

Probiotici e Allergopatie

Diego Peroni

Università di Pisa

Microbioma, disbiosi e malattia

Probiotici e Allergia

Conclusioni



XXX CONGRESSO NAZIONALE

SIAAIC

Società Italiana di Allergologia,
Asma ed Immunologia Clinica



FIRENZE 6/9 APRILE 2017 | WWW.SIAAIC2017.ORG

diego.peroni@unipi.it



Transforming Life: A Broad View of the Developmental Origins of Health and Disease Concept from an Ecological Justice Perspective.

S. Prescott, Int. J. Environ. Res. Public Health 2016, 13, 1075

The holobiont view of human life underscores that we are assemblages of different species—**persistent symbionts**—that make up an **ecological unit**.

The human host and its microbiome (trillions of microbes and their collective genomes) are therefore an **ecological community**.

In turn, the holobiont operates within its own ecological theater—that is, the often inequitable biotic and abiotic neighborhood.

Transforming Life: A Broad View of the Developmental Origins of Health and Disease Concept from an Ecological Justice Perspective.

S. Prescott, Int. J. Environ. Res. Public Health 2016, 13, 1075

Functions of the microbiome include, but are not limited to:

- ✓ “education” of the immune system,
- ✓ protection against pathogens,
- ✓ maintenance of barriers to the external environment,
- ✓ nutrient production and extraction, increasing bioavailability of dietary phytochemicals, lipid metabolism, provision of short chain fatty acids, production of bioactive metabolites, and
- ✓ detoxification of environmental toxins

Collectively these benefits can be described as **ecosystem services**.

ORIGINAL ARTICLE

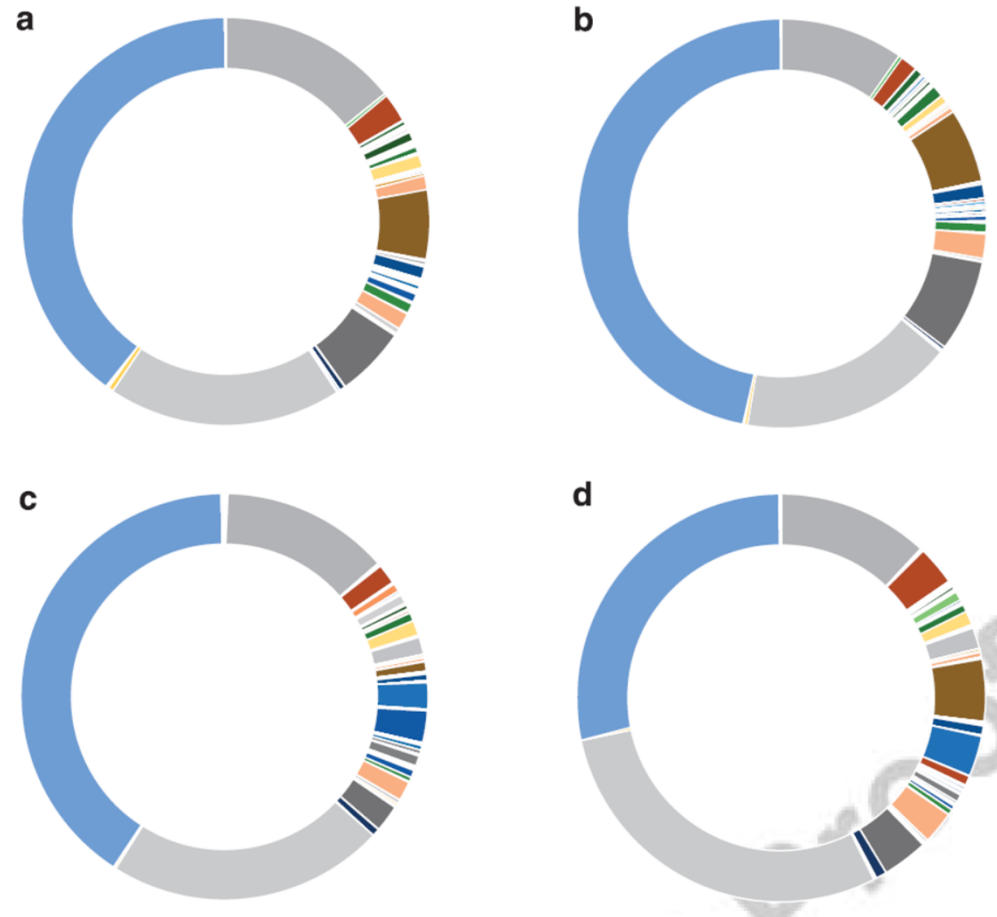
Microbiota network and mathematic microbe mutualism in colostrum and mature milk collected in two different geographic areas: Italy versus Burundi

Lorenzo Drago^{1,2}, Marco Toscano¹, Roberta De Grandi², Enzo Grossi³, Ezio M Padovani⁴ and Diego G Peroni^{5,6}

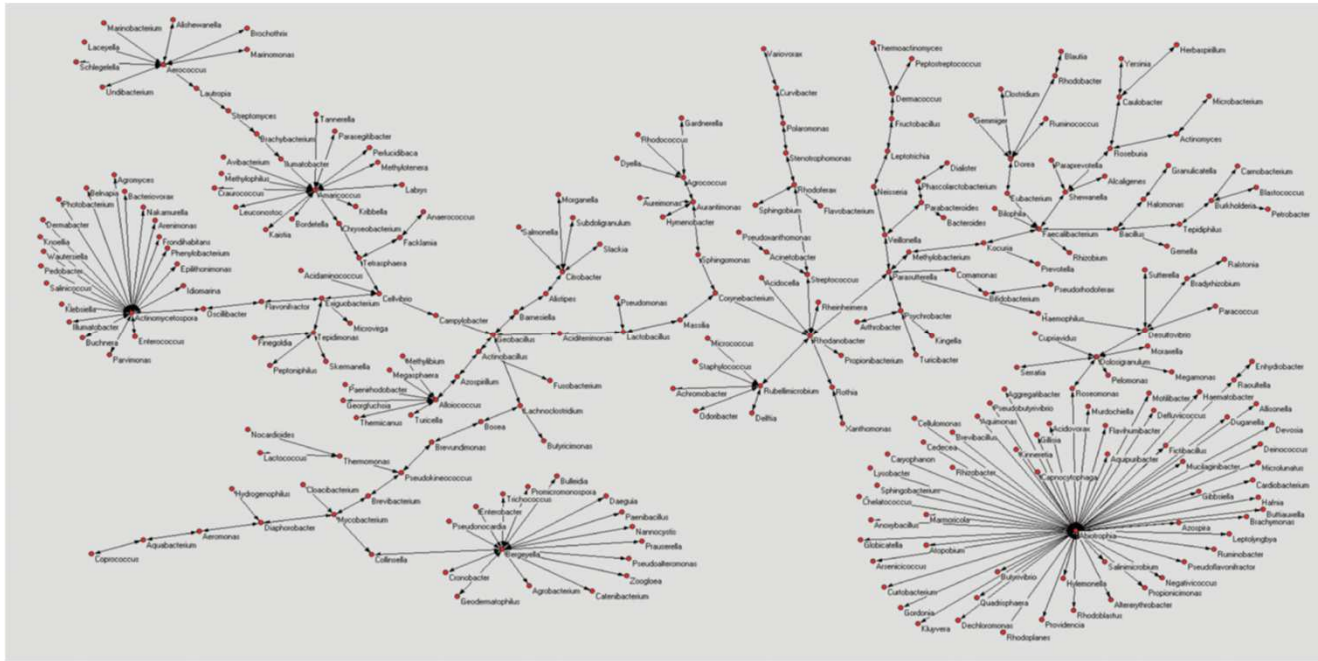
Bacterial distribution in each type of milk sample:

- (a) Italian colostrum;
- (b) Italian mature milk;
- (c) Burundian colostrum;
- (d) Burundian mature milk

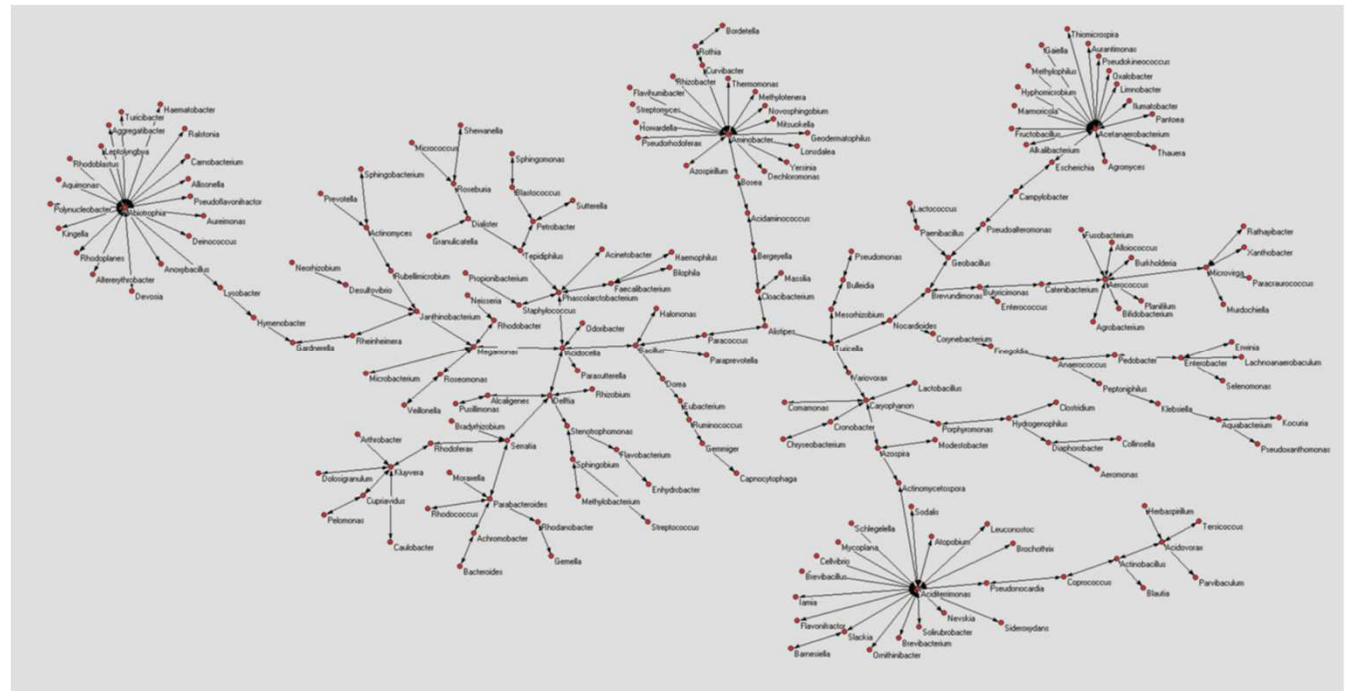
- Mothers from Burundi and Verona
- Colostrum and mature milk (1 mo.)
- Bacterial DNA extraction and 16S gene sequencing
- The auto-contractive map



Colostrum from Italy



Mature milk from Italy



ORIGINAL ARTICLE

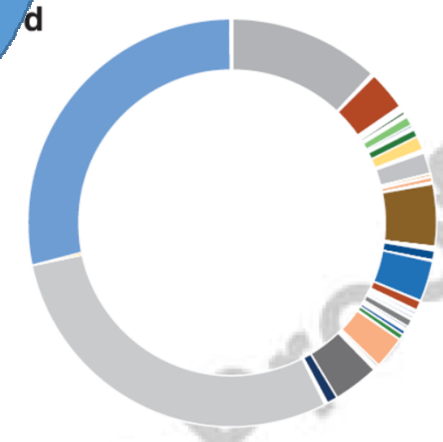
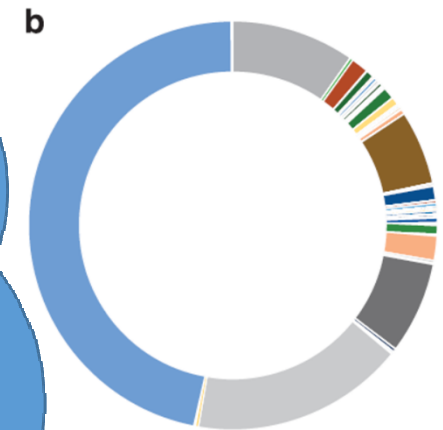
Microbiota network and mathematic microbe mutualism in colostrum and mature milk collected in two different geographic areas: Italy versus Burundi

Lorenzo Drago^{1,2}, Marco Toscano¹, Roberta De C. ¹, Grossi ¹, Medovani⁴
and Diego G Peroni^{5,6}

The microbiota of human milk is a dynamic, and complex, ecosystem with different bacterial networks among different populations containing diverse microbial hubs and central nodes, which change during the transition from colostrum to mature milk.

