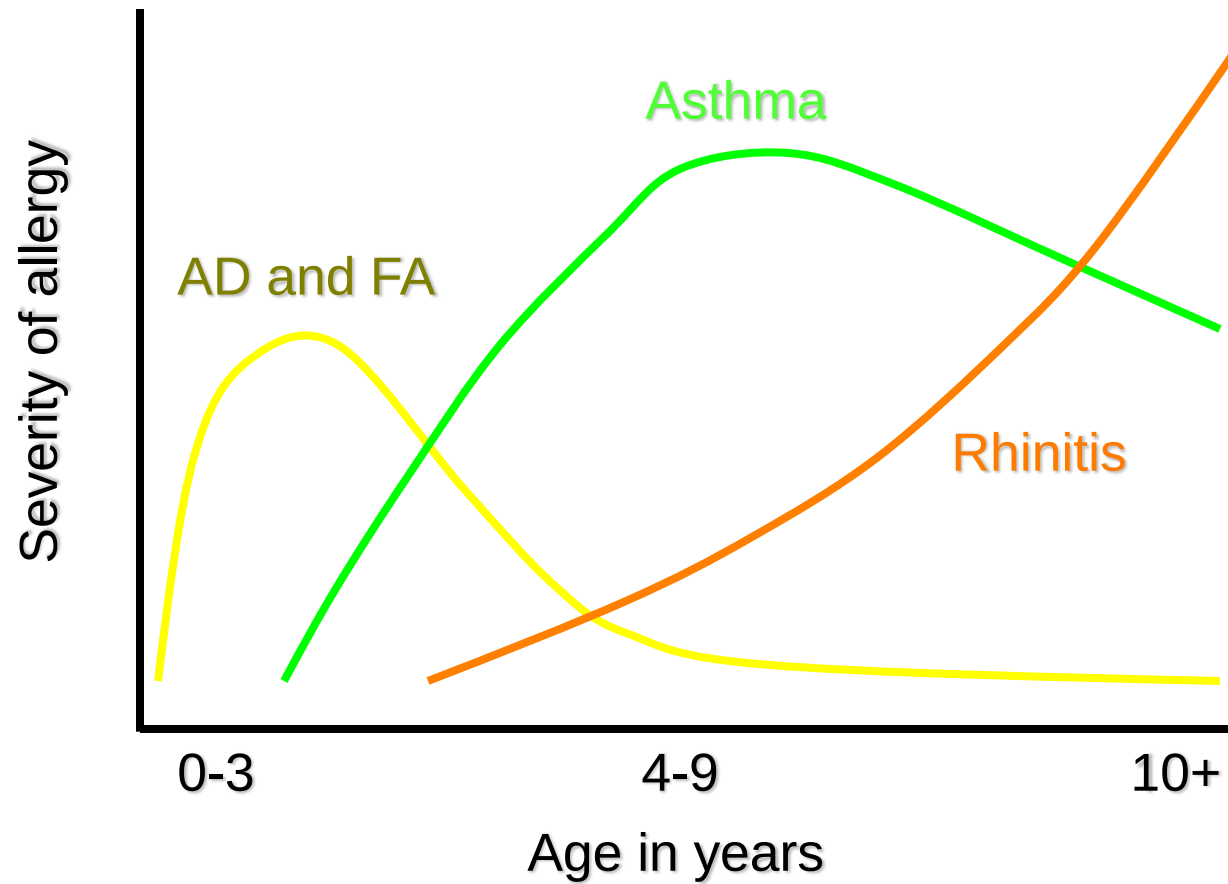
Facial angioedema

Atopic dermatitis in infancy



- Affects up to 10% of infants.
- Significant burden of disease and cost
- Requires treatment with moisturisers and topical steroid creams
- Early-onset moderate to severe atopic dermatitis is a marker of IgE-mediated food allergies and atopy.

The atopic march



T-Lymphocytes

T-helper 1



IFN- γ
IL-2

Regulatory
T-cells



TGF- β
IL-10

T-helper 2



IL-4
IL-5
IL-13

INFECTION

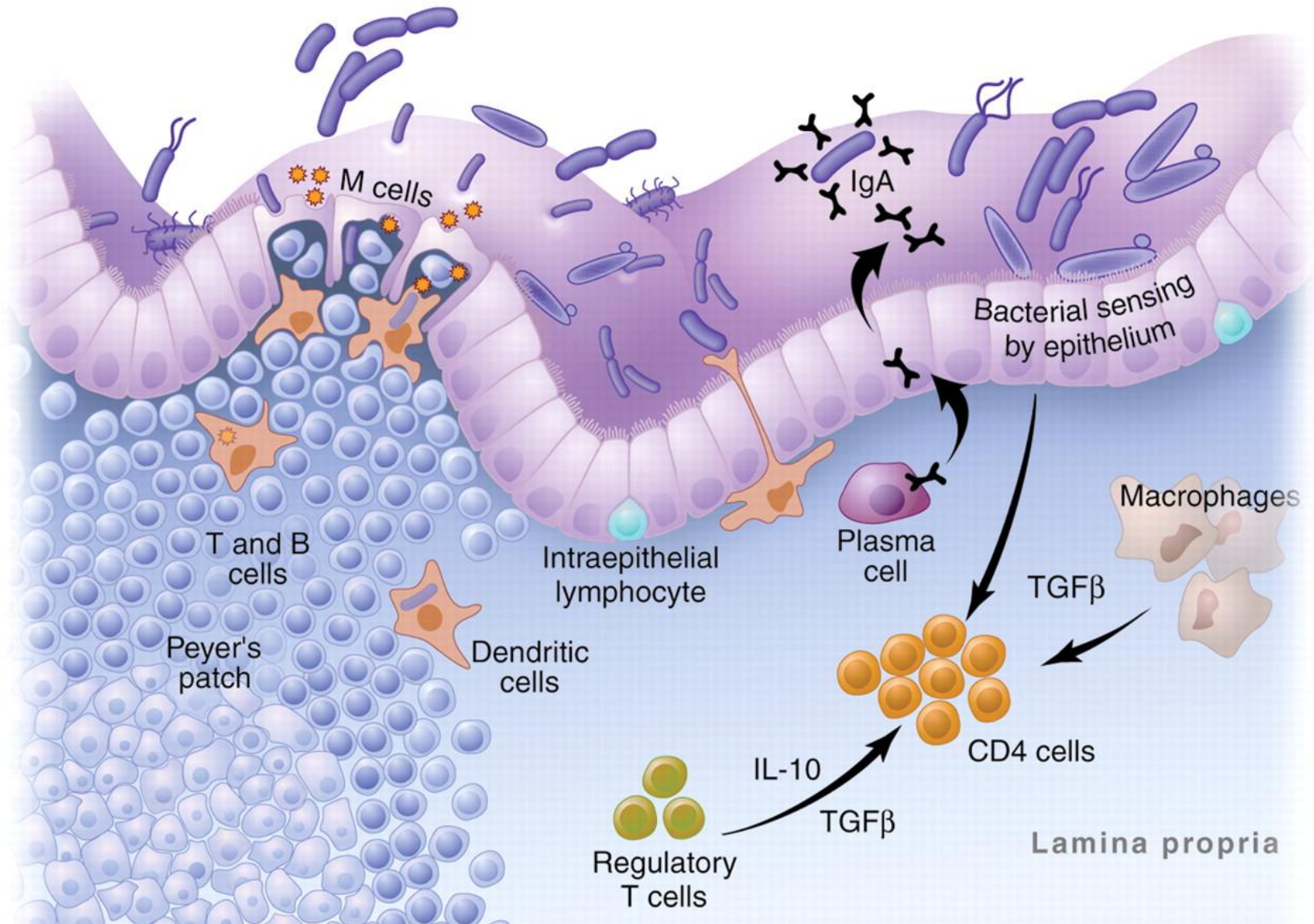
Autoimmunity



ALLERGY

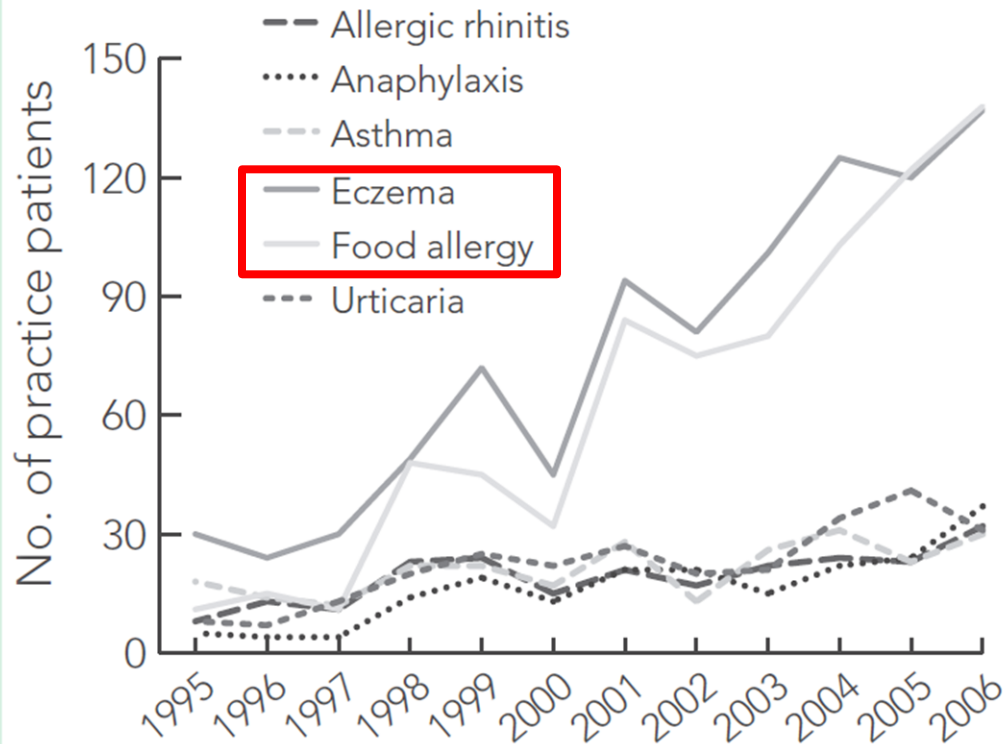
Parasitic infection

Gastrointestinal antigen processing



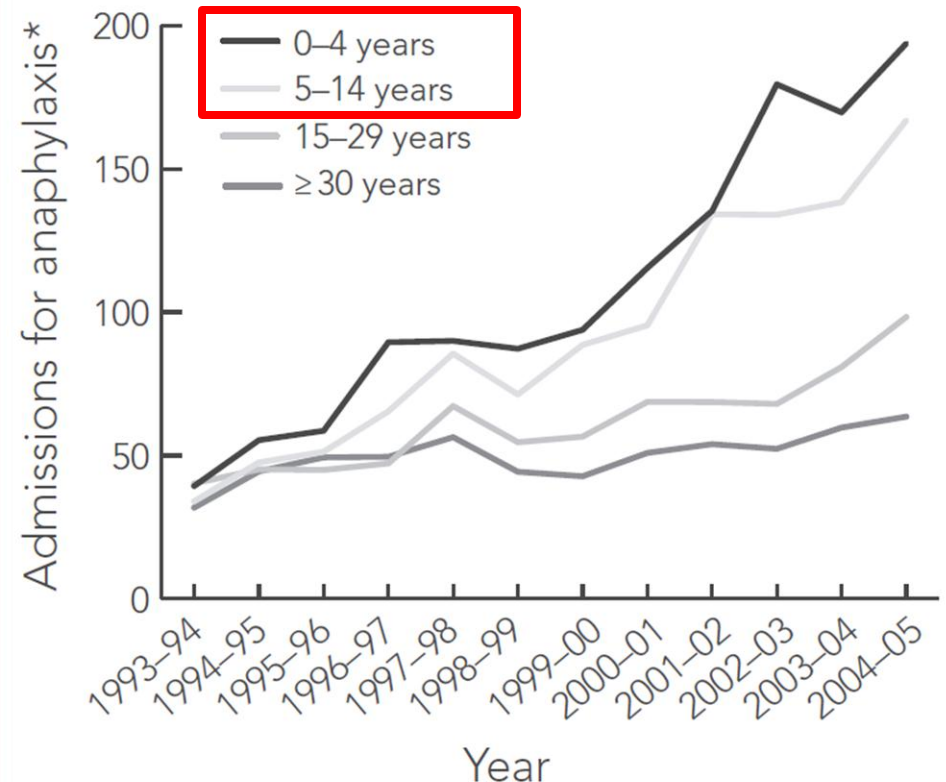
Epidemiology of food allergy in Australia

1 Time trends in allergy-related disorders in children aged 0–5 years referred to an Australian Capital Territory private practice



Mullins R. *MJA* 2007;186:618-21

3 Age-adjusted Australian hospital admission rates for anaphylaxis in the financial years 1993–94 to 2004–05



* Rate per million population.



