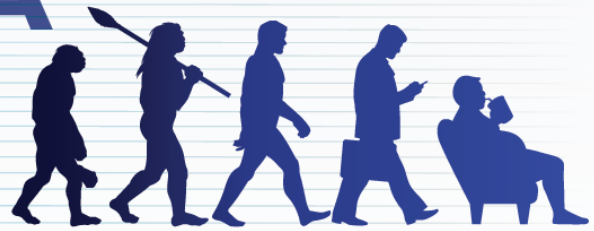
DIABETE ED OBESITÀ

SI PUÒ INVERTIRE LA ROTTA?



COSA ABBIAMO GUADAGNATO E COSA ABBIAMO PERSO

CONGRESSO CONGIUNTO

SID-AMD-SIEDP-SIE-ANIED-OSDI

SESSIONE I ESPLORIAMO L'OBESITÀ

MODERATORI: ***Manuela Albertelli, Mara Boschetti***

Microbioma è la chiave dell'obesità? Si/No è solo un'ipotesi

Flavia Prodam

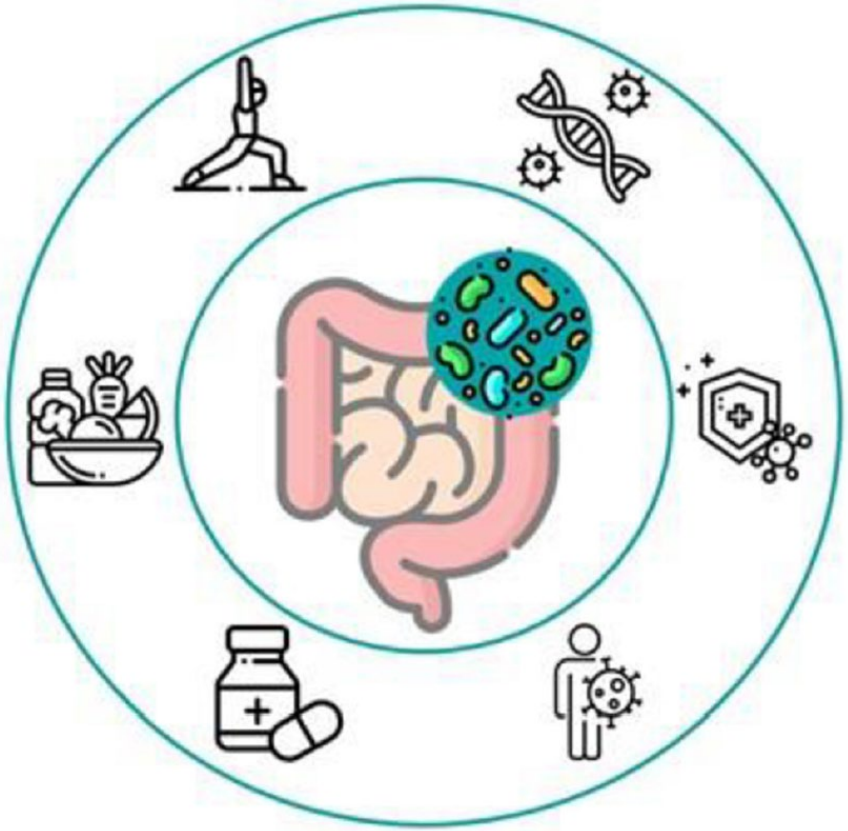
DISCLOSURES

Abiogen; Amryt; Astra Zeneca; Boheringer; Difass International; Caelus Health; Menarini; Novartis; Novo Nordisk; Probiotical , Sanofi; Therascience

INFLUENCERS

SANITIZZAZIONE
TIPO DI PARTO
ALLATTAMENTO
DIETA

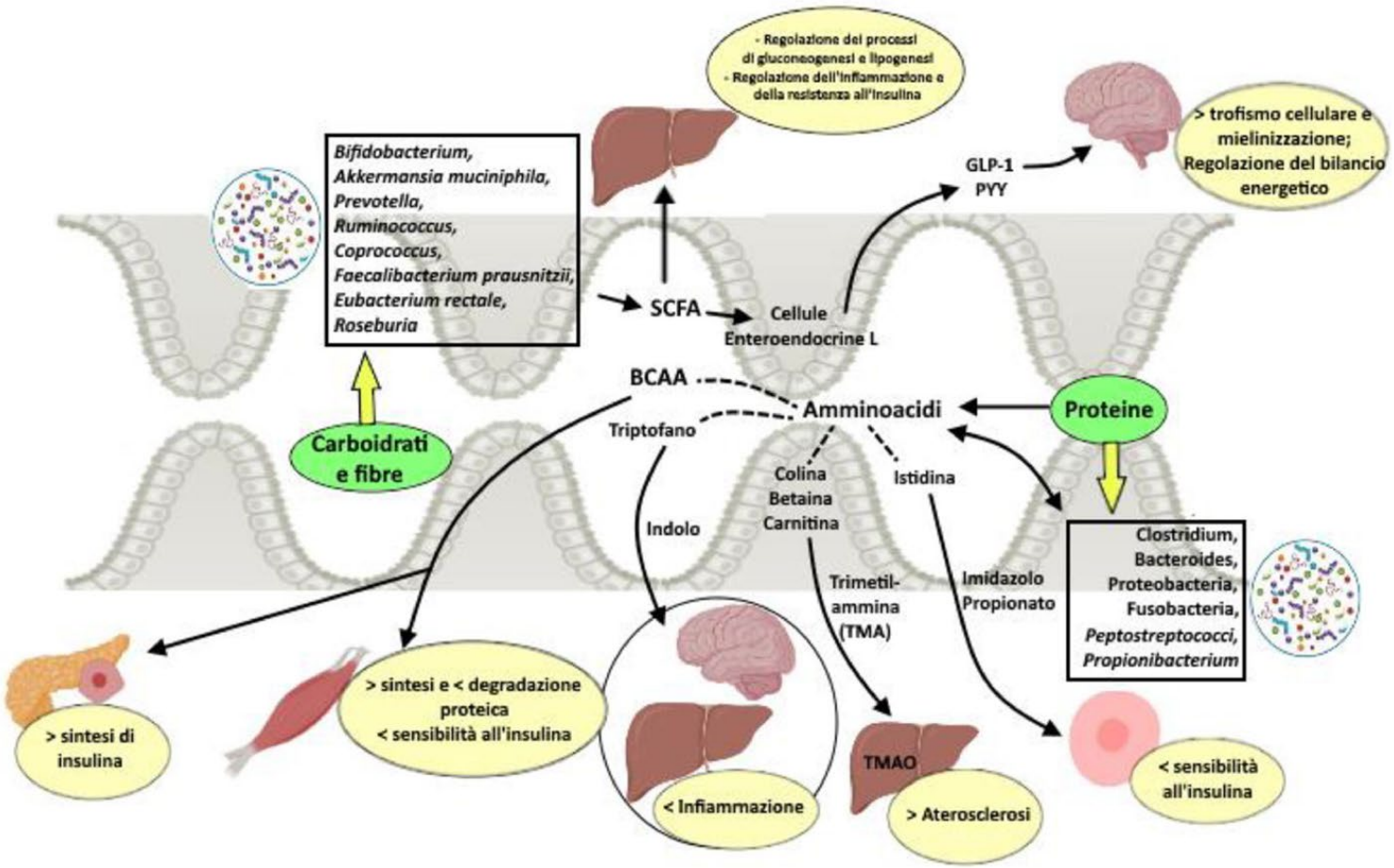
Composizione (Kcal, grassi, fibre, carne..)
Cottura
Addittivi naturali (zafferano..)
Addittivi artificiali:
Conservanti (acido benzoico, sodio benzoato, nitriti/nitrati, diossido di zolfo/solfiti..)
Dolcificanti
Emulsionanti e stabilizzanti
Aromi, addensanti, antiagglomeranti, antiossidanti...
Altro (diossido di titanio..)



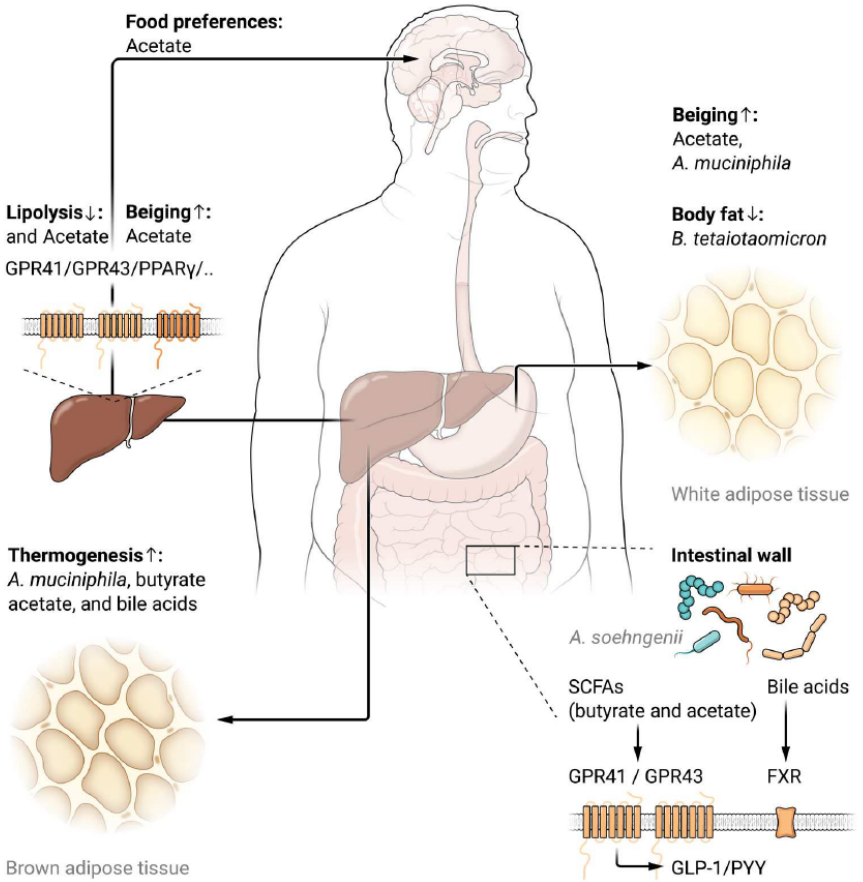
ESERCIZIO FISICO
SONNO
STRESS
FARMACI
IMMUNITA'
GENETICA