Bacterial distribution in each type of milk sample:

- (a) Italian colostrum;
- (b) Italian mature milk;
- (c) Burundian colostrum;
- (d) Burundian mature milk



ORIGINAL ARTICLE

Microbiota network and mathematic microbe mutualism in colostrum and mature milk collected in two different geographic areas: Italy versus Burundi

Lorenzo Drago^{1,2}, Marco Toscano¹, Roberta Peroni¹, and Diego G Peroni^{5,6}

Bacterial distribution in each type of milk sample:

- (a) Italian colostrum;
- (b) Italian mature milk;
- (c) Burundian colostrum;
- (d) Burundian mature milk

Bacterial relations changed within the same population, underlying that **colostrum and mature milk are different** not only for protein and fat content but also for the microbiota composition.

We believe **some bacterial genera are essential in the first phase of lactation**, and for this reason, they have a pivotal role in colostrum, while **other microorganisms are fundamental in the long-term nutrition of newborns**

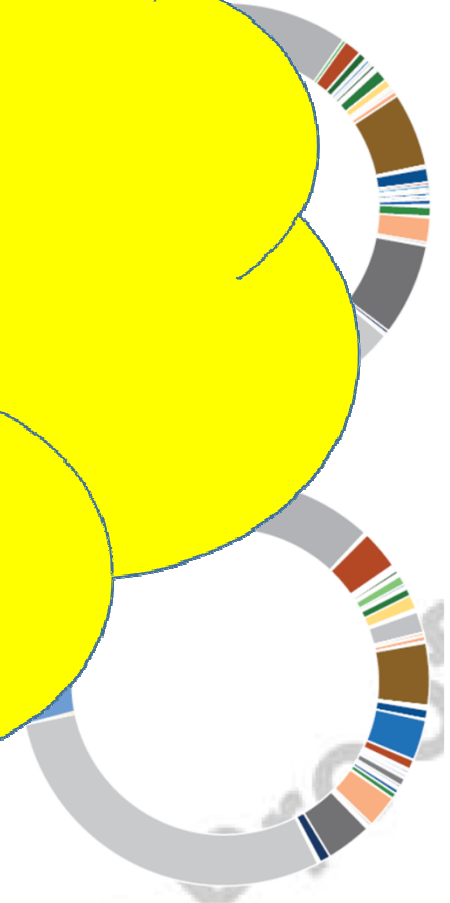
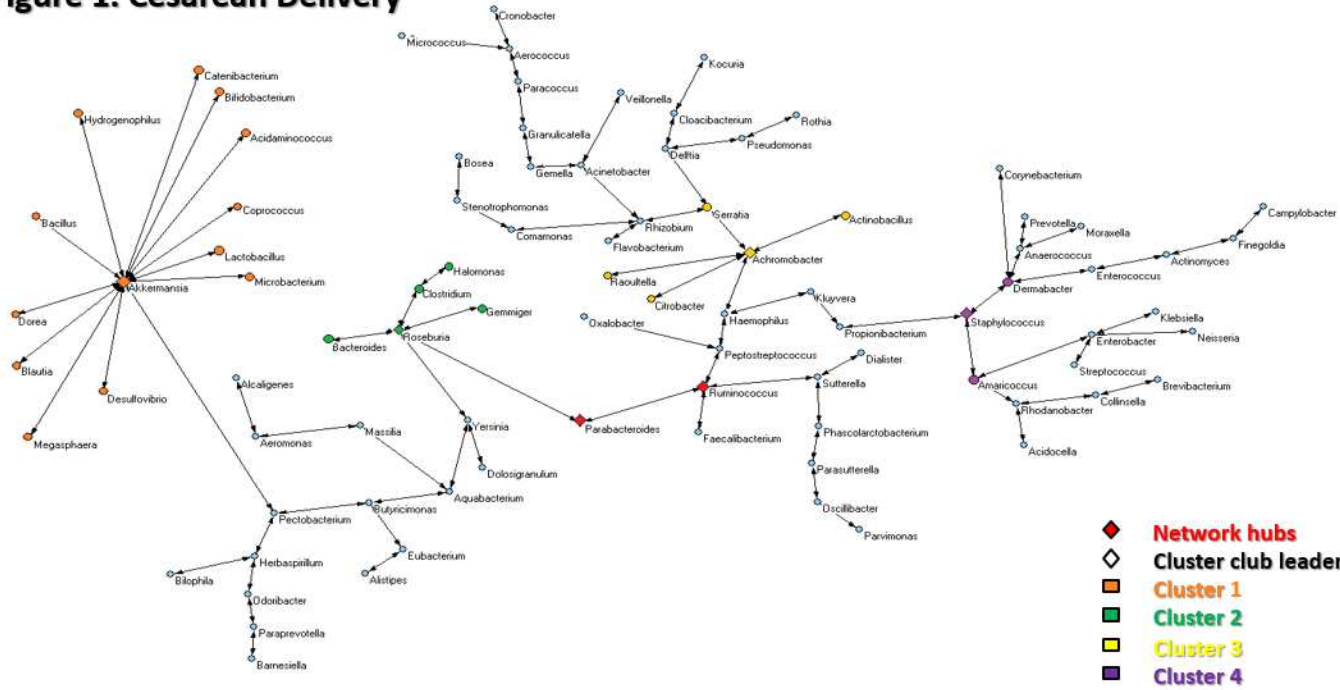
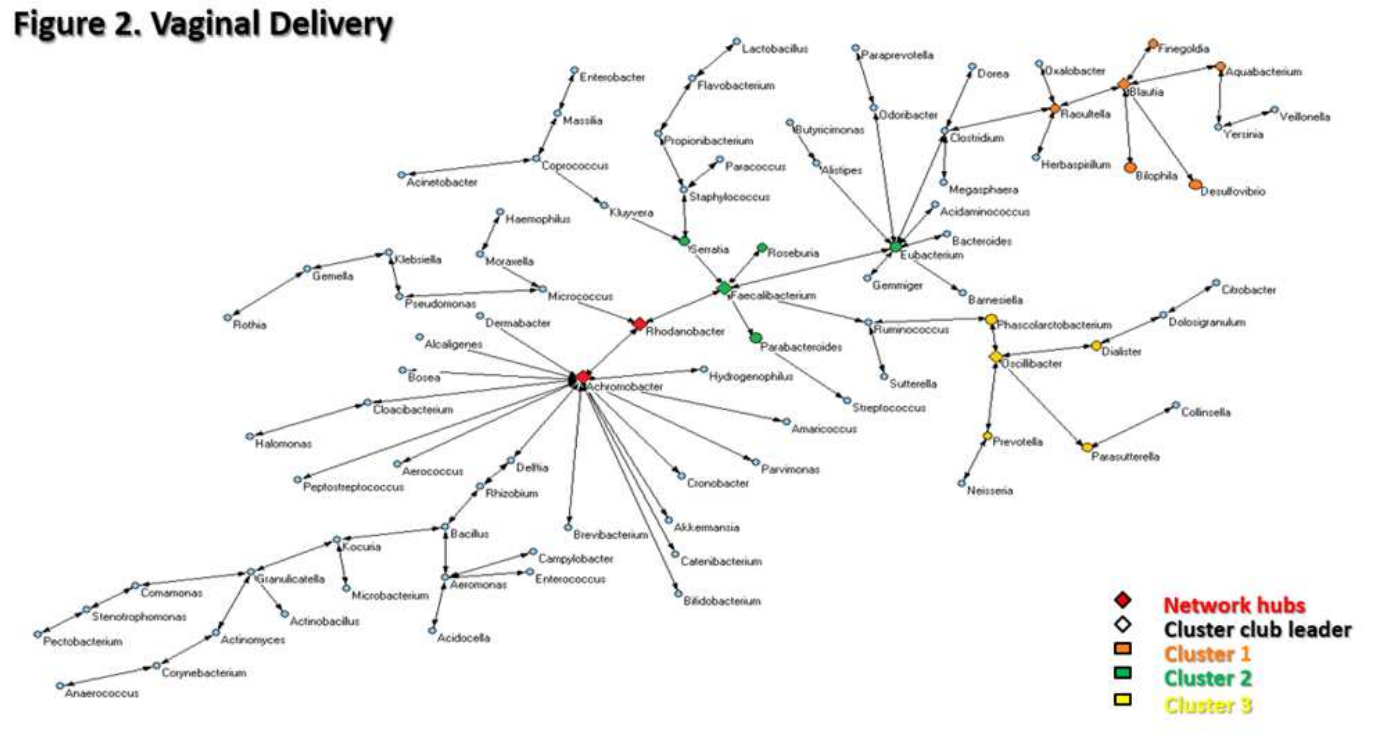


Figure 1. Cesarean Delivery



Colostrum in ..