Food allergy in Australia

1995-2005

Increase in hospital admissions for food anaphylaxis increased by 350%

Challenge proven food allergy at 12 mo

Egg 8.9% (sensitisation 16.5%)

Peanut 3.0% (sensitisation 8.9%)

Sesame 0.8% (sensitisation 2.5%)

ALLERGY PREVENTION



“... children who lived on farms had lower prevalences of asthma and atopy and were exposed to a greater variety of environmental microorganisms than the children in the reference group.”

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Exposure to Environmental Microorganisms and Childhood Asthma

Markus J. Ege, M.D., Melanie Mayer, Ph.D., Anne-Cécile Normand, Ph.D., Jon Genuneit, M.D., William O.C.M. Cookson, M.D., D.Phil., Charlotte Braun-Fahrländer, M.D., Dick Heederik, Ph.D., Renaud Piarroux, M.D., Ph.D., and Erika von Mutius, M.D., for the GABRIELA Transregio 22 Study Group

ABSTRACT

BACKGROUND

Children who grow up in environments that afford them a wide range of microbial exposures, such as traditional farms, are protected from childhood asthma and atopy. In previous studies, markers of microbial exposure have been inversely related to these conditions.

METHODS

From University Children's Hospital Munich, Munich (M.J.E., E.M.); Institute of Animal Hygiene, Technische Universität München, Freising (M.M.); and the Institute of Epidemiology, University of Ulm, Ulm (J.G.) — all in Germany; Chrono-environnement Laboratory, University of

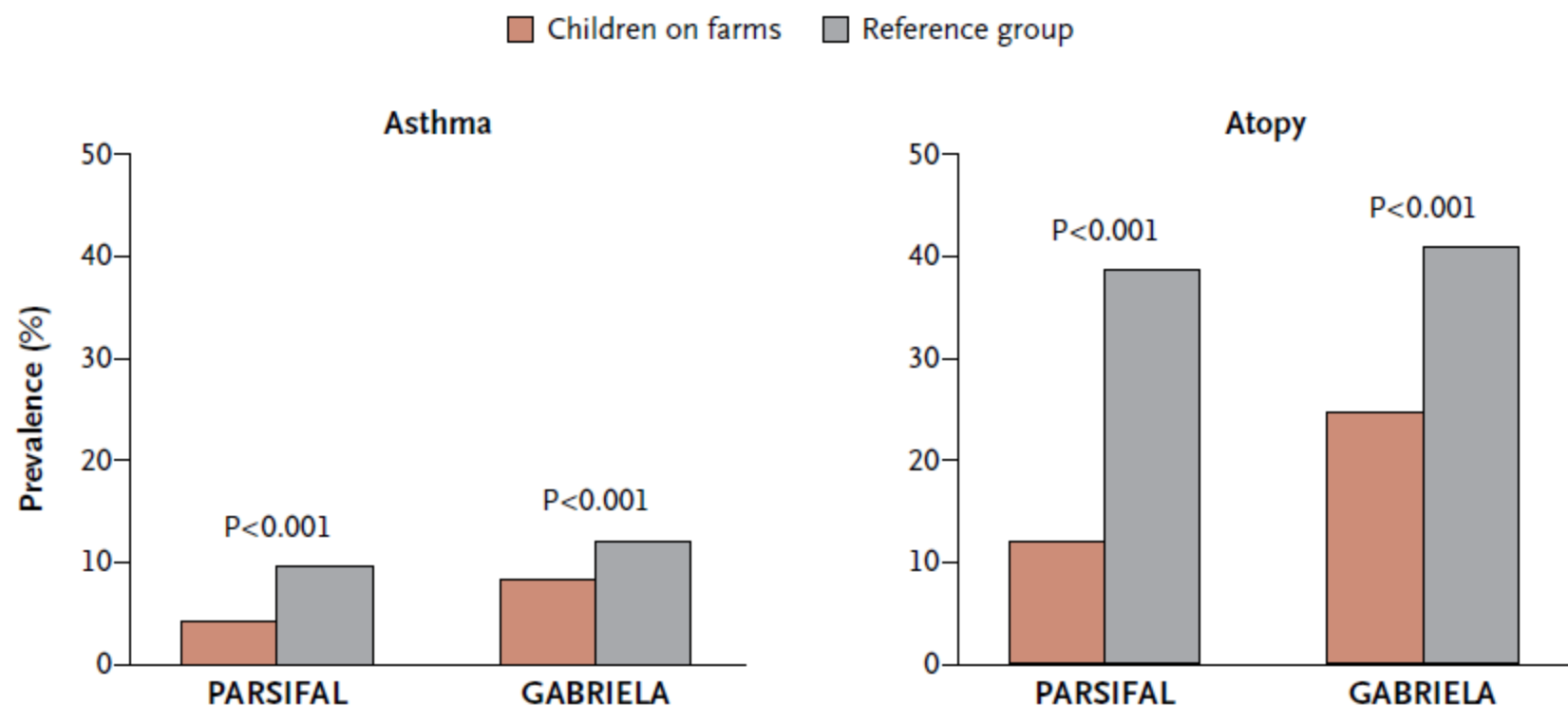


Figure 1. Prevalence of Asthma and Atopy among Children Living on Farms as Compared with Reference Groups. The PARSIFAL study population included 6843 school-age children 6 to 13 years of age, and the GABRIELA study population included 9668 children between 6 and 12 years of age. Calculations of prevalence in GABRIELA were weighted on the basis of the total number of children who were eligible for inclusion in the study (34,491 children).

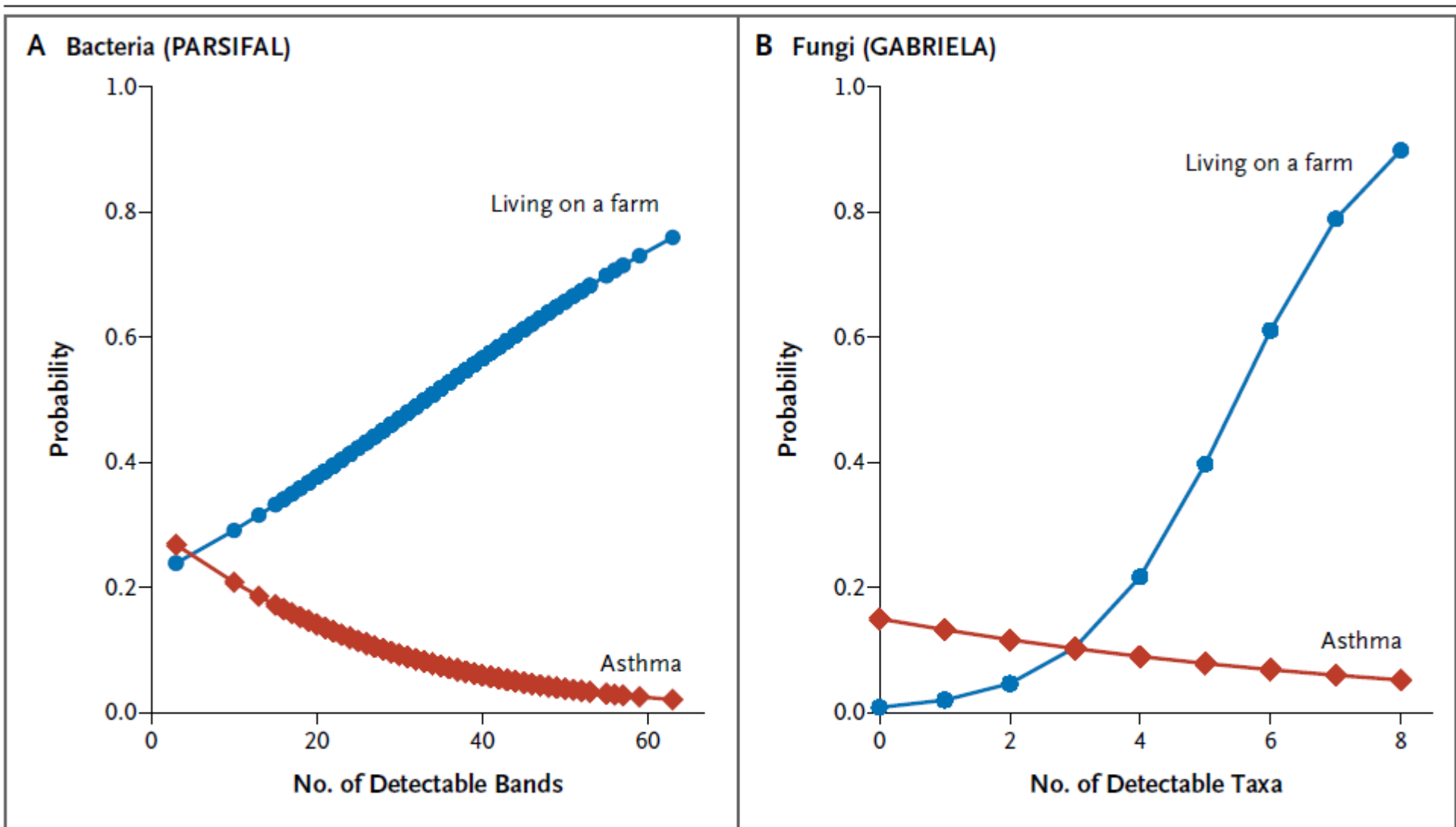


Figure 3. Relationship between Microbial Exposure and the Probability of Asthma.

In both the PARSIFAL study and GABRIELA, the range of microbial exposure was inversely associated with the probability of asthma.

Breast milk



Breast milk
is the best
source of
nutrition for
the first six
months of life

- Specific nutrient mix
- Psychosocial benefits/mother-infant relationship
- Nucleotides
- Growth factors
- Protection from respiratory and gastrointestinal infection (IgA)
- Immune modulation
sIgA, TGF- β , LCPUFA

Maternal elimination diets

■ Pregnancy

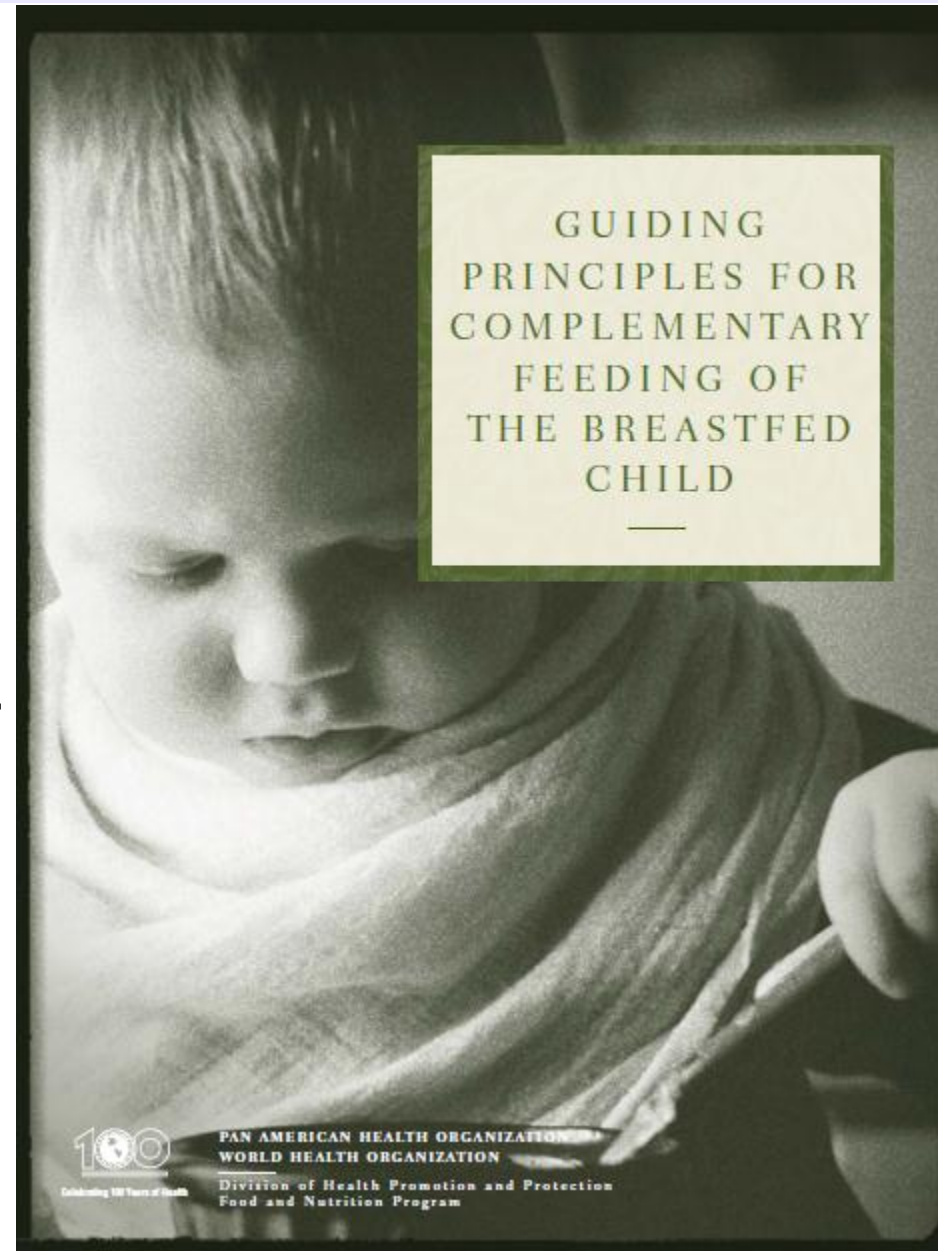
- No evidence for primary allergy prevention
- May cause adverse nutritional outcomes for mother and fetus (SGA)
- May paradoxically increase sensitisation?