Antoniotti V...Prodam F . L'endocrinologo 2023

INFLUENCERS E MECCANISMI



GLUCOSE METABOLISM



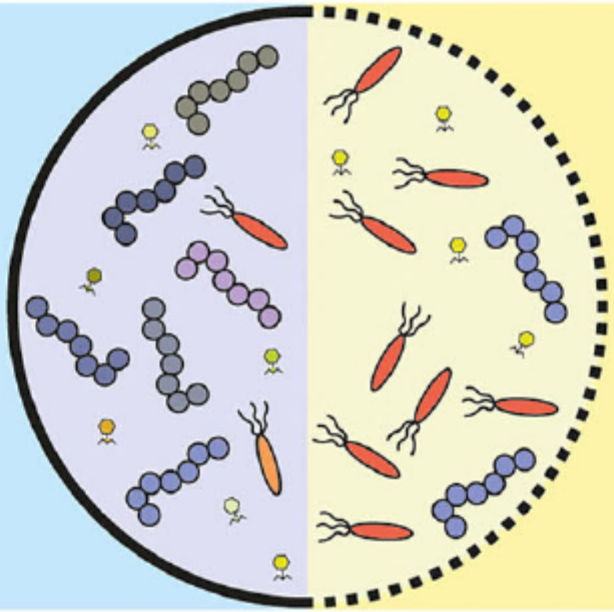
METAINFLAMMATION

De Wit DF et al. Science Transl Med 2023

Antoniotti V...Prodam F . L?endocrinologo 2023

OBESITA'

Lean phenotype
Symbiosis
Controlled pathogens
Byturate producers
Balanced SCFAs profile
Balanced energy harvest
Appropiate immune response
Anti-inflammatory microbiota
Tight intestinal barrier



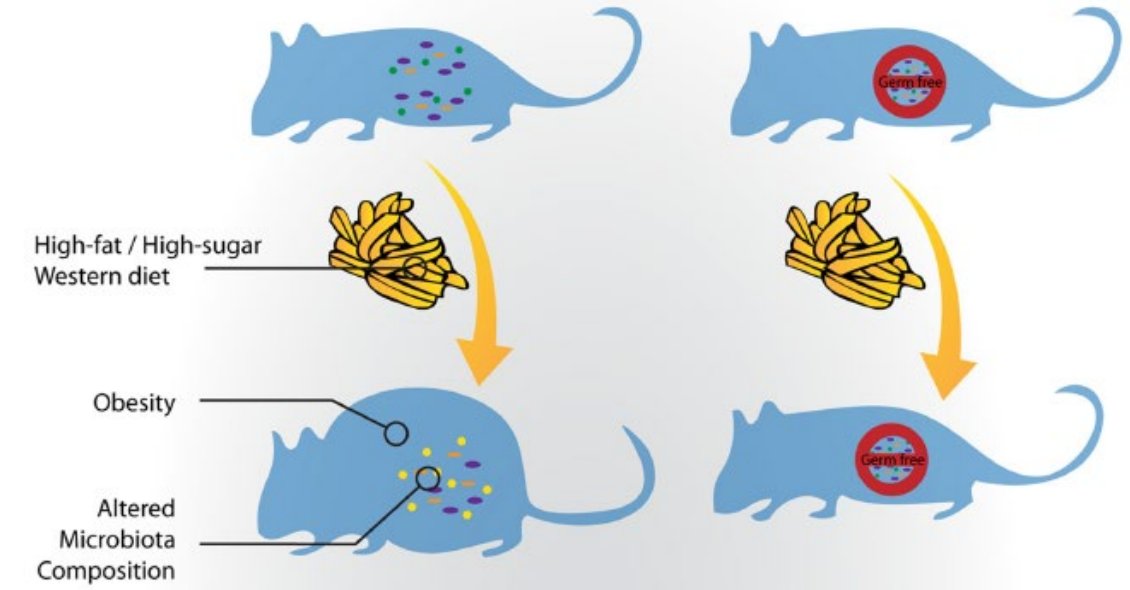
Obese phenotype
"Dysbiosis"
Expansion of pathogens
Loss of butyrate producers
Disturbed SCFAs profile
Increaesd energy harvest
Disturbed immune response
Pro-inflammatory microbiota
"Leaky" gut

+++LPS

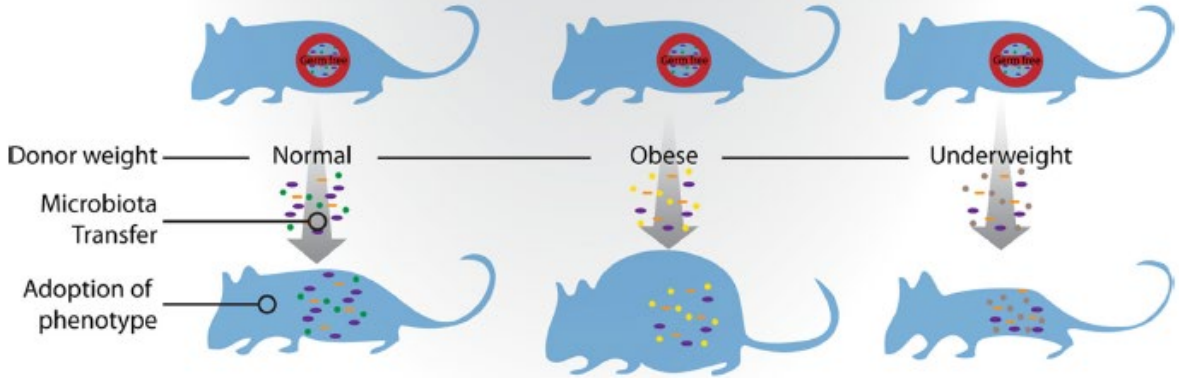
Scheithauer TPM et al. Front Imm 2020

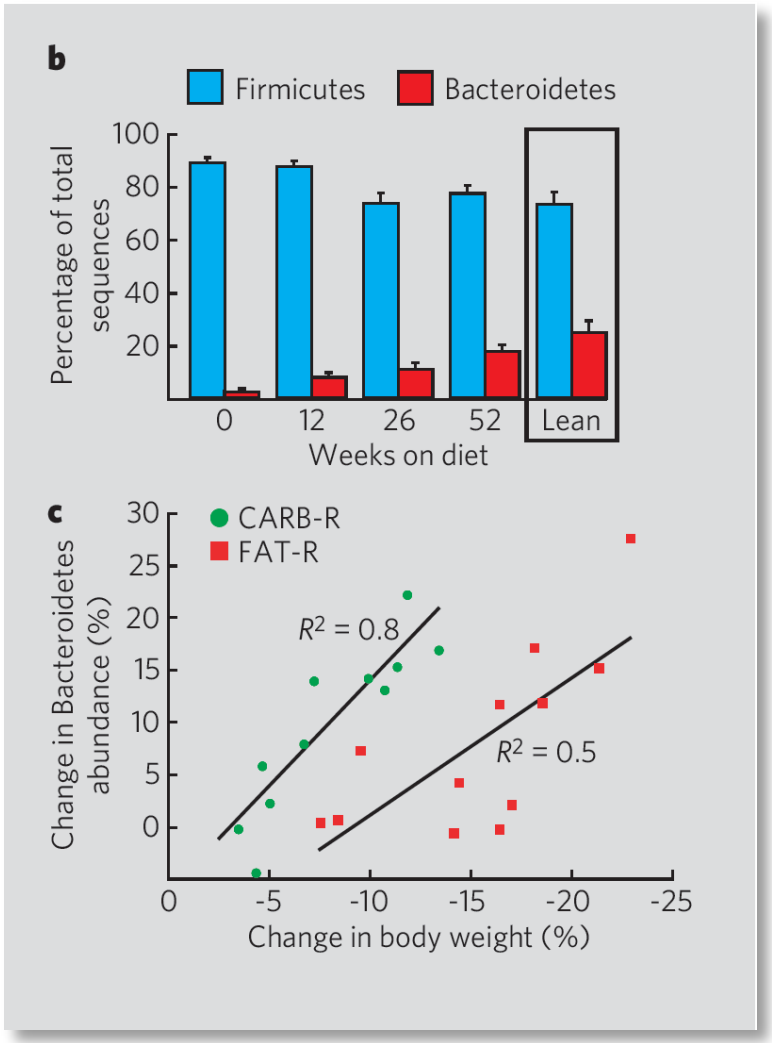
An obesity-associated gut microbiome with increased capacity for energy harvest

