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Presidente
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sulla Alimentazione e sulla Salute (UNIPSAS)
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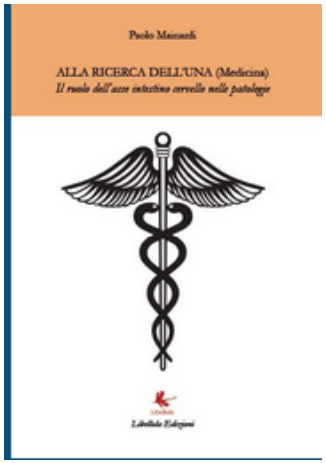
www.Protocollorestart.it
www.UnaMedicina.it

Cremona, TELECOLOR 21 Aprile '20

La Medicina e la Nutrizione, oggi, nell'era del Microbiota

Come cambiano molti concetti fondamentali,
verso una "Una-Medicina" che curi il Microbiota per consentirgli di prendersi cura di noi



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How Knowledge on Microbiota may be Helpful to Establish an Optimal Diet for Health Maintenance

Paolo Mainardi[1,*], Paolo Carta[2], Michele Mainardi[3] and Pasquale Striano[3]

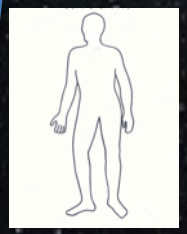
We Are Not Alone in This Endless Universe

10^{13} germ and somatic cells

≈ 80 kg

24,000 genes

Cellular body

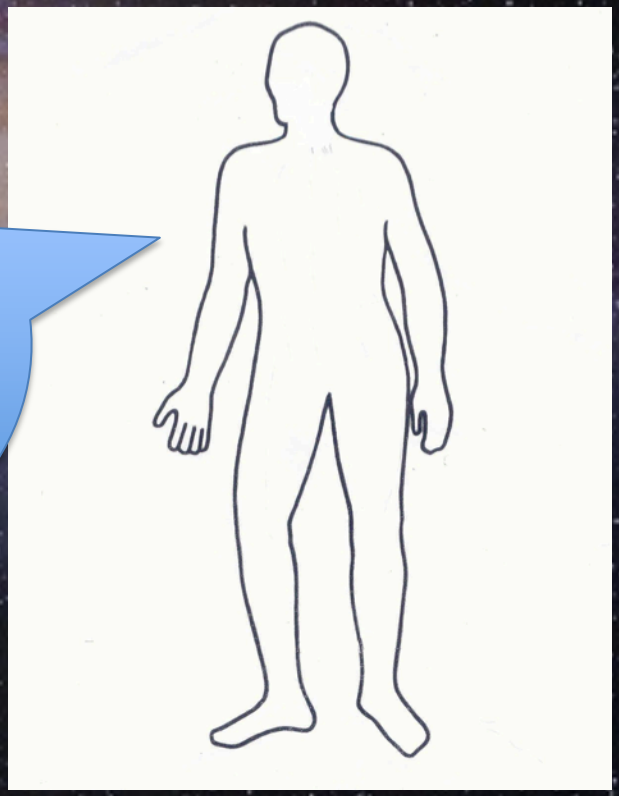


10^{14} bacteria

1.13 kg

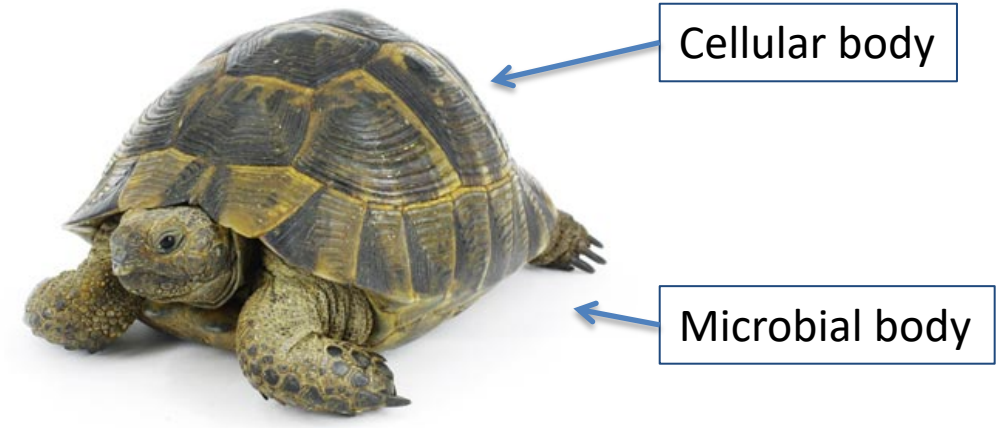
3-4 million genes

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.

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

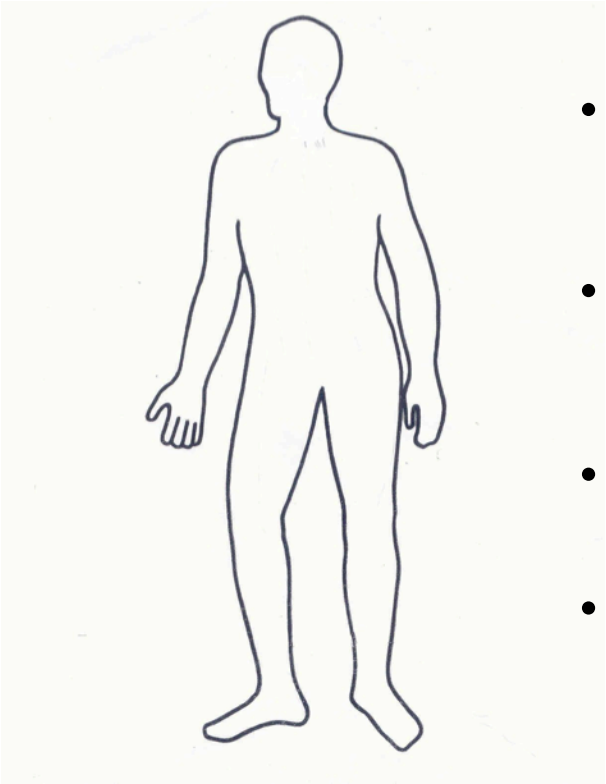


"Surprisingly, each of us can be identified by the DNA of our gut microbes".

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**

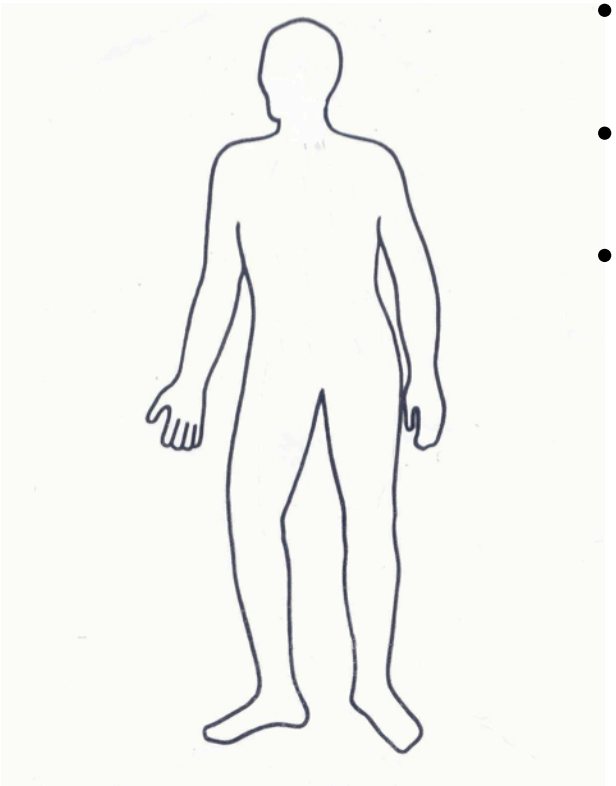
Microbial body controls:



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.)
- **Metabolic diseases** (Clavel T, Desmarchelier C, Haller D, Gérard P, Rohn S, Lepage P, Daniel H. Intestinal microbiota in metabolic diseases: from bacterial community structureand 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 coreintestinal 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:

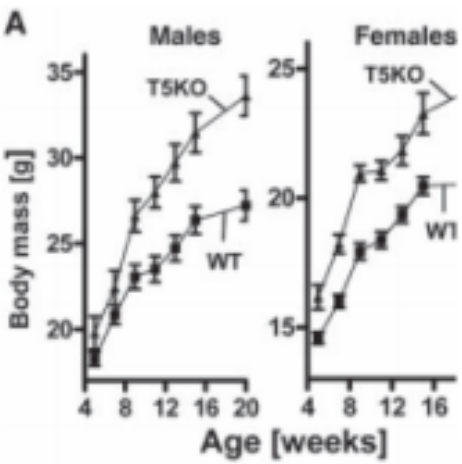


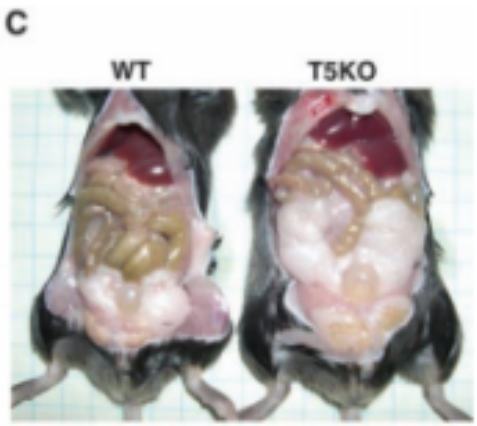
- **Parkinson's**: Qian Y, Yang X, Xu S, Wu C, Song Y, Qin N, Chen SD, Xiao Q. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. Brain Behav Immun.2018 Mar 2. pii: S0889-1591(18)30028-X.
- **Alzheimer's** (Di Sabatino A, Lenti MV, Cammalleri L, Corazza GR, Pilotto A. Frailty 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.)
- **...**

Review essays

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

Joe Alcock[1], Carlo C. Maley[2)3)4)] and C. Athena Aktipis[2)3)4)5)]*





Wexler HM. Bacteroides: the Good, the Bad, and the Nitty-Gritty. Clinical Microbiology Reviews. 2007;20(4):593-621.

