

Microbi-ota/oma: alimenti, nutrizione e metabolismo

Lorenzo M Donini



THE ITALIAN MICROBIOME INITIATIVE FOR IMPROVED HUMAN HEALTH AND AGRI-FOOD PRODUCTION



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UNIVERSITÀ DI ROMA

Dipartimento di Medicina Sperimentale

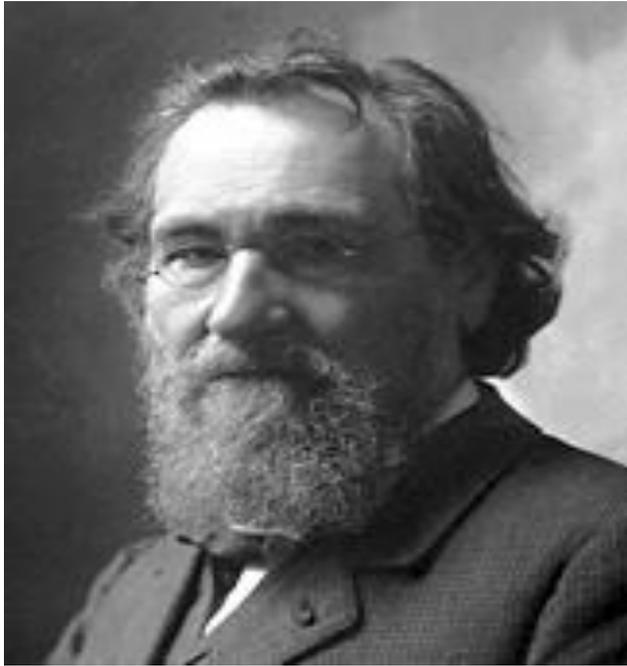
**Sezione di Fisiopatologia Medica,
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Endocrinologia**



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Faculty/Presenter Disclosure

- **Relationships with commercial interests:** I currently have, or I have had in the past years, an affiliation or financial interest with business corporation(s):
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- **Conflict of interest:** no conflict of interest to declare.
- The Author is an advocate of Mediterranean diet.



Ilya I. Metchnikoff (1845-1916)

(Nobel in immunologia 1908)

Nel suo libro, **The Prolongation of Life: Optimistic Studies**, egli ipotizzò che la lunga aspettativa di vita della popolazioni bulgare fosse associata alla frequente assunzione di batteri lattici contenuti nei latti fermentati bulgari

*"The dependence of the intestinal microbes on the food makes it possible to adopt measures to **modify the flora** in our bodies and to **replace the harmful microbes by useful microbes**"*

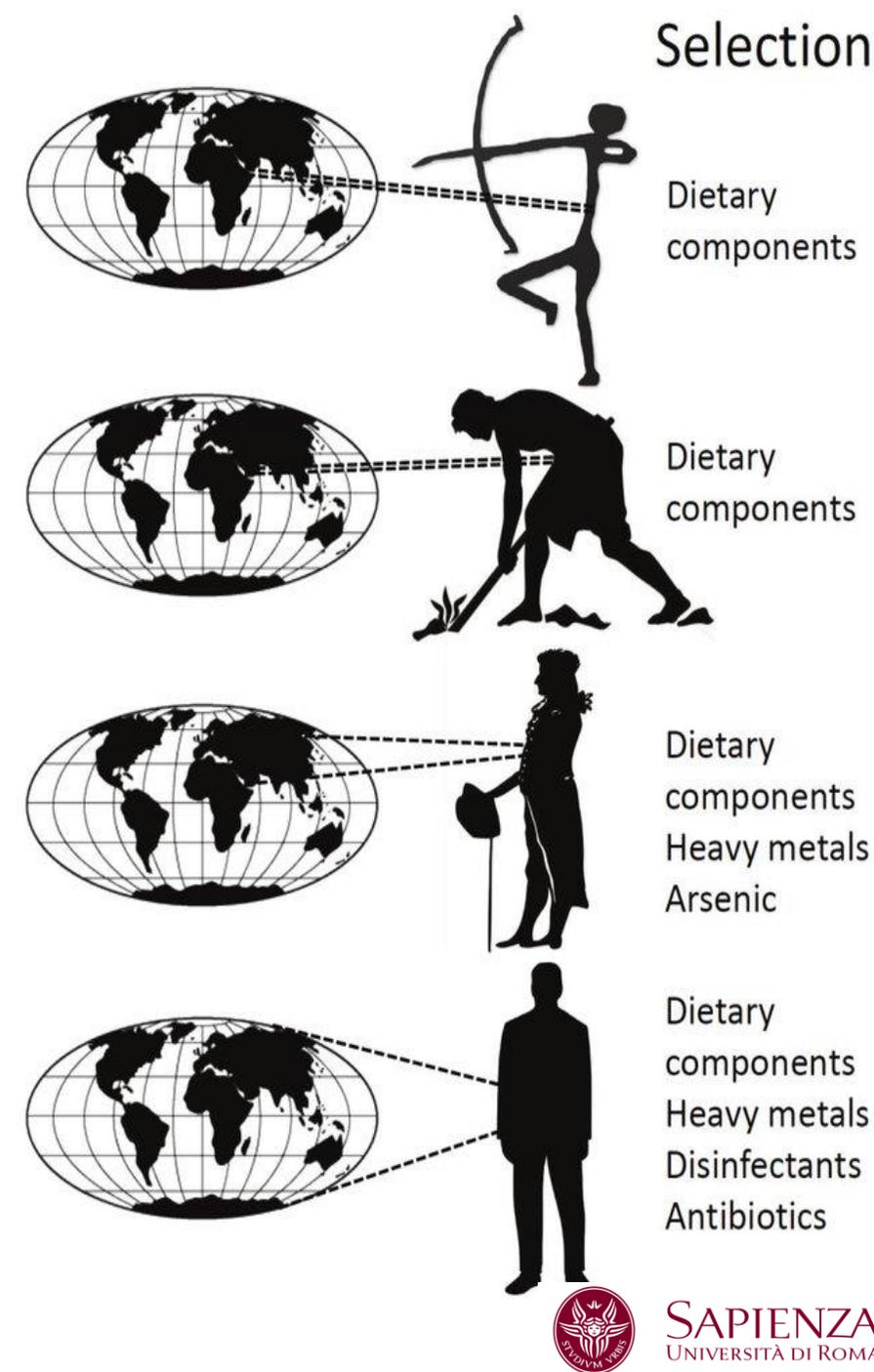
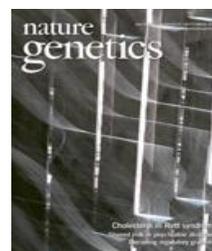
Metchnikoff, E. (1907) The Prolongation of Life. New York: GP Putman's Sons.