Figure 2. Vaginal Delivery

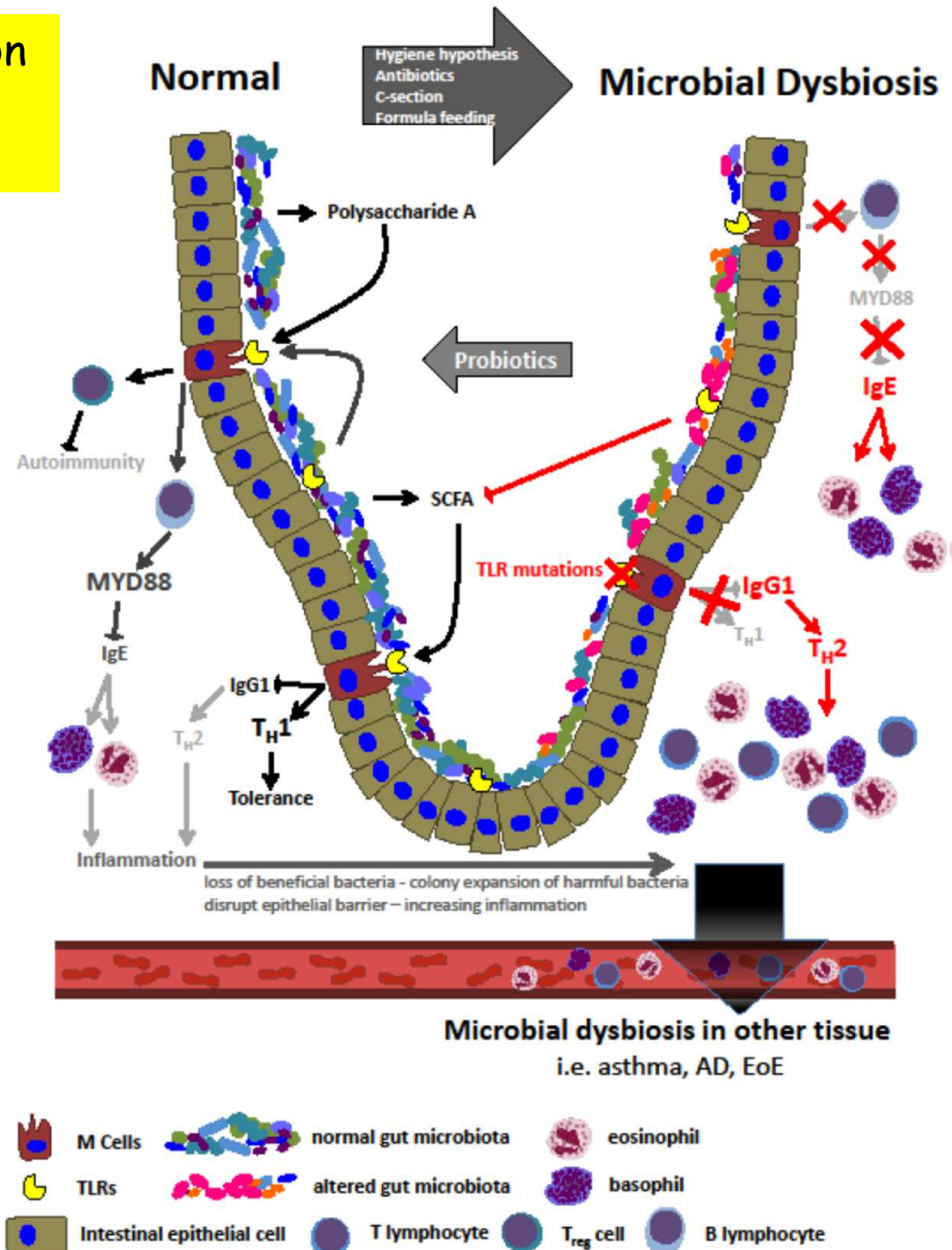


Microbiome and its Impact on Gastrointestinal Atopy.
Muir, Allergy 2016

Commensal bacteria and their role in the development of tolerance.

Commensal colonization decreases IgE-basophil axis and increases TLR stimulation thus promoting tolerance.

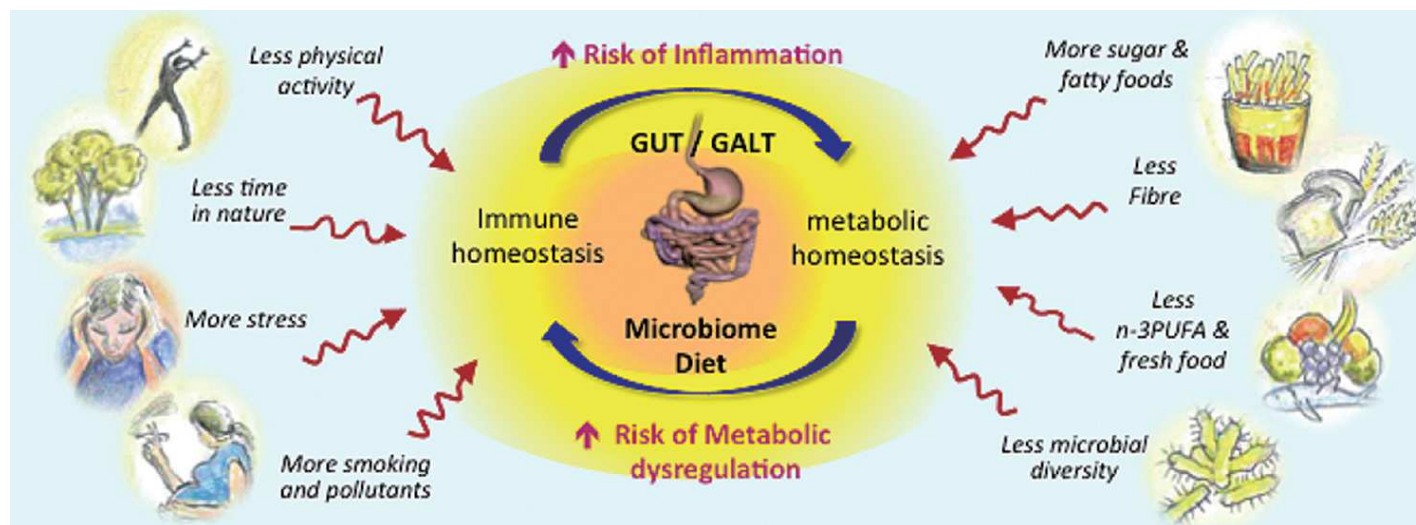
Dysbiosis and ineffective TLR signaling leads to enhanced Th2 response and IgE mediated disease.



Transforming Life: A Broad View of the Developmental Origins of Health and Disease Concept from an Ecological Justice Perspective.

S. Prescott, Int. J. Environ. Res. Public Health 2016, 13, 1075

Dysbiosis is a term that translates as “difficult living” or “life in distress”; given neighborhood grey space, massive health disparities, matters of economic and environmental injustices, biodiversity losses, climate change, rapid urbanization and other threats to ecosystems, it has been argued that dysbiosis can apply at the individual, neighborhood and global level.



Transforming Life: A Broad View of the Developmental Origins of Health and Disease Concept from an Ecological Justice Perspective.

S. Prescott, Int. J. Environ. Res. Public Health 2016, 13, 1075

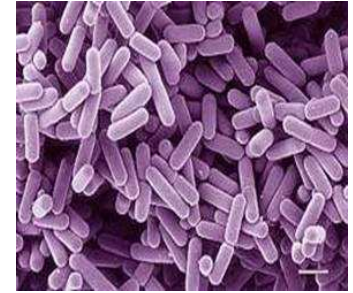
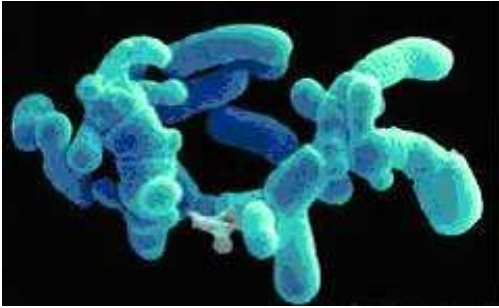
The drivers of microbial dysbiosis (e.g., **westernized/ultra-processed diet, stress, alcohol, tobacco, circadian disruptions, antibiotic use**, et al.) are slanted toward the SES disadvantaged in developed nations, and increasingly so in developing nations.

The presence of grey space (an environment maintained by marketing forces and absence of policy that could otherwise transform opportunity for health) accompanies disadvantage and contributes to what has been referred to as “dysbiotic drift”.

Probiotics are
“live microorganisms that, when
administered in adequate amounts,
confer a health benefit on the host”

Thus, viability is considered to
be a fundamental
requirement for probiotics

Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014;11:506



In humans, by far, the most commonly used probiotics are bacteria from the genus *Lactobacillus* or *Bifidobacterium*, and a yeast, *Saccharomyces boulardii*.

However, novel probiotics are an area of current investigation.

Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014;11:506

Table 3 Effects of probiotics in children

Condition	Effect of probiotics as a group	Examples of probiotics with documented or promising efficacy	Ref
Acute gastroenteritis (treatment)	Approximately 1-day reduction in the duration of diarrhoea	ESPGHAN Strong recommendation ▶ <i>Lactobacillus</i> GG ▶ <i>S. boulardii</i> Weak recommendation ▶ <i>L. reuteri</i> DSM 17938 ▶ <i>Lactobacillus</i> GG ▶ <i>S. boulardii</i> ▶ <i>Lactobacillus</i> GG	2 3 6 7
Antibiotic-associated diarrhoea (prevention)	Reduced risk	Promising ▶ <i>Lactobacillus</i> GG ▶ <i>L. reuteri</i> DSM 17938	10 14 15
Nosocomial diarrhoea (prevention)	Reduced risk	WAO suggests the use of probiotics in select high-risk populations to reduce the risk of eczema; however, there is no clear indication regarding which probiotic(s) to use	25 26
Infections in children attending day care centres (prevention)	Reduced risk	No clear indications from scientific societies regarding which probiotic strain(s) should be recommended	27
Allergy (prevention)	Reduced risk of eczema	No clear indications which strain(s) to use Promising ▶ <i>S. boulardii</i>	32 33
NEC (prevention)	Reduced risk of NEC and mortality in infants who were born <1500 g	▶ <i>L. reuteri</i> DSM 17938 (documented in breastfed infants)	35–4
<i>H. pylori</i> infection	Reduced risk of side effects and increased eradication rate	More studies are needed to identify beneficial strains. Promising ▶ <i>Lactobacillus</i> GG ▶ VSL#3	42–4
Infantile colic (management)	Reduced crying time	ESPGHAN/ECCO ▶ <i>E. coli</i> Nissle 1917 ▶ VSL#3	50
Abdominal pain- related functional gastrointestinal disorders	Certain probiotics reduced intensity of pain (especially in patients with irritable bowel syndrome) Limited evidence suggests that probiotics added to standard therapy may provide modest benefits	ECCO/ESPGHAN: not recommended	54
Induction of remission in ulcerative colitis	Insufficient evidence	ESPGHAN/NASPGHAN: not recommended	44
Induction of remission in Crohn's disease	Until more data are available, the use of probiotics should be considered investigational		

What are the indications for using probiotics in children?

Hania Szajewska. Arch Dis Child 2015

Some questions were asked:
should

If

Search data meta-
als or their
s.

Considering
that probiotics have
strain-specific effects,
the main focus was on
data on individual
probiotic strains, not on
probiotics in general.

The MEDLINE database was searched for evidence-based clinical practice guidelines, developed by scientific societies.

Probiotici e Allergopatie

Diego Peroni

Università di Pisa

Microbioma, disbiosi e malattia

Probiotici e Allergia

Conclusioni



XXX CONGRESSO NAZIONALE

SIAAIC

Società Italiana di Allergologia,
Asma ed Immunologia Clinica



FIRENZE 6/9 APRILE 2017 | WWW.SIAAIC2017.ORG

diego.peroni@unipi.it



de Silva D. **EAACI** Food Allergy and Anaphylaxis Guidelines Group. Primary prevention of food allergy in children and adults: systematic review. *Allergy* 2014;69:581.

Muraro A. **EAACI** Food Allergy and Anaphylaxis Guidelines Group. **EAACI** food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy* 2014;69:590

There is no evidence to support the use of probiotics (also prebiotics) for food allergy prevention

Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials.