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

Joe Alcock[1], Carlo C. Maley[2)3)4)] and C. Athena Aktipis[2)3)4)5)]*

Selective influence of diet on microbiota:

Prevotella ⟷ Carbohydrates

Bifidobacteria ⟷ Fibers

Bacteroidetes ⟷ Some Fats

Wu GD, Chen J, Hoffmann C, et al. Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes. Science (New York, N.y). 2011;334(6052):105-108. doi:10.1126/science.1208344.

Urinary metabolites in Chocolate indifferent and Chocolate desidering

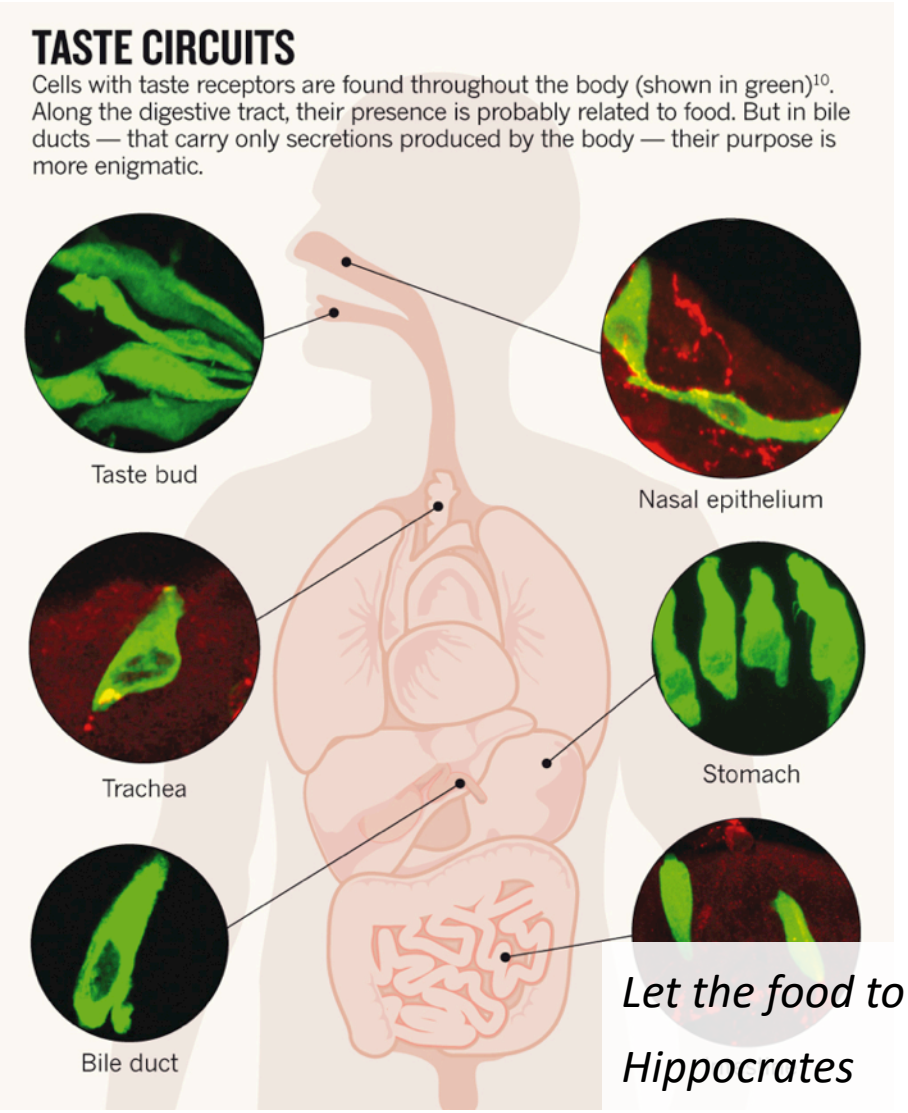
	4-HPA	4-cresol sulfate	PAG	2-HHP	hippurate	trigonelline
4-HPA		-0.3(0.0860)*	0.6 (0.01×10^{-3})**	0.1 (0.5620)	-0.3 (0.0620)*	0.3 (0.0560)*
4-cresol sulfate	0.1 (0.3990)		0.3 (0.0220)**	0.1 (0.5450)	0.0 (0.8150)	0.1 (0.4570)
PAG	0.3 (0.0540)**	0.5 (0.0010)**		0.1 (0.3490)	-0.2 (0.1120)	0.3 (0.0340)**
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 ^{1}H 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 multicolinearity 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.

Taste receptors to produce anticipatory response to foods or pathogens.



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

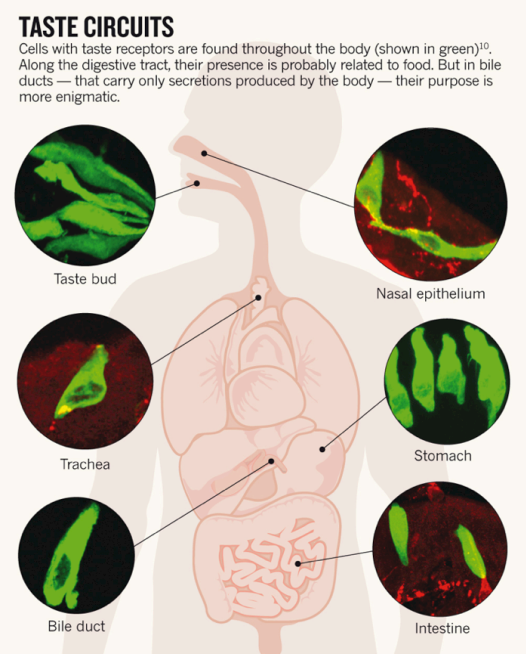
✓ **The main role of digestive system is to protect gut ecosystem**

✓ **By the food we can talk with microbiota**

✓ **Food information goes beyond the nutritional aspect**

Let the food to be the medicine and the medicine to be the food.

Hippocrates



6 gusti:

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

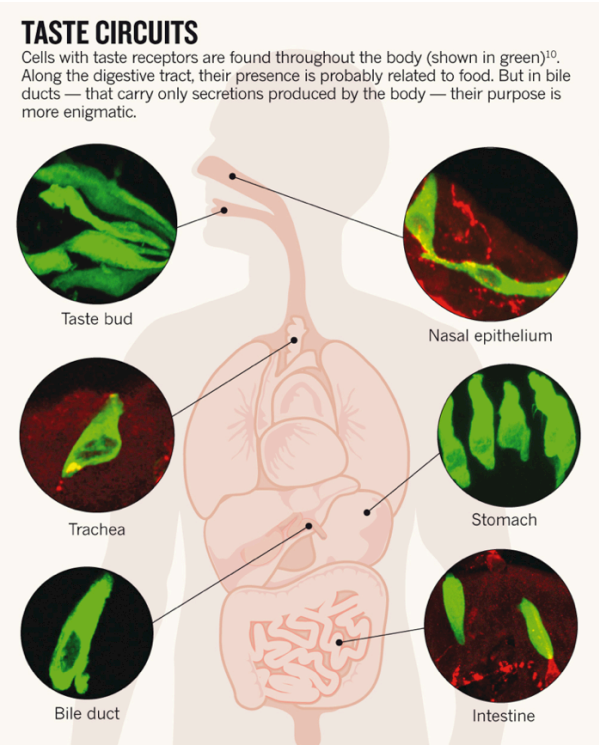
scatenano una frenetica attività cerebrale: le emozioni e i ricordi (regioni emotive del cervello)

6 gusti:

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

una potente salvaguardia contro il consumo di cibi potenzialmente pericolosi

Taste receptors response to bitter-tasting compunds in airway



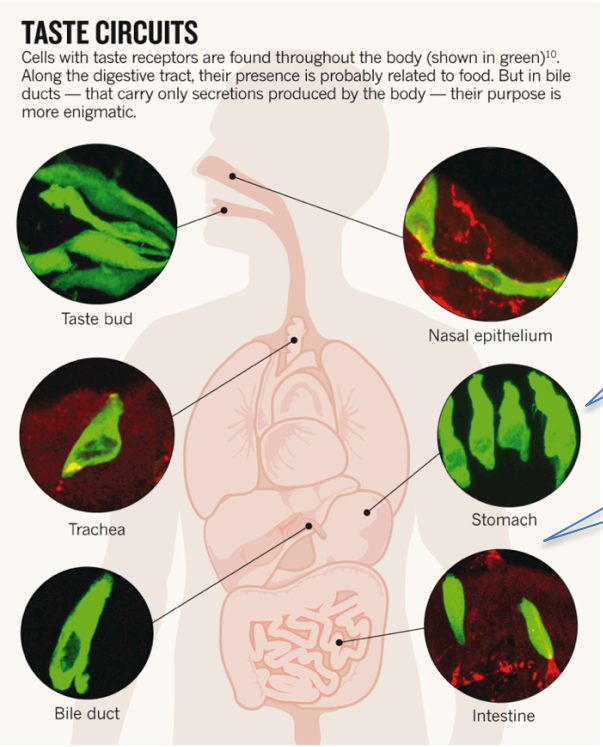
Bitter receptors are also found on cilia on human airway epithelium cells

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 bitter-tasting compunds



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.

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

Wrongulator è il passatempo per ufficio più divertente che mai!
Effettuando i calcoli con questa calcolatrice otterrai sempre il risultato errato!

Intolleranze alimentari?

Allergie?

Sono dovute ad un errore della risposta dei recettori del gusto = ad una disbiosi intestinale.

Ha senso fare il calcolo delle calorie alimentari?

Ha senso suddividere il cibo in Grassi, Carboidrati e Proteine?

Caloria Alimentare= calore emesso da 1 g di cibo se BRUCIATO

OPINION

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

Come ti senti oggi? Chiedilo al microbiota

- ✓ 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.

