IX Jornada CODiNuCoVa

“MyNewGut: de la investigación en microbiota a la práctica clínica”

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Valencia

Educación y Nutrición

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MyNewGut: gut microbiota, diet and obesity

The burden of obesity

THE LANCET

Obesity 2015

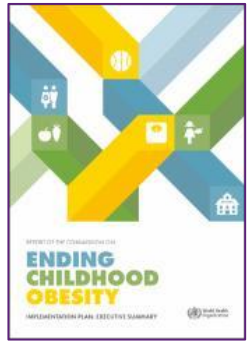
Published: February 18, 2015

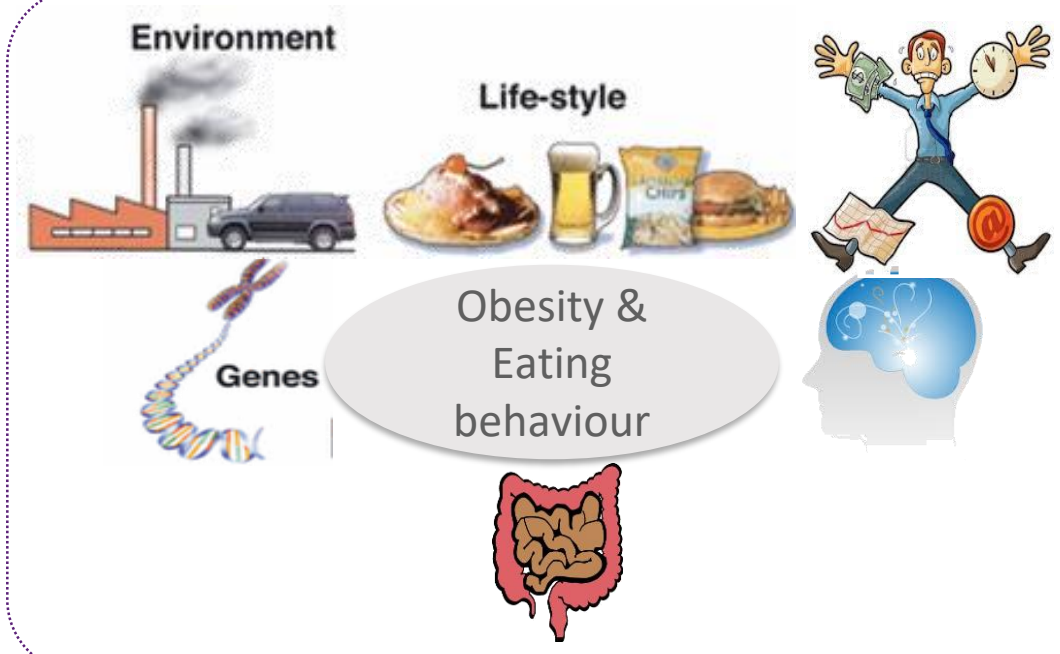
Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking

Christina A Roberto, Boyd Swinburn, Corinna Hawkes, Terry T-K Huang, Sergio A Costa, Marice Ashe, Lindsey Zwicker, John H Cawley, Kelly D Brownell

World Health Organization

Childhood Obesity Surveillance Initiative (2017) - Number of obese children has increased tenfold in the last 40 years.



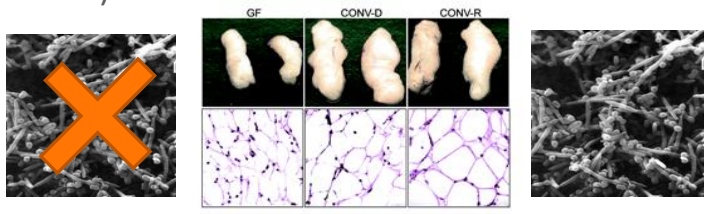


Evidence of the role of gut microbiota in obesity

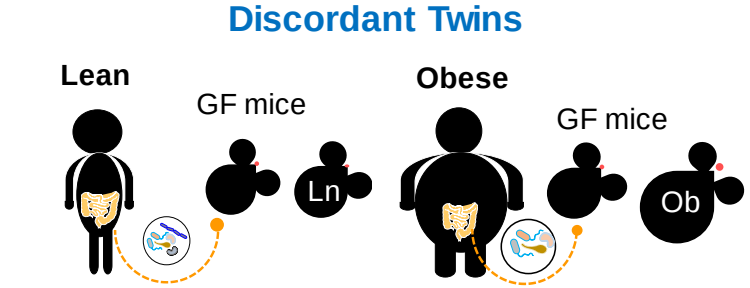
Lessons form germ-free animal models

- Germ-free mice are more resistant to diet-induced obesity (DIO), suggesting that gut microbiota is essential for obesity development

  (Bäckhed et al., 2004; Leone et al., 2015; Martinez-Guryn et al. 2018).

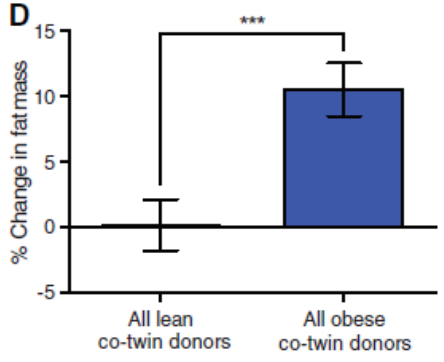


- Faecal transference from mouse/human to GF mice allows recapitulation of the obese or lean metabolic phenotype (Ridaura et al. 2013)



Science
AAAS

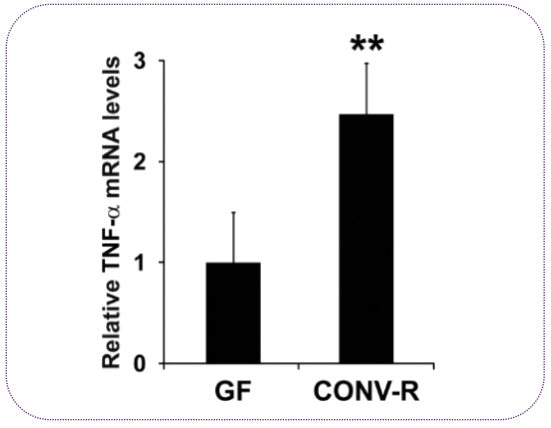
Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice
Vanessa K. Ridaura *et al.*
Science **341**, (2013);
DOI: 10.1126/science.1241214