Sequencing ancient calcified dental plaque shows changes in oral microbiota with dietary shifts of the Neolithic and Industrial revolutions

Christina J Adler, Keith Dobney, Laura S Weyrich, John Kaidonis, Alan W Walker, Wolfgang Haak, Corey J A Bradshaw, Grant Townsend, Arkadiusz Sołtysiak, Kurt W Alt, Julian Parkhill & Alan Cooper

Nature Genetics 45, 450–455 (2013) doi:10.1038/ng.2536



The composition of oral microbiota remained unexpectedly constant between Neolithic and Medieval times, after which cariogenic bacteria became dominant, apparently during the Industrial Revolution.

1. **hunter-gatherers** dental calculus had fewer bacterial related to caries or periodontal diseases
2. in **Neolithic farmers** these bacteria are more frequent (\Leftarrow increased use of soft CHO foods)
3. oral microbiome remains stable in the **medieval farmers'**
4. **post-industrial modern humans** carry dominantly cariogenic bacteria, (e.g. *S. mutans*) and show less diversity in the oral cavity.



Modulazione dietetica del microbiota intestinale



The Food-Gut Human Axis: The Effects of Diet on Gut Microbiota and Metabolome

Current Medicinal Chemistry, 2017, 24, 1-15

Maria De Angelis^{a,*}, Gabriella Garruti^b, Fabio Minervini^a, Leonilde Bonfrate^{a,c},
Piero Portincasa^c and Marco Gobetti^d

DIETARY COMPONENTS MODULATE THE MICROBIAL METABOLIC PATHWAYS

- With the dietary introduction of **polymers (fibers, proteins, lipid, polyphenols)** that are **not digested by human hydrolytic enzymes**, humans acquired an adaptable and rapidly evolving bacterial metagenome.
- Depending on the type of polymers available at intestinal level, microbial metabolism is mainly directed to:
 - **saccharolytic pathways** mainly lead to the release of SCFA, showing immune-modulating and anti-inflammatory properties
 - **proteolytic pathways** lead to degradation of proteins, peptides and free amino acids, producing BCAA, ammonia, N-nitroso compounds, phenols and hydrogen sulphide
- Because of the different actions of the metabolic products derived from the saccharolytic or proteolytic pathways, it is generally believed that **health is fostered when the balance is shifted towards the saccharolytic pathways.**

A diet characterised by an unbalanced supply of:

- **macronutrients** (high fat and/or high-protein and/or low complex CHO)
- and/or other **nutritional/bioactive molecules** (low intake of fibers and/or polyphenols and/or high intake of alcohol)

leads to:

- **dysbiosis** [increasing the number of potentially pathogenic and proinflammatory bacterial species (e.g. decrease in Bifidobacteria and Bacteroidetes and increase in Firmicutes and Proteobacteria)]
- a reduced synthesis of **beneficial metabolites** (e.g. SCFA, vitamins)
 - butyrate provides **E for colonic epithelial cells**; acetate and propionate reach the liver and peripheral organs, where they are substrates for **gluconeogenesis** and **lipogenesis**
 - SCFAs control **colonic gene expression and** suppress **inflammation**
- an increased amount of potentially **toxic compounds** (e.g. BCAA, ammonia, N-nitroso compounds, phenols and hydrogen sulphide)
- an increase of **endotoxemia, intestinal permeability** and **inflammation** (due to increase in LPS and/or microbial DNA)



