8 e 9 MARZO 2019 BERGAMO HOTEL EXCELSIOR SAN MARCO Piazza della Repubblica, 6

Responsabile Scientifico: Fabio Pace

MICROBIOTA INTESTINALE E SVILUPPO DI ALLERGOPATIE

Enza D'Auria

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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.,¹⁰ 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

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





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



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

SISTEMA IMMUNE = LEARNING DEVICE



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









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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. 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

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MICROBIAL RELATED FACTORS INCREASING RISK OF ALLERGY





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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)



JAMA Pediatrics | Original Investigation

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



Adjusted Hazard Ratio (aHR)

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

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, I² 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 <u>no statistically significant association between</u> <u>breastfeeding and food allergy development</u> (OR 1.02, 95% CI 0.88-1.18; I² 86%).

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....

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

	Microbiota at 3 mos	nths		Microbiota at 1 year				
Infants analysed Bodiversity metric	Non-sensitized Median (IQR)	Sensitized Median (IQR)	Р	Non-sensitized Median (IQR)	Sensitized Median (IQR)	Р		
All infants	(<i>N</i> = 154)	(N = 12)		(<i>N</i> = 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		

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

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.

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

(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

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 <i>Bacteroidetes</i> and greater abundance of <i>Clostridium</i> 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}
llergic sensitization	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 <i>Clostridium difficile</i> at 1 mo associated with eczema throughout the first 6 y of life. Colonization with <i>Lactobacillus paracasei</i> at 1 mo inversely associated with risk of atopic dermatitis at	van Nimwegen et al, 2011 ³ Penders et al, 2010 ³⁸
	2 y of age.	
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 <i>Bifidobacterium bifidum</i> at 1 wk of age in sensitized children at 5 v 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 <i>Lachnospira</i> , <i>Veillonella</i> , <i>Rothia</i> , and <i>Faecalibacterium</i> during first 100 d in children classified as high risk of developing asthma in childhood (children with atopy and/or wheeze at 1 v).	Arrieta et al, 2015 ³⁴
	Lower microbiota diversity at 1 wk and 1 mo in children developing asthma by 7 v of age.	Abrahamsson et al. 2014 ³⁶
	Colonization by Clostrianum difficile at 1 mo of age associated with asthma at 6 y of age.	van Nimwegen et al, 2011 ³
	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

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.

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

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Prevenzione?

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

	Probio	tics	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
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: Tau ² = 0.0	7: Chi ² =	64.73. d	df = 28 (P	< 0.00	01); l ² = 57	%	
Test for overall effect: Z =	3.65 (P =	0.0003	3)		<i></i>		0.1 0.2 0.5 1 2 5 10 Favours Probiotics Favours Control