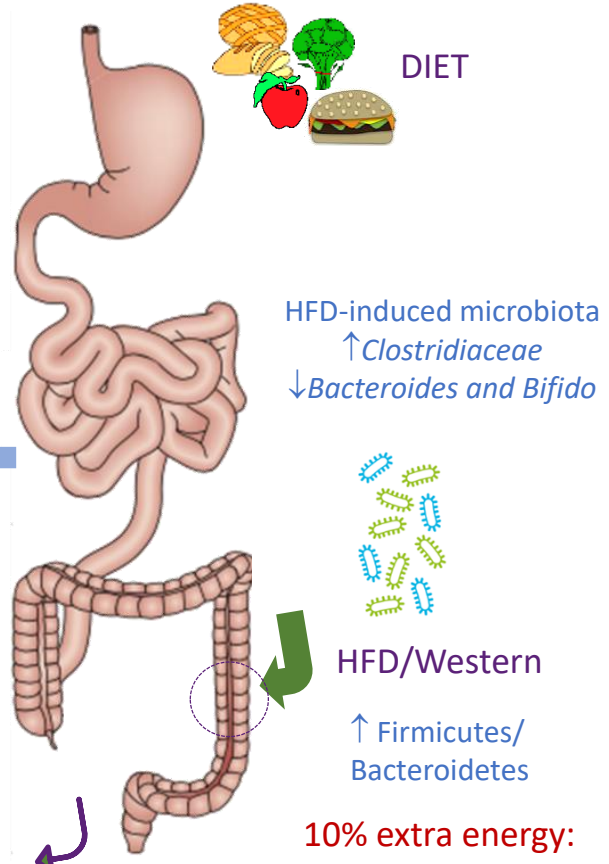
How gut microbiota contributes to obesity?

Lessons form germ-free animal models

- Extraction of energy *(Bäckhed et al., 2004)*
- Lipid digestion and absorption
  (Semova et al. 2012; Martinez-Guryn et al. 2018)
- Inflammatory tone (*Reigstad et al. 2009, Sanz 2018*)



Increased inflammatory makers in colonized fed Western diet but not in GF mice

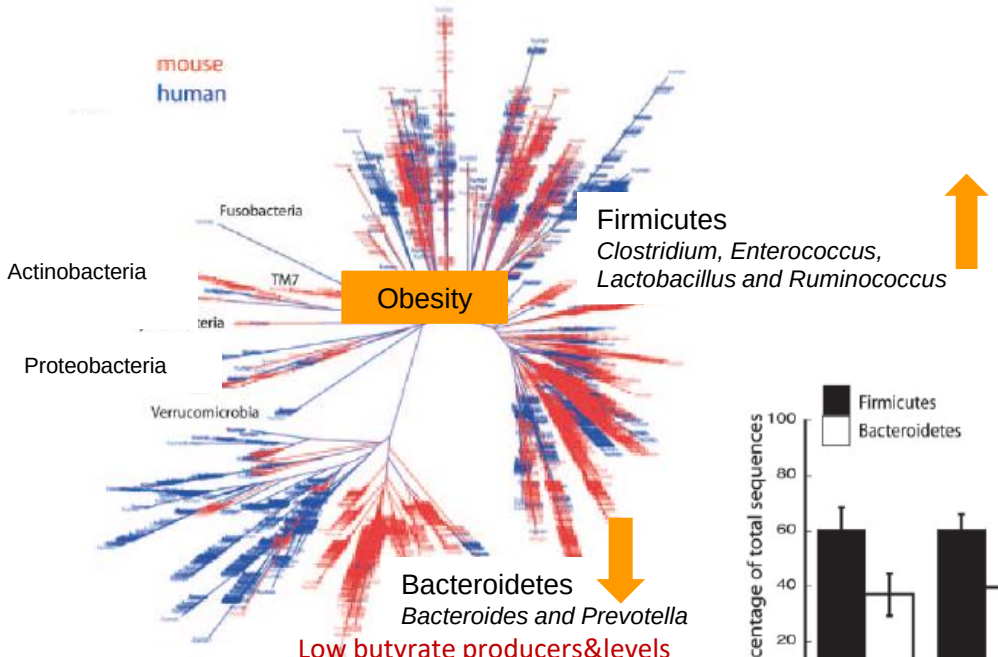


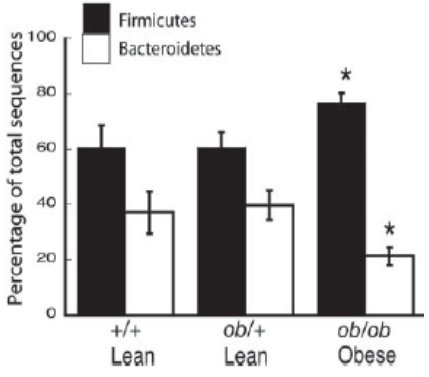
Intestinal dysbiois associated with in human obesity

Obesity alters gut microbial ecology

PNAS Free Full Text

Ruth E. Ley†, Fredrik Bäckhed†, Peter Turnbaugh†, Catherine A. Lozupone‡, Robin D. Knight§, and Jeffrey I. Gordon†¶



