

XLIII Congresso Nazionale



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Società Italiana
di Neurologia Pediatrica

BOLOGNA
17-20 ottobre 2018

Asse intestino-cervello nel disturbo del comportamento alimentare

Paolo Mainardi

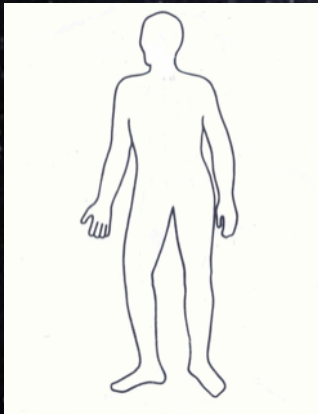
Asse microbiota- intestino-cervello nel disturbo del comportamento alimentare

We Are Not Alone in This Endless Universe

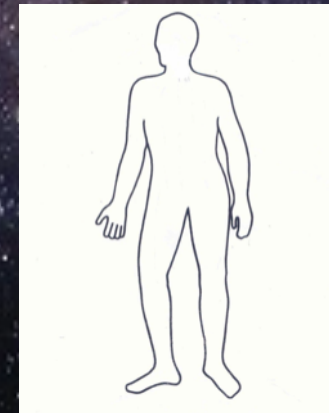
Human body



Cellular body



Microbial body



Shivaji S. **We are not alone**: a case for the human microbiome in extra intestinal diseases. Gut Pathog. 2017 Mar 7;9:13.

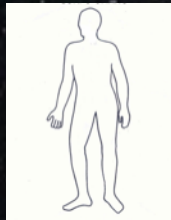
We Are Not Alone in This Endless Universe

10^{13} germ and somatic cells

≈ 80 kg

24,000 genes

Cellular body

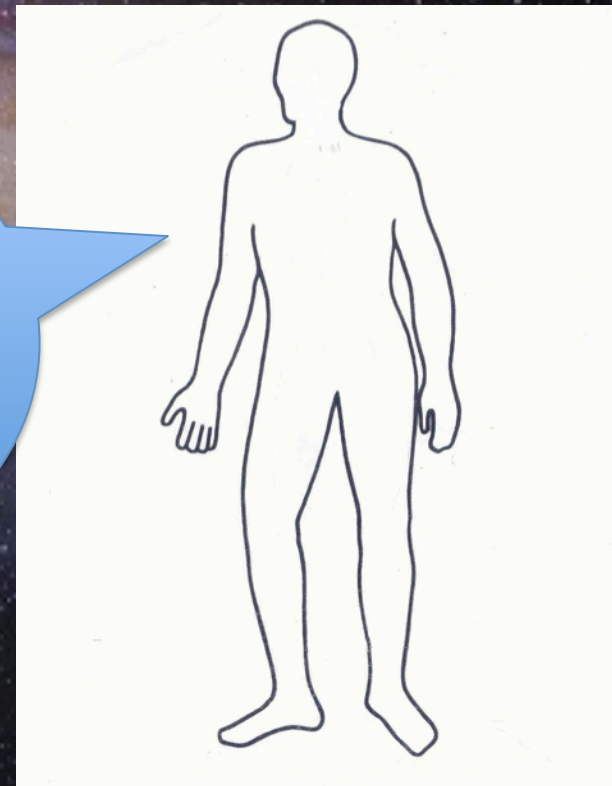


10^{14} bacteria

1.13 kg

3-4 million genes

Microbial body



Shivaji S. **We are not alone:** a case for the human microbiome in extra intestinal diseases. Gut Pathog. 2017 Mar 7;9:13.

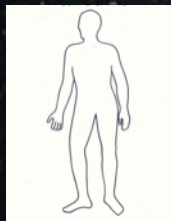
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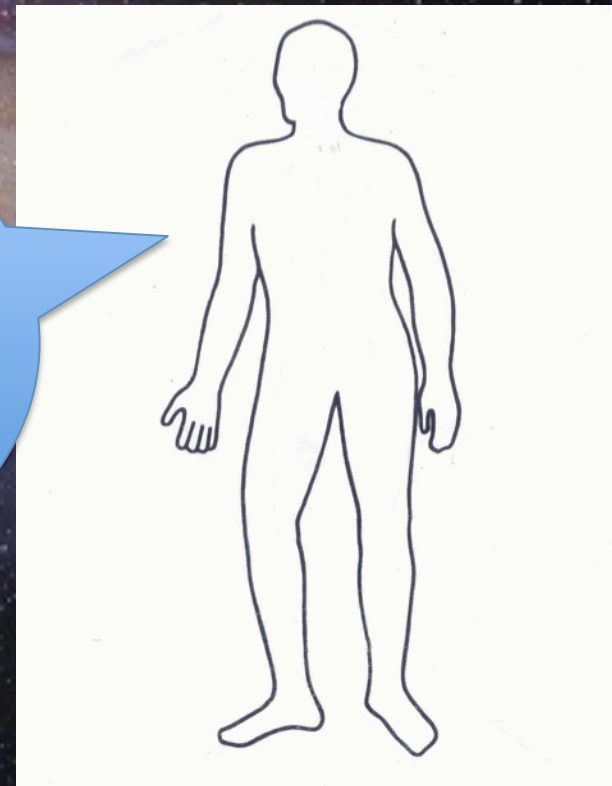


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R= Unità geniche/ massa

R= Energia/ massa

Fisica delle particelle \neq Fisica classica

R1= 24000/80

R2= 4000000/1.13



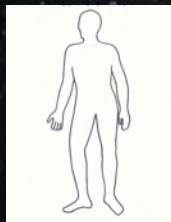
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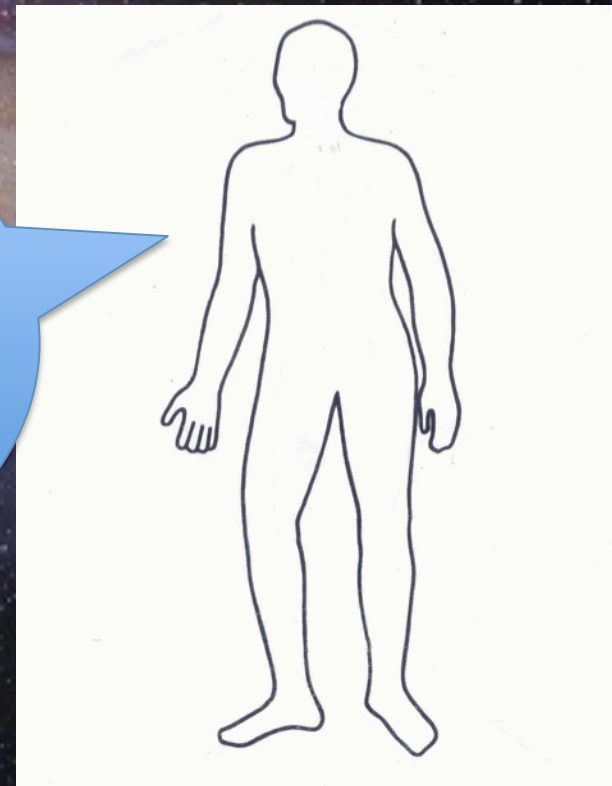


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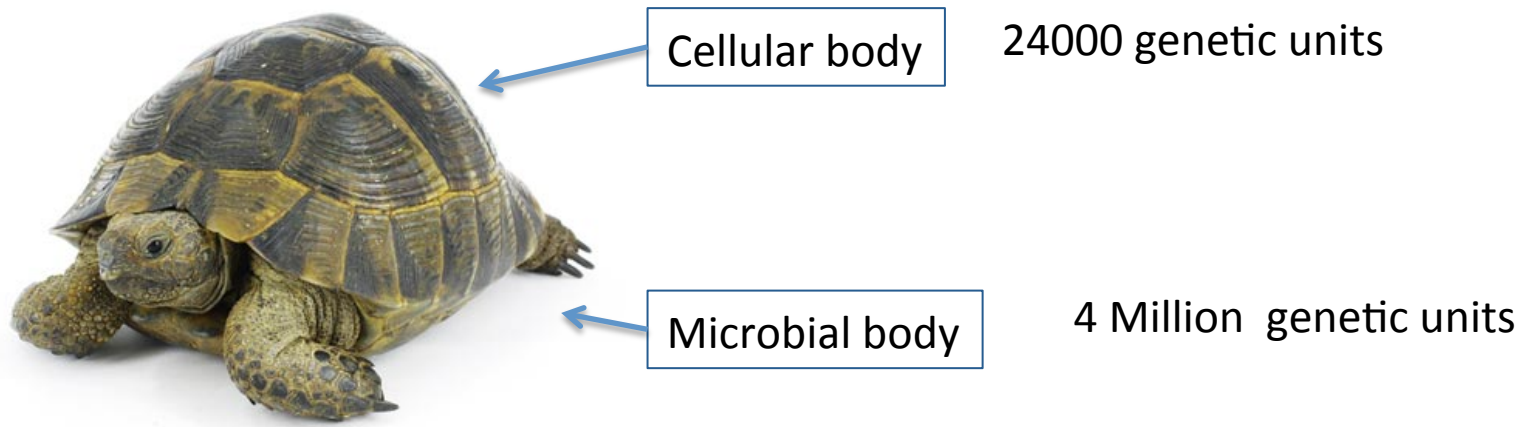
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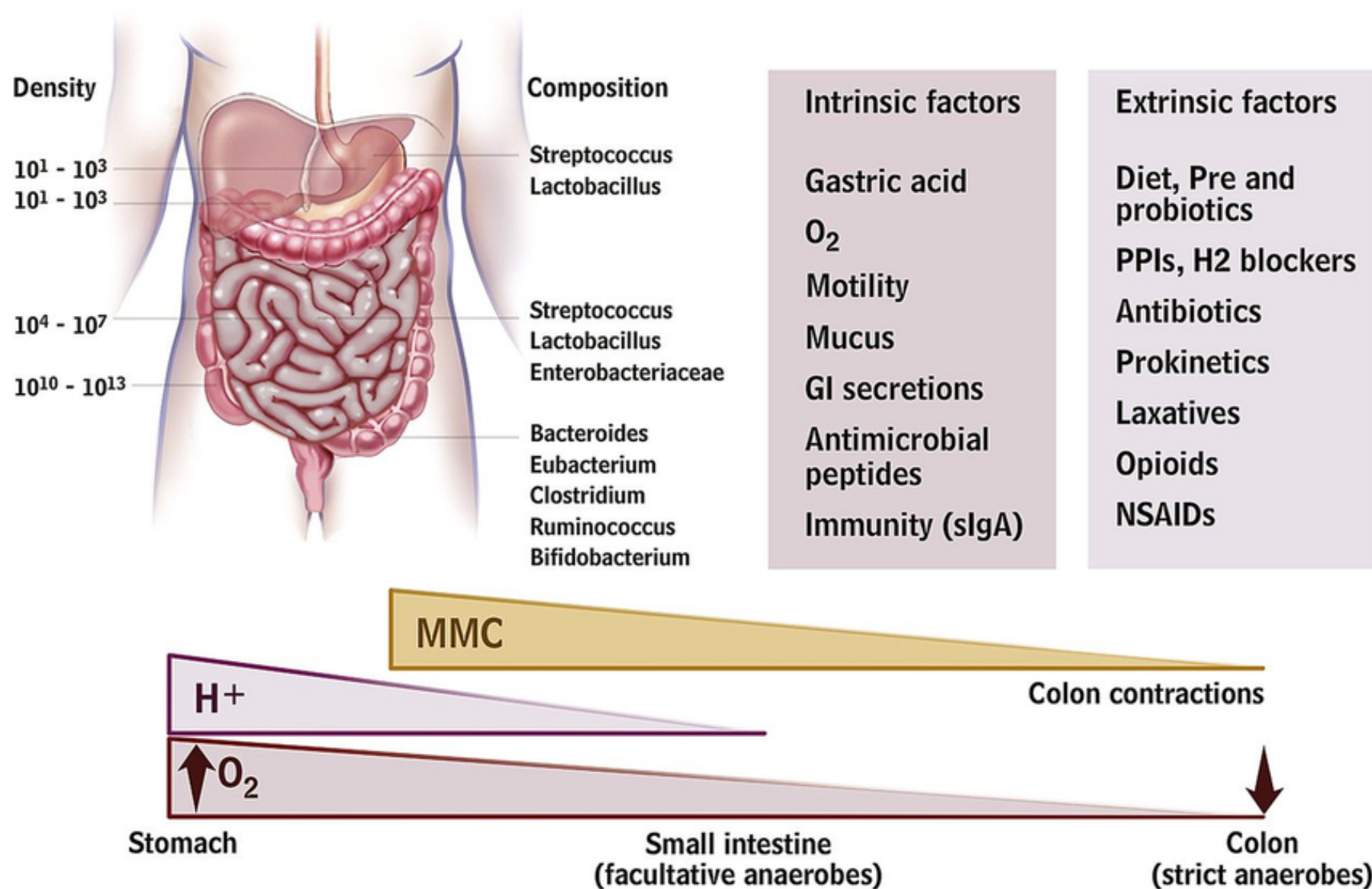
- **Microbial body is ten time cellular body**



“Surprisingly, each of us can be identified by the DNA of our gut microbes”.

George Weinstock, Genoma Institute, Washington University

- **It compensates for our genetic damage**
- **It is able to repair our DNA**
- **It is able to modify our genetic expression**



THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.

YOU CALL
THIS LIVING?

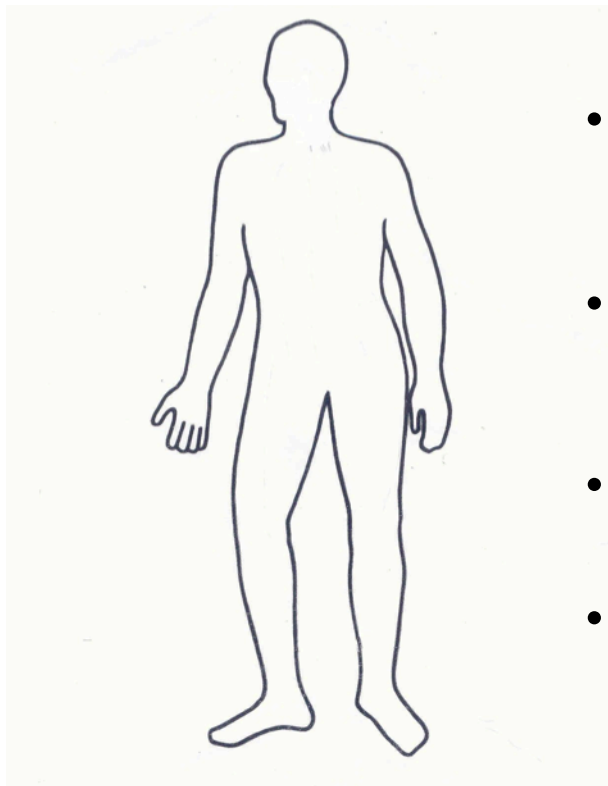
6/15/12
HABITAT 66
GARY

Physiological functions, i.e.:

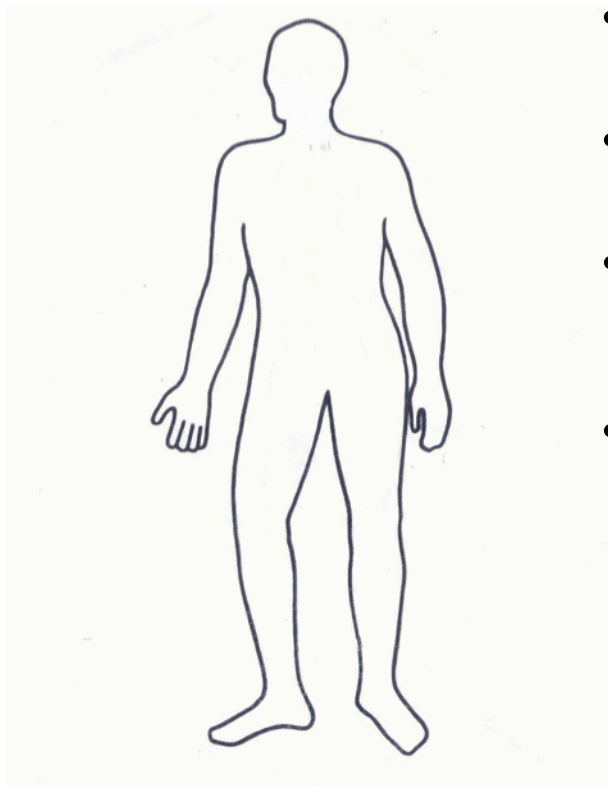
- **Blood pressure** (Yang T, Zubcevic J. Gut-Brain Axis in Regulation of Blood Pressure. Front Physiol. 2017 Oct 25;8:845).
- **Plasma levels of cholesterol** (Gérard P. Metabolism of cholesterol and bile acids by the gut microbiota. Pathogens. 2013 Dec 30;3(1):14-24.)

Microbial body controls:

- **Metabolic diseases** (Clavel T, Desmarchelier C, Haller D, Gérard P, Rohn S, Lepage P, Daniel H. Intestinal microbiota in metabolic diseases: from bacterial community structure and functions to species of pathophysiological relevance. Gut Microbes. 2014 Jul 1;5(4):544-519)
- **Heart functions** (Luedde M, Winkler T, Heinsen FA, Rühlemann MC, Spehlmann ME, Bajrovic A, Lieb W, Franke A, Ott SJ, Frey N. Heart failure is associated with depletion of core intestinal microbiota. ESC Heart Fail. 2017 Aug;4(3):282-290)
- **Kidney functions** (Jiang S, Xie S, Lv D, Wang P, He H, Zhang T, Zhou Y, Lin Q, Zhou H, Jiang J, Nie J, Hou F, Chen Y. Alteration of the gut microbiota in Chinese population with chronic kidney disease. Sci Rep. 2017 Jun 6;7(1):287)0
- **Neuroendocrine system** (Farzi A, Fröhlich EE, Holzer P. Gut Microbiota and the Neuroendocrine System. Neurotherapeutics. 2018 Jan;15(1):5-22)
- ...