Human gut microbes associated with obesity



B Germ-free animals adopt phenotype of microbiota donor

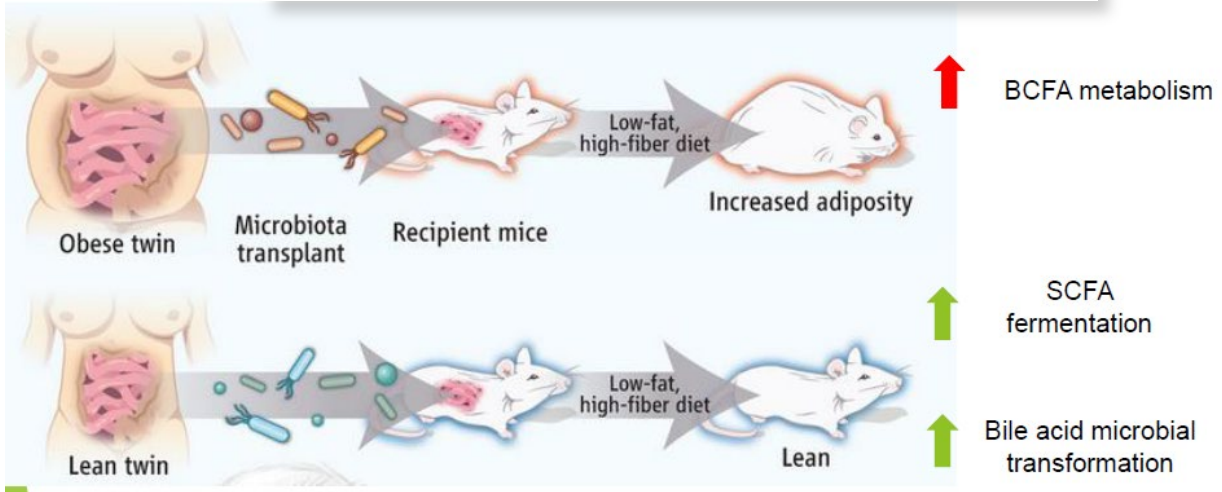




Ley RE et al. Nature 2006

Turnbaugh PJ. et al. Nature 2006

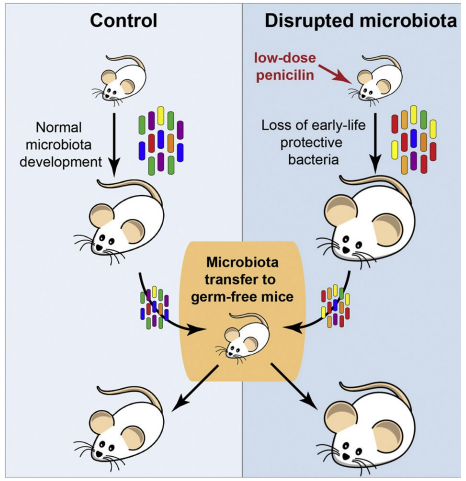
Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice



Results and Discussion: The intact uncultured and culturable bacterial component of Ob co-twins' fecal microbiota conveyed significantly greater increases in body mass and adiposity than those of Ln communities. Differences in body composition were correlated with differences in fermentation of short-chain fatty acids (increased in Ln), metabolism of branched-chain amino acids (increased in Ob), and microbial transformation of bile acid species (increased in Ln and correlated with down-regulation of host farnesoid X receptor signaling). Cohousing Ln and Ob mice prevented development of increased adiposity and body mass in Ob cage mates and transformed their microbiota's metabolic profile to a leanlike state. Transformation correlated with invasion of members of Bacteroidales from Ln into Ob microbiota. Invasion and phenotypic rescue were diet-dependent and occurred with the diet representing the lower tertile of U.S. consumption of saturated fats and upper tertile of fruits and vegetables but not with the diet representing the upper tertile of saturated fats and lower tertile of fruit and vegetable consumption. These results reveal that transmissible and modifiable interactions between diet and microbiota influence host biology.

Ridaura VK et al. Science 2013

Altering the Intestinal Microbiota during a Critical Developmental Window Has Lasting Metabolic Consequences



Acquisition of the intestinal microbiota begins at birth, and a stable microbial community develops from a succession of key organisms. Disruption of the microbiota during maturation by low-dose antibiotic exposure can alter host metabolism and adiposity. We now show that low-dose penicillin (LDP), delivered from birth, induces metabolic alterations and affects ileal expression of genes involved in immunity. LDP that is limited to early life transiently perturbs the microbiota, which is sufficient to induce sustained effects on body composition, indicating that microbiota interactions in infancy may be critical determinants of long-term host metabolic effects. In addition, LDP enhances the effect of high-fat diet induced obesity. The growth promotion phenotype is transferrable to germ-free hosts by LDP-selected microbiota, showing that the altered microbiota, not antibiotics per se, play a causal role. These studies characterize important variables in early-life microbe-host metabolic interaction and identify several taxa consistently linked with metabolic alterations.

Cox LM et al. Cell 2014

JAMA Pediatr. 2014 Nov;168(11):1063-9. doi: 10.1001/jamapediatrics.2014.1539.

Association of antibiotics in infancy with early childhood obesity.

Bailey LC[1], Forrest CB[1], Zhang P[2], Richards TM[3], Livshits A[2], DeRusso PA[1].

Antibiotic Exposure in Infancy and Risk of Being Overweight in the First 24 Months of Life

Antti Saari, MD[a,b], Lauri J. Virta MD, PhD[c], Ulla Sankilampi MD, PhD[b], Leo Dunkel MD, PhD[d], Harri Saxen MD, PhD[e]

Eur J Pediatr (2014) 173:25–32
DOI 10.1007/s00431-013-2178-1

REVIEW

Obesity and infection: two sides of one coin

Giulia Genoni · Flavia Prodam · Agostina Marolda · Enza Giglione · Irene Demarchi · Simonetta Bellone · Gianni Bona

Gastroenterology. 2016 Jul;151(1):120-129.e5. doi: 10.1053/j.gastro.2016.03.006. Epub 2016 Mar 18.

Administration of Antibiotics to Children Before Age 2 Years Increases Risk for Childhood Obesity.

Scott FI[1], Horton DB[2], Mamtani R[3], Haynes K[4], Goldberg DS[5], Lee DY[6], Lewis JD[5].

J Pediatr. 2016 Sep;176:105-113.e2. doi: 10.1016/j.jpeds.2016.06.015. Epub 2016 Jul 8.

Early Life Antibiotic Exposure and Weight Development in Children.

Mbakwa CA[1], Scheres L[2], Penders J[3], Mommers M[2], Thijs C[2], Arts IC[4].

Weight gain by gut microbiota manipulation in productive animals

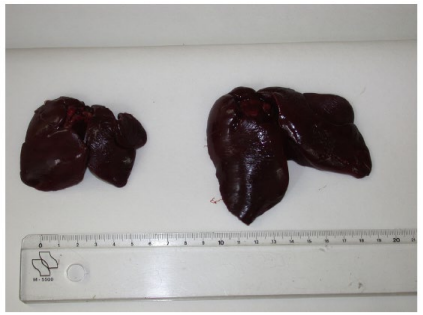
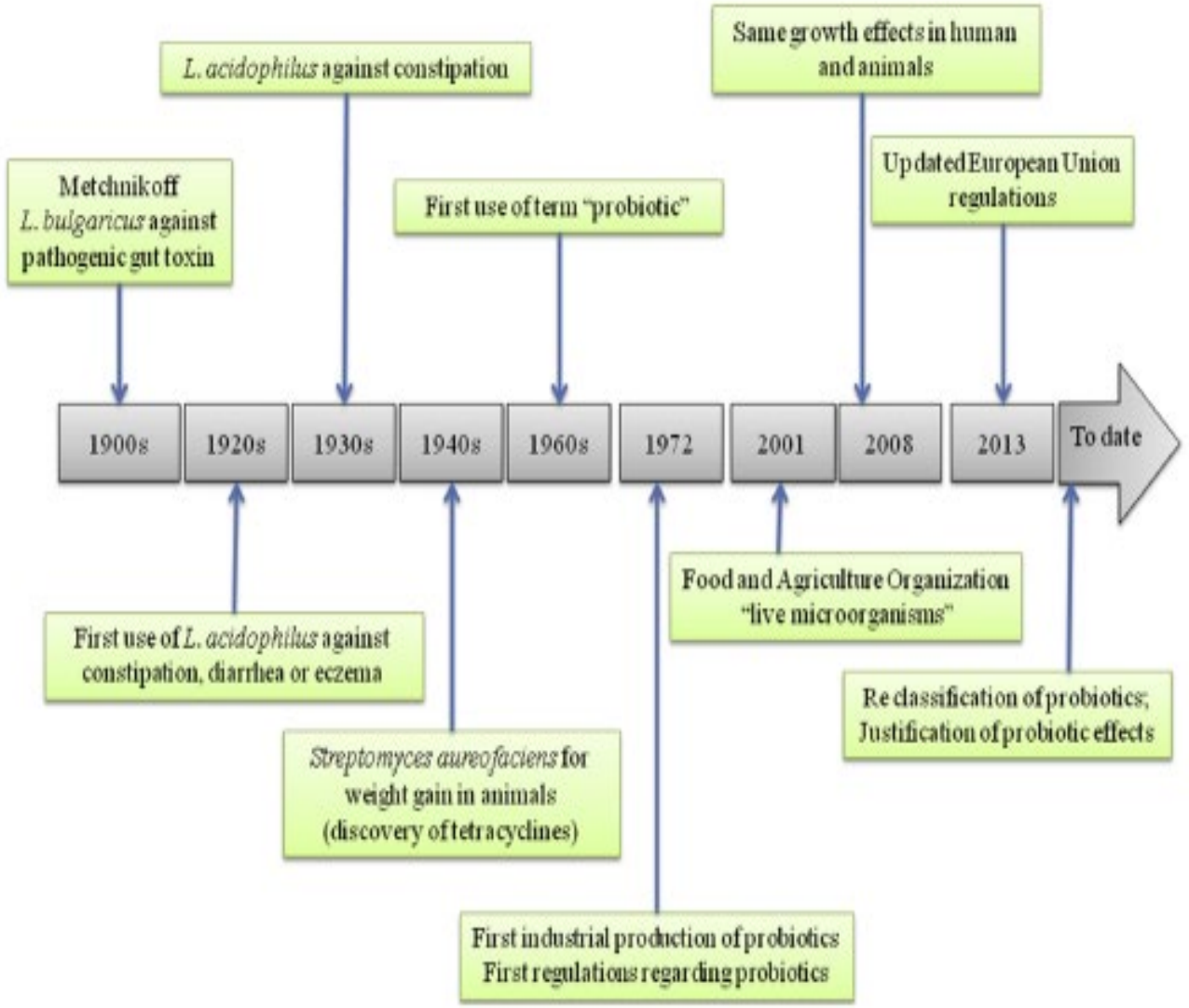
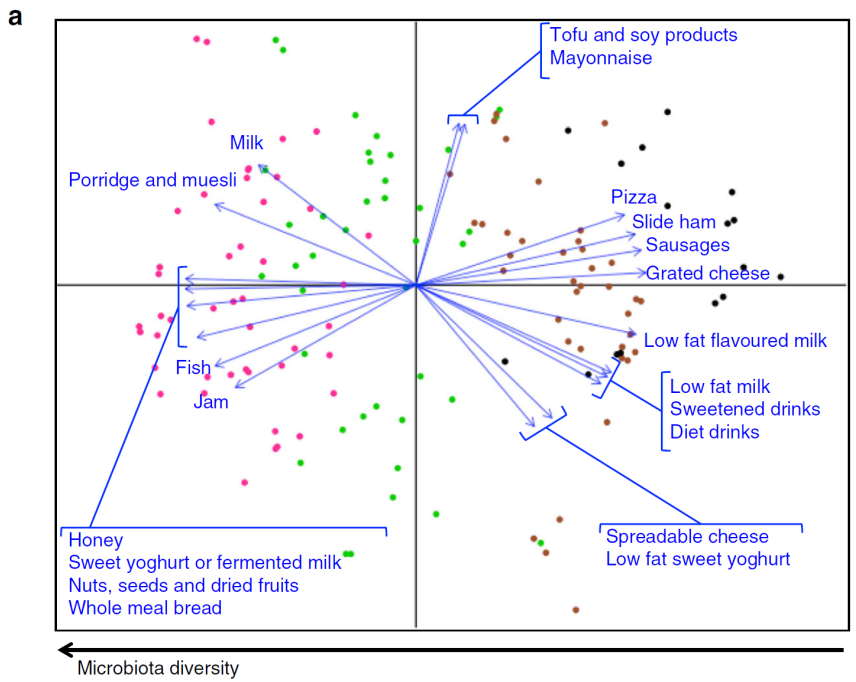