Cuello-Garcia, JACI, 2015;136:952

Outcomes	No. of participants (studies)	Quality of evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	
				Risk with no probiotics	Risk difference with probiotics
Eczema, follow-up: range, 6-24 mo	2657 (10 RCTs)*	●○○○ Very low †‡§	0.80 (0.64-0.93)	Study population 289 per 1000	58 fewer per 1000 (104 fewer to 20 fewer)
Atopic eczema, follow-up: range, 6-36 mo	2218 (7 RCTs)*	●○○○ Very low †‡§¶	0.62 (0.51-0.76)	Study population 198 per 1000	73 fewer per 1000
Asthma/wheezing, follow-up: range, 6-36 mo	1733 (6 RCTs)				
Food allergy, follow-up: range, 6-24 mo	295 (2 RCTs)				
Allergic rhinitis, follow-up: range, 12-36 mo	1465 (4 RCTs)				
Any allergy, follow-up: range, 6-24 mo	1152 (3 RCTs)				
Adverse events, follow-up: range, 6-36 mo	642 (2 RCTs)	Very low †‡§ ††		196 per 1000	6 more per 1000 (59 fewer to 102 more)
Nutritional status assessed with growth and weight, follow-up: range, 3-36 mo	454 (1 RCT)	●○○○ Very low § ††	Not estimable	Mean nutritional status: 0 infants only in the control group	SMD, 0 higher (0.18 lower to 0.18 higher)

Key messages

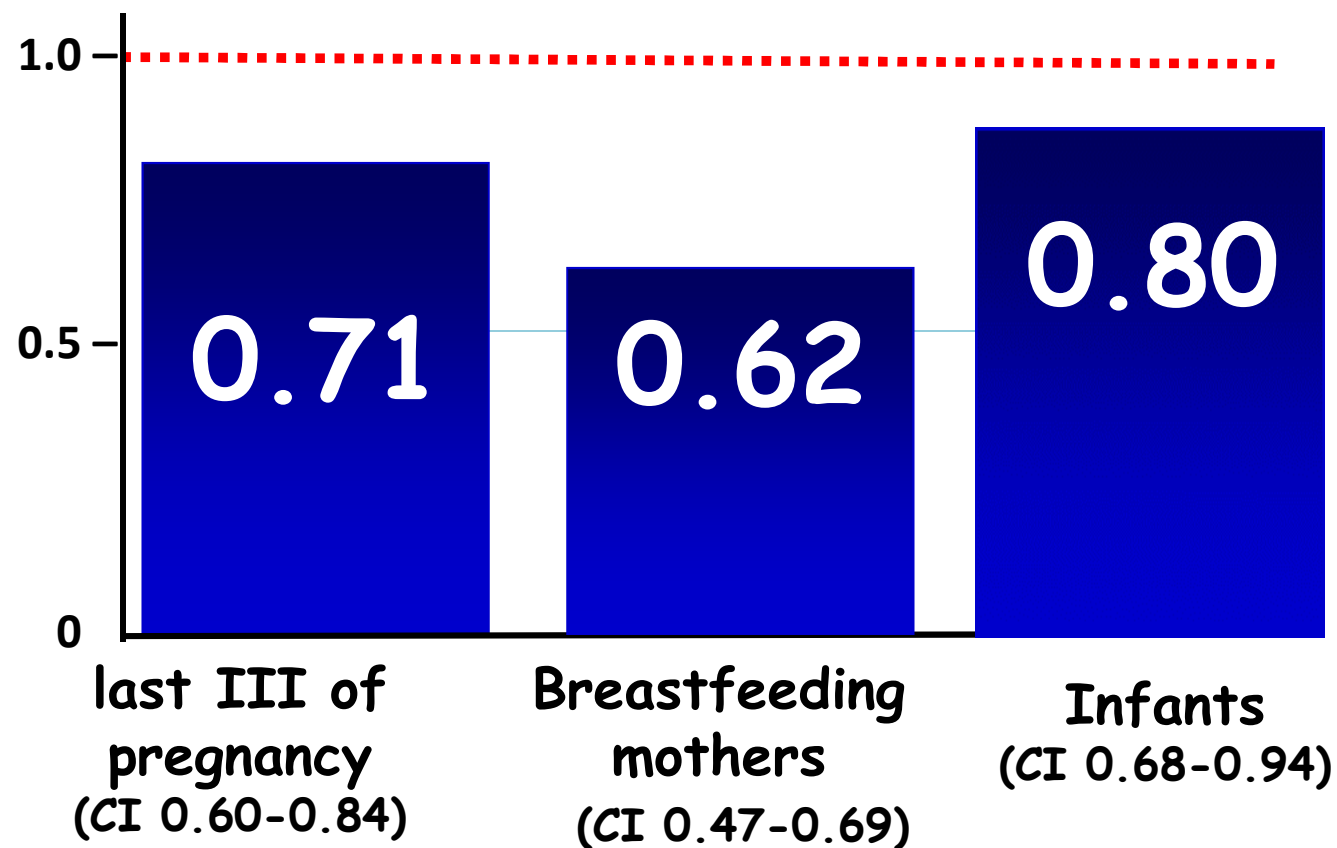
- Probiotics given to pregnant women, breast-feeding mothers, and/or infants reduced the risk of eczema in infants.
- Currently available evidence does not indicate that probiotics prevent the development of other allergies.
- Design of future studies should consider the weaknesses identified regarding the risk of bias and indirectness of the evidence.

World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): probiotics.

Fiocchi A, Pawankar R, Cuello-Garcia C, et al. World Allergy Organ J 2015;8:4.

- ✓ A systematic review.
- ✓ 29 publications
- ✓ 12 various probiotics single or in combination
- ✓ Except for LGG none in more than one trial

Relative Risk For Reducing the risk of eczema with supplementation in



World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): probiotics.

Fiocchi A, Pawankar R, Cuello-Garcia C, et al. World Allergy Organ J 2015;8:4.

✓ A systematic review.

✓ 29 published

✓ 17 probiotics in controlled trials

✓ Except for one trial

In line with the EAACI, the WAO experts agreed that probiotic supplementation cannot be recommended for reducing the risk of allergy in children.

However, the WAO considered that there is a likely net benefit from using probiotics for preventing eczema...

...ing mothers (CI 0.47-0.69)

Infants CI 0.68-0.94

80

WAO suggests:

- "a) using probiotics in pregnant women at high risk for having an allergic child;
- b) using probiotics in women who breastfeed infants at high risk of developing allergy; and
- c) using probiotics in infants at high risk of developing allergy."

✓ A sys
review

✓ 29 pu

✓ 12 va
probiot
in combin

✓ F
n

All recommendations were conditional and supported by a very low quality of evidence.

eventing

ners
CI 0.47-0.69)

Infants
CI 0.68-0.94

Recommendations on probiotics in allergy prevention should not be based on pooling data from different strains

Hania Szajewska. JACI 2015

One important limitation of the WAO guidelines is the lack of answers to the most important practical questions.

Which probiotic(s) should be used to reduce the risk of eczema?

When should one start the administration of probiotics with proven efficacy?

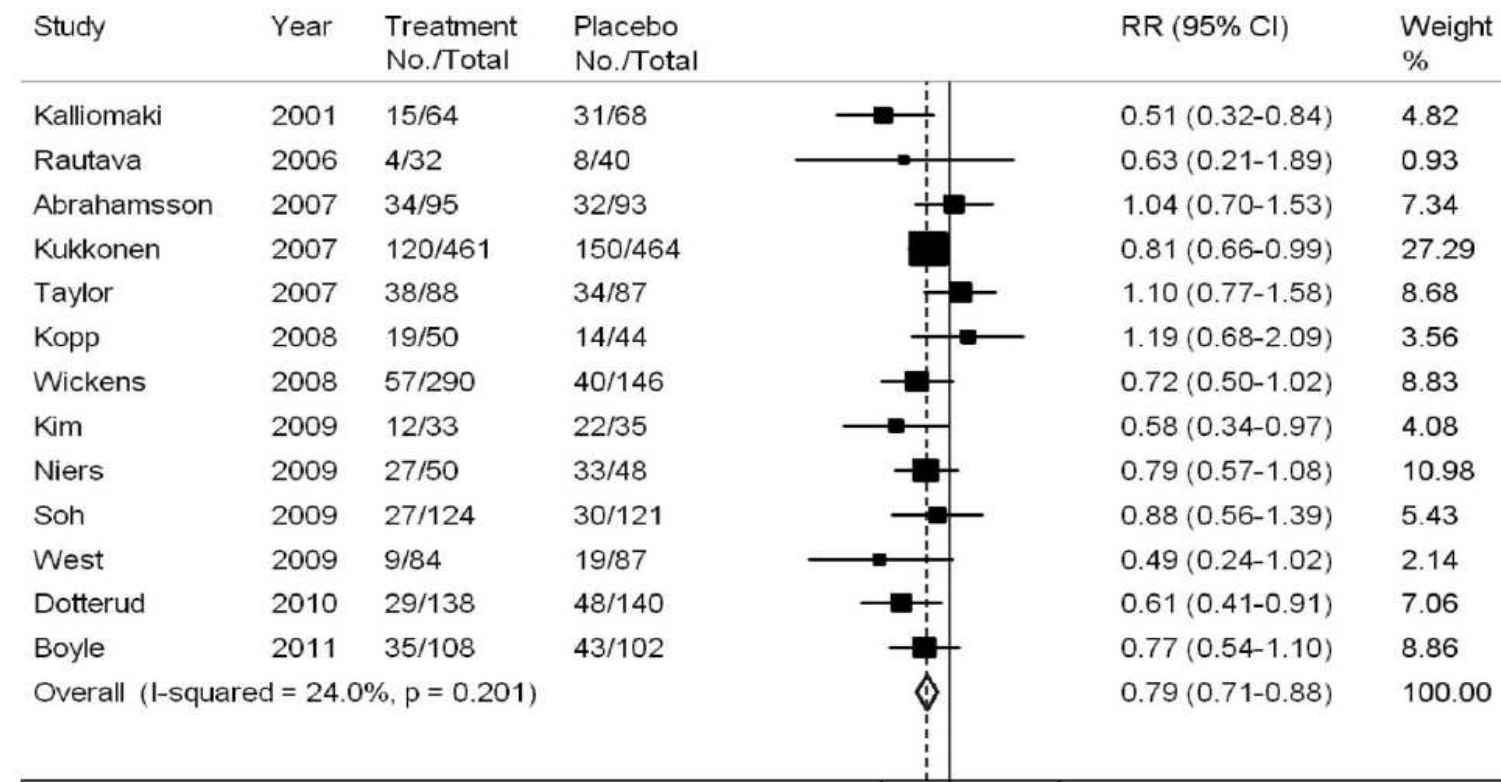
When should one stop?

What is the dose of an effective probiotic?

Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis

Pelucchi C, Epidemiology 2012; 23:402

✓ meta-analysis of randomized controlled trials to investigate whether probiotic use during pregnancy and early life **decreases the incidence of atopic dermatitis** and immunoglobulin E (IgE)-associated atopic dermatitis in infants and young children.

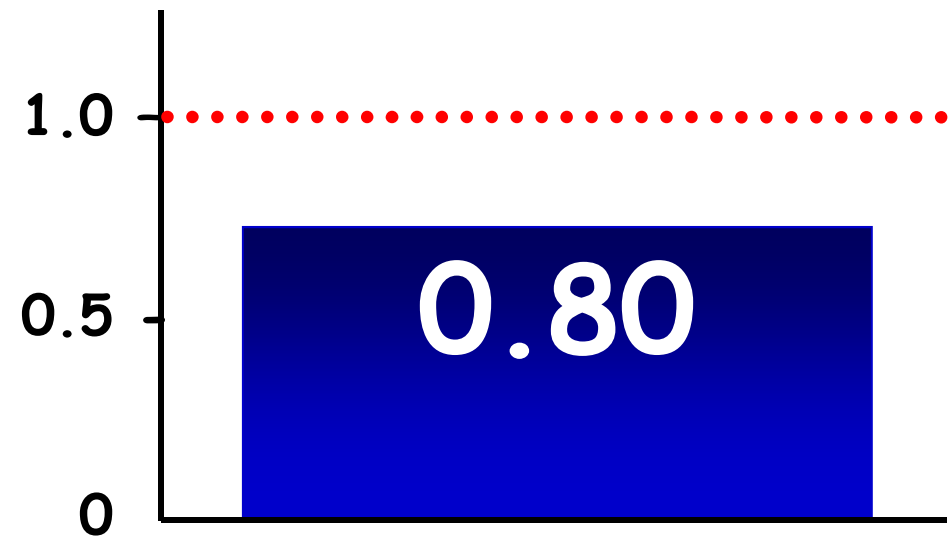


Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis

Pelucchi C, Epidemiology 2012; 23:402

- ✓ meta-analysis of randomized controlled trials to investigate whether probiotic use during pregnancy and early life decreases the incidence of atopic dermatitis and immunoglobulin E (IgE)-associated atopic dermatitis in infants and young children.