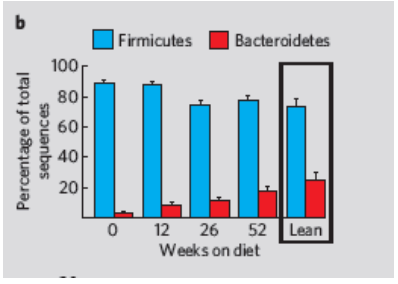


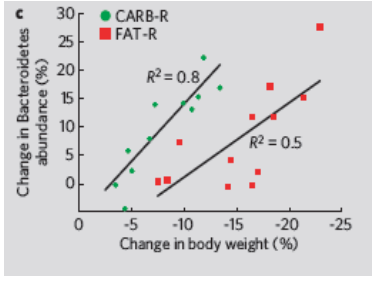
ob/ob 50% fewer Bacteroidetes

MICROBIAL ECOLOGY

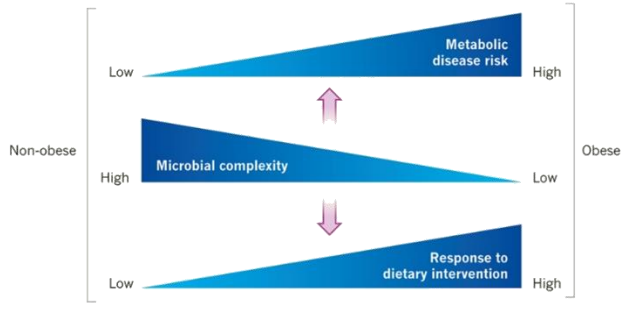
Human gut microbes associated with obesity

Ley et al, Nature 2006





FAT-R, fat restricted, CARB-R, carbohydrate restricted



Looking for a Signal in the Noise: Revisiting Obesity and the Microbiome *Sze & Schloss MBio. 2016; 23;7, 4*

Sanz Y, et al. Pharmacol Res. 2013 Mar;69(1):144-55. Ley et al. (2006). Proc Natl Acad Sci U S A.102:11070-5. Verdam et al. Obesity (Silver Spring). 2013 Mar 21.

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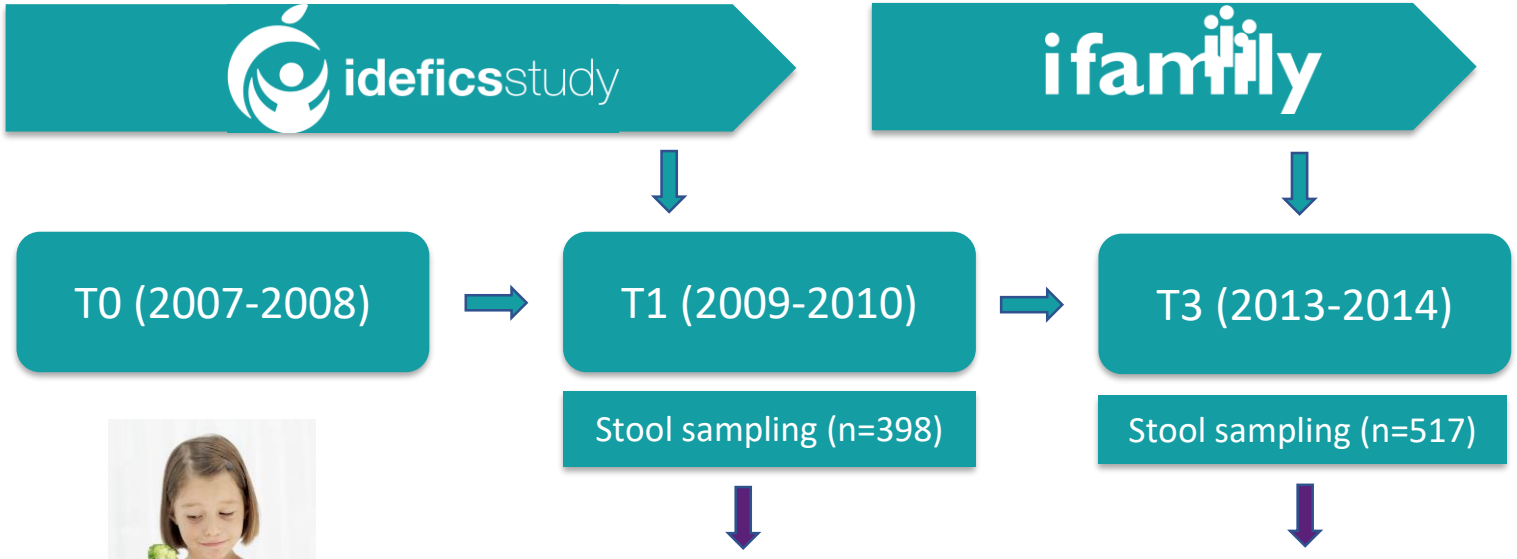
Why we are not there yet? What is missing?

- Does the microbiota play a role in obesity onset/ What is the predictive value for human obesity?
- What matters for obesity, gut microbiota, metabolites or both?
- Which microbes play a role in obesity?
- Which are the underlying mechanisms of action?