■ Lactation

No evidence for primary allergy prevention, but suitable if allergic symptoms in breast-fed infant

WHO guidelines 2003

- Global guidelines
- Exclusive breast feeding for 6 months
- Frequent on-demand breast feeding until 2 years or beyond
- Responsive feeding
- WHO Guidelines currently under review in countries with high prevalence of allergies
- **Commence complementary feeding from 4-6 months?**



Considerations for infant feeding guidelines

Nutrition:

- Protein
- Energy
- Micronutrients:
 - Iron, zinc
 - Iodine
 - Vitamin D, B₁₂
 - DHA

Immune modulation:

- Prevention of allergy/atopy
- Autoimmune disease:
 - Coeliac disease
 - T1 diabetes
 - MS? IBD?

Developmental aspects:

- Oro-motor skills
- 'Readiness' for solids
- Development of taste preferences
- Choking

Growth:

- Weight gain
- Linear growth
- Head growth
- Prevention of obesity and cardiovascular disease

Transfer of passive immunity:

- Prevention of respiratory and gastrointestinal infection (rotavirus, RSV)

Developing world:

- Infection / HIV
- Vertical transmission
- Malnutrition
- Poor sanitation
- Poverty
- Conflict

International Infant Feeding Guidelines

	WHO 2003	AAP 2008	ESPHGHAN 2008	ASCI 2008
Exclusive breast feeding	6 mo	4-6 mo	(4-) 6mo	4-6 mo
Introduction of solids	After 6mo	4-6mo	17-26 wk	4-6 mo
Maternal elimination diet	---	No	---	No
Delayed introduction of highly allergenic foods	Yes	No	No Gluten 4-7mo	No
Partially hydrolysed formula for allergy prevention (if breast feeding not possible)	---			Yes
Other comments	Global guideline	---	No vegan diets in infancy	New food 2-3d

Delayed introduction of food allergens

Cow's milk

Hen's egg

Peanut

American College for Asthma, Allergy and Immunology suggests delayed introduction

Milk after 12 mo

Egg after 2 yrs

Nuts/peanut after 3 yrs

Fiocchi et al. - Ann Asthma Allergy Immunol 2006;37:10-20

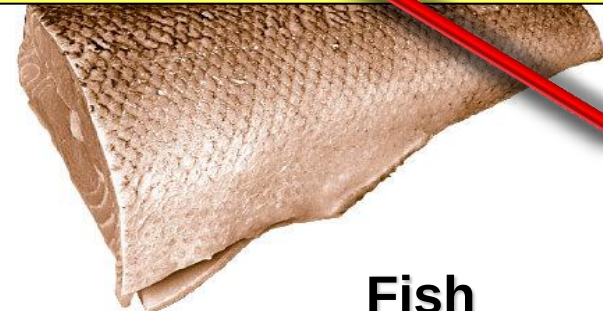
Nuts



Soya bean



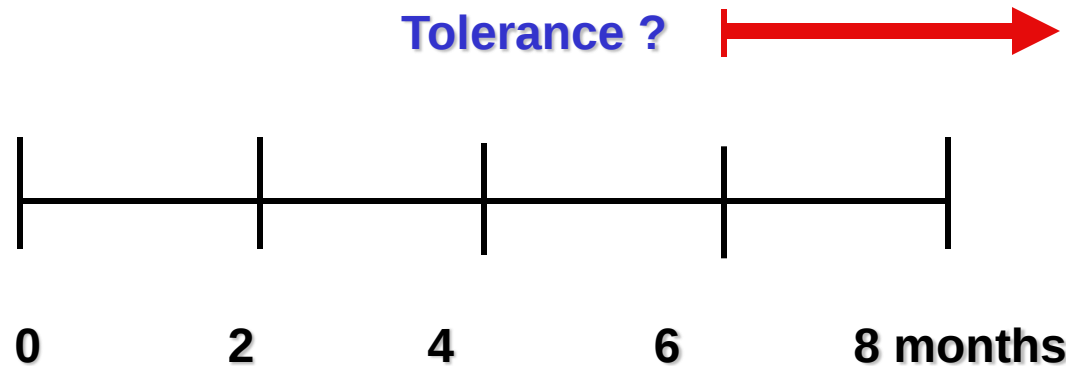
Shellfish



Fish

'Window of opportunity' for tolerance?

Increased IgE wheat allergy after 6 mo



← Tolerance ? →
Increased coeliac disease
and islet cell autoimmunity
before 3mo and after 7 mo

Poole JA et al. *Pediatrics* 2006;117:2175-82

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

Myléus A et al., *J Pediatr Gastroenterol Nutr* 2009;49:170-6

Prescott SL et al. , *Pediatr Allergy Immunol* 2008; 19: 375-80

Dietary introduction of egg

- HealthNuts Study Australia (2589 infants)
- Compared risk of egg allergy by age of introduction
- Food challenge to egg if SPT ≥ 1 mm

Variable	No.*	Egg allergy (%)	Adjusted	
			OR (95% CI)	<i>P</i> value, trend
Age at introduction of egg (mo)†				
4-6	485	5.6	1.0	<.001
7-9	933	7.8	1.3 (0.8-2.1)	
10-12	730	10.1	1.6 (1.0-2.6)	
>12	98	27.6	3.4 (1.8-6.5)	

Earlier introduction of egg from 4-6 months may protect against egg allergy

INFANT FEEDING ADVICE

ascia

australasian society of clinical immunology and allergy inc.

www.allergy.org.au

FEEDING GUIDE:

EXAMPLES ONLY:

Specific food choices will depend on what the family eats

1

Start with smooth, pureed foods

Start with plain cereals (e.g. rice, oats, semolina) then add other foods such as smooth, cooked vegetables and smooth, cooked fruits, pureed meats.

2

Move on to mashed foods and finger foods

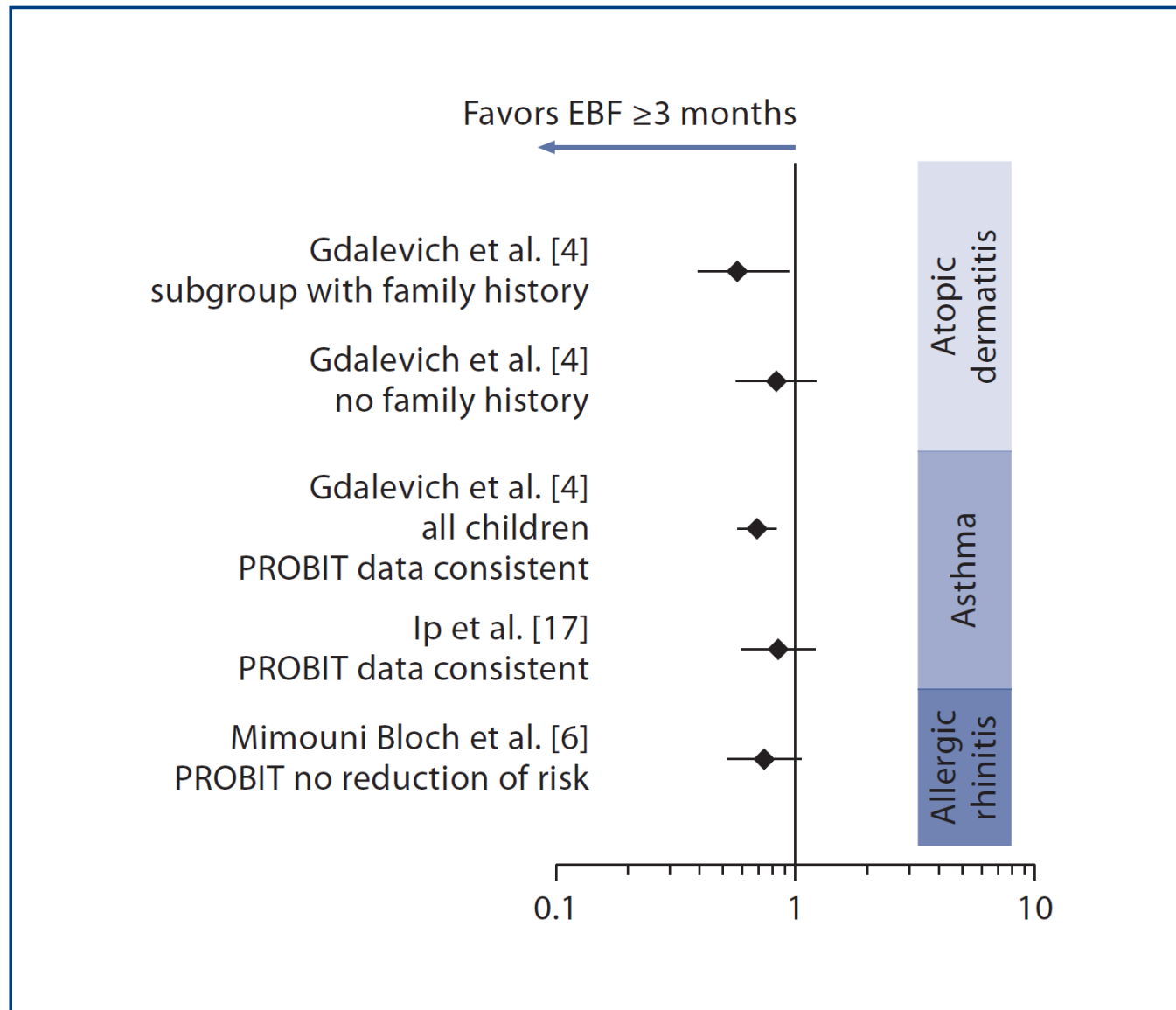
Meats and fish and a wider variety of vegetables. Fresh fruits and wider variety of cereals and legumes. Yoghurt, egg custard and nut pastes.

3

Move on to a chopped texture. Drinks can be offered from a cup
(from a developmental perspective, this is usually around 8 months)

Continue to increase variety as above (e.g. bread, crackers, pasta, wheat based breakfast cereals, cow's milk on cereal, cheese, egg, fish, other seafood, nut products and foods containing nuts).

