



Fondazione IRCCS Ca' Granda  
Ospedale Maggiore Policlinico  
Università degli Studi di Milano



## Il neonato a termine: latte materno e quale altro latte?

Lorella Gianni

U.O.C. di Neonatologia e  
Terapia Intensiva Neonatale  
Direttore: Prof. Fabio Mosca



## Bioactive Functions of Milk Proteins: a Comparative Genomics Approach



Lactation provides the essential nutrients required by the smallest and most altricial neonate to the largest and most precocial offspring [13] (Fig. 1). The ability to provide easily digestible, balanced nutritional components supported evolution of different developmental and reproductive strategies [13]. In the ancestral history of mammalian evolution, milk has evolved not only for nutritional value but also the earliest mechanism through which mothers signal biochemically to their offspring by providing factors in milk that play a significant part in improving health of the young [17–21].

*per la mamma*



Diabete mellito di tipo 2  
(maggior durata di  
allattamento -32%)



Depressione post  
partum

Diminuzione del rischio  
dose dipendente

Tumore al seno  
(Per ogni aumento di 12 mesi nella durata  
cumulativa di allattamento  
sii ha una riduzione del rischio del 4.3%)

Tumore ovarico  
(una maggior durata di  
allattamento si associa a una  
riduzione del rischio del 30%)

*per il bambino*



Obesità  
(-13%)



### Diminuzione del rischio dose dipendente



Diabete tipo II  
(-35%)

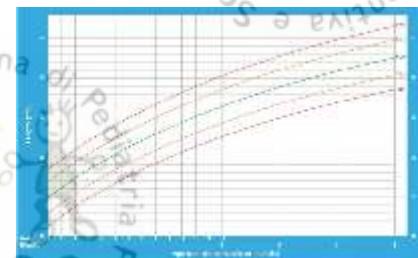
- Patologie infettive (diarrea, infezioni respiratorie, otite)
- Mortalità e ospedalizzazione secondaria a patologie infettive
- SIDS (-36%)
- Leucemia (-19%)

Promozione sviluppo cognitivo





Macro e micronutrienti  
molecole di segnale



Pattern di crescita e  
composizione  
corporea

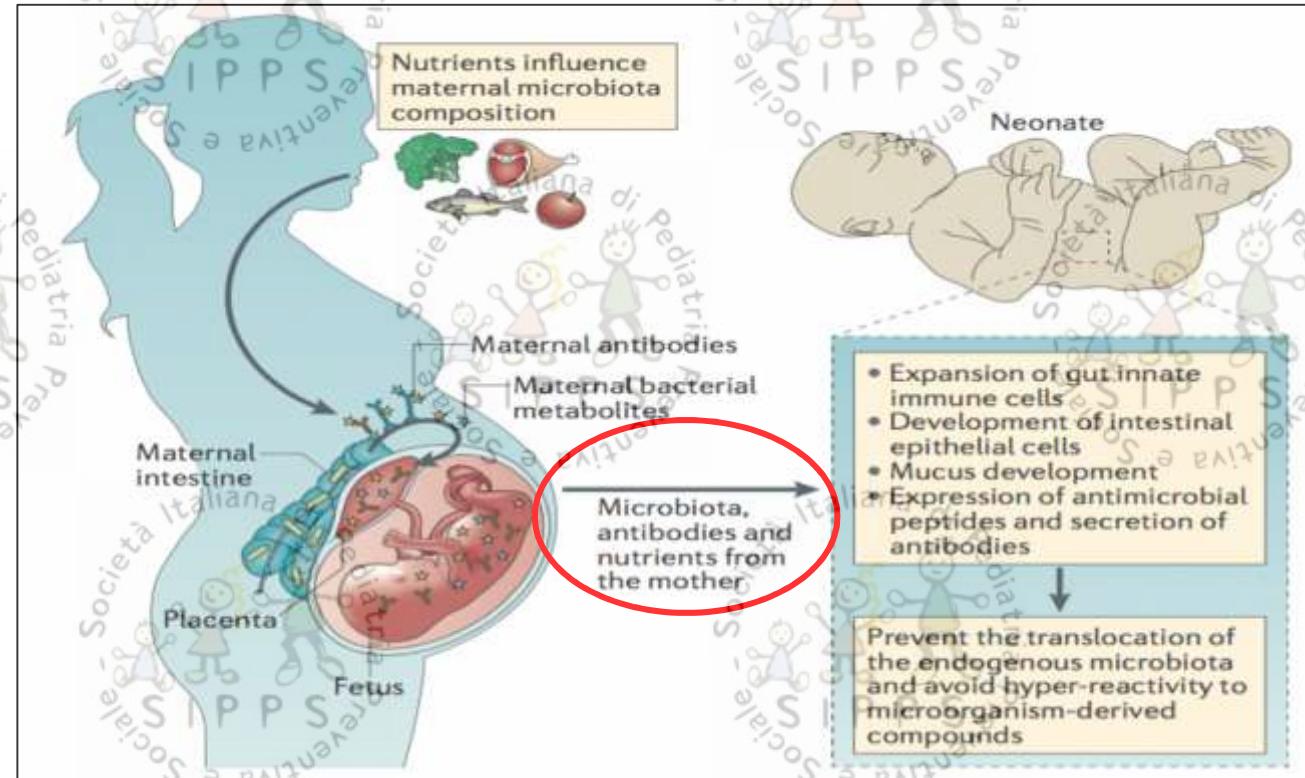
Quali sono i potenziali meccanismi  
attraverso cui il latte materno promuove lo  
stato di salute dell'individuo?

Modulazione del sistema  
immune e dello sviluppo del  
microbiota intestinale



# Il microbiota materno “allena” il sistema immunitario feto-neonatale alla tolleranza dei microorganismi commensali

MacPherson AJ, Nat Rev Immunol 2017



È dimostrato il passaggio transplacentare diretto di microorganismi vivi

Placenta as a sterile environment?  
Not so much!

Limitazione alla traslocazione e alla reattività immunologica verso antigeni del microbiota materno

## Human milk is a putative innate immune system

### Mother's Milk: A Purposeful Contribution to the Development of the Infant Microbiota and Immunity

Kathy L. Doherty<sup>1,2</sup>, Beth Hollander<sup>3</sup>, Anna Bassani<sup>4</sup> and Pia S. Forman<sup>5,6</sup>

<sup>1,2</sup>Centre for Immunobiology and Infection, Imperial College London, London, United Kingdom; <sup>3</sup>Microbiology Research Group, Imperial College London, United Kingdom; <sup>4</sup>Medical Research Institute, University of Lorraine, Nancy, France; <sup>5</sup>Department of Pediatrics, Division of Infectious Diseases, University of Southern California, Los Angeles, CA, United States; <sup>6</sup>Department of Pediatrics and Adolescent Medicine, and Immunology, University of Southern California, Los Angeles, CA, United States

Breastfeeding confers protection against respiratory and gastrointestinal infections and is associated with a reduced risk of inflammatory diseases such as asthma, atopy, diabetes, obesity, and inflammatory bowel disease (1–7). Prolonged and exclusively breastfed infants have improved cognitive development (8, 9). Human milk continues the transfer of immunity from mother to child that started *in utero*, providing a nurturing environment that protects against infection and develops the infant intestinal mucosa, microbiota, and their own immunologic defenses. Breast milk is a specialized secretion in which immune response is highly targeted against microorganisms in the mother's gut and airway, providing an important defense against the same pathogens likely encountered by her infant (10). More recent studies suggest that breast milk not only provides passive protection

Il latte materno contribuisce a completare l'imprinting iniziato dalla mamma in gravidanza!

## Factors Affecting Gastrointestinal Microbiome Development in Neonates

Clara Yieh Lin Chong<sup>1</sup>, Frank H. Bloomfield<sup>1,2,3</sup> and Justin M. O'Sullivan<sup>1,\*</sup>

<sup>1</sup> Liggins Institute, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand; clara.chong@auckland.ac.nz (C.Y.L.C.); f.bloomfield@auckland.ac.nz (F.H.B.)

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Received: 13 February 2018; Accepted: 21 February 2018; Published: 28 February 2018

Ingredients in breast milk  
can help to establish a  
healthy community of  
microorganisms in the infant  
gut!

Nature 2018

## Breastfeeding and microbiota

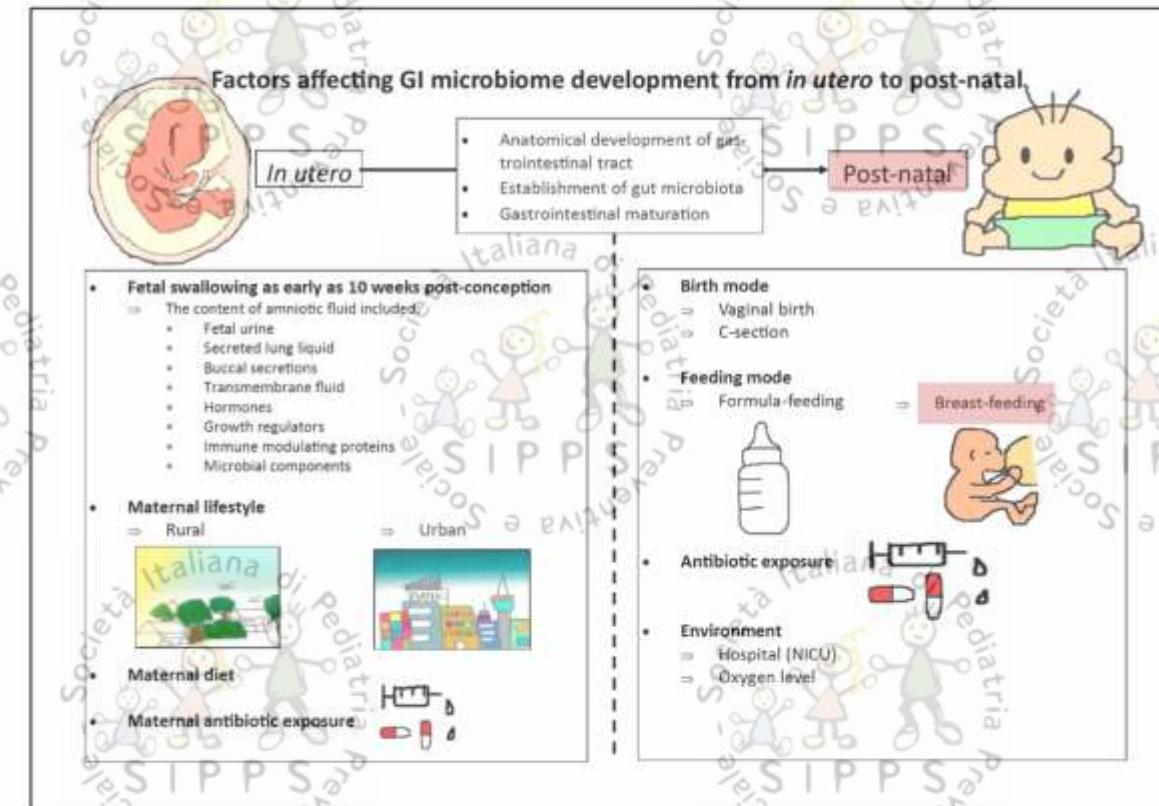


Figure 1. Factors from *in utero* to post-natal life that have been shown to affect the establishment of the gastrointestinal (GI) microbiome.

## ARTICLE

DOI: 10.1038/s41467-018-05472

OPEN

## Meta-analysis of effects of exclusive breastfeeding on infant gut microbiota across populations

Nhan T. Hu<sup>1</sup>, Fan Li<sup>2</sup>, Kathleen A. Lao-Sarwar<sup>3,4</sup>, Hsin M. Tu<sup>5,6</sup>, Bryan P. Brown<sup>7,8,9</sup>, Pa S. Fannaraj<sup>2</sup>, Jeffrey M. Bender<sup>9</sup>, Maghan B. Azad<sup>10</sup>, Amanda L. Thompson<sup>11</sup>, Scott T. Wass<sup>12</sup>, M. Andrea Accarino-Perrin<sup>13,14</sup>, Augusto A. Istrail<sup>14</sup>, Anita I. Kozyrskyj<sup>4</sup>, Heather R. Isipan<sup>15,16</sup>, Grace M. Aldrovandi<sup>2</sup> & Louise Kuhn<sup>1</sup>

**b**

Study	DD	SE
Subramanian et al., 2014 (Bangladesh)	0.26	0.0718
Azad et al., 2015 (Canada)	0.33	0.1583
Bender et al., 2016 (Haiti)	-0.11	0.3474
Wood et al., 2018 (South Africa)	0.31	0.2235
Pannaraj et al., 2017 (USA(GA/FL))	0.37	0.1492
Sordillo et al., 2017 (USA(CA/MA/MO))	0.77	0.1971
Thompson et al., 2015 (USA(NC))	0.30	0.4239

Fixed effect model

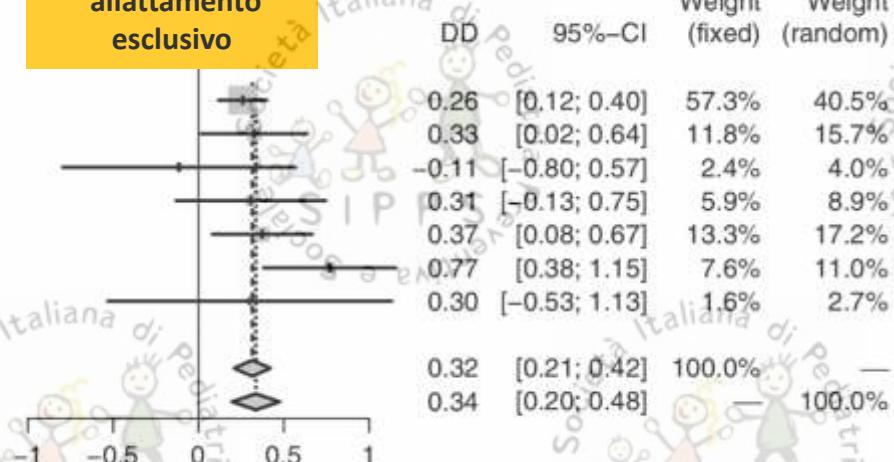
Random effects model

Heterogeneity:  $I^2 = 21\%$ ,  $\tau^2 = 0.0074$ ,  $p = 0.27$ 

1825 stool samples with 684 infants

## Increased bacterial diversity in non exclusively breast fed infants

Allattamento non  
esclusivo  
vs  
allattamento  
esclusivo

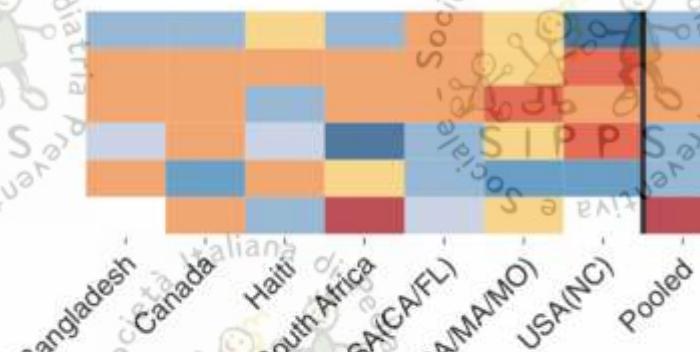


ARTICOLO

OPEN

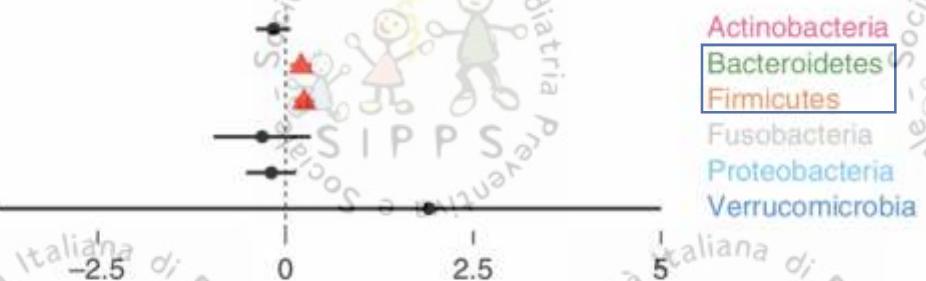
## Meta-analysis of effects of exclusive breastfeeding on infant gut microbiota across populations