Altered Microbiota in:



- **Parkinson's**: Qian Y, Yang X, Xu S, Wu C, Song Y, Qin N, Chen SD, Xiao Q. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. Brain Behav Immun. 2018 Mar 2. pii: S0889-1591(18)30028-X.
- **Alzheimer's** (Di Sabatino A, Lenti MV, Cammalleri L, Corazza GR, Pilotto A. Frailty and the gut. Dig Liver Dis. 2018 Mar 16)
- **ALS** (Brenner D, Hiergeist A, Adis C, Mayer B, Gessner A, Ludolph AC, Weishaupt JH. The fecal microbiome of ALS patients. Neurobiol Aging. 2018 Jan;61:132-137.)
- **Huntington's**
- **MS** (Tremlett H, Waubant E. Gut microbiome and pediatric multiple sclerosis. Mult Scler. 2018 Jan;24(1):64-68).
- **Autism** (Campion D, Ponzo P, Alessandria C, Saracco GM, Balzola F. Role of microbiota in the autism spectrum disorders. Minerva Gastroenterol Dietol. 2018 Mar 30.)
- **Epilepsy** (Xie G, et al. WJ. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J Gastroenterol. 2017 Sep 7;23(33): 6164-6171)
- **PANDAS** (Quagliariello A, et al. Gut Microbiota Profiling and Gut-Brain Crosstalk in Children Affected by Pediatric Acute-Onset Neuropsychiatric Syndrome and Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. Front. Microbiol. 9:675-)

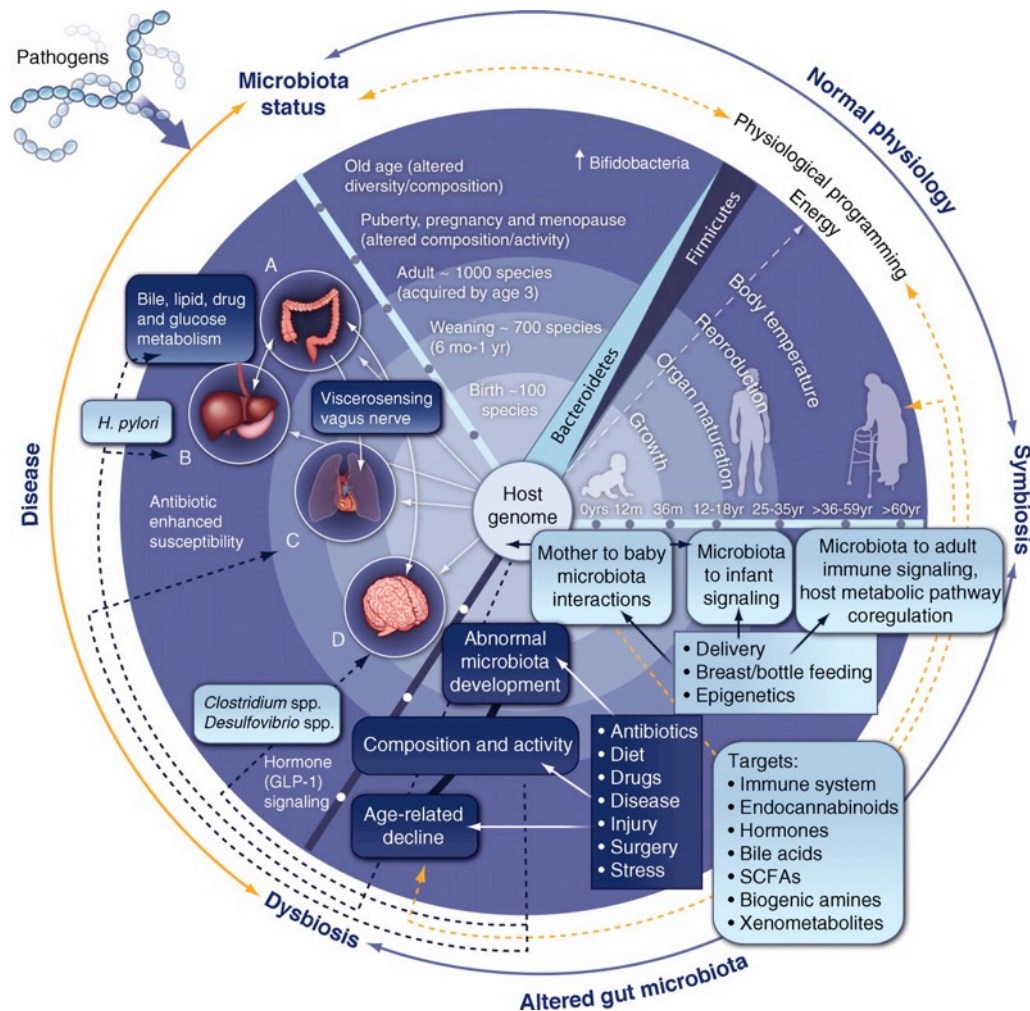
Intestinal Microbiota: A moderator in health and diseases.

4573 articles on pubmed

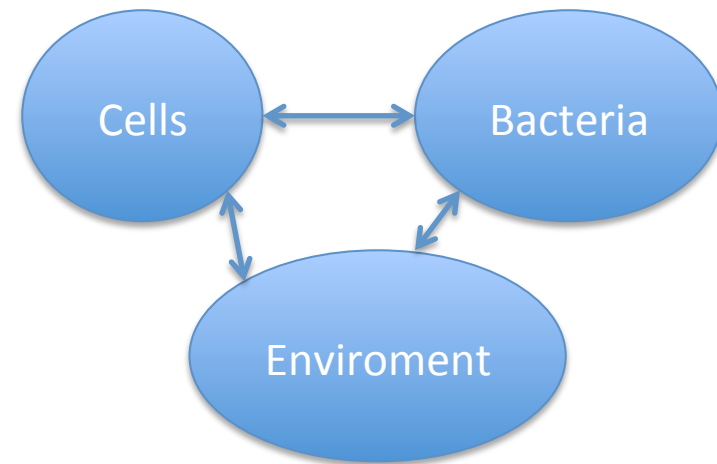


Feng Q, Chen W-D and Wang Y-D (2018) Gut Microbiota: An Integral Moderator in Health and Disease. Front. Microbiol. 9:151

THE GUT MICROBIOTA

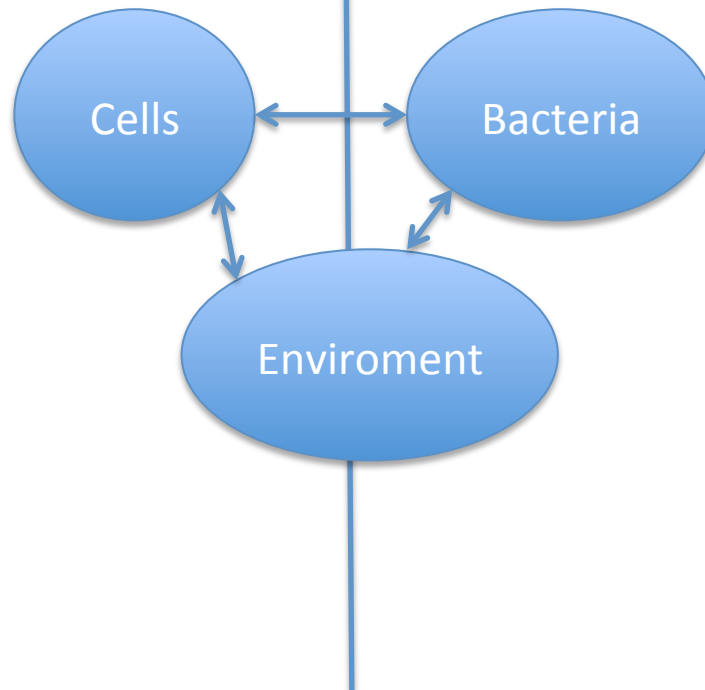


... Gut microecological imbalance caused by various biogenic and abiogenic agents and factors can produce different epigenetic abnormalities and the onset and progression of metabolic diseases associated ...



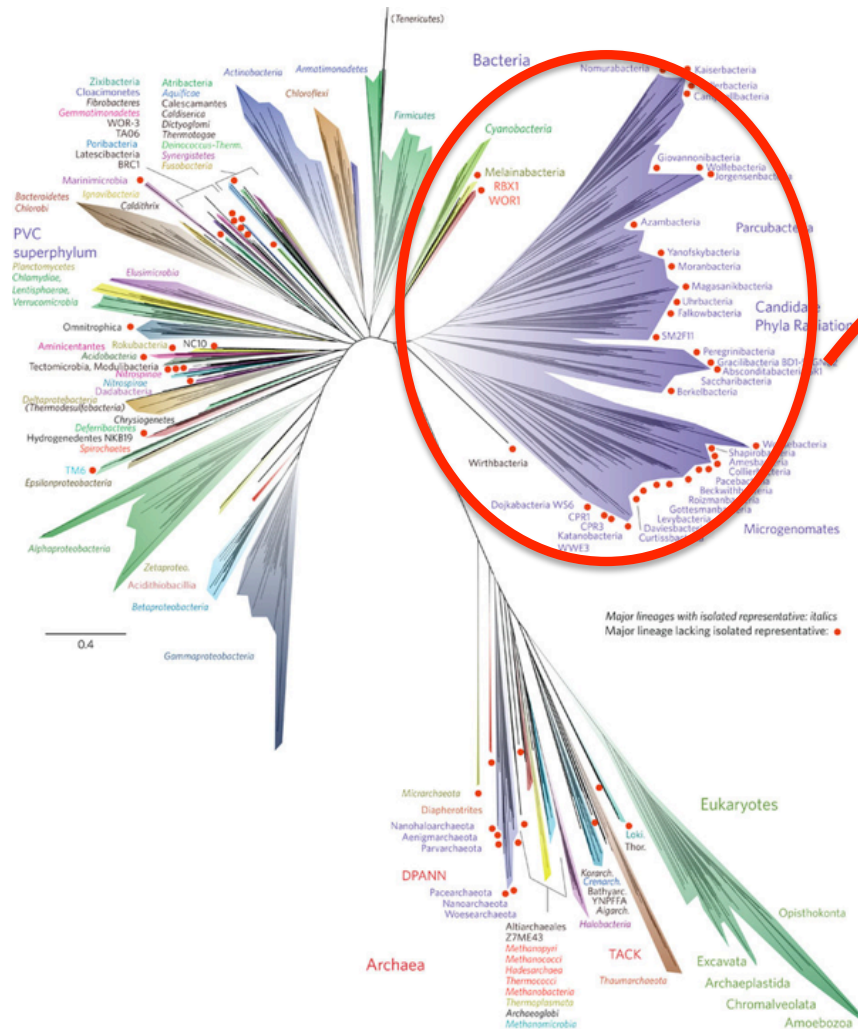
Malattia

Salute



A new tree of life:

grouped by evolutionary distance and not by taxonomy

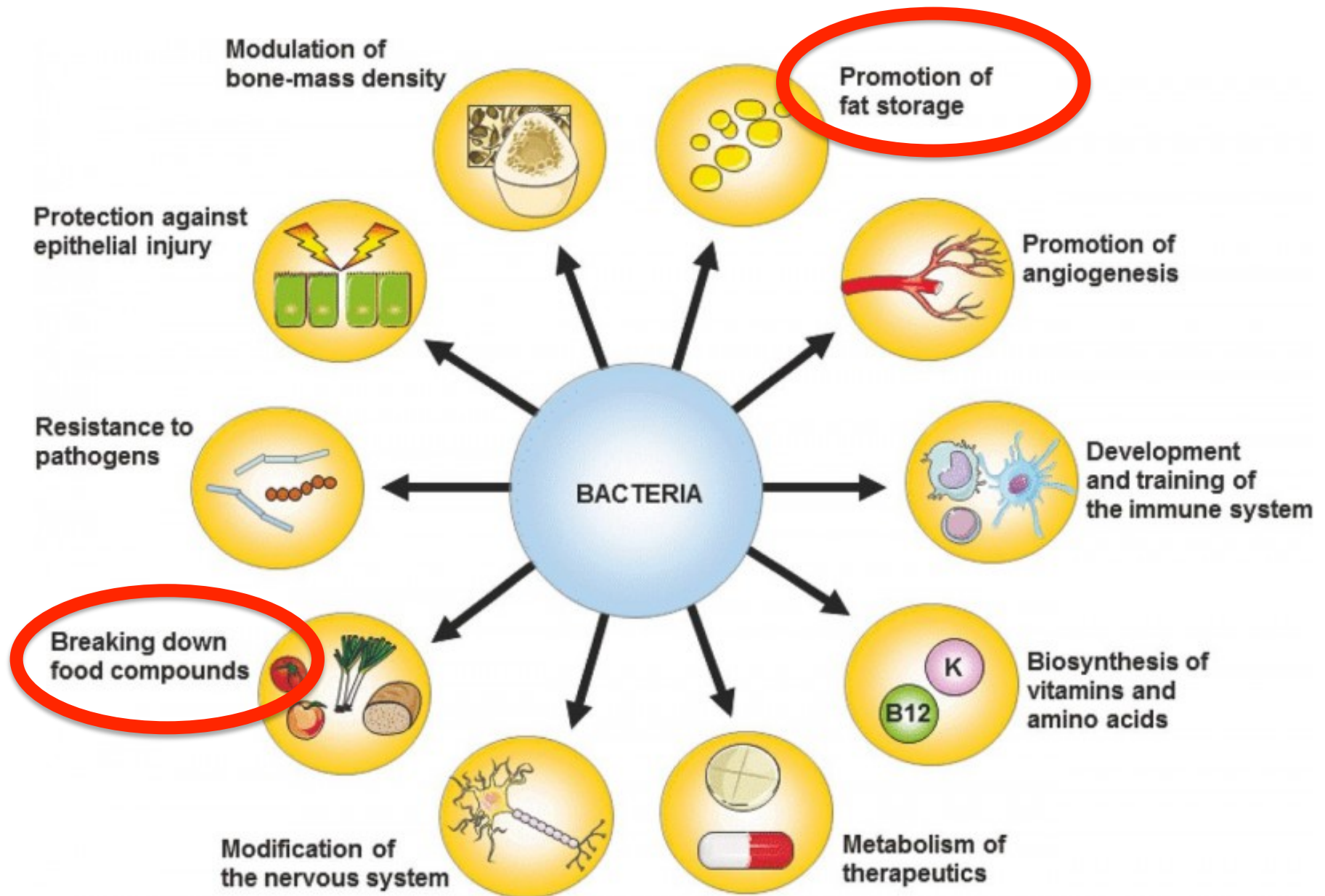


A new view of the tree of life

Laura A. Hug^{1†}, Brett J. Baker², Karthik Anantharaman¹, Christopher T. Brown³, Alexander J. Probst¹, Cindy J. Castelle¹, Cristina N. Butterfield², Alex W. Hernsdorf², Yuki Amano⁴, Kotaro Ise⁴, Yohey Suzuki⁵, Natasha Dudek⁶, David A. Relman^{7,8}, Kari M. Finstad⁹, Ronald Amundson⁹, Brian C. Thomas¹ and Jillian F. Banfield^{1,9*}

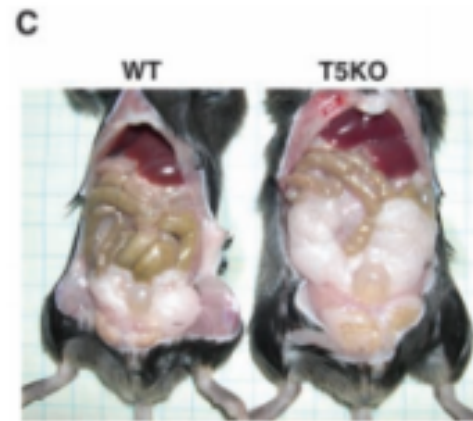
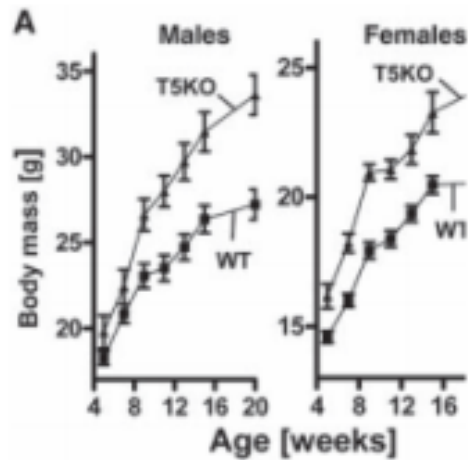
there is a large new branch, described as "candidate phyla radiation", only recently discovered and composed only of symbiont extremophile bacteria

"This incredible diversity means that there is a very incredible number of organisms we are just beginning to learn about the peculiarities, which could change our understanding of biology,"



Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms

Joe Alcock¹⁾, Carlo C. Maley^{2)3)4)*} and C. Athena Aktipis²⁾³⁾⁴⁾⁵⁾



I batteri vivono sulla Terra da 3.5 miliardi di anni, l'uomo da mezzo milione di anni

- ✓ Oltre tre miliardi di anni di evoluzione hanno affinato le capacità di batteri di sfruttare i loro ambienti.
- ✓ Milioni di anni di coevoluzione di batteri e dei loro ospiti presumibilmente hanno selezionato quei batteri che meglio manipolano i loro ospiti

Bacteria influence host appetite:

The bacteria in the gut possess several mechanisms for influencing the physiology of their hosts and, in particular, **can influence the preferences of their hosts for certain nutrients**

Positive feedback between gut microbiota and appetite:

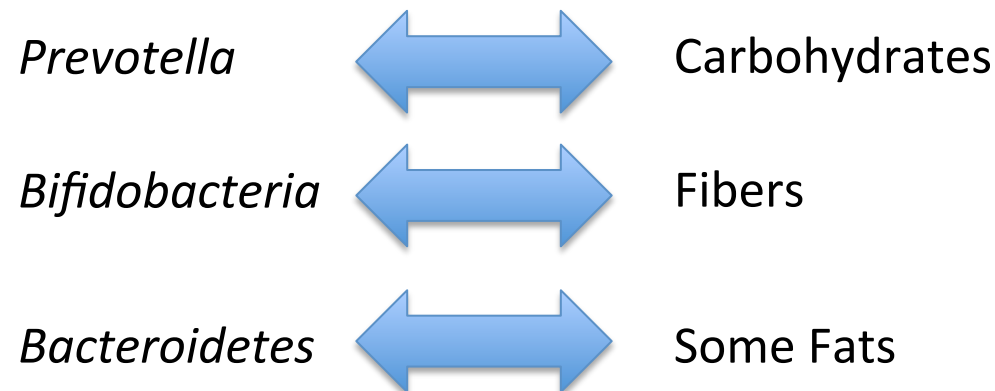
Un sistema di selezione basato su un feedback tra i nutrienti consumati e la composizione batterica intestinale porta ad una stabile attrazione verso particolari alimenti determinando il comportamento alimentare.



