MICROBIOTA INTESTINALE E SVILUPPO DI ALLERGOPATIE

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Il trend epidemiologico..

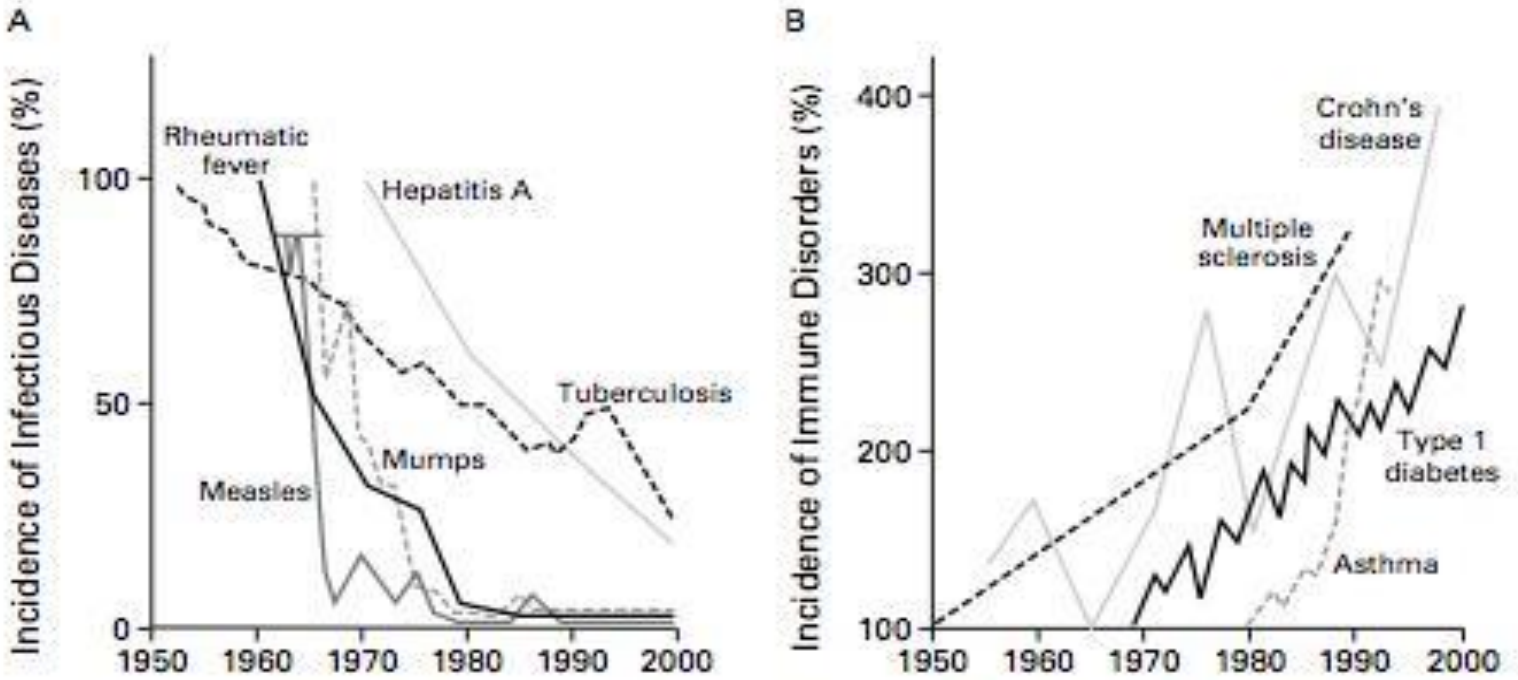


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[12] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

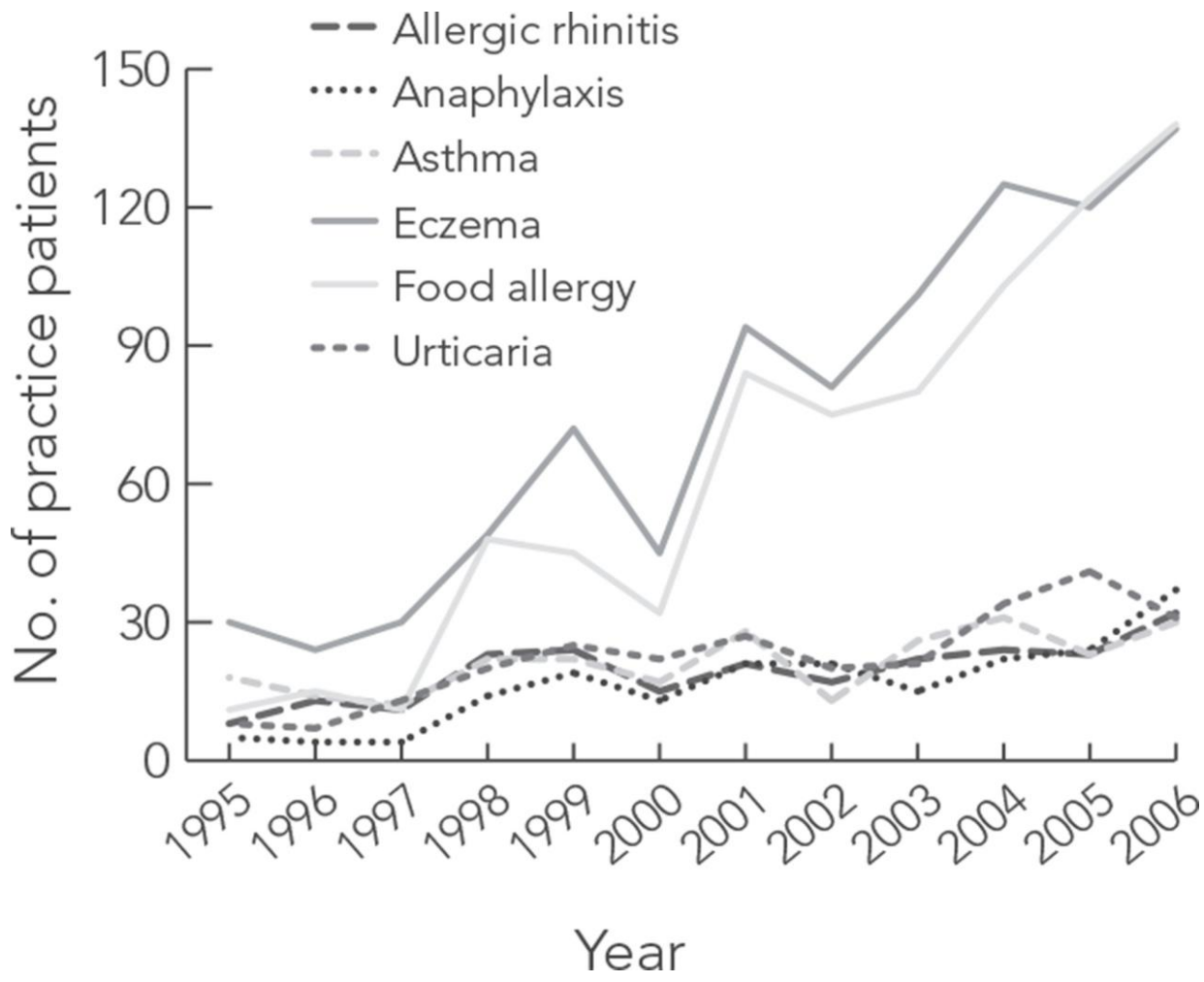
The 21st Century: a new set of problems

New epidemics of ‘early’ onset NCDs

- Allergy and immune disease
- Childhood obesity and associated NCDs
- Mental ill-health: young people

Inflammation and immune dysregulation are major elements of these conditions

Consequence of rapid environmental change on human health



Time trends in allergy-related disorders in children aged 0–5 years

Mullins, MJA 2007

The Hygiene Hypothesis

The facts "…could be explained if allergic diseases were prevented by infection in early childhood…"

Strachan, DP (1989) Hay fever, hygiene, and household size. BMJ, 229 (6710). pp. 1259-1260. ISSN 0959-8138

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Prof. David Strachan

Strachan BMJ 1989; 299:1259–60

Epidemiological studies carried out in Finland, Denmark and the United Kingdom now confirm that childhood infections **do not protect** against allergic disorders

Benn CS et al *British Medical Journal 2004*

Dunder T et al *Archives of Pediatric & Adolescent Medicine 2007*

Bremner SA et al Allergy 2008

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Da **“The Hygiene Hypothesys”** a **“Microbiota Hypothesys”**

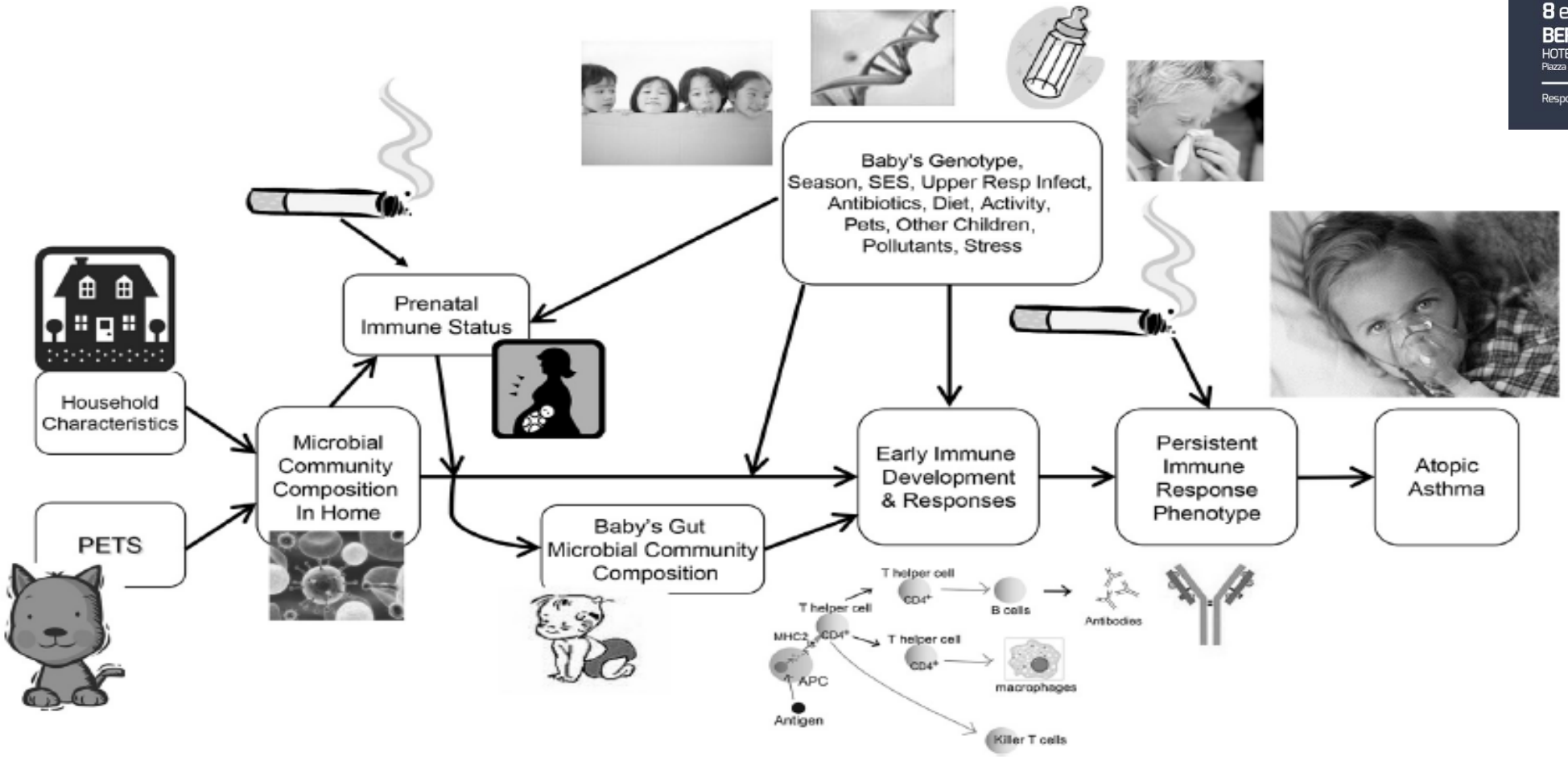


Fig 1. Causal pathway relating the environment, infant gut microbiota, and pediatric allergy and atopic asthma.