Han T,<sup>1</sup> Li F,<sup>1</sup> Kathleen A. Lee-Sherer,<sup>1,2</sup> Hein M, Tun,<sup>3</sup> Bryan P, Brown,<sup>4</sup> K. S, Pis S, Parvarej,<sup>5</sup> Nitro, M, Benders,<sup>6</sup> Meghan B, Azad,<sup>10</sup> Amanda L, Thompson,<sup>7</sup> Scott T, Weiss,<sup>8</sup> M, Andrea Avramovic-Panić,<sup>12</sup> Augusto A, Litorjau,<sup>13</sup> Anita L, Kozyrskyj,<sup>9</sup> Heather B, Jaspar,<sup>10</sup> Grace M, Alcock,<sup>11</sup> & Louise Kamm,<sup>1</sup>



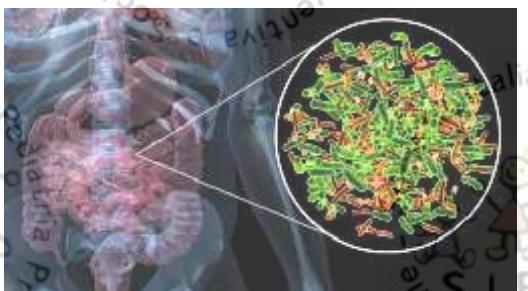
## Altered microbioma in non exclusively breast fed infants

Allattamento non esclusivo  
vs  
allattamento esclusivo





## Perché è importante la modulazione dello sviluppo del microbiota?





## Can Postbiotics Represent a New Strategy for NEC?

Fabio Mosca, Maria Lorella Gianni, and Maria Rescigno



**Table 1** Main functions associated with gut microbiota

### Modulation of gene expression

Development of mucus and barrier function

Immune function development

Metabolism

Microbial production of nutrients (i.e., vitamins, amino acids, short-chain fatty acids)

Modulation of neural signaling (gut-brain axis)

Modulation of immune response locally and outside the local environment (i.e., gut-lung axis)

Digestion of complex macromolecules

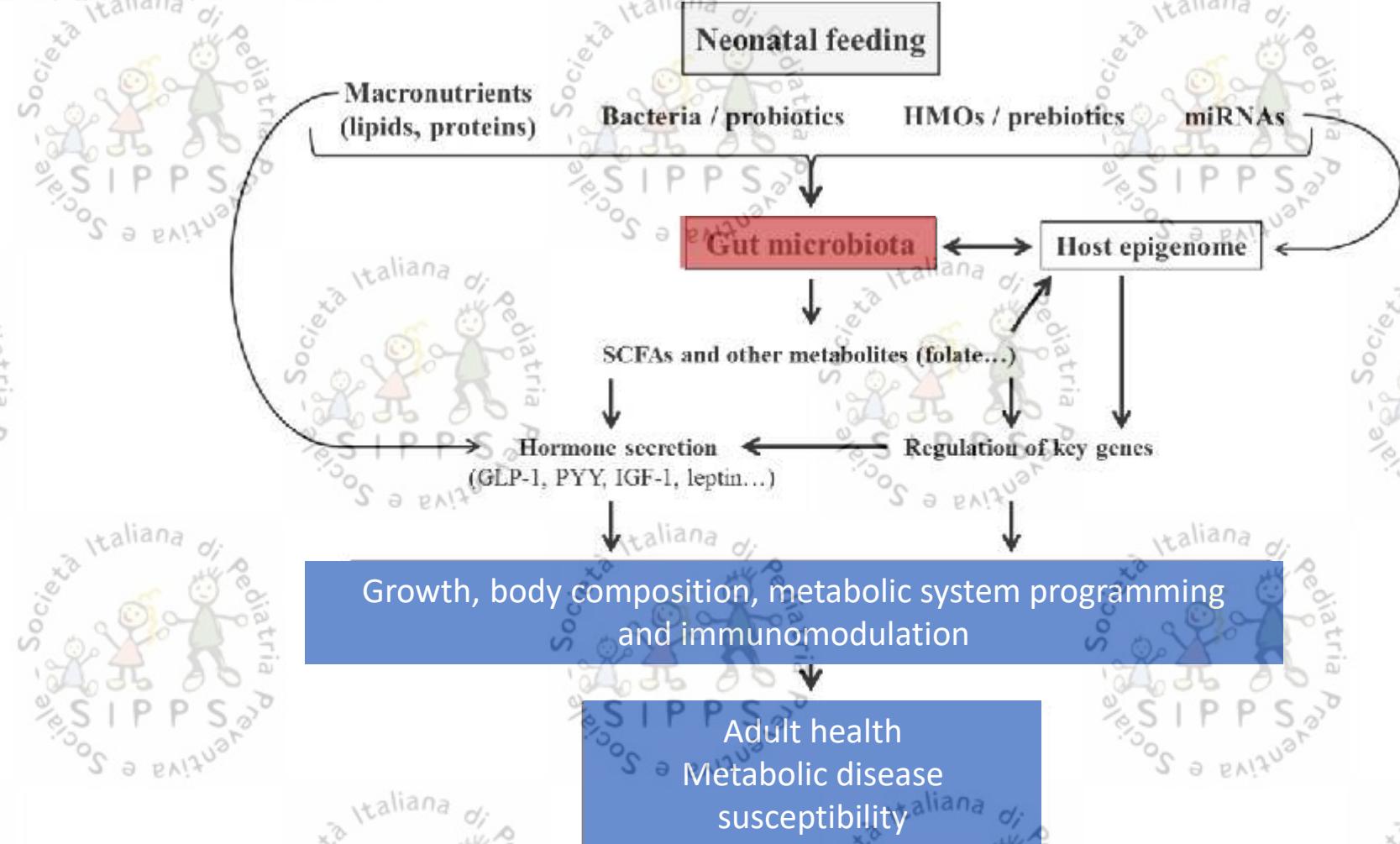
## Effects of infant formula composition on long-term metabolic health

Marion Lemare, Isabelle Le Huérou-Luron, Sophie Blat

### To cite this version:

Marion Lemare, Isabelle Le Huérou-Luron, Sophie Blat. Effects of infant formula composition on long-term metabolic health. *Journal of Developmental Origins of Health and Disease*, Cambridge University Press, 2018, 9 (3), 459-473-589. 10.1017/S204074417000931. hal-01723901

## Effects on composition on gut microbiota: a possible mechanistic link?

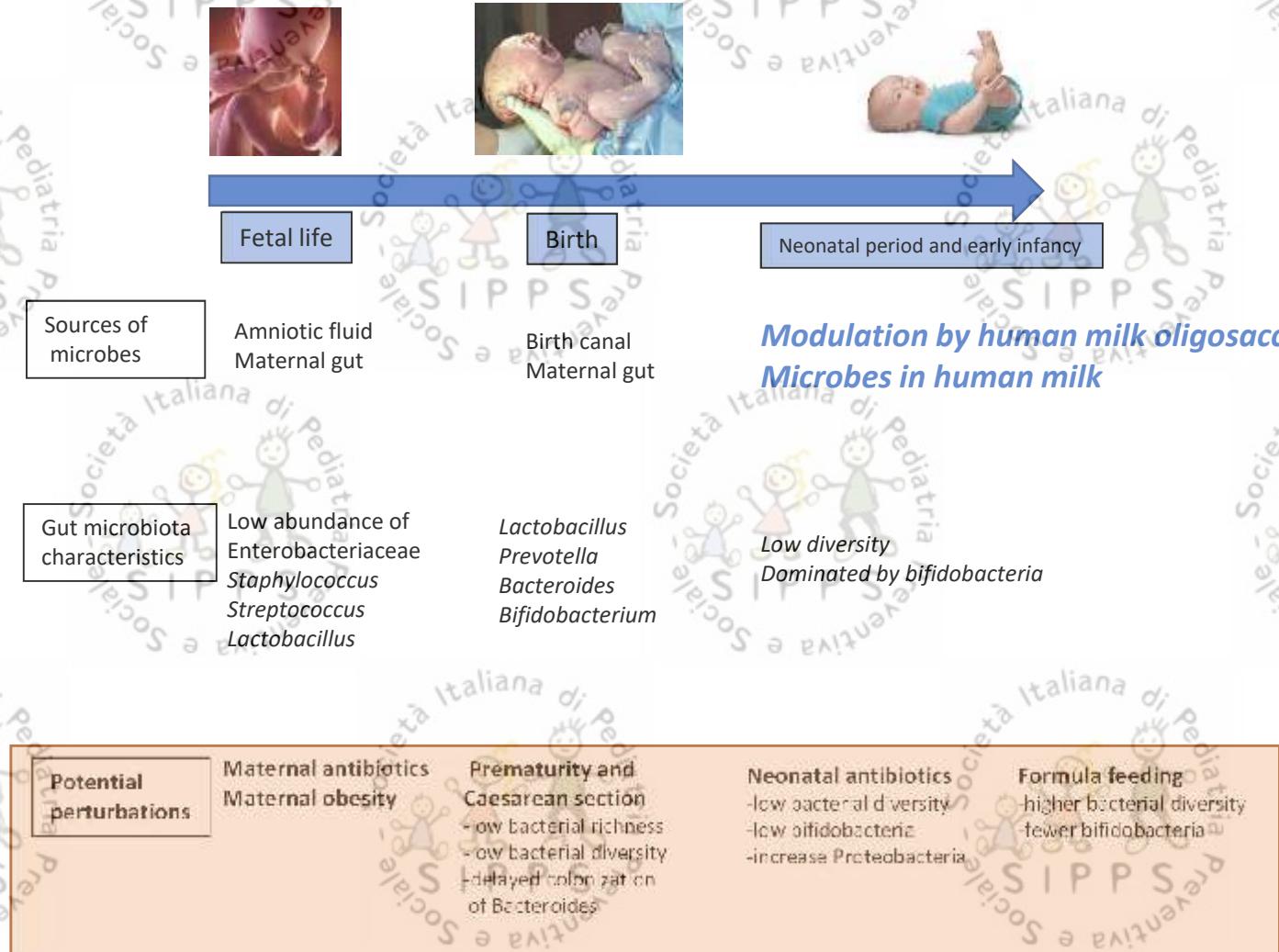


**Fig. 2. Long-term metabolic health: the potential pathways involving gut microbiota**

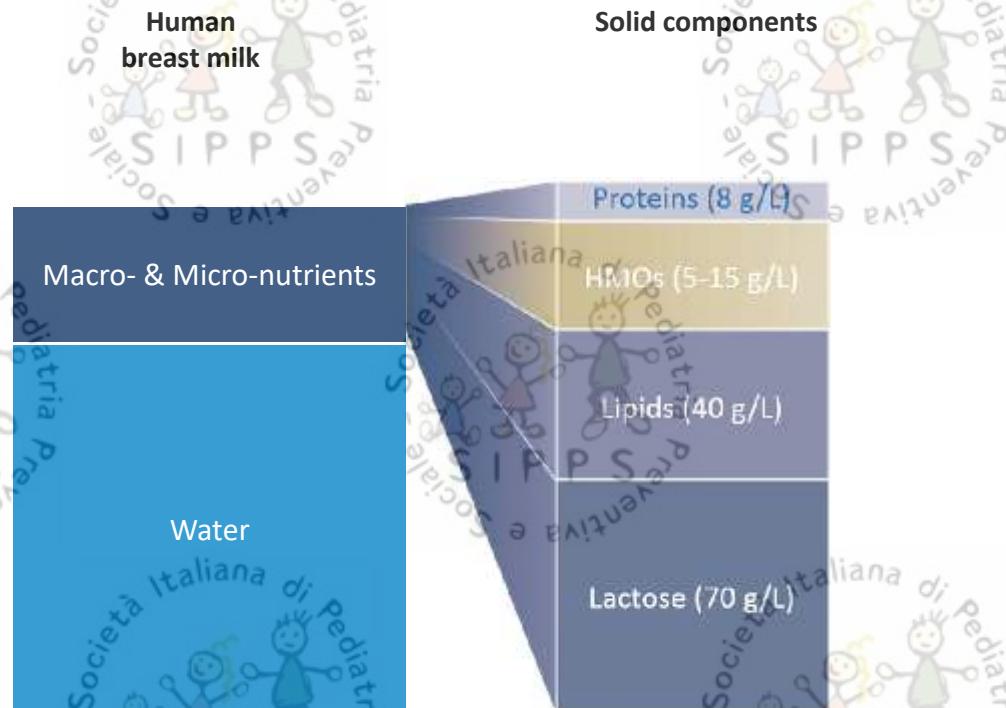
HMOs, human milk oligosaccharides; miRNAs, non-coding microRNAs; SCFAs, short-chain fatty acids; GLP-1, glucagon-like peptide-1; PYY, peptide YY; IGF-1, insulin-like growth factor-1

Modified

# G E N E T I C S



## OLIGOSACCARIDI



Zivkovic A et al. PNAS 2010;108 (Suppl 1):4653; Austin et al. Nutrients 2016;8:pii: E346;  
Sprenger et al. PlosONE 2017;12:e0171814; Kunz et al. JPGN 2017;64:789

➤ Gli oligosaccaridi sono la terza componente più abbondante del latte materno e sono caratterizzati da una elevata complessità strutturale (5-15 g/L)