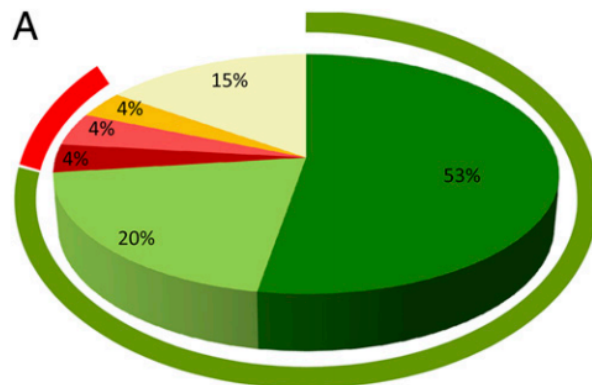
Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms

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Selective influence of diet on microbiota:



- Microbi che digeriscono alghe marine in Giappone
- Microbi che digeriscono la cellulosa in Africa

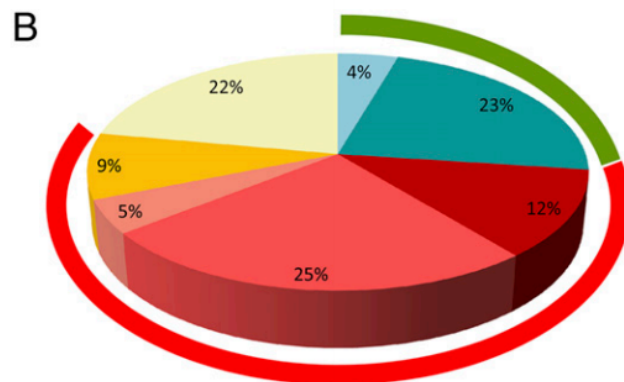


BF

- Prevotella } Bacteroidetes
- Xylanibacter }
- Acetitomaculum } Firmicutes
- Faecalibacterium }
- Subdoligranulum }
- Others }



village of
in Burkin

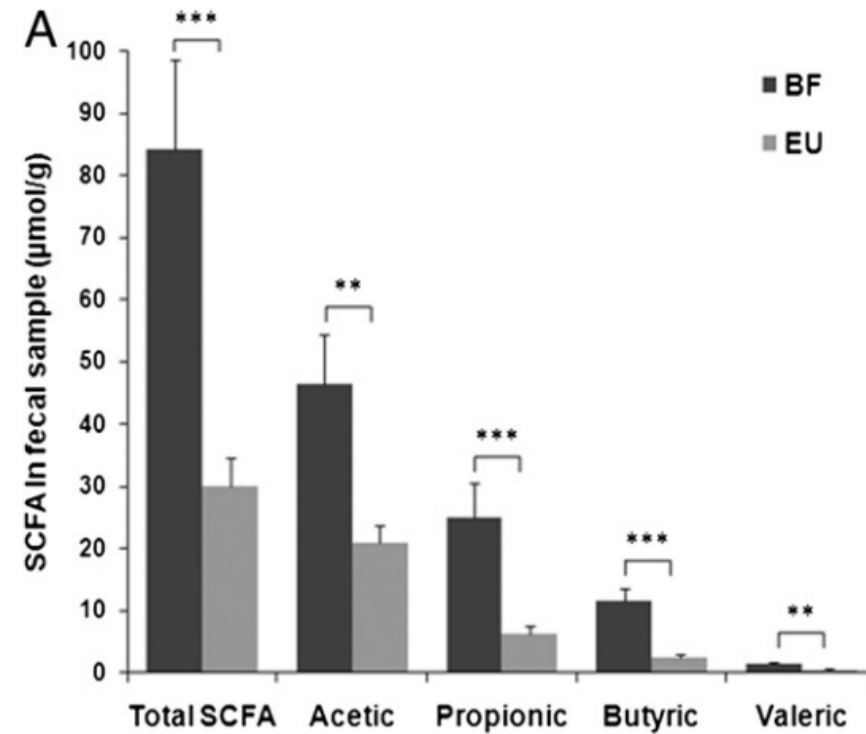


EU

- Alistipes } Bacteroidetes
- Bacteroides }
- Acetitomaculum } Firmicutes
- Faecalibacterium }
- Roseburia }
- Subdoligranulum }
- Others }



Firenze



De Filippo C, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proceedings of the National Academy of Sciences of the United States of America. 2010;107(33):14691-14696.

An altered F/B ratio carry out to altered metabolism

$$F/B_{\gamma\text{-PAN}} < F/B_{\text{ctrl}}$$

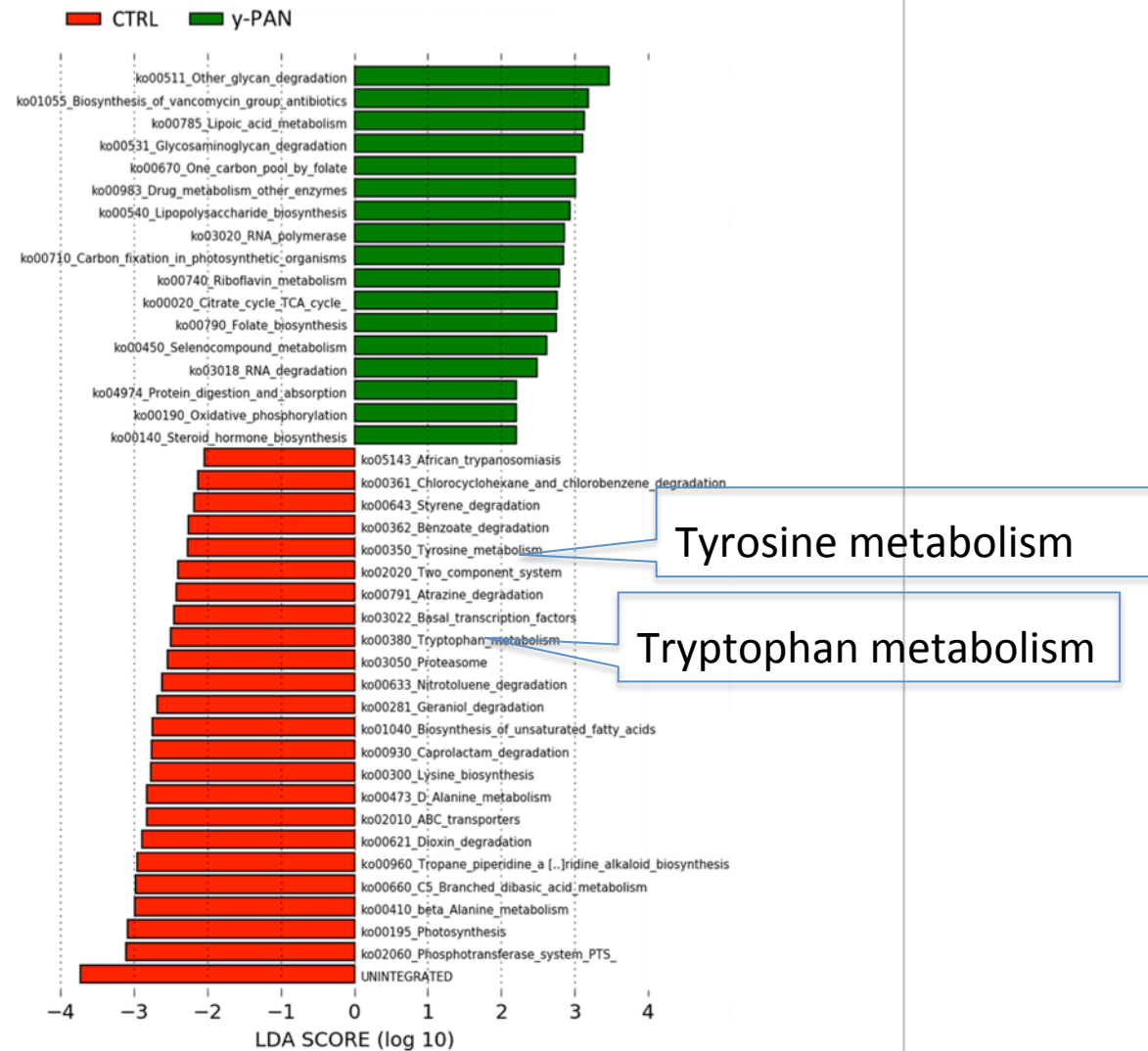


FIGURE 6 | KEGG biomarkers associated with the γ-PAN and CTRL groups. A linear discriminant effect size (LeFse) analysis has been performed (α value = 0.05, logarithmic LDA score threshold = 2.0).

Urinary metabolites in Chocolate indifferent and Chocolate desiring

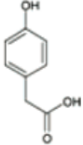

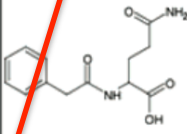
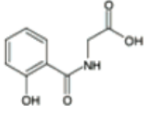
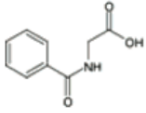
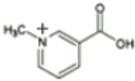
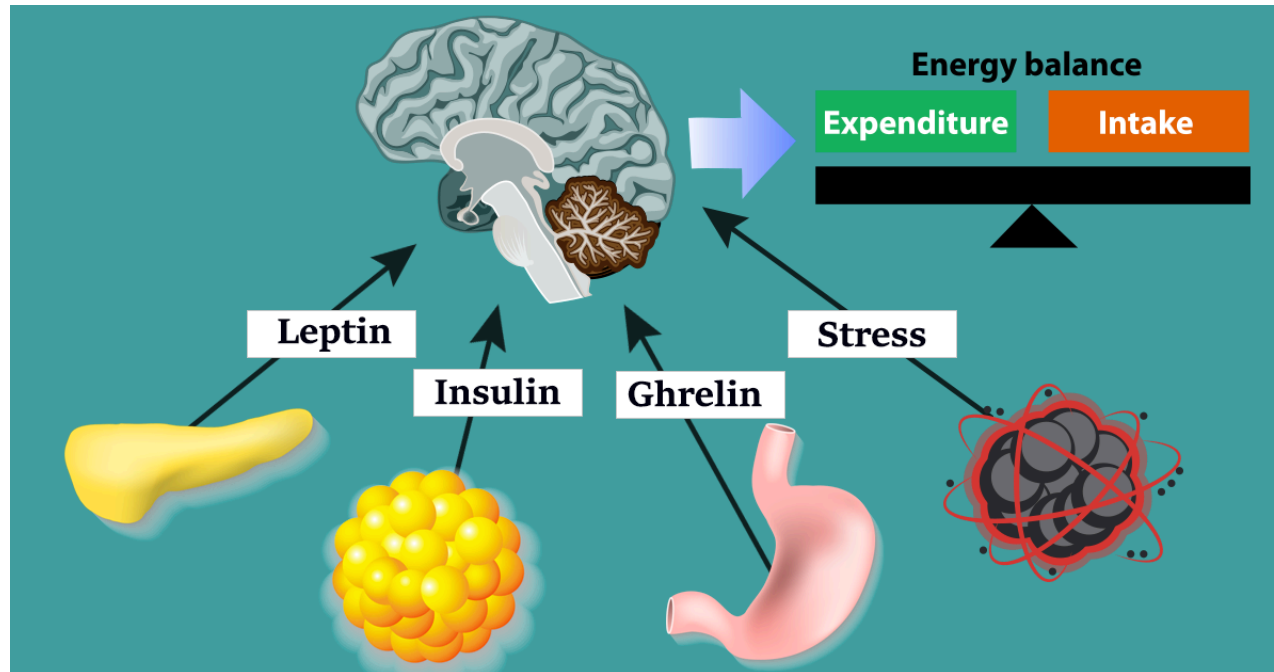
						
	4-HPA	4-cresol sulfate	PAG	2-HHP	hippurate	trigonelline
4-HPA		-0.3 (0.0860) *	0.6 (0.01x10 ⁻³) **	0.1 (0.5620)	-0.3 (0.0620) *	0.3 (0.0560) *
4-cresol sulfate	0.1 (0.3990)		0.3 (0.0220) **	0.1 (0.5450)	0.0 (0.8150)	0.1 (0.4570)
PAG	0.3 (0.0540) **	0.5 (0.0010) *		0.1 (0.3490)	-0.2 (0.1120)	0.3 (0.0340) **
2-HHP	-0.1 (0.6850)	0.2 (0.3240)	0.1 (0.5310)		-0.1 (0.4740)	-0.1 (0.3880)
hippurate	-0.1 (0.5800)	0.3 (0.0850) *	0.2 (0.2160)	0.3 (0.0300) **		0.0 (0.9950)
trigonelline	0.1 (0.4940)	0.1 (0.5560)	0.2 (0.1850)	0.3 (0.0470) **	-0.1 (0.7360)	

Figure 5. Correlation matrix between urinary host and microbial metabolites in “chocolate indifferent” and “chocolate desiring” individuals. This figure reports the Pearson correlation coefficients between ¹H NMR intensities scaled to the noise level obtained from the different aromatic metabolites and their respective *P*-values calculated at the confidence levels of 95% (**) and 90% (*) for the “chocolate desiring” (CD, blue) and the “chocolate indifferent” (CI, red) subjects. Positive and negative correlations show the multicollinearity between metabolites whose concentrations are interdependent such as in the case of a substrate–product biochemical reaction or under some common regulatory mechanisms across different pathways. Phenylacetylglutamine (PAG) shows significant and non-class specific correlations with 4-hydroxyphenylacetate (4-HPA) and 4-cresol sulfate, two microbial metabolites, which may indicate a relationship between microflora activity and the host liver and kidney metabolism. However, the correlations of 2-hydroxyhippurate (2-HHP) with hippurate and trigonelline are specifically observed in the CI group, while the CD group is characterized by the correlation of trigonelline with PAG. These observations highlight a class-specific microbial modulation of dietary flavonoids and niacin metabolism. Moreover, the conversion of 4-HPA to 4-cresol sulfate exhibits a negative correlation in the urine profiles of CD subjects confirming an already established substrate–product biochemical relationship associated with the gut activity of *C. difficile*. Interestingly, this relationship shows a non-significant correlation in the CI individuals. These findings suggest differential mammalian–microbial metabolism for the considered metabolites between the “chocolate desiring” and the “chocolate indifferent” individuals.

Microbiota dei golosi diverso da quello dei non golosi

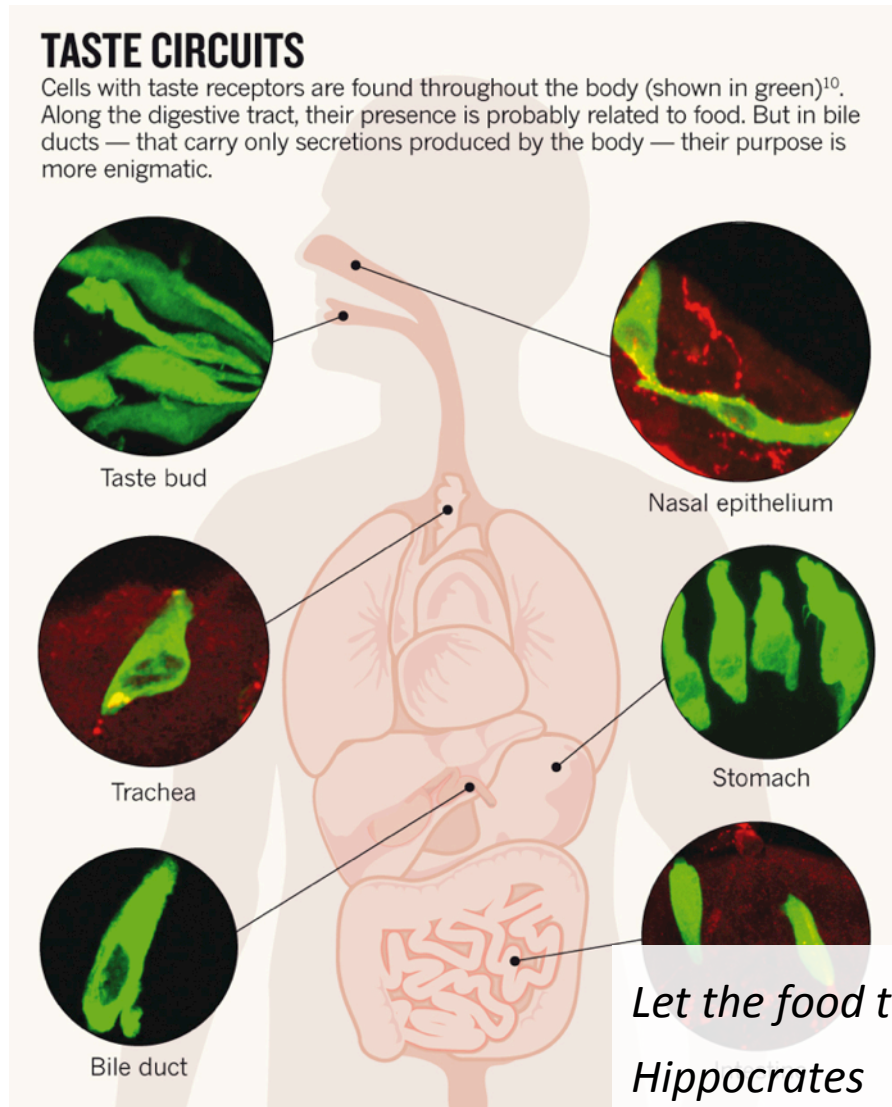
Rezzi S, et al. Human metabolic phenotypes link directly to specific dietary preferences in healthy individuals. J Proteome Res. 2007 Nov;6(11): 4469-77.