Gut microbiota as predictor of human obesity

Prospective study in children of four years



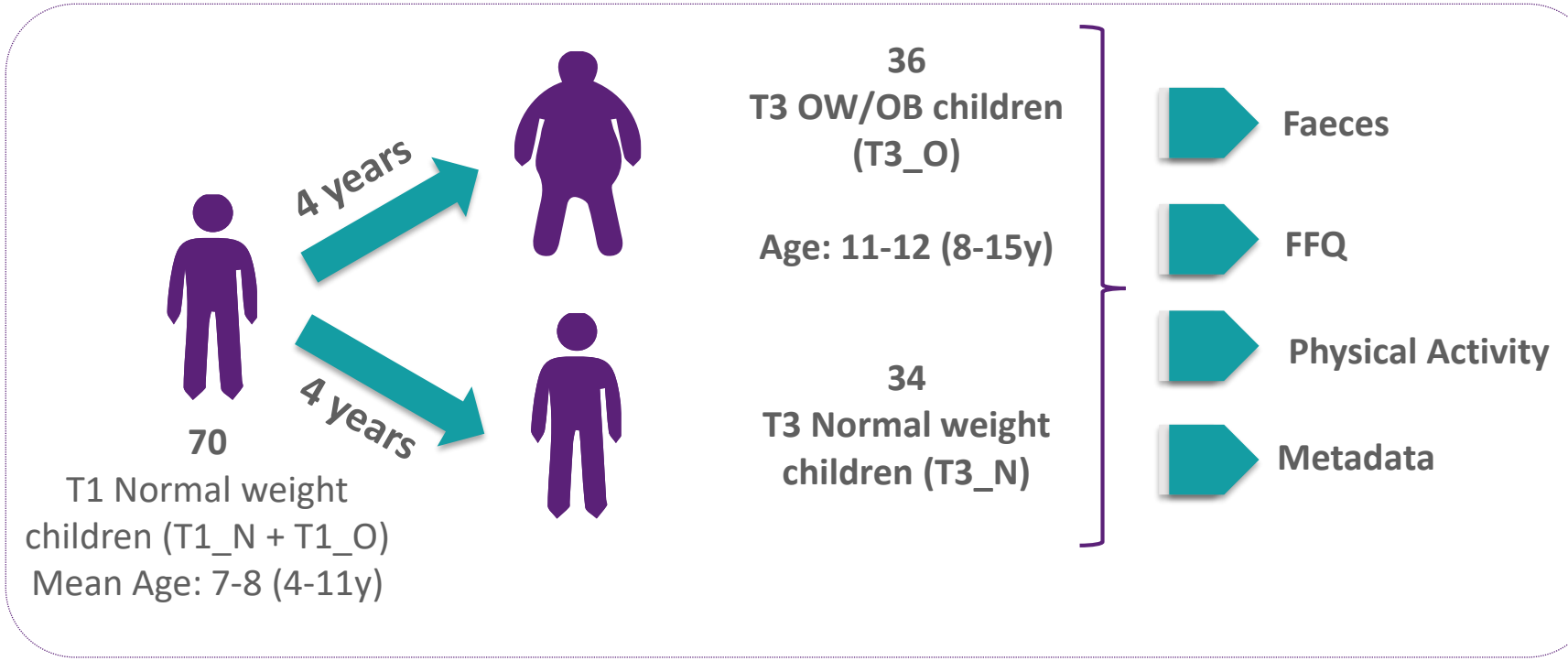
Diet
Physical activity
Metabolic
Inflammatory markers
etc.

Children with stool samples in IDEFICS (T1) and I.Family (T3) → n=97

Weight development	n (%)
stayed normal weight (controls)	34 (35.1%)
gained excessive weight (cases)	36 (37.1%)
lost weight	11 (11.3%)
chronical overweight/obesity	11 (11.3%)
chronical underweight	5 (5.2%)

Rampelli et al. Commun Biol. 2018; 7;1:222.

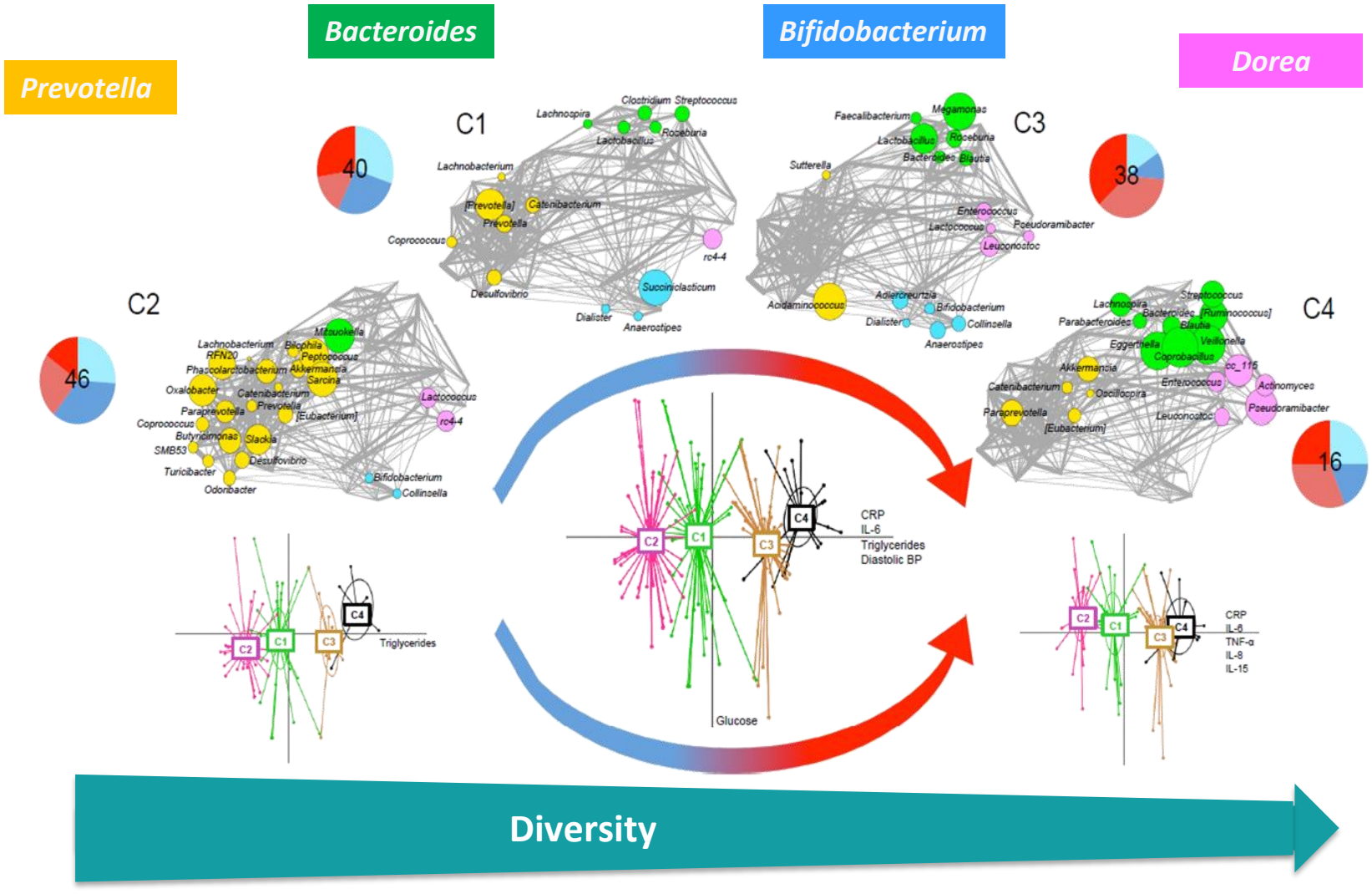
Longitudinal analysis of gut microbiome and other variables



- 16S rRNA sequencing of 140 samples → 56,485 ± 22,321 reads/sample
- 20,360 OTUs

Rampelli et al. Commun Biol. 2018; 7;1:222.