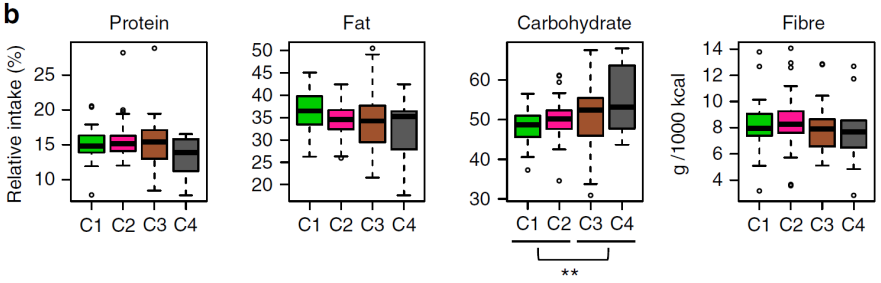
Fig. 3. Increase liver mass in chicken after probiotic treatment.

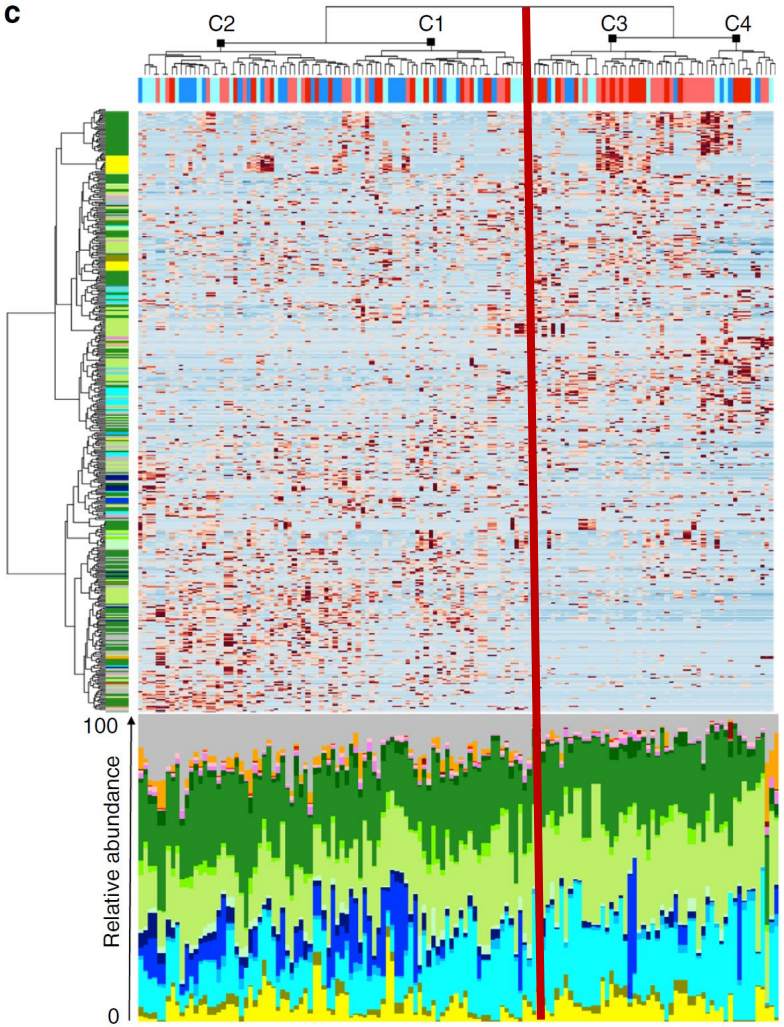


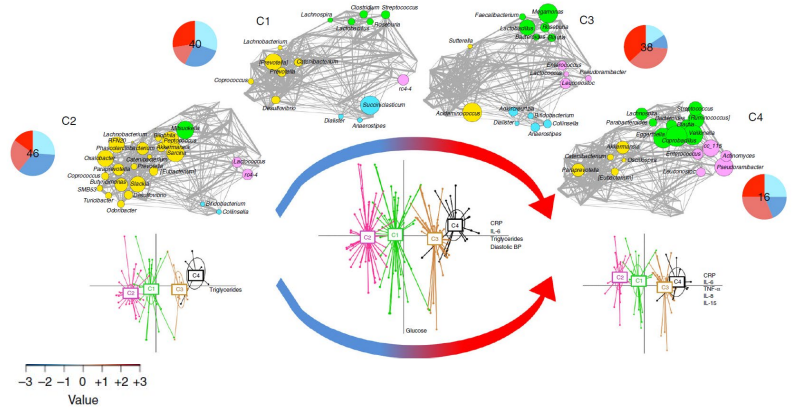
Angelakis E Microb Pathog 2017

Pre-obese children's dysbiotic gut microbiome and unhealthy diets may predict the development of obesity

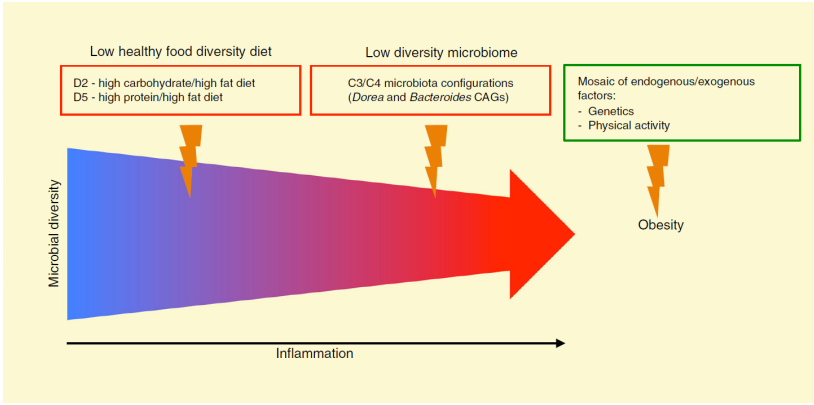








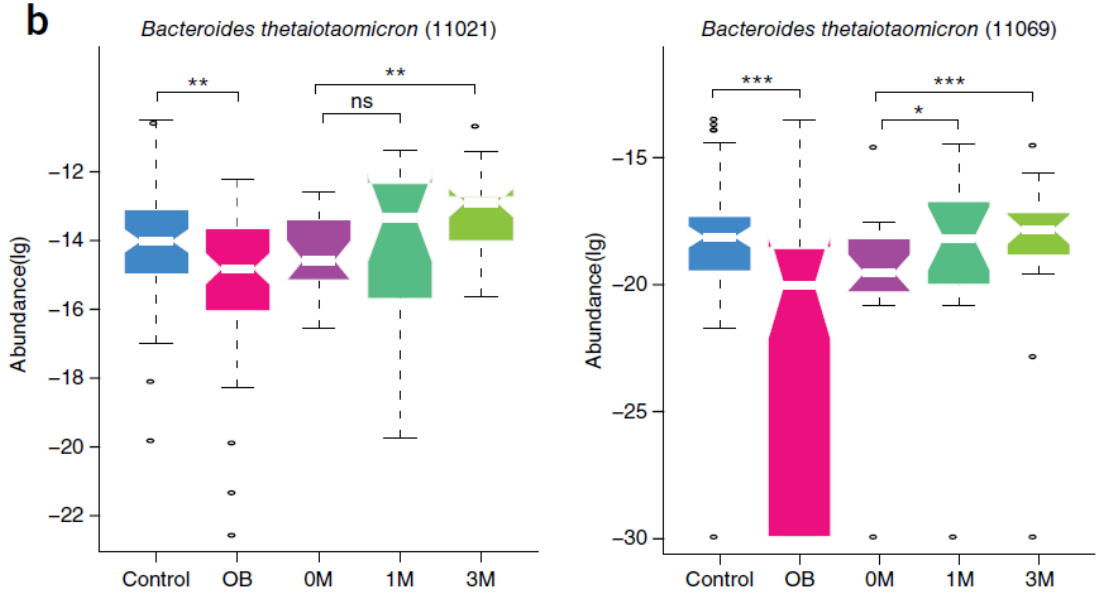
Children normal weight T1
Children normal weight T3
Children OB/OW T1
Children OB/OW T3