Modelli alimentari e microbiota intestinale



Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population

Evdokia K. Mitsou¹, Aimilia Kakali¹, Smaragdi Antonopoulou¹, Konstantinos C. Mountzouris², Mary Yannakoulia¹, Demosthenes B. Panagiotakos¹ and Adamantini Kyriacou¹*



Intriguing associations between gut microbiota characteristics and consumption of **stimulants or snacks and junk food**

- inverse relation of **stimulant consumption** with the prevalence of faecal *S. aureus* \Leftarrow more acidic stool pH, systemic antimicrobial activity of coffee and tea polyphenols against a wide range of pathogenic micro-organisms;
- higher consumption of **snack and junk food** products was characterised by:
 - increased counts of *E. coli* and suppressed presence of lactobacilli and butyrate-producing Firmicutes members \Rightarrow potential detrimental inflammatory gut microbiota milieu;
 - Increased faecal levels of the branched SCFA iso-valerate \Leftarrow bacterial catabolism of animal protein;
 - elevated amount of propionate in faeces \Leftarrow increased dietary intake of propionate salts, common preservatives in the food industry;
- negative association of **soda consumption** with levels of *A. muciniphila* (mucin-degrading bacterium) \Rightarrow possible beneficial effects against obesity and T2DM.



Urbanization and the gut microbiota in health and inflammatory bowel disease

JULY 2018 | VOLUME 15

Tao Zuo, Michael A. Kamm, Jean-Frédéric Colombel and Siew C. Ng

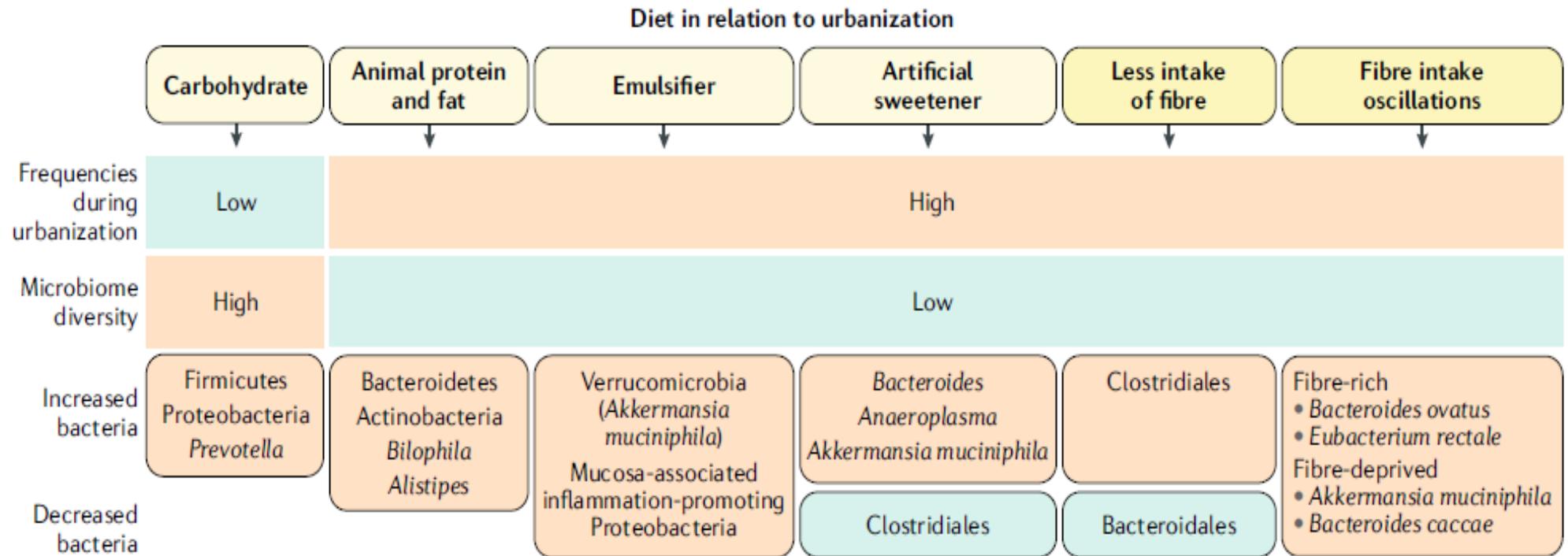


Fig. 2 | Diet changes during urbanization and effects on the gut microbiota. Urbanization is associated with a decrease in the intake of carbohydrates (including natural fibre) and an increase in the consumption of animal proteins, fats and food additives, such as emulsifiers and artificial sweeteners, all of which can lead to a diminished gut microbial diversity.