Gut Microbiota modifies Serum Leptin and Ghrelin Levels

Queipo-Ortuño MI, Seoane LM, Murri M, et al. Gut Microbiota Composition in Male Rat Models under Different Nutritional Status and Physical Activity and Its Association with Serum Leptin and Ghrelin Levels. Sanz Y, ed. PLoS ONE. 2013;8(5):e65465.

Taste receptors to produce anticipatory response to foods or pathogens.



- They recognize food
- Memorized it
- To produce fast response

- ✓ **The main role of digestive system is to protect gut ecosystem**
- ✓ **By the food we can talk with microbiota**
- ✓ **Food information goes beyond the nutritional aspect**

How do you feel? Interoception: the sense of the physiological condition of the body

A. D. Craig

L'interocezione è una consapevolezza interna soggettiva nel momento in cui si sente un'emozione nel corpo.

Di contro le posture, espressioni facciali ed i gesti, esprimono esternamente stati emotivi interni, comunicandoli agli altri



- ✓ The subjective process of feeling emotions requires the participation of brain regions that are involved in the mapping and/or regulation of our **continuously changing internal states** — that is, in **homeostasis**.
- ✓ **These feelings help to guide behavioural decisions that affect survival and quality of life** by producing a 'perceptual landscape' that represents the emotional significance of a particular stimulus that is being experienced, or of a projected future action by means of a further 'as-if-body loop' mechanism.

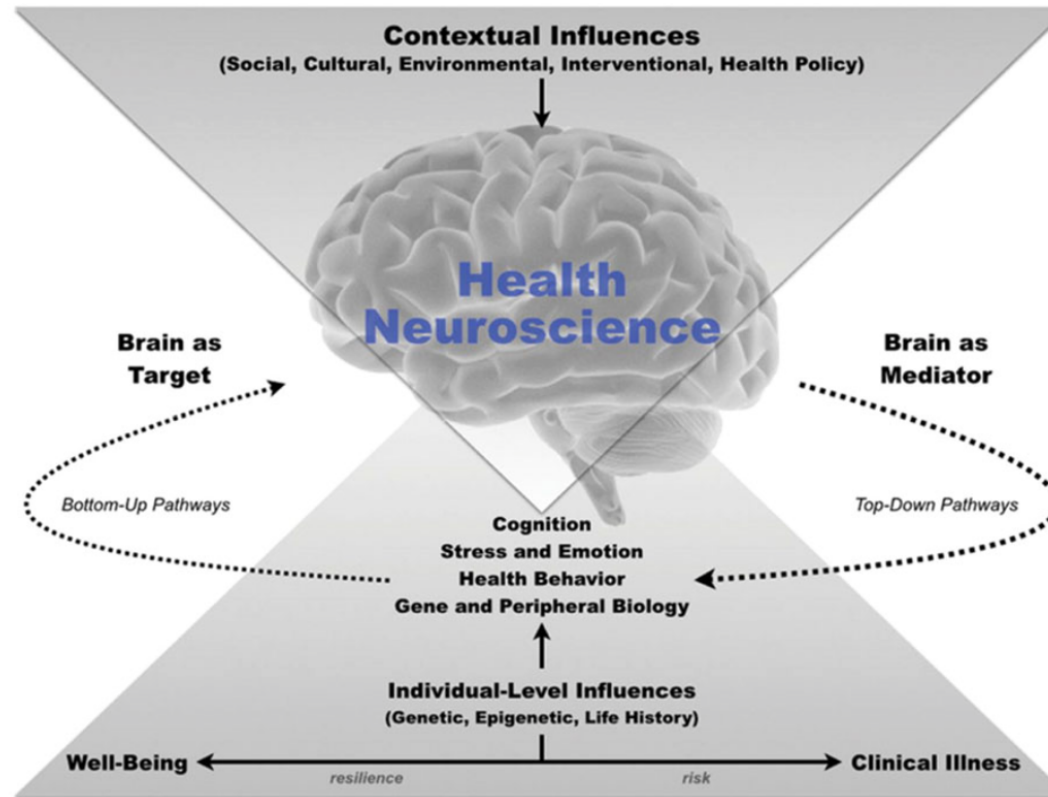


Figure 1. Conceptual model defining the interdisciplinary field of health neuroscience. Reprinted with permission from Ref. 1.

Questo intimo colloquio regola i normali processi digestivi e li integra con il completo stato fisico ed emozionale del corpo.

Il cibo ed il sesso fondamentali per garantire la sopravvivenza della specie.

il cibo e il sesso hanno la stessa localizzazione cerebrale, gli stessi circuiti neuroendocrini e gli stessi ormoni che li controllano, di conseguenza sono stimulate le stesse molecole del cervello.

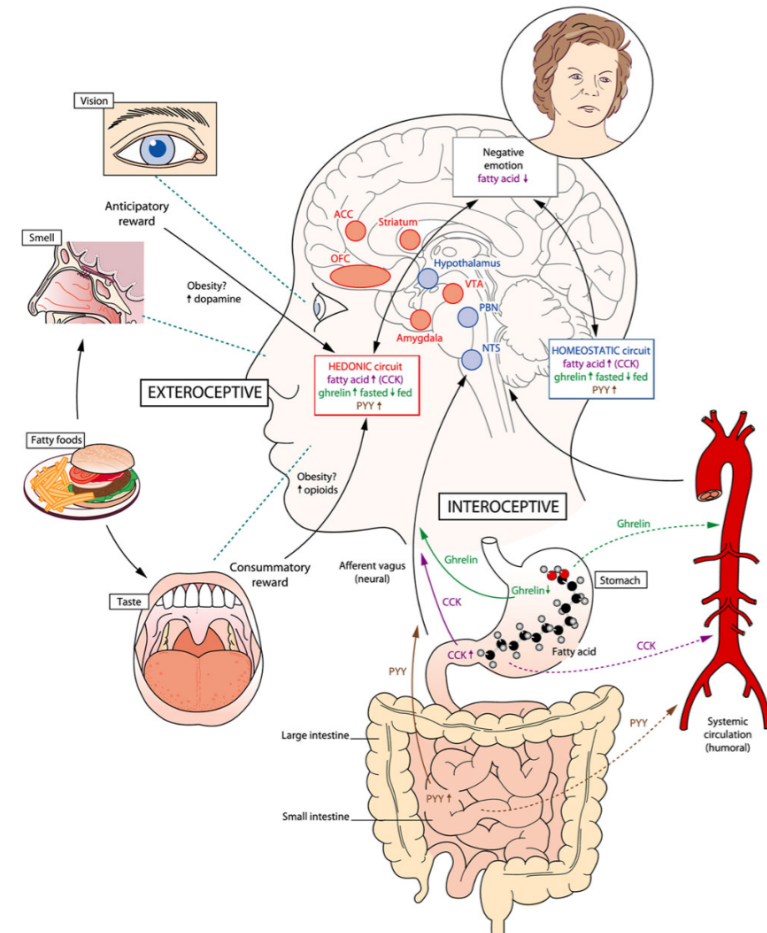
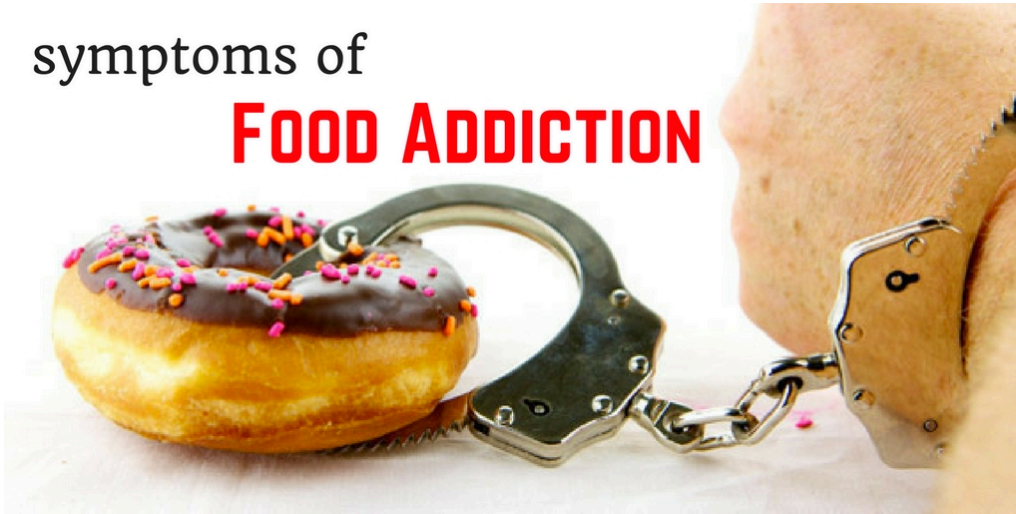


Figure 2. The gut-brain axis from a nutritional neuroscience perspective: interoceptive and exteroceptive gut-brain signaling pathways influencing homeostatic and hedonic appetite and feeding regulation. PYY, peptide YY₃₋₃₆; CCK, cholecystokinin; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; VTA, ventral tegmental area; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex. Reprinted with permission from Ref. 12.

symptoms of

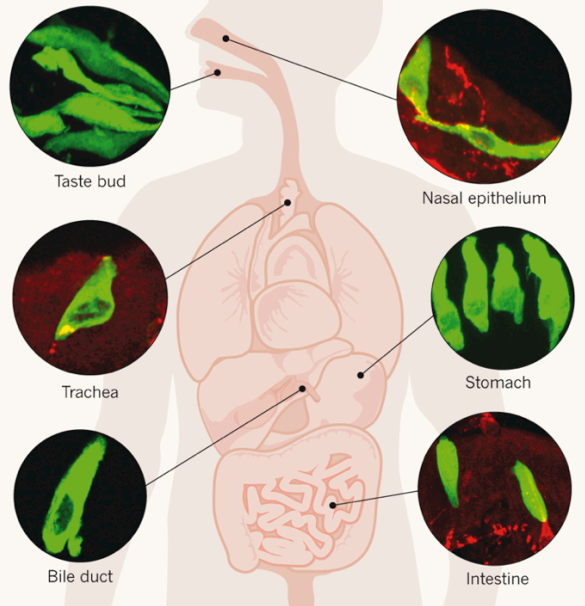
FOOD ADDICTION



- ✓ These deep-rooted connections between the senses and the brain can make it hard to change dietary habits
- ✓ Junk foods and sweet drinks are often described as addictive.
- ✓ It's not a classic chemical addiction, where a single drug hits a single receptor, but a widespread activation of eager taste receptors supercharging a powerful brain response.

TASTE CIRCUITS

Cells with taste receptors are found throughout the body (shown in green)¹⁰. Along the digestive tract, their presence is probably related to food. But in bile ducts — that carry only secretions produced by the body — their purpose is more enigmatic.

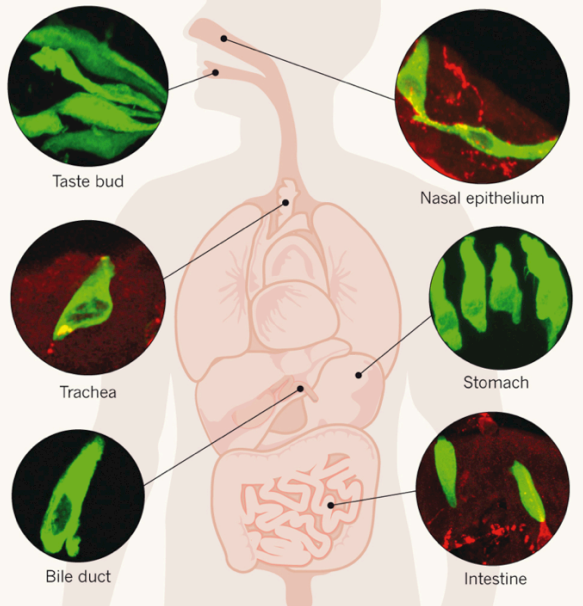


6 gusti:

- dolce,
- aspro,
- salato,
- amaro,
- saporito (umami)
- e grasso.

TASTE CIRCUITS

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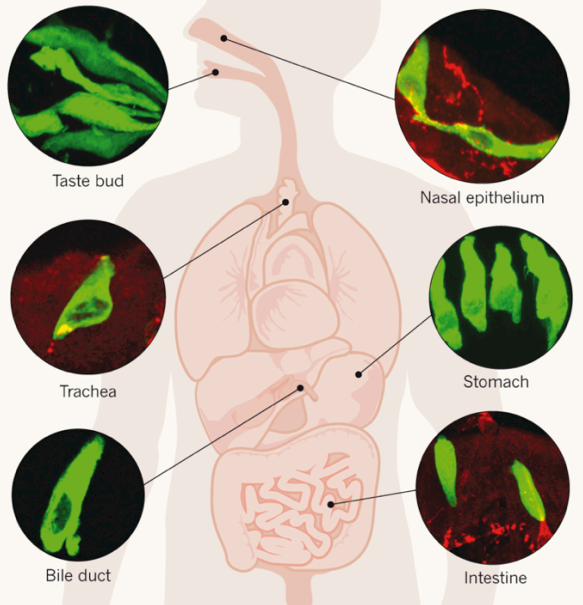
6 gusti:

- **dolce,**
- aspro,
- **salato,**
- amaro,
- **saporito (umami)**
- e grasso.

- ✓ scatenano una frenetica attività cerebrale che influenza profondamente gli stati d'animo, le emozioni e i ricordi (regioni emotive del cervello)

TASTE CIRCUITS

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6 gusti:

- dolce,
- aspro,
- salato,
- **amaro,**
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- ✓ una potente salvaguardia contro il consumo di cibi potenzialmente pericolosi.
- ✓ Alcuni cibi amari causano una risposta molto rapida – nausea e/o vomito

I bambini tendono ad evitare cibi che hanno sostanze chimiche amare, come i cavolini di Bruxelles

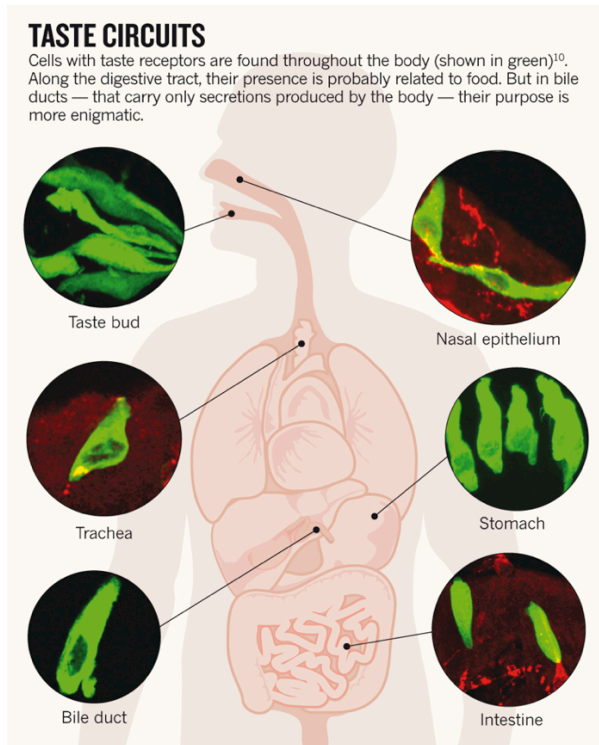
in dosi gestibili, i sapori amari possono essere tollerati e persino assaporati - come il sacro caffè mattutino.

Not only on the tongue

- ✓ the receptors that detect bitter, sweet and umami are not restricted to the tongue
- ✓ They are distributed throughout the stomach, intestine and pancreas, where they aid the digestive process by influencing appetite and regulating insulin production.
- ✓ They have also been found in the airways, where they have an impact on respiration, and even on sperm, where they affect maturation

A better understanding of what they do and how they work could have implications for treating conditions ranging from allergy, diabetes to infertility.

Taste receptors response to bitter-tasting compounds in airway



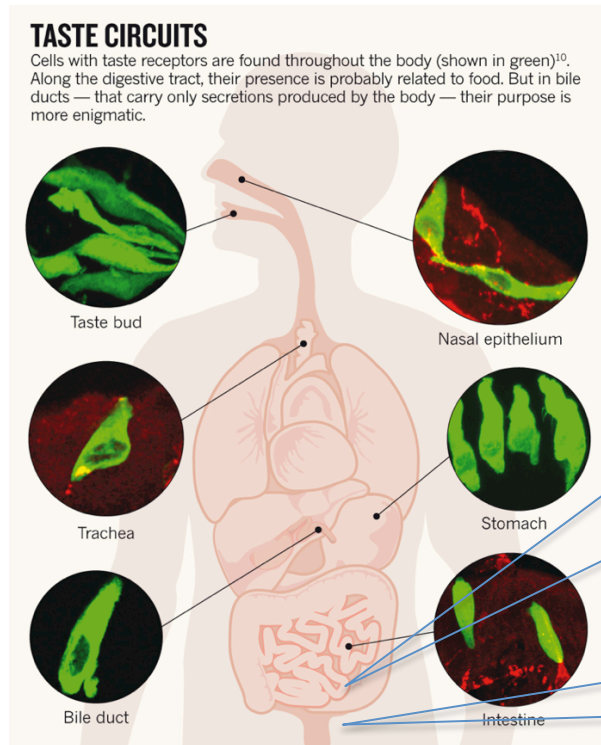
Bitter receptors are also found on cilia on human airway epithelium cells

When are stimulated by bitter compounds, such as nicotine or quinine, the cilia waved back and forth vigorously, **helping to clear the airways of irritating compounds**

“they stop breathing,
they cough and sneeze,”

This response is to stop the irritant from being inhaled deep into the lungs

Taste receptors response to bitter- and umami tasting compounds in testes



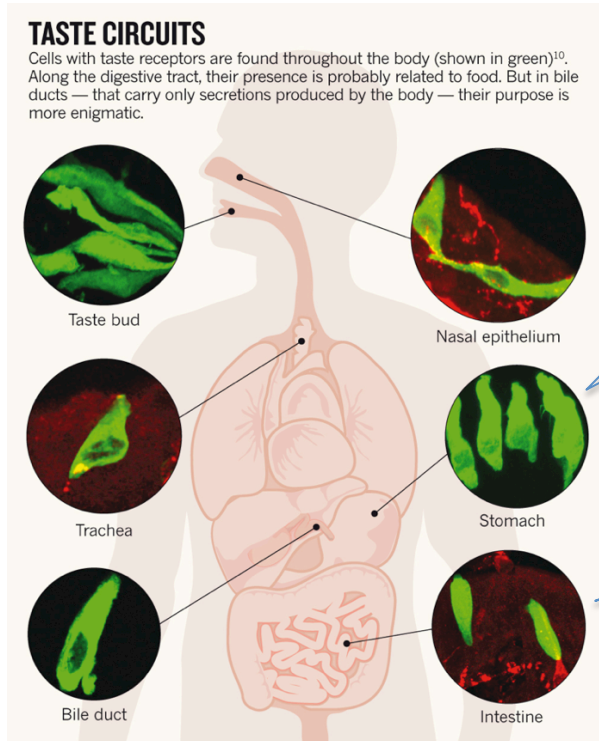
The bitter receptor T2R5 is also found in the testes; deleting these cells leads to smaller testes and a huge reduction in the number of mature sperm

The umami receptor keeps the sperm in a quiet state until it reaches an egg.