RR for IgE associated atopic dermatitis



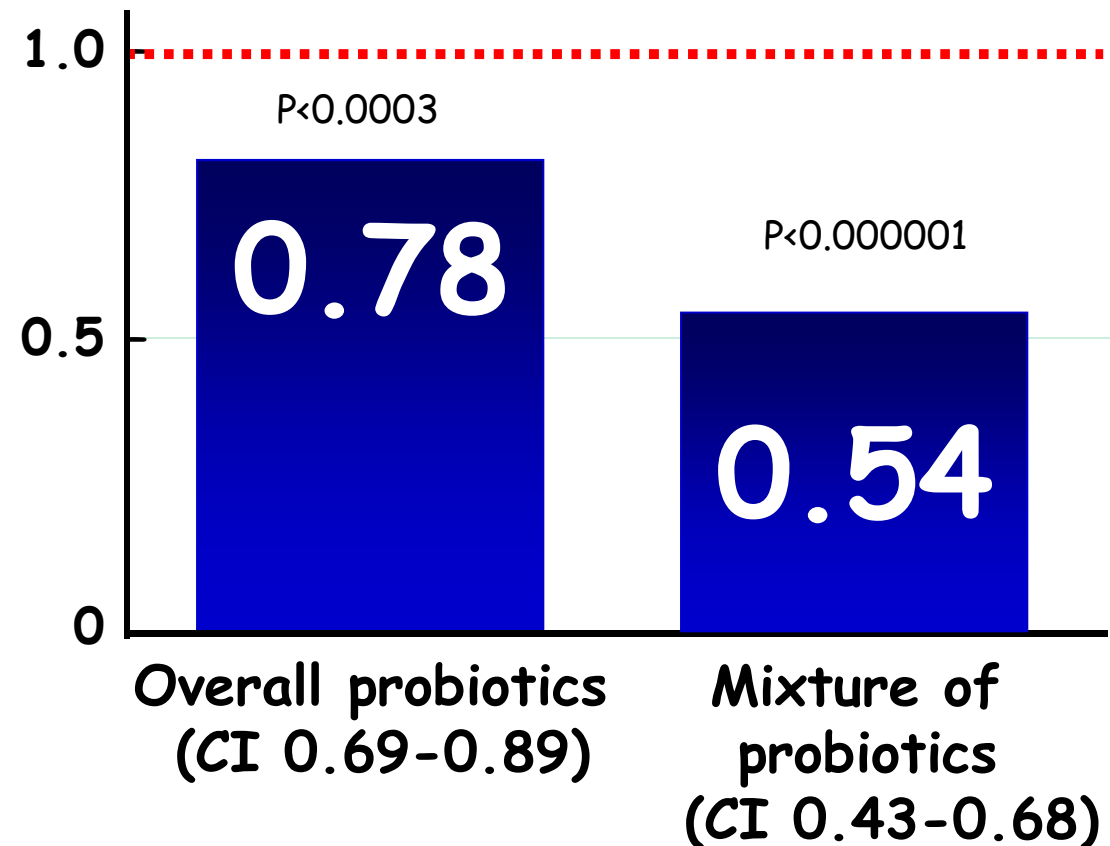
Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis.

Zuccotti G and *Task Force on Probiotics of the Italian Society of Neonatology, *Allergy* 2015; 70:1376

✓ systematic review and meta-analysis

✓ 17 studies, reporting data from 4755 children (2381 in the probiotic group)

Relative Risk For Reducing the risk of eczema

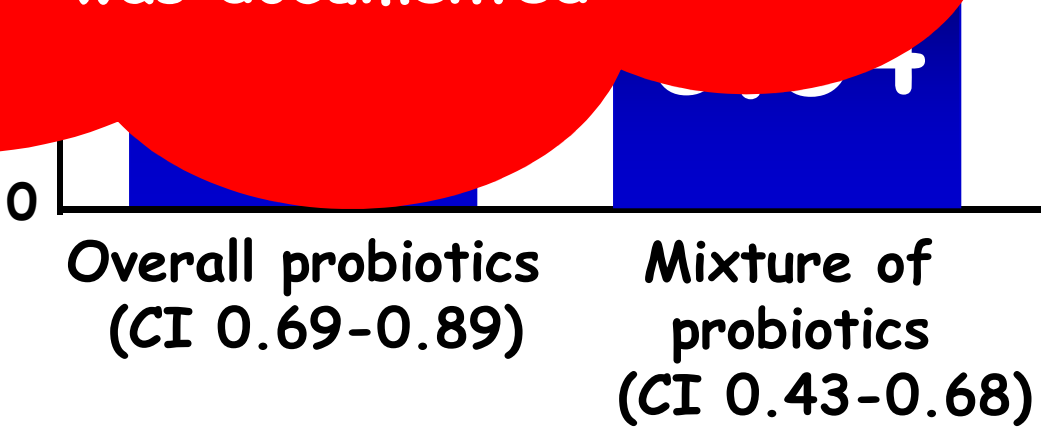


Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis.

Zuccotti G and *Task Force on Probiotics of the Italian Society of Neonatology, Allergy 2015; 70:1376

- ✓ systematic review and meta-analysis
- ✓ 17 studies reporting data from 4755 children (25% in the probiotic group)

No significant difference in terms of prevention of asthma (RR 0.99 [95% CI: 0.77-1.27], P = 0.95), wheezing (RR 1.02 [95% CI: 0.89-1.17], P = 0.76) or rhinoconjunctivitis (RR 0.91 [95% CI: 0.67-1.23], P = 0.53) was documented



What are the indications for using probiotics in children?

Hania Szajewska. Arch Dis Child 2015

Probiotics as a group reduce the risk of eczema.

However, it would be premature to support the routine use of probiotics for preventing eczema.

Data regarding which probiotic products should be administered, at what dosages and the most effective dosing schedule are needed

One important question is whether probiotics should be used in children with eczema.

Which probiotics should be used?

When should probiotics be used? What is the most effective dosing schedule?

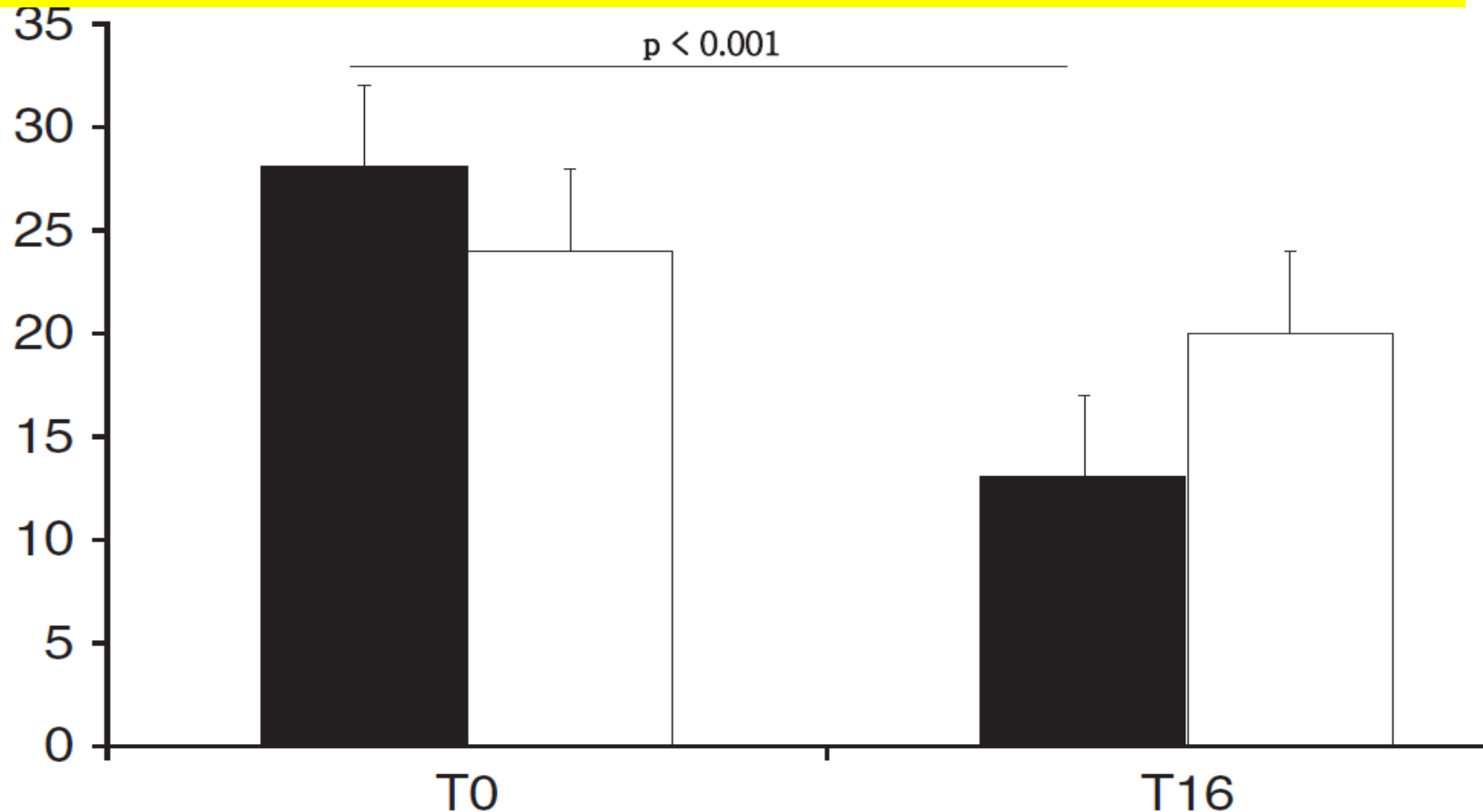
When should probiotics be used?

What is the dose of an effective probiotic?

Changing of Fecal Flora and Clinical Effect of *L. salivarius* LS01 in Adults With Atopic Dermatitis.

Drago L, J Clin Gastroenterol 2012;46:S56.