The depletion of the microbial ecosystem caused by low fibre intake is transmissible over generations and becomes irreversible. Frequent dietary oscillations between fibre-rich and fibre-deprived diets in modern urban lifestyles have a detrimental effect on the gut microbiota. Processed fibre is not as protective as natural fibre to the diversity of the gut microbiota.



Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Carlotta De Filippo^a, Duccio Cavalieri^b, Monica Di Paola^b, Matteo Ramazzotti^c, Jean Baptiste Poulet^d, Sebastien Massart^d, Silvia Collini^b, Giuseppe Pieraccini^e, and Paolo Lionetti^{b,1}

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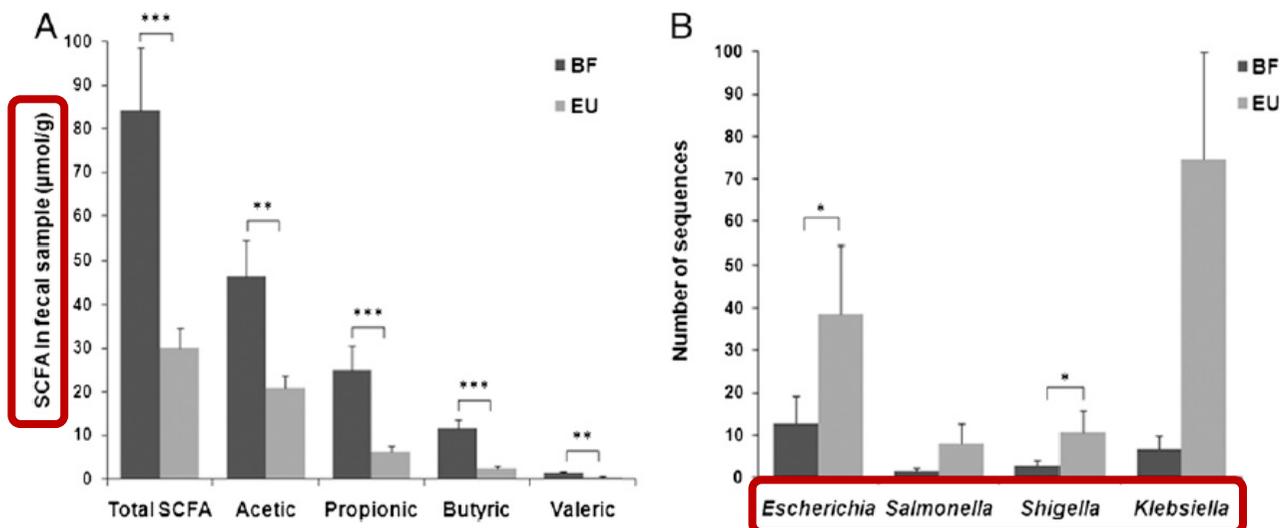


Fig. 3. SCFA-producing bacteria could help to prevent establishment of some potentially pathogenic intestinal bacteria. (A) Quantification of SCFAs in fecal samples from BF and EU populations by SPME-GC-MS. (B) Number of sequences relative to principal *Enterobacteriaceae* genera, in BF and EU children microbiota. Mean values (\pm SEM) are plotted. Asterisks indicate significant differences (one-tailed Student t test of all data points: * $P < 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$).

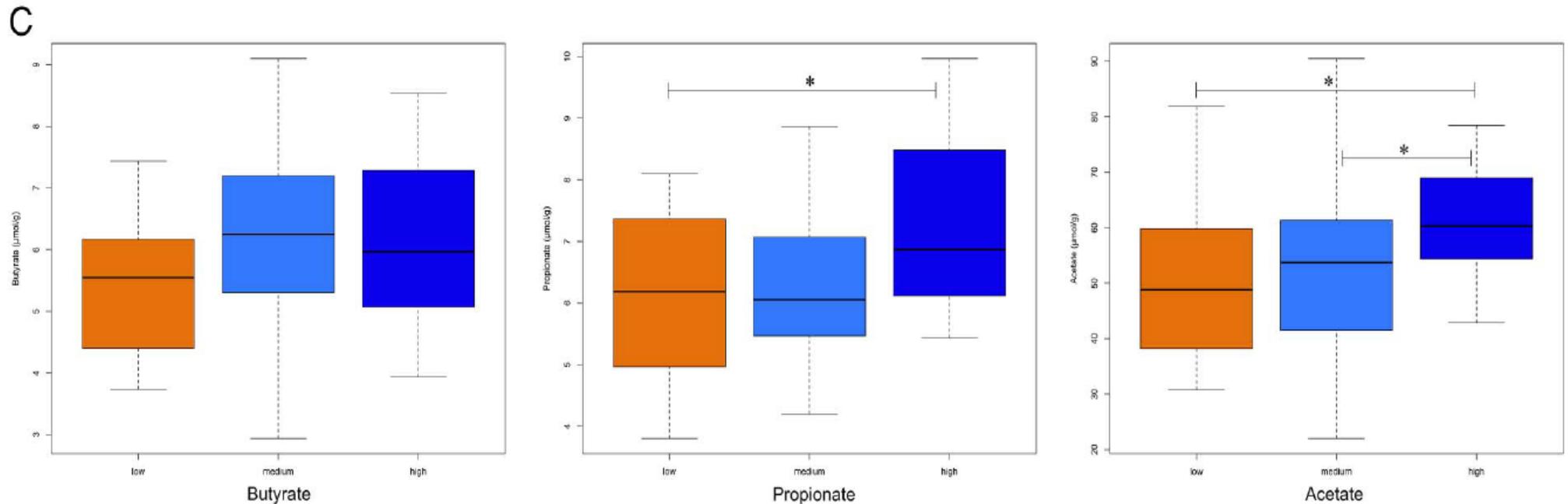
Microbiota coevolved with the diet of Burkina Faso (BF) individuals, allowing them to maximize the E intake from indigestible components, such as plant polysaccharides, by producing high levels of **SCFAs that supply the host with an additional amount of energy**. Given that enhanced ability to obtain energy-rich food is considered to be one factor that has driven human evolution.