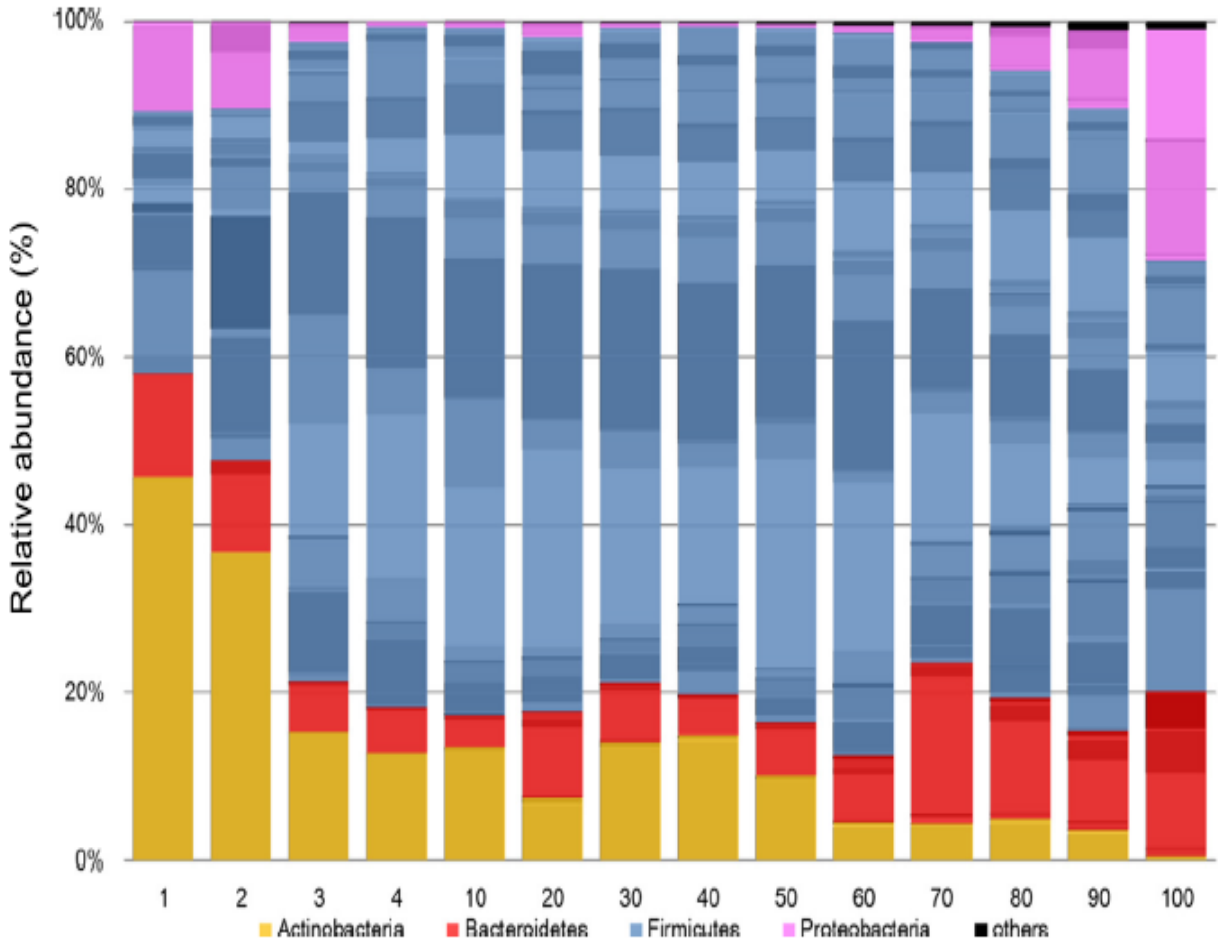
Johnson CC, Ownby DR. Translational Research 2017

SISTEMA IMMUNE = LEARNING DEVICE

Before

After

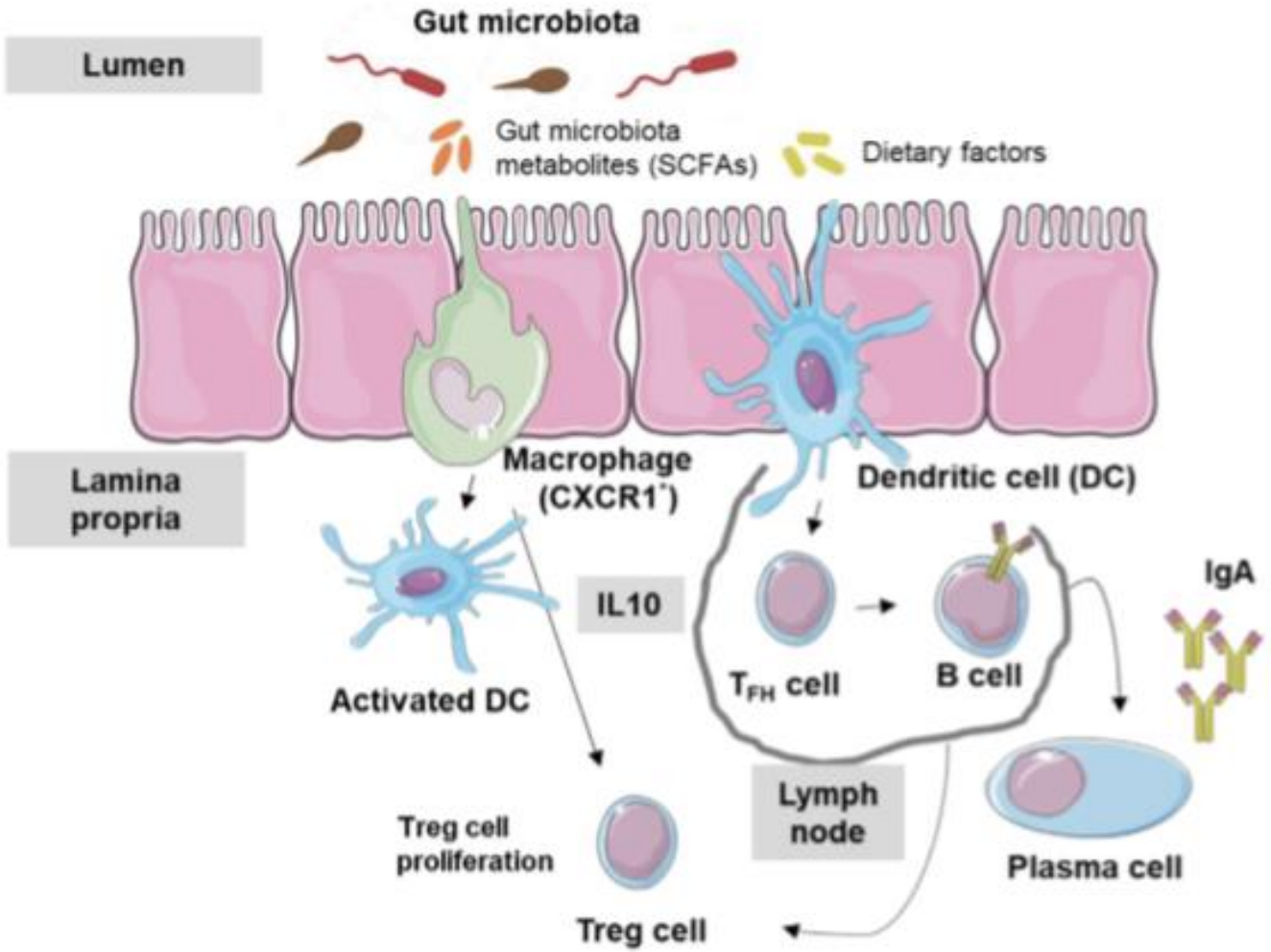
The succession process of intestinal bacterial colonizers culminates in the establishment of a stable “climax community” of microbes resembling the adult microbiota by 3 years of age, with studies in Western populations demonstrating maturation as soon as 1 year.



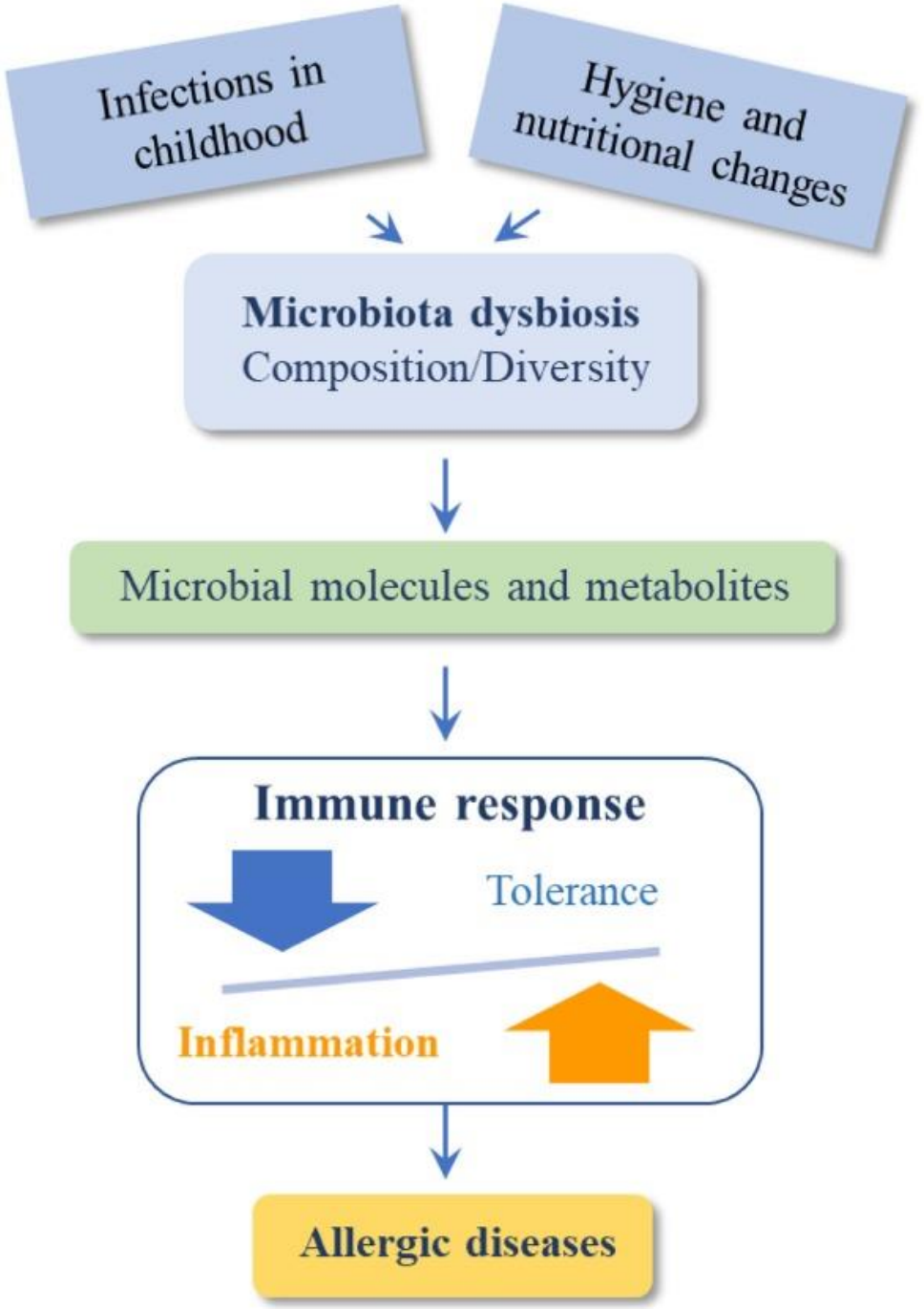
…..

Dogra S et al. mBio. 2015
Hesla HM et al. FEMS Microbiol Ecol 2014
Backhed F et al Cell Host Microbe 2015
Odamaki et al. BMC Microbiology 2016

NETWORK DI TOLLERANZA IMMUNOLOGICA



Pascal M et al Front. Immunol.2018



Pascal M et al Front. Immunol.2018

The intestinal microflora in allergic Estonian and Swedish 2-year-old children

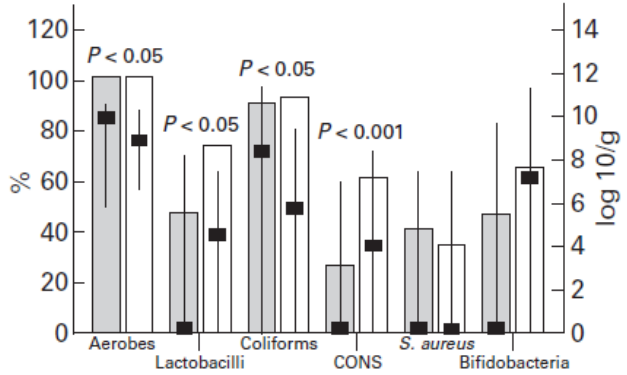


Fig. 1. Intestinal microflora of 13 allergic (grey) and 16 nonallergic (white) Estonian children. The results are presented as colonization rate (%, columns) and counts (log CFU/g, range and median, lines and filled symbols).

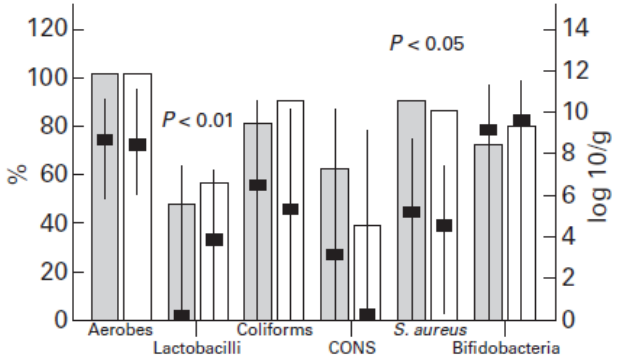


Fig. 2. Intestinal microflora of 14 allergic (grey) and 19 nonallergic (white) Swedish children. The results are presented as colonization rate (%, columns) and counts (log CFU/g, range and median, lines and filled symbols).