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

Study or Subgroup Total Venets Tota		Experim	ental	Contr	lon		Risk Ratio	Risk Ratio	Risk of Bias	
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Total events 42 47 Hereforgenety. Not applicable Feet for versal effect Z = 0.76 (P = 0.45) 1.12. LGG to pregnant women & linfants - eczema 18.24 mo Califormal 2001 15 64 31 66 35.5% 0.51 [0.31, 0.86] Subtrati (95% Ch 178 1174 100.0% 0.33 [0.48, 1.76] Subtrati (95% Ch 16 178 1177 4100.0% 0.33 [0.48, 1.76] Subtrati (95% Ch 16 178 1177, df = 1 (P = 0.18), P = 2% Test for swents 2007 (1P = 1.77, df = 1 (P = 0.18), P = 44% Subtrati (95% Ch 23 53 41 62 100.0% 0.86 [0.46, 0.94] Subtrati (95% Ch 23 53 41 62 100.0% 0.83 [0.48, 1.76] Subtrati (95% Ch 23 53 41 62 100.0% 0.86 [0.46, 0.94] Subtrati (95% Ch 23 53 41 62 100.0% 0.85 [0.46, 0.94] Subtrati (95% Ch 23 53 41 62 100.0% 0.85 [0.46, 0.94] Subtrati (95% Ch 23 53 41 62 100.0% 0.83 [0.59, 1.45] Chai events 23 24 1 Hereogenetic, Not applicable Test for swents ender Z = 2.32 (P = 0.69), P = 0% Subtrati (95% Ch 26 92 28 92 100.0% 0.83 [0.59, 1.45] Chai events 23 41 Hereogenetic, Not applicable Test for swents effect Z = 0.12 (P = 0.69), P = 0% Subtrati (95% Ch 26 92 28 92 100.0% 0.93 [0.59, 1.45] Chai events 23 41 Hereogenetic, Not applicable Test for swents effect Z = 0.22 (P = 0.75) Hereogenetic, Not applicable Test for swents effect Z = 0.22 (P = 0.75) Hereogenetic, Not applicable Test for swents effect Z = 0.22 (P = 0.75) Hereogenetic, ChP = 2.23, df = 4 (P = 0.69), P = 0% Subtrati (95% Ch 26 92 28 92 100.0% 0.93 [0.59, 1.45] Dial mont of ucome assessment (detection bias) B) Allocation concealment (selection bias) B) Allocation concealment (selection bias) B) Allocation concealment (selection bias) B) Binding of concealment (selection bias) B)	Boyle 2011 Subtotal (95% CI)	42	122	47	120	100.0%	0.88 [0.63, 1.22] 0.88 [0.63, 1.22]	•		
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Test for overall effect: Z = 0.32 (P = 0.75) Test for subgroup differences: Chi ^a = 2.23, df = 4 (P = 0.69), i ^a = 0% Risk of bias legend A) Random sequence generation (selection bias) B) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) E) Incomplete outcome data (attrition bias) E) Selective reporting (reporting bias) (B) Other bias	leterogeneity: Not a	pplicable								
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rest for subgroup differences: Chi ² = 2.23, df = 4 (P = 0.69), i ² = 0% Favours LGG Favours control Random sequence generation (selection bias) B) Allocation concealment (selection bias) B) Allocation concealment (selection bias) B) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) B) D) Binding of outcome assessment (detection bias) B) E) Incomplete outcome data (attrition bias) B) C) Selective reporting (reporting bias) B)							Lo Lo	01 0.1 1 10 100	t .	
Nandom sequence generation (selection bias) B) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) E) Incomplete outcome data (attrition bias) E) Selective reporting (reporting bias)	est for subgroup di	fferences: 0	chi# = 2.	23, df = 4	(P = 0	.69), I ^a = 0	1%	Favours LGG Favours control		
A) Random sequence generation (selection bias) 3) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) b) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) E) Incomplete outcome data (attrition bias) E) Selective reporting (reporting bias) 3) Other bias	tisk of bias legend									
B) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (affrition bias) F) Selective reporting (reporting bias) S) Othere bias	A) Random sequen	ice generat	ion (seli	ection bia	is)					
C) Blinding of participants and personnel (performance bias) D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) F) Selective reporting (reporting bias) 3) Others bias	B) Allocation concea	alment (sel	ection b	ias)						
D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) E) Selective reporting (reporting bias) 3) Other bias	C) Blinding of partic	ipants and	personn	nel (perfo	rmanc	e bias)				
E) Incomplete outcome data (attrition bias) F) Selective reporting (reporting bias) 3) Other bias	D) Blinding of outco	me assess	ment (d	detection	bias)					
F) Selective reporting (reporting bias)	E) Incomplete outco	me data (a	thrition b	ias)	2000					
G) Other blas	F) Selective reportin	a (reporting	bias)							
	G) Other bias	a coperant	and a large							