High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome

Gut 2016;65:1812–1821. doi:10.1136/gutjnl-2015-309957

Francesca De Filippis,¹ Nicoletta Pellegrini,² Lucia Vannini,^{3,4} Ian B Jeffery,^{5,6} Antonietta La Storia,¹ Luca Laghi,^{3,4} Diana I Serrazanetti,⁴ Raffaella Di Cagno,⁷ Ilario Ferrocino,⁸ Camilla Lazzi,² Silvia Turroni,⁹ Luca Cocolin,⁸ Patrizia Brigidi,⁹ Erasmo Neviani,² Marco Gobbetti,⁷ Paul W O'Toole,^{5,6} Danilo Ercolini¹



Correlations between SCFA levels and diet

[box plots showing abundance of soluble butanoate, propanoate and acetate in faecal samples of omnivore subjects grouped according to adherence to the MD (* $p < 0.05$ and ** $p < 0.01$)]





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Current Medicinal Chemistry, 2017, 24, 1-15

Maria De Angelis^{a,*}, Gabriella Garruti^b, Fabio Minervini^a, Leonilde Bonfrate^{a,c},
Piero Portincasa^c and Marco Gobetti^d

- Compared to gluten-containing diet (GCD), **gluten-free diet** (GFD) affects the composition of gut microbiota and metabolome of healthy subjects.
- Probably due to lower content of dietary fibers and resistant starch of GFD, elimination of gluten containing cereals in healthy subjects drives to a modification of the composition and immunological properties of the intestinal microbiota.
 - lower level of healthy-related bacteria (mainly *Bifidobacterium* sp., *Lactobacillus* sp., *F. prausnitzii*)
 - higher number of potentially unhealthy bacteria (*Enterobacteriaceae*)
- Consequently, the exclusion of some cereals from GFD seems to drive to **intestinal dysbiosis**, together with **modification of the immunological properties**.



Microbiota intestinale & metabolismo dell'ospite



Functional interactions between the gut microbiota and host metabolism

Valentina Tremaroli^{1,2} & Fredrik Bäckhed^{1,2,3}

NATURE | VOL 489 | 13 SEPTEMBER 2012



Microbial processing of food constituents

- Products of microbial metabolism act as **signalling molecules** and influence the host's metabolism.
- **Microbial products directly affect intestinal function** but may also affect the liver and brain, as well as adipose and muscle tissue, which consequently may affect the level of obesity and the associated comorbidities
- **Microbial enzymatic activities** can act directly on the fermentation of polysaccharides and bile-acid metabolism, or act in conjunction with the host on the metabolism of choline

The complex network of communication between the GI tract and brain encompasses the CNS, the gut microbiota, the autonomic nervous system, the enteric nervous system, as well as the neuroimmune and neuroendocrine systems .

The **microbiota-brain-gut axis** communicates via humoral signaling molecules, hormonal components in addition to neuronal routes.



The Impact of Starvation on the Microbiome and Gut-Brain Interaction in Anorexia Nervosa

Jochen Seitz^{1*†}, Meriem Belheouane^{2†}, Nina Schulz¹, Astrid Dempfle³, John F. Baines^{2†} and Beate Herpertz-Dahlmann^{1†}

 **frontiers**
in Endocrinology

published: 12 February 2019
doi: 10.3389/fendo.2019.00041

HORMONES & NEUROTRANSMITTER

Gut microbes are influenced by hormones and neurotransmitters and in turn affect hormonal and neurotransmitter secretion:

- there are microbes producing **dopamine, serotonin, norepinephrine, GABA** and **insulin**;
- germ free (GF) mice, exhibited a 25% increased **TSH** level, but decreased plasma **catecholamine** and **serotonin** levels;
- **leptin** is associated with an increased abundance of Bifidobacterium and Lactobacillus and a decreased abundance of Bacteroides and Prevotella, while **ghrelin** shows inverse relationships;
- gut bacteria are thought to help regulate **orexin** release from neuroendocrine cells which in turn influences local neural communication in the gut as well as CNS functions of hunger signaling;
- microbiota depletion in germ-free mice impairs the **thermogenic capacity of BAT** by blunting the increase in the expression of uncoupling protein 1 (UCP1) and reducing the browning process of WAT.