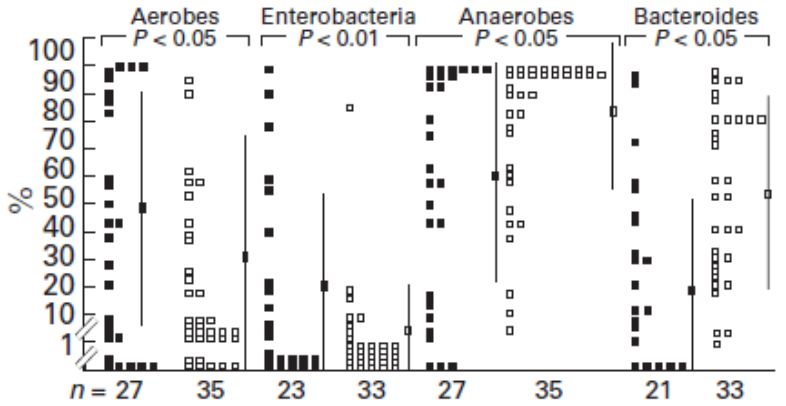
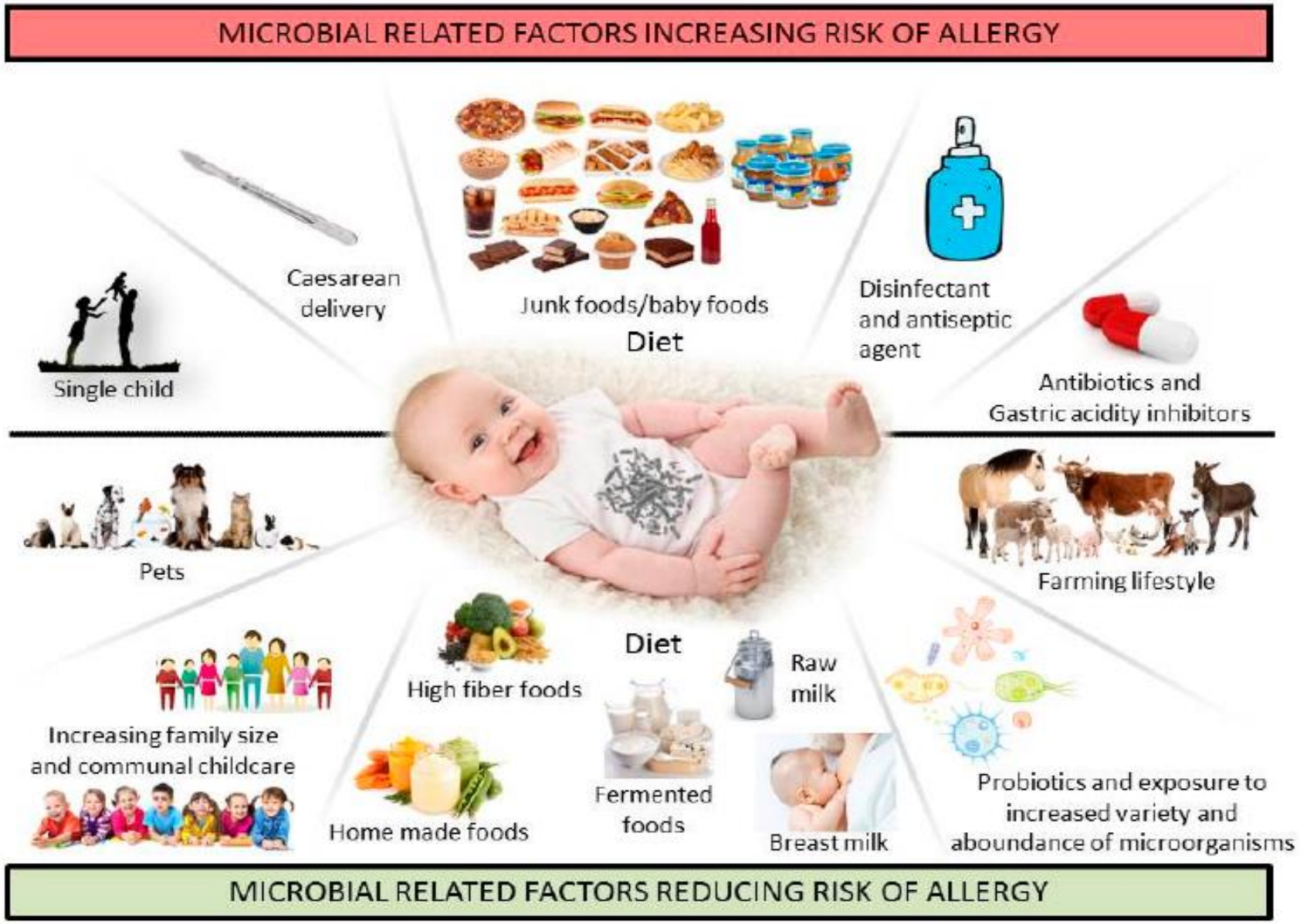


Fig. 3. Relative amounts of aerobic and anaerobic microorganisms, enterobacteria and bacteroides, expressed as a percentage of the total microbial faecal flora in allergic ($n = 27$, filled symbols) and nonallergic ($n = 35$, open squares) 2-year old children.

The allergic children in Estonia and Sweden were less often colonized with lactobacilli (P < 0.01), as compared with the nonallergic children in the two countries. The proportions of aerobic bacteria of the intestinal flora were also higher in the allergic children (P< 0.05), while the opposite was true for anaerobes (P< 0.05).

Bjorksten B et al Clin Exp Allergy 1999

top ten
in gastroenterologia
10ª EDIZIONE
8 e 9 MARZO 2019
BERGAMO
HOTEL EXCELSIOR SAN MARCO
Piazza della Repubblica, 6
Responsabile Scientifico: Fabio Pace



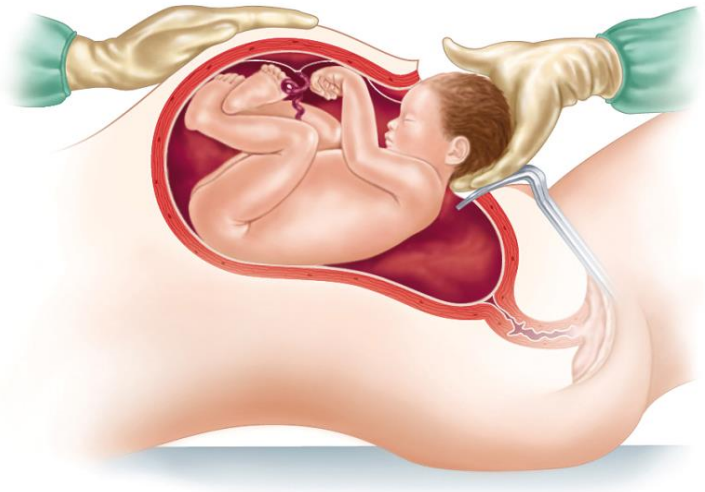
Aitoro et al Nutrients. 2017

Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood

Table 4 Combined effect of type of delivery and parental atopy on the development of food allergy

Group	All neonates (n = 459)	Term-born neonates (n = 379)
Vaginal delivery—no parental atopy	Reference group	Reference group
Cesarean section—no parental atopy	2.02 (0.58–7.06)	2.84 (0.72–11.2)
Vaginal delivery—parental atopy	3.05 (0.54–17.36)	3.76 (0.60–23.5)
Cesarean section—parental atopy	**10.0 (3.06–32.7)**	**11.3 (2.93–43.5)**

Logistic regression models.
Parental atopy refers to the presence of atopy in any parent.
Statistically significant values are presented in bold.



Possibili meccanismi:

- ≠ della microflora intestinale neonato ↓ Actinobacteria e Bacteroidetes phyla, ↑ Firmicutes in CS
- < «stress», effetto su maturazione S.I
- **…**

Papathoma et al Pediatric Allergy and Immunology 27 (2016)

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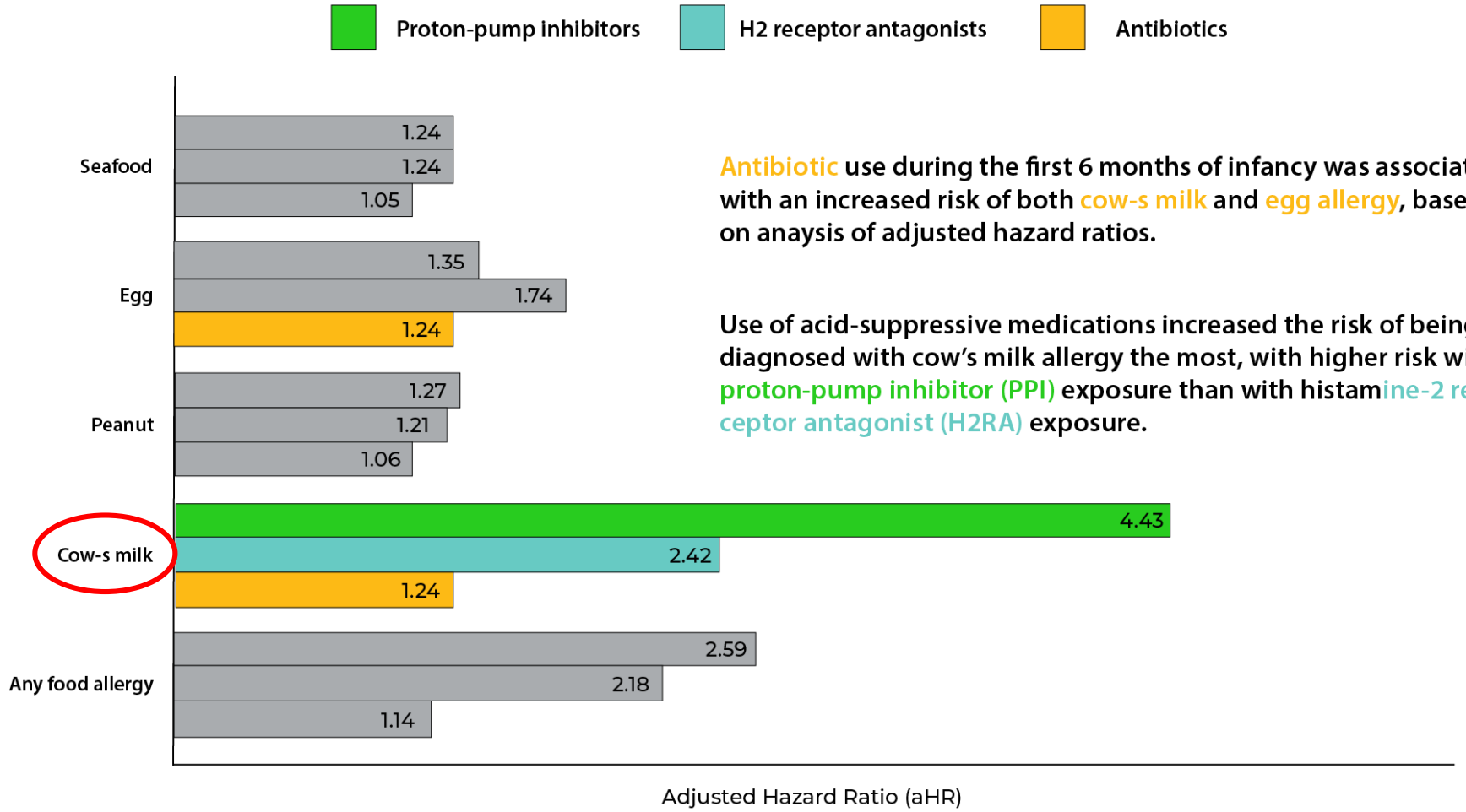
JAMA Pediatrics | Original Investigation

Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood



Antibiotic use during the first 6 months of infancy was associated with an increased risk of both cow-s milk and egg allergy, based on anaysis of adjusted hazard ratios.

Use of acid-suppressive medications increased the risk of being diagnosed with cow's milk allergy the most, with higher risk with proton-pump inhibitor (PPI) exposure than with histamine-2 receptor antagonist (H2RA) exposure.

Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM, Association Between Use of Acid-Suppressive and Antibiotics During Infancy and Allergic Diseases in Early Childhood, JAMA Pediatr. Published online April 02, 2018. doi:10.1001/jamapediatrics.2018.0315

The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation

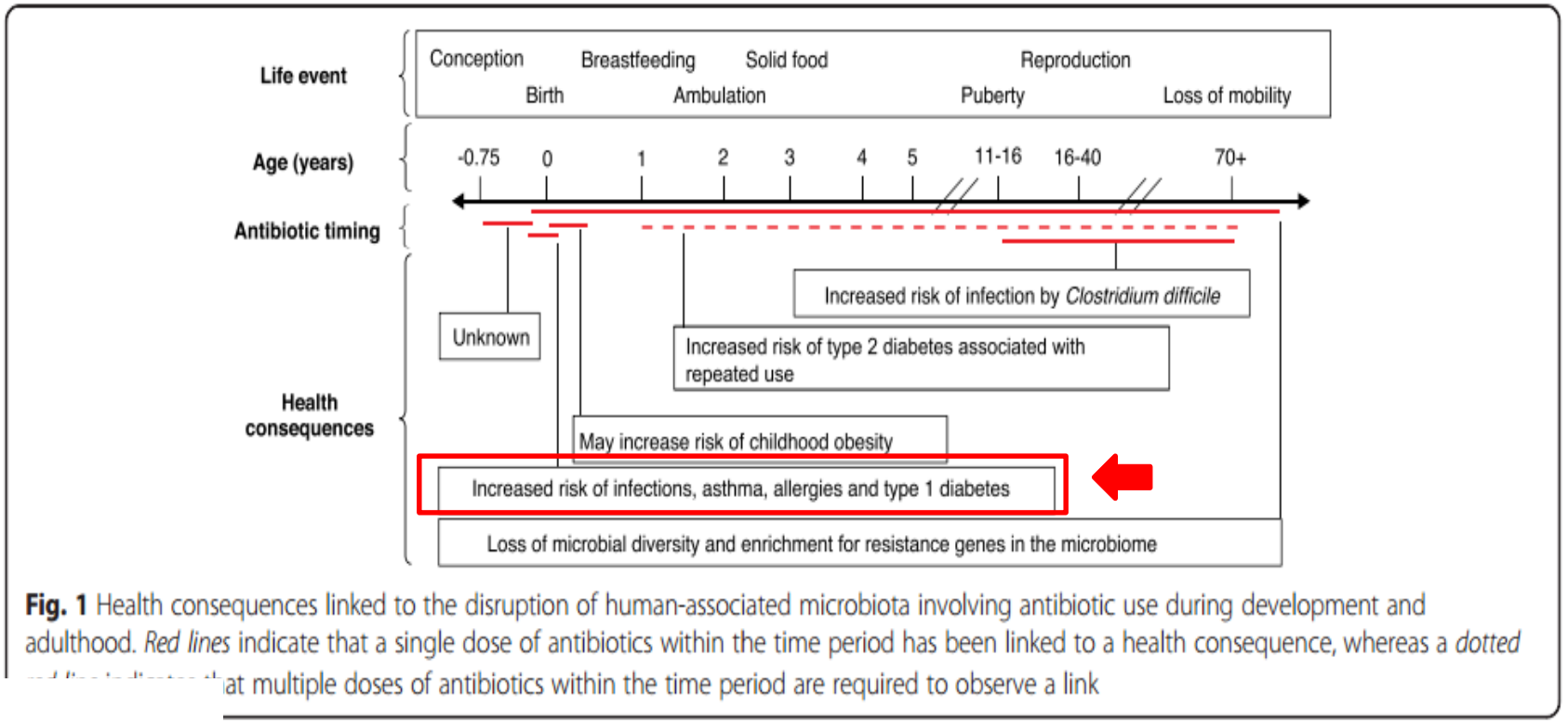


Fig. 1 Health consequences linked to the disruption of human-associated microbiota involving antibiotic use during development and adulthood. *Red lines* indicate that a single dose of antibiotics within the time period has been linked to a health consequence, whereas a *dotted* [illegible] multiple doses of antibiotics within the time period are required to observe a link

Langdon et al. Genome Medicine 2016

Pascal M et al Front. Immunol.2018

BREASTFEEDING E ALLERGIE: EVIDENZE

DERMATITE ATOPICA

- **No evidence of breastfeeding protective effect on eczema development** at 6–7 years of age, but some protection against severe eczema

SAAC Phase Three Study Group. Allergol. Immunopathol. 2011

- **Weak evidence that exclusive breastfeeding for more than 3–4 months reduced the risk of eczema up to 2 years** (OR 0.74; 0.57,0.97, I^2 62%); no effect after the age of 2

Lodge et al. Acta Paed 2015

ASMA

- "More vs less breastfeeding" was associated with a 22% reduced risk of asthma (OR 0.78, 95% CI 0.74, 0.84), strongest effects observed before two years of age (Dogaru et al. Am J Epidemiol 2014)
- There is some evidence that breastfeeding is protective for asthma (5-18 years): 10% reduced risk (OR 0.90, 95% CI 0.84, 0.97), with stronger associations in low- and middle-income countries (Lodge et al. Acta Paed 2015)
- **In both reviews, significant heterogeneity was observed (I^2 = 71% and 63%, respectively)**

ALLERGIA ALIMENTARE

- The most recent meta-analysis showed **no statistically significant association between breastfeeding and food allergy development** (OR 1.02, 95% CI 0.88-1.18; I^2 86%).