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

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

	Probio	tic	Place	bo		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI		
West 2008	7	89	7	90	4.0%	1.01 [0.37, 2.76]			
Abrahamsson 2007	14	117	14	115	8.3%	0.98 [0.49, 1.97]			
Kalliomaki 2001	9	77	3	82	2.5%	3.19 [0.90, 11.37]	· · · · ·		
Niers 2009	5	78	8	78	3.5%	0.63 [0.21, 1.83]			
Wickens 2008a (HN001)	31	159	17	79	14.5%	0.91 [0.54, 1.53]			
Wickens 2008b (HN019)	37	158	18	80	16.4%	1.04 [0.63, 1.71]	+		
Kukkonen 2007	58	610	63	613	34.9%	0.93 [0.66, 1.30]	+		
Taylor 2007	8	111	5	115	3.4%	1.66 [0.56, 4.91]			
Ou 2012	14	95	11	96	7.4%	1.29 [0.62, 2.69]			
Dotterud 2010	8	211	12	204	5.2%	0.64 [0.27, 1.54]			
Total (95% CI)		1705		1552	100.0%	0.99 [0.81, 1.21]	•		
Total events	191		158				T T		
Heterogeneity: Tau ² = 0.00); Chi ² = 6.	57, df =	= 9 (P = 0	.68); 12	= 0%				
Test for overall effect: Z =	0.10 (P = 1	0.92)	1 14 173 1 1 1 2 1				Favours Probiotic Favours Placebo		

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

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

	Experime	ental	Contr	lor		Risk Ratio	Risk Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG	
2.1.1 LGG during pre	gnancy onl	y-2y						SCOND CO	
Boyle 2011 Subtotal (95% CI)	27	122	29	120	100.0%	0.92 [0.58, 1.45] 0.92 [0.58, 1.45]	-		
Total events	27		29						
Heterogeneity: Not ap	plicable								
Test for overall effect	Z = 0.38 (P	9 = 0.71)						
2.1.2 LGG to pregnan	it women 8	infant	s - 18-24	mo					
Kopp 2008	13	50	4	44	37.6%	2.86 [1.01, 8.13]			
Ou 2012 Subtotal (95% CI)	13	64 114	9	62 106	52.4% 100.0%	1.40 [0.64, 3.04] 1.83 [0.93, 3.62]	-	3386688	
Total events	26		13						
Heterogeneity: Tau ^a = Test for overall effect	0.04; Chi ^a Z = 1.74 (P	= 1.17,	df=1 (P)	= 0.28); I²= 15%				
2.1.3 LGG to pregnar	t women 8	infant	5 - 36-48	mo					
Kalliomaki 2003	3	53	1	54	9.2%	3.06 10.33, 28,461			
Ou 2012	14	65	11	64	90.8%	1.25 [0.62, 2.55]		2200000	
Subtotal (95% CI)		118		118	100.0%	1.36 [0.69, 2.68]			
Total events	17		12						
Heterogeneity: Tau [#] = Test for overall effect	0.00; Cihi* Z = 0.89 (P	= 0.56, = 0.37	df≃1 (P)	= 0.45); I*= 0%				Wheezing/asthma
2.1.4 LGG to pregnan	t women 8	infant	s - 7 y				1000	100000000000000	
Kalliomaki 2007 Subtotal (95% CI)	9	53 53	3	62 62	100.0%	3.51 [1.00, 12.30] 3.51 [1.00, 12.30]			
Total events	9		3						
Heterogeneity: Not ap	oplicable		25						
Lest for overall ellect	Z = 1.90 (P	= 0.05	2						
2.1.5 LGG to infants of	only - 5 y								
Cabana 2017	9	92	16	92	100.0%	0.56 [0.26, 1.21]			
Subtotal (95% CI)		92		92	100.0%	0.56 [0.26, 1.21]			
Total events	9		16						
Heterogeneity: Not ap	oplicable								
Test for overall effect	Z=1.48 (P	= 0.14	9						
						5	05 0.2 1 5 20	f.	
Test for subgroup diff	ferences: C	h≓= 0	36 df = 4	P = 0	05) (*= 5	7 3%	Favours LGG Favours control		
Risk of bias legend	erences. e		50, 41 - 4	4-0	0007,1 - 0				
(A) Random sequent	ce generati	on (sel	ection bia	(a)					
(B) Allocation concea	iment (sele	ction b	ias)						
(C) Blinding of particip	pants and p	erson	nel (perfo	rmanc	e blas)				
(D) Blinding of outcor	ne assess	ment (o	detection i	bias)					
(E) incomplete outcom	me data (at	trition t	ias)						
(F) Selective reporting	(reporting	bias)							
(G) Other bias									

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).

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.