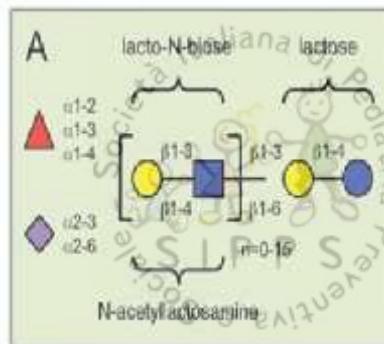
(Newburg et al. 1986; Kunz et al. 2000)

➤ La loro produzione richiede il 10% dell'energia richiesta alla mamma per produrre il latte

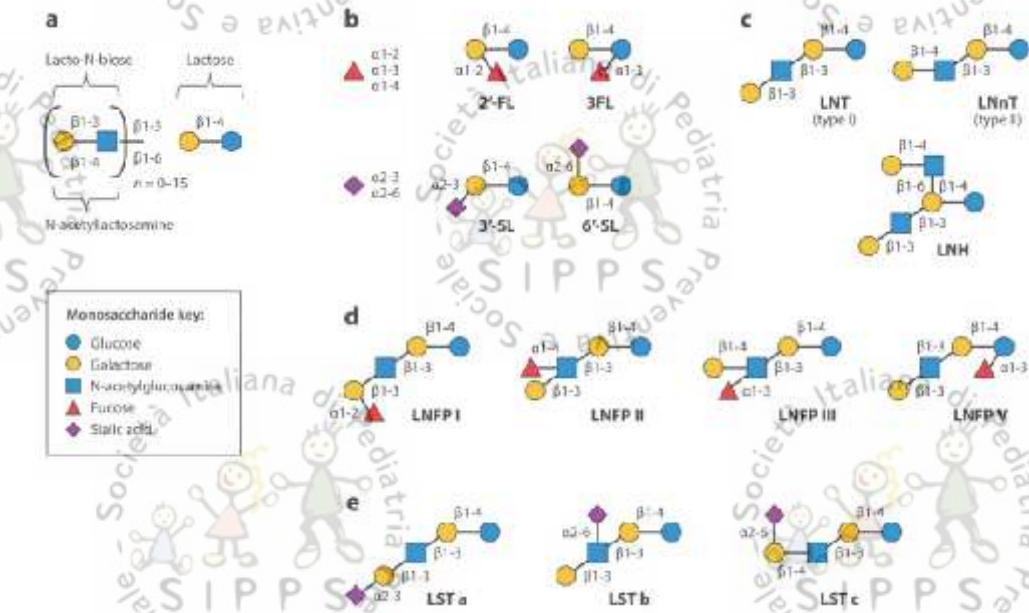
➤ Sono state identificate circa 200 strutture differenti

➤ Le implicazioni funzionali relative alla diversità strutturale degli oligosaccaridi rappresentano una importante area di ricerca

## 5 monosaccardi sono i “building blocks” degli HMOs



**Different building blocks and linkages lead to different HMOs**



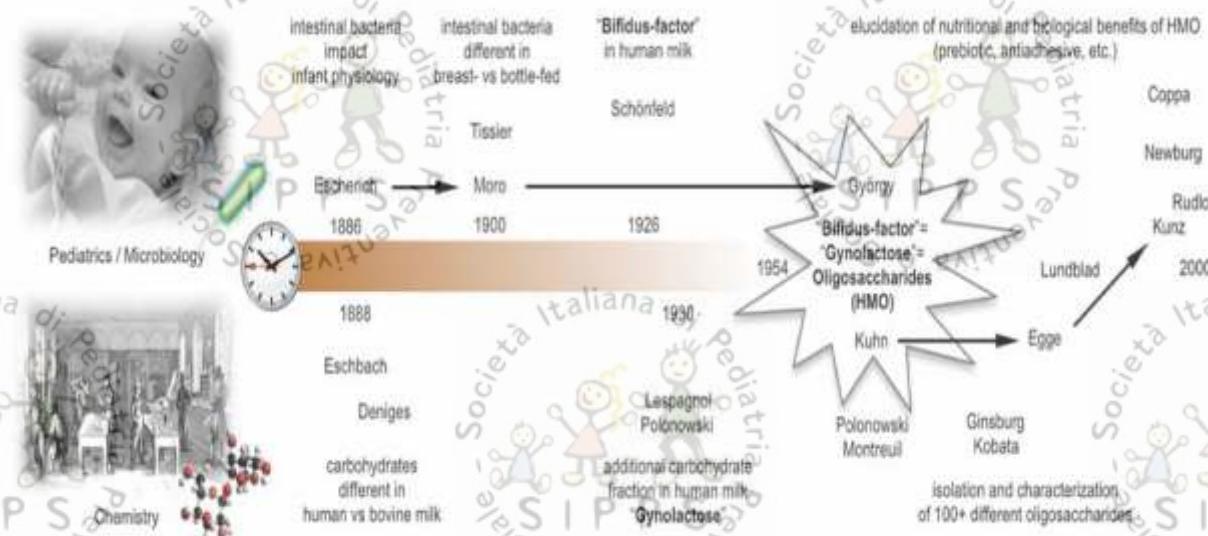
Glycobiology vol. 22 no. 9 pp. 1147-1162, 2012  
doi:10.1093/glycob/cws074  
Advance Access publication on April 18, 2012

REVIEW

## Human milk oligosaccharides: Every baby needs a sugar mama

Lars Bode

### OLIGOSACCARIDI: metabolismo e funzioni

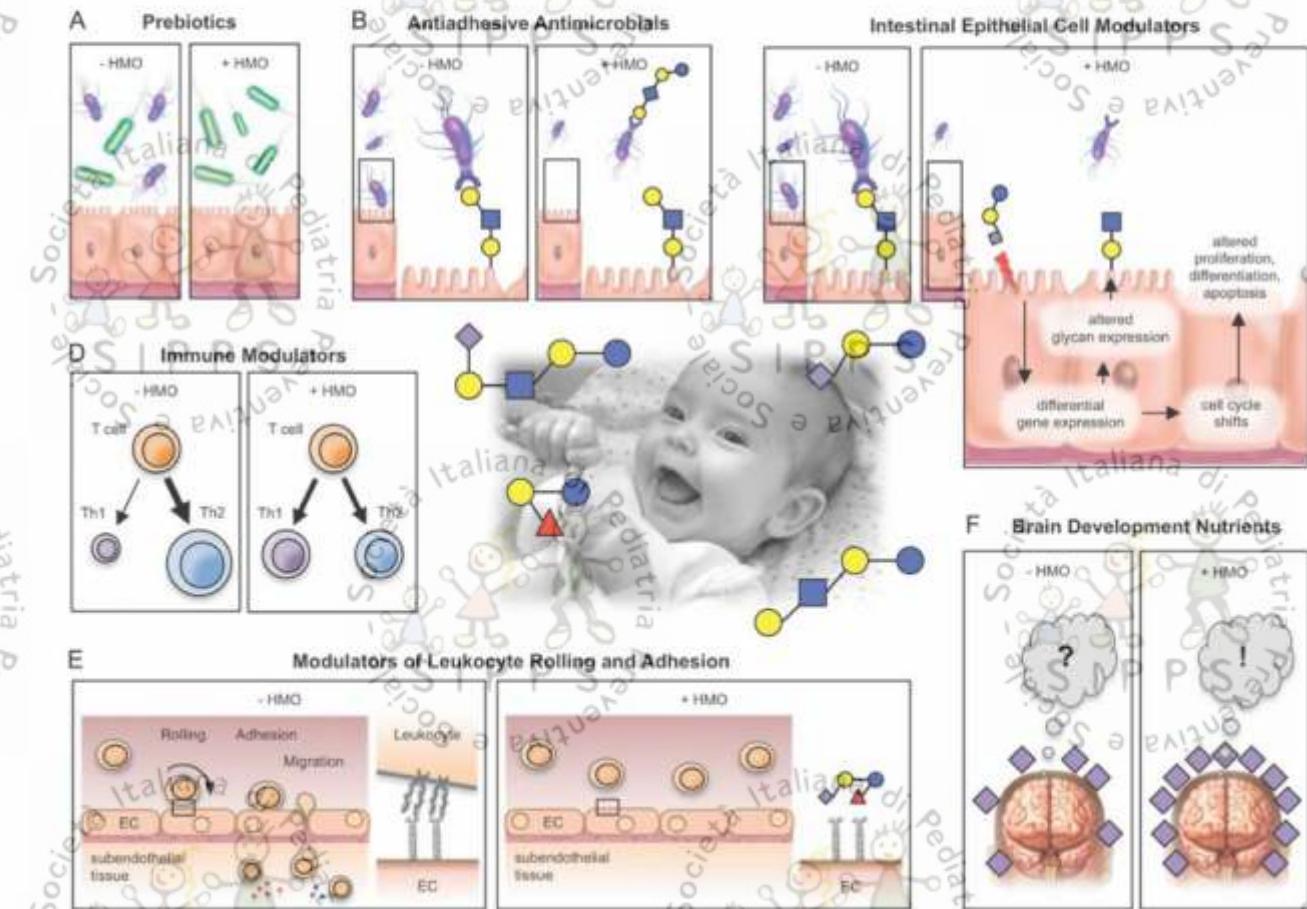


REVIEW

# Human milk oligosaccharides: Every baby needs a sugar mama

Lars Bode

## OLIGOSACCARIDI: metabolismo e funzioni





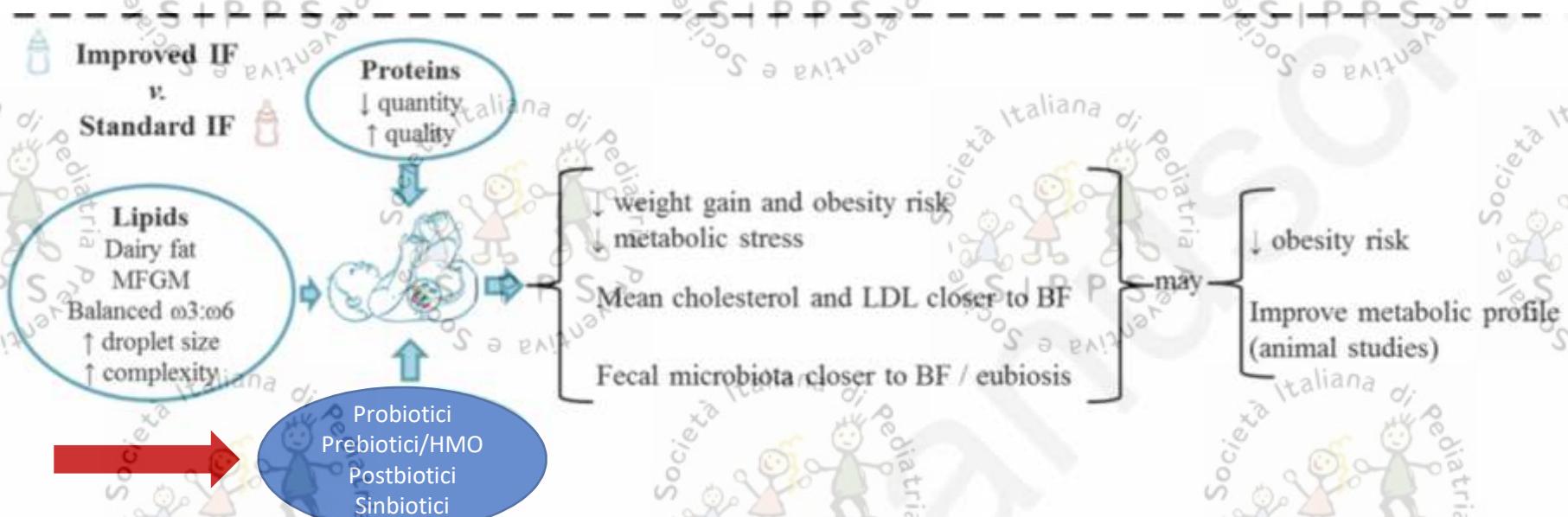
Come possiamo utilizzare le evidenze scientifiche oggi disponibili per migliorare gli effetti funzionali dei latte di formula in mancanza del latte materno?

# Effects of infant formula composition on long-term metabolic health

Marion Lemaire, Isabelle Le Huérou-Luron, Sophie Blat

## To cite this version:

Marion Lemaire, Isabelle Le Huérou-Luron, Sophie Blat. Effects of infant formula composition on long-term metabolic health. *Journal of Developmental Origins of Health and Disease*, Cambridge University Press, 2018, 9 (6), pp.573-589. <https://doi.org/10.1017/S2040174417000964>. hal-01723931



**Fig. 1. Short- and plausible long-term effects of neonatal feeding**

IF, infant formula; v., versus; FA, fatty acid; HMOs, human milk oligosaccharides; IGF-1, insulin-like growth factor-1; IR, insulin resistance; TG, triglycerides; TD2, type-2 diabetes; CHD, coronary heart disease; MFGM, milk fat globule membrane; LDL, low density lipoprotein; BF, breastfed infants