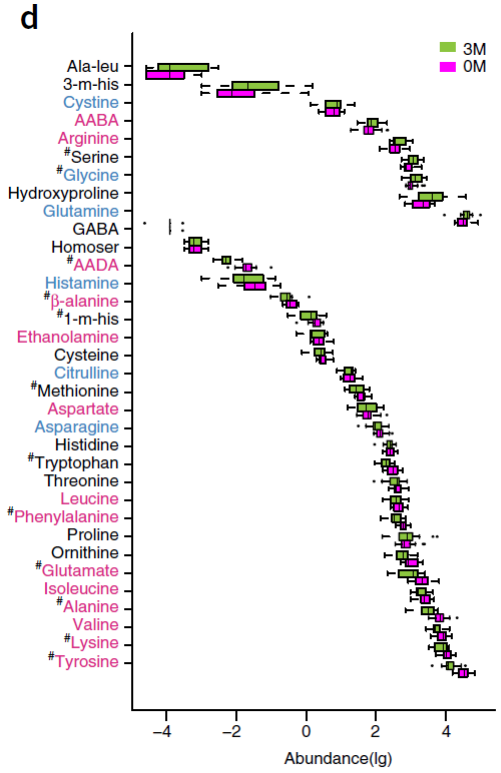


Rapelli S et al, Communic Biol 2019

Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention

Emerging evidence has linked the gut microbiome to human obesity. We performed a metagenome-wide association study and serum metabolomics profiling in a cohort of lean and obese, young, Chinese individuals. We identified obesity-associated gut microbial species linked to changes in circulating metabolites. The abundance of *Bacteroides thetaiotaomicron*, a glutamate-fermenting commensal, was markedly decreased in obese individuals and was inversely correlated with serum glutamate concentration. Consistently, gavage with *B. thetaiotaomicron* reduced plasma glutamate concentration and alleviated diet-induced body-weight gain and adiposity in mice. Furthermore, weight-loss intervention by bariatric surgery partially reversed obesity-associated microbial and metabolic alterations in obese individuals, including the decreased abundance of *B. thetaiotaomicron* and the elevated serum glutamate concentration. Our findings identify previously unknown links between intestinal microbiota alterations, circulating amino acids and obesity, suggesting that it may be possible to intervene in obesity by targeting the gut microbiota.



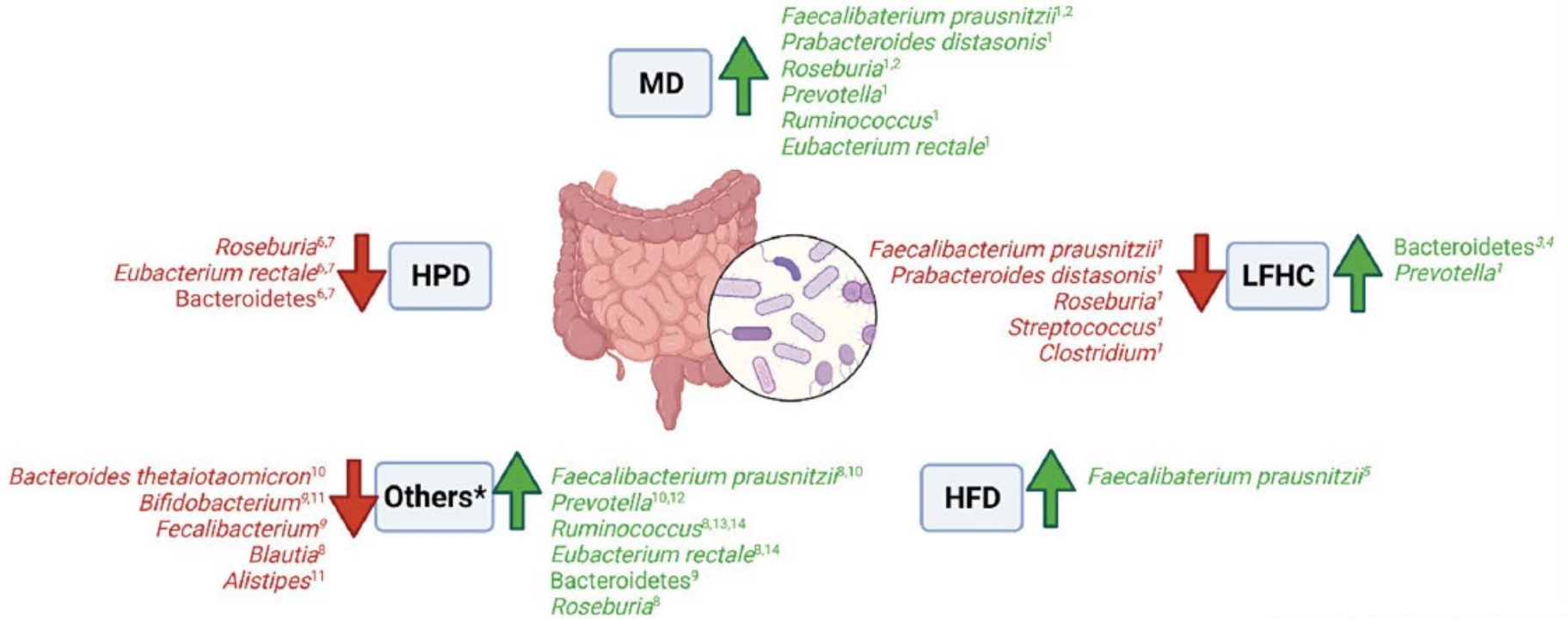


Liu R et al. Nature 2017

Targeting microbiota in dietary obesity management: a systematic review on randomized control trials in adults

Marina Caputo, Stella Pigni, Valentina Antoniotti, Emanuela Agosti, Alice Caramaschi, Alessandro Antonioli, Gianluca Aimaretti, Marcello Manfredi, Elisa Bona & Flavia Prodam

This review aimed to systematically organize the body of evidence on microbiota deriving from dietary trials in adult obesity giving the most certain phylogenetic, and metabolomic signatures in relation to both the host metabolism and phenotype changes published until now. We retrieved 18 randomized control trials on 1385 subjects with obesity who underwent several dietary interventions, including standard diet and healthy dietary regimens. Some phyla and species were more related to diets rich in fibers and others to healthy diets. Weight loss, metabolism improvements, inflammatory markers decrease were specifically related to different microorganisms or functions. The *Prevotella/Bacteroides* ratio was one of the most reported predictors. People with the burden of obesity comorbidities had the most significant taxonomic changes in parallel with a general improvement. These data emphasize the possibility of using symbiotic approaches involving tailored diets, microbiota characteristics, and maybe drugs to treat obesity and metabolic disorders. We encourage Authors to search for specific phylogenetic associations beyond a too generally reported Firmicutes/Bacteroides ratio.



Crit Rev Food Sci Nutr 2022

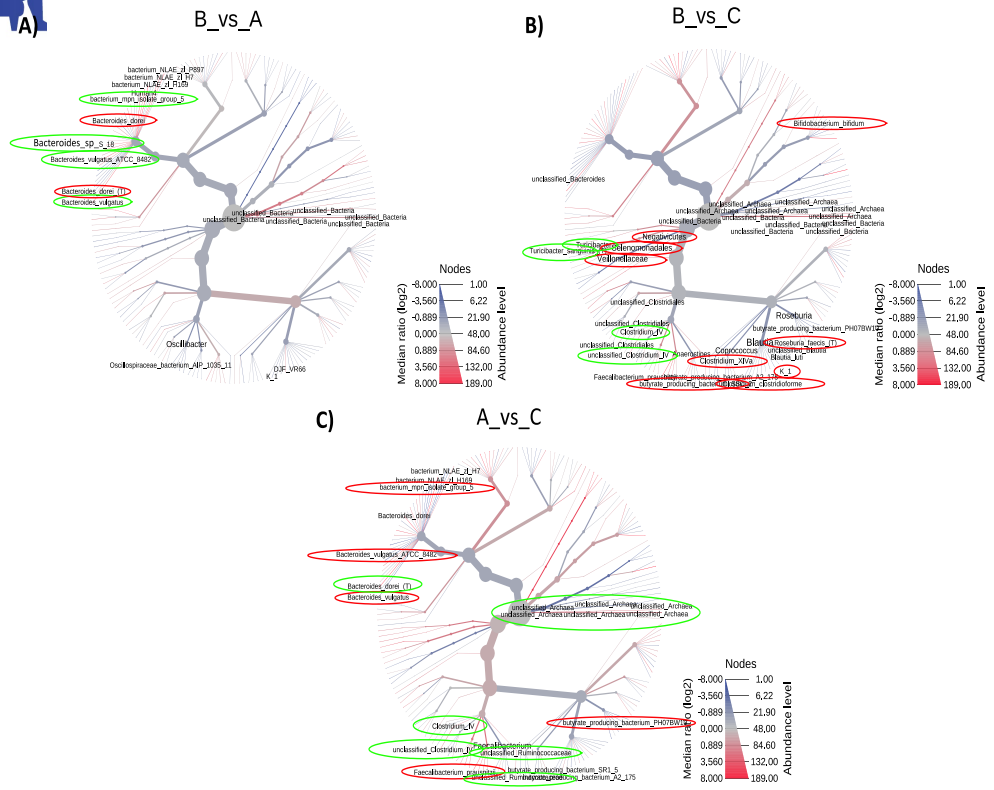


Figure 3. Heat tree of percentage of carbohydrate intake.
Heat trees report the effect of the treatment on hierarchical structure of taxonomic classifications (median abundance, non-parametric Wilcoxon Rank Sum test). Heat tree analysis was performed using R metacoder package of MicrobiomeAnalyst. CLASS: percentage of consumed carbohydrates (A<45%, B=45-55%, C> 55%). In A, red ellipses highlight species more represented in A group, while green ellipses indicate species more present in B group; in B red ellipses highlight species more represented in C group, while green ellipses indicate species more present in B group; in C, red ellipses highlight species more represented in C group, while green ellipses indicate species more present in A group.