		Experim	ental	Contr	lo		Risk Ratio	Risk Ratio	Risk of Bias	
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG	
í	3.1.2 LGG to pregnan	t women &	& infants	s - 18 mo)					
	Ou 2012 Subtotal (95% CI)	12	64 64	12	62 62	100.0%	0.97 [0.47, 1.99] 0.97 [0.47, 1.99]		2200000	
	Total events Heterogeneity: Not ap	12 plicable		12						
	Test for overall effect.	Z = 0.09 (F	P = 0.93)						
	3.1.3 LGG to pregnan	t women a	& infant	s-3-4 y						
	Kalliomaki 2003	10	53	5	54	30.0%	2.04 [0.75, 5.56]	+		
	Ou 2012 Subtotal (95% CI)	15	65 118	13	64 118	70.0%	1.14 [0.59, 2.19] 1.35 [0.78, 2.35]	-	2200000	
	Total events	25		18						
	Heterogeneity: Tau ² = Test for overall effect	0.00; Chi ² Z = 1.08 (F	= 0.92, = 0.28	df=1 (P)	= 0.34); lª = 0%				
	3.1.4 LGG to pregnan	it women &	& infants	s-7y						
	Kalliomaki 2007 Subtotal (95% CI)	12	53 53	6	62 62	100.0%	2.34 [0.94, 5.81] 2.34 [0.94, 5.81]	-		Allergic rhinitis
	Total events Heterogeneity: Not ap Test for overall effect.	12 oplicable Z = 1.83 (F	^o = 0.07)	6						
	3.1.5 LGG to infants of	only - 5 y								
	Cabana 2017 Subtotal (95% CI)	4	92 92	5	92 92	100.0%	0.80 [0.22, 2.88]			
	Total events Heterogeneity: Not ap Test for overall effect.	4 oplicable Z = 0.34 (F	P = 0.73	5						
							0.0	01 0.1 1 10 100		
	Test for subgroup diff	ferences: C	chi# = 2.1	82, df = 3	(P = 0	42), I ^e = 0	%	Favours LGG Favours control		
	Risk of bias legend									
	(A) Random sequence	ce generati	on (sele	ection bia	is)					
	(B) Allocation concea	Iment (sele	ection bi	ias)						
	(C) Blinding of particip	pants and	personn	iel (perfo	rmano	e bias)				
	(D) Blinding of outcom	ne assess	ment (d	etection	otas)					
	(E) Selective reporting	reportion	bias)	1031						
	(G) Other bias	1 Faharand	i sinal							
	fel seres eres									

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).

Probiotics for Prevention of Atopy and Food Hypersensitivity in Early Childhood

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

	Probiot	lics	Contr	ol		Risk Ratio	Risk R	atio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Randor	n, 95% Cl
2.1.1 Prenatal and po	stnatal							
Abrahamsson 2007	26	76	26	72	30.0%	0.95 [0.61, 1.47]		
Kim 2009	12	31	15	29	18.0%	0.75 [0.43, 1.32]		
Niers 2009	2	46	3	47	1.9%	0.68 [0.12, 3.89]		
Wickens 2008	44	290	31	146	33.4%	0.71 [0.47, 1.08]	-=+	
Wu 2010	11	34	18	36	16.7%	0.65 [0.36, 1.16]		
Subtotal (95% CI)		477		330	100.0%	0.77 [0.61, 0.98]	●	
Total events	95		93					
Heterogeneity: Tau ² =	0.00; Chi ²	= 1.36,	df = 4 (P	9 = 0.85); I ² = 0%			
Test for overall effect:	Z = 2.13 (F	P = 0.03	3)					
2.1.2 Prenatal only								
Boyle 2011	31	107	29	101	100.0%	1.01 [0.66, 1.55]		
Subtotal (95% CI)		107		101	100.0%	1.01 [0.66, 1.55]	•	
Total events	31		29					
Heterogeneity: Not app	olicable							
Test for overall effect:	Z = 0.04 (F	P = 0.9	7)					
2.1.3 Postnatal only								
Rautava 2006	2	32	3	40	5.9%	0.83 [0.15, 4.69]		
Soh 2009	7	124	6	121	15.6%	1.14 [0.39, 3.29]		
Taylor 2006	32	88	20	86	78.5%	1.56 [0.97, 2.51]	t.	-
Subtotal (95% CI)		244		247	100.0%	1.43 [0.94, 2.18]		
Total events	41		29					
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.70,	df = 2 (P	9 = 0.71); I ² = 0%			
Test for overall effect:	Z = 1.69 (F	P = 0.09	9)					
							0.01 0.1 1	10 100

FIGURE 4. Effect of probiotic supplementation on food hypersensitivity.