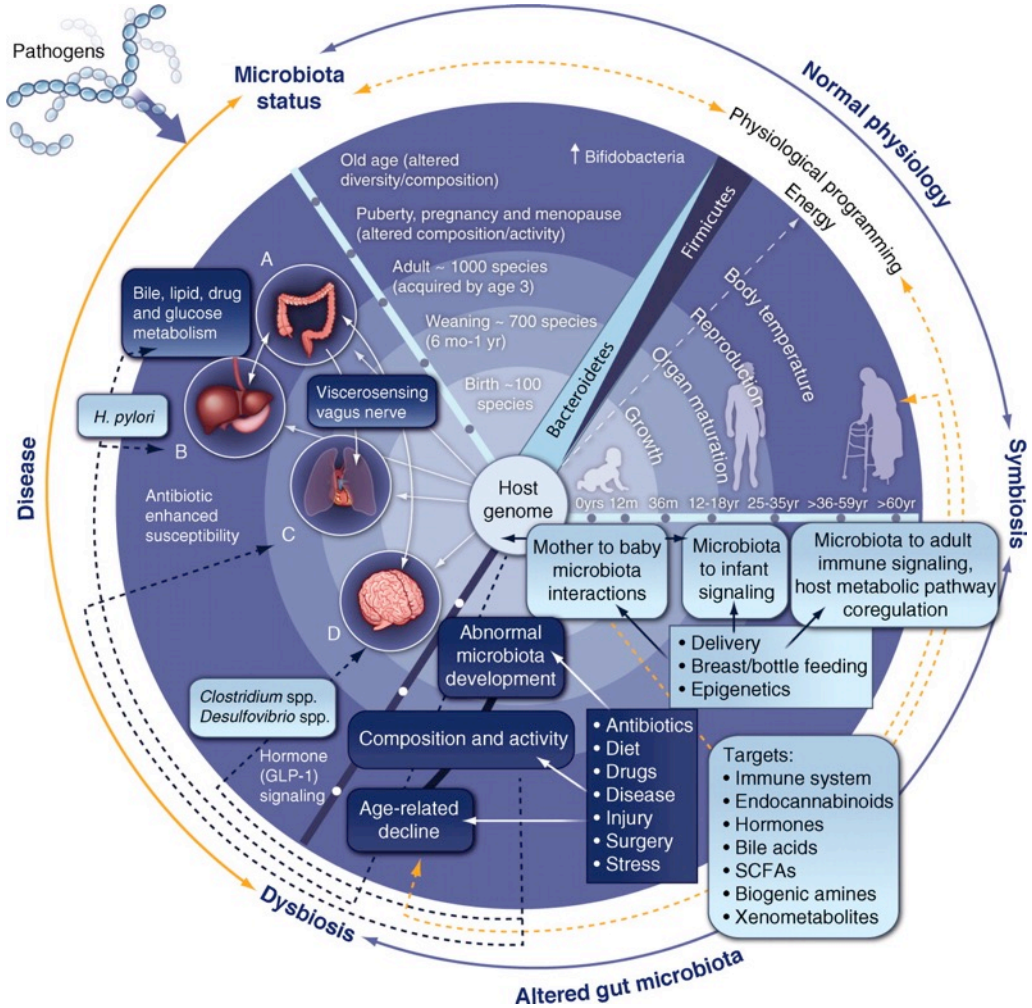
Intestinal Microbiota:

A moderator in health and diseases.

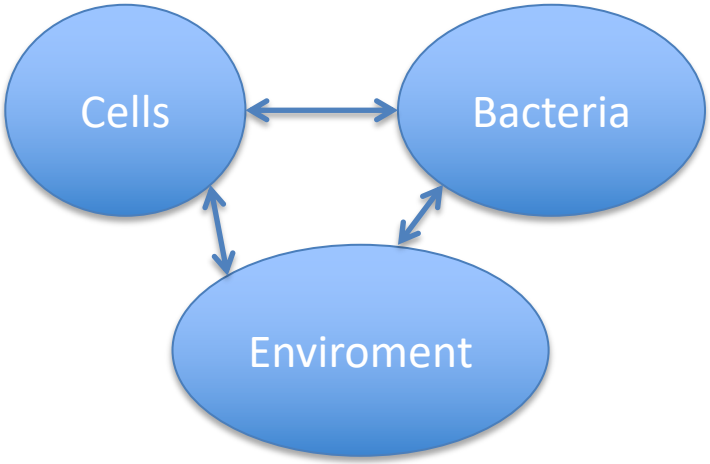
4573 articles on pubmed

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 …

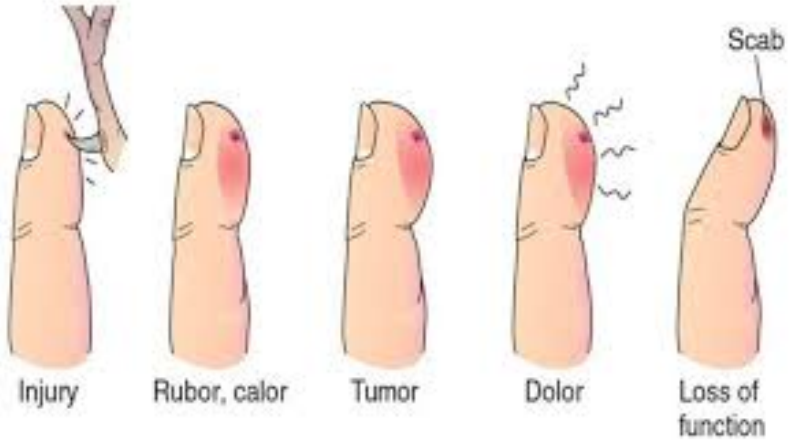


Shenderov BA et al: Gut indigenous microbiota and Epigenetics. Microbial Ecology in Health & Disease 2012, 23: 17195 -

Microbiota orchestrates inflammatory processes

Dysregulation of gut microbiota and chronic inflammatory disease

*In addition to their barrier function, Intesinal 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***

Koh, J. H., & Kim, W.-U. (2017). Dysregulation of gut microbiota and chronic inflammatory disease: from epithelial defense to host immunity. Experimental & Molecular Medicine, 49(5), e337–.

Inflammatory cascade:

Pro- and anti-inflammatory

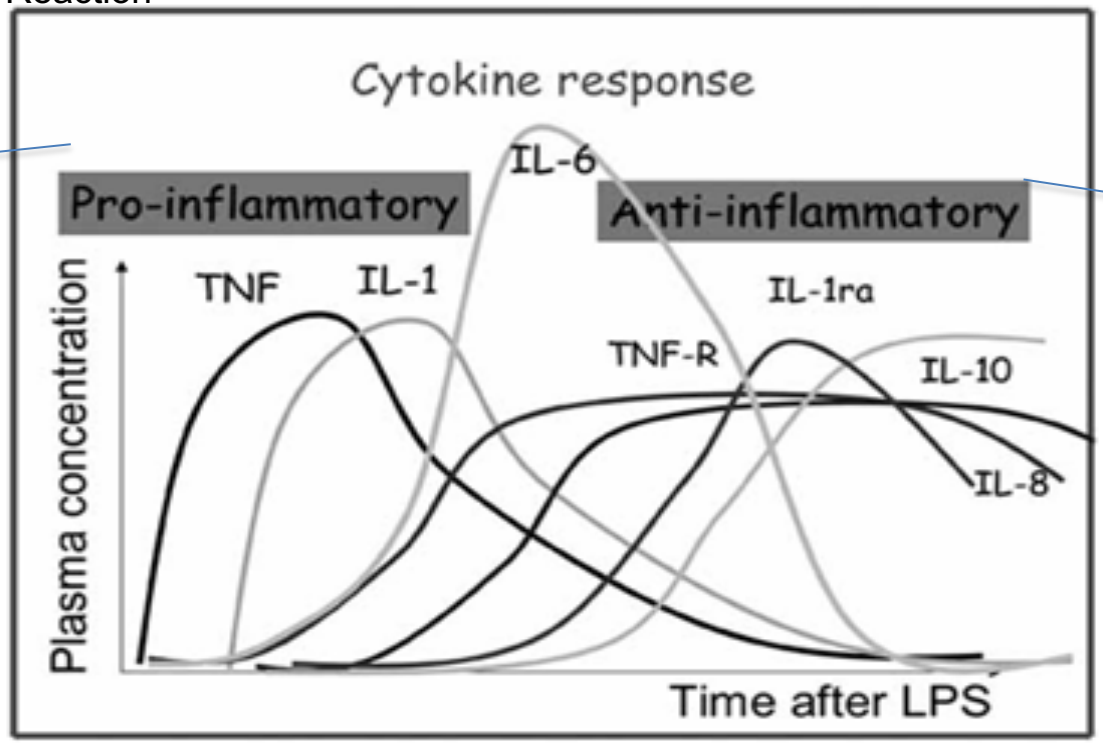
Modulate from APR to CPR

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

APR: Acute Phase Reaction

CPR. Chronic Phase Reaction

Demoliscono



Ricostruiscono

In CNS:

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

Andreasen AS, Krabbe KS, Krogh-Madsen R, Taudorf S, Pedersen BK, Møller K. Human Endotoxemia as a model of systemic inflammation. Curr Med Chem. 2008;15(17):1697-705.