Mammary epithelial cells express Tas2Rs, and their expression is **downregulated in breast cancer cells**.

Tas2Rs act on apoptosis signaling.

Taste receptors response to carbohydrates and proteins



T1R3 receptors secrete ghrelin, **encouraging eating** when important nutrients are available .

The sweet receptor on L cells produce the gastrointestinal incretin hormone GLP-1, which stimulates insulin production and sends a **satiety signal to the brain**

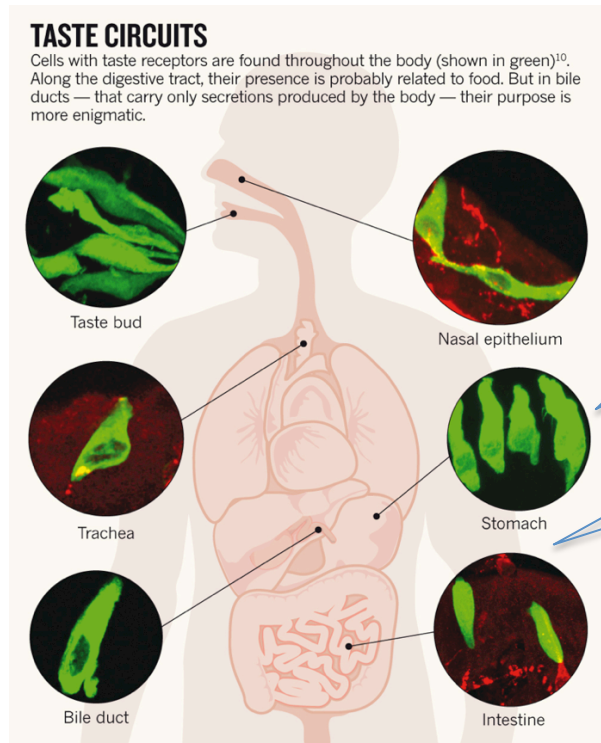
Jang,H.J.et al.Proc.NatlAcad.Sci.USA104, 15069–15074 (2007).

- ✓ Blocking or deleting these sweet receptors decreases insulin release
- ✓ This 'second tasting' triggers glucose transport into the cells and bloodstream, and the faster this happens, the more insulin will be released.

It was surprising that artificial sweeteners, which were thought to influence only the tongue, also trigger changes in the gut

Margolskee, R. F. et al. Proc. Natl Acad. Sci. USA 104, 15075–15080 (2007).

Taste receptors response bitter-tasting compounds



Initially, T1R3 receptors secrete ghrelin, **encouraging eating** when important nutrients are available .

But after 30 minutes, food intake decreased, as did gastric emptying, keeping the food in the stomach

This curbs the appetite by prolonging the sense of fullness and satiety — perhaps to prevent the ingestion of toxic food.

The Romans drank wine infused with bitter herbs to prime the appetite and prevent over-eating.

Microbiota alters taste receptors

- Germ-free mice had altered TRs for fat on tongues and on intestine.

(Duca FA et al. 2012 Increased oral detection, but decreased intestinal signaling for fats in mice lacking gut microbiota. PLoS ONE 7: e39748)

- Germ-free mice preferred more sweets, have more sweet TRs in gut vs normal mice.

(Swartz T et al. 2012 Up-regulation of intestinal type 1 taste receptor 3 and sodium glucose luminal transporter-1 expression and increased sucrose intake on mice lacking microbiota. Br J Nutr 107:621)

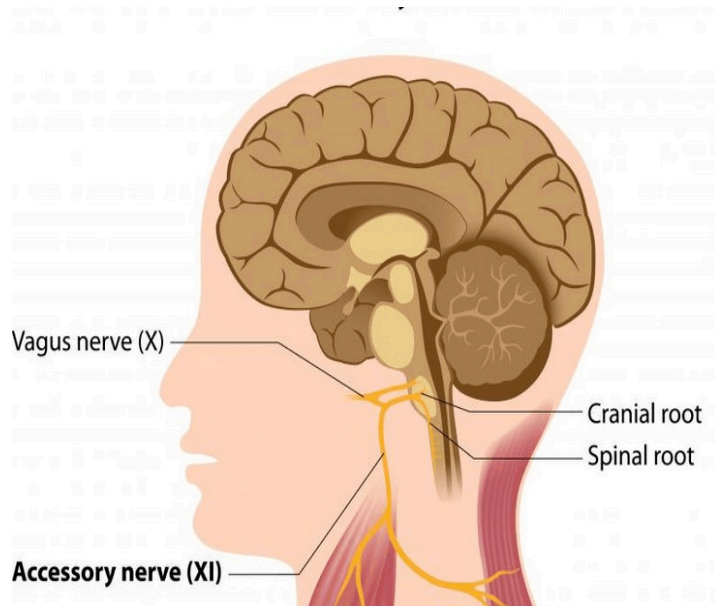
- Gastric bypass surgery modifies TR, change microbiota and alters satiety and food preferences.

(Miras AD, le Roux CW. 2013 Mechanisms underlying weight loss after bariatric surgery. Nat Rev Gastroenterol Hepatol 10:575-84)

Microbes could influence food preferences by altering receptor expression or transduction

Microbiota can influence hosts through neural mechanisms

- ✓ The vagus nerve is a central actor in this communication, connecting 100 million neurons of ENS to the brain
- ✓ Enteric nerves have receptors that react to particular bacteria and to bacteria metabolites, i.e. SCFAs

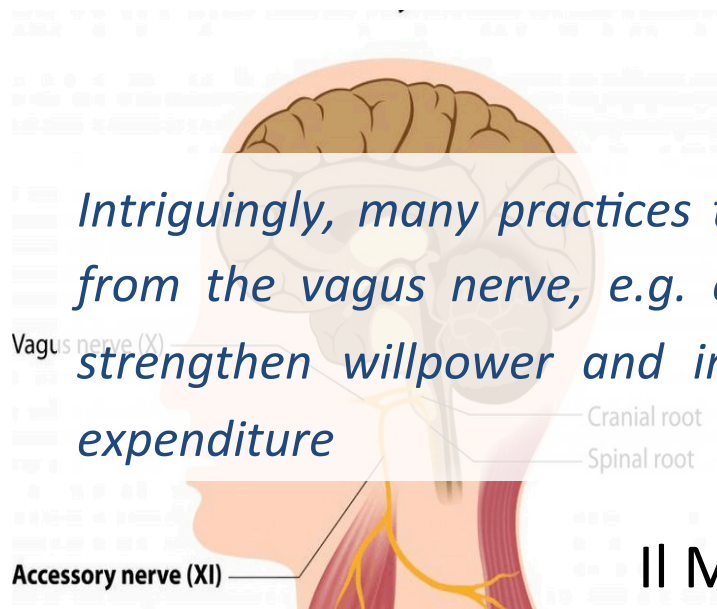


- ✓ Vagus nerve regulates eating behaviour and body weight:
 - ✓ Its transection cause drastic weight loss
 - ✓ Its stimulation, i.e. by NE, drive to excessive eating behaviours

- *Then, gut microbes producing adrenergic neurochemicals may contribute to overeating by Vagus nerve*
- *Microbes have opportunities to manipulate vagus nerve traffic in order to control host eating*

Microbiota can influence hosts through neural mechanisms

- ✓ The vagus nerve is a central actor in this communication, connecting 100 million neurons of ENS to the brain
- ✓ Enteric nerves have receptors that react to particular bacteria and to bacteria metabolites, i.e. SCFAs



Intriguingly, many practices that are known to enhance parasympathetic outflow from the vagus nerve, e.g. exercise, yoga, and meditation, are also thought to strengthen willpower and improve accuracy of food intake relative to energy expenditure

Il Microbiota altera la percezione di se stessi

WARNING: to increase vagus activity is not always associated with health.

One study linked parasympathetic vagus activity with weight loss in patients with anorexia nervosa.

Microbiota orchestrates inflammatory processes

Dysregulation of gut microbiota and **chronic inflammatory** disease

*In addition to their barrier function, Intestinal Epithelial Cells (IECs) serve as ‘mediators’, maintaining a **balanced relationship between gut microbes and the host immune system** by secreting **cytokines**, chemokines and hormones.*

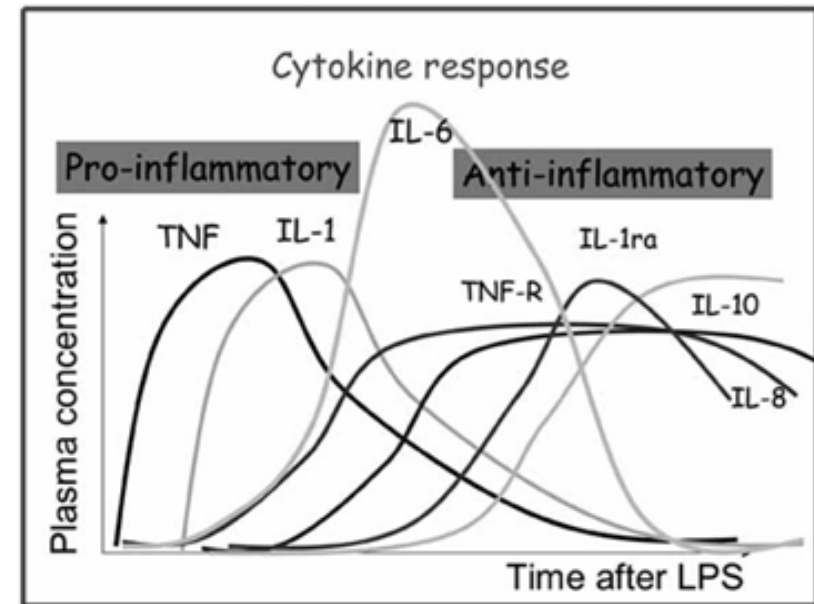
*Thus, dysfunction of the IECs leads to perturbation of the gut microbiota and enhances susceptibility to **intestinal inflammation***

Inflammatory cascade:

Pro- and anti-inflammatory Modulate from APR to CPR

APR: Acute Phase Reaction

CPR: Chronic Phase Reaction



- **The Pro-Inflammatory Cytokines produce necrosis**
- **The Anti-inflammatory Cytokines rebuild tissues**

In CNS:

- The Pro-inflammatory cytokines inhibit synaptogenesis and neurogenesis,
- The Anti-inflammatory cytokines restart Synpatogenesis and neurogenesis processes

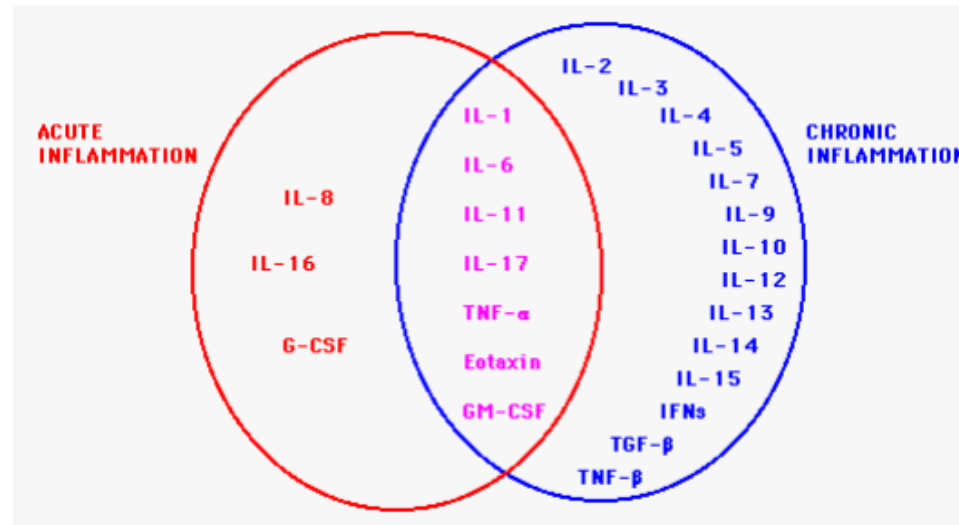


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

In Chronic Inflammation are produced different anti-inflammatory cytokines: unable to rebuilt tissues, unble to restart synaptogenesis and neurogenesis processes in CNS

***Stig Bengmark, Acute and “chronic” phase reaction - a mother of disease.
Clinical Nutrition (2004) 23, 1256–1266***

Cytokine-related Mechanisms of Apoptosis

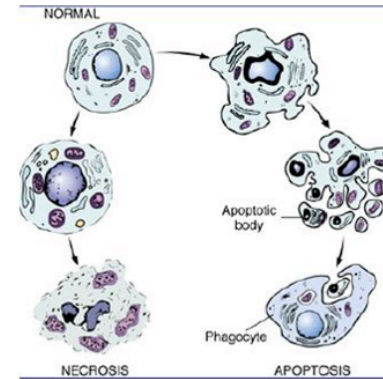
Meccanismi di morte cellulare

• Apoptosi

- Morte programmata
- Contrazione
- Corpi apoptotici

• Necrosi

- Morte accidentale
- Espansione
- Infiammazione



- Cytokines participate in neuronal development in brain functioning. Inappropriate activity can produce different neurological symptoms

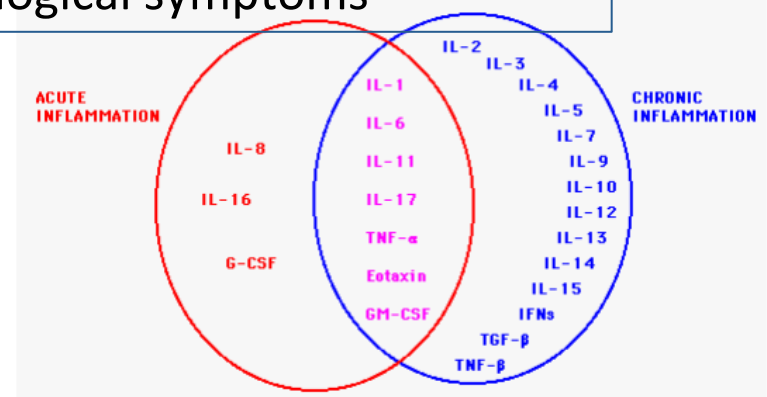


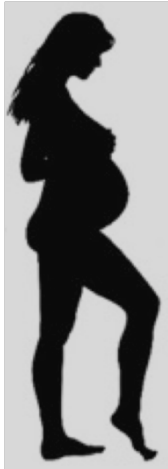
FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

when does the problem originate?



- **Impact of Maternal Stress in Pregnancy on Brain Function of the Offspring**

Udagawa J, Hino K. Impact of Maternal Stress in Pregnancy on Brain Function of the Offspring. *Nihon Eiseigaku Zasshi*. 2016;71(3):188-194.



Metabolic changes during pregnancy:

- Same nutritional intake
- Increased energy extraction by foods:

Leptin (ng/ml) ^f	30.72 (±1.83)	37.58 (±2.47)	0.0008
Cholesterol (mmol/l) ^f	4.76 (±0.09)	6.37 (±0.12)	1.72 × 10 ⁻³³
Insulin (mU/l) ^f	6.48 (±0.59)	10.92 (±0.88)	1.01 × 10 ⁻⁸
Homeostatic model assessment (HOMA) ^f	1.35 (±0.12)	2.28 (±0.19)	1.93 × 10 ⁻⁷
Quantitative insulin sensitivity check index (QUICKI) ^f	0.39 (±0.01)	0.35 (±0.00)	2.39 × 10 ⁻⁹
Glucose (mmol/l)	4.65 (±0.03)	4.61 (±0.05)	0.5799
GHbA1c1 (%) ^f	5.01 (±0.03)	5.23 (±0.03)	9.92 × 10 ⁻¹⁰

Cell 150, 470–480, August 3, 2012 ©2012 Elsevier Inc.

Cell

Host Remodeling of the Gut Microbiome and Metabolic Changes during Pregnancy

Omry Koren,¹ Julia K. Goodrich,¹ Tyler C. Cullender,¹ Ayumi Spor,^{1,11} Kari Laitinen,^{1,11} Helene Kling Bäckhed,^{1,2} Antonio Gonzalez,³ Jeffrey J. Warner,^{1,12} Lázaro T. Anguiano,¹ Rob Knight,^{1,13} Fredrik Bäckhed,^{1,2} Erika Isaksson,⁴ Soope Saarnimäki,⁵ and Ruth E. Ley^{1,14}

- the microbiota undergoes profound changes in T3 vs T1
- It is not due to nourish the fetus, but to realize his tissues by anti-inflammatory cytokines

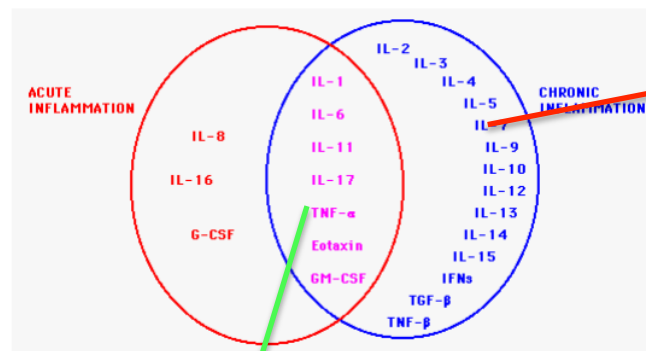


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

Houston, we have a problem!

No-problems



when does the problem originate?