Zhang et al Medicine. 2016

Favours probiotics Favours control

7 SUPPLEMENTAZIONE & IMMUNOMODULAZIONE

8 e 9 MARZO 2019 BERGAMO HOTEL EXCELSIOR SAN MARCO Pazza della Repubblica, 6

Responsabile Scientifico: Fabio Pace

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

	lgE-mediated (n =	= 21) cor	mpared to control Infan	ts	Non-IgE-mediated ($n = 20$) compared to control infants				
	Univariate		Multivariable**		Univariate		Multivariable**		
	Odds ratio	p	Odds ratio	р	Odds ratio	р	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 likely reverse causality	as					
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 medica- tion					3.312 (1.13–9.75)	0.030	Not included in anal likely reverse cause	lysis as ality	

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

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)

•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.

8 e 9 MARZO 2019 BERGAMO HOTEL EXCELSIOR SAN MARCO Pazza della Repubblica. 6

Responsabile Scientifico: Fabio Pace

Trattamento?

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

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

ORIGINAL RESEARCH

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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

	Probio	tic	Placel	bo		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI		
1.2.1 No tolerance at 6 months									
Berni Canani et.al. 2012	11	27	22	28	20.7%	0.52 [0.32, 0.85]			
Hol, et.al. 2008	24	55	26	56	23.2%	0.94 [0.62, 1.42]			
Subtotal (95% CI)		82		84	44.0%	0.71 [0.40, 1.27]	-		
Total events	35		48						
Heterogeneity: Tau ² = 0.12; Chi ² = 3.29, df = 1 (P = 0.07); i ² = 70%									
Test for overall effect: Z = 1.15 (P = 0.25)									
1.2.2 No tolerance at 12 m	onths								
Berni Canani et.al. 2012	5	27	13	28	11.6%	0.40 [0.16, 0.97]			
Hol, et.al. 2008	12	55	10	56	14.1%	1.22 [0.58, 2.59]			
Subtotal (95% CI)		82		84	25.7%	0.72 [0.24, 2.14]			
Total events	17		23						
Heterogeneity: Tau ² = 0.45;	ChF = 3.	57, df =	= 1 (P = 0	.06); l²	= 72%				
Test for overall effect: Z = 0	.60 (P = 0).55)							
1.2.3 No tolerance at >2 ye	ears								
Berni Canani, et.al. 2017	19	98	44	95	21.8%	0.42 [0.26, 0.66]			
Cukrowska et.al. 2010	4	21	6	19	8.6%	0.60 [0.20, 1.82]			
Subtotal (95% CI)		119		114	30.4%	0.44 [0.29, 0.67]			
Total events	23		50				—		
Heterogeneity: Tau ² = 0.00; Chl ² = 0.36, df = 1 (P = 0.55); l ² = 0%									
Test for overall effect: Z = 3	.79 (P = 0).0002)							
Total (95% CI)		283		282	100.0%	0.63 [0.43, 0.92]	•		
Total events	75		121						
Heterogeneity: Tau ² = 0.11; Chl ² = 11.33, df = 5 (P = 0.05); l ² = 56%									
Test for overall effect: Z = 2.40 (P = 0.02) Favours Problems Favours Prob									
Test for subgroup differences: Chl ² = 1.96, df = 2 (P = 0.37), l ² = 0%									

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

ORIGINAL RESEARCH

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

8 e 9 MARZO 2019 BERGAMO HOTEL EXCELSIOR SAN MARCO Pazza della Repubblica, 6

Responsabile Scientifico: Fabio Pace

SOTTOGRUPPO 2 Analisi basata sul ceppo di probiotico utilizzato

CONCLUSIONE:

"Although the mean difference favors probiotic use, the CI is wide \rightarrow the results are not precise."