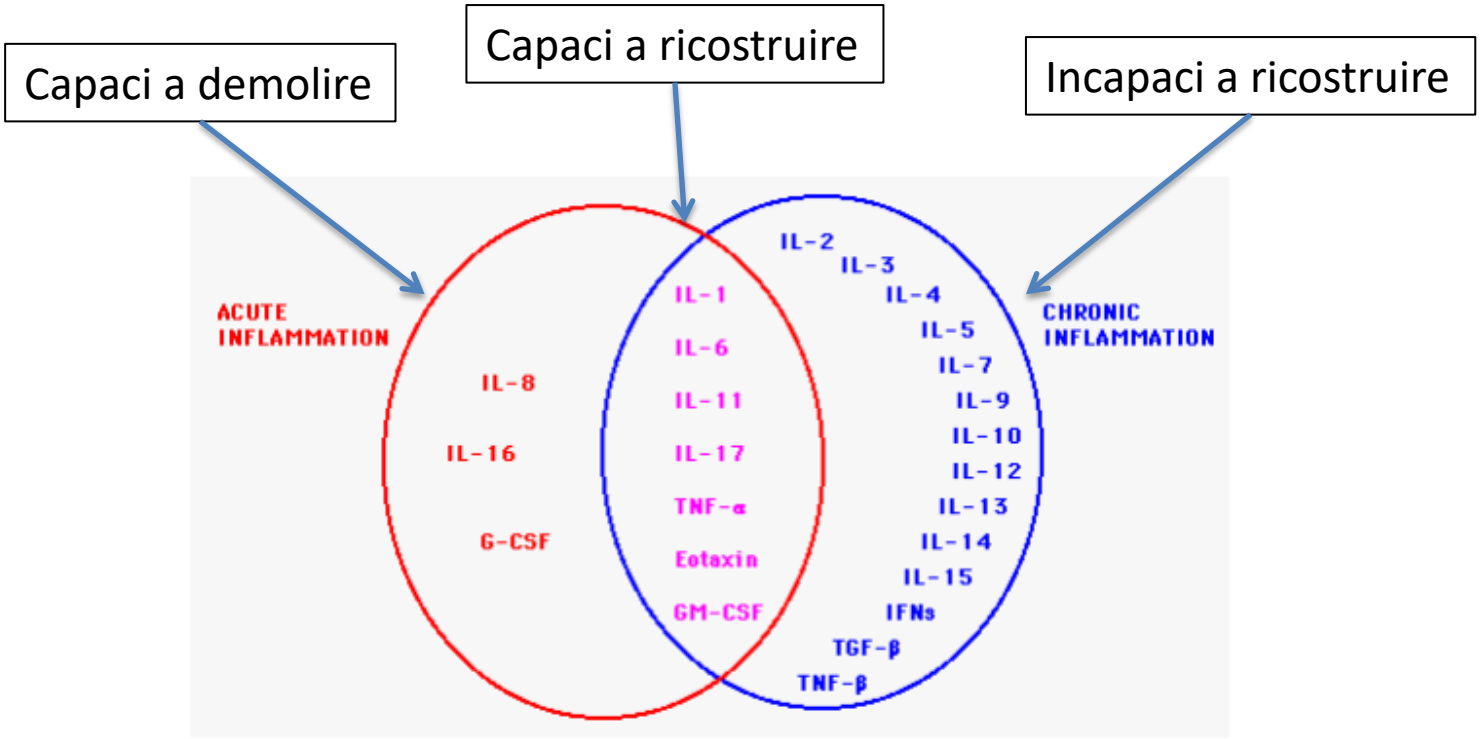
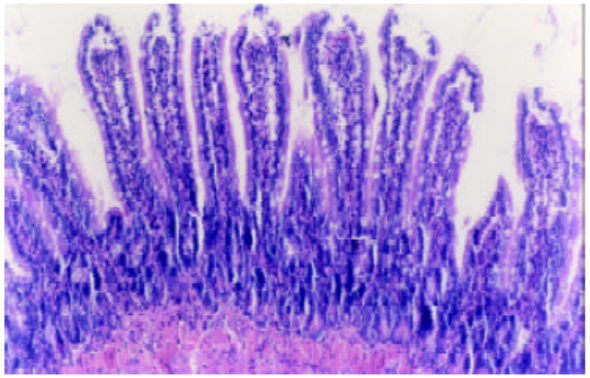


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

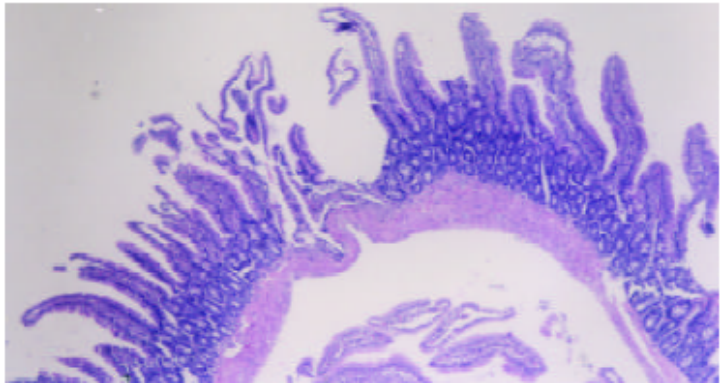
In Chronic Inflammation are produced different anti-inflammatory cytokines: unable to rebuilt tissues, unble to restart synaptogenesis and neurogenesis processes in CNS

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

3 days after TBI collapses the intestinal membrane

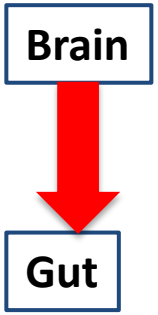


Before TBI



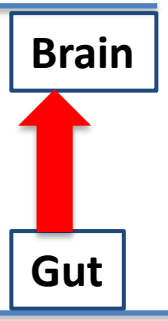
3 days After TBI

Hang Ch et al, Intestinal mucosa structure after TBI. World J Gastroenterol 2003,9 (12) 2776-2781



IL-6 elevation in the brain is involved in the mediation of autism-like behaviors through ***impairments of neuroanatomical structures*** *and neuronal plasticity*

Wei H, Alberts I, Li X. Brain IL-6 and autism. Neuroscience. 2013 Nov 12;252:320-5.



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

Goines PE, Ashwood P. Cytokine dysregulation in autism spectrum disorders (ASD): possible role of the environment. Neurotoxicol Teratol. 2013 Mar-Apr;36:67-81.

Brain, Behavior, and Immunity 22 (2008) 797–803

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Invited Review

The role of cytokines in the pathophysiology of epilepsy

Annamaria Vezzani *, Silvia Balosso, Teresa Ravizza

Mario Negri Institute for Pharmacological Research, Department of Neuroscience, Via G La Masa, 19 Milano, Italy

*Brain inflammation is not a predisposing factor for seizures, but it is the **physiopathogenetic cause** of them.*

Metabolic changes during pregnancy:

- Same nutritional intake
- Increased energy extraction by foods:

Cell

Host Remodeling of the Gut Microbiome and Metabolic Changes during Pregnancy

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.

- **the microbiota undergoes profound changes in T3 vs T1**
- **<u>It is not due to nourish the fetus, but to realize his tissues by anti-inflammatory citokines</u>**

Houston, we have a problem!

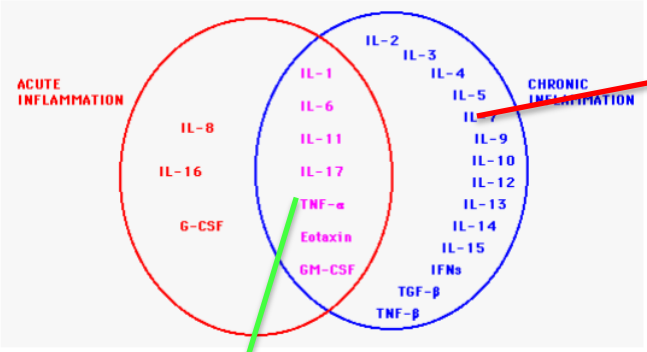
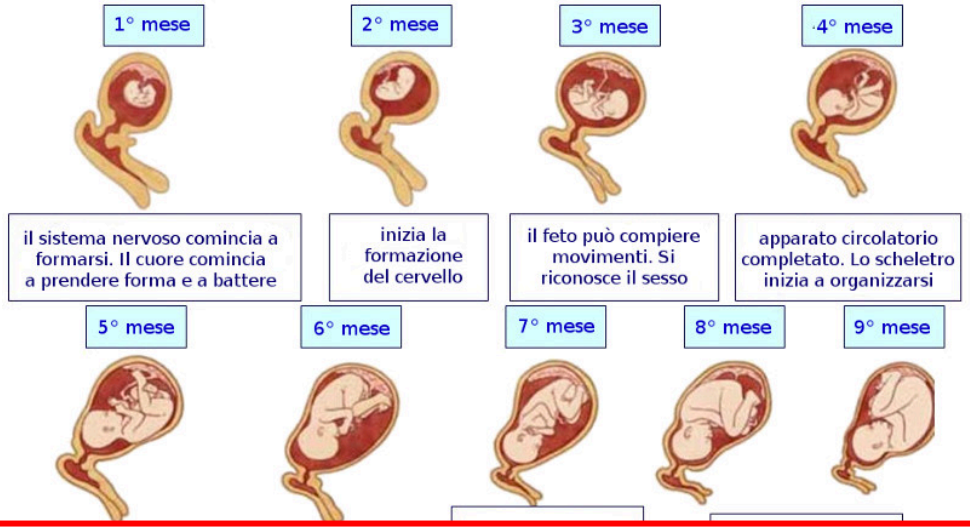