Breast feeding and allergy risk

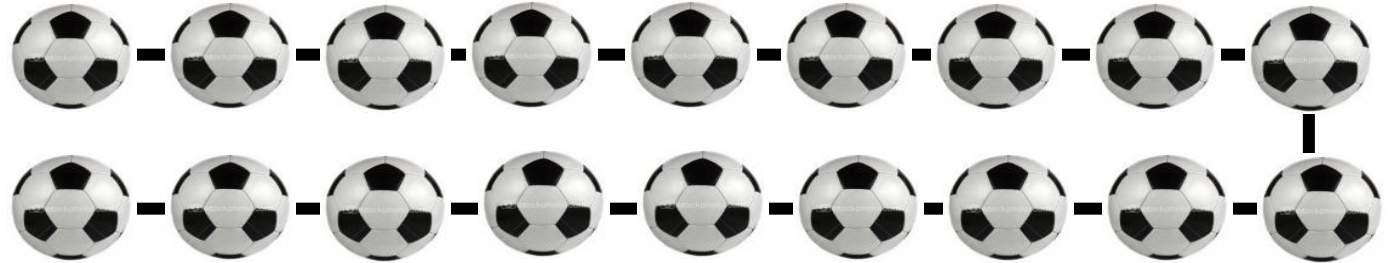


Key Messages

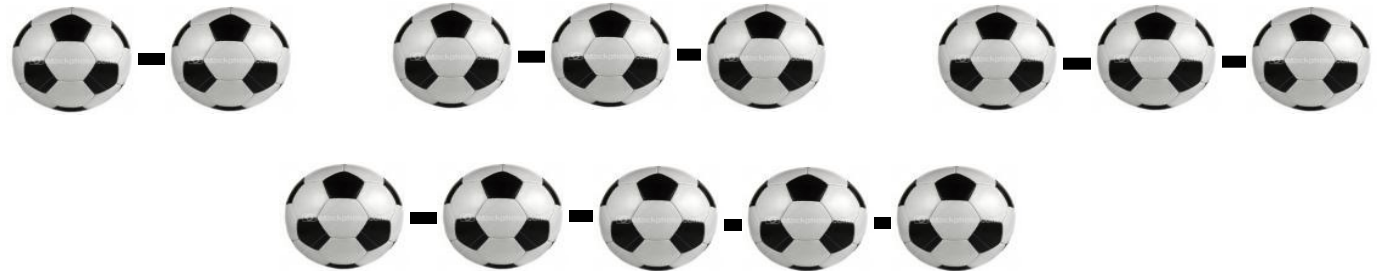
- Exclusive breastfeeding for at least 3 months reduces the risk of atopic dermatitis, at least during infancy.
- No clear risk reduction is evident, however, for asthma, allergic rhinitis, positive allergen skin tests, or food allergy.
- Future epidemiologic and basic laboratory research should explore interactions between specific allergy-promoting genes and infant feeding, as well as effects of other nutritional (e.g. specific micronutrients) and environmental exposures on the risk of allergic disease.

Hydrolysed and amino acid-based formulae

pHF



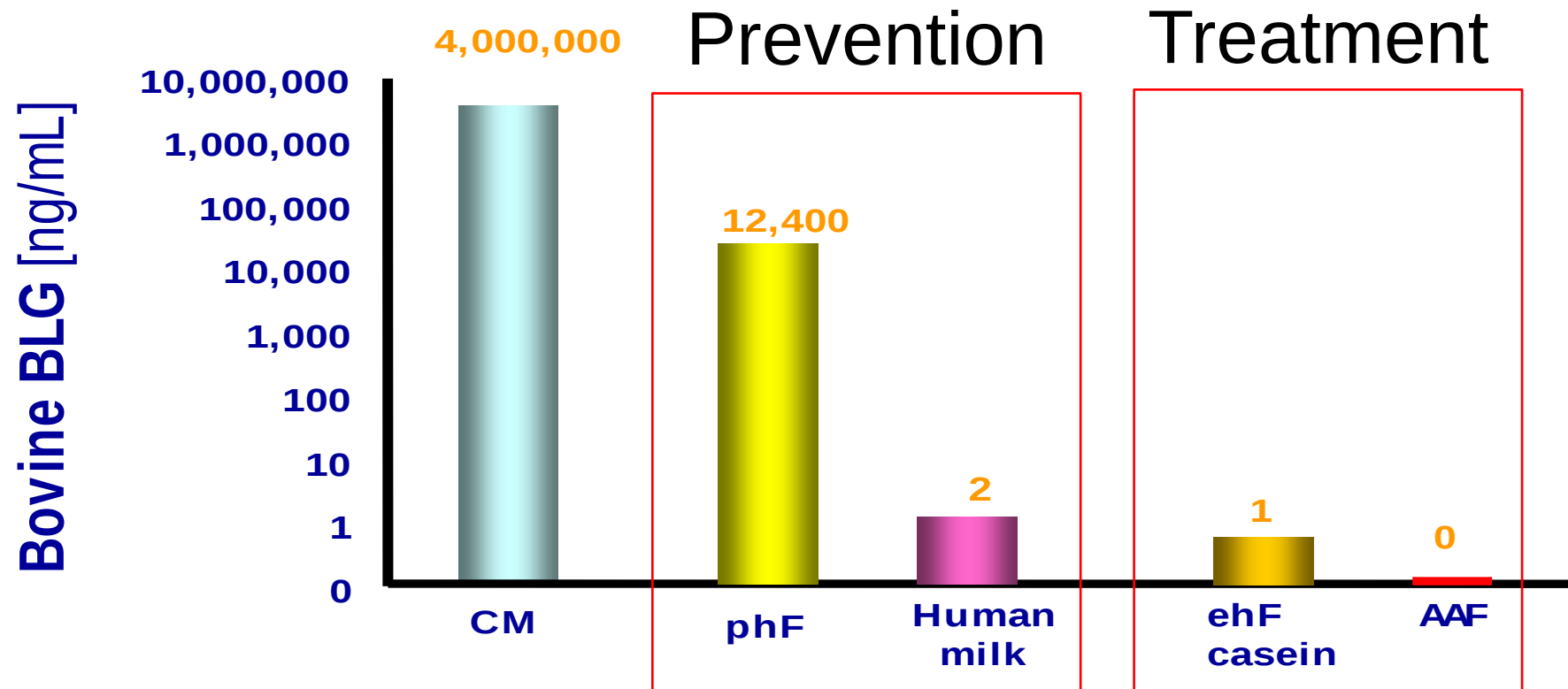
eHF



AAF



Levels of BLG in Human Milk and Infant Formulae



Background

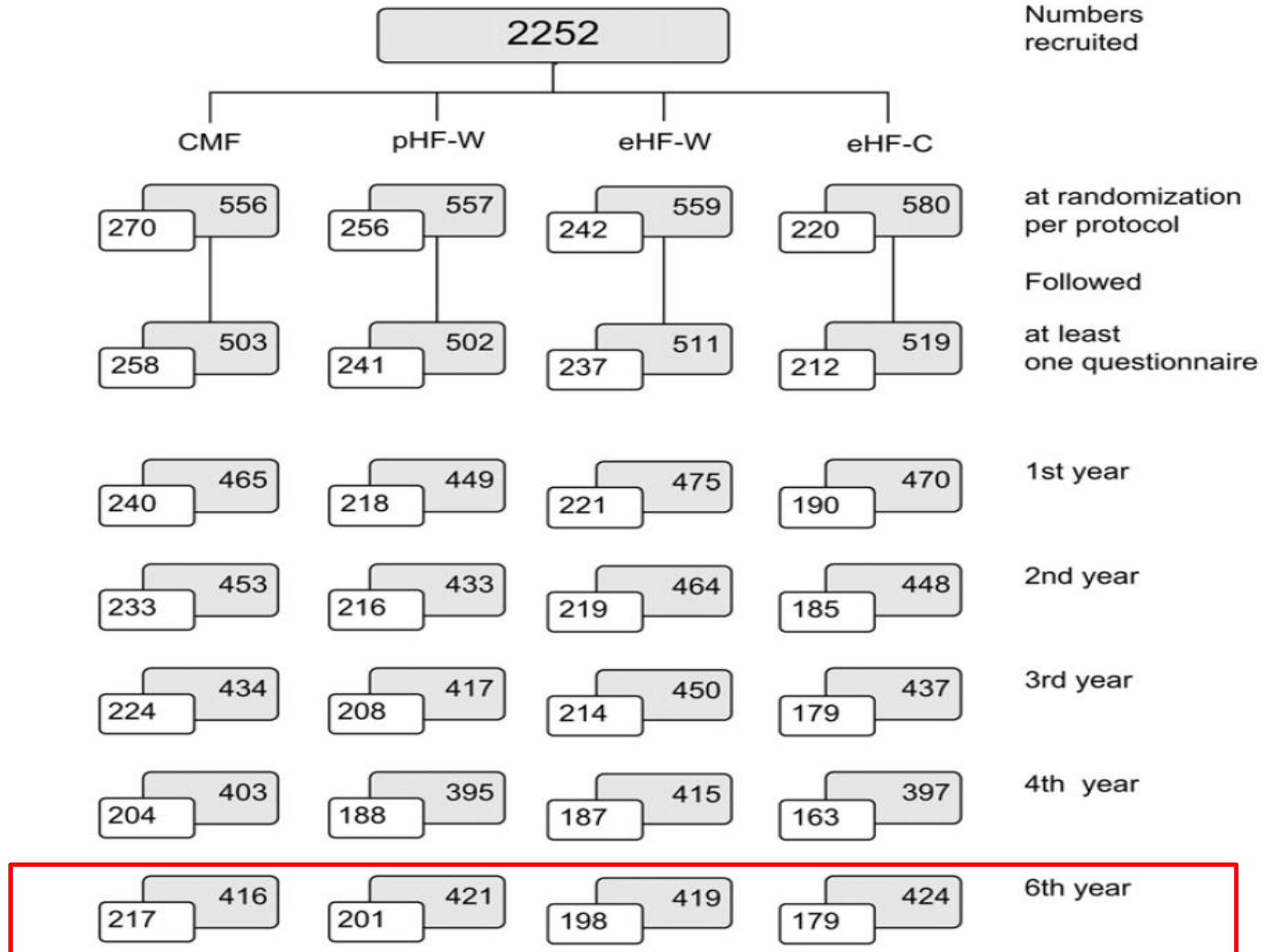
- Largest randomised clinical trial on effect of 3 hydrolysed formulas on allergy prevention (n=2252)
- Non-interventional arm to study effect of breast feeding (n=3739)
- Funded by German government
- Published follow-up to 6 years

Randomised trial (n=2252)

(at time of cessation of breast feeding)

- Standard cow's milk-based formula (CMF)
- Partially hydrolysed whey (pHF-W)
- Extensively hydrolysed whey (eHF-W)
- Extensively hydrolysed casein (ehF-C)

GINI Study: Recruitment and follow-up to 6 years



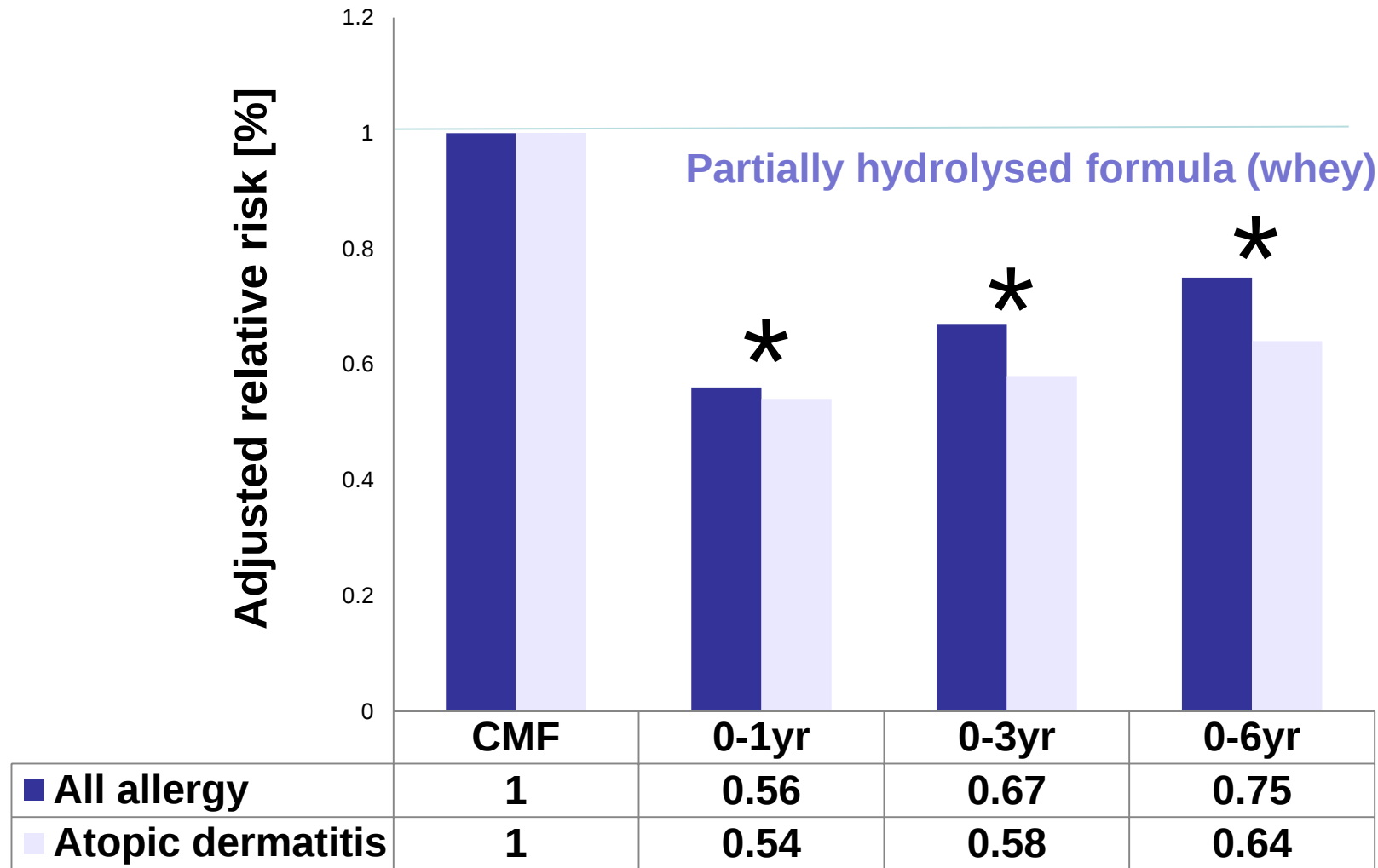
German Infant Nutritional Intervention (GINI) Study