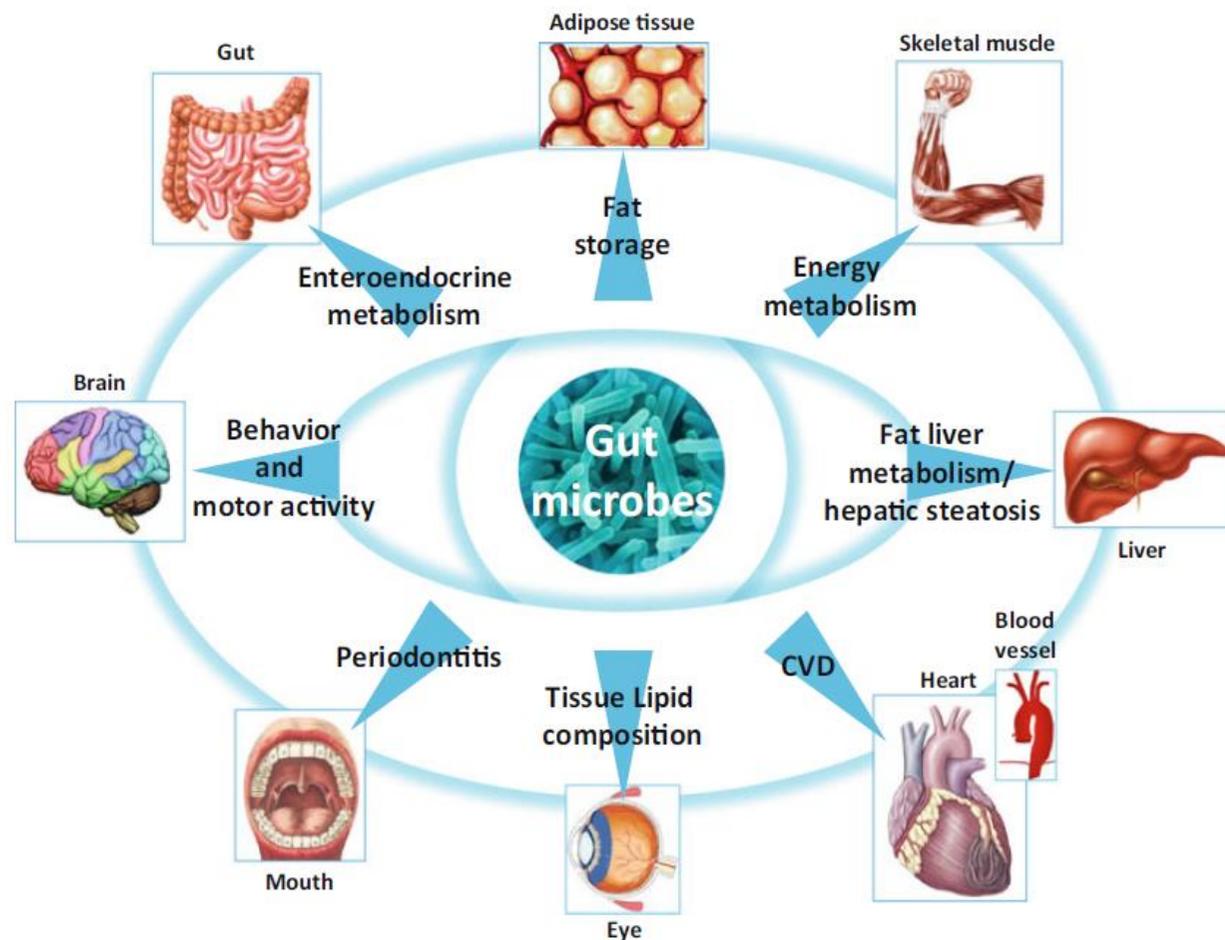


Gut microbiota and diabetes: from pathogenesis to therapeutic perspective

Rémy Burcelin · Matteo Serino · Chantal Chabo · Vincent Blasco-Baque · Jacques Amar

Multiple-sited impact of gut microbiota on whole host metabolism.

Gut microbes have been shown or proposed to have an impact on adipose tissue and liver fat storage, skeletal muscle energy metabolism, fat liver metabolism and hepatic steatosis, atherosclerosis and cardiovascular diseases, tissue lipid composition in the retina lens, periodontitis, behavior and motor activity, and enteroendocrine metabolism.