Four microbiota compositional clusters based on co-abundance of genera



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Rampelli et al. Commun Biol. 2018; 7;1:222.

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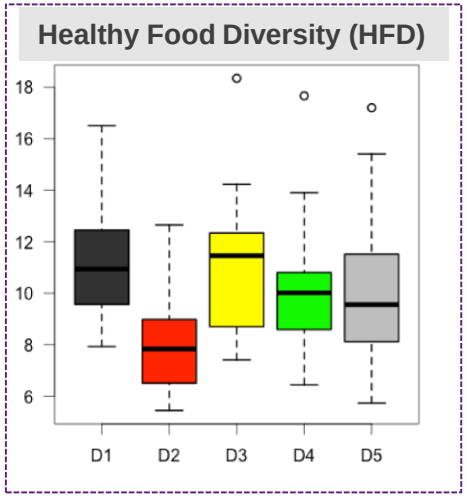
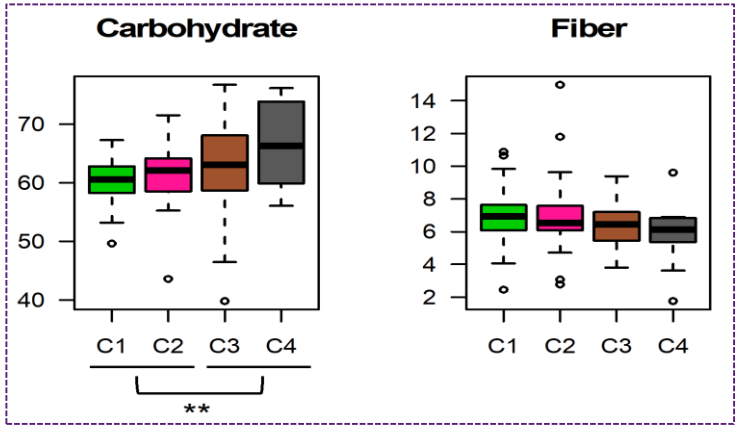
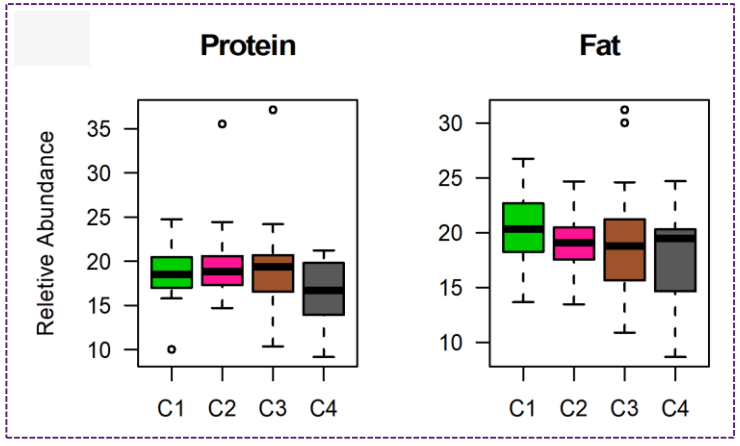
Dietary patters co-segregates with microbiota clusters

D2/D5 dietary patters related to C3/C4 microbiota clusters and low diversity

D1 – low protein/low carbohydrate
D2 – high carbohydrate/high fat
D3 – high carbohydrate/high fibre
D4 – low protein/low fat
D5 – high protein/high fat