SCORAD index in probiotic (black bars) and placebo (open bars) groups



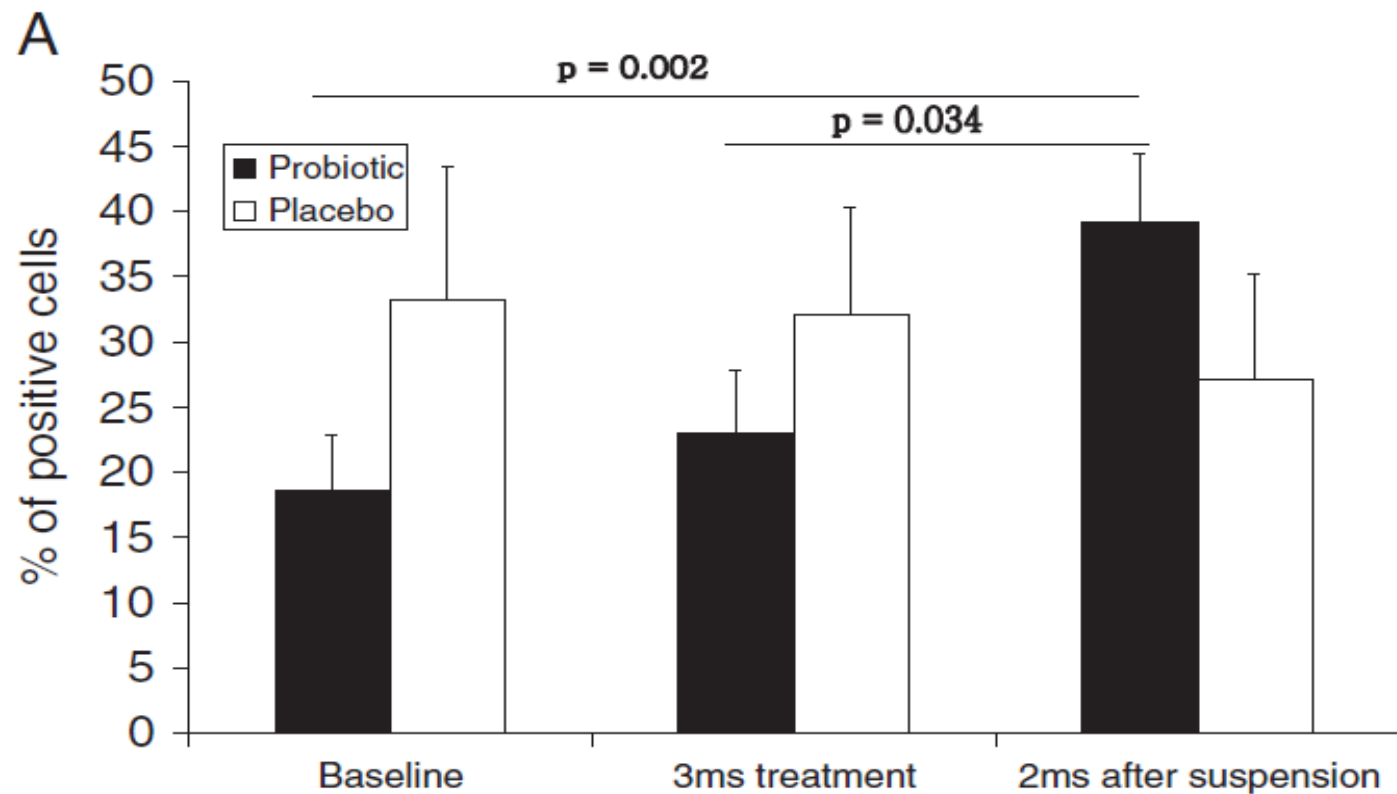
Probiotics Reduce Gut Microbial Translocation and Improve Adult Atopic Dermatitis. Iemoli, J Clin Gastroenterol 2012;46:S33

48 pts were enrolled
(randomization ratio 2:1)

treated with a combination
(Lactobacillus salivarius and
Bifidobacterium breve or
placebo (maltodextrin) for
12 weeks.

Clinical efficacy was
assessed from baseline by
changes in the SCORAD
index and DLQ index
improvement.

Regulatory T cells: TGF- β -secreting and IL-10-secreting regulatory T cells



Effects of probiotics for the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials

Kim Ann Allergy 2014;113:217

- ✓ 25 randomized controlled trials (n = 1,599).



Significant differences in SCORAD values favoring probiotics over the control were observed:

- overall (mean - 4.51),
- in children 1 to 18 yrs old (- 5.74),
- in adults (- 8.26).

Effects of probiotics for the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials

Kim Ann Allergy 2014;113:217

However,
the effectiveness
of probiotics in
infants (< 1 yr old)
with AD was
not proved.

Significant differences in SCORAD values favoring probiotics over the control were observed:

- overall (mean - 4.51),
- in children 1 to 18 yrs old (- 5.74),
- in adults (- 8.26).

Effects of probiotics for the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials

Kim Ann Allergy 2014;113:217

The overall result of this meta-analysis suggests that **probiotics could be an option for the treatment of AD**, especially for moderate to severe AD in children and adults.

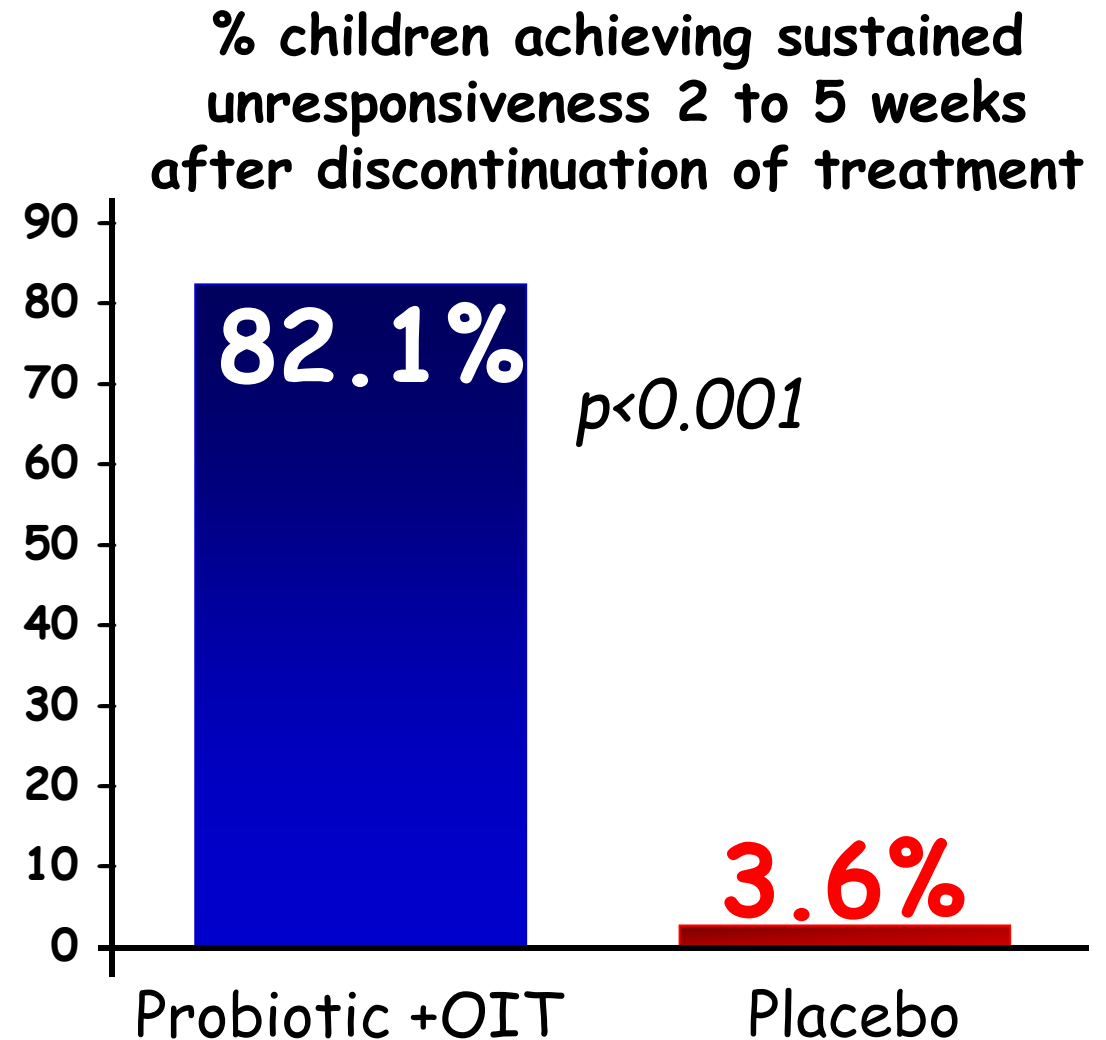
Significant differences in SCORAD values favoring probiotics over the control were observed:

- overall (mean - 4.51),
- in children 1 to 18 yrs old (- 5.74),
- in adults (- 8.26).

Administration of a probiotic with peanut oral immunotherapy: A randomized trial

Tang MLK, *J Allergy Clin Immunol* 2015; 135:737-44

- ✓ *Lactobacillus rhamnosus* CGMCC 1.3724 and peanut OIT (probiotic and peanut oral immunotherapy) or placebo.
- ✓ 62 children (1-10 years) with peanut allergy.
- ✓ Sustained unresponsiveness 2 to 5 weeks after discontinuation of treatment.



Probiotici e Allergopatie

Diego Peroni

Università di Pisa

Microbioma, disbiosi e malattia

Probiotici e Allergia

Conclusioni



XXX CONGRESSO NAZIONALE

SIAAIC

Società Italiana di Allergologia,
Asma ed Immunologia Clinica



FIRENZE 6/9 APRILE 2017 | WWW.SIAAIC2017.ORG

diego.peroni@unipi.it

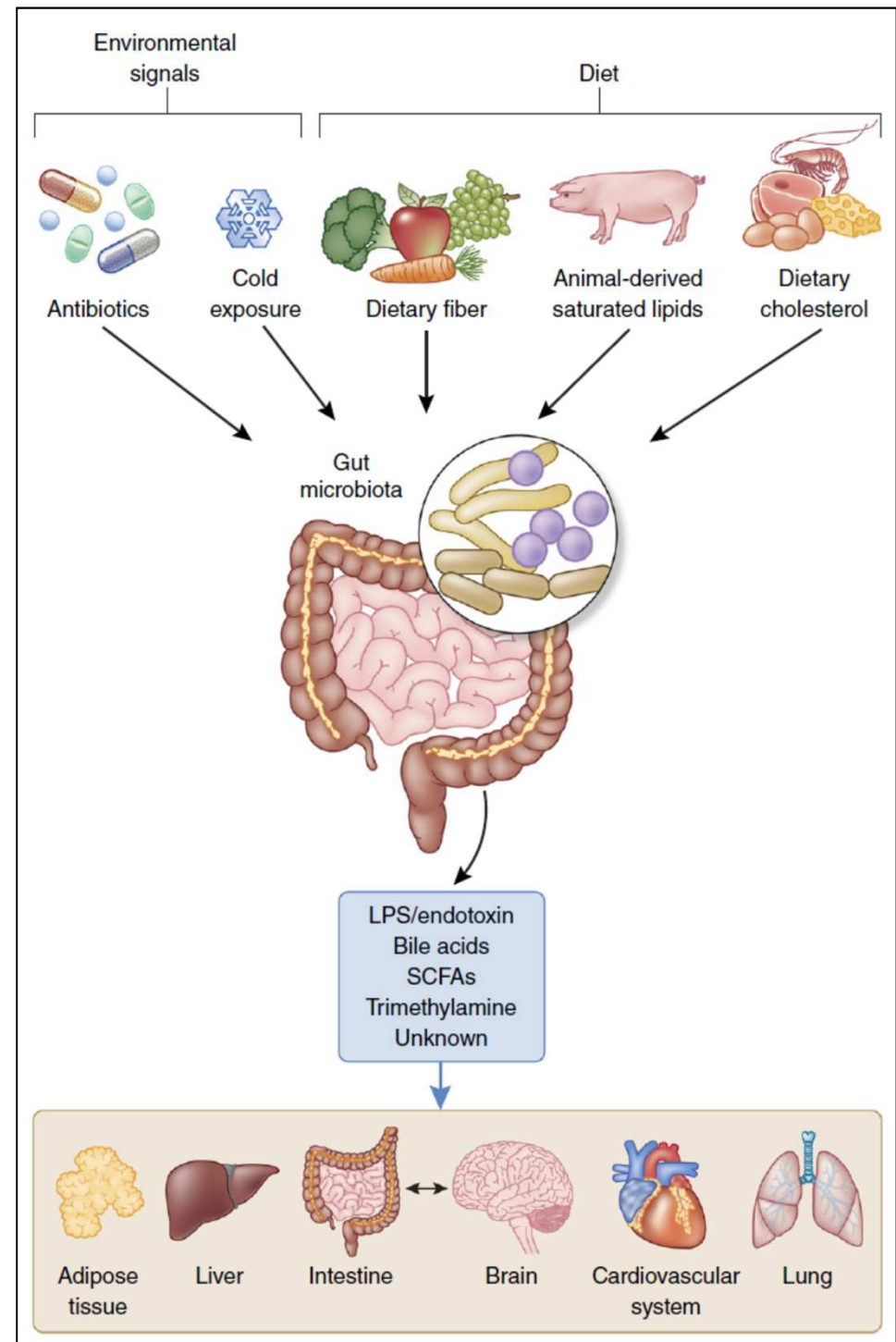


Signals from the gut microbiota to distant organs in physiology and disease. Schroeder BO, Nature Med, 2016: 22:1079

Gut microbiota convert environmental signals and dietary molecules into signaling metabolites to communicate with the host.