	Probio	tic	Placel	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.3.1 LGG strain							
Berni Canani et.al. 2012	5	27	13	28	17.3%	0.40 [0.16, 0.97]	
Berni Canani, et.al. 2017	19	98	44	95	60.7%	0.42 [0.26, 0.66]	
Subtotal (95% CI)		125		123	78.0%	0.41 [0.28, 0.62]	
Total events	24		57				
Heterogeneity: Chi ² = 0.01	, df = 1 (P :	= 0.92)	; l² = 0%				
Test for overall effect: Z =	4.25 (P < 0	.0001)					
1.3.2 Mixed strain							
Cukrowska et.al. 2010	4	21	6	19	8.6%	0.60 [0.20, 1.82]	
Hol, et.al. 2008	12	55	10	56	13.5%	1.22 [0.58, 2.59]	
Subtotal (95% CI)		76		75	22.0%	0.98 [0.53, 1.81]	•
Total events	16		16				
Heterogeneity: Chi ² = 1.07	, df = 1 (P	= 0.30)	; l² = 7%				
Test for overall effect: Z =	0.06 (P = 0	.95)					
Total (95% Cl)		201		198	100.0%	0.54 [0.39, 0.75]	•
Total events	40		73				
Heterogeneity: Chi2 = 6.20	, df = 3 (P :	= 0.10)	; l² = 52%				
Test for overall effect: Z =	3.64 (P = 0	.0003)					U.US U.2 1 5 20
Test for subgroup difference	es: Chi² =	5.28 d	f = 1 (P =	0.02)	l ² = 81.09	2	Favours Problotic Favours Placebo

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 Bacteroides diversity all'età di 1 mese Proteobacteria diversity a 12 mesi p-value 0.004 p-value 0.01 p = 0.04

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

	Experimental Control						Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2004 Viljanen	12.1	16.8	80	9.8	13.2	74	7.8%	2.30 [-2.45, 7.05]	·
2005 Weston	22.6	4.92	28	33.8	4.85	28	9.0%	-11.20 [-13.76, -8.64]	
2006 Folster	35.3	15.2	26	31.6	14.5	27	5.8%	3.70 [-4.30, 11.70]	
2007 Gruber	22.5	14.6	54	17.9	13.6	48	7.3%	4.60 [-0.87, 10.07]	
2009 Niers	20.4	10.9	50	21	10.5	48	8.1%	-0.60 [-4.84, 3.64]	
2010 Gerasimov	27.9	9.9	43	32.4	7.7	47	8.4%	-4.50 [-8.19, -0.81]	
2010 Shafiei	41.9	15.4	43	39.9	11.6	18	6.3%	2.00 [-5.06, 9.06]	·
2010 Woo	28.8	5.4	41	35.8	5.85	34	9.0%	-7.00 [-9.57, -4.43]	
2011 Gore	12.5	5.33	45	11.8	3.48	47	9.2%	0.70 [-1.15, 2.55]	i +
2011 Wu KG	27.4	12.7	27	36.3	14.9	27	6.1%	-8.90 [-16.28, -1.52]	
2012 Yavuz	12.4	7.2	20	15.3	6.1	20	8.1%	-2.90 [-7.04, 1.24]	
2012 Youngshin	20.6	9.2	45	23.2	8.2	46	8.5%	-2.60 [-6.18, 0.98]	
2015 Wang IJ	25.76	19.23	51	40.1	15.58	53	6.5%	-14.34 [-21.08, -7.60]	
Total (95% CI)			553			517	100.0%	-3.07 [-6.12, -0.03]	•
Heterogeneity: Tau ² =	25.20: (Chi r = 9	5.65, d	f = 12 (P	< 0.000	001); P	= 87%		
Test for overall effect	Z=1.98	(P = 0)	05)						-20 -10 0 10 20
		v •.	,						Favours [experimental] Favours [control]

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

Huang et al. Frontiers in Cellular and Infection Microbiology 2017

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