Microbiota intestinale & malattie dismetaboliche

*... ovvero il mai risolto dilemma:
chi è nato prima, l'uovo o la gallina ?*

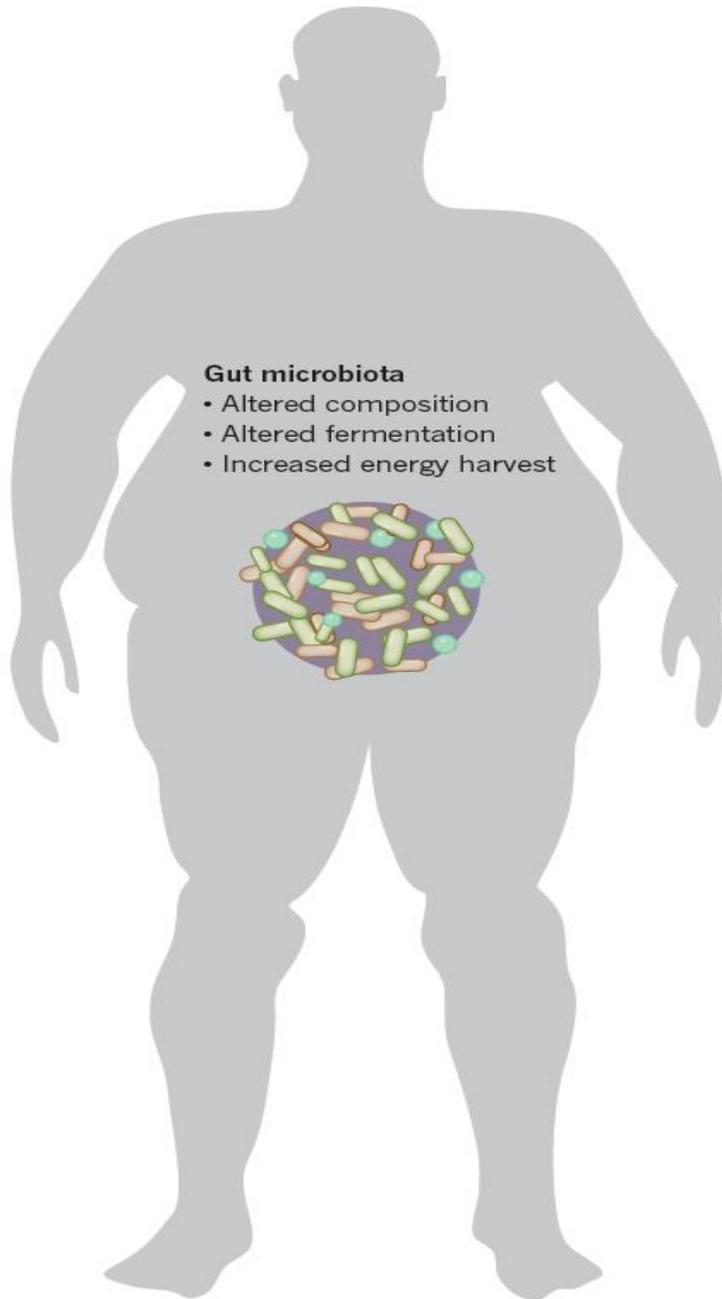


Functional interactions between the gut microbiota and host metabolism

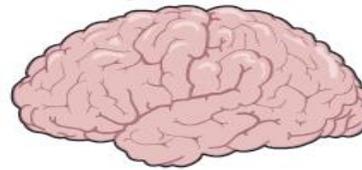


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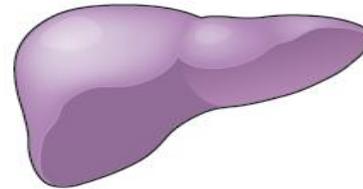
Valentina Tremaroli^{1,2} & Fredrik Bäckhed^{1,2,3}



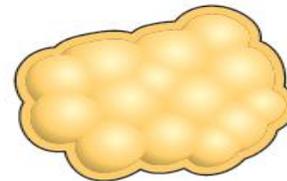
Brain
↓ Satiety



Liver
↑ Short-chain fatty acids
↑ Inflammation



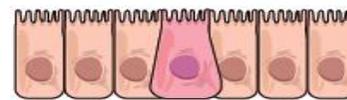
Adipose tissue
↑ Triglyceride incorporation
↑ Inflammation



Muscle
↓ Fatty-acid oxidation



Epithelium
↑ Permeability of the epithelium
↓ PYY/GLP-1 from L-cells



Alterations to the composition and metabolic capacity of gut microbiota in **obesity** promote adiposity and influence metabolic processes in peripheral organs, such as the **control of satiety** in the brain; the **release of hormones from the gut** (shown as PYY and GLP-1); and the **synthesis, storage or metabolism of lipids** in the adipose tissue, liver and muscle.