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

No-problems

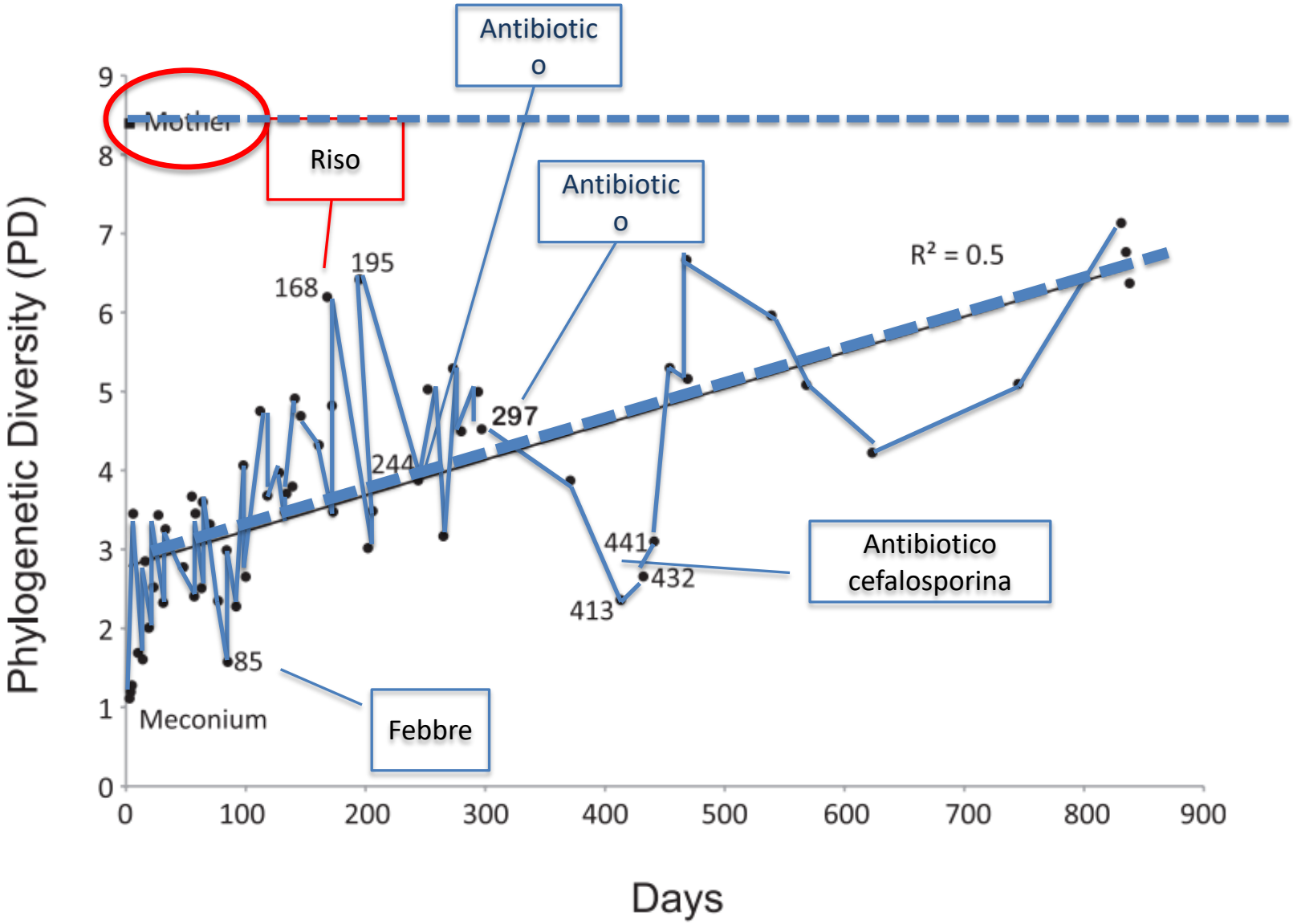
PROGRAMMA DI MATURAZIONE FETALE



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

Indici di fattori di rischio:

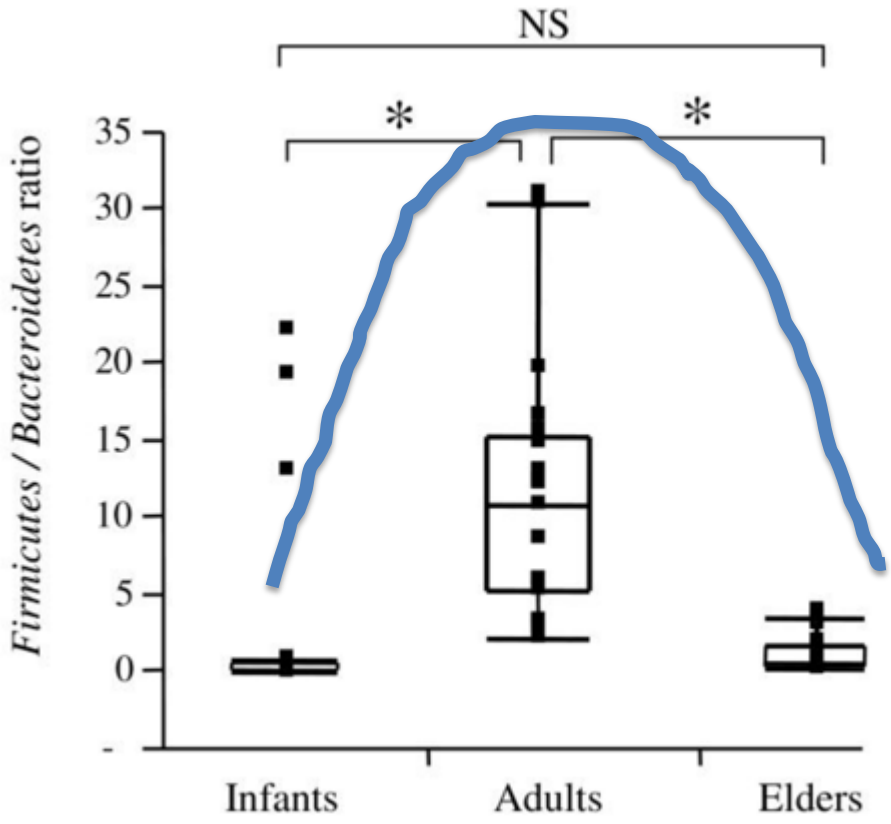
- Parti podalici
- Parti prematuri
- Aborti spontanei
- Infertilità
- …

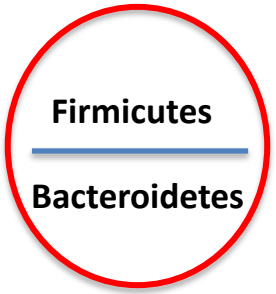


Jeremy E. Koenig et al. Succession of microbial consortia in the developing infant gut microbiome Proceedings of the National Academy of Sciences Mar 2011, 108 (Supplement 1) 4578-4585;

Firmicutes/Bacteroidetes ratio vs ageing

getting old you will be children again





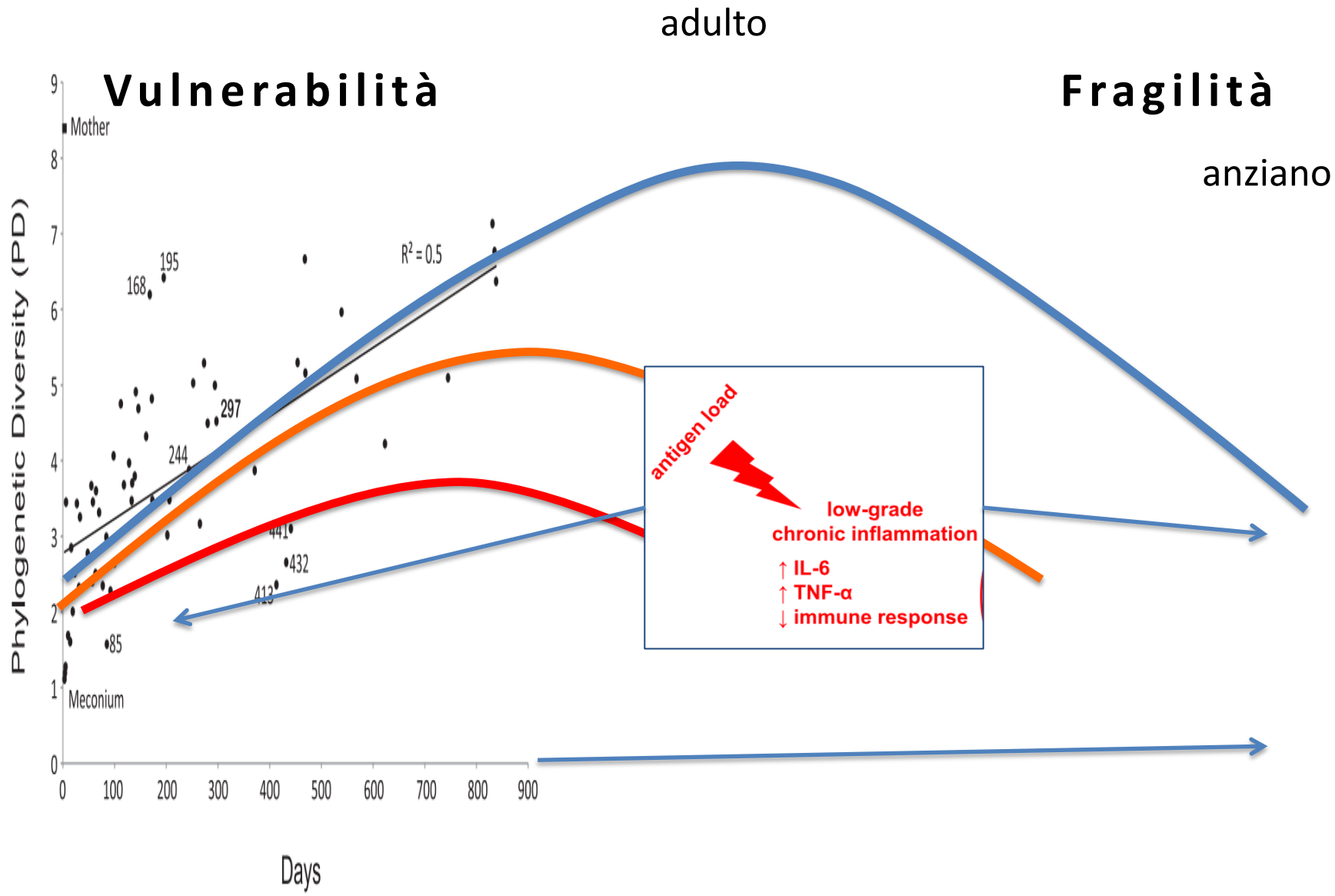
Infants: N=21, from 3 weeks to 10 months

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

Invecchiando si torna bambini.