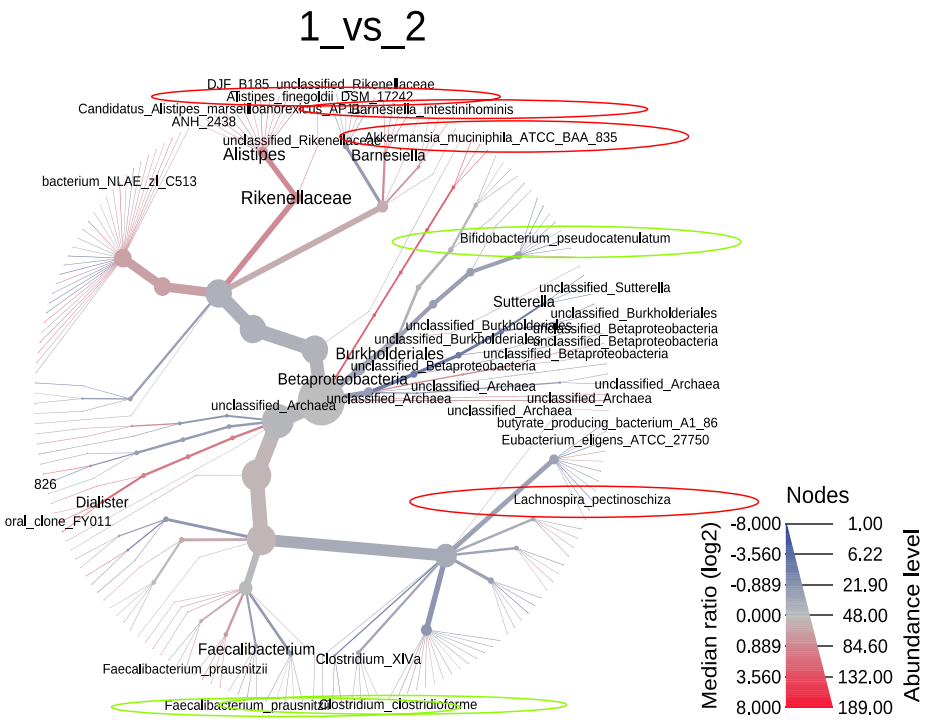
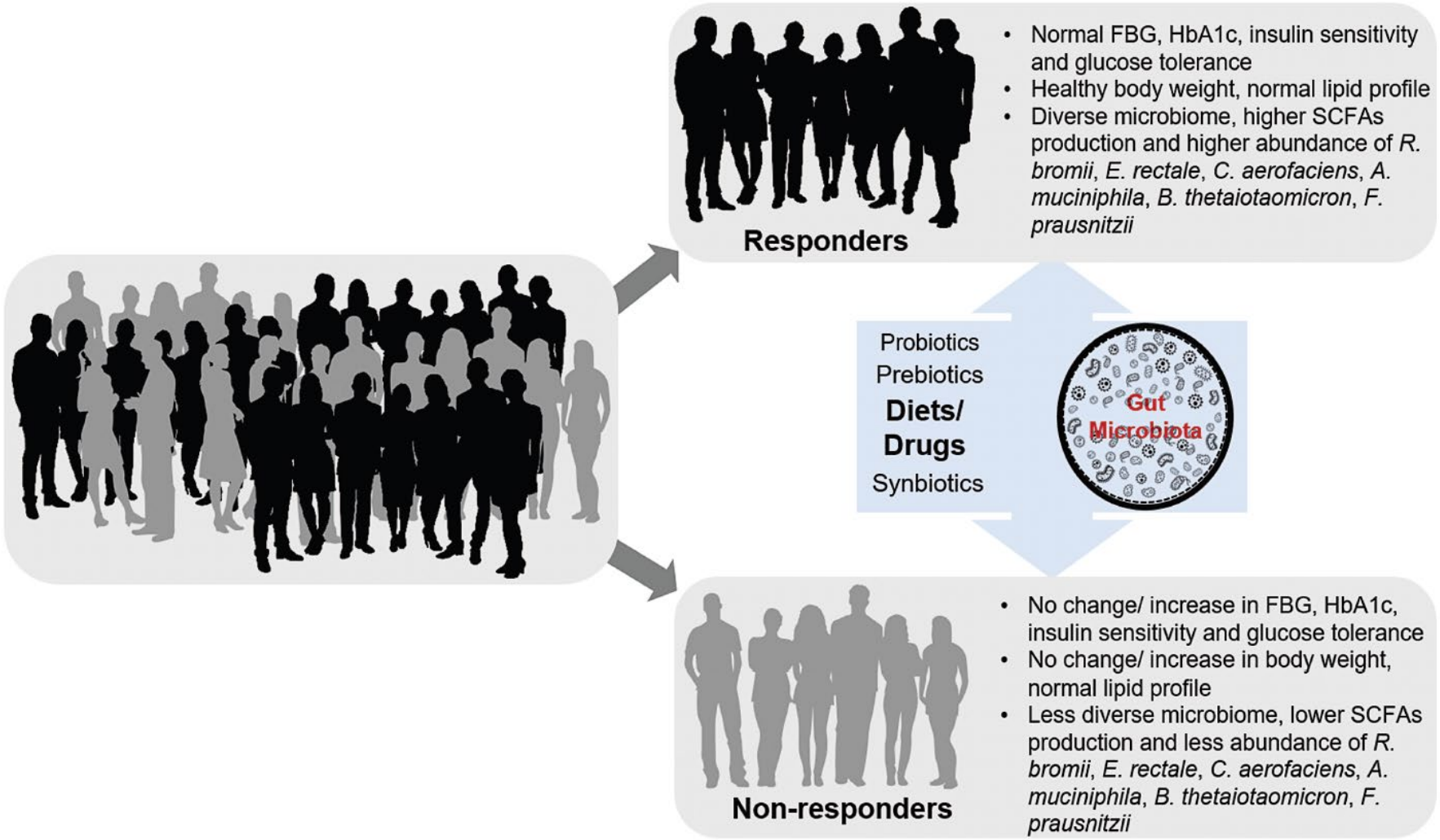


Figure 4. Heat tree of HOMA-IR ≥95° percentile
Heat trees report the effect of the treatment on hierarchical structure of taxonomic classifications (median abundance, non-parametric Wilcoxon Rank Sum test). Heat tree analysis was performed using R metacoder package of MicrobiomeAnalyst. CLASS: HOMA-IR 95: 1=HOMA-IR < 95° percentile; 2≥ 95° percentile. Red ellipses highlight species more represented in 1 group, while green ellipses indicate species more present in 2 group.