Lodge et al. Acta Paed 2015

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Review

Human Milk and Allergic Diseases: An Unsolved Puzzle

"The main challenge in the analyses of these data was **significant heterogeneity** in the definitions of breastfeeding, which are not always consistent with WHO recommendations, and in phenotyping of for health outcomes"

"It is well established that **breastfeeding confers protection** against both short-term adverse outcomes (including reduced morbidity and mortality from neonatal infections) and long-term events including reduction in blood pressure, type 2 diabetes, increased IQ and better educational achievements in later life (even when adjusted for family socio-economic status).
[…]
Based on these data, current UNICEF and WHO recommendations are "**every infant should be exclusively breastfed for the first six months of life….**

Nutrients **2017**, *9*, 894; doi:10.3390/nu9080894

Infant gut microbiota and food sensitization: associations in the first year of life

Table 2. Faecal microbiota richness and diversity at 3 months and 1 year of age, according to food sensitization at 1 year

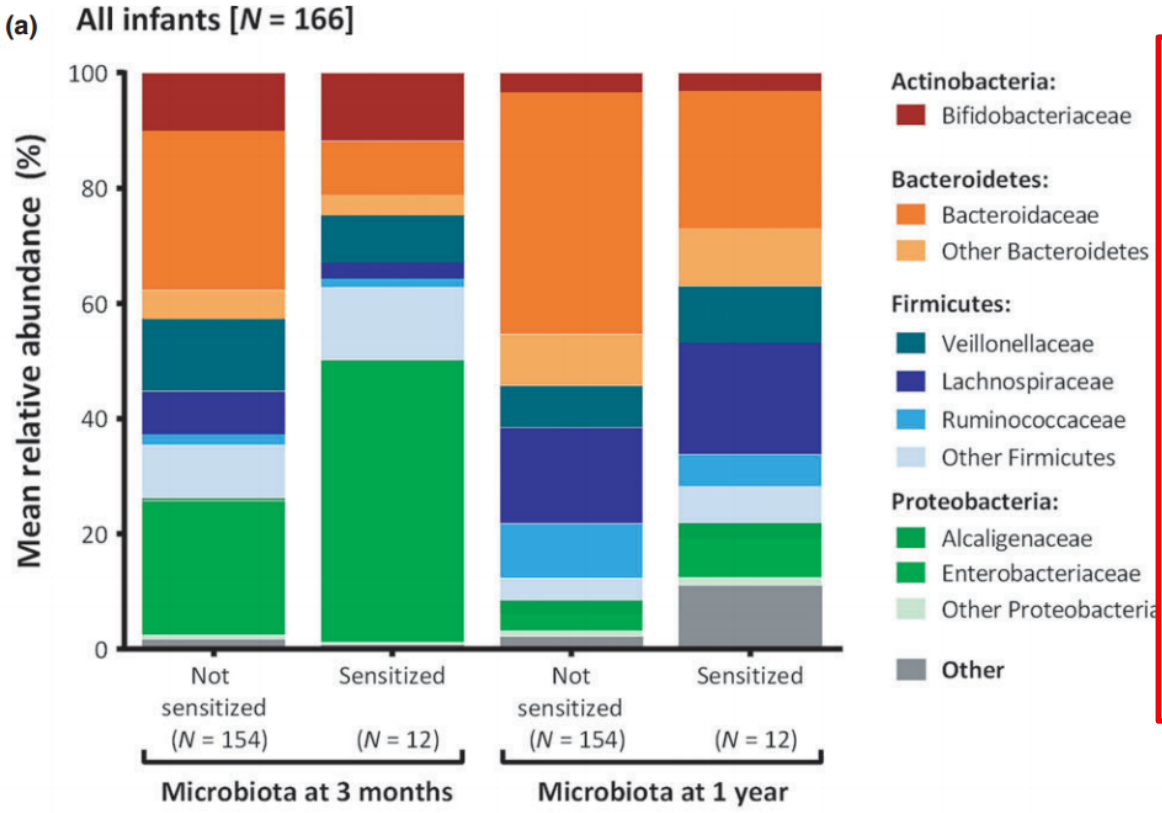
	Microbiota at 3 months			Microbiota at 1 year		
Infants analysed Bodiversity metric	Non-sensitized Median (IQR)	Sensitized Median (IQR)	*P*	Non-sensitized Median (IQR)	Sensitized Median (IQR)	*P*
All infants	(*N* = 154)	(*N* = 12)		(*N* = 154)	(*N* = 12)	
Chao1 richness	28.0 (25.7–30.3)	25.0 (23.7–27.0)	**0.02**	34.9 (33.0–37.0)	36.2 (33.3–38.0)	0.30
Shannon diversity	1.94 (1.53–2.25)	1.55 (1.18–2.19)	0.20	2.24 (1.99–2.55)	2.29 (1.89–2.92)	0.63
Incident sensitization only*	(*N* = 154)	(*N* = 10)		(*N* = 154)	(*N* = 10)	
Chao1 richness	28.0 (25.7–30.3)	25.0 (23.9–26.0)	**0.03**	34.9 (33.0–37.0)	36.9 (33.3–38.2)	0.31
Shannon diversity	1.94 (1.53–2.25)	1.55 (1.14–2.48)	0.34	2.24 (1.99–2.55)	2.29 (1.93–2.87)	0.72
'Undisturbed' subgroup†	(*N* = 34)	(*N* = 4)		(*N* = 34)	(*N* = 4)	
Chao1 richness	28.2 (26.7–30.3)	24.8 (22.7–25.5)	**0.01**	34.8 (33.5–36.7)	34.7 (31.8–37.3)	0.57
Shannon diversity	1.82 (1.50–2.23)	1.22 (0.81–1.76)	0.09	2.26 (2.14–2.66)	2.47 (2.20–2.67)	0.63

Richness and diversity measures calculated at family level of taxonomy. Comparisons by nonparametric Kruskal–Wallis test.
IQR, interquartile range.
*Excludes sensitized infants with unknown or diagnosed food allergy before initial sampling at 3 months.
†Excludes children with major microbiota-disrupting exposures before initial sampling at 3 months (i.e. caesarean delivery, antibiotic exposure or complementary feeding).

- From the population-based Canadian Healthy Infant Longitudinal Development (CHILD) study:
- The Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study recruited 3624 pregnant women, most partners and 3542 eligible offspring
- Environmental and biological sampling, innate and adaptive immune responses, gene expression, DNA methylation, gut microbiome and nutrition studies complement repeated environmental and clinical assessments to age 5.

Subbarao P, et al. Thorax 2015
M. B. Azad et al Clinical & Experimental Allergy 2015

Infant gut microbiota and food sensitization: associations in the first year of life



- This study of 166 infants represents a subset of the larger Canadian Healthy Infant Longitudinal Development (CHILD) national population-based birth cohort.
- Microbiome analyses were conducted by Illumina 16S rRNA sequencing for an unselected subsample comprising the first 166 enrolled infants with available fecal samples at 3 months and 1 year of age, and complete allergy skin prick testing results at 1 year.
- Food sensitization at 1 year was determined by skin prick testing

(a) Mean relative abundance of dominant families (those with overall median relative abundance > 1% at either sampling time)

Enterobacteriaceae were overrepresented and **Bacteroidaceae** were underrepresented in the gut microbiota of food-sensitized infants at 3 months (P=**0.002**; P=**0.09**) and 1 year (P=**0.004**; P=**0.01**), whereas lower microbiota richness was evident only at 3 months (P=0.02)

M. B. Azad et al Clinical & Experimental Allergy 2015

RUOLO DEL MICROBIOTA NELLO SVILUPPO DI MALATTIA

DISBIOSI INTESTINALE e ALLERGIE

Table 2
Studies on the association between infant intestinal microbiota and development of allergic disease and related conditions published in the past 5 years[a]

Allergic disease	Association with gut microbiota	Study
Atopic dermatitis or eczema	Lower relative abundance of gram-positive Ruminococcaceae at 1 wk of age in infants developing IgE-associated eczema by 2.5 y of age.	West et al, 2015[35,b]
	Greater diversity at 18 mo of age; lower abundance of *Bacteroidetes* and greater abundance of *Clostridium* clusters IV and XIVa (Firmicutes phylum) at 18 mo in infants with eczema at 2 y of age.	Nylund et al, 2013[29,b]
	Lower microbiota diversity at 1 wk in infants with eczema at 12 mo of age.	Ismail et al, 2012[40,b]
	Lower microbiota diversity at 1 mo; lesser diversity of phylum Bacteroidetes and genus *Bacteroides* at 1 mo; lower abundance of Proteobacteria at 12 mo in children with IgE-associated eczema at 2 y of age.	Abrahamsson et al, 2012[30]
	Colonization by *Clostridium difficile* at 1 mo associated with eczema throughout the first 6 y of life.	van Nimwegen et al, 2011[31]
	Colonization with *Lactobacillus paracasei* at 1 mo inversely associated with risk of atopic dermatitis at 2 y of age.	Penders et al, 2010[38]
Allergic sensitization	Lower microbiota richness at 3 mo; higher Enterobacteriaceae/Bacteroidaceae ratio at 3 and 12 mo in food-sensitized children at 1 y.	Azad et al, 2015[33]
	Fewer Lactobacilli in the first weeks of life; lower colonization with *Bifidobacterium bifidum* at 1 wk of age in sensitized children at 5 y of age.	Johansson et al, 2011[41]
	Lower microbiota diversity at 1 and 12 mo in sensitized children during the first 6 y of life.	Bisgaard et al, 2011[39,b]
	Lower levels of *Escherichia coli* at 4 mo and 1 y, higher levels of *Bifidobacterium longum* at 1 y, and lower levels of *Bacteroides fragilis* at 2 y of age in sensitized infants.	Storro et al, 2011[37]
Asthma or asthma risk	Decreased relative abundances of *Lachnospira*, *Veillonella*, *Rothia*, and *Faecalibacterium* during first 100 d in children classified as high risk of developing asthma in childhood (children with atopy and/or wheeze at 1 y).	Arrieta et al, 2015[34]
	Lower microbiota diversity at 1 wk and 1 mo in children developing asthma by 7 y of age.	Abrahamsson et al, 2014[36]
	Colonization by *Clostridium difficile* at 1 mo of age associated with asthma at 6 y of age.	van Nimwegen et al, 2011[31]
	Colonization with *Bacteroides fragilis* group and/or to *Clostridium coccoides* subcluster XIVa at 3 wk associated with increased risk of asthma at 3 y of age.	Vael et al, 2011[32]

[a]Includes studies from past 5 years in which microbiota were analyzed before allergic disease outcome.
[b]Infants at high risk of allergic disease.

Bridgman SL, et al., Ann Allergy Asthma Immunol 2016

Allergic diseases	Study	Result
Eczema	Nylund et al. BMC Microbiology 2013	Composition of the microbiota did not differ between study groups at age of 6 months, but was significantly different at age of 18 months as assessed by MCPP (p=0.01). Probiotic Lactobacillus rhamnosus GG supplementation in early infancy was observed to have minor long-term effects on the microbiota composition
Allergic rhinoconjunctivitis, eczema, asthma	Abrahamsson et al., Clinical & Experimental Allergy 2014	Allergic rhinoconjunctivitis, eczema and positive skin prick reactivity at 7 years of age did not associate with the gut microbiota diversity. Neither was asthma associated with the microbiota composition later in infancy (at 12 months).
Asthma, atopic dermatitis	Bisgaard J allergy clin immunol 2011	Bacterial diversity in the early intestinal flora 1 and 12 months after birth was inversely associated with the risk of allergic sensitization. There was no association with the development of asthma or atopic dermatitis.

Dati non conclusivi!

DISBIOSI INTESTINALE e ALLERGIE

data from large longitudinal cohorts is required to confirm which deviations in microbial development in early infancy are important in the later development of atopic disease…

…including those that might present novel targets for intervention

Prevenzione?

Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abrahamsson 2007 (1)	34	95	32	93	4.2%	1.04 [0.70, 1.53]
Abrahamsson 2013 (2)	20	94	17	90	2.9%	1.13 [0.63, 2.01]
Bottcher 2008	21	51	19	53	3.5%	1.15 [0.71, 1.87]
Boyle 2011 (3)	42	122	47	120	4.7%	0.88 [0.63, 1.22]
Boyle 2011 (4)	35	108	43	102	4.5%	0.77 [0.54, 1.10]
Huure 2008 (5)	7	72	12	68	1.7%	0.55 [0.23, 1.32]
Kalliomaki 2001 (6)	15	64	31	68	3.3%	0.51 [0.31, 0.86]
Kim 2010 (7)	6	33	14	35	1.8%	0.45 [0.20, 1.04]
Kim 2010 (8)	7	35	17	42	2.1%	0.49 [0.23, 1.05]
Kim 2010 (9)	8	43	16	46	2.2%	0.53 [0.26, 1.12]
Kopp 2008 (10)	14	50	12	44	2.5%	1.03 [0.53, 1.98]
Niers 2009 (11)	6	50	15	52	1.7%	0.42 [0.18, 0.99]
Niers 2009 (12)	23	50	30	48	4.3%	0.74 [0.51, 1.07]
Niers 2009 (13)	27	50	33	48	4.8%	0.79 [0.57, 1.08]
Ou 2012 (14)	16	64	11	62	2.4%	1.41 [0.71, 2.79]
Ou 2012 (15)	24	72	17	72	3.2%	1.41 [0.83, 2.39]
Ou 2012 (16)	16	65	16	64	2.8%	0.98 [0.54, 1.80]
Prescott 2008 (17)	31	74	25	76	4.0%	1.27 [0.84, 1.94]
Rautava 2002 (18)	4	27	14	30	1.4%	0.32 [0.12, 0.85]
Rautava 2012 (19)	20	70	44	62	4.1%	0.40 [0.27, 0.60]
Rautava 2012 (20)	21	73	44	62	4.2%	0.41 [0.27, 0.60]
Taylor 2007 (21)	23	89	20	88	3.3%	1.14 [0.67, 1.92]
Taylor 2007 (22)	38	88	34	87	4.5%	1.10 [0.77, 1.58]
Wickens 2008 (23)	23	157	43	159	3.7%	0.54 [0.34, 0.85]
Wickens 2008 (24)	38	158	43	159	4.3%	0.89 [0.61, 1.30]
Wickens 2012 (25)	49	146	56	143	4.9%	0.86 [0.63, 1.16]
Wickens 2012 (26)	37	136	56	143	4.6%	0.69 [0.49, 0.98]
Wickens 2013 (27)	26	112	43	129	4.0%	0.70 [0.46, 1.06]
Wickens 2013 (28)	41	133	43	129	4.5%	0.92 [0.65, 1.32]
Total (95% CI)		**2381**		**2374**	**100.0%**	**0.78 [0.69, 0.89]**
Total events	672		847			

Heterogeneity: Tau² = 0.07; Chi² = 64.73, df = 28 (P < 0.0001); I² = 57%

Test for overall effect: Z = 3.65 (P = 0.0003)

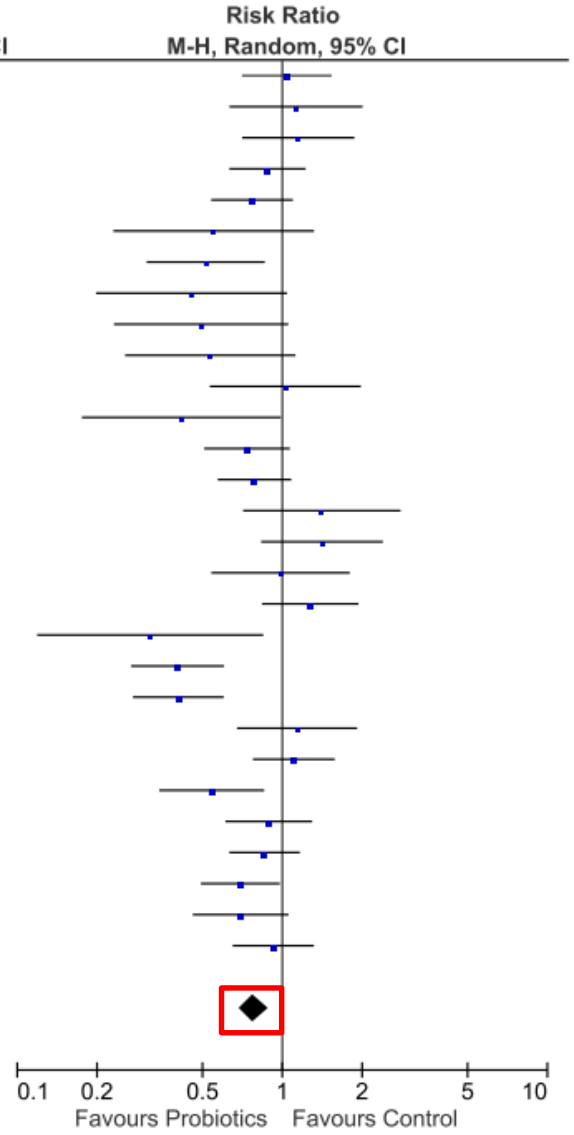


Figure 2 Forest plot showing the association between probiotics and eczema. M-H: Mantel–Haenszel method.

Zuccotti et al., Allergy 2015

Probiotics and primary prevention of atopic dermatitis: a meta-analysis of randomized controlled studies

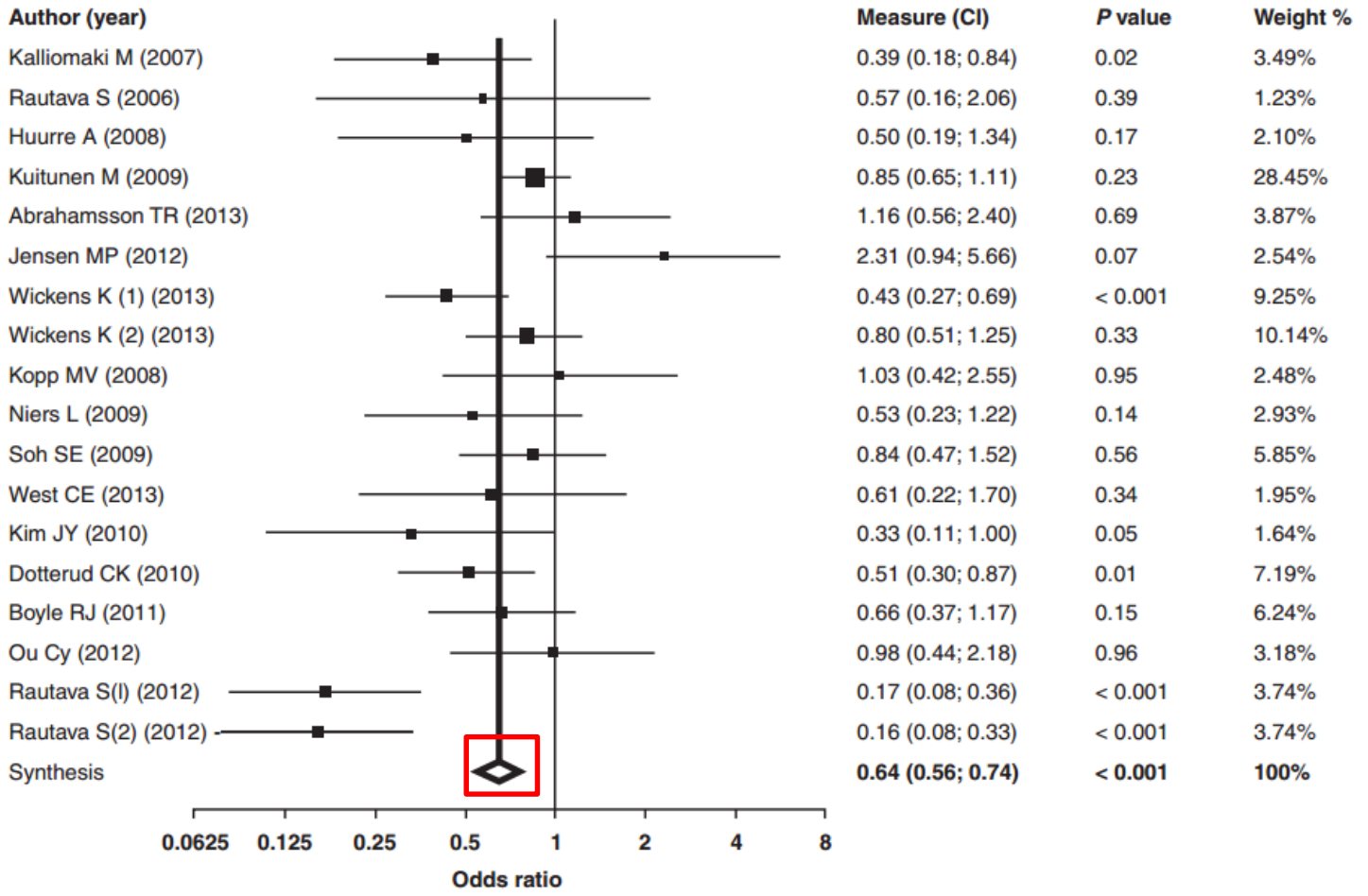


Figure 2 General meta-analysis of studies regarding administration of probiotics and primary prevention of atopic dermatitis.

Heterogeneity: Q statistic (51.57; P < 0.001), and I2 (67.04%; 95% CI = 46.03–79.87)

Panduru et al. JEADV 2015

Lactobacillus rhamnosus GG in the Primary Prevention of Eczema in Children: A Systematic Review and Meta-Analysis

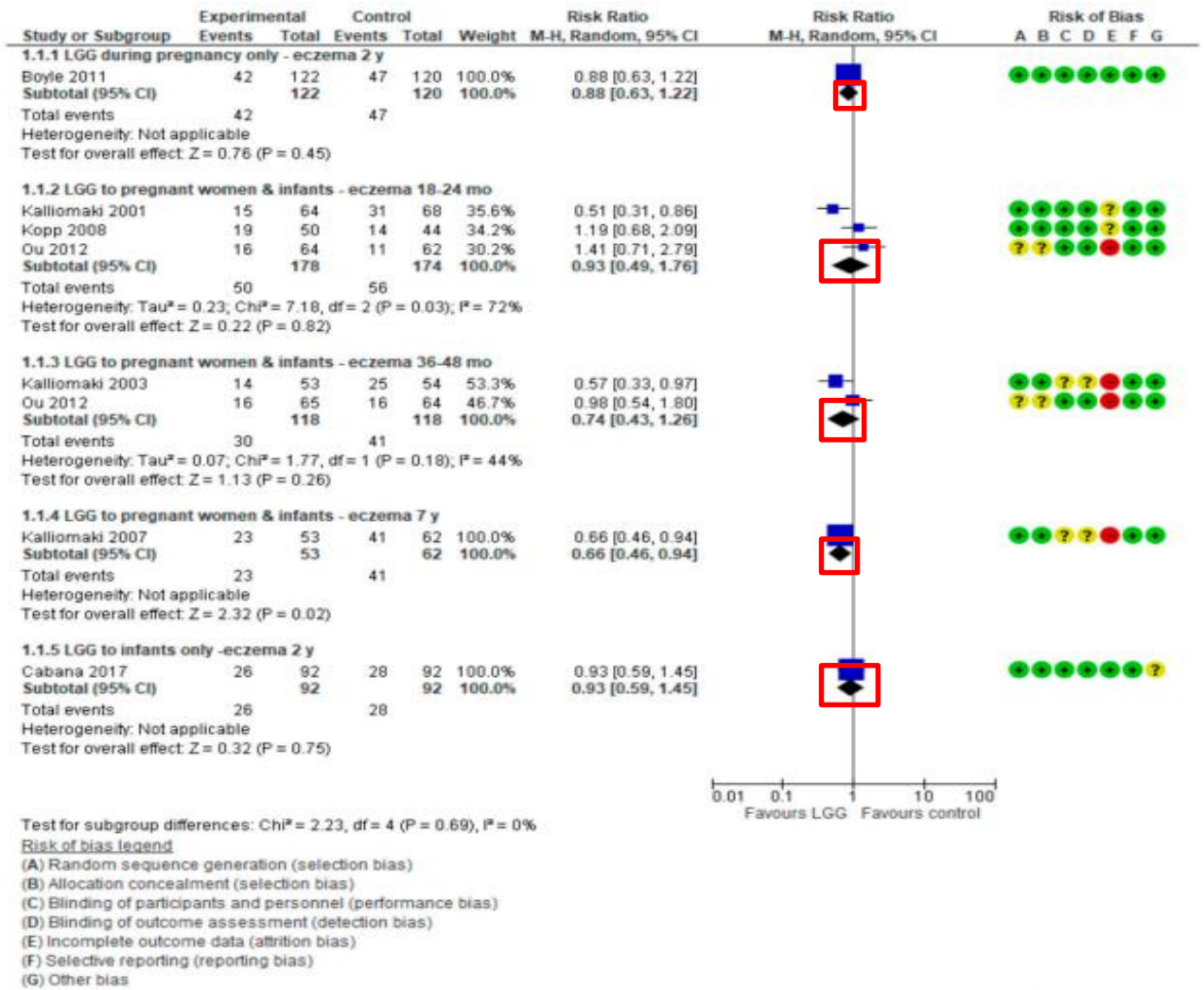


Figure 3. Primary outcome: Effect of LGG supplementation on eczema (data presented based on the timing of LGG administration and the timing of assessment).