Ridotta diversità ceppi:

- Ridotta capacità di riparare i danni
- Ridotta capacità a rigenerare i tessuti
- Ridotta capacità a scremare linfociti T
- Ridotta capacità a controllare organi

…

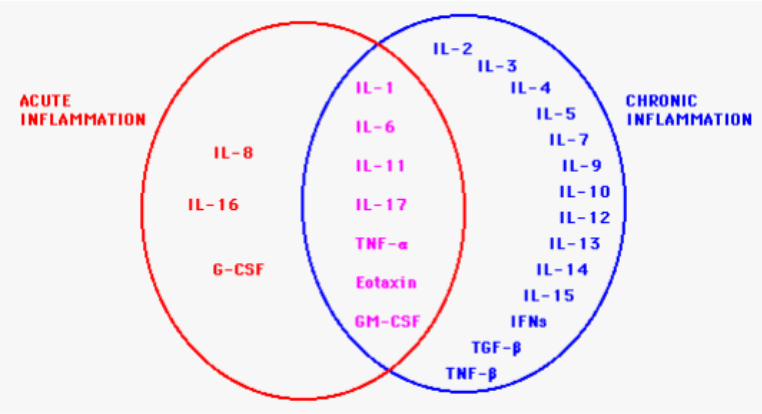
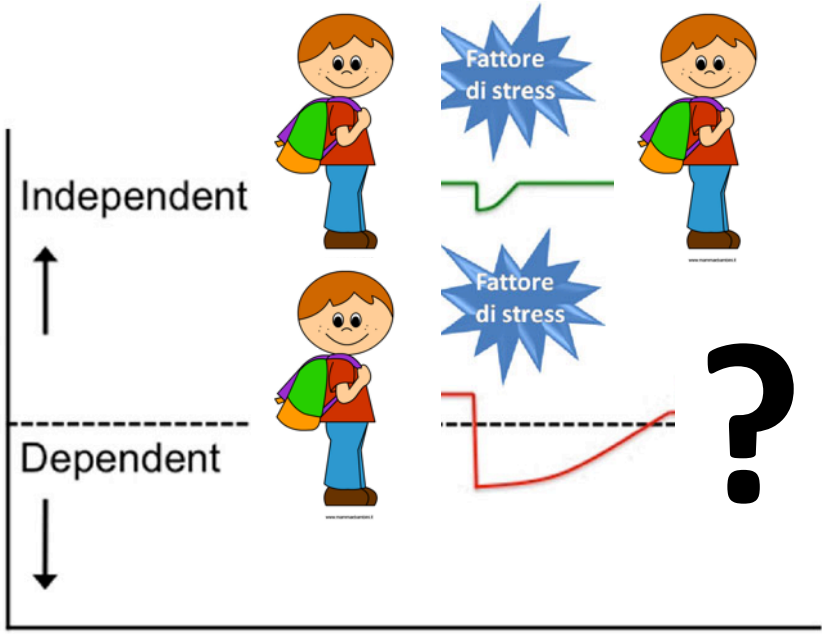
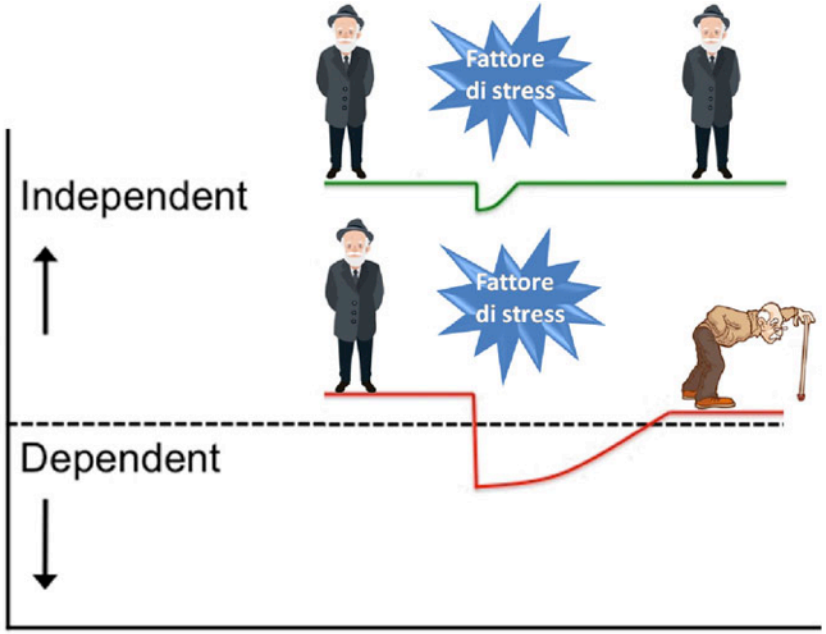
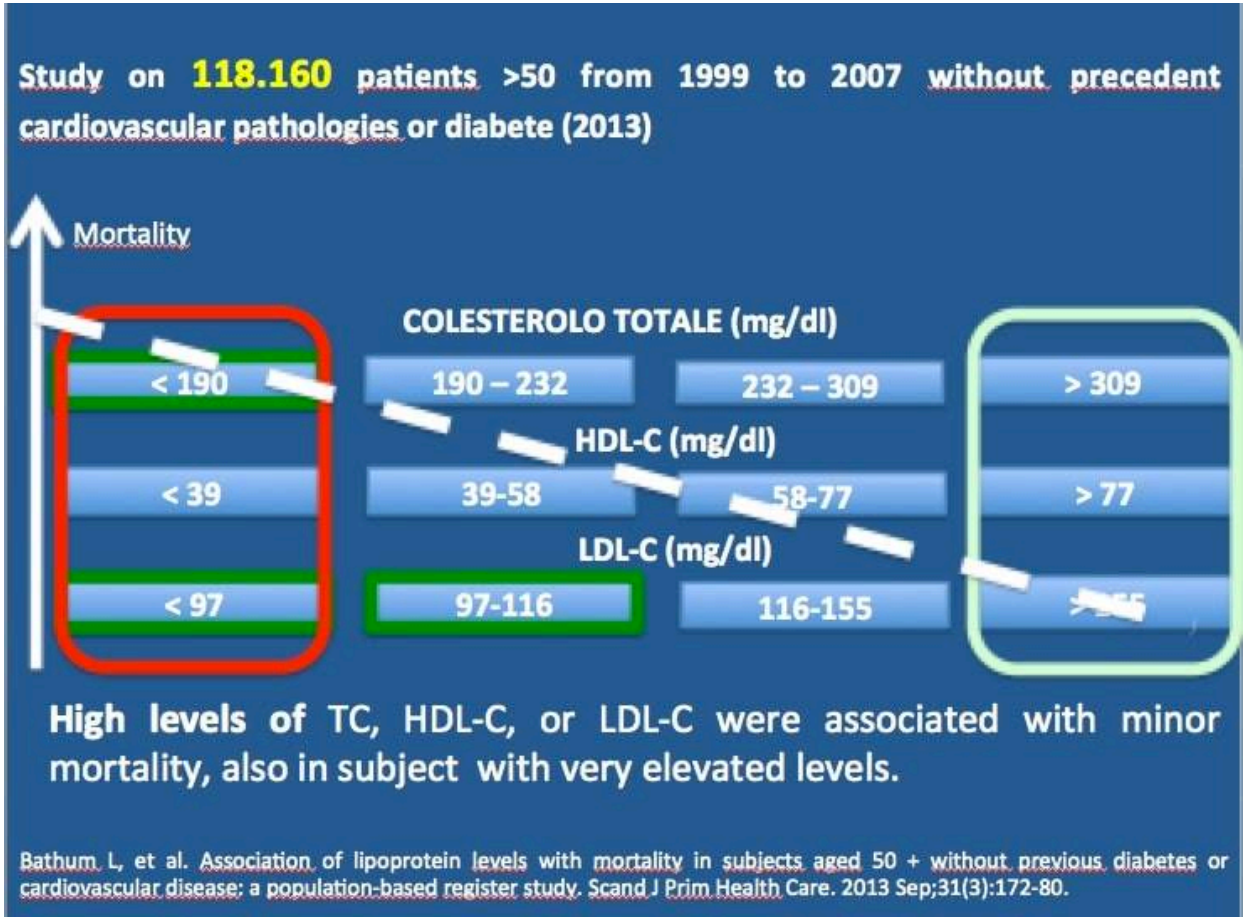


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.







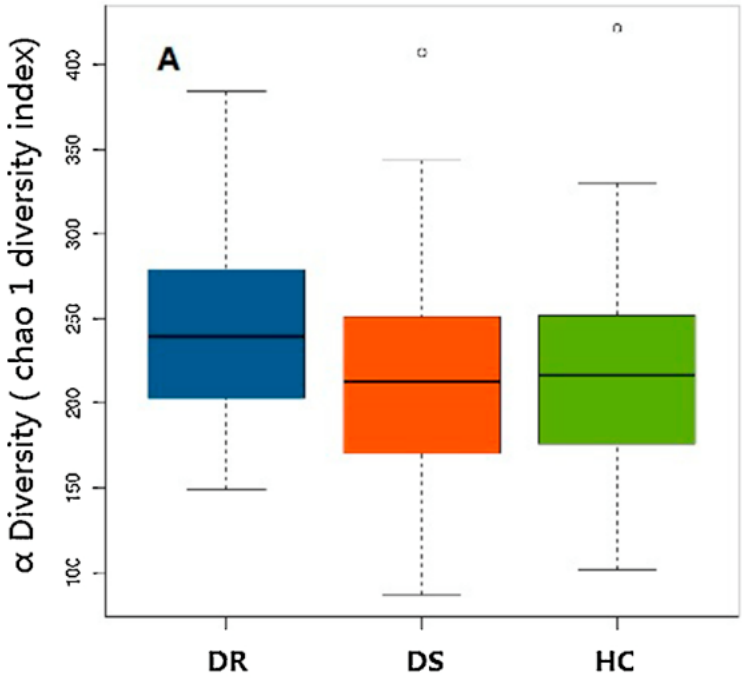
Studio su 70 pz ricoverati per Covdi19 vs 80 controlli: Colesterolo totale : 140 mg/dl vs 190 mg/dl

Si stimano circa 6 milioni di italiani positivi al COVID19, almeno 5 milioni sono asintomatici

Hu, X, Chen D, Wu L, He G, Ye W. Low Serum Cholesterol level among patients with COVID-19 infection in Wenzhou, China (February 21, 2020).