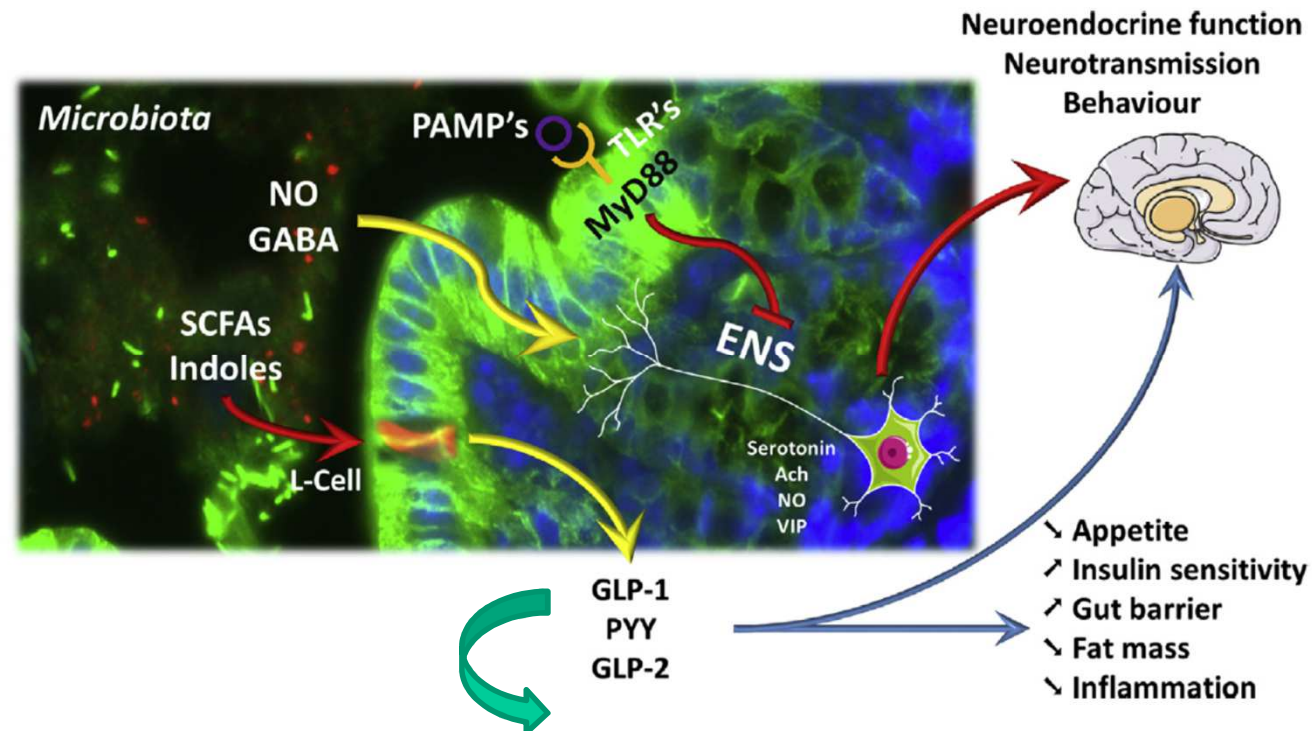
At the top of the figure are indicated factors that can alter the composition of the gut microbiota.

The gut microbiota converts these inputs into metabolites, which can signal to different organs and tissues in the host, as indicated below.



How gut microbes talk to organs: The role of endocrine and nervous routes.

Cani PD, Molecular Metabolism, 2016; 5:743

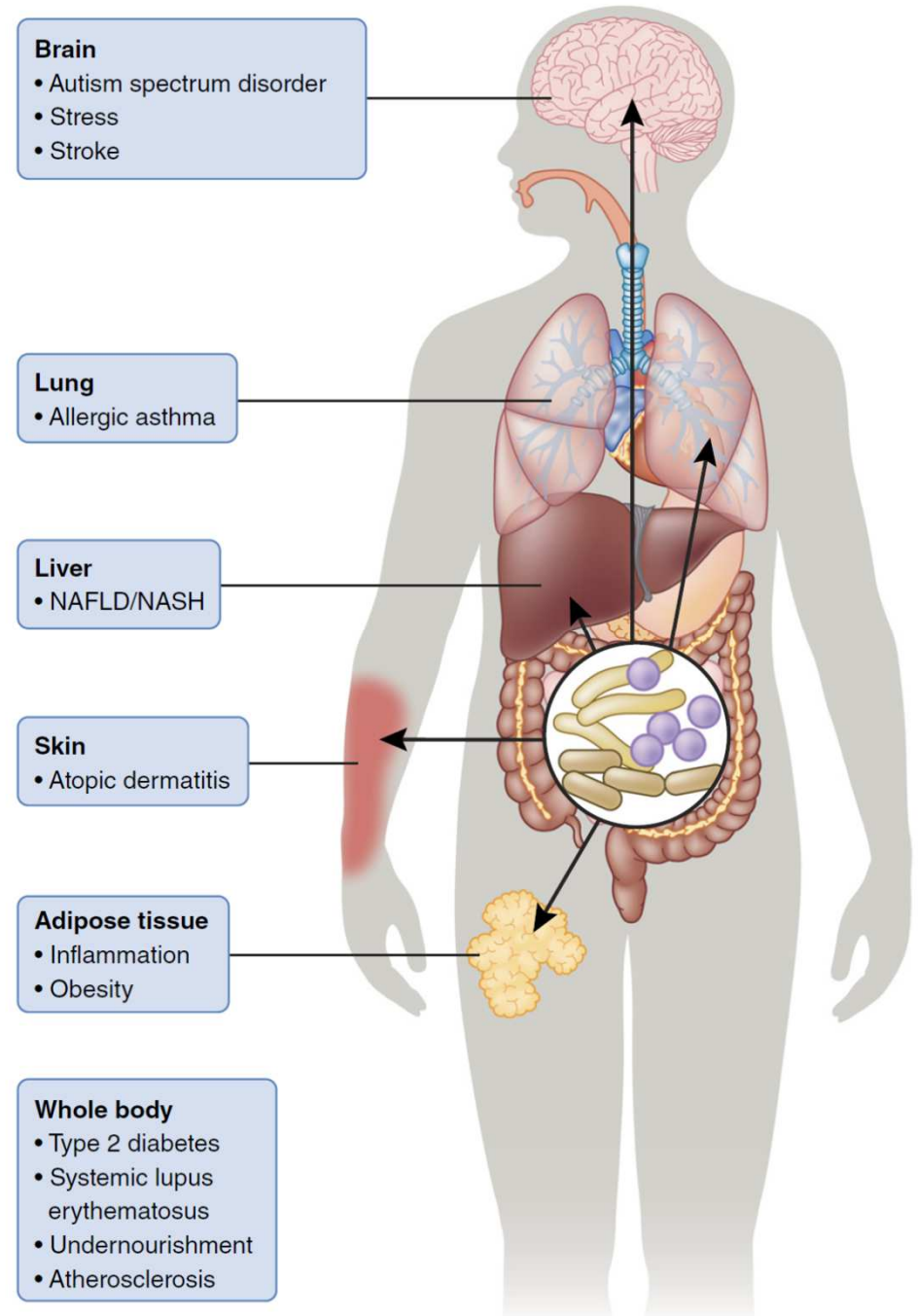


Secretion of such hormones control **appetite, gut barrier, and glucose homeostasis** (e.g., insulin sensitivity) via direct interactions with organs but also through nervous routes. Similar to what is observed in the brain, different neurotransmitters or molecules (produced by intestinal microbes), such as nitric oxide (NO) as well as g-aminobutyric acid (GABA), act through the enteric nervous system (ENS). **Secondary messengers**, including NO, serotonin, acetylcholine (Ach) or vasoactive intestinal polypeptide (VIP) release, are involved in the gut to peripheral organ and brain communication, leading to the control of different behaviors (e.g., food intake, anxiety, stress)

Signals from the gut microbiota to distant organs in physiology and disease. Schroeder BO, Nature Med, 2016: 22:1079

Obesity in humans has been associated with reduced microbial diversity as compared to lean controls.

However, it is at present unknown whether the reduced **microbial diversity** contributes to obesity or merely reflects the obesogenic lifestyle and dietary habits, because **diets without fiber dramatically reduce microbial diversity and the capacity to metabolize complex carbohydrates**



Signals from the gut microbiota to distant organs in physiology and disease. Schroeder BO, Nature Med, 2016: 22:1079

Obesity in humans has been associated with reduced microbial diversity as compared to lean controls.

However, it is at present unknown whether the reduced microbial diversity is a cause or a consequence of obesity.

The gut microbiota actively communicates with the host, similarly to other human organs, and we are only just beginning to decipher their signals and their relevance for human health and disease.