Leptin regulates gut microbiota, through either its central effect or via the induction of obesity



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The Impact of Starvation on the Microbiome and Gut-Brain Interaction in Anorexia Nervosa

Jochen Seitz^{1†}, Meriem Belheouane^{2†}, Nina Schulz¹, Astrid Dempfle³, John F. Baines^{2†}
and Beate Herpertz-Dahlmann^{1†}

Gut microbiome:

- Microbe diversity reduced
- Altered bacterial community-structures
- More protein-fermenting and less butyrate-producing taxa (probably feed on mucin and aggravate gut permeability/ inflammation)

Immunology:

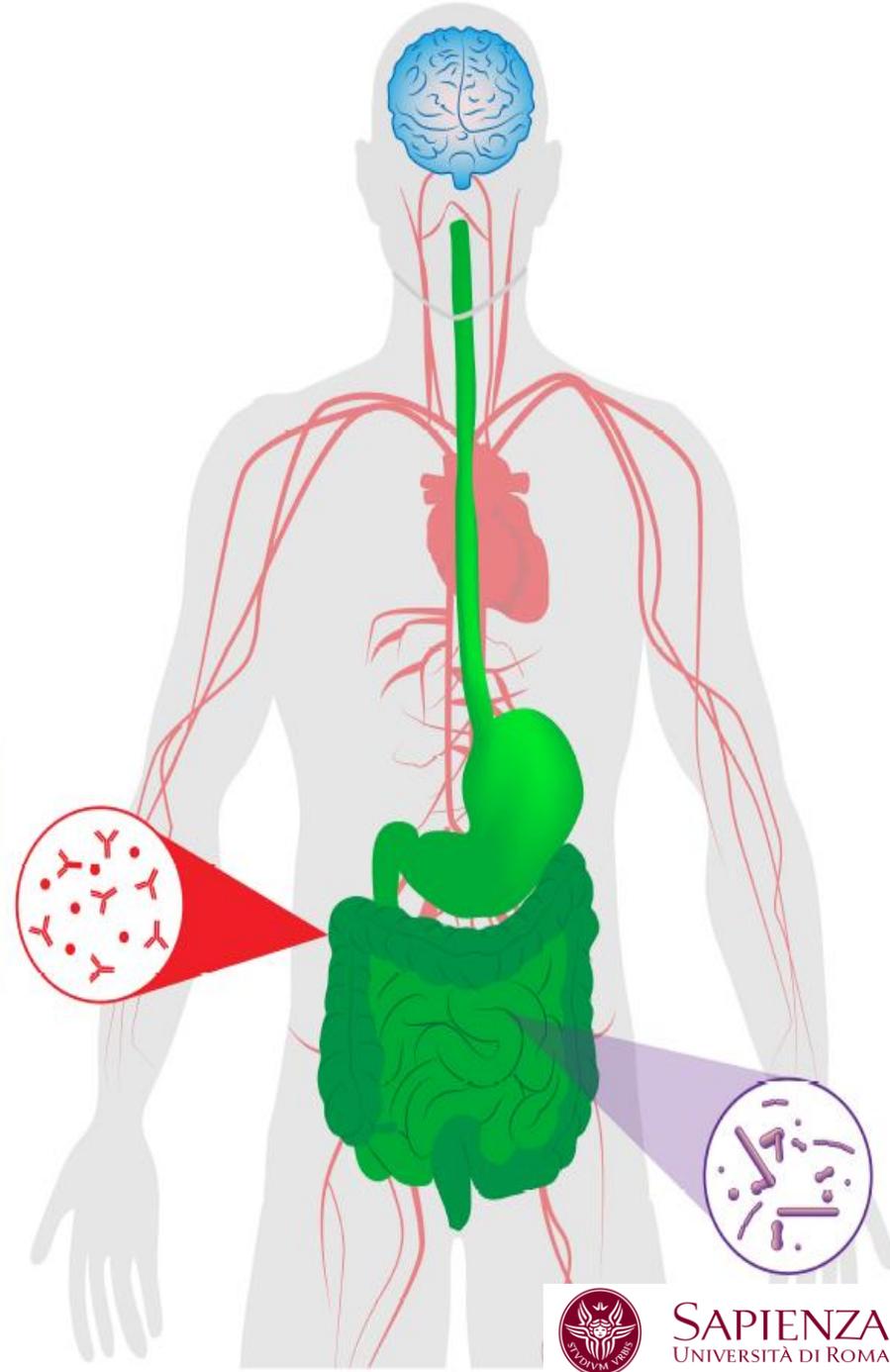
- Bacterial antigens traverse intestinal wall
- Low grade inflammation in AN
- Antibodies against hunger/satiety hormones in AN

Intestinal tract:

- Microbes degrade nutrients and regulate gut permeability
- Production of increased fecal branched-chain fatty acid in AN
- Increased gut permeability in AN animal model

Brain/Behavior:

- Microbes interact with brain („Gut-Brain Axis“)
- Microbes influence cell neogenesis, learning, mood, anxiety
- Microbial diversity reduced in AN and linked to depression and ED symptoms



Non so voi,
ma io
nemmeno.



Snoopy Forever