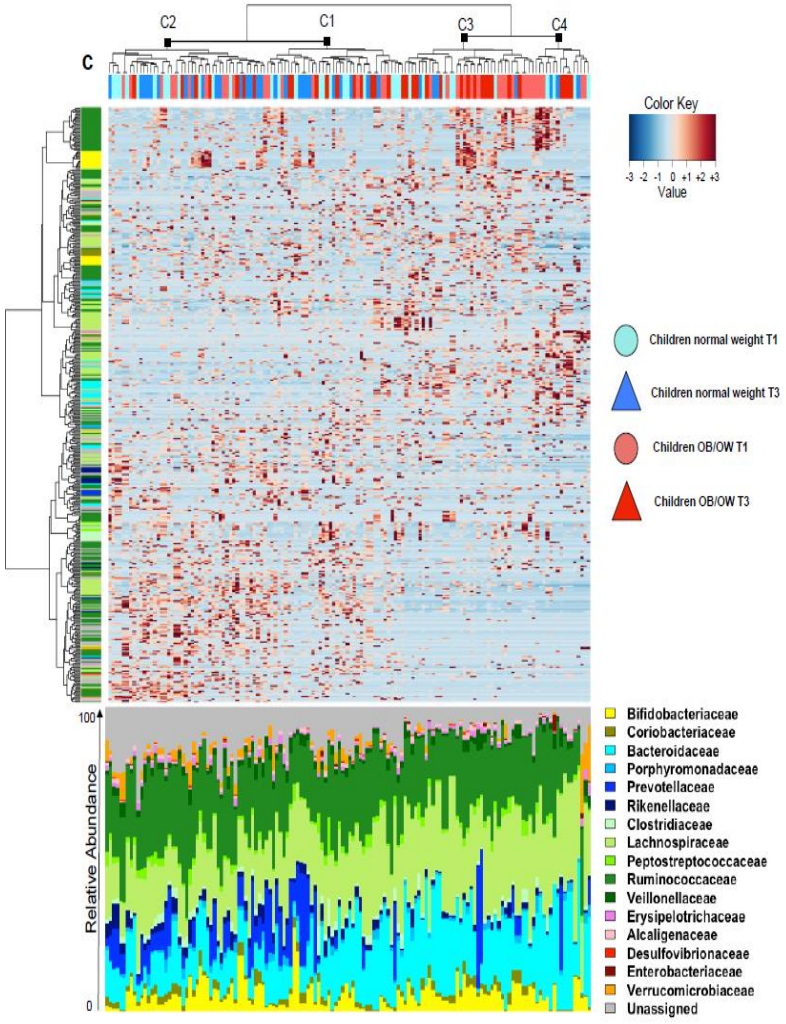


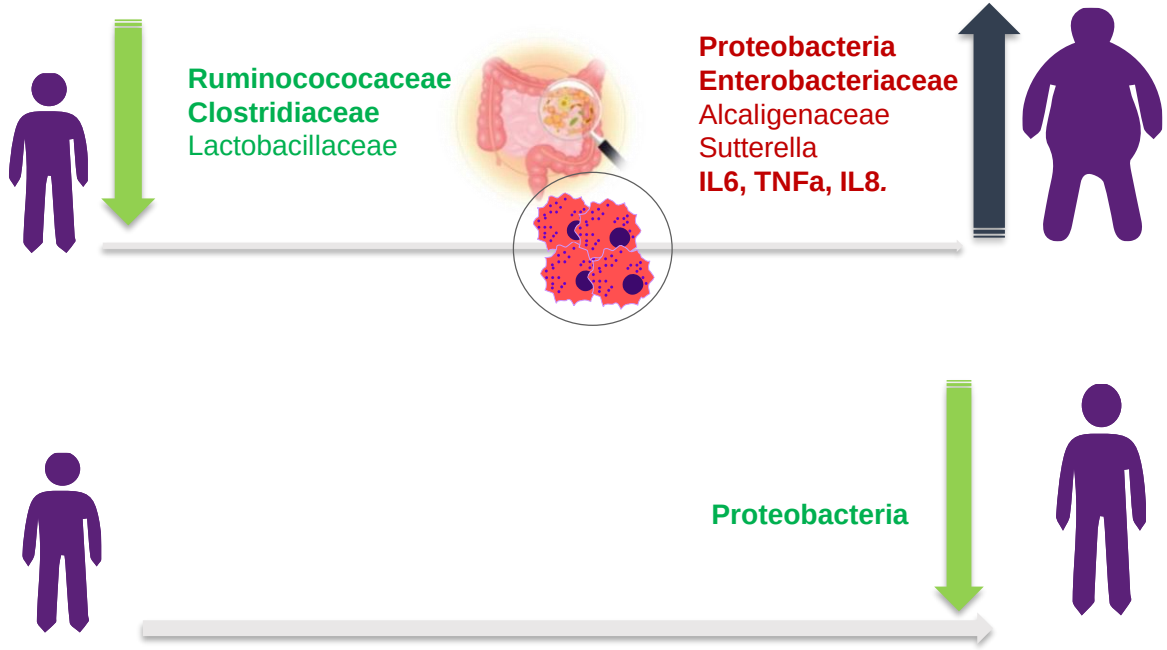




Rampelli et al. Commun Biol. 2018; 7;1:222.

Transition from normal weight to obesity in childhood





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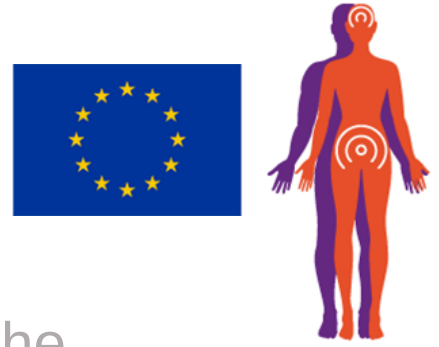
Why we are not there yet? What is missing?