TABLE II. PP analysis: adjusted relative risk from marginal log-binomial models with generalized estimating equations by study formula in comparison with cow's milk feeding

	No. of followed children (N = 988)			
	CMF (N = 270)	pHF-W (N = 256)	eHF-W (N = 242)	eHF-C (N = 220)
AM*†				
Cumulative incidence, birth to 1 y				
Cases (%)	50 (21.1)	26 (12.0)	35 (16.0)	24 (12.8)
aRR (95% CI)	1	0.56 (0.37-0.86)	0.73 (0.50-1.07)	0.60 (0.39-0.92)
Cumulative incidence, birth to 3 y				
Cases (%)	97 (41.7)	62 (29.0)	74 (33.7)	44 (23.9)
aRR (95% CI)	1	0.67 (0.51-0.89)	0.82 (0.64-1.07)	0.60 (0.44-0.83)
Cumulative incidence, birth to 6 y				
Cases (%)	128 (55.7)	96 (45.46)	89 (42.2)	71 (39.0)
aRR (95% CI)	1	0.75 (0.60-0.93)	0.78 (0.63-0.97)	0.67 (0.53-0.85)
AD‡				
Cumulative incidence, birth to 1 y				
Cases (%)	40 (16.8)	21 (9.7)	30 (13.6)	18 (9.6)
aRR (95% CI)	1	0.54 (0.34-0.87)	0.73 (0.47-1.12)	0.54 (0.33-0.89)
Cumulative incidence, birth to 3 y				
Cases (%)	78 (33.5)	42 (19.5)	56 (25.6)	30 (16.2)
aRR (95% CI)	1	0.58 (0.41-0.82)	0.76 (0.56-1.04)	0.51 (0.34-0.75)
Cumulative incidence, birth to 6 y				
Cases (%)	90 (39.1)	58 (27.4)	64 (29.9)	41 (22.5)
aRR (95% CI)	1	0.64 (0.48-0.86)	0.74 (0.56-0.98)	0.55 (0.39-0.76)

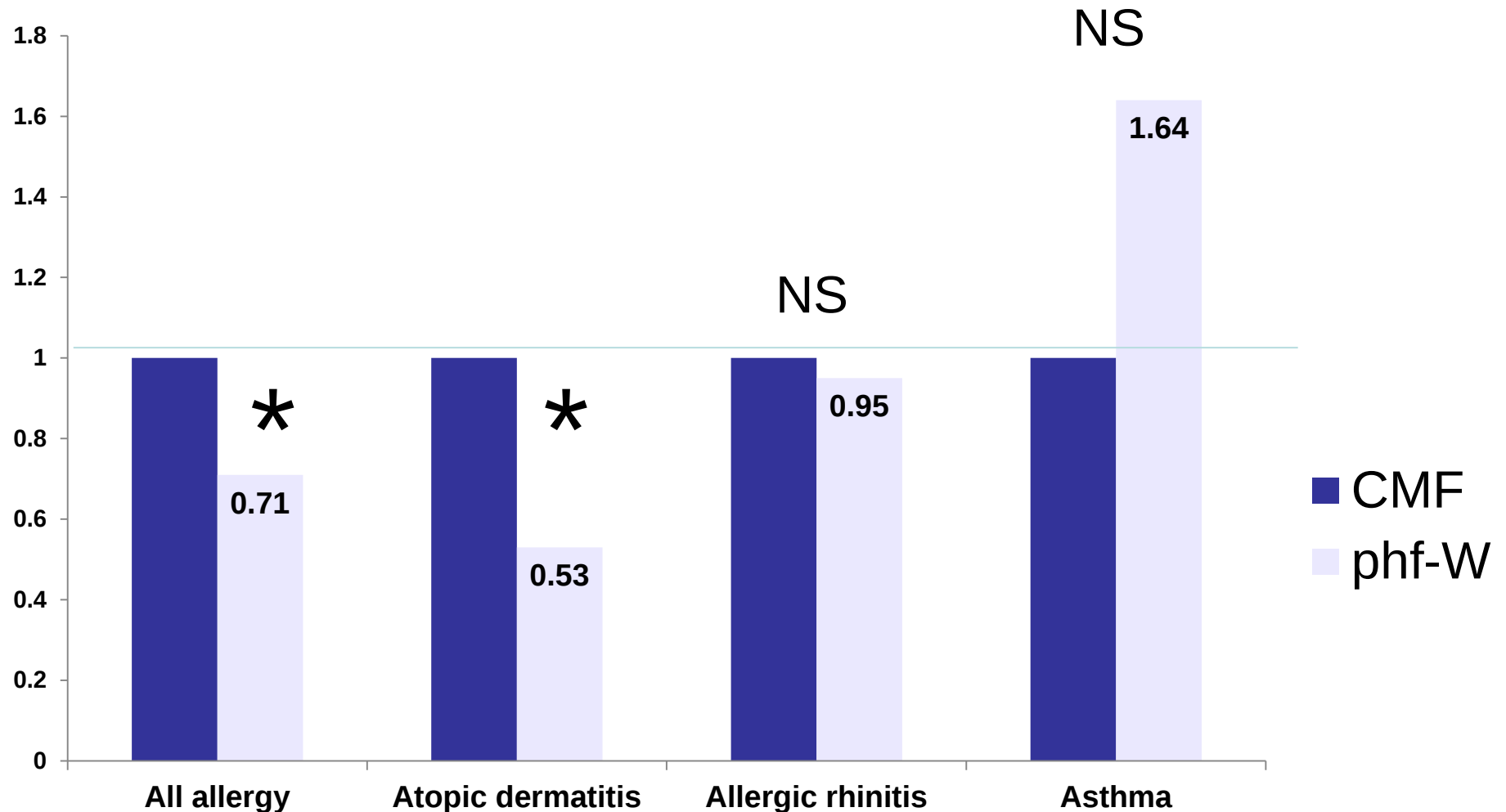
German Infant Nutritional Intervention (GINI) Study