Altered composition of the gut microbiome in patients with drug-resistant epilepsy

- ✓ patients with drug-resistant epilepsy (DR) are characterized by the over-expression of rare microbial lineages.



DR: drug resistant

DS: drug sensitive

HR: Health controls

Peng A, Qiu X, Lai W, Li W, Zhang L, Zhu X, He S, Duan J, Chen L. Altered composition of the gut microbiome in patients with drug-resistant epilepsy. Epilepsy Res. 2018 Sep 24;147:102-107.

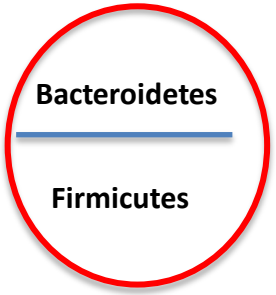
SCIENTIFIC REPORTS

OPEN

Analysis of gut microbiota profiles and microbe-disease associations in children with autism spectrum disorders in China

Received: 14 March 2018
Accepted: 24 August 2018
Published online: 18 September 2018

Mengxiang Zhang[1,2], Wei Ma[3], Juan Zhang[4], Yi He[1,2] & Juan Wang[1,2]



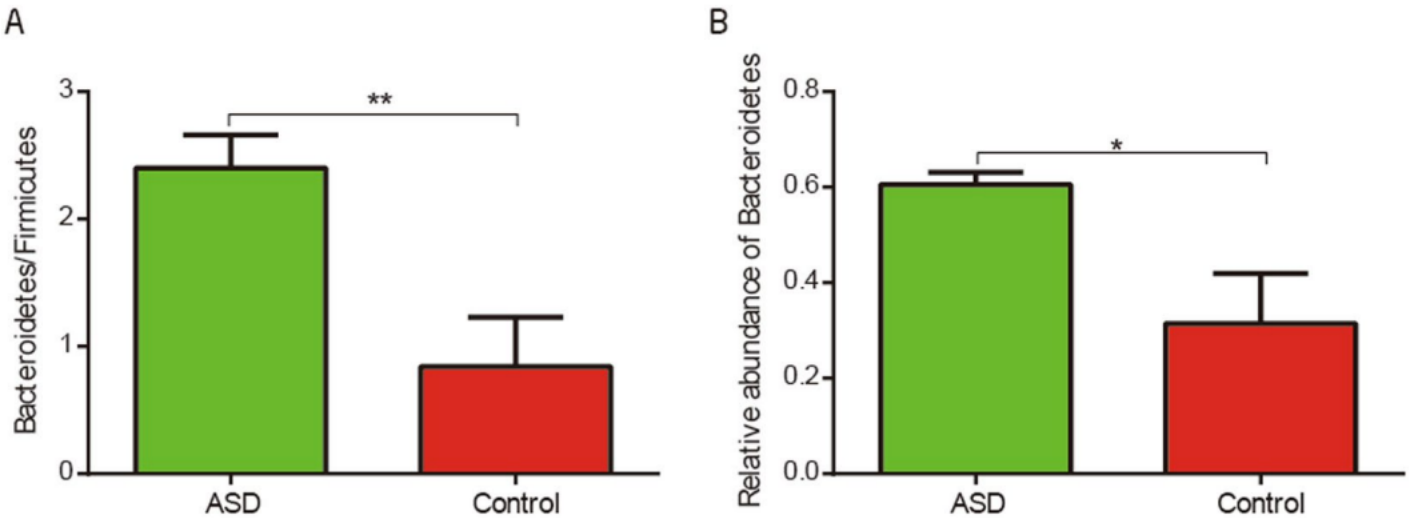
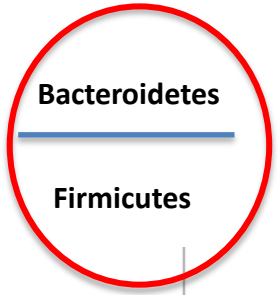


Figure 1. (**A**) Comparison of the ratio of *Bacteroidetes/Firmicutes* between ASD children and typical development children (**$p < 0.005$, Wilcoxon rank-sum test). (**B**) Box plot representation of the relative abundance of *Bacteroidetes* (*FDR-corrected $p < 0.05$, Wilcoxon rank-sum test). The boxes represent the mean ± Standard Error of Mean (SEM).

Gut Microbiota Profiling and Gut-Brain Crosstalk in PANDAS

Disequilibrium between **Firmicutes** and **Bacteroidetes (F/B)**



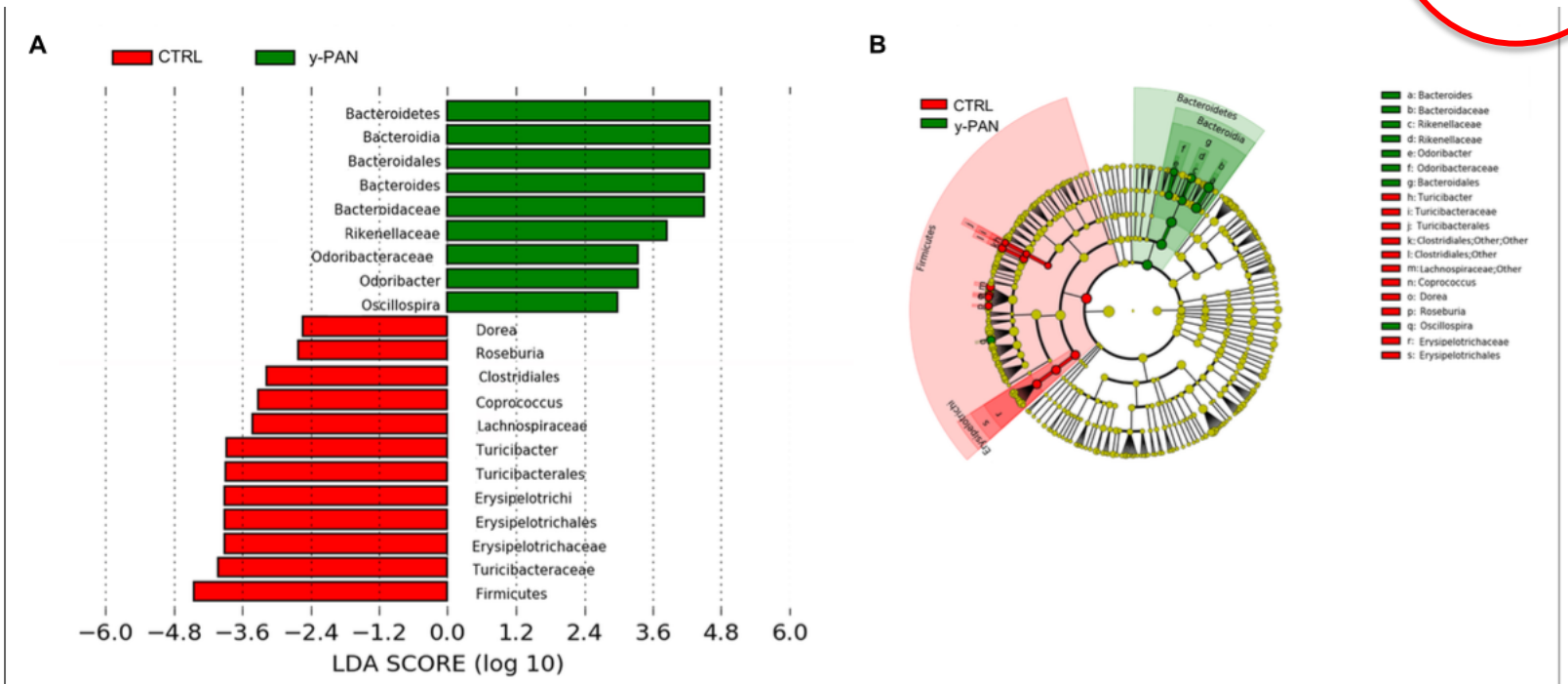


FIGURE 5 | OTU biomarkers associated with y-PAN and CTRL groups. **(A)** A linear discriminant effect size (LeFse) analysis was performed (α value = 0.05, logarithmic LDA score threshold = 2.0). **(B)** The cladogram represents the phylogenetic relationship of significant OTUs associated with each group.

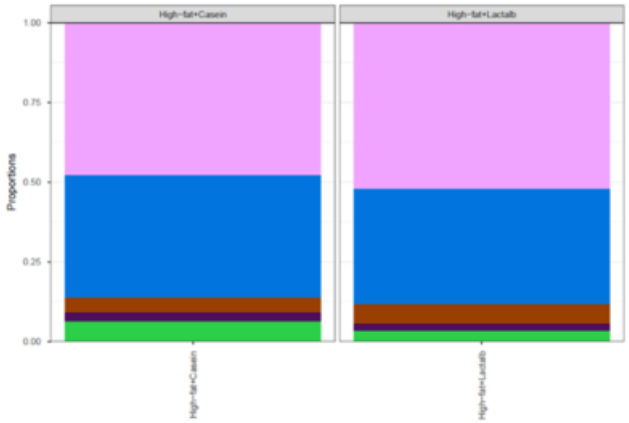
Quagliariello A, et al. Gut Microbiota Profiling and Gut–Brain Crosstalk in Children Affected by Pediatric Acute-Onset Neuropsychiatric Syndrome and Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. Front. Microbiol. 9:675.