- Does the microbiota play a role in obesity onset/ What is the predictive value for human obesity?
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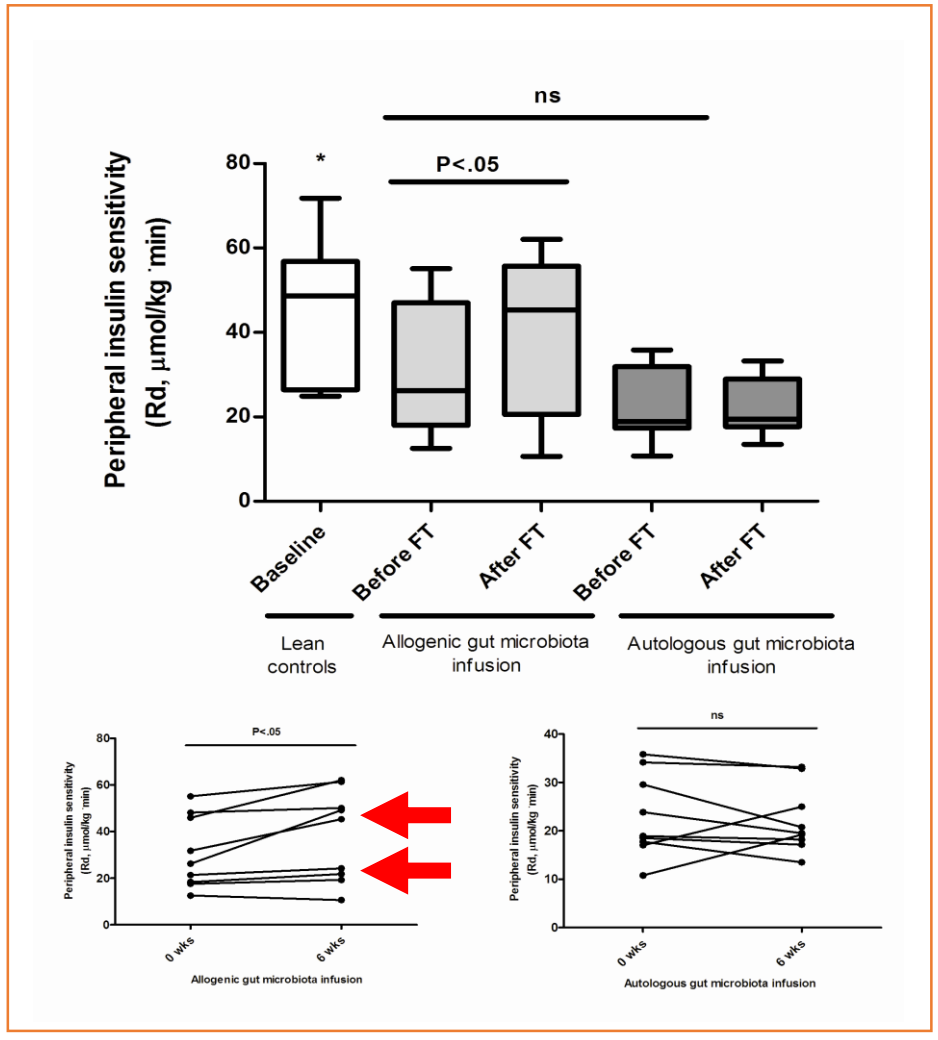
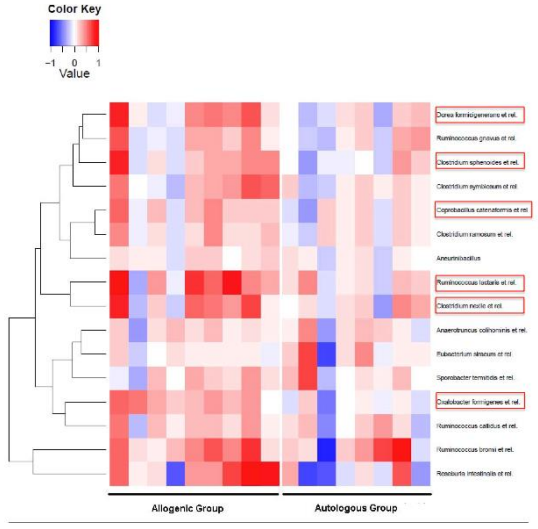
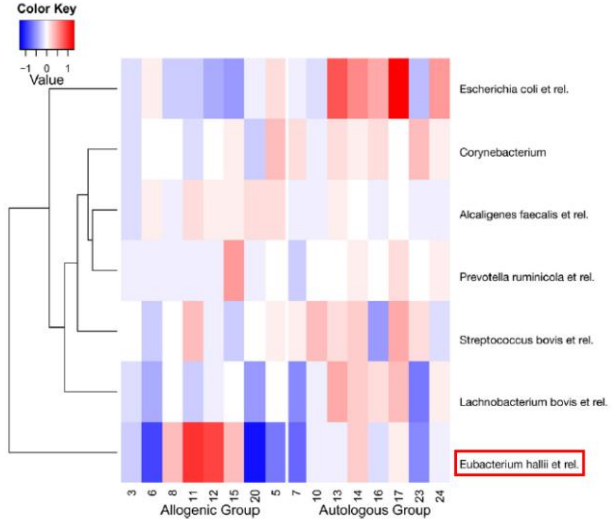
Lean microbiota improves insulin sensitivity in MetSyn





Lean donor FMT increased SCFA butyrate producers

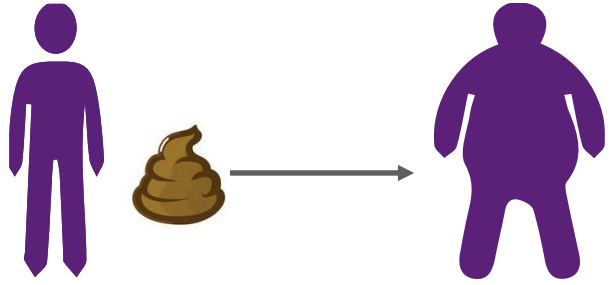


Vrieze, Gastroenterology 2012: Kootte, Cell Metabolism 2017

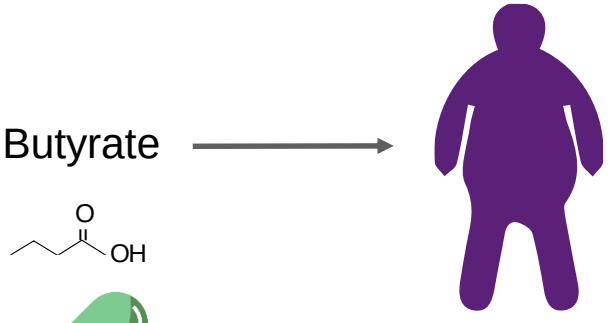
Effects of FMT or butyrate in overweight with MetSyn

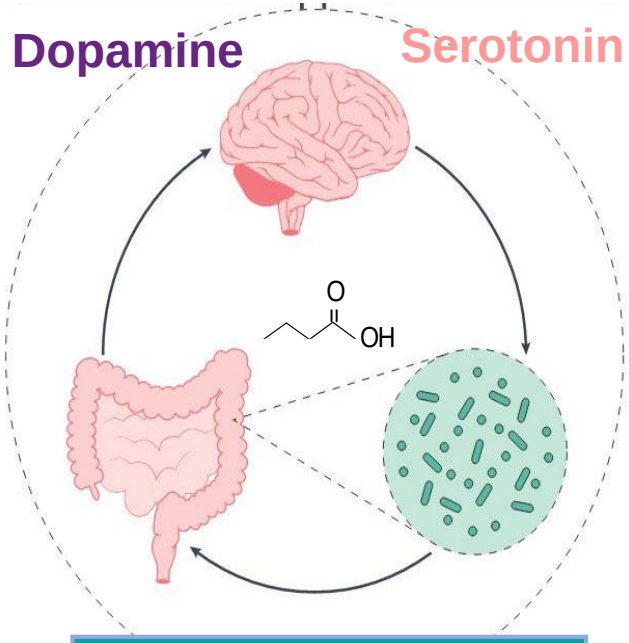
FMT leads to ↑ brain dopamine receptor expression correlated to *Prevotella* and *Bacteroides uniformis*

N=12 MetSyn
Placebo tablets 4 wks
Aloctonous FMT

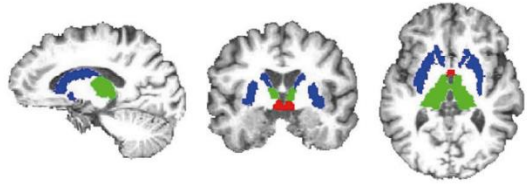


N=12 male/female
MetSyn
Butyrate tablets 4 wks
Placebo (autologous) FMT





Donor microbiota's effect



Hartstra et al., Mol Metab. 2020 Sep 8:101076. doi: 10.1016/j.molmet.2020.101076.