Preventive effect of pHF-W on allergic disease 0-6 yrs

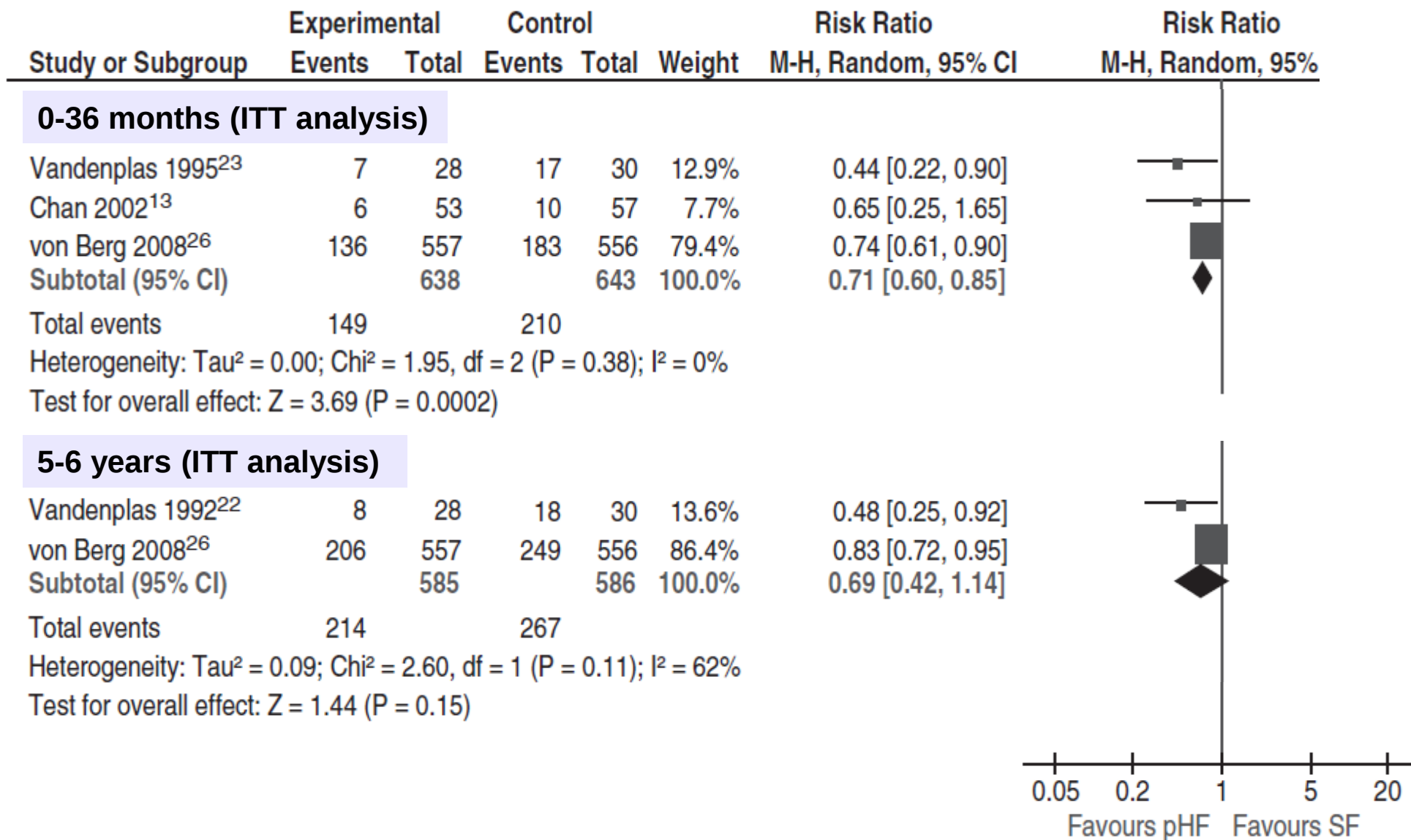


German Infant Nutritional Intervention (GINI) Study

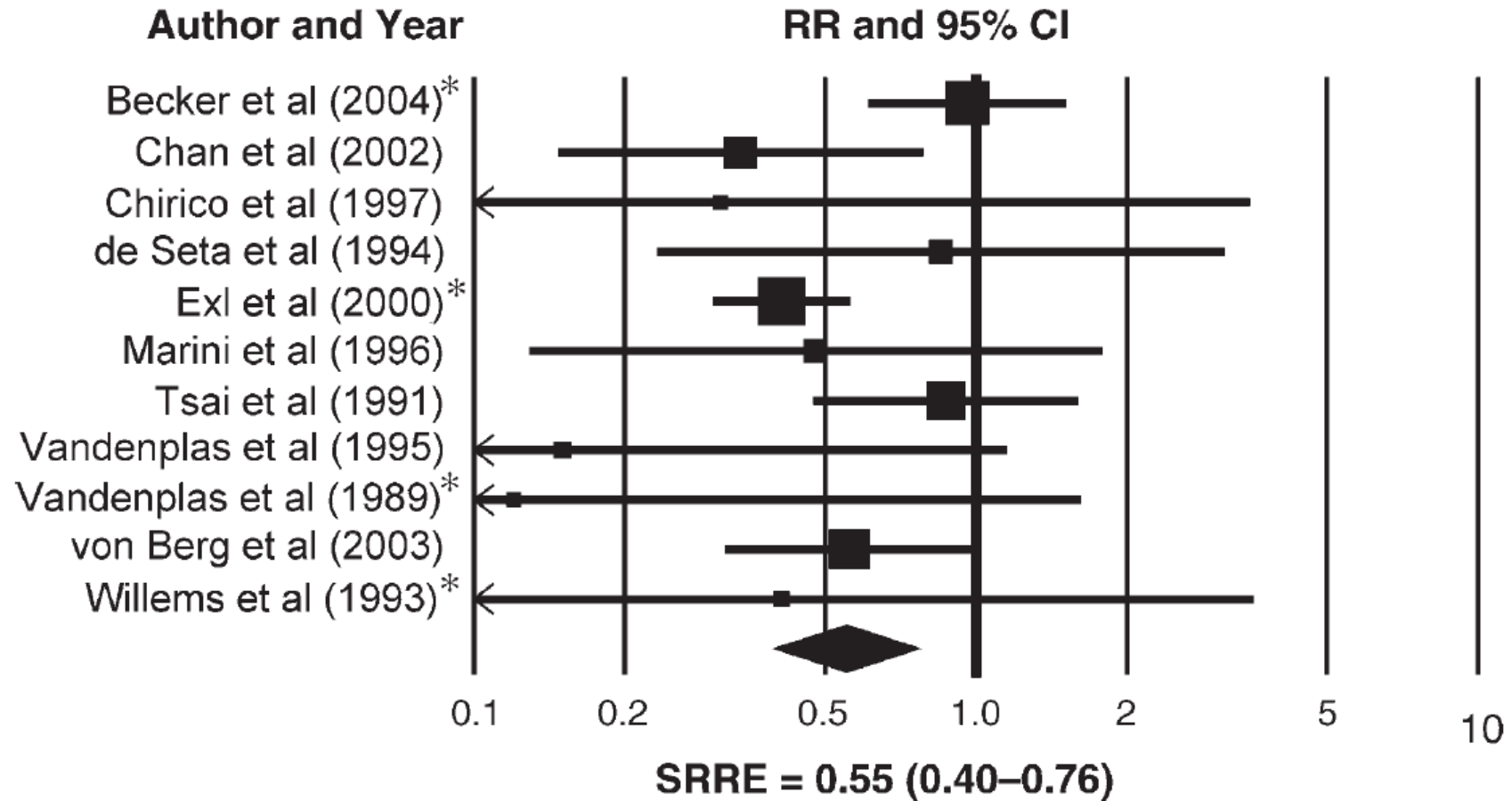
Effect of pHF-W on allergic disease at 4-6 yrs of age



Meta-analysis of allergy prevention pHF vs CMF



Meta-analysis pHF vs CMF in prevention of atopic dermatitis



Clinical implications

If exclusive breast feeding is not possible, early nutritional intervention with partially hydrolysed whey formula in high-risk children has a preventive effect against atopic dermatitis.

Extensively hydrolysed formula

- Few studies on eHF for allergy prevention available
- Contains contaminant amounts of intact cow's milk protein (similar to breast milk)
- Casein ehF reduced risk of CMA and eczema, compared to cow's milk formula (adj. OR 0.51; 95% CI 0.28-0.92)
- Cost high (role for supplemental feeding?)

ehF has similar preventive effect against CMA or atopic dermatitis as pHF, but is more costly

Soy formula

Not generally recommended in infants under 6 months of age

- risk of concomitant soy allergy
- phyto-oestrogens
- phytate content
- aluminium content (soy beverages)

Soy formula currently not recommended for primary allergy prevention

Amino acid-based formula

- No studies on allergy prevention available
- Does not contain food protein antigens
- Does not stimulate oral tolerance
- Costly

AAF not recommended for primary allergy prevention

Clinical implications

Infant soy formula and amino-acid based formula are **not** recommended for the prevention of allergic disorders.



Clinical Report—Probiotics and Prebiotics in Pediatrics

Dan W. Thomas, MD, Frank R. Greer, MD, and COMMITTEE
ON NUTRITION; SECTION ON GASTROENTEROLOGY,
HEPATOLOGY, AND NUTRITION

KEY WORDS

probiotics, prebiotics, pediatrics, supplements, nutrition

ABBREVIATIONS

LGG—*Lactobacillus rhamnosus* GG

FOS—fructo-oligosaccharide

IBD—inflammatory bowel disease

RCT—randomized controlled trial

CI—confidence interval

RR—relative risk

OR—odds ratio

NEC—necrotizing enterocolitis

CUC—chronic ulcerative colitis

IBS—irritable bowel syndrome

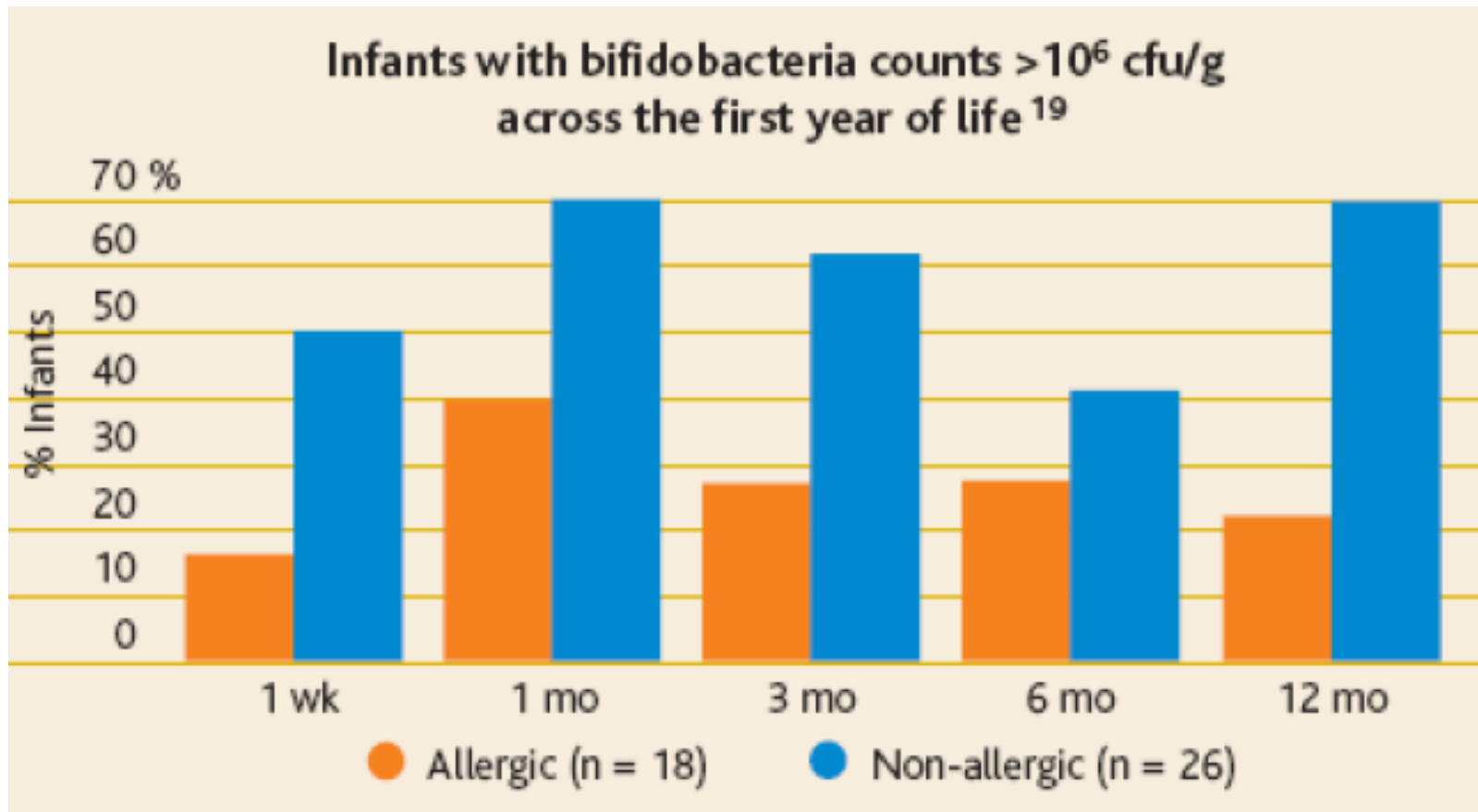
GOS—galacto-oligosaccharide

abstract

FREE

This clinical report reviews the currently known health benefits of probiotic and prebiotic products, including those added to commercially available infant formula and other food products for use in children. Probiotics are supplements or foods that contain viable microorganisms that cause alterations of the microflora of the host. Use of probiotics has been shown to be modestly effective in randomized clinical trials (RCTs) in (1) treating acute viral gastroenteritis in healthy children; and (2) preventing antibiotic-associated diarrhea in healthy children. There is some evidence that probiotics prevent necrotizing enterocolitis in very low birth weight infants (birth weight between 1000 and 1500 g), but more studies are needed. The results of RCTs in which probiotics were used to treat childhood *Helicobacter*

Prevalence of faecal bifidobacteria in allergic and healthy infants



Effects of probiotics depend on

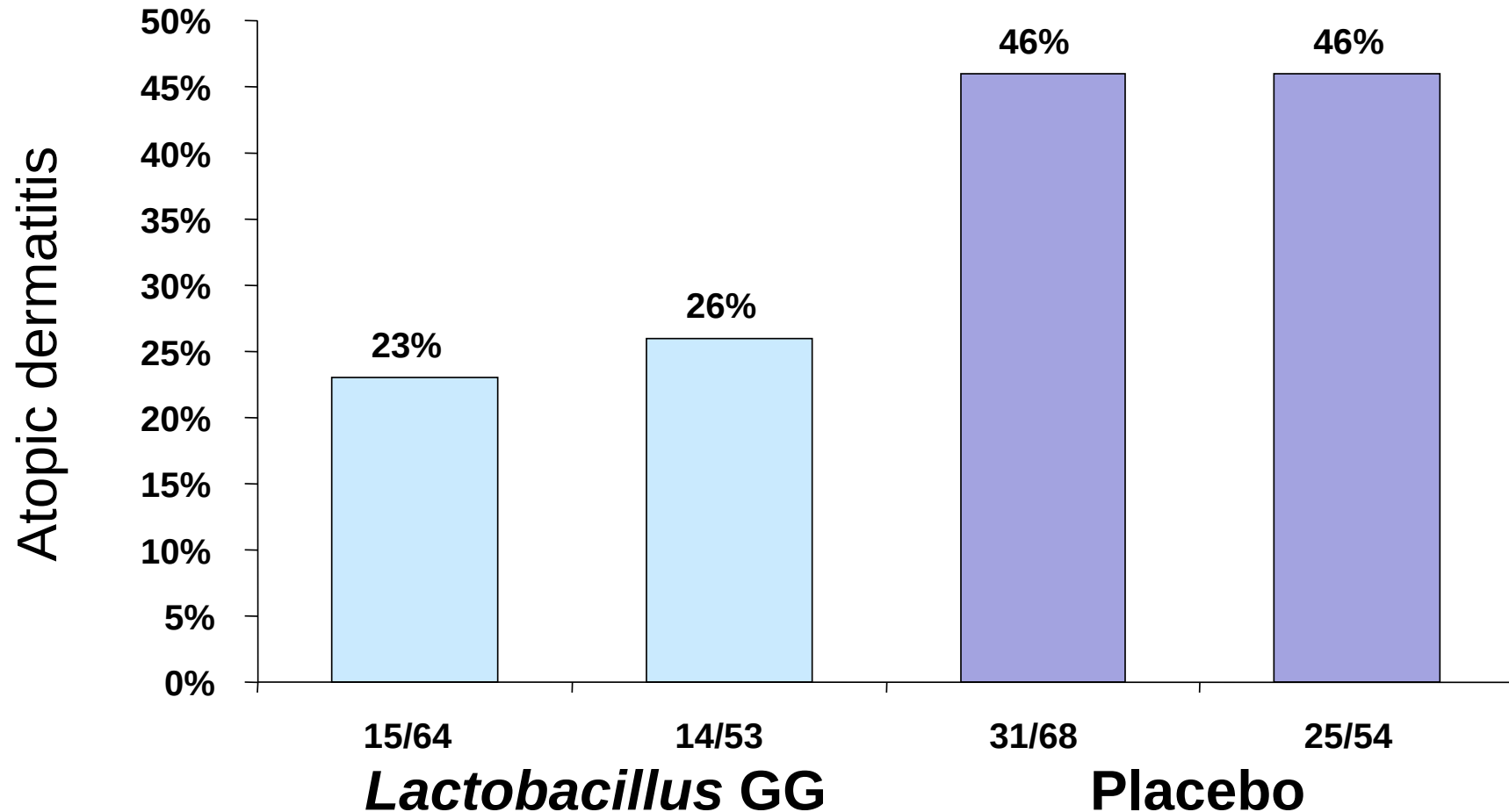
- Probiotic strain
- Dose
- Timing and duration of administration
- Disease-specific outcomes

Prevention of atopic dermatitis with probiotics

- First clinical study demonstrating a preventive effect of pre- and postnatal supplementation with ***Lactobacillus rhamnosus GG*** on atopic dermatitis (AD)
- LGG given to mother 4 weeks before birth and 6 months postnatally (or placebo)
- Perinatal Finnish cohort with high allergy risk
- Rate of eczema reduced by about 50% (23% vs 46% at 12 mo)
- Lower prevalence of AD maintained at follow-up to 7 years.