Prodam F et al. manuscript in preparation

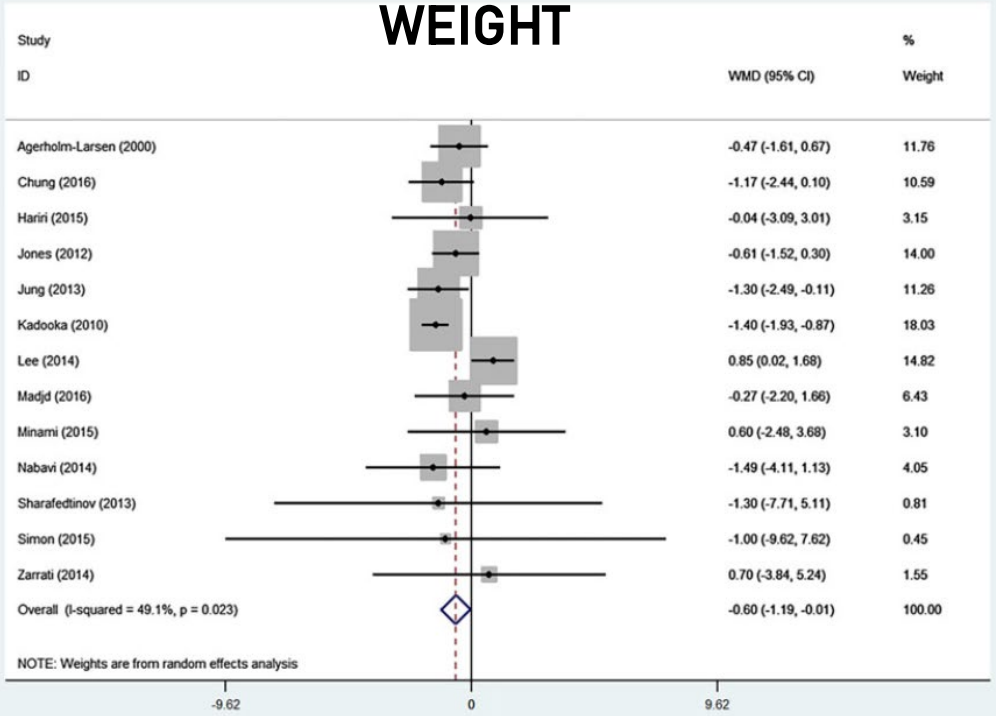
INTERVENTI



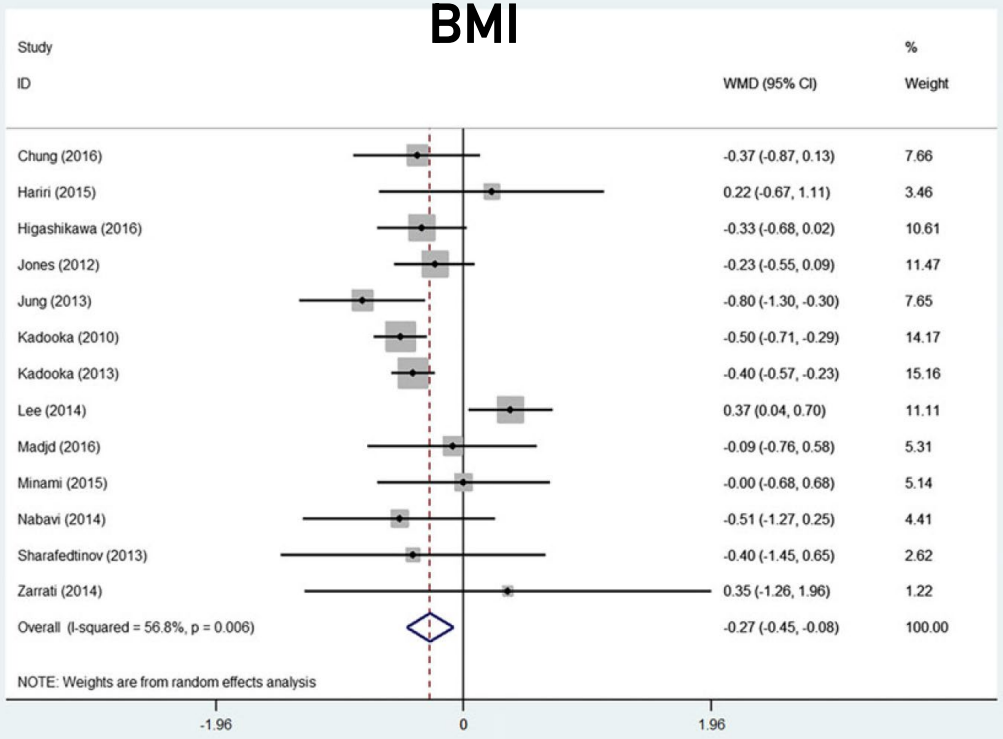
Mishra SP et al. JCEM 2021

INTERVENTI

WEIGHT



BMI

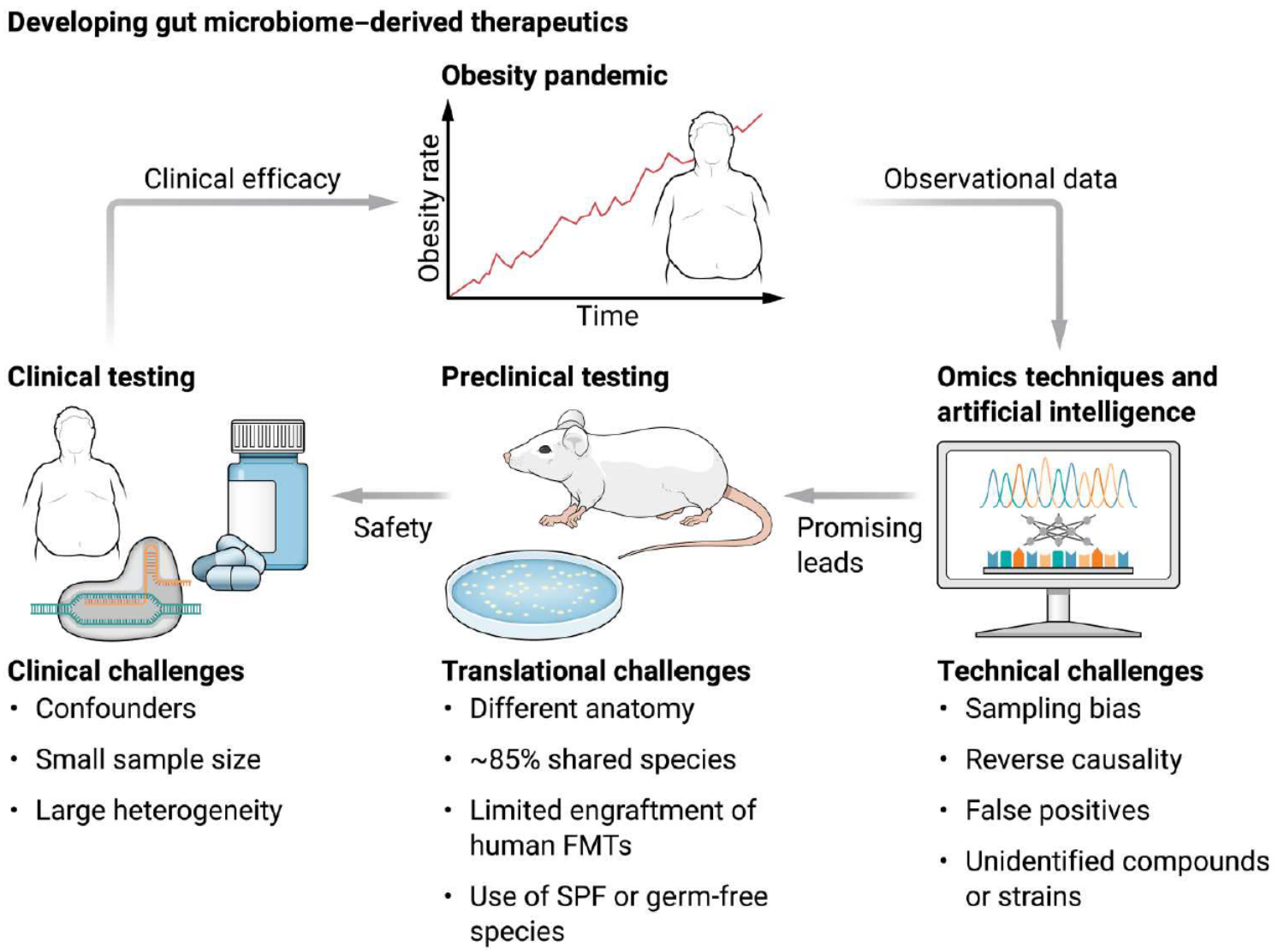


1946-2016
957 subjects (63% F)
BMI: 27.6 Kg/m2

Duration: 3-12 weeks
Yogurth, fermented milk
Lactobacilli; Enterococcus; Streptococcus; Bifidobacteria

Borgeraas H et al. Obes Rev 2017

INTERVENTI



De Wit DF et al. Science Transl Med 2023

INTERVENTI

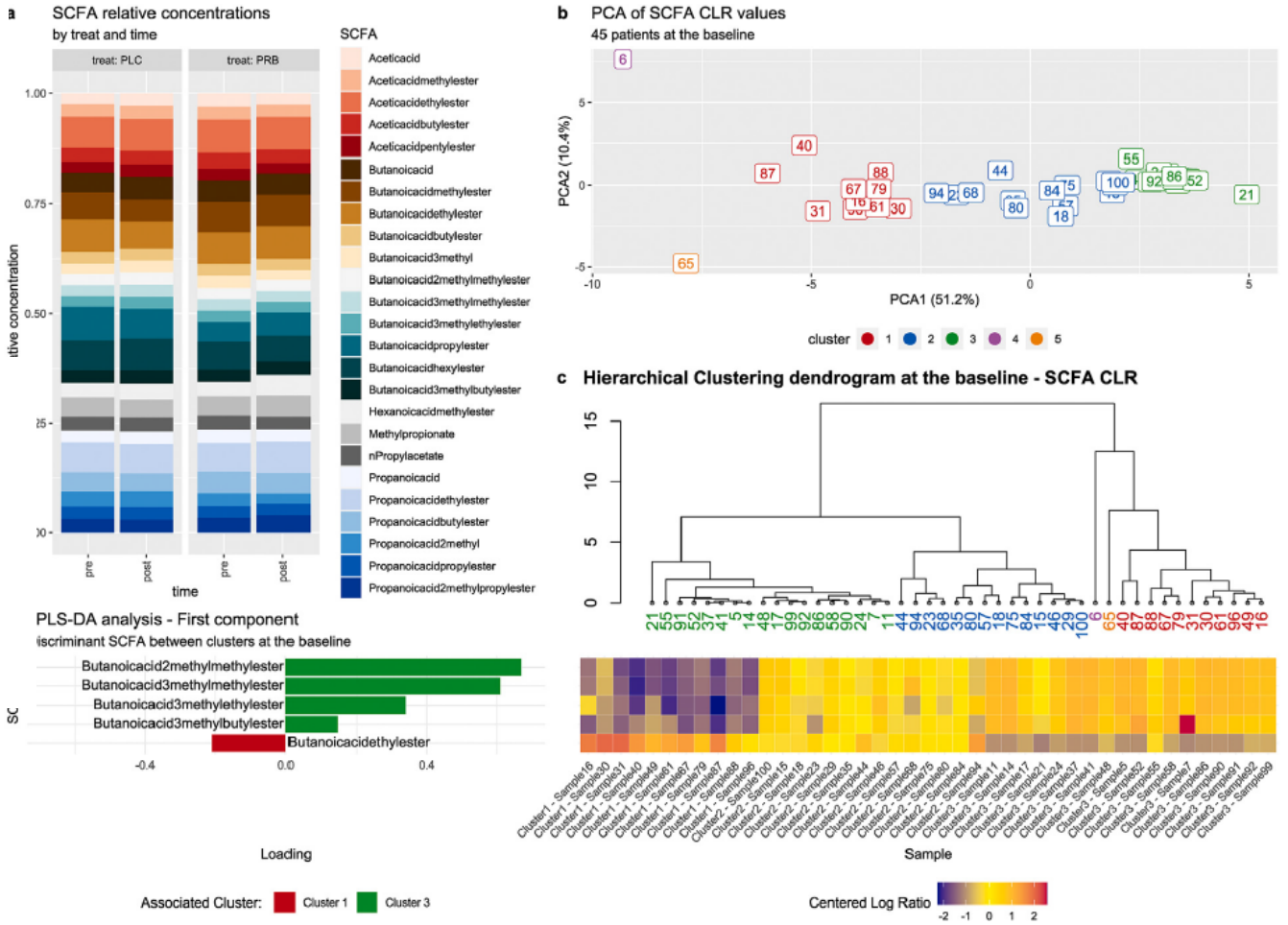
Randomized Control Trials

Supplementation with *Bifidobacterium breve* BR03 and B632 strains improved insulin sensitivity in children and adolescents with obesity in a cross-over, randomized double-blind placebo-controlled trial

Arianna Solito [a, 1], Nicole Bozzi Cionci [b, 1], Matteo Calgaro [c], Marina Caputo [d, e], Lucia Vannini [b], Iderina Hasballa [e], Francesca Archero [a], Enza Giglione [a], Roberta Ricotti [a], Gillian Elisabeth Walker [d], Antonella Petri [a], Emanuela Agosti [d], Giorgio Bellomo [f], Gianluca Aimaretti [e], Gianni Bona [a], Simonetta Bellone [a], Angela Amoruso [g], Marco Pane [g], Diana Di Gioia [b], Nicola Vitulo [c, **], Flavia Prodam [a, d, e, *]