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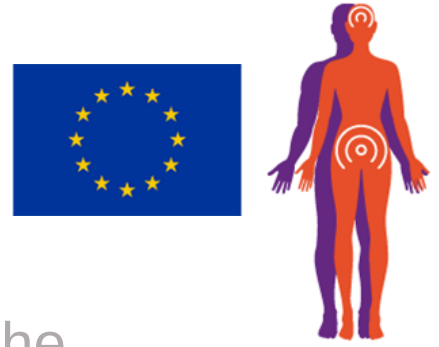

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How to tackle obesity? Which bacteria can help?

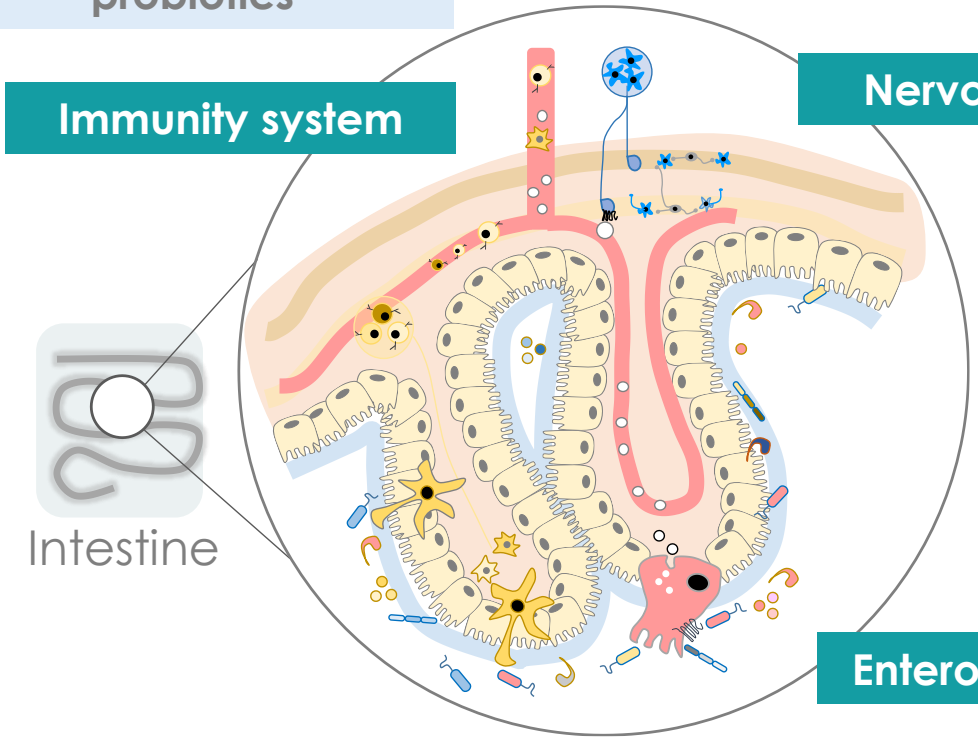
- Life style changes: hypocaloric diets and exercise
- Drugs

New generation of probiotics

Microbiota restoration and functional gain

Immunity system

Nervous system



Enteroendocrine system

↓ Inflammation

↑ Insulin sensitivity

↑ Neuroendocrine signaling

↓Intake

Obesity prevention

METABOLIC HEALTH

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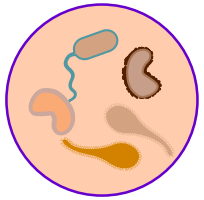
How to find microbiome-based solutions?

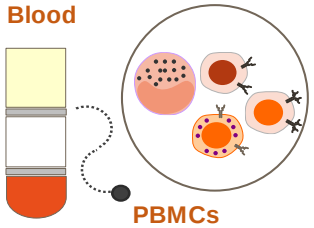
MyNewGut

Observational studies

Healthy diets-metabolism



Bacterial isolation

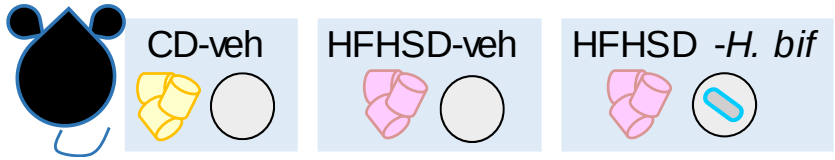


In vitro assays

Ensayos in vivo

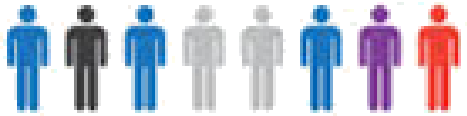
B. uniformis

Holdemanella sp.

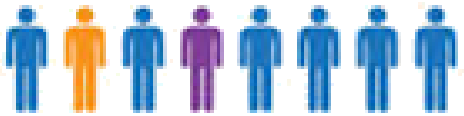


Animal models of Diet-Induced Obesity (DIO)

PROBIOTIC



PLACEBO



Intervention studies

In summary

- The individual's microbiota might help to predict the risk of developing obesity. A combination of unhealthy dietary patters and low diverse microbiota configurations and increases in Proteobacteria precede the development of obesity in children.
- A healthy gut microbiota influences the dopaminergic system via the gut-brain axis, increasing food intake control in humans with MetSyn.
- Different intestinal bacteria improve metabolism through complementary mechanisms, which could help to combat obesity and its complications
- *B. uniformis* exerts anti-inflammatory effects increasing IL10, IL33 and Tregs, likely involving TLR5 signaling.
- *Holdemanella* sp. improves glucose metabolism by improving GLP-1 production and signaling through endocrine and neuro-paracrine routes

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