- **Neonatal inflammatory pain and systemic inflammatory responses as possible environmental factors in the development of autism spectrum disorder of juvenile rats.**

The first 1000 days of life set the tone for the whole of the lifespan.

May be linked with the bacterial phylogenetic diversity?

In the first 1000 days of life, new born arrives to have a microbiota like mother's one at T1

By Caesarean section or too medicalized deliveries risks taking the midwife's one

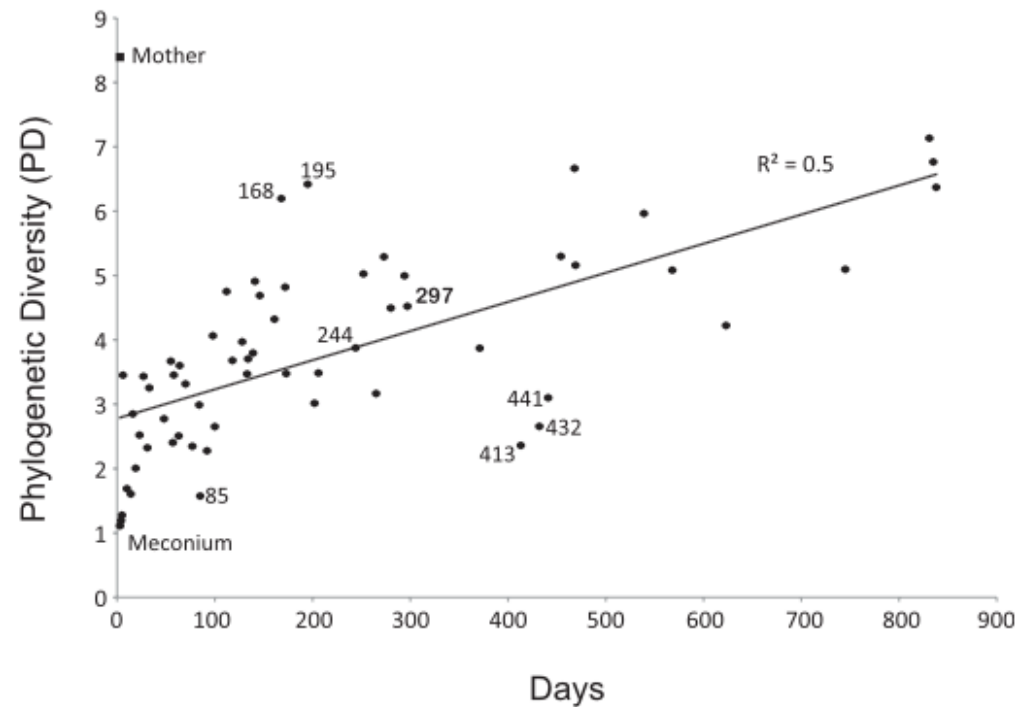
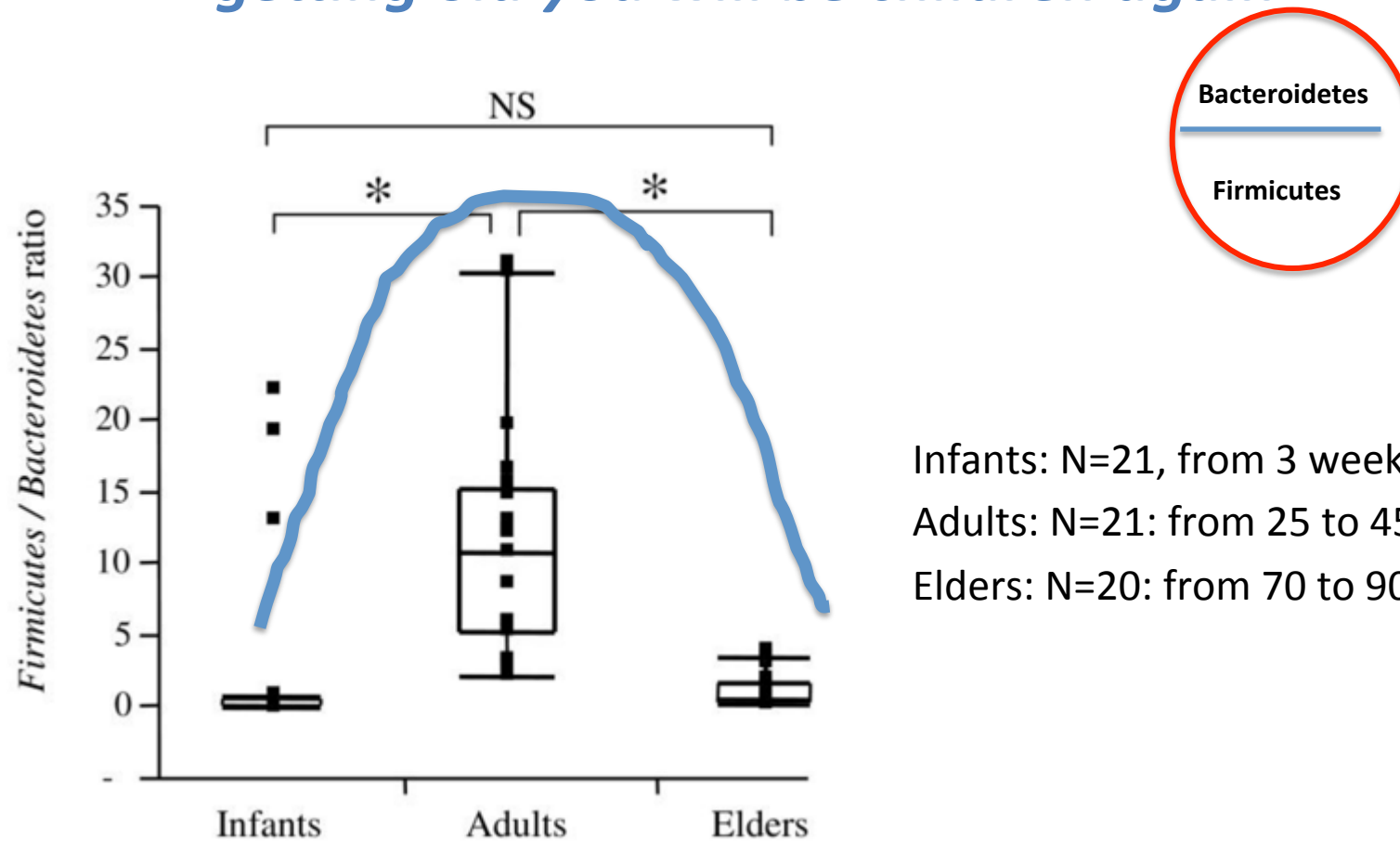


Fig. 1. Bacterial PD of the infant gut microbiota over time. PD provides a measure of the diversity within a community based on the extent of the 16S rRNA phylogenetic tree that is represented by that community. Symbols are fecal samples. The mother's fecal sample, collected at day 3, is denoted as a filled square.

Firmicutes/Bacteroidetes ratio vs ageing

getting old you will be children again



Infants: N=21, from 3 weeks to 10 months

Adults: N=21: from 25 to 45 years

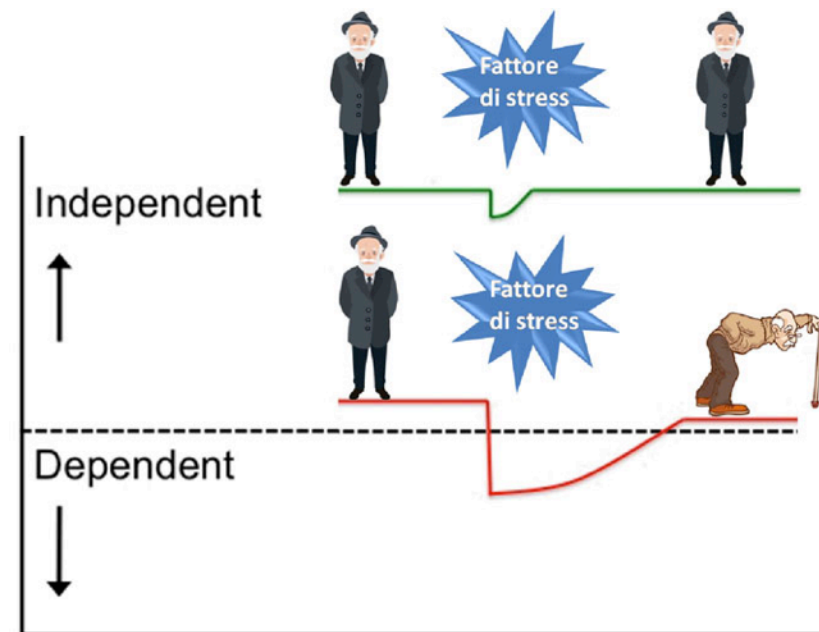
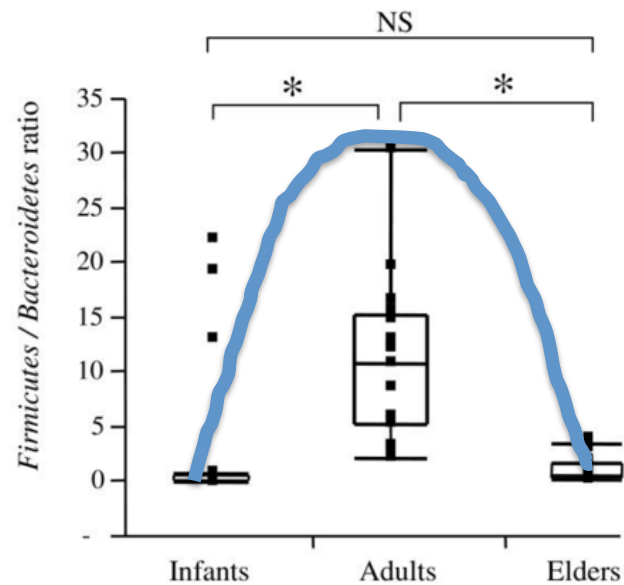
Elders: N=20: from 70 to 90 years

Mariat D, Firmesse O, Levenez F, Guimarães V, Sokol H, Doré J, Corthier G, Furet JP. The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. BMC Microbiol. 2009 Jun 9;9:123

Frailty in older people

Frailty is the most problematic expression of population ageing.

It is a **state of vulnerability** to **poor resolution of homeostasis** following a stress and is a **consequence of cumulative decline in multiple physiological systems over a lifespan**.



The frail gut is characterised by a low-grade chronic mucosal inflammation, impaired immune response, increased permeability, and reduced microbiota diversity

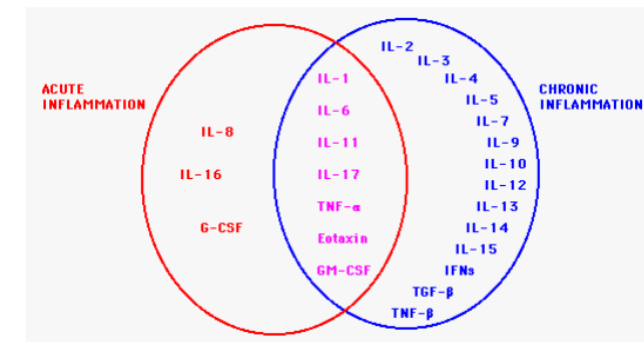
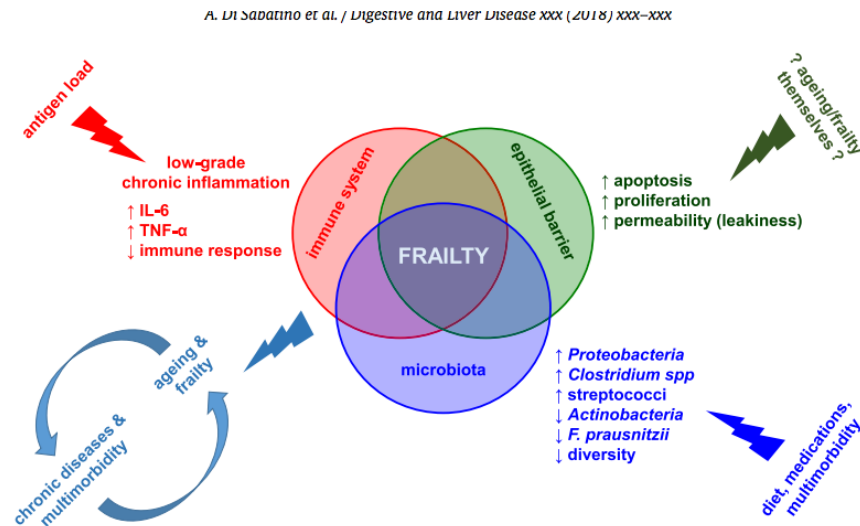


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

A reduced microbiota diversity carry out to **Chronic Inflammation**:

A type of inflammation unable to repair tissues continually damaged by stressor

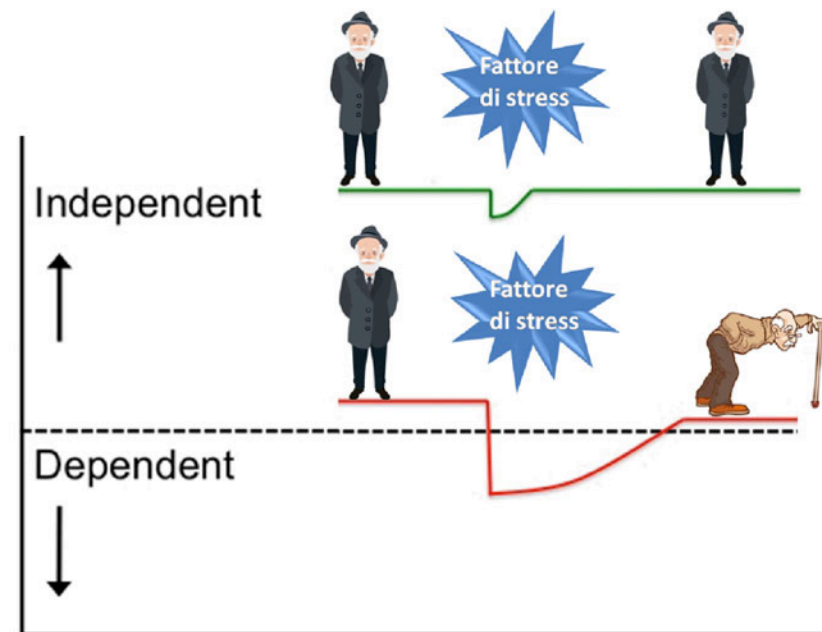
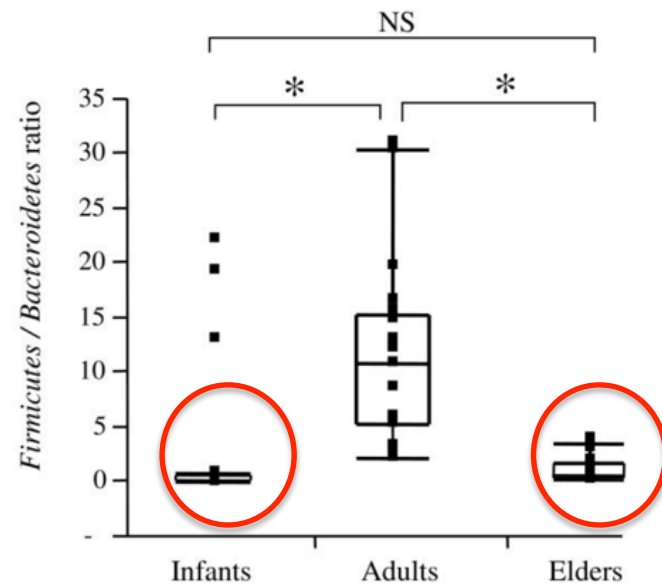
Fintanto che sono capace a ripararmi, l'agente stressogeno non mi causa problemi

Di Sabatino A, Lenti MV, Cammalleri L, Corazza GR, Pilotto A. Frailty and the gut. Dig Liver Dis. 2018 Mar 16. pii: S1590-8658(18)30228-7.

Frailty in older people

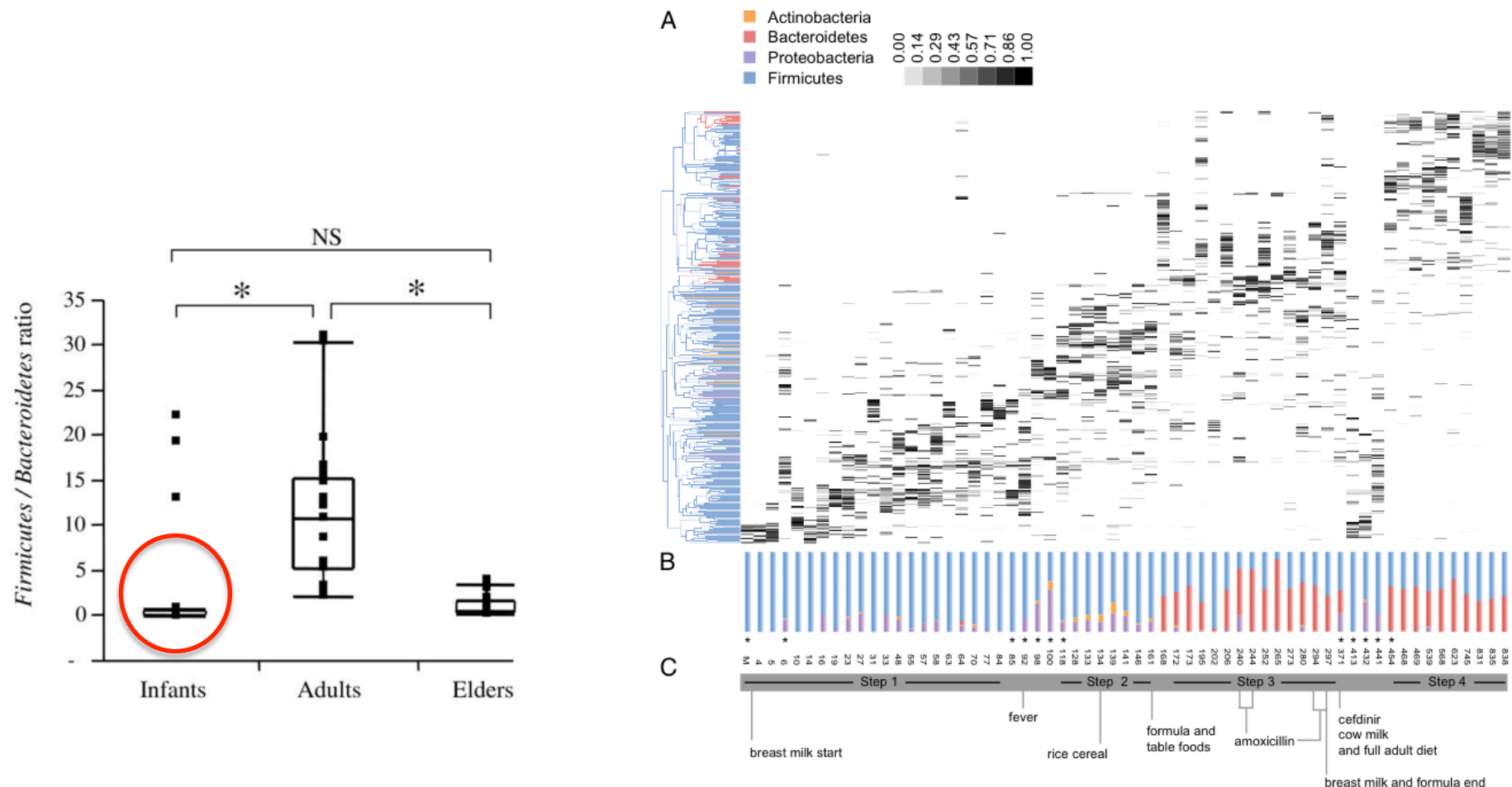
Frailty is the most problematic expression of population ageing. It is a state of vulnerability to **poor resolution of homeostasis following a stress** and is a consequence of cumulative decline in multiple physiological systems over a lifespan.