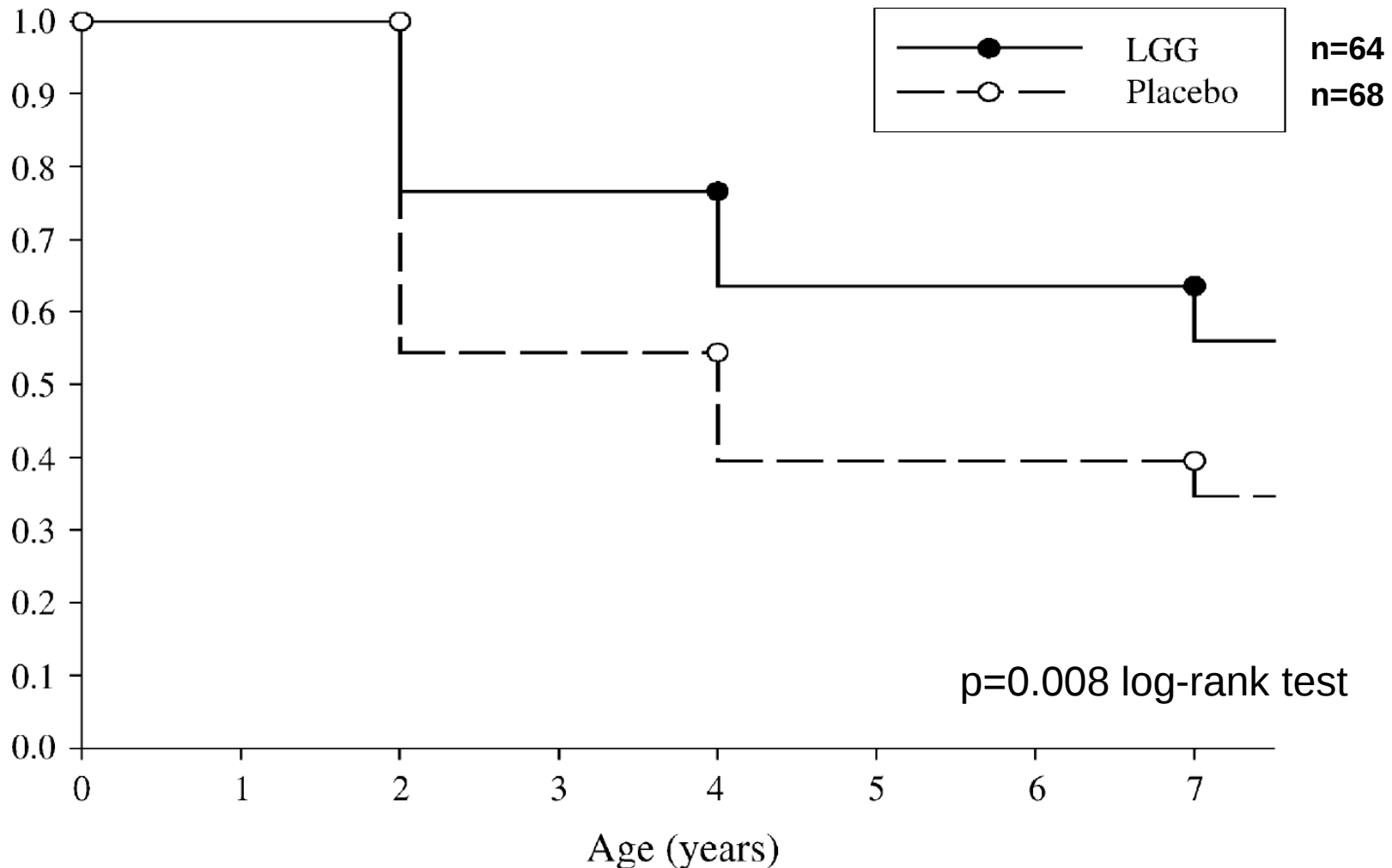
Prevention of atopic dermatitis with probiotics

2 years OR (CI) 0.51 (0.32-0.84)
4 years OR (CI) 0.57 (0.33-0.97)



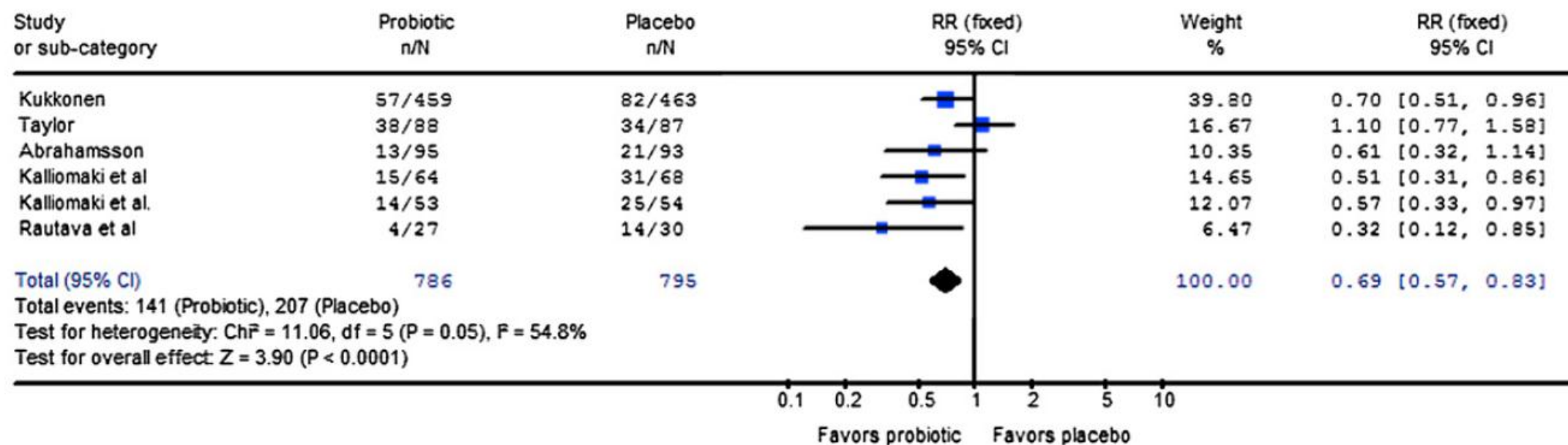
Prevention of atopic dermatitis with probiotics

7-year follow-up of infants without eczema



Meta-analysis on probiotics prevention of atopic dermatitis

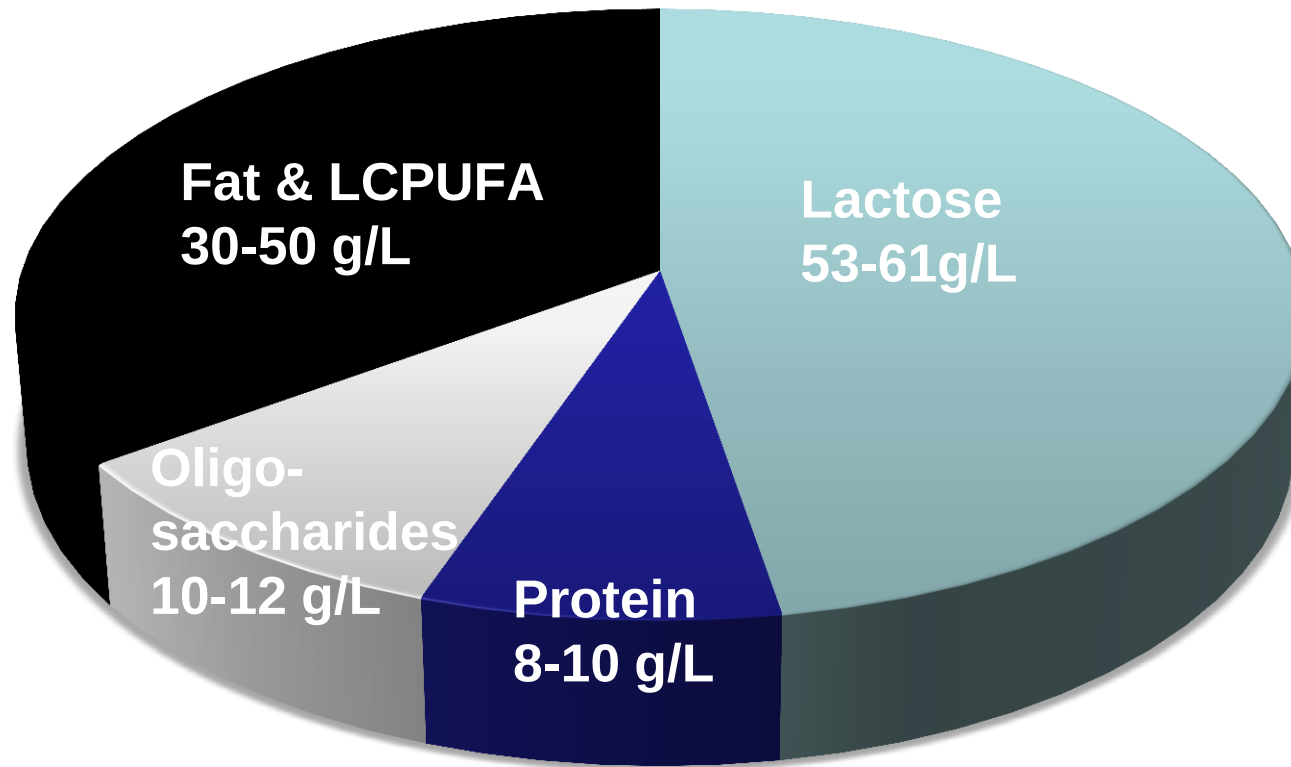
Review: Probiotics for pediatric atopic dermatitis
Comparison: Probiotic vs placebo
Outcome: **Primary prevention studies**



Clinical implications

Supplementation with specific probiotic bacteria (*L. rhamnosus* GG) significantly reduces the risk of atopic dermatitis in high-risk infants and has a long-term preventive effect.