British Journal of Nutrition (2019), 121, 1097–1107
doi:10.1017/S0007114519000461

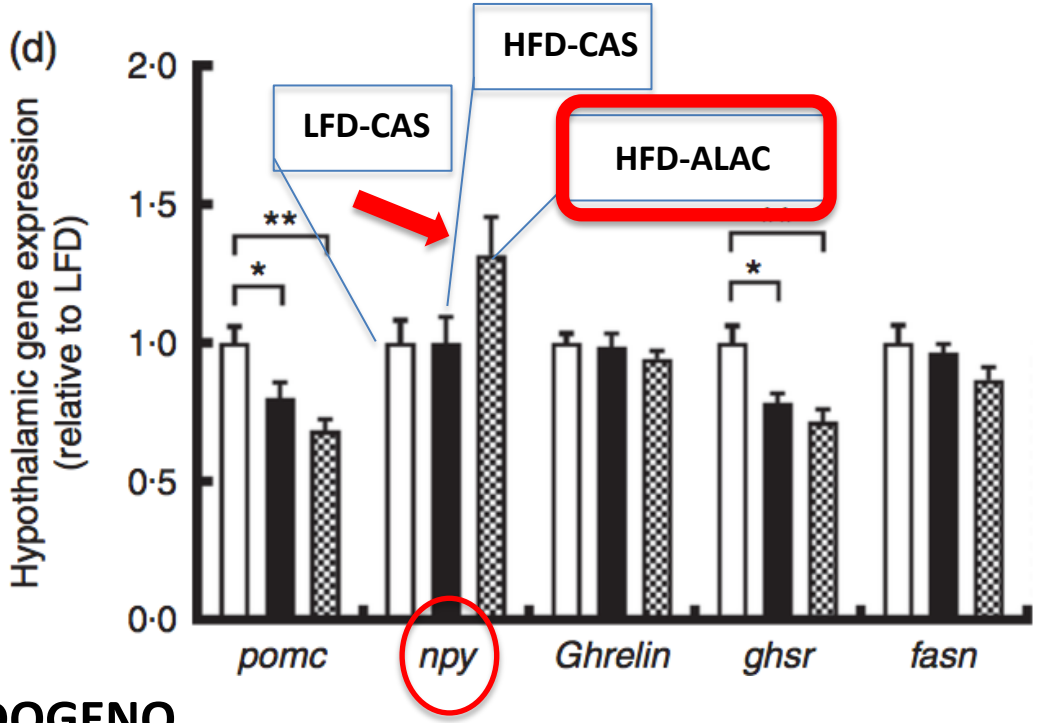
Dietary α-lactalbumin alters energy balance, gut microbiota composition and intestinal nutrient transporter expression in high-fat diet-fed mice

Serena Boscaini[1,2,3], Raul Cabrera-Rubio[1,2], John R. Speakman[4,5], Paul D. Cotter[1,2], John F. Cryan[2,3] and Kanishka N. Nilaweera[1,2]*

(b)



Ripristina il microbiota



NPY: Anticonvulsivo ENDOGENO

Alpha-lactalbumin in epilepsy

Preclinical activity profile of α-lactoalbumin, a whey protein rich in tryptophan, in rodent models of seizures and epilepsy

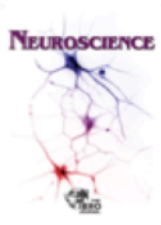
Rita Citraro[1], Francesca Scicchitano[1], Salvatore De Fazio[1], Riccardo Raggio[2], Paolo Mainardi[3], Emilio Perucca[4], Giovambattista De Sarro[1,*], Emilio Russo[1].

More than 400 animals, experimental models:

- GEPR-9 rats
- Pilocarpine
- MES test
- WAG Rij rats

Main results:

- Repeated daily administrations are needed
- **It is able to control both types of seizures induced by Pilocarpine (*)**



Neuroscience 226 (2012) 282–288

PROTECTIVE ACTIVITY OF α-LACTOALBUMIN (ALAC), A WHEY PROTEIN RICH IN TRYPTOPHAN, IN RODENT MODELS OF EPILEPTOGENESIS

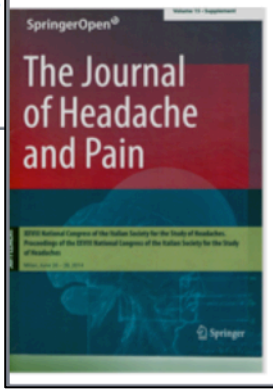
E. RUSSO,[a,*] F. SCICCHITANO,[a] R. CITRARO,[a] R. AIELLO,[a] C. CAMASTRA,[a] P. MAINARDI,[b] S. CHIMIRRI,[a] E. PERUCCA,[c] G. DONATO[a] AND G. DE SARRO[a]

- Adiogenic mice: after 3 weeks of daily adminsitrations, the seizures control last for one month since the end of treatment..

(*) Mainly for this result, ALAC entered in the NIH new drug program screening

Alpha-lactalbumin in Headache

- After 3 months: MoA (da 9.81±2.44 a 6.18±1.73 attachs/month)
- Bristol stool test: type 2 stool (from 64% to 38%)
- The decrease in MoA correlates with decreasing in intestinal inflammation



Alpha-lactalbumin in autism

UNICUSANO
Università degli Studi Niccolò Cusano - Telematica Roma

Master in "NUTRIZIONE CLINICA"

ASSE INTESTINO-CERVELLO E PATOLOGIE COLLEGATE:
l'importanza dell'alimentazione e dell'integrazione prebiotica e probiotica per la riduzione dei sintomi nei bambini affetti da disturbo dello spettro autistico

Candidato: DR. ANDREA TURATTO
Relatore: PROF. CARMELO RIZZO

Alpha-lactalbumin is reported in a Thesis of Master of Nutrition on the basis of results on autism.

Venerdi 29 Novembre

08.30 - 10.00 VISITA POSTER
Moderatori: Mauro Budetta (Salerno), Maurizio Viri (Novara), Antonella Palmieri (Genova), I**rene Bagnasco (Torino)**, Laura Siri (Savona), Maria Fulvia De Leva (Napoli), Gaetano Terrone (Napoli), Valentina Marchiani (Bologna), **Alessandro Orsini (Pisa)**
Poster su disturbi del sonno del gruppo di Torino (Bagnasco) e di Pisa (Orsini)

11.30 - 13.00 Comunicazioni orali selezionate – N. 3 Sessioni parallele

TERAPIA Moderatori: Pasquale Parisi (Roma), Gianluca Casara (Bolzano)

C29: L'UTILIZZO DEL SERPLUS (A-LATTOALBUMINA) IN SOGGETTI CON PANDAS/PANS: LA NOSTRA ESPERIENZA
L. Sabino, F. Greco, M. Motta, E. Pusturino, C. Oliva, G. Gangi, T. Timpanaro, P. Mainardi, P. Pavone

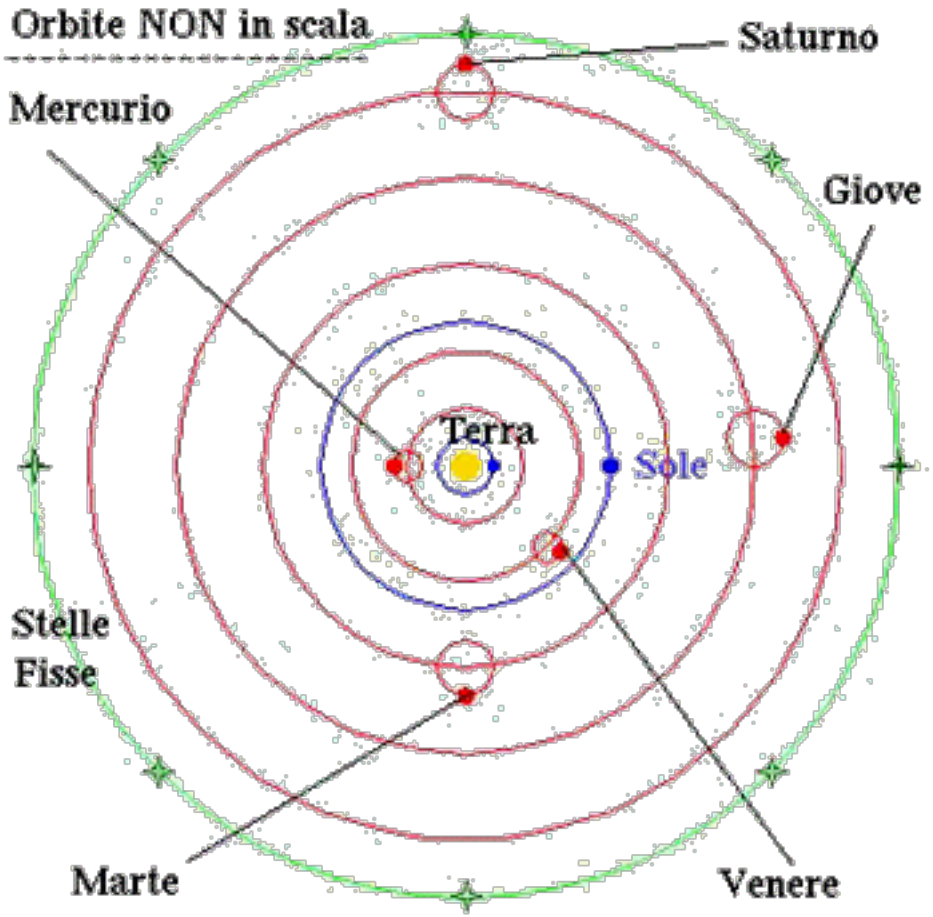
C45: RUOLO DELLA ALFA-LATTOALBUMINA (ALAC) NEL TRATTAMENTO PREVENTIVO DELLA EMICRANIA SENZ'AURA PEDIATRICA
N. Ruotolo, F. Precenzano, M. Esposito, V. Lanzara, E. Lauria, M. Carotenuto

Medicina è una scienza non esatta?

Corpo umano come una grande bottiglia dove poter introdurre ciò che manca

Vitamina D
Melatonina
BCAAs
…

Senza aggiornare le conoscenze anche l'esplorazione dell'Universo sarebbe una scienza non esatta.



Looking towards a new medicine:

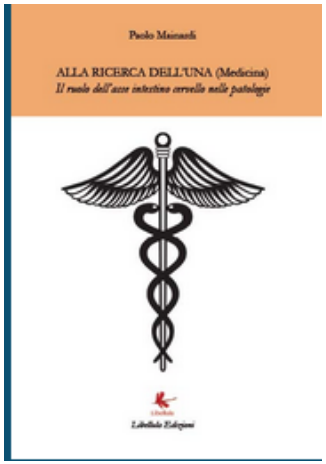
- **MORE POWERFUL THAN ANY DRUGS**

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

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