Modified

## Production of HMOs using microbial hosts – from cell engineering to large scale production

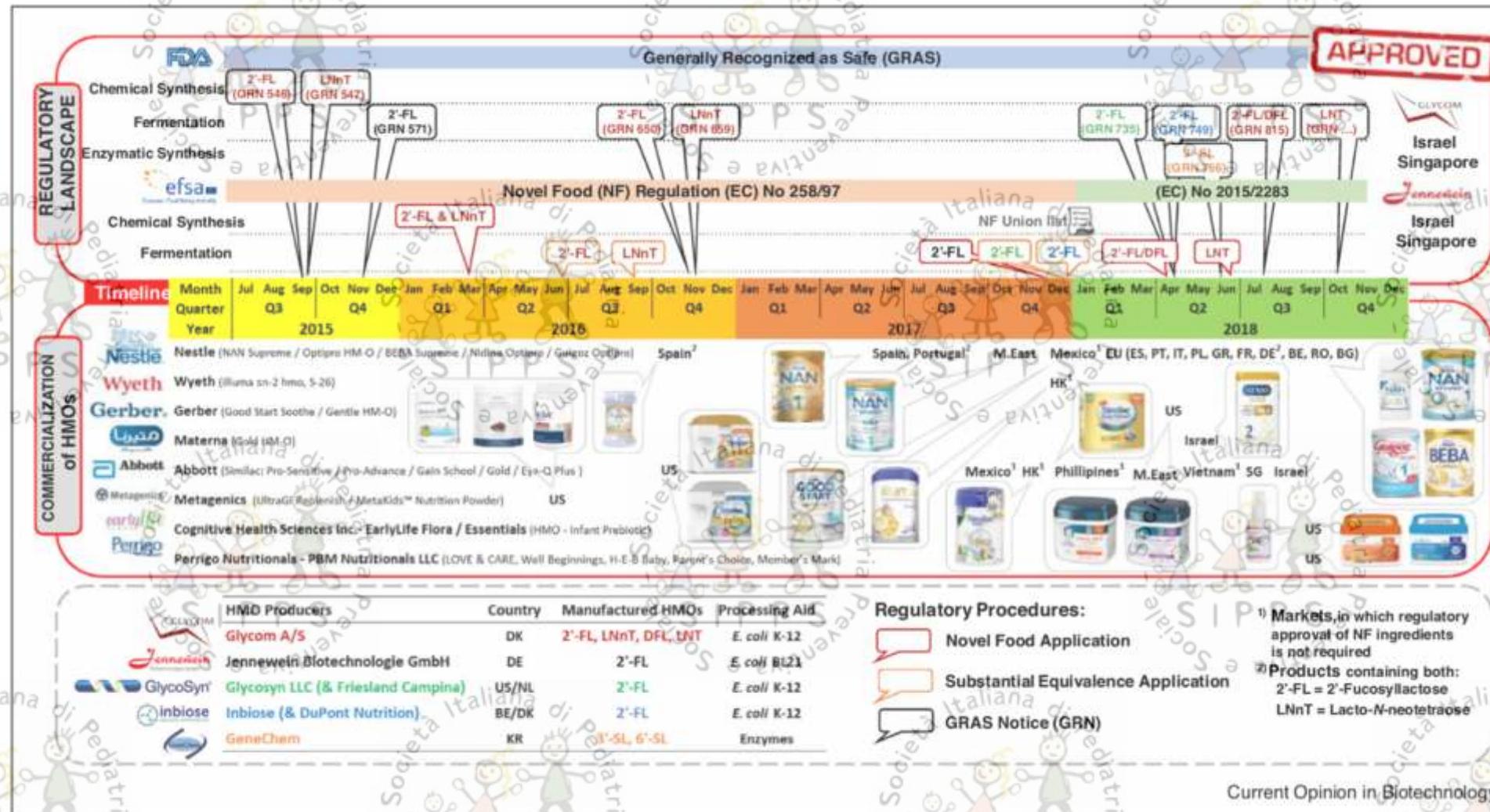
Katrine Bych<sup>1</sup>, Marta Hanna Mikš<sup>1,2</sup>, Ted Johanson<sup>1</sup>,  
Markus Jondelius Hederos<sup>1</sup>, Louise Kristine Vignæs<sup>1</sup> and  
Peter Becker<sup>1</sup>

**Current Opinion in Biotechnology 2019, 56C:130–137**

This review comes from a themed issue on **Food biotechnology**

Edited by Rute Neves and Herwig Bachmann

## Shift alla biotecnologia





Quali possono essere le implicazioni terapeutiche  
della supplementazione con HMO strutturalmente  
identici a quelli presenti nel latte materno?

**Similar to Those Who Are Breastfed, Infants Fed a Formula Containing 2'-Fucosyllactose Have Lower Inflammatory Cytokines in a Randomized Controlled Trial<sup>1-4</sup>**

Karen C Coohran,<sup>5</sup> Barbara J Marinaz,<sup>6</sup> Jeffery S Oliver,<sup>7</sup> Julie A Wilder,<sup>7</sup> Edwina G Barron,<sup>7</sup> and Richard H Buck,<sup>8</sup>

<sup>5</sup> Research Diet sponsor and <sup>6</sup> Department of Anthropology, University of Colorado, CO; and <sup>7</sup> Cytelis Biopharmaceuticals, Inc., Albuquerque, NM.

RCT

(307 alimentati con formula; 107 allattati al seno)

**TABLE 1.** Energy, macronutrient, GOS, and 2'FL concentrations in the control and EFs

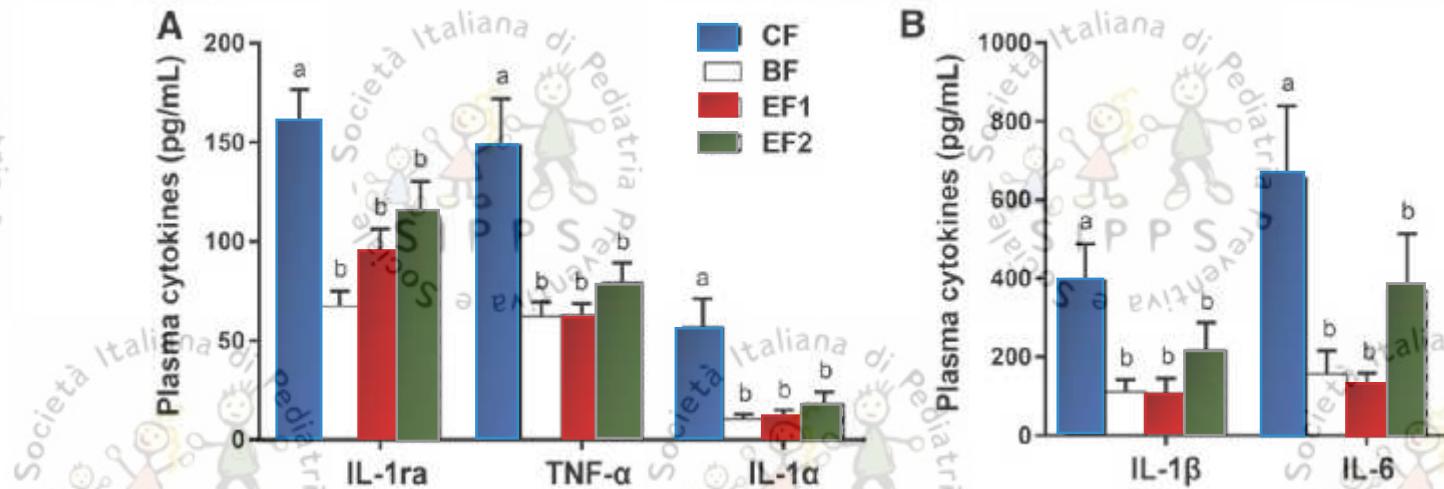
Ingredient	CF	EF 1	EF 2
Energy, kcal/dL	64.3	64.3	64.3
Protein	13.3	13.3	13.3
Fat	34.7	34.7	34.7
Total carbohydrate	69.0	69.0	69.0
GOS	2.4	2.2	1.4
2'FL	—	0.2	1.0

All values are expressed as g/L unless otherwise indicated. 2'FL = 2'-fucosyllactose; CF = control formula; EF = experimental formula; GOS = galactooligosaccharides.

## Similar to Those Who Are Breastfed, Infants Fed a Formula Containing 2'-Fucosyllactose Have Lower Inflammatory Cytokines in a Randomized Controlled Trial<sup>1–4</sup>

Karen C Goehring,<sup>1</sup> Barbara J Marangi,<sup>1</sup> Jeffrey S Olson,<sup>1</sup> Julie A Wilder,<sup>1</sup> Edward G Barrett,<sup>2</sup> and Rachael H Buck,<sup>3\*</sup>

<sup>1</sup>Research and Development and Regulatory Affairs, Mead Johnson Nutrition, Indianapolis, and <sup>2</sup>Exercise Response Research Institute, Albuquerque, NM

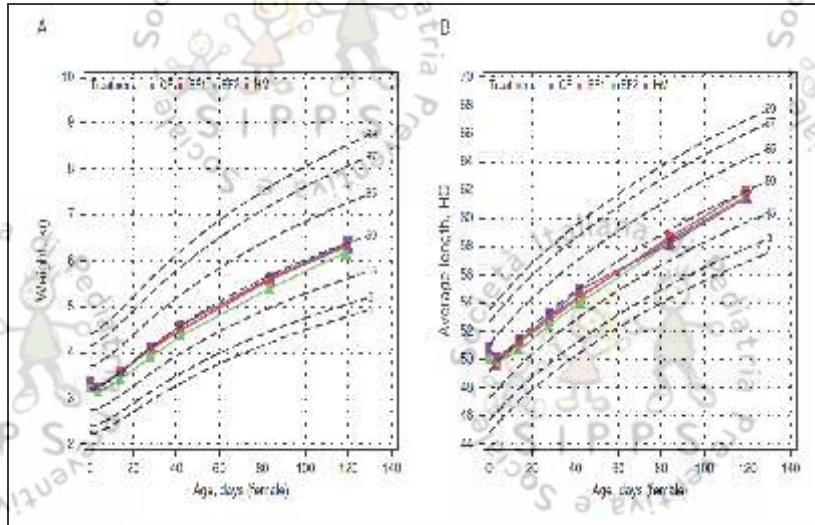


I lattanti alimentati con formule supplementate con 2'FL producevano quantità di citochine simili agli allattati al seno e significativamente inferiori a quelle prodotte dai lattanti alimentati con formula di controllo

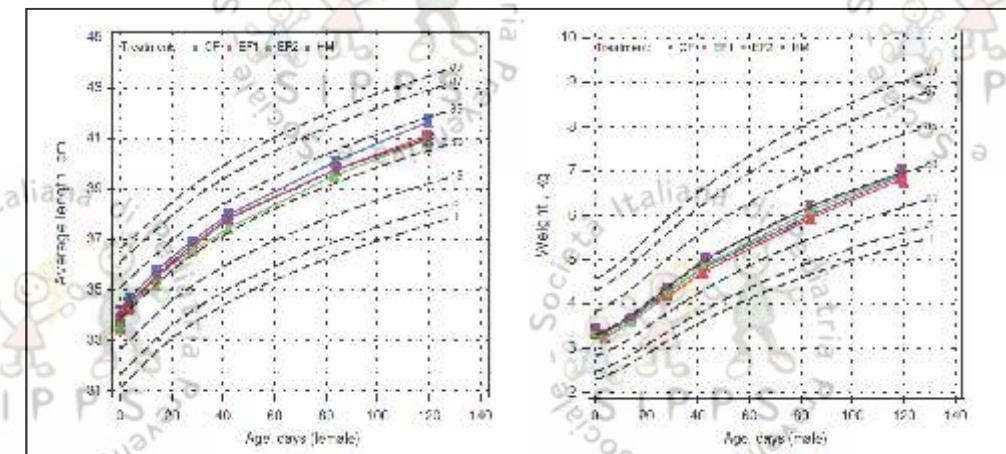
## Infants Fed a Lower Calorie Formula With 2'FL Show Growth and 2'FL Uptake Like Breast-Fed Infants

Sophora J. Marriage, Richard H. Buck, Karen C. Gashring, Jeffrey S. Oliver, and Jennifer A. Williams

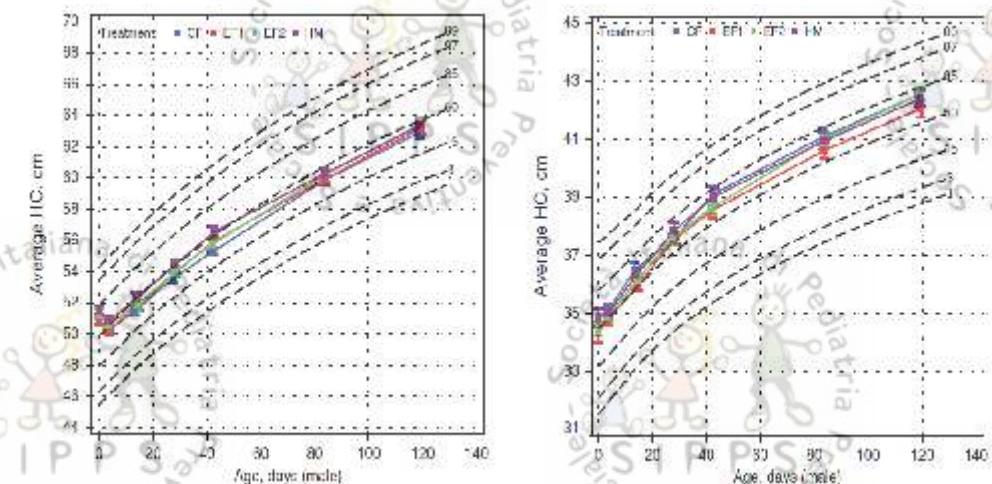
Weight



Length



Head circumference



**Non vi sono differenze significative nella crescita per quanto riguarda i parametri antropometrici durante la durata dello studio**

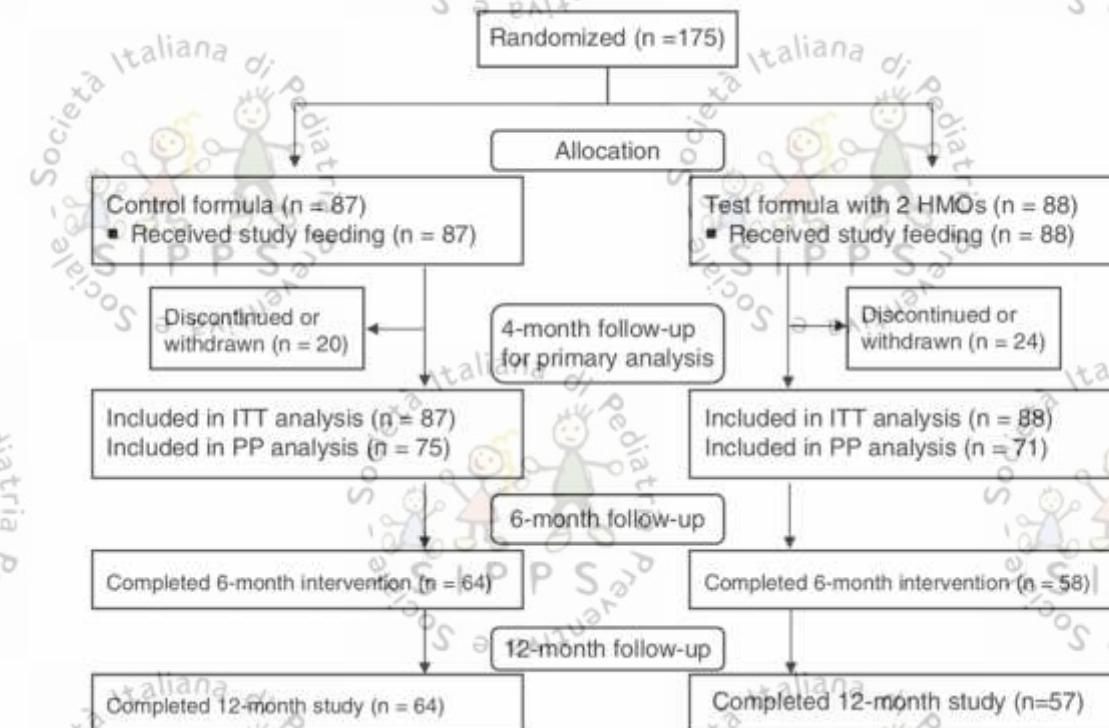
OPEN

# Effects of Infant Formula With Human Milk Oligosaccharides on Growth and Morbidity: A Randomized Multicenter Trial

\*Giuseppe Puccio, <sup>†</sup>Philippe Alliet, <sup>\*</sup>Cinzia Cajozzo, <sup>‡</sup>Elke Janssens, <sup>\*</sup>Giovanni Corsetto,  
<sup>||</sup>Norbert Sprenger, <sup>§</sup>Susan Werummont, <sup>¶</sup>Delphine Egli, <sup>||</sup>Laura Gosoniu, and <sup>\*</sup>Philippe Steenhout