Composition of breast milk solids



88-90% water

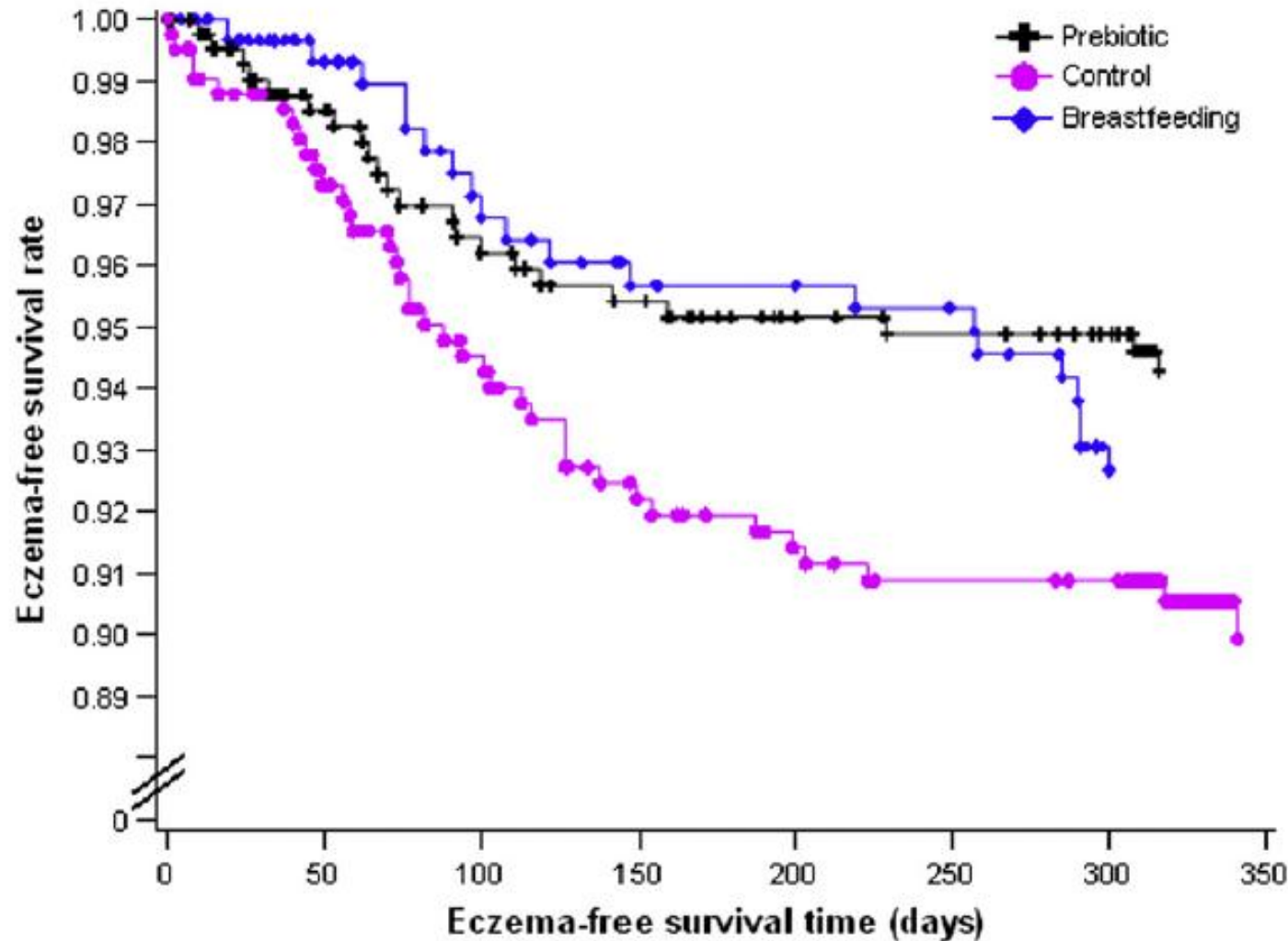
Prebiotics

- Complex oligosaccharides
- Occur in breast milk
- Promote faecal bifidobacteria
- Result in lower stool pH
- **3 types (manufactured):**
 - Short chain galacto-oligosaccharides (sc-GOS)
 - Long chain fructo-oligosaccharides (lc-FOS)
 - Pectin-derived acidic oligosaccharides (pAOS)
- May have preventive effect for atopic dermatitis

Prebiotics and atopic dermatitis risk

- European multi-centre randomised, controlled trial
- Healthy low-risk infants from 8 weeks to 12 months
- Randomised to standard infant formula supplemented with **sc-GOS**, **lc-FOS** and pectin-derived acidic oligo-saccharides (**p-AOS**) (n=414), or unsupplemented standard formula (n=416). Breast fed infants (n=300) also followed.
- Prebiotics reduced incidence of atopic dermatitis by 44% at 12 months of age (severity not affected)
- Number needed to treat in order to prevent 1 case of atopic dermatitis was 25 infants.

Prebiotics and atopic dermatitis risk



Atopic dermatitis

- Prebiotic 5.7%

- Control 9.7%

$p = 0.04$

Clinical implications

Formula supplementation with prebiotic oligosaccharides reduced the risk of atopic dermatitis in low-risk infants at 12 months of age. Long-term data are not available.

Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial



OPEN ACCESS

D J Palmer *research fellow*¹, T Sullivan *statistician*², M S Gold *consultant paediatric allergist*³, S L Prescott *consultant paediatric allergist*⁴, R Heddle *clinical immunologist*⁵, R A Gibson *professor of functional foods*⁶, M Makrides *professor of human nutrition*^{1 3}

¹Women's and Children's Health Research Institute, 72 King William Road, North Adelaide, South Australia, 5006, Australia; ²Data Management and Analysis Centre, University of Adelaide, Adelaide, South Australia, 5005, Australia; ³School of Paediatrics and Reproductive Health, University of Adelaide, North Adelaide, South Australia, 5006; ⁴Princess Margaret Hospital for Children, Perth, Western Australia, 6008, Australia; ⁵SA Pathology, Royal Adelaide Hospital, Adelaide, South Australia, 5005; ⁶School of Agriculture, Food and Wine, University of Adelaide, Glen Osmond, South Australia, 5064, Australia

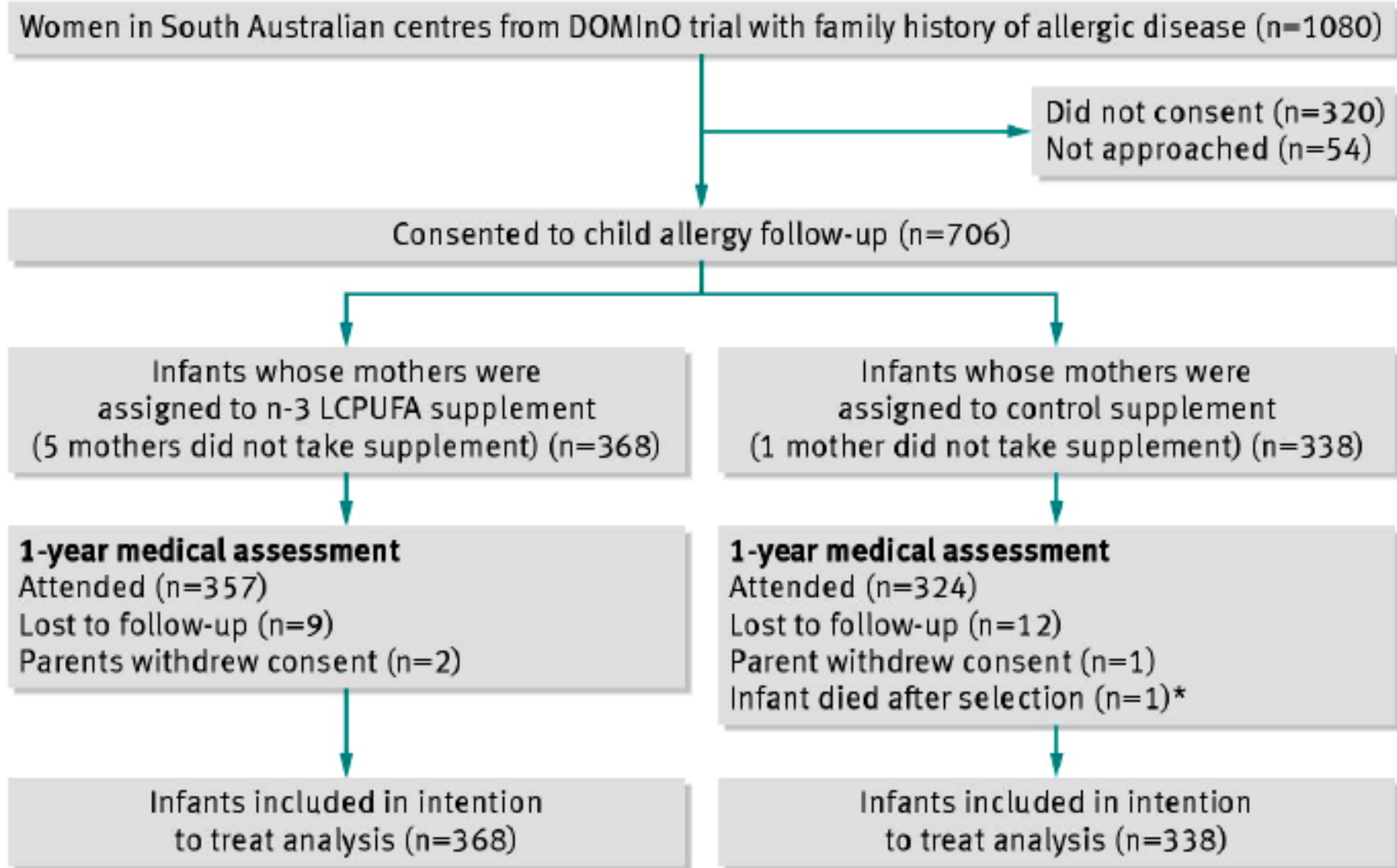
Fish oil supplementation during pregnancy

- Significant increase in dietary ω -6 fatty acids since onset of allergy epidemic
- Diets high in ω -3 long chain polyunsaturated fatty acids (LCPUFA) may have immune modulating effects and reduce risk of IgE-sensitisation
- Two previous trials have suggested that fish oil supplementation during pregnancy reduces risk of IgE-mediated allergic disease (eczema, food allergy)

Fish oil supplementation during pregnancy

- Cohort of high-risk infants (FHx allergies)
- High-dose supplementation with fish oil (n=368)
 - 3 x 500mg capsules
 - = 800mg docosahexaenoic acid (DHA)
 - + 100mg eicosapentaenoic acid (EPA)or control intervention (vegetable oil; n=338)
- Taken from 21 weeks' gestation until delivery
- Assessment for allergies by blood and skin tests
- Follow-up of infants to 12 months of age
- Primary outcomes eczema or food sensitisation

DOMInO trial



DHA/EPA during pregnancy: results

Table 2| Clinical allergy assessment outcomes at 12 months of age.

Outcome	n-3 LCPUFA* (n=368)	Control* (n=338)	Unadjusted relative risk (95% CI)	Unadjusted P value	Adjusted† relative risk (95% CI)	Adjusted† P value
Allergic disease with sensitisation:	32 (9)	43 (13)	0.68 (0.43 to 1.05)	0.08	0.70 (0.45 to 1.09)	0.12
Eczema with sensitisation	26 (7)	39 (12)	0.61 (0.38 to 0.98)	0.04	0.64 (0.40 to 1.03)	0.06
Food allergy with sensitisation	11 (3)	11 (3)	0.94 (0.40 to 2.22)	0.88	0.96 (0.41 to 2.25)	0.93
Sensitisation with/without allergic disease:	53 (14)	67 (20)	0.73 (0.52 to 1.02)	0.07	0.75 (0.53 to 1.04)	0.08
Egg sensitisation	34 (9)	52 (15)	0.61 (0.40 to 0.91)	0.02	0.62 (0.41 to 0.93)	0.02
Peanut sensitisation	15 (4)	22 (7)	0.62 (0.33 to 1.18)	0.15	0.63 (0.34 to 1.19)	0.16
Cows' milk sensitisation‡	6 (2)	3 (1)		0.51		
Allergic disease without sensitisation	63 (17)	53 (16)	1.10 (0.79 to 1.55)	0.57	1.10 (0.79 to 1.55)	0.57

LCPUFA=long chain polyunsaturated fatty acid.

*All data are based on analysis of 50 imputed datasets; values are numbers (percentages).

†Adjusted for centre, parity, maternal history, and sex.

‡Fisher's exact test using original data; adjusted/imputed analyses not done owing to rarity of outcomes (n-3 LCPUFA group, n=349; control group, n=317).

DHA/EPA during pregnancy

- High-dose intervention in at-risk population
- Study failed to show an overall reduction in IgE-mediated allergic disease at 12 months
- Decreased prevalence of eczema and egg sensitisation in the DHA/EPA supplemented group
- Clinical significance unclear
- Further prospective studies needed

Summary and recommendations

- In view of the general increase in food allergy and atopic dermatitis, allergy prevention has become a major public health priority.
- Exclusive breast feeding for at least 4-6 months is the most important strategy in the primary prevention of food allergy and allergic disorders.
- Maternal elimination diets and prolonged avoidance of food allergens are not considered effective in preventing allergies.

Summary and recommendations

- If exclusive breast feeding is not possible, supplemental feeding with a partially hydrolysed formula should be considered.
- Supplementation with specific probiotic bacteria or prebiotics also significantly reduces the risk of atopic dermatitis.
- High-dose supplementation with fish oil during pregnancy may prevent eczema and egg sensitisation in young infants.