Eczema

Szajewska et al., Nutrients 2018, 10, 1319

Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis

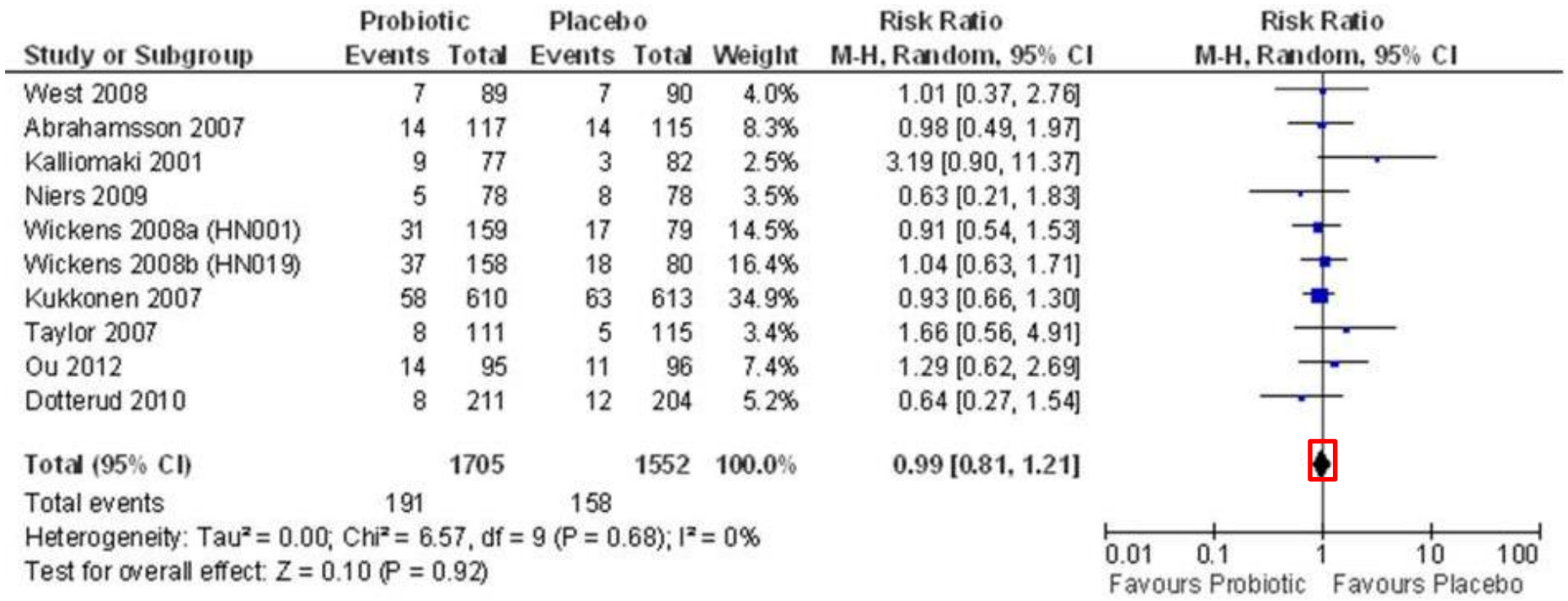


Fig 2 Probiotic supplementation during pregnancy or infancy and doctor diagnosed asthma in children. The longest available follow-up data (intention to treat) were extracted from each contributing trial. Trials are sorted in order of decreasing duration of follow-up. df=degrees of freedom; M-H=Mantel-Haenszel

Azad MB et al. BMJ 2013

Lactobacillus rhamnosus GG in the Primary Prevention of Eczema in Children: A Systematic Review and Meta-Analysis

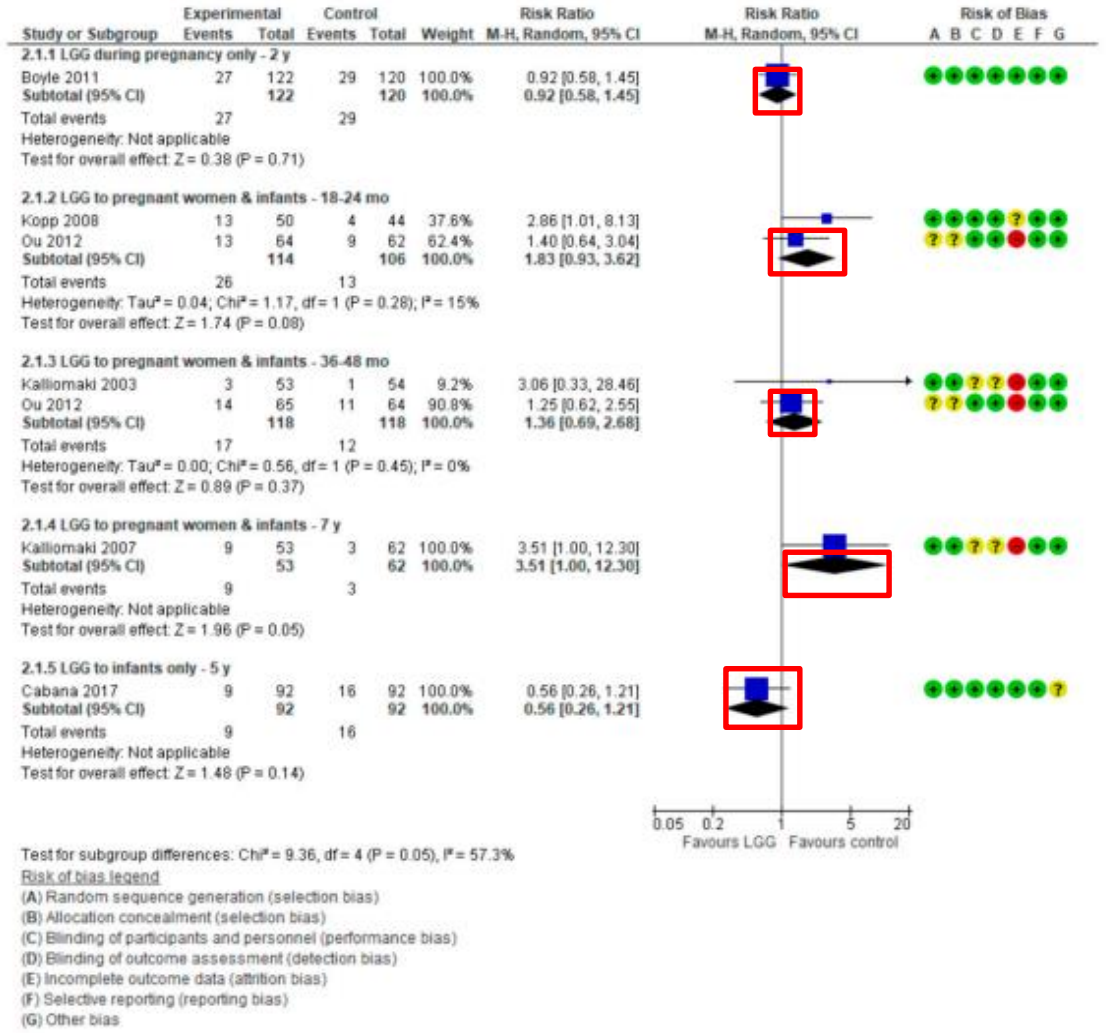


Figure 4. Secondary outcome: Effect of LGG supplementation on wheezing/asthma (data presented based on the timing of LGG administration and the timing of assessment).

Wheezing/asthma

Szajewska et al., Nutrients 2018, 10, 1319

Lactobacillus rhamnosus GG in the Primary Prevention of Eczema in Children: A Systematic Review and Meta-Analysis

For data on allergic rhinitis/sneezing, see Figure 5.

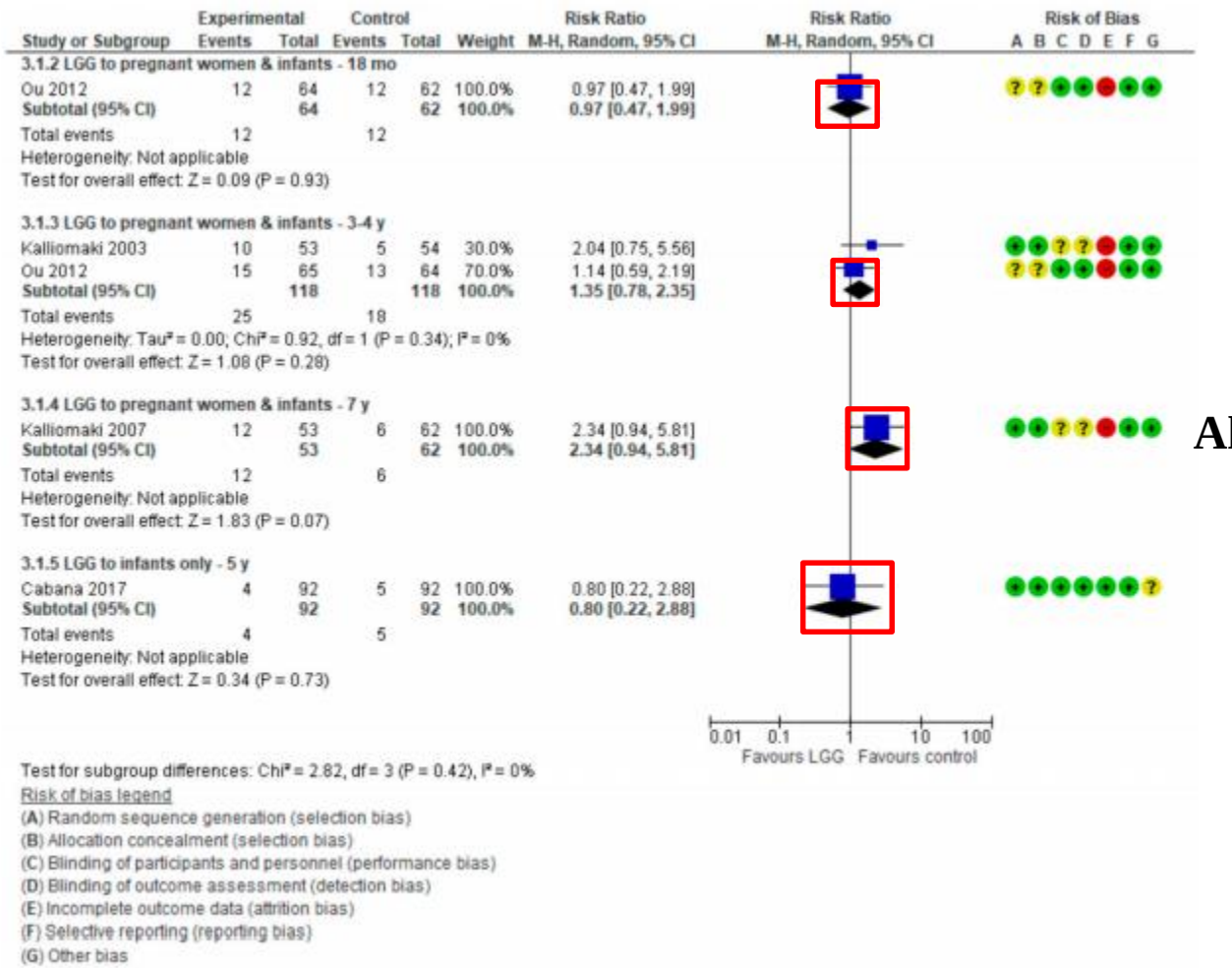


Figure 5. Secondary outcome: Effect of LGG supplementation on allergic rhinitis (data presented based on the timing of LGG administration and the timing of assessment).

Allergic rhinitis

Szajewska et al., Nutrients 2018, 10, 1319

Probiotics for Prevention of Atopy and Food Hypersensitivity in Early Childhood

A PRISMA-Compliant Systematic Review and Meta-Analysis of Randomized Controlled Trials

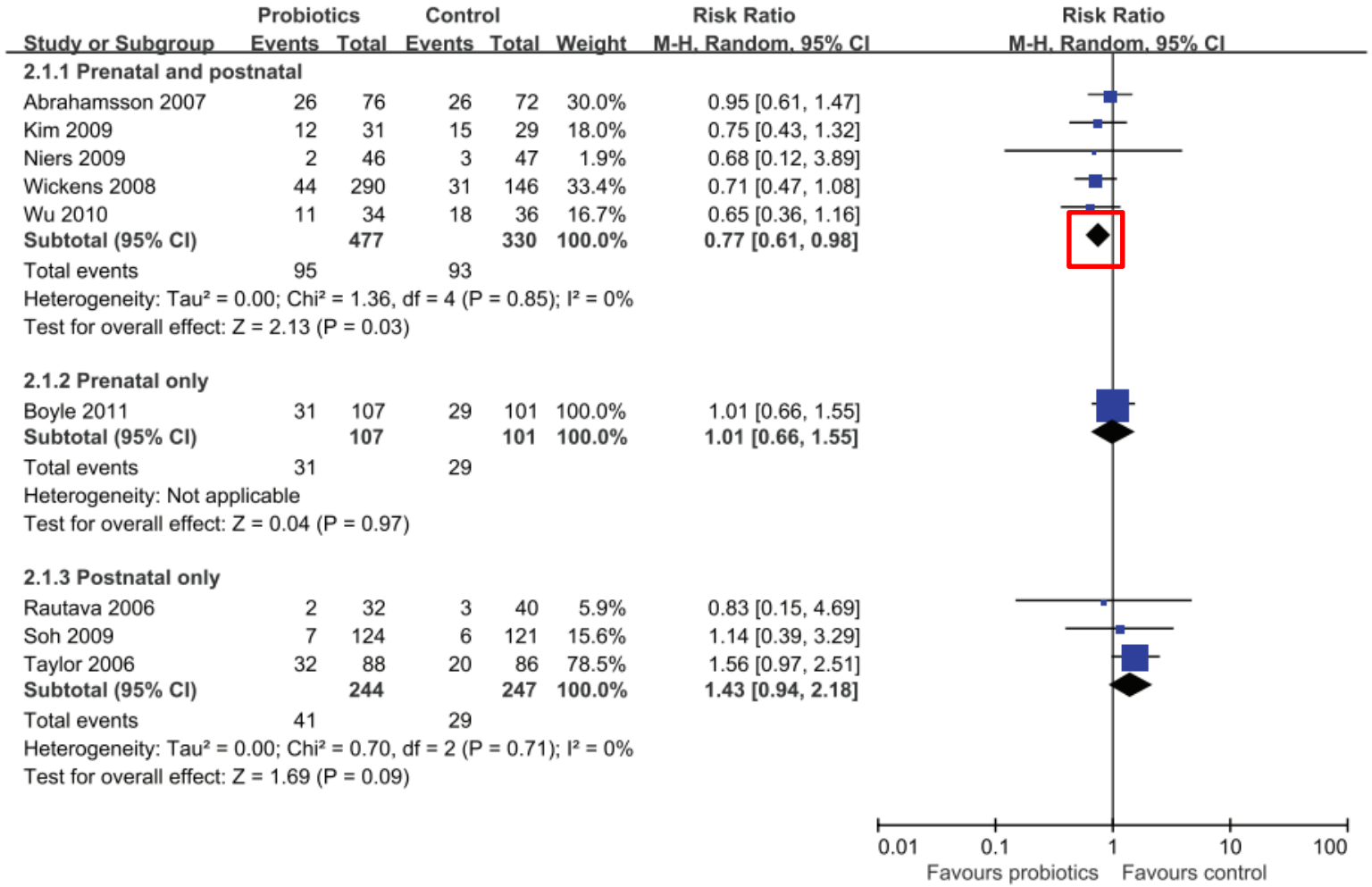


FIGURE 4. Effect of probiotic supplementation on food hypersensitivity.