Proteine  
intere,  
formula di  
controllo

Stessa formula ma  
con 1.0 g/L 2'FL e  
0.5 g/L LNT

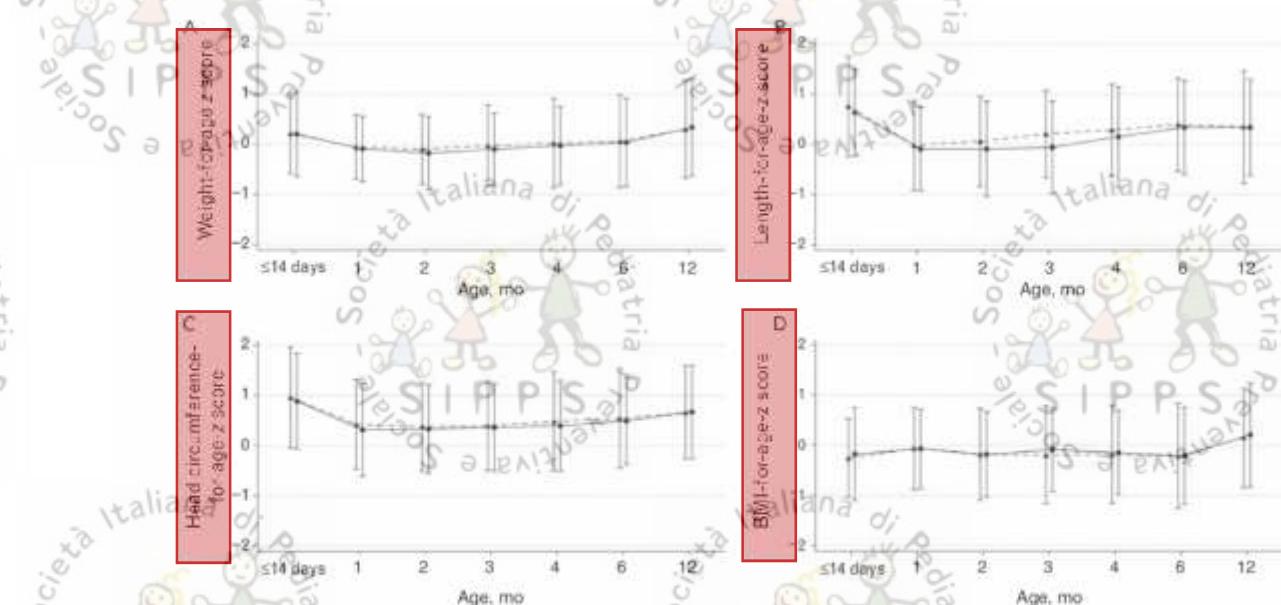


OPEN

## Effects of Infant Formula With Human Milk Oligosaccharides on Growth and Morbidity: A Randomized Multicenter Trial

<sup>1</sup>Giovanni Puccio, <sup>1</sup>Philippe Allot, <sup>1</sup>Cinzia Cofazzo, <sup>1</sup>Elke Janssens, <sup>1</sup>Giovanni Corsello,  
<sup>2</sup>Norbert Sprenger, <sup>3</sup>Susan Wermuth, <sup>4</sup>Delphine Eghi, <sup>5</sup>Laura Gerosa, and <sup>6</sup>Philippe Sicennecourt

(JPGN 2017;64: 624–631)



**FIGURE 2.** Anthropometric z scores for weight-for-age (A), length-for-age (B), head circumference-for-age (C) and BMI-for-age (D) from enrollment to 12 months of age based on the 2006 World Health Organization Child Growth Standards. Triangles/dashed line = control; Circles/solid line = test. BMI = body mass index.

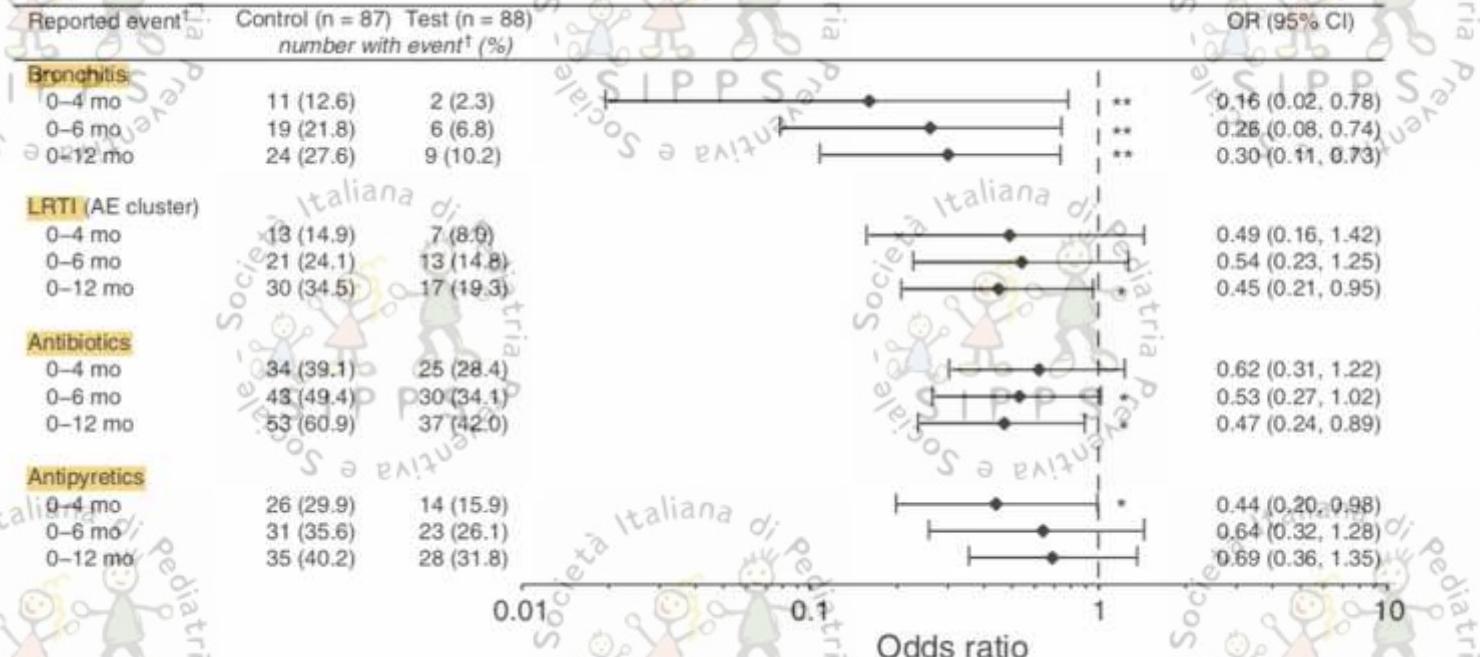
La crescita e la tolleranza gastroenterica è sovrapponibile in entrambi i gruppi durante tutto lo studio  
la formula supplementata appare sicura e ben tollerata

OPEN

# Effects of Infant Formula With Human Milk Oligosaccharides on Growth and Morbidity: A Randomized Multicenter Trial

Giuseppe Puccio,<sup>1</sup> Philippe Alliet,<sup>1</sup> Cinzia Cajozzo,<sup>2</sup> Elke Janssens,<sup>3</sup> Giovanni Corsello,<sup>4</sup> Norbert Sprenger,<sup>5</sup> Susan Wernimont,<sup>6</sup> Delphine Egli,<sup>7</sup> Laura Gosoniu,<sup>8</sup> and Philippe Steenhout<sup>9</sup>

(JPGN 2017;64: 624–631)



Riduzione del rischio di sviluppare bronchite, infezioni delle basse vie respiratorie nei primi due anni di vita, minor uso di antibiotici 0-12 mesi, minor uso di antipiretici 0-4 mesi nei soggetti che hanno assunto la formula supplementata

Review  
Human Milk Oligosaccharides: 2'-Fucosyllactose (2'-FL) and Lacto-N-Neotetraose (LNnT) in Infant Formula

Yvan Vandenplas<sup>1,2</sup>, Bernard Berger<sup>2</sup>, Virgilio Paolo Cannella<sup>3</sup>, Janusz Kielasyk<sup>4</sup>,  
Hanna Legatowska<sup>5</sup>, Manuel Sanchez-Tarazona<sup>6,7</sup>, Natasja Migacheva<sup>8</sup>, Jean-Marc Massolmann<sup>9</sup>,  
Jean-Charles Picard<sup>10</sup>, Mike Pozzani<sup>11</sup>, Atul Singhai<sup>11</sup> and Martin Wobitsch<sup>12</sup>

**Abstract:** The authors reviewed the published evidence on the presence of oligosaccharides in human milk (HMO) and their benefits in *in vitro* and *in vivo* studies. The still limited data of trials evaluating the effect of mainly 2'-fucosyllactose (2'-FL) on the addition of some of HMOs to infant formula were also reviewed. PubMed was searched from January 1990 to April 2018. The amount of HMOs in mother's milk is a dynamic process as it changes over time. Many factors, such as duration of lactation, environmental, and genetic factors, influence the amount of HMOs. HMOs may support immune function development and provide protection against infectious diseases directly through the interaction of the gut epithelial cells or indirectly through the modulation of the gut microbiota, including the stimulation of the bifidobacteria. The limited clinical data suggest that the addition of HMOs to infant formula seems to be safe and well tolerated, inducing a normal growth and suggesting a trend towards health benefits. HMOs are one of the major differences between cow's milk and human milk, and available evidence indicates that these components do have a health promoting benefit. The addition of one or two of these components to infant formula is safe, and brings infant formula closer to human milk. More prospective, randomized trials in infants are needed to evaluate the clinical benefit of supplementing infant formula with HMOs.

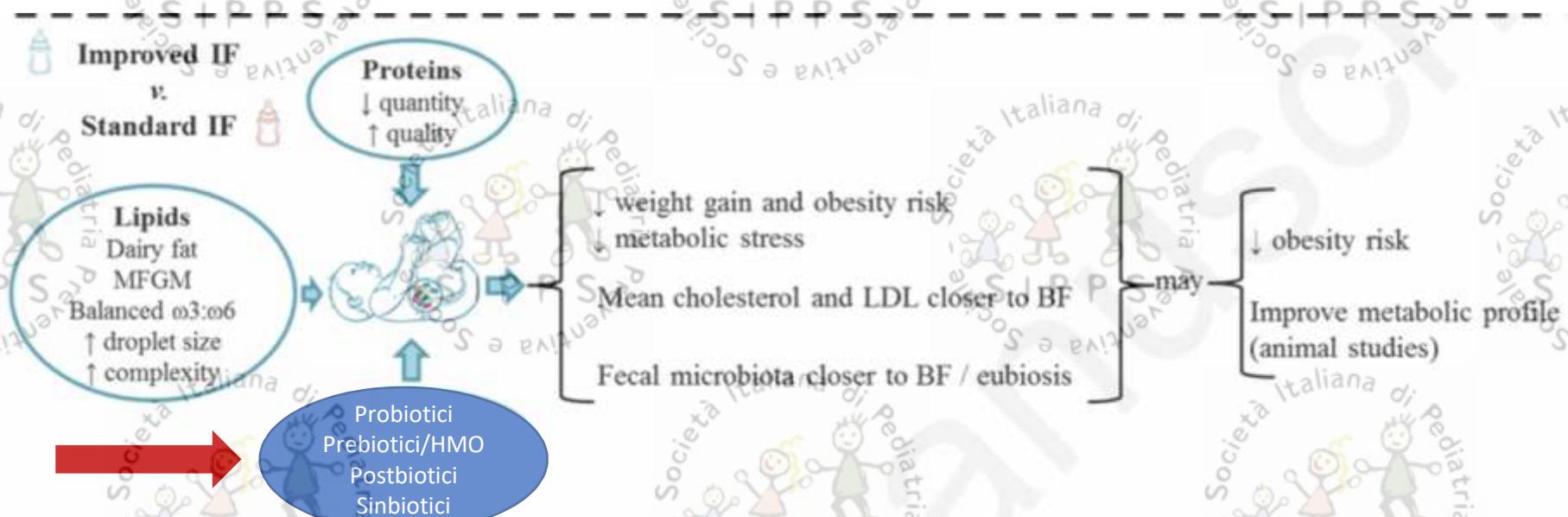
**Keywords:** breast feeding; formula feeding; human milk oligosaccharide; 2-fucosyllactose; Lacto-N-neotetraose; microbiota; bifidobacteria

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**Fig. 1. Short- and plausible long-term effects of neonatal feeding**

IF, infant formula; v., versus; FA, fatty acid; HMOs, human milk oligosaccharides; IGF-1, insulin-like growth factor-1; IR, insulin resistance; TG, triglycerides; TD2, type-2 diabetes; CHD, coronary heart disease; MFGM, milk fat globule membrane; LDL, low density lipoprotein; BF, breastfed infants

Modified

# Postbiotics: what else?

K. Tsilingiri and M. Rescigno

Istituto Europeo di Oncologia, Department of Experimental Oncology, via Adamello 16, 20139 Milan, Italy;  
katerina.tsilingiri@ieo.eu

Received: 3 August 2012 / Accepted: 12 October 2012

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## Abstract

The use of probiotics and synbiotics in the food industry or as food supplements for a balanced diet and improved gut homeostasis has been blooming for the past decade. As feedback from healthy consumers is rather enthusiastic, a lot of effort is currently directed in elucidating the mechanisms of interaction between beneficial microbes and barrier and immune function of the host. The use of probiotics or synbiotics for treating certain pathologies has also been examined, however, the outcome has not always been favourable. In most cases, the effect of the administered probiotic is evident when the bacteria are still alive at the time they reach the small and large intestine, suggesting that it is dependent on the metabolic activity of the bacteria. Indeed, in some occasions it has been shown that the culture supernatant of these bacteria mediates the immunomodulatory effect conferred to the host. Recent work on relevant probiotic strains has also led to the isolation and characterisation of certain probiotic-produced, soluble factors, here called postbiotics, which were sufficient to elicit the desired response. Here, we summarise these recent findings and propose the use of purified and well characterised postbiotic components as a safer alternative

el disease, where

many of the beneficial biological effects associated with the gut microbiota  
are driven by bacterial metabolic by-products

Aguilar-Toalá et al. 2018



## Can Postbiotics Represent a New Strategy for NEC?

Fabio Mosca, Maria Lorella Gianni, and Maria Rescigno

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2

3

Moreover, postbiotics offer a safety advantage over probiotics since they decrease the risk for microbial translocation and infection and prevent potential detrimental effects shown by probiotics within an already pro-inflammatory context (Tsilingiri et al. 2012). Other side effects reported in association with probiotic use are diffusion of antibiotic resistance gene and prevention of normal colonization of other microflora. Further, we do not know what will be in the long run the effect of early colonization with predominant strains of probiotics both on microbiota maturation and immune system development (Klaenhammer et al. 2012).