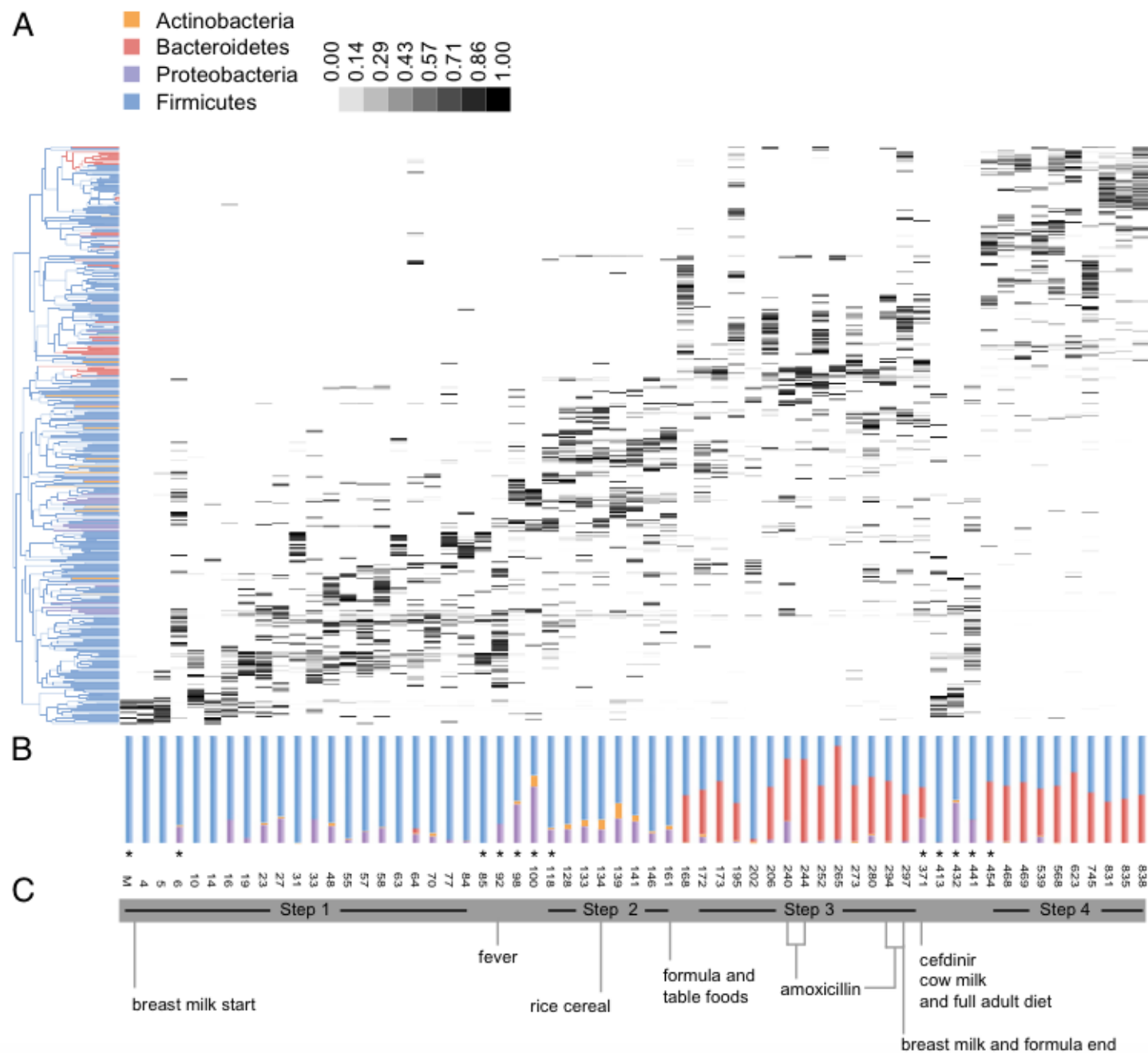
LIKE VULNERABILITY IN THE FIRST 1000 DAYS OF LIFE



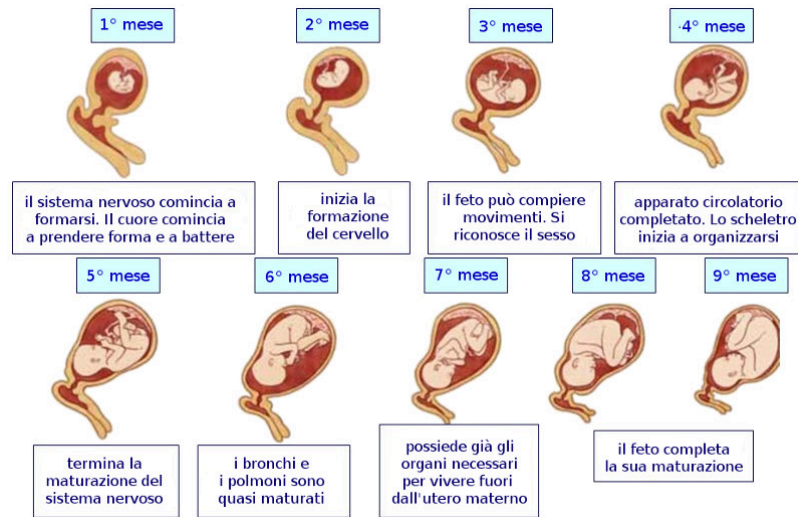
Frailty in newborns and in infants

- Weaning ends at 7 years
- It is equivalent to bring the digestive system to gym: it has to be gradual and progressive.
- Microbiota has to be perturbed by stressful agents, but the strength of stress must be comparable with that of the microbiota.





PROGRAMMA DI MATURAZIONE FETALE



the neonatologist, and then the pediatric neurologist, must know the entire clinical history of the child.



The relationship between premature birth and obesity among children aged 10 to 17 years in the U.S.

Tabitha Young

*Presented to the Public Health Faculty at the University of Michigan-Flint
in partial fulfillment of the requirements for the Master of Public Health*

- ✓ Adolescents that were born premature tended to have body weights other than the normal ranging either too high or too low.
- ✓ These results suggest that prematurity may play some role in weight gain

Intestinal dysbiosis in anorexia

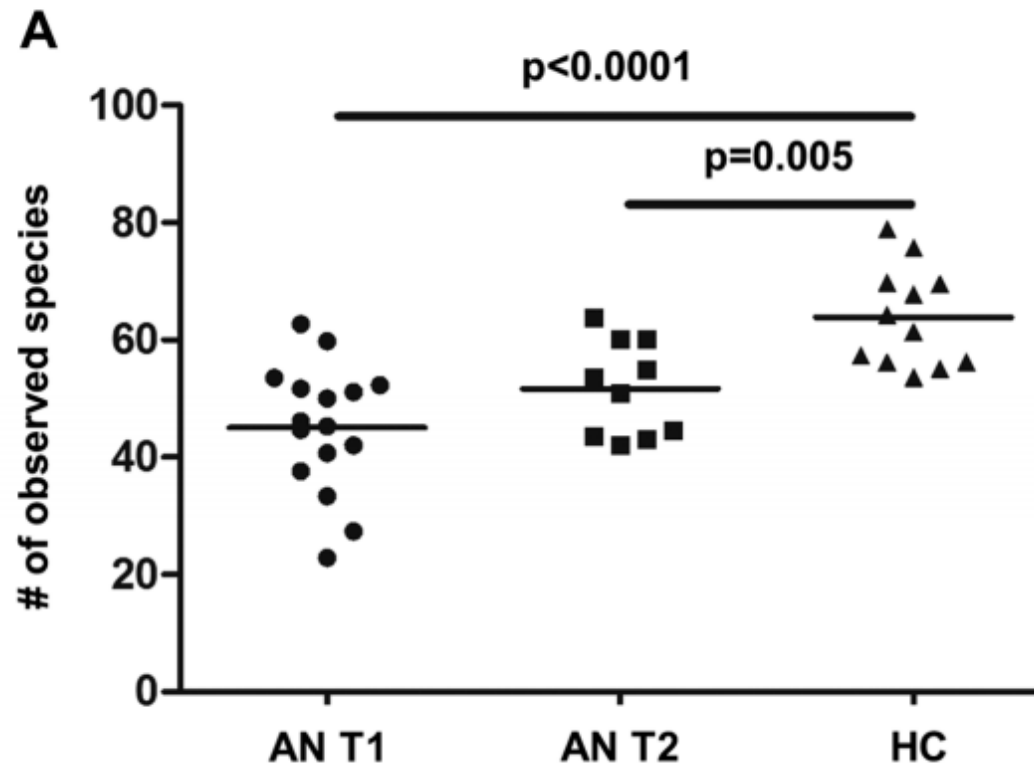
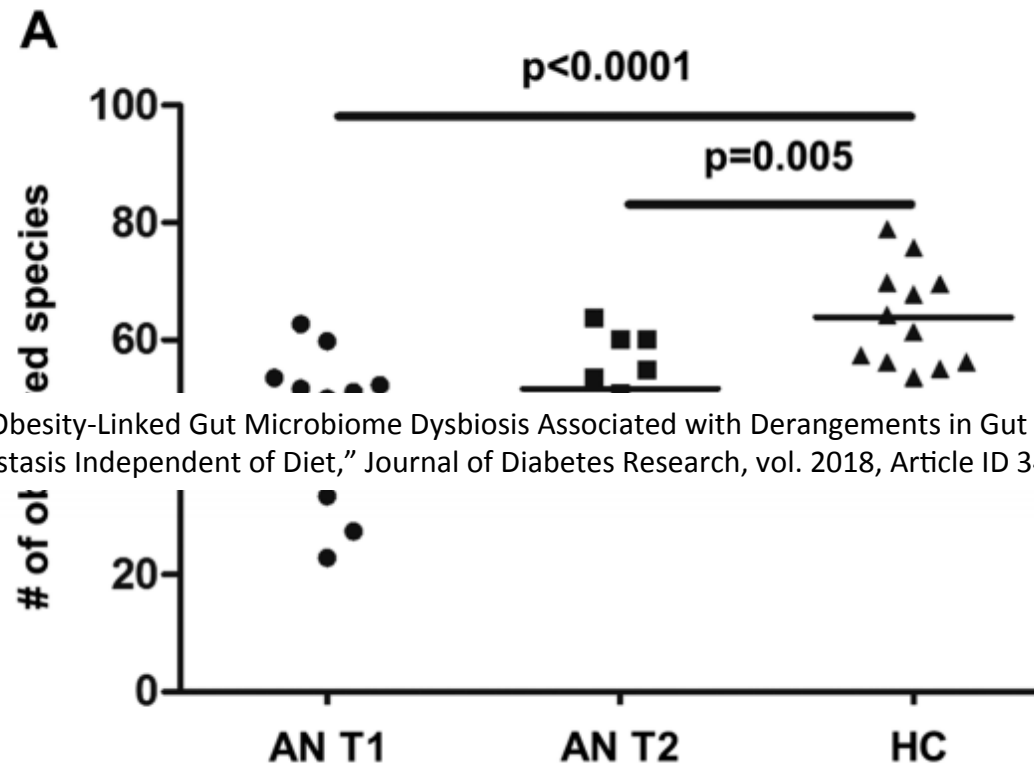


Figure 3.

Alpha diversity in samples from patients with anorexia nervosa (AN) at hospital admission (T1; n=16) and discharge (T2; n=10) and a healthy comparison group (HCG; n=12).

Intestinal dysbiosis in anorexia and in obesity










Ravinder Nagpal, et al., "Obesity-Linked Gut Microbiome Dysbiosis Associated with Derangements in Gut Permeability and Intestinal Cellular Homeostasis Independent of Diet," *Journal of Diabetes Research*, vol. 2018, Article ID 3462092, 9 pages, 2018.

Figure 3.

Alpha diversity in samples from patients with anorexia nervosa (AN) at hospital admission (T1; n=16) and discharge (T2; n=10) and a healthy comparison group (HCG; n=12).

Kleiman SC, et al. The Intestinal Microbiota in Acute Anorexia Nervosa and During Renourishment: Relationship to Depression, Anxiety, and Eating Disorder Psychopathology. *Psychosomatic medicine*. 2015;77(9):969-981.

Bristol Stool Test to explore the Gut Microbiota

BRISTOL STOOL CHART			
	Type 1	Separate hard lumps	SEVERE CONSTIPATION
	Type 2	Lumpy and sausage like	MILD CONSTIPATION
	Type 3	A sausage shape with cracks in the surface	NORMAL
	Type 4	Like a smooth, soft sausage or snake	NORMAL
	Type 5	Soft blobs with clear-cut edges	LACKING FIBRE
	Type 6	Mushy consistency with ragged edges	MILD DIARRHEA
	Type 7	Liquid consistency with no solid pieces	SEVERE DIARRHEA

Gut

Gut microbiota composition associated with stool consistency

Authors: G. First

Gut

Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates

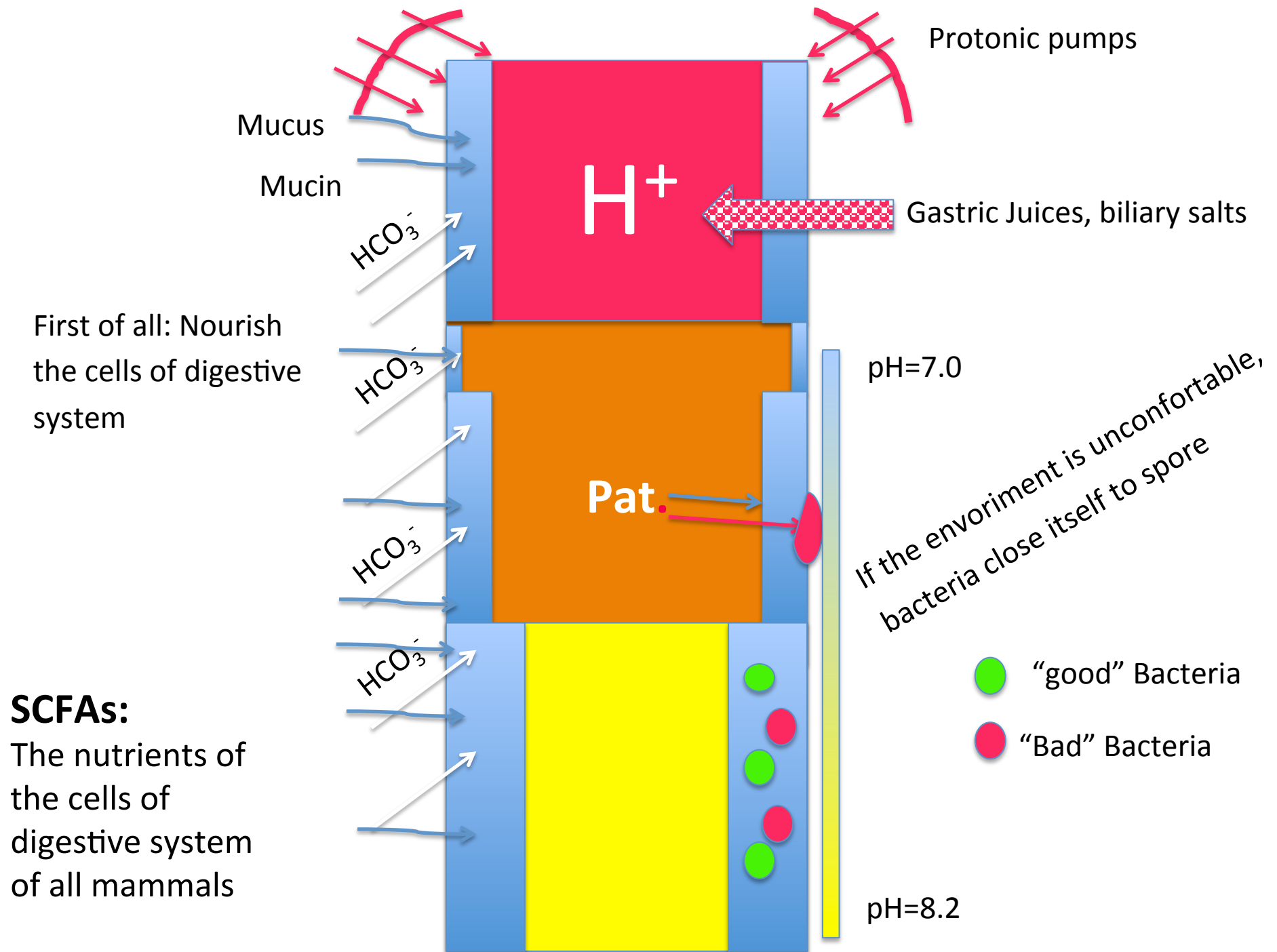
Doris Vandeputte,^{1,2,3} Gwen Falony,^{1,2} Sara Vieira-Silva,^{1,2} Raul Y Tito,^{1,2,3}
Marie Joossens,^{1,2,3} Jeroen Raes^{1,2,3}

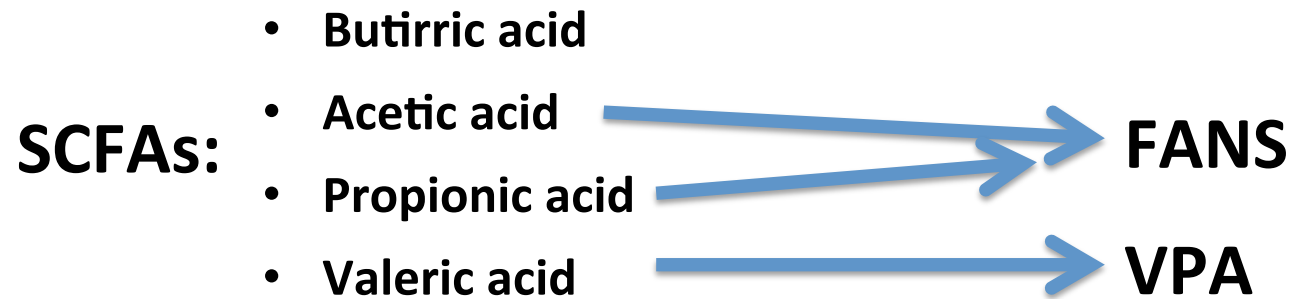
GUT

Gut microbiota composition associated with stool consistency

E F Tigchelaar, M J Bonder, S A Jankipersadsing, J Fu, C Wijmenga and A Zhernakova

Gut published online August 14, 2015





SCFAs= Histone-deacetylase inhibitor = **Intestinal disinflammation**

Saturated fats in the diet allow us to obtain SCFAs.