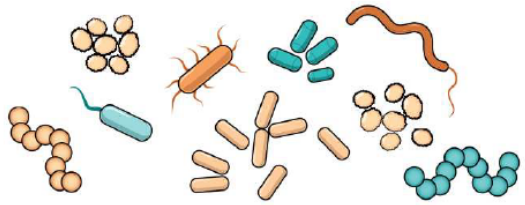
Results: All subjects (M/F 54/47) completed the first 8 weeks, and 82 (M/F 43/39) the last part without adverse events. Mixed-effects models revealed a carry-over effect on many variables in the entire study, narrowing the analysis to the first 8 weeks before the wash-out periods. All subjects improved metabolic parameters, and decreased weight and *Escherichia coli* counts. Probiotics improved insulin sensitivity at fasting (QUICKI, 0.013 CI95%0.0–0.03) and during OGTT (ISI, 0.654 CI95%-0.11–1.41). Cytokines, GLP1, and target microbial counts did not vary. Of 25 SCFAs, acetic acid and acetic acid pentyl-ester relative abundance remained stable in the probiotics, while increased in the placebo ($p < 0.02$). A signature of five butanoic esters identified three clusters, one of them had better glucose responses during probiotics.

Conclusion: An 8 weeks treatment with *B. breve* BR03 and B632 had beneficial effects on insulin sensitivity in youths with obesity. Microbiota functionality could influence metabolic answers to probiotics. Long-term studies to confirm and enrich our findings are justified. Tailored probiotic treatments could be an additional strategy for obesity.

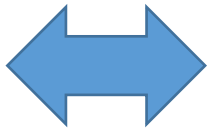


Clin Nutr 2021

FUTURO PROSSIMO



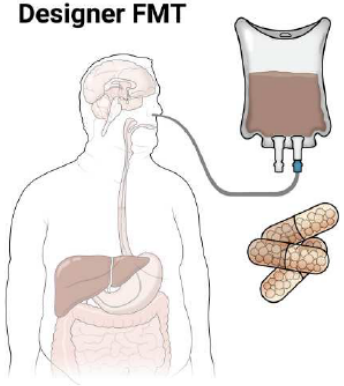
Microbiome



DRUGS

- Metformin
- Statins
- GLP-1 antagonists

Designer FMT

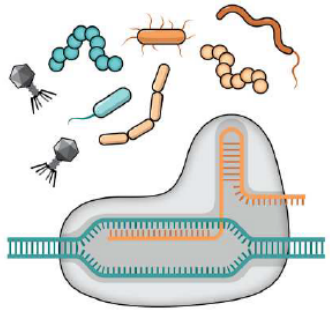


- Fecal virome transplant
- FMT after diet-induced weight loss
- Encapsulated FMT

Pre-, pro-, and postbiotics

- Indole derivatives
- Short-chain fatty acids
- *A. soehngenii*
- *A. muciniphila*

Genetically engineered strains



- *E. coli* Nissle 1917 modified strains
- *A. soehngenii*

Horvath A et al. Endocr Diab Metab 2023

De Wit DF et al. Science Transl Med 2023

FUTURO PROSSIMO

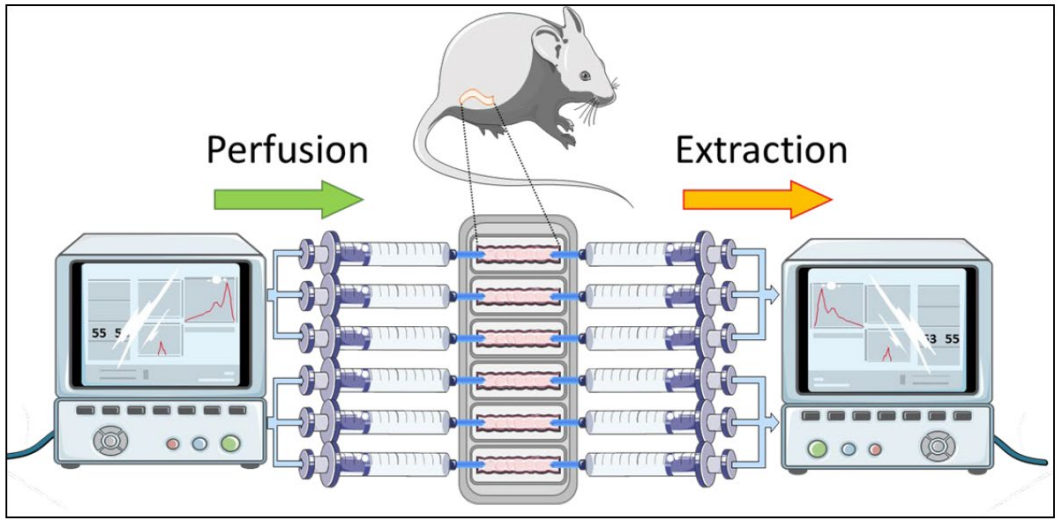
Communication

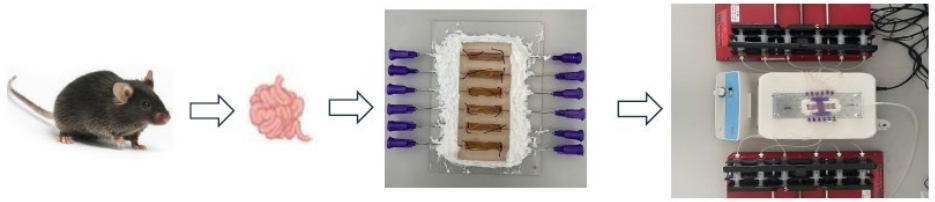
The Gut-Ex-Vivo System (GEVS) Is a Dynamic and Versatile Tool for the Study of DNBS-Induced IBD in BALB/C and C57BL/6 Mice, Highlighting the Protective Role of Probiotics

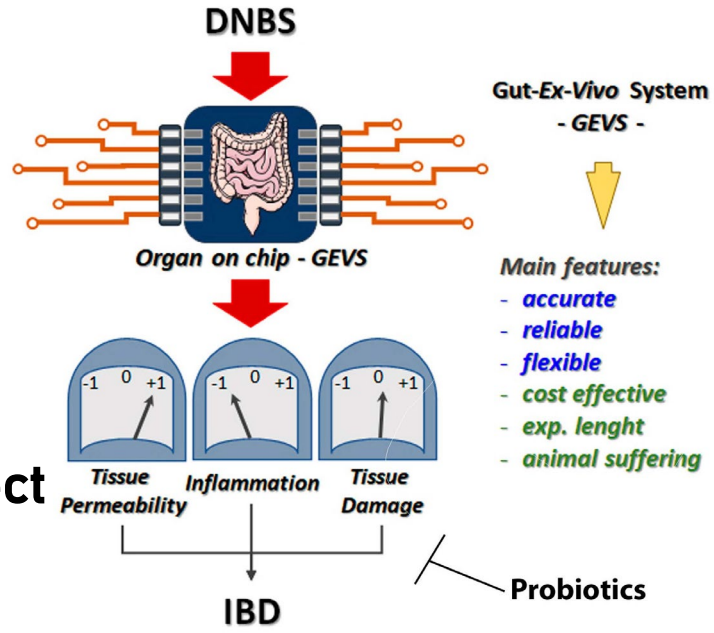
Romina Monzani [1,†], Mara Gagliardi [1,†], Nausicaa Clemente [2], Valentina Saverio [1], Elżbieta Pańczyszyn [1], Claudio Santoro [3], Nissan Yissachar [4], Annalisa Visciglia [5], Marco Pane [5], Angela Amoruso [5] and Marco Corazzari [3,*]

NODES
Nord Ovest Digitale E Sostenibile

ecs-nodes.eu







SPOKE 5 MR3

+

NUTRIAGE project

Biology 2022

FOOD FOR TOUGHT

- ✓ Il microbiota nell'obesità è differente in composizione e funzione
- ✓ Il metabolismo microbico influenza il metabolismo dell'ospite
- ✓ La signature microbiologica può influenzare la risposta a terapie metaboliche, diete e trattamenti con probiotici, prebiotici, postbiotici, prodotti del metabolismo microbico e FMT
- ✓ Ripristinare un microbiota "sano" potrebbe non significare ridurre l'obesità
- ✓ Sono necessari studi traslazionali, studi longitudinali e RCT su popolazioni numerose finalizzati ad una medicina di precisione (signature-based)
- ✓ In attesa di ulteriori evidenze, si suggerisce di evitare l'abuso di terapie antibiotiche in età neonatale ed infantile

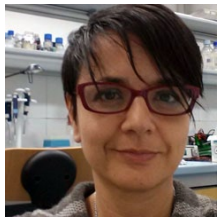
THANKS TO…


Salvatore Sutti,


Provera Alessia


Aessandro Antonioli,


Sabrina Tini


Nicoletta Filigheddu,


Simone Reano,


Marco Corazzari


Marina Caputo,


Valentina Antoniotti,


Marcello Manfredi,


Daniele Spadaccini,

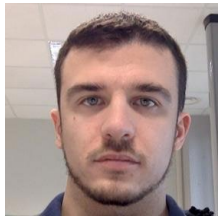

Marco Arlorio,


Jean D Coisson,


Valentina Saverio

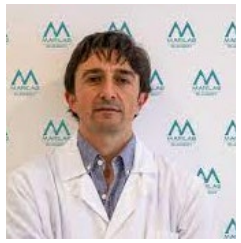

Ilario Ferrocino,


Luca S Cocolin,
PO, DiSAFA


Davide Raineri,


Annalisa Chiocchetti


Elisa Bona,


Massimiliano Caprio,


Maria Felicia Faienza,

NUTRICIA RESEARCH FOUNDATION