**Different set of postbiotics, characterized by specific biological activities, may be produced according to the type of probiotic strains employed and the fermentation process used (Tsilingiri and Rescigno 2013; Aguilar-Toaláa et al. 2018).**

**Postbiotics are mainly obtained from Lactobacillus and Bifidobacterium strains; however, some authors have investigated Streptococcus and Faecalibacterium species as a source of postbiotics (Tsilingiri and Rescigno 2013; Aguilar-Toaláa et al. 2018).**



## Can Postbiotics Represent a New Strategy for NEC?

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**Table 3** Main effects exerted by postbiotics

### Local effects on the gut epithelium

Immunomodulating

Anti-inflammatory

Antimicrobial

Enhancement of the intestinal barrier function

### Systemic effects on organ/tissue

Antioxidant

Hypocholesterolemic

Antihypertensive

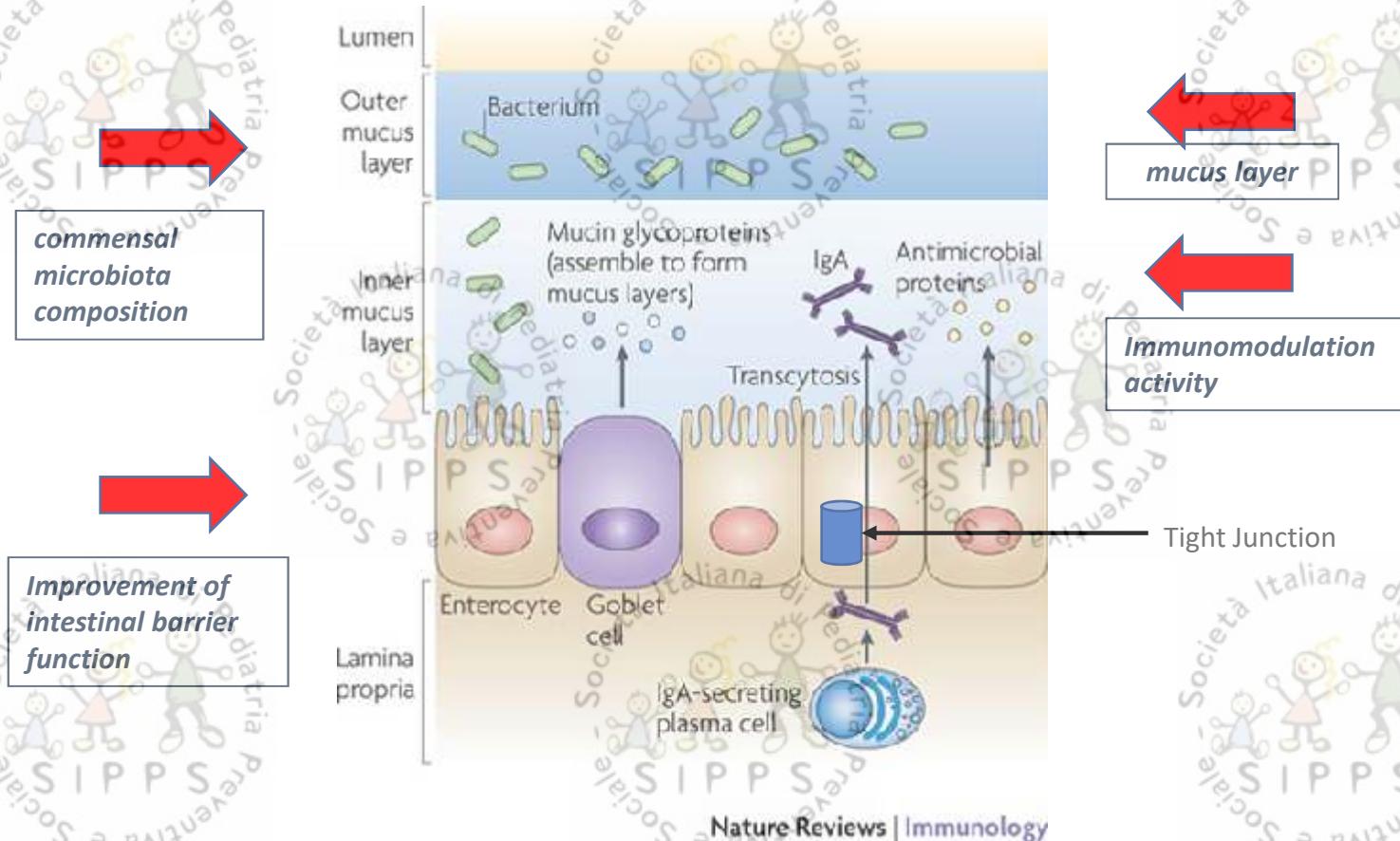
Antiobesogenic

Antiproliferative

Anxiolytic

Antidepressants

# The host-microbiota interface



Hooper et al., *Nat. Rev. Immunol.* 2010



Quali evidenze scientifiche sono disponibili relativamente all'utilizzo dei postbiotici nel neonato?



# **Lactobacillus paracasei fermented infant formula favors the maturation of the immune system, gut microbiota and metabolome more similarly to human milk than standard formula: evidence from a randomized controlled clinical trial.**

## **Aim**

To compare the activities of **two different dietary regimens** (standard formula and *Lactobacillus paracasei* CBA L74 fermented formula) with the reference group of breastfed infants on **immune defense mechanisms** (antimicrobial peptides, IgAs), **the microbiota** and its **metabolome**.

# Subjects

## Inclusion criteria

- Healthy full term newborns, with a **gestational age 37-41 weeks** and a birth weight adequate for gestational age (10 e 90° centile according to the World Health Organization charts)
- Maternal agalactia
- Controindications to breastfeeding

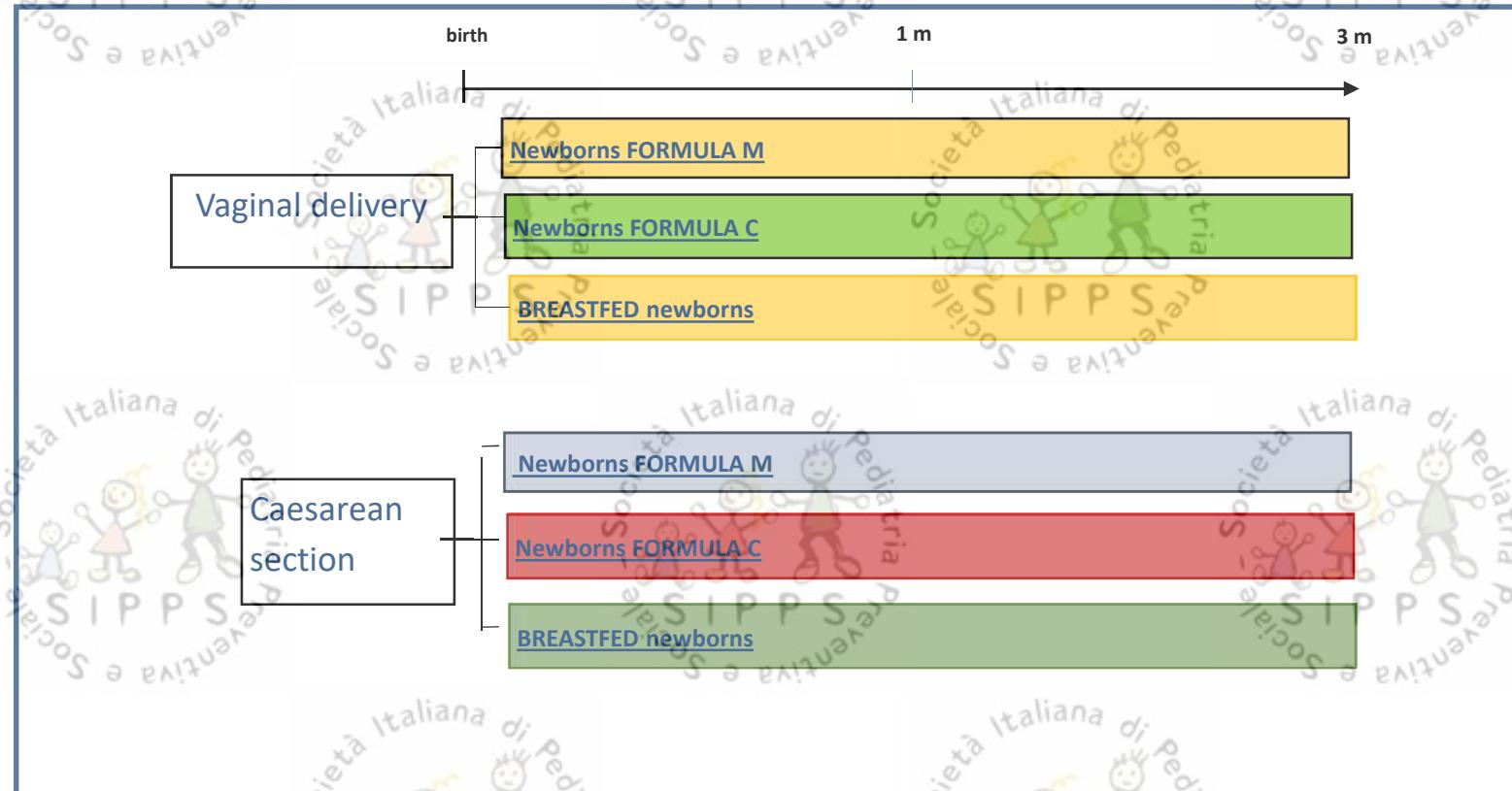
## Exclusion criteria

- Newborns with a birth weight < 10 or > 90° centile according to the World Health Organization charts
- Newborns with congenital and/or chromosomal diseases and/or cardiac, gastroenteric, respiratory, neurological, metabolic diseases
- Perinatal infections
- Family history positive for cow's milk protein allergy
- Newborns born to parents that will move within 3 months from birth

## Reference group

- **Exclusively breast fed newborns for the first three months of life.**

# Lactobacillus paracasei fermented infant formula favors the maturation of the immune system, gut microbiota and metabolome more similarly to human milk than standard formula: evidence from a randomized controlled clinical trial.



## Composition of the study formulas

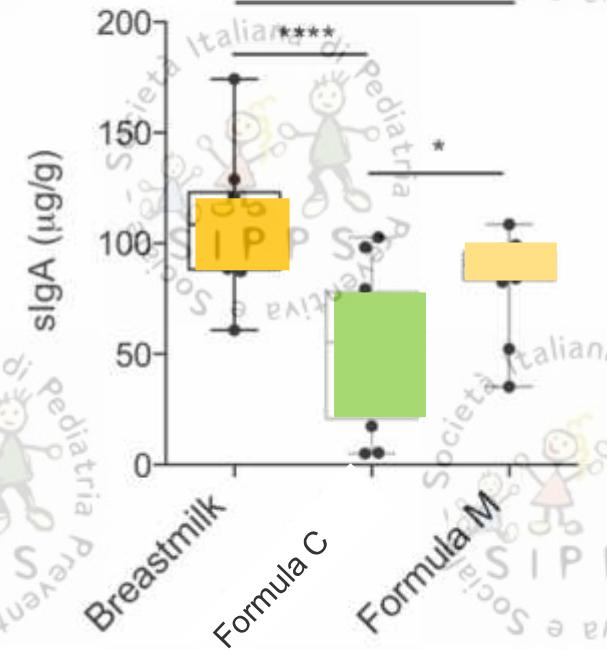
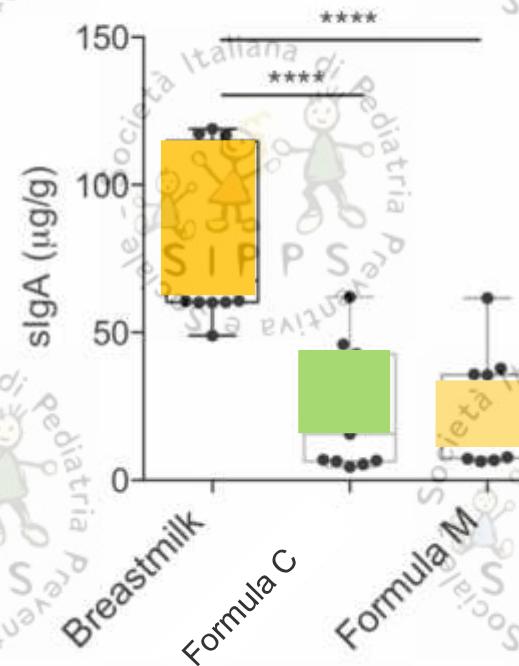
Products	Package	Macronutrients/100 ml	Functional ingredients
Fermented Formula (M)	800 g	Energy: 69 kcal Lipids: 3.6 g Carbohydrates: 7.4 g Proteins: 1.4 g	<ul style="list-style-type: none"><li>Nucleotides (3,4 g/100 ml)</li><li>GOS (0,4g/100 ml)</li><li>Fermented milk with L.paracasei CBA L74 (2.34% out of 100 g powder)</li></ul>
Control Formula (C)	800 g	Energy: 68 kcal Lipids: 3.6 g Carbohydrates: 7.3 g Proteins: 1.4 g	<ul style="list-style-type: none"><li>Nucleotides (3,4 g/100 ml)</li><li>GOS (0,4g/100 ml)</li></ul>