Ketogenic diet: Fats/Carbohydrates ratio 4:1 or 3:1

Then, rich in saturated fats and butter

KD nourishes and disinflames intestine

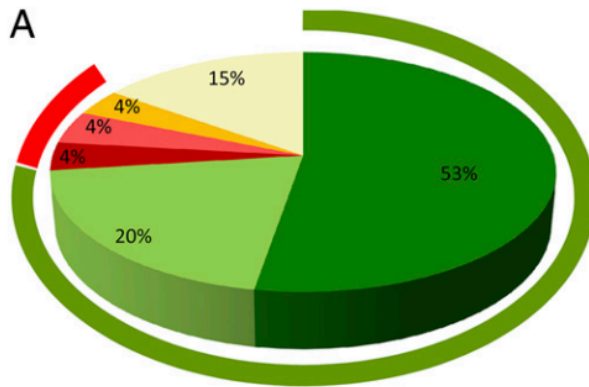
Does the butter hurt?

Kim CH, Park J, Kim M. Gut Microbiota-Derived Short-Chain Fatty Acids, T Cells, and Inflammation. Immune Network. 2014;14(6):277-288. doi:10.4110/in.2014.14.6.277.

Waldecker M(1), Kautenburger T, Daumann H, Busch C, Schrenk D. Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. J Nutr Biochem. 2008 Sep;19(9):587-93.

Butyric acid has been suggested:

- as an alternative approach in **autoimmune and inflammatory diseases**,
- against **bacterial infections**,
- reduce cell proliferation in **colon cancer**,
- **reduce blood sugar**,
- **insulin resistance**,
- **dyslipidemia and gluconogenesis** comparable to metformin.
- has protective action in experimental models of **muscular spinal atrophy**,
- as well as reducing **muscular atrophy from aging**,
- has therapeutic action on **allergic rhinitis**,
- improves **cardiac functions**,
- **reduces alcohol intake in dependent animals**,
- protects against severe **acute lung injury at a distance caused by burns**.
- ...

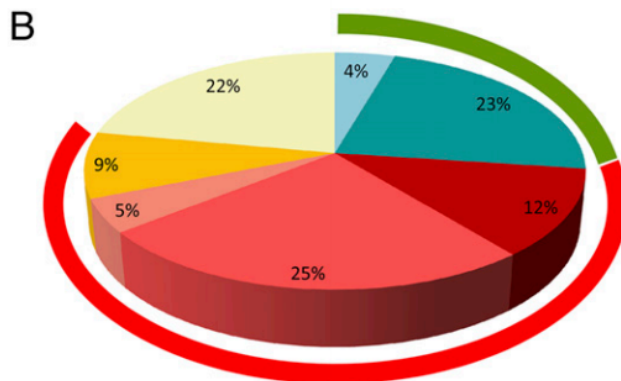


BF

- Prevotella] Bacteroidetes
- Xylanibacter]
- Acetivomaculum] Firmicutes
- Faecalibacterium]
- Subdoligranulum]
- Others]



La dieta ottimale deve nutrire le cellule del digerente e mantenerlo allenato ad affrontare cibi complessi

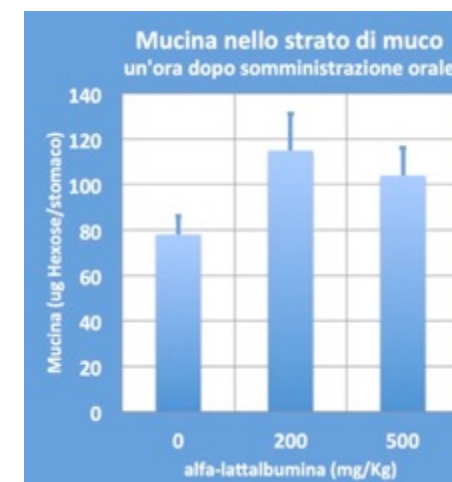
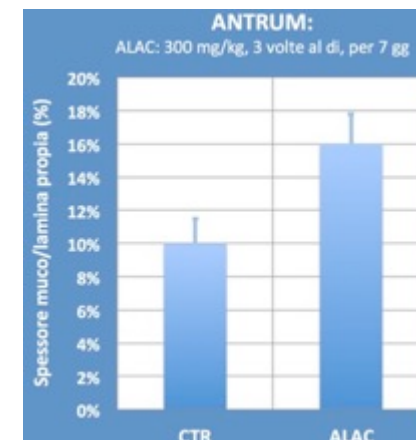
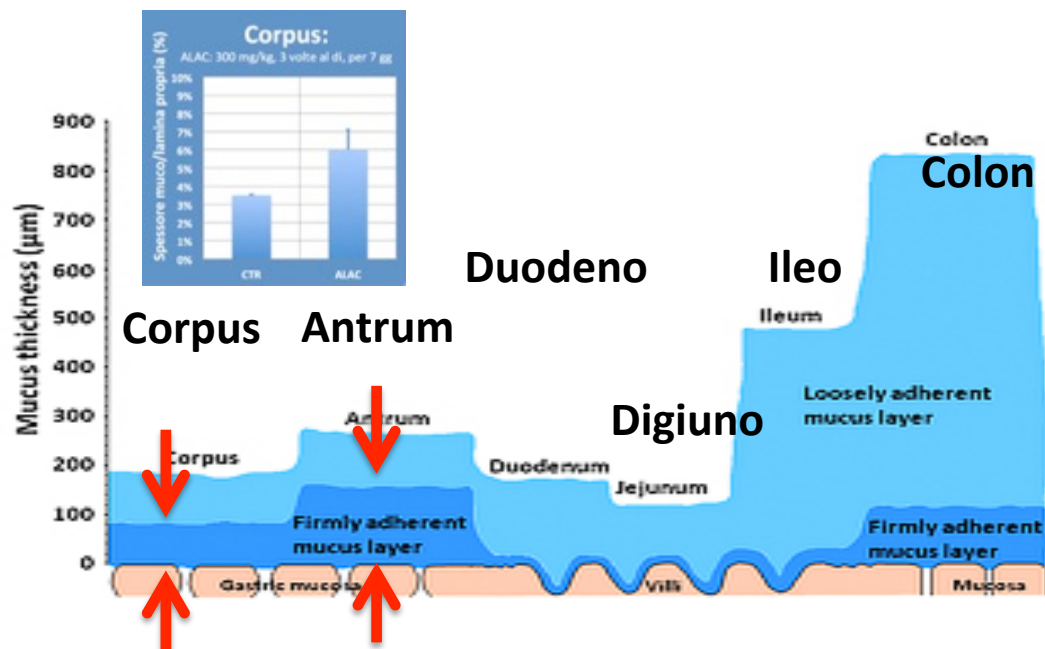


EU

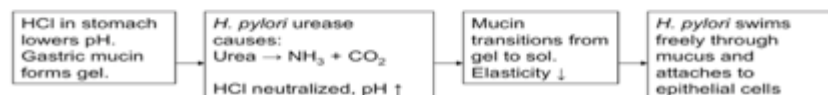
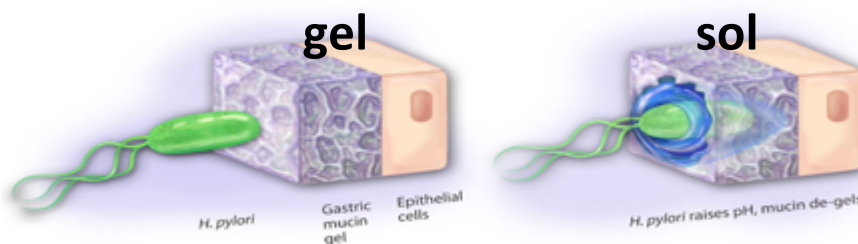
- Alistipes] Bacteroidetes
- Bacteroides]
- Acetivomaculum] Firmicutes
- Faecalibacterium]
- Roseburia]
- Subdoligranulum]
- Others]



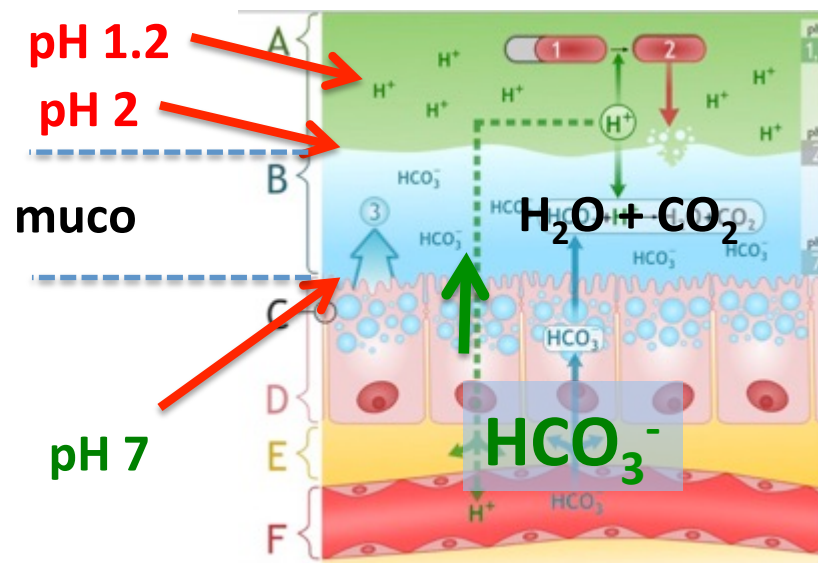
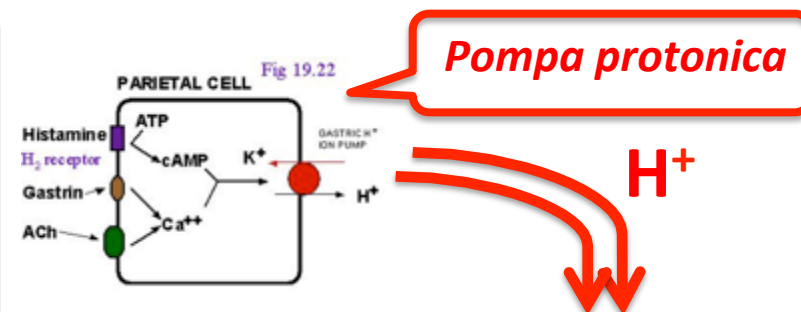
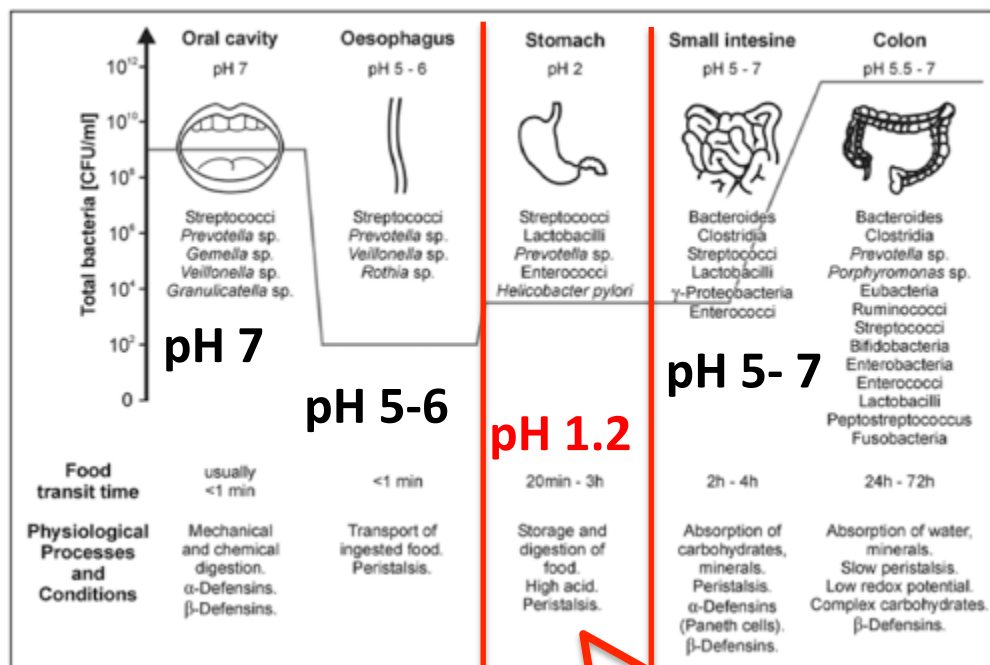
Azioni intestinali dell'alfa-lattoalbumina



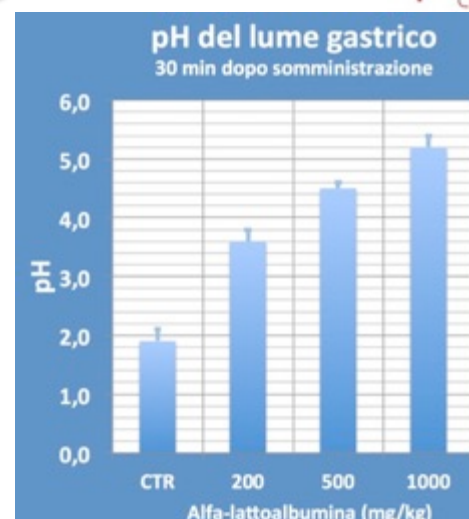
H. PYLORI CROSSING MUCUS LAYER OF STOMACH



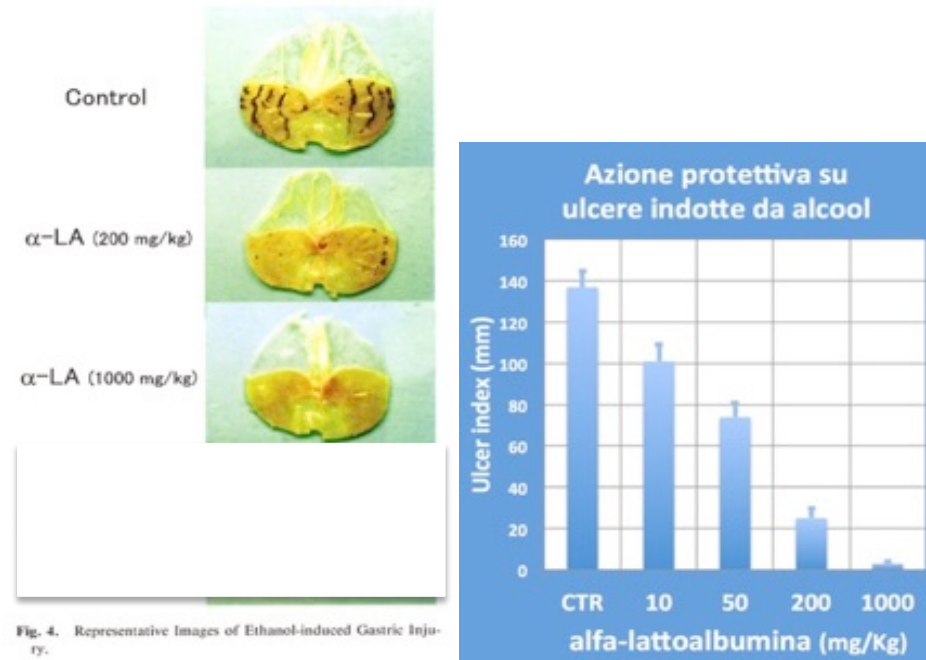
- gastrite cronica
- atrofia gastrica
- ...



Demolisce cibo e Agenti patogeni



Alpha-lactalbumin protects in a dose-dependent manner from gastric ulcers induced by alcohol or stress



Biosci. Biotechnol. Biochem., 65 (5), 1104–1111, 2001



New Biological Function of Bovine α -Lactalbumin: Protective Effect against Ethanol- and Stress-induced Gastric Mucosal Injury in Rats

Hiroshi MATSUMOTO,[†] Yukiko SHIMOKAWA, Yoshihiko USHIDA, Tomohiro TOIDA, and Hirotoshi HAYASAWA

Biochemical Research Laboratory, Morinaga Milk Industry Co. Ltd., Zama, Kanagawa 228-8583, Japan

Looking towards a new medicine:



- MORE POWERFUL THAN ANY DRUGS

restore the powerful of endogenous self-repair and control mechanisms

Take – home message:

Cure the microbiota to allow it to take care of you.

Looking for the One Medicine

THANK YOU FOR YOUR ATTENTION