Zhang et al Medicine. 2016

SUPPLEMENTAZIONE & IMMUNOMODULAZIONE

Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention

prebiotics for allergy prevention under certain conditions. The relatively low quality evidence, limited comparative studies and large heterogeneity between studies, have collectively hampered recommendations on specific probiotic strains, specific timing and specific conditions for the most effective preventive management. At the same time the risk of using available products is low. While further research is needed before specific practice guidelines on supplement probiotics and prebiotics, it is equally important that the underlying dietary and lifestyle factors of dysbiosis are addressed at both the individual and societal levels.

Incidence and risk factors for food hypersensitivity in UK infants: results from a birth cohort study

Table 4 Univariate and multivariable analyses for infants with food hypersensitivity, IgE-mediated food allergy and non-IgE-mediated hypersensitivity

	IgE-mediated (n = 21) compared to control infants				Non-IgE-mediated (n = 20) compared to control infants			
	Univariate		Multivariable**		Univariate		Multivariable**	
	Odds ratio	p	Odds ratio	p	Odds ratio	p	Odds ratio	p
Eczema (at initial assessment)	17.83* (2.89–∞)	<0.001	18.67**** (1.03–338.41)	0.048				
Rhinitis (at initial assessment)	3.94 (1.31–11.83)	0.023	4.80**** (1.19–19.36)	0.027	2.96 (0.92–9.52)	0.087		
Maternal atopy	11.54 (1.47–90.35)	0.003						
Vitamin D supplement during pregnancy	8.68*** (0.66–∞)	0.097						
Age at first egg from any source, months	1.05 (1.00–1.11)	0.026	Not included in analysis as likely reverse causality					
Dog in the home	3.24 (1.00–10.48)	0.076			4.37 (1.38–13.80)	0.015	19.49 (1.17–325.93)	0.039
Wheeze associated with upper respiratory tract	2.84 (1.01–7.98)	0.052						
Healthy eating dietary pattern score, arbitrary units	0.36 (0.20–0.66)	0.001	0.32**** (0.16–0.66)	0.012	0.34 (0.19–0.62)	<0.001	0.28 (0.09–0.87)	0.028
Maternal age, years					0.87 (0.78–0.99)	0.037		
Paternal age, years					0.893 (0.803–0.992)	0.035		
Maternal food hypersensitivity					2.790 (0.994–7.831)	0.055		
Other household smoking					5.133 (1.32–19.95)	0.023		
Consumed probiotics whilst breastfeeding					3.31 (1.13–9.75)	0.084	45.41 (3.41–604.67)	0.004
Age at first solid, months					0.84 (0.73–0.97)	0.021	0.60 (0.40–0.89)	0.011
Milk overlap, months					0.94 (0.88–1.00)	0.037		
Received anti-reflux medication					3.312 (1.13–9.75)	0.030	Not included in analysis as likely reverse causality	

Adjusted and unadjusted odds ratios (95 % confidence intervals (CI) and p values) are presented for all factors significant in the multivariate model

* Factors associated with hypersensitivity at a p value <0.1 were entered into a multivariable analysis using SPSS. A stepwise backwards selection process was used

** For multivariable analysis p values are only given for those variables included in the final model

*** Exact logistic regression model used to estimate parameters

**** Firthlogit approach to fit a logistic model by penalized maximum likelihood regression (accessed via STATA)

Grimshaw et al. Clin Transl Allergy (2016

Fibra ed acidi grassi a catena corta (SCFAs)

•La fibra alimentare (polisaccaridi ed oligosaccaridi di origine vegetale) giunge al colon non digerito dove viene fermentato dalla flora batterica→ produzione di acidi grassi a catena corta (short chain fatty acids- SCFAs, acetato , propionato, butirrato).

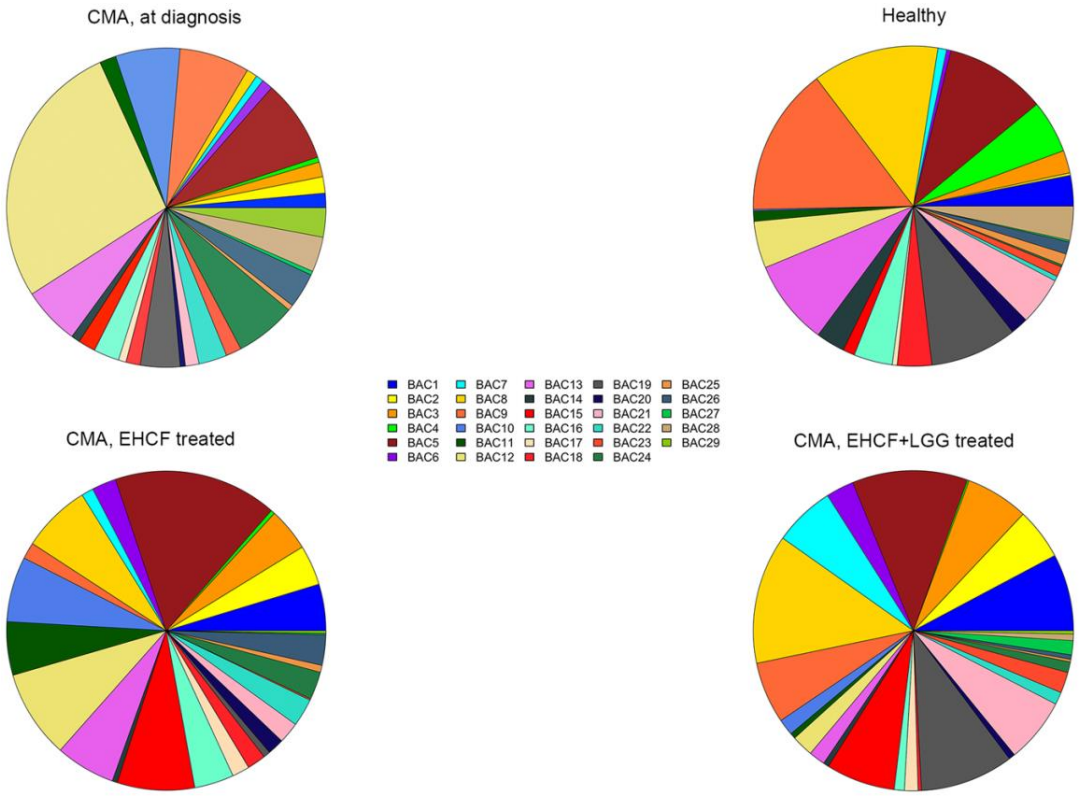
• La produzione di SCFAs dipende dalla composizione del microbiota e dalla quantità di carbonio a disposizione. Per esempio una dieta ricca in lipidi alterna la composizione del microbiota riducendo la quota di batteri in grado di fermentare la fibra e produrre acidi grassi → ridotta produzione di SCFA.

•Dieta ricca in frutta, verdura e fibra→ aumentata produzione di SCFAs. Gli SCFA agiscono direttamente sul sistema immunitario del GALT oppure attraverso l'attivazione dei GPCR, favorendo risposta immunitaria protettiva nei confronti delle malattie allergiche.

Immunological Reviews. 2017;278:277–295.

Trattamento?

Gut microbiota composition and butyrate production in children affected by non-IgE-mediated cow's milk allergy



- Case control study
- 46 non-IgE-mediated CMA subjects
- 23 healthy children
- Evaluation of gut microbiota composition and fecal butyrate levels in children affected by non-IgE-mediated CMA

CONCLUSIONI: EHCF + LGG resulted in a Bacteroides diversity pattern similar to that seen in healthy controls. Butyrate concentrations, was more evident in children treated with EHCF + LGG

Berni Canani et al Scientific reports 2018

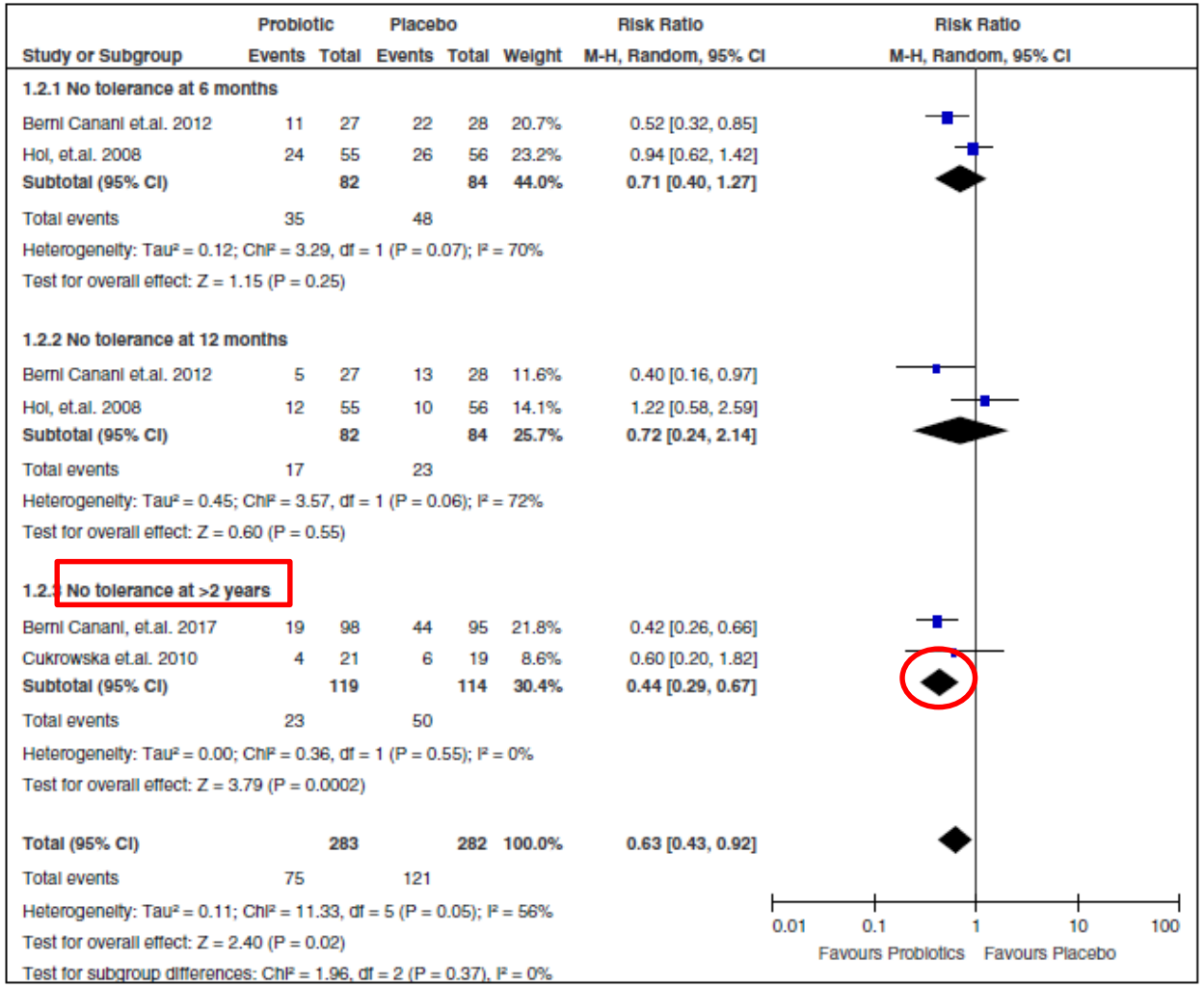
ORIGINAL RESEARCH Open Access

Probiotics as treatment for food allergies among pediatric patients: a meta-analysis

9 RCTs: 895 pazienti con APLV (età 1mese - <2anni)

- Primary outcome: miglioramento sintomi (SCORAD)
- Secondary outcome:
- induzione tolleranza