**IGA**

**A**

**Vaginal delivery**

**Enrolment**



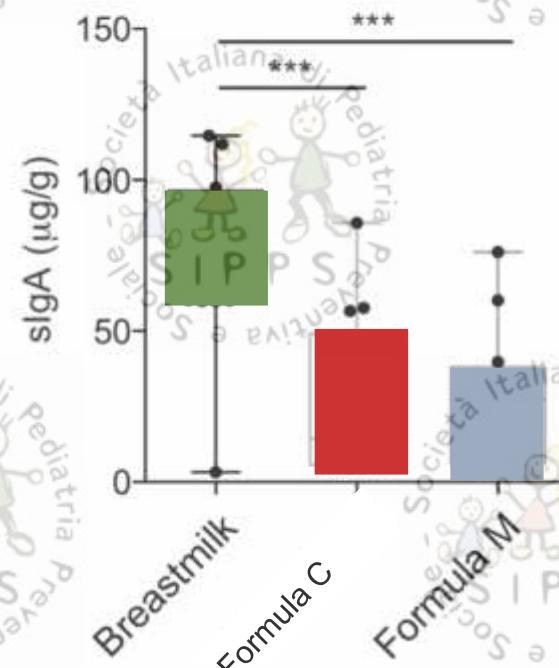
\* $P < 0.05$ ; \*\*\* $P < 0.001$

**IGA**

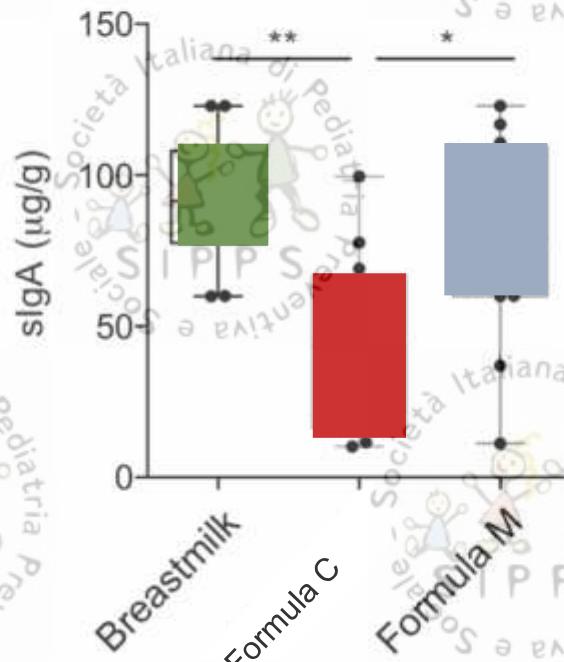
**B**

**Cesarean section**

**Enrolment**

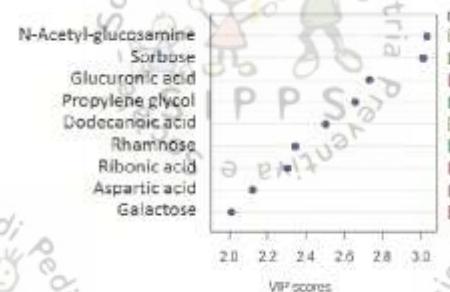
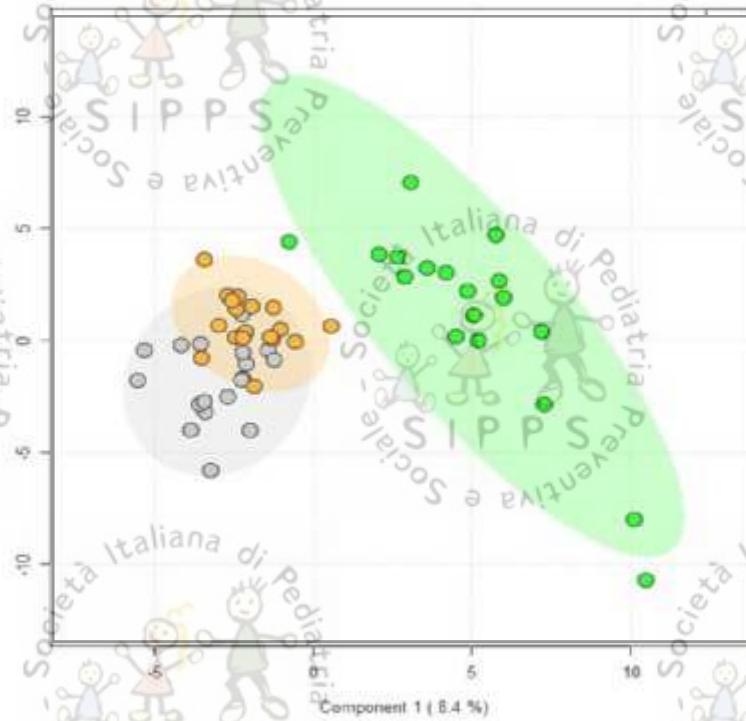


**Visit 2**



\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$

## Metabolomic analysis

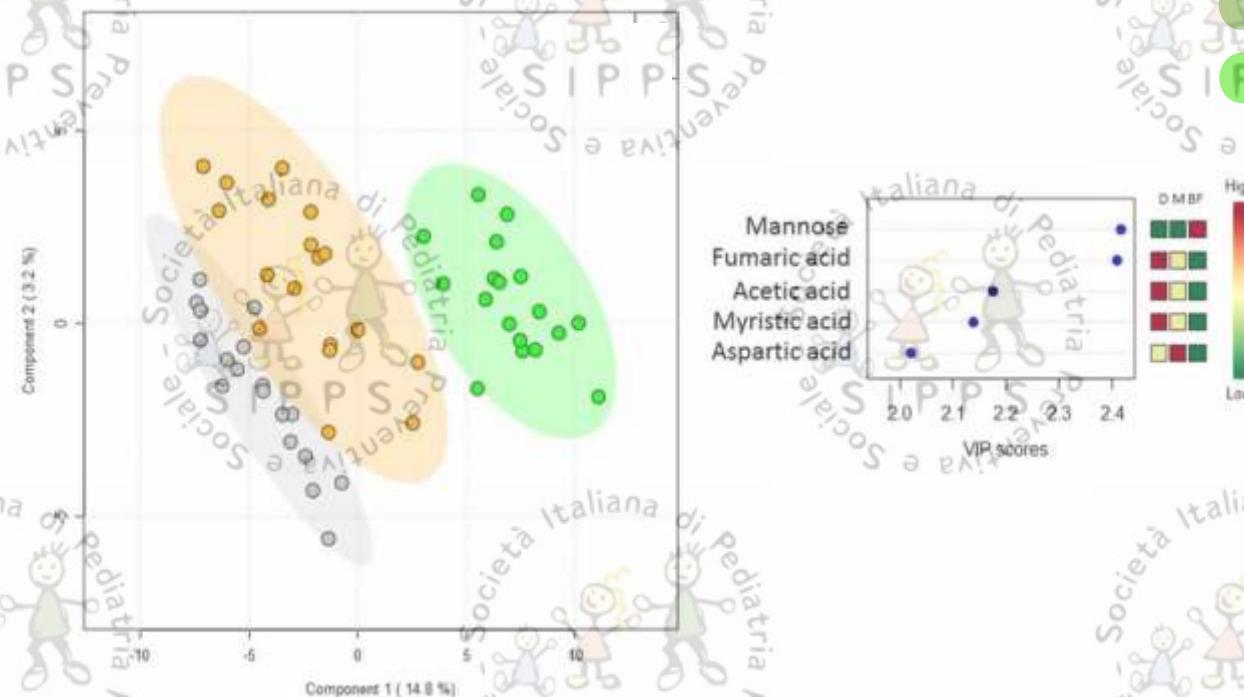


### Arruolamento

- Formula C
- Formula M
- Breastfed

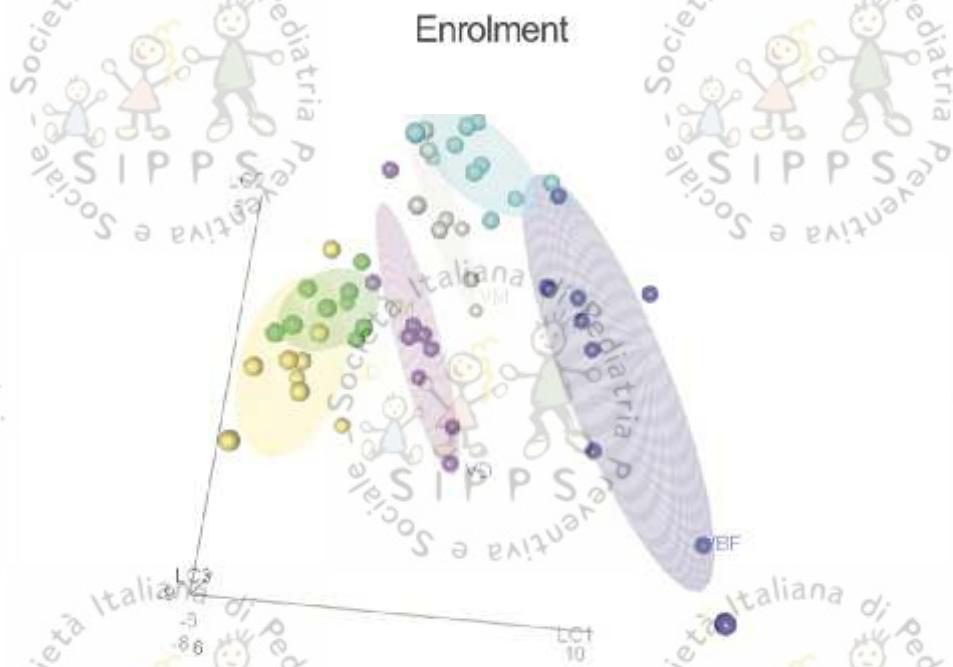
**At enrollment formula fed infants demonstrated a differentiation in fecal metabolites compared to breastfed infants.  
No differences among the two study formulas.**

## Metabolomic analysis



At 3 months, although fecal metabolites of formula fed infants were still different compared to those of breastfed infants, the metabolome of formula M fed infants was more similar to that of the reference group

# Metabolomic analysis



Breastfed infants born from a vaginal delivery were clearly separated and distant from the other groups with a different clusterization of fecal metabolites already at enrolment, suggesting that both mode of delivery and feeding impact on metabolite composition already in the first week of life

Arruolamento

Vaginal delivery  
breastfed

Caesarean section  
breastfed

Vaginal delivery  
Formula M

Vaginal delivery  
Formula C

Caesarean section  
Formula M

Caesarean section  
Formula C

## Metabolomic analysis

### Metabolomic analysis

3 mesi

Vaginal delivery  
breastfed

Caesarean section  
breastfed

Vaginal delivery  
Formula M

Vaginal delivery  
Formula C

Caesarean section  
Formula M

Caesarean section  
Formula C



At 3 months although formula fed infants remained different from breastfed infants, formula M fed infants had a pattern of fecal metabolites more similar to that of breastfed infants compared to formula C fed infants.

## **Lactobacillus paracasei fermented infant formula favors the maturation of the immune system, gut microbiota and metabolome more similarly to human milk than standard formula: evidence from a randomized controlled clinical trial.**

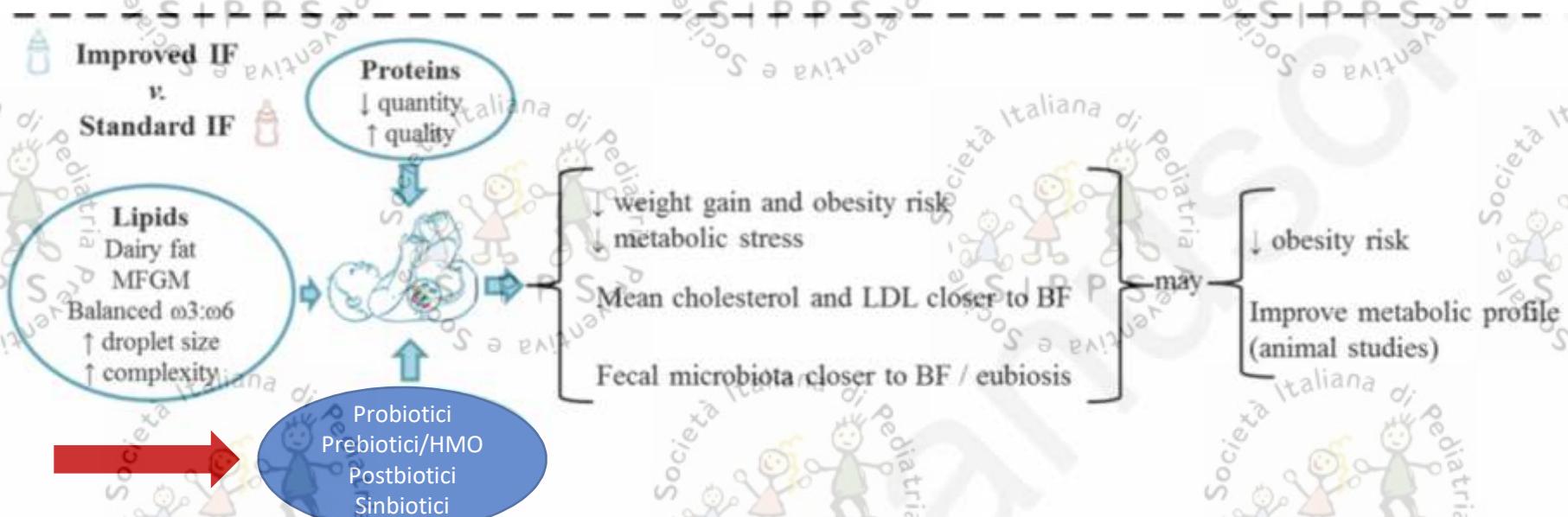
In conclusion, to our knowledge, this is the first randomized controlled trial that compares the metabolome, microbiota and immune system maturation in three nutrition dietary regimens in infants according to the mode of delivery. In spite of the short follow up and small sample size we clearly observed significant statistical differences in the three dietary regimens in terms of both the metabolome and sIgA induction, positioning the fermented formula as a closer substitute of breast milk than a standard formula. Indirectly, these results suggest that most of the beneficial activities of breast milk may be provided by its microbiota-associated metabolites and indicate that the analysis of the metabolome may be more accurate than that of the microbiota in small size groups to assess the effect of nutrition.