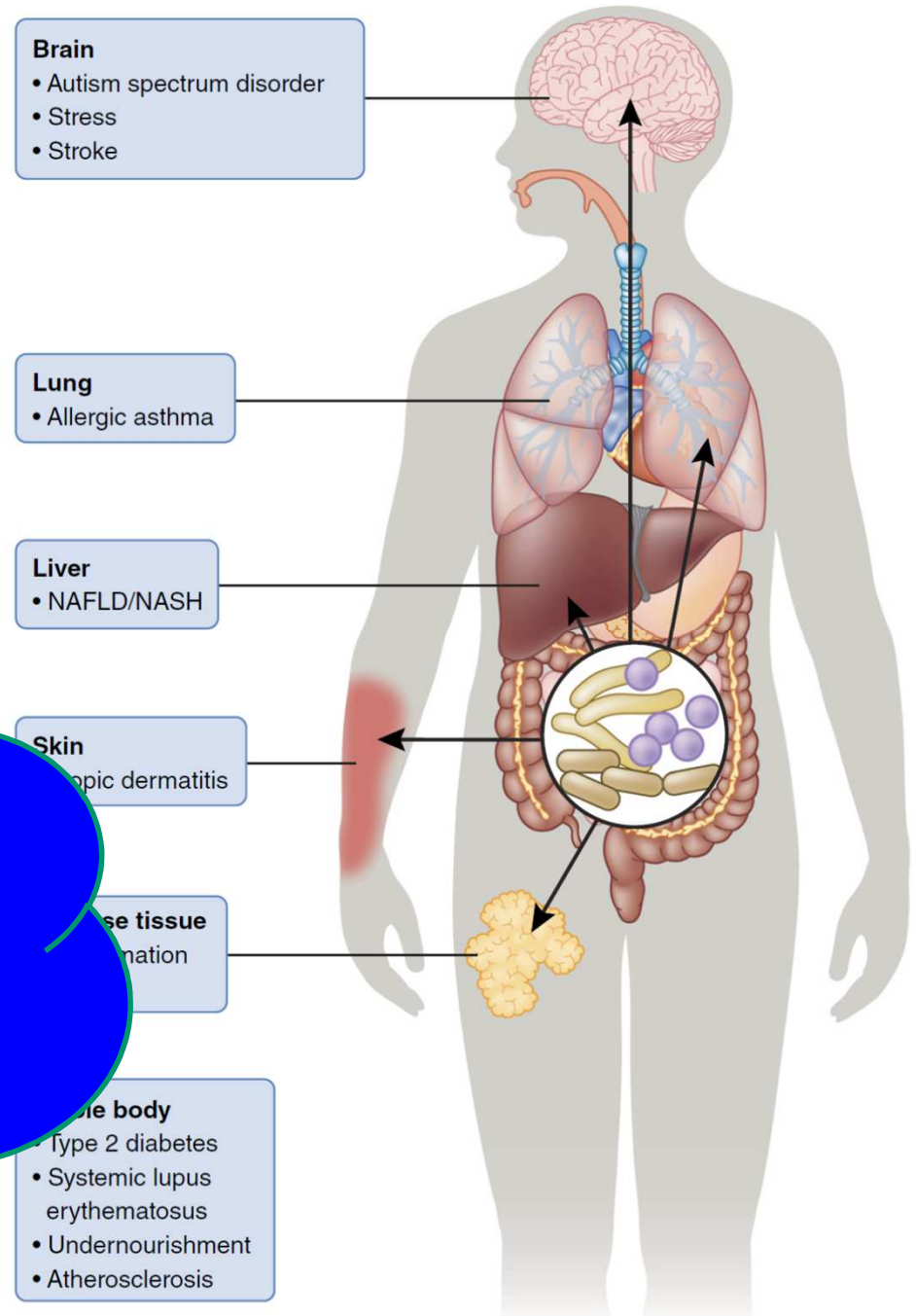
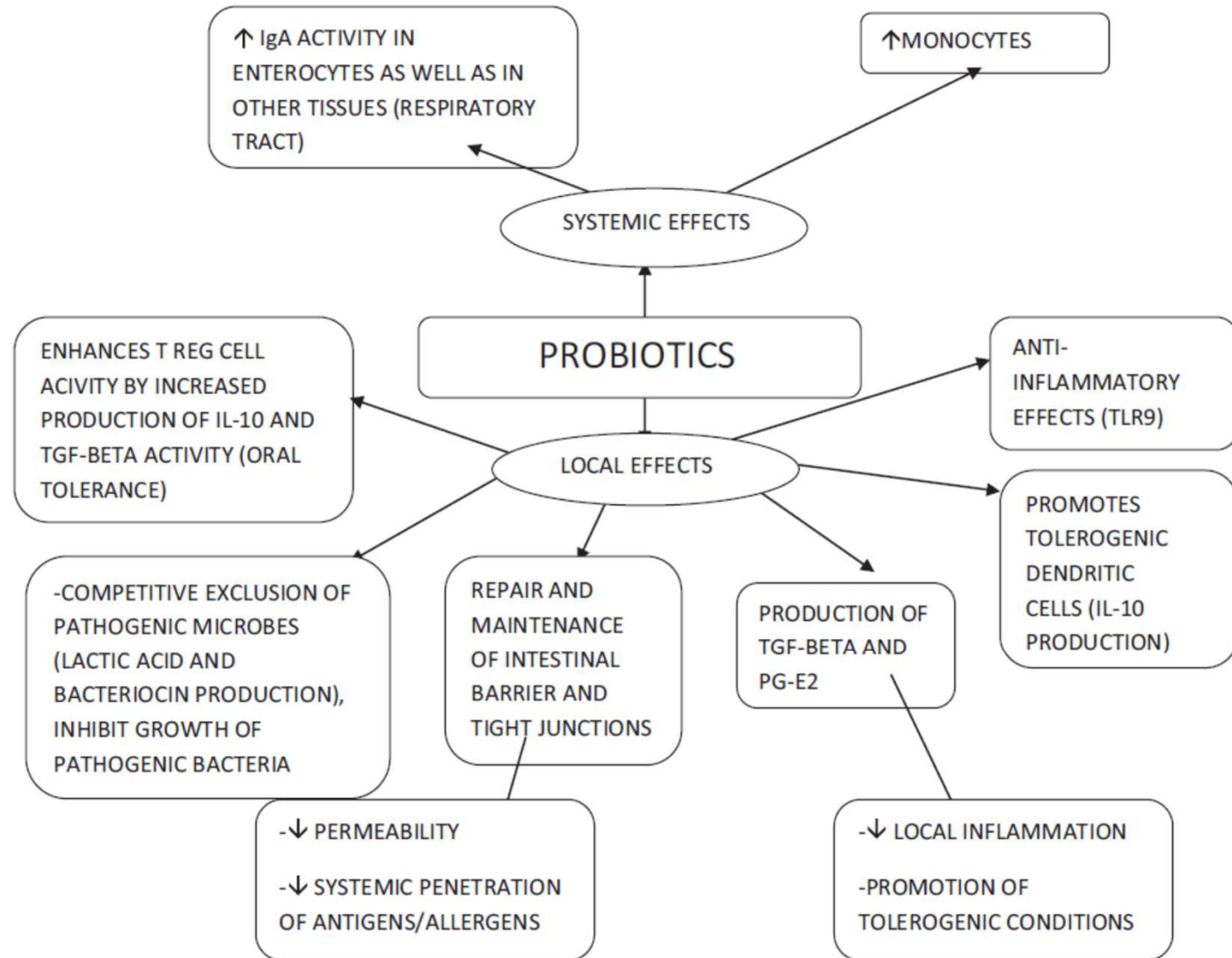


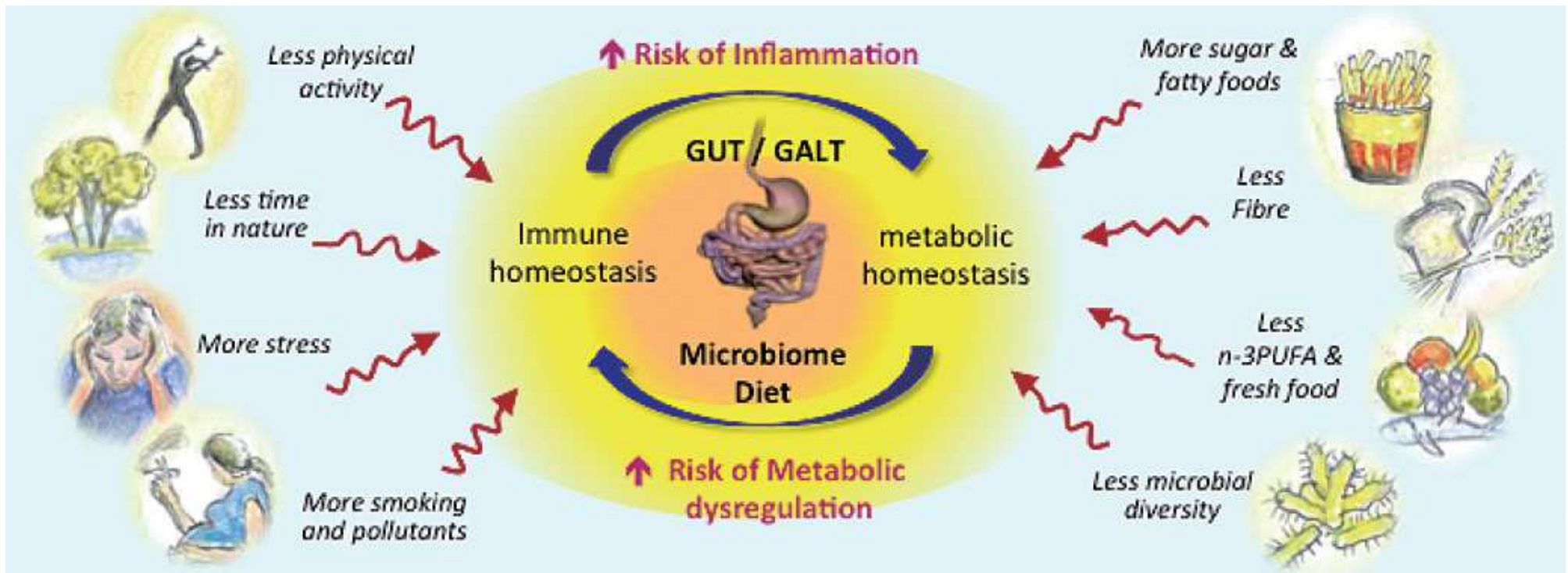
Table 3 Effects of probiotics in children

Condition	Effect of probiotics as a group	Examples of probiotics with documented or promising efficacy
Acute gastroenteritis (treatment)	Approximately 1-day reduction in the duration of diarrhoea	ESPGHAN Strong recommendation ▶ <i>Lactobacillus</i> GG ▶ <i>S. boulardii</i> Weak recommendation ▶ <i>L. reuteri</i> DSM 17938 ▶ <i>Lactobacillus</i> GG ▶ <i>S. boulardii</i> ▶ <i>Lactobacillus</i> GG
Antibiotic-associated diarrhoea (prevention)	Reduced risk	Promising ▶ <i>Lactobacillus</i> GG ▶ <i>L. reuteri</i> DSM 17938
Nosocomial diarrhoea (prevention)	Reduced risk	
Infections in children attending day care centres (prevention)	Reduced risk	
Allergy (prevention)	Reduced risk of eczema	WAO suggests the use of probiotics in select high-risk populations to reduce the risk of eczema; however, there is no clear indication regarding which probiotic(s) to use
NEC (prevention)	Reduced risk of NEC and mortality in infants who were born <1500 g	No clear indications from scientific societies regarding which probiotic strain(s) should be recommended
<i>H. pylori</i> infection	Reduced risk of side effects and increased eradication rate	No clear indications which strain(s) to use Promising ▶ <i>S. boulardii</i>
Infantile colic (management)	Reduced crying time	▶ <i>L. reuteri</i> DSM 17938 (documented in breastfed infants)
Abdominal pain- related functional gastrointestinal disorders	Certain probiotics reduced intensity of pain (especially in patients with irritable bowel syndrome)	More studies are needed to identify beneficial strains. Promising ▶ <i>Lactobacillus</i> GG ▶ VSL#3
Induction of remission in ulcerative colitis	Limited evidence suggests that probiotics added to standard therapy may provide modest benefits	ESPGHAN/ECCO ▶ <i>E. coli</i> Nissle 1917 ▶ VSL#3
Induction of remission in Crohn's disease	Insufficient evidence	ECCO/ESPGHAN: not recommended
Functional constipation	Until more data are available, the use of probiotics should be considered investigational	ESPGHAN/NASPGHAN: not recommended

Primary prevention of allergy - Will it soon become a reality? Van Bever PAI 2016, 27:6



Many life style risk factors for NCDs have both immune and metabolic effects.



These are also the logical targets to prevention inflammation and metabolic dysregulation.

Prescott S, Allergol Int. 2014;63(1):11-20