SOTTOGRUPPO 1:
Analisi basata sul raggiungimento della tolleranza

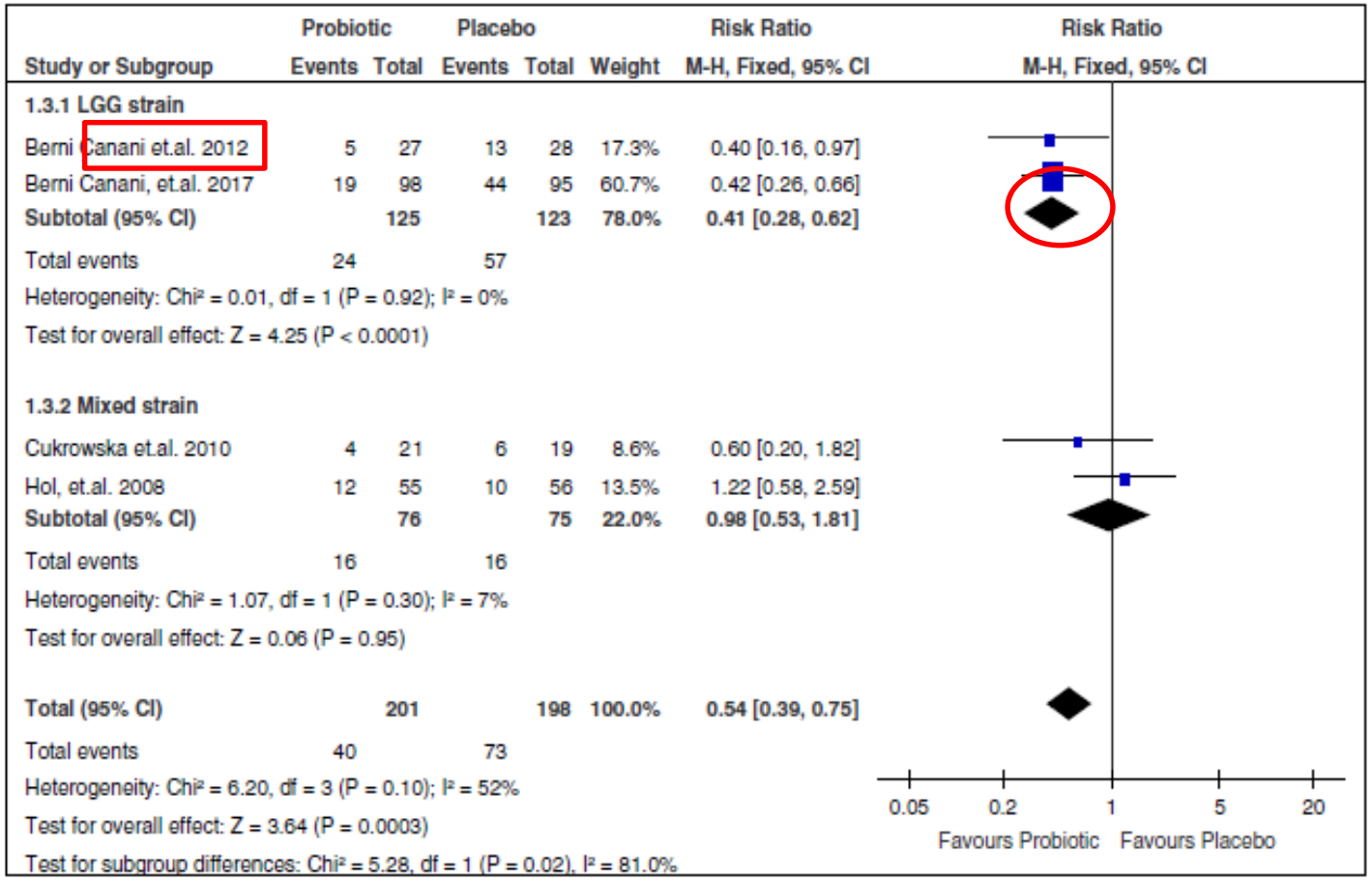


ORIGINAL RESEARCH Open Access

Probiotics as treatment for food allergies among pediatric patients: a meta-analysis

SOTTOGRUPPO 2: Analisi basata sul ceppo di probiotico utilizzato

CONCLUSIONE: *"Although the mean difference favors probiotic use, the CI is wide → the results are not precise."*



Tan-Lim and Esteban-Ipac *World Allergy Organization Journal* (2018) 11:25

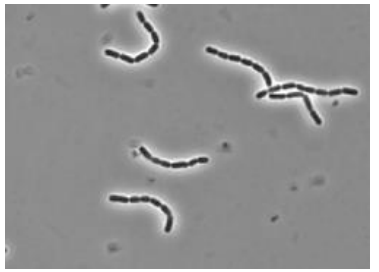
Probiotici e immunoterapia orale

TABLE III. Clinical outcomes

	PPOIT group	Placebo group	RR,* NNT,† or mean difference‡
2-wk Sustained unresponsiveness			
n (%)	23/28 (82.1)	1/28 (3.6)	23 (3.33-158.84)*§
			1.27 (1.06-1.59)†
2-wk Sustained unresponsiveness, sensitivity 1			
n (%)	23/31 (74.2)	1/31 (3.2)	23 (3.31-159.93)*§
			1.41 (1.14-1.84)†
2-wk Sustained unresponsiveness, sensitivity 2			
n (%)	23/31 (74.2)	4/31 (12.9)	5.75 (2.25-14.69)*§
			1.63 (1.24-2.39)†
Desensitization			
n (%)	26/29 (89.7)	2/28 (7.1)	12.55 (3.28-47.99)*§
			1.21 (1.03-1.47)†
Peanut SPT at T1			
Mean (SD), n	4.83 (3.98), 29	14.54 (5.63), 27	−9.71 (−12.31 to −7.11)‡§
Peanut SPT at T3			
Mean (SD), n	4.46 (4.44), 28	14.75 (6.09), 28	−10.29 (−13.14 to −7.43)‡

T1 refers to the last day of treatment, and T3 refers to 3 months after the end of treatment.
*RR (95% CI).
†NNT (95% CI).
‡Mean difference (95% CI).
§$P < .001$.

…This is a promising therapy in the context of the increase in peanut allergy incidence and the unlikely natural resolution of peanut allergy …

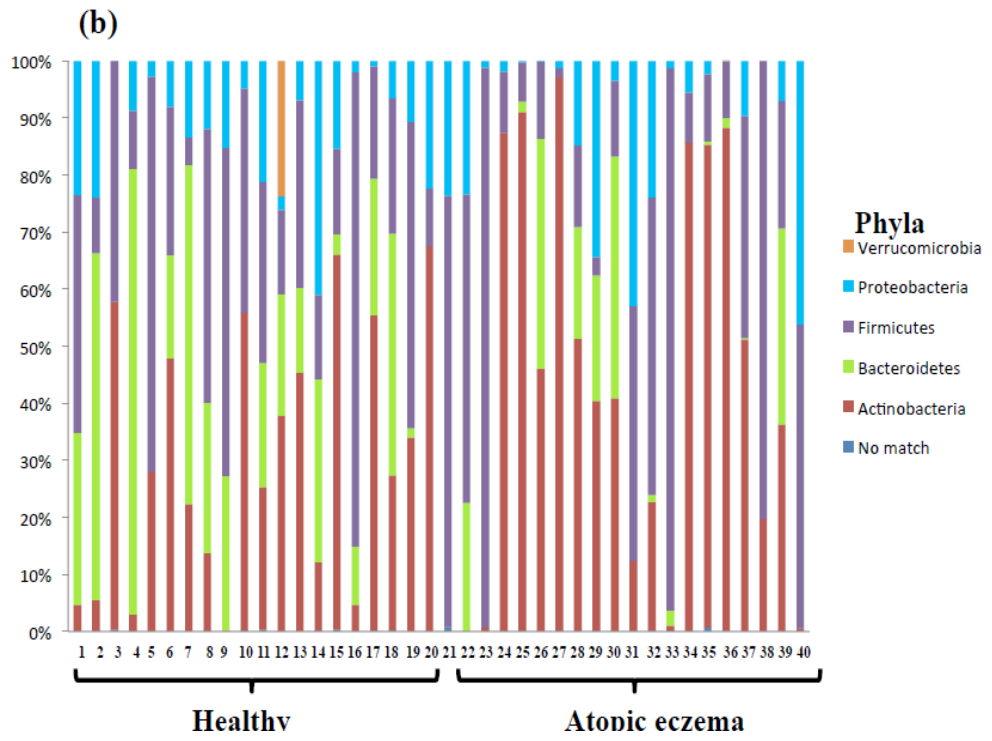


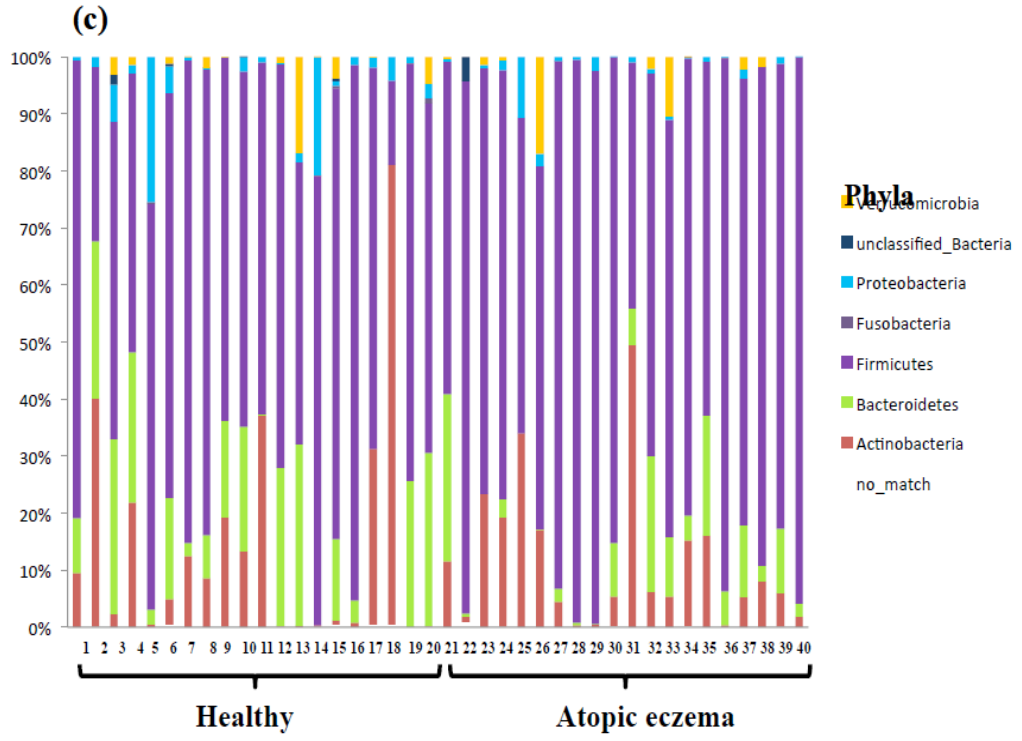
Lactobacillus rhamnosus

Tang et al. J Allergy Clin Immunol 2015

Dermatite atopica e “disbiosi” intestinale

Abbondanza relativa di alcuni phyla batterici nei campioni di feci ad uno (b) e 12 mesi (c) di età in 20 bambini che hanno sviluppato eczema atopico e 20 bambini senza manifestazioni allergiche





Total Microbiota diversity all’età di un mese p-value 0.004
Bacteroides diversity all’età di 1 mese p-value 0.01
Proteobacteria diversity a 12 mesi p = 0.04

Abrahamsson TR et al. J Allergy Clin Immunol. 2012

Probiotics for the Treatment of Atopic Dermatitis in Children: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

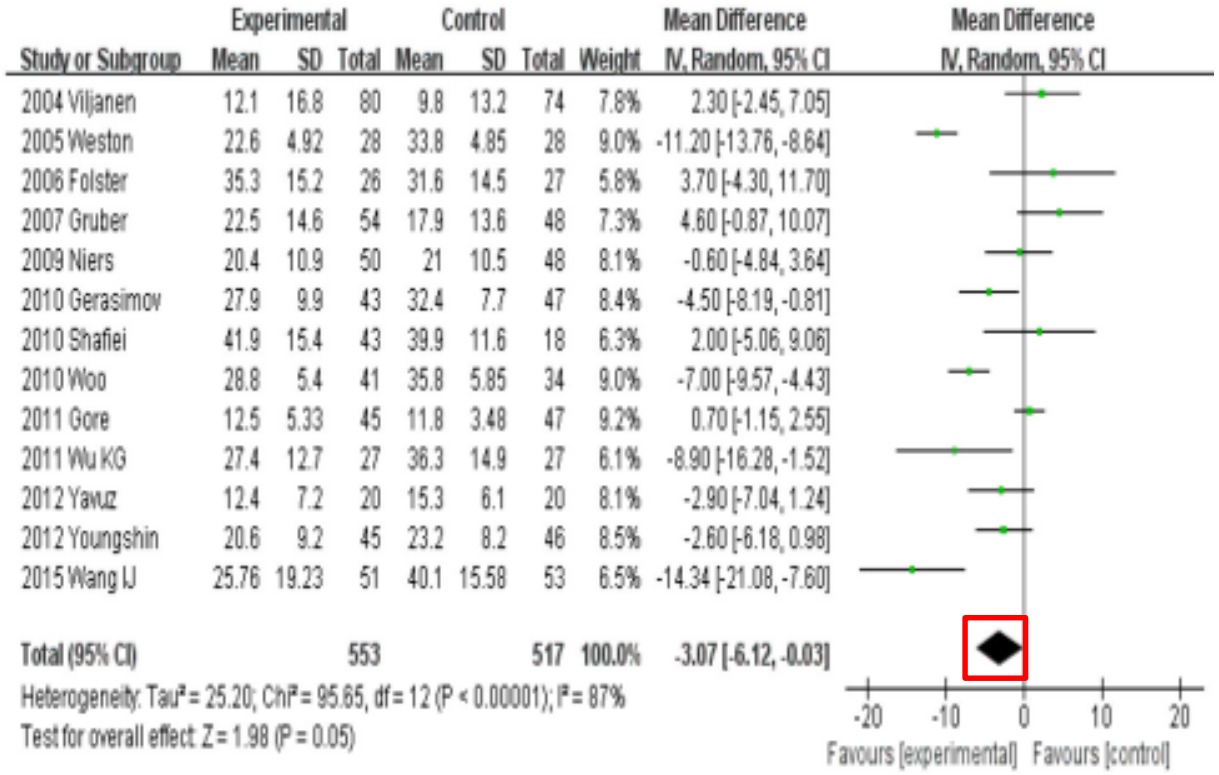


FIGURE 3 | MD scoring with probiotics treatment compared to control and placebo interventions. 95%CI, 95% confidence interval.

Dai probiotici ai postbiotici…

EFFICACY OF FERMENTED RICE FLOUR FOR THE TREATMENT OF ATOPIC DERMATITIS: RANDOMIZED, DOUBLE BLIND CONTROLLED TRIAL

NCT03042624

Lactobacillus paracasei CBA-L74

In conclusione…

- Further studies with larger number of well characterized patients and controls are needed to dissect the role of microbiome in allergic diseases…

- ... despite some limitations, interventions with probiotics, prebiotics, and/ or synbiotics **show promise for the development of a preventive therapy**, either by restoring altered microbiome functionality due to dysbiosis or as a boosting of immunological system in specific immunotherapy…

- Because of the multiplicity of factors involved, strategies to preserve or manipulate the microbiota will probably require a **personalised approach** tailored to individual genetics and lifestyle factors

GRAZIE