# Effects of infant formula composition on long-term metabolic health

Marion Lemaire, Isabelle Le Huérou-Luron, Sophie Blat

## To cite this version:

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**Fig. 1. Short- and plausible long-term effects of neonatal feeding**

IF, infant formula; v., versus; FA, fatty acid; HMOs, human milk oligosaccharides; IGF-1, insulin-like growth factor-1; IR, insulin resistance; TG, triglycerides; TD2, type-2 diabetes; CHD, coronary heart disease; MFGM, milk fat globule membrane; LDL, low density lipoprotein; BF, breastfed infants

Modified

- Current symbiotic approaches have focused on the most well-characterised probiotics, which belong to the genera *Bifidobacterium* and *Lactobacillus*
- The function of symbiotics can be either complementary or synergistic

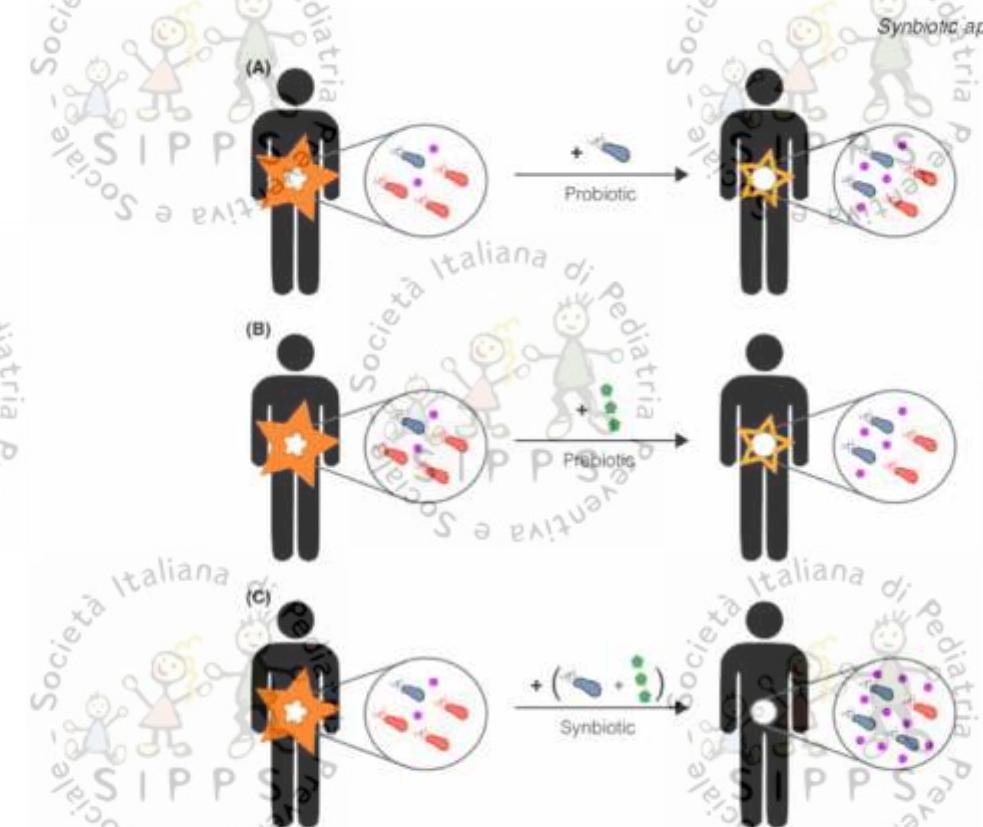


Fig. 1. Schematic illustrating the synergistic effect on a subject's gut microbiota of administering a lactic acid-producing probiotic (A) and an associated prebiotic (B) as a symbiotic formulation (C). In this example, the symbiotic aims to boost the production of lactic acid, depicted in purple, in order to reduce intestinal inflammation.

REVIEW

Open Access

## Synbiotics, probiotics or prebiotics in infant formula for full term infants: a systematic review

Vary N Mugambi<sup>1\*</sup>, Alfred Musoke<sup>2,3</sup>, Marie A Lennox<sup>1</sup>, Taryn Young<sup>1</sup> and Renéé Blaauw<sup>4</sup>

**Table 7 Summary of findings table: Synbiotic studies**

Effects of infant formula containing Synbiotics on clinical outcomes in full term infants				
Outcomes	Illustrative comparative risks* (95% CI)		Measure of effect (95% CI)	No of Participants (studies) / Quality of the evidence (GRADE)
	Assumed risk Conventional formula	Corresponding risk Infant formula with synbiotics		
<b>Weight gain (g/day) for boys</b> Follow-up: mean 4 months	The mean (SD) weight gain (g/day) in control group was 30.9 (6.1)	Mean (SD) weight gain in synbiotic group was 31.8 (5.9)	MD (95% CI): 0.90 (-1.95 to 3.75)	81 (1 study)
<b>Weight gain (g/day) for girls</b> Follow-up: mean 4 months	The mean (SD) weight gain (g/day) in control group was 26.9 (6)	Mean (SD) weight gain in synbiotic group was 27.8 (6)	MD (95% CI): 0.90 (-1.81 to 3.61)	86 (1 study)
<b>Length gain (mm/mo) for boys</b> Follow-up: mean 4 months	The mean (SD) length gain (mm/month) for boys in control group ranged from 32.6 (3.6) to 35.1 (4.4)	The mean length gain (mm/mo) for boys in the intervention groups was <b>0.75 higher</b> (0.66 lower to 2.17 higher)	MD (95% CI): 0.75 (-0.56 to 2.17)	120 (2 studies)
<b>Length gain (mm/mo) for girls</b> Follow-up: mean 4 months	The mean length gain (mm/month) for girls in the control groups ranged from 31.2 (3.7) to 32.2 (4.6)	The mean length gain (mm/mo) for girls in the intervention groups was <b>0.75 higher</b> (0.63 lower to 2.13 higher)	MD (95% CI): 0.75 (-0.63 to 2.13)	138 (2 studies)
<b>Head circumference gain (mm/mo) for boys</b> Follow-up: 4 to 6 months	The mean head circumference gain (mm/month) for boys in the control groups ranged from 17.4 (2.9) to 18.4 (2.3)	The mean head circumference gain (mm/mo) for boys in the intervention groups was <b>0.06 lower</b> (0.96 lower to 0.85 higher)	MD (95% CI): -0.06 (-0.96 to -0.85)	126 (2 studies)
<b>Head circumference gain (mm/mo) for girls</b> Follow-up: 4 to 6 months	The mean head circumference gain (mm/month) for girls in the control groups ranged from 15.5 (3) to 16.7 (2.4)	The mean head circumference gain (mm/mo) for girls in the intervention groups was <b>0.05 lower</b> (0.94 lower to 0.85 higher)	MD (95% CI): -0.05 (-0.94 to 0.85)	138 (2 studies)
<b>Stool frequency (evacuations per day)</b> Follow-up: 4 to 6 months	The mean (SD) stool frequency (evacuations per day) in the control group ranged from 1.4 (0.49) to 1.8 (0.9)	The mean stool frequency (evacuations per day) in the intervention groups was <b>0.28 higher</b> (0.08 to 0.48 higher)	MD (95% CI): 0.28 (0.08 to 0.48)	176 (2 studies)

**There is not enough evidence to state that supplementation of term infant formula with synbiotics does result in modification of growth and clinical outcomes in full term infants**

## Safety of a New Synbiotic Starter Formula

Yvan Vandenplas, Antonis Analitis\*, Chara Iozouvara†, Athina Kourtzoglou†, Anastasia Drakou†,  
Manos Tsouvalas†, Antigoni Mavroudi†, Ioannis Xinias†

Department of Pediatrics, University Ziekenhuis Brussels, Vrije Universiteit Brussel, Brussels, Belgium; \*Department of Hygiene, Epidemiology and Medical Statistics, Faculty of Medicine, National and Kapodistrian University of Athens, Athens; †3rd Pediatric Department, Hippocrateion Hospital, Thessaloniki, Greece

**Purpose:** Breastfeeding is the best way to feed all infants, but not all infants can be (exclusively) breastfed. Cow's milk based infant formula is the second choice infant feeding.

**Methods:** The safety of a new synbiotic infant formula, supplemented with *Bifidobacterium lactis* and fructo-oligo-saccharides, with lactose and a whey/casein 60/40 protein ratio was tested in 280 infants during 3 months.

**Results:** The median age of the infants at inclusion was 0.89 months. Weight evolution was in accordance with the World Health Organization growth charts for exclusive breastfed infants. The evolution of all anthropometric parameters (weight-for-length z score and body mass index-for-age z score) was within the normal range. The incidence of functional constipation (3.2%), daily regurgitation (10.9%), infantile crying and colic (10.5%) were all significantly lower than the reported median prevalence for a similar age according to literature (median value of 7.8% for functional constipation, 26.7% for regurgitation, 17.7% for infantile colic).

**Conclusion:** The new synbiotic infant starter formula was safe, resulted in normal growth and was well tolerated. Functional gastro-intestinal manifestations (functional constipation, regurgitation and colic) were significantly lower than reported in literature. Synbiotics (*Bifidobacterium lactis* and fructo-oligosaccharides) in cow's milk based infant formula bring the second choice infant feeding, formula, closer to the golden standard, exclusive breastfeeding.

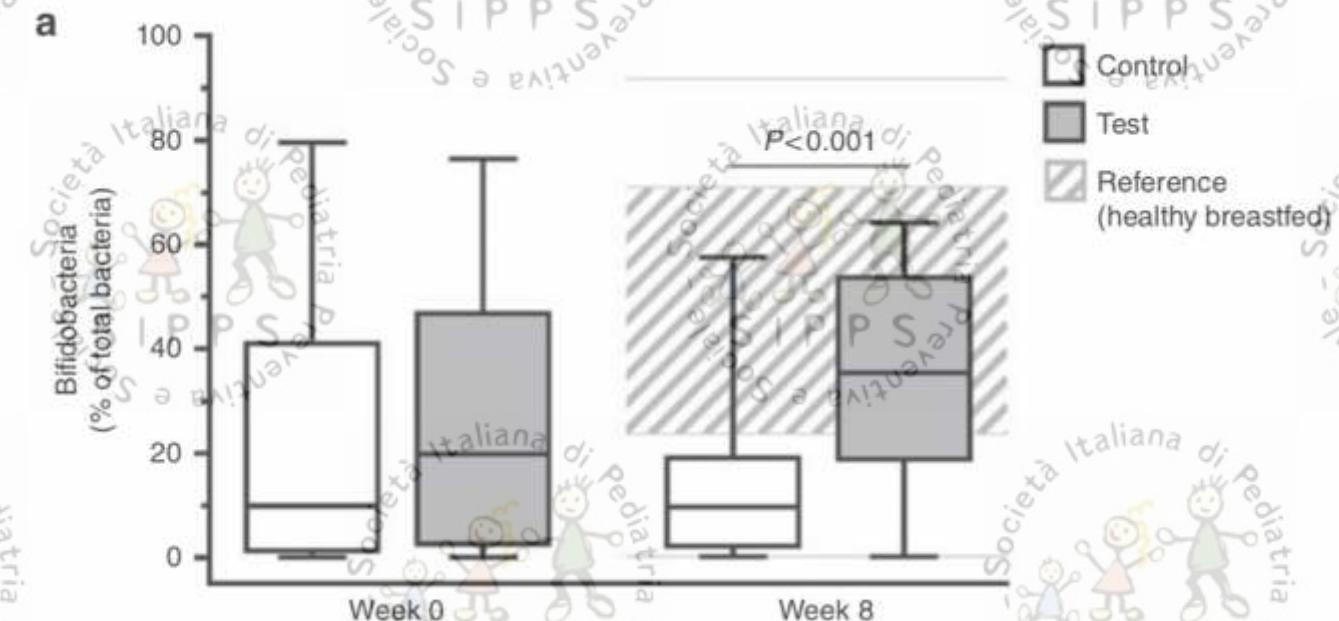
**Key Words:** Functional gastrointestinal disorder, Growth, Infant formula, Prebiotics, Probiotics, Synbiotics

Open

## A synbiotic-containing amino-acid-based formula improves gut microbiota in non-IgE-mediated allergic infants

David C.A. Candy<sup>1</sup>, Marleen T.J. Van Ampting<sup>2</sup>, Manon M. Oude Nijhuis<sup>2</sup>, Harm Wopereis<sup>3</sup>, Assad M. Butt<sup>1</sup>, Diego G. Peroni<sup>4</sup>, Yvan Vandenplas<sup>5</sup>, Adam T. Fox<sup>6</sup>, Neil Shah<sup>7</sup>, Christina E. West<sup>8</sup>, Johan Garssen<sup>8</sup>, Lucien P. Harthoorn<sup>2</sup>, Jan Knol<sup>2</sup> and Louise J. Michaelis<sup>10</sup>, on behalf of the ASSIGN study group<sup>11</sup>

Volume 83 | Number 3 | March 2018



Supplementation with specific synbiotics resulted in levels of bifidobacteria approximating levels of breastfed group infants

## A randomized synbiotic trial to prevent sepsis among infants in rural India

Fredrik Persson<sup>1</sup>, Sathyanarayana Perumal<sup>2</sup>, Arun G. Patel<sup>3</sup>, Rishabh Chaturvedi<sup>4</sup>, Arjun Jayaraman<sup>5</sup>, Arun K. Agarwal<sup>6</sup>, Subbarao G. Mooppan<sup>7</sup>, Praveen R. Mehta<sup>8</sup>, Renu Goyal<sup>9</sup>, Leena D. Solanki<sup>10</sup>, J. Geeta Menon<sup>11</sup>, Agnieszka P. Rutkowska<sup>12</sup>

### Lactobacillus plantarum plus fructooligosaccharide

**Table 2 | Effect of synbiotic treatment on sepsis and other morbidities in the first 60 days of life**

Outcome variables	Control n=2,278 (%)	Synbiotic n=2,278 (%)	RR (95% CI)	NNT (95% CI)	P value
Death and sepsis (primary outcome)	206 (9.0)	123 (5.4)	0.60 (0.48, 0.74)	27 (19, 47)	<0.001
Deaths	4 (0.2)	6 (0.3)	1.50 (0.42, 5.31)	NA*	0.526†
<b>Sepsis (A + B + C)</b>	<b>202 (8.9)</b>	<b>117 (5.1)</b>	<b>0.58 (0.46, 0.72)</b>	<b>27 (19, 44)</b>	<b>&lt;0.001</b>
A. Sepsis/pSBI—culture-positive septicaemia	27 (1.2)	6 (0.3)	0.22 (0.09, 0.53)	108 (71, 232)	<0.001
Gram-negative sepsis	16 (0.7)	4 (0.2)	0.25 (0.08, 0.75)	190 (110, 699)	0.007
Gram-positive sepsis	11 (0.5)	2 (0.1)	0.18 (0.04, 0.82)	253 (142, 1,169)	0.012
B. Sepsis/pSBI— culture-negative sepsis (Culture-negative clinical sepsis warranting hospitalization and IV antibiotics)	36 (1.6)	19 (0.8)	0.53 (0.30, 0.92)	134 (72, 890)	0.021
C. Sepsis/pSBI—LRTI (LRTIs requiring antibiotic therapy)	139 (6.1)	92 (4.0)	0.66 (0.51, 0.88)	48 (30, 126)	0.002
Diarrhoea	59 (2.6)	12 (0.5)	0.20 (0.11, 0.38)	48 (36, 74)	<0.001
Local infections (including >10 pustules, oral thrush, conjunctivitis)	33 (1.5)	16 (0.7)	0.48 (0.27, 0.88)	134 (74, 677)	0.015
Abscess/ otitis media	11 (0.5)	5 (0.2)	0.45 (0.16, 1.33)	NA*	0.133*
Omphalitis	13 (0.6)	3 (0.1)	0.23 (0.07, 0.81)	228 (128, 1,045)	0.014

These findings suggest that a large proportion of neonatal sepsis in developing countries could be effectively prevented using a synbiotic containing *L. plantarum* ATCC-202195.

## Considerazioni conclusive

- La nutrizione nelle prime epoche della vita svolge un ruolo cruciale nel guidare l'imprinting della risposta immunitaria feto-neonatale.
- Il latte materno umano è un sistema biologico estremamente complesso, la cui composizione si caratterizza per la presenza sia di nutrienti che di fattori bioattivi non nutrizionali, che contribuiscono all'estrinsecazione dei numerosi benefici associati all'allattamento nel breve e nel lungo termine
- La ricerca è indispensabile per poter migliorare gli effetti funzionali dei latte di formula in mancanza del latte materno

*Thank you for your attention!*