

# Obesitas, microbiota en inflammatie

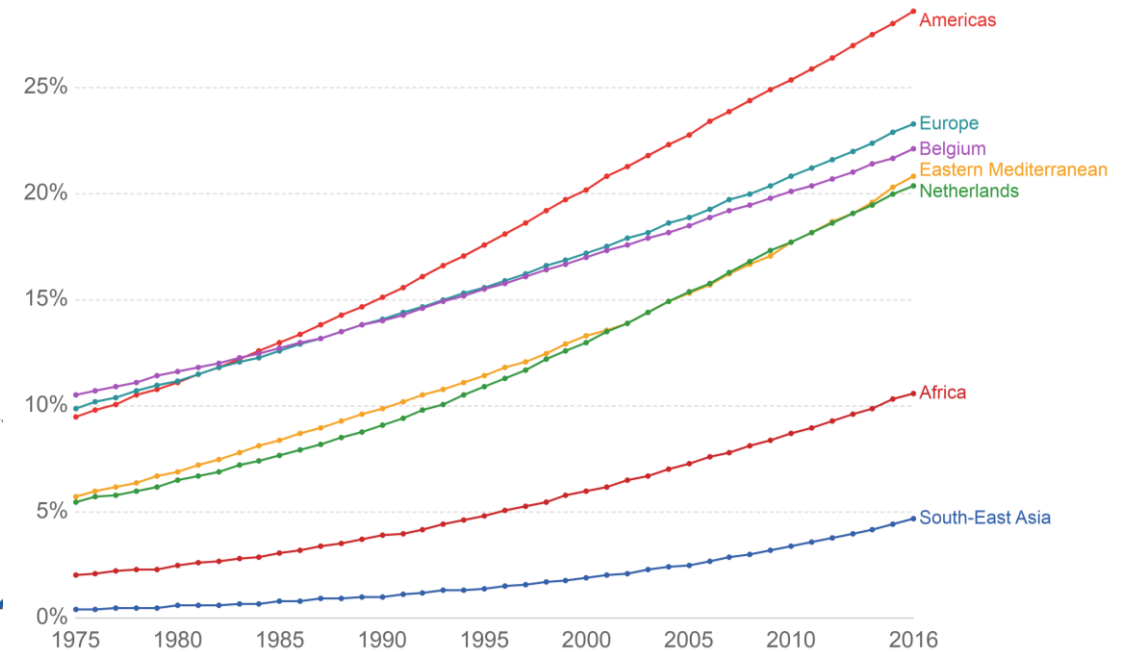
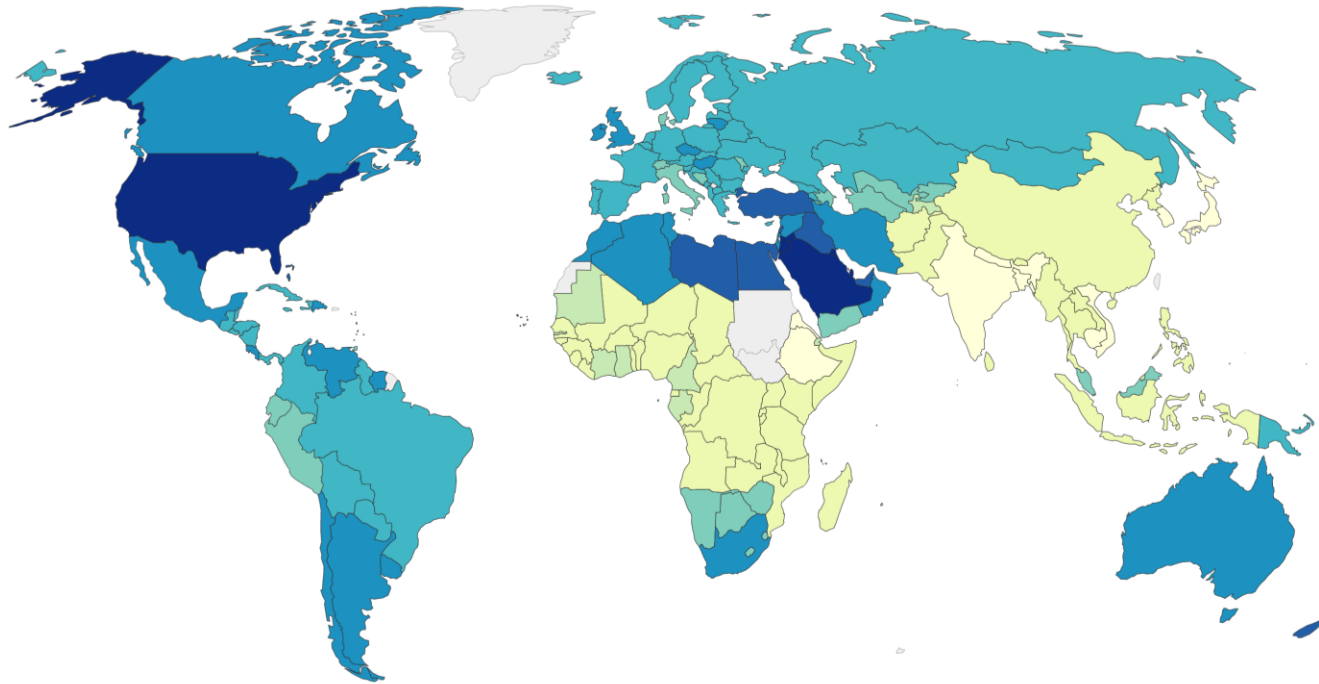
Kristin Verbeke

Translational Research in Gastrointestinal Disorders

KU Leuven, Leuven, België



# The obesity epidemic



Source: WHO, Global Health Observatory

OurWorldInData.org/obesity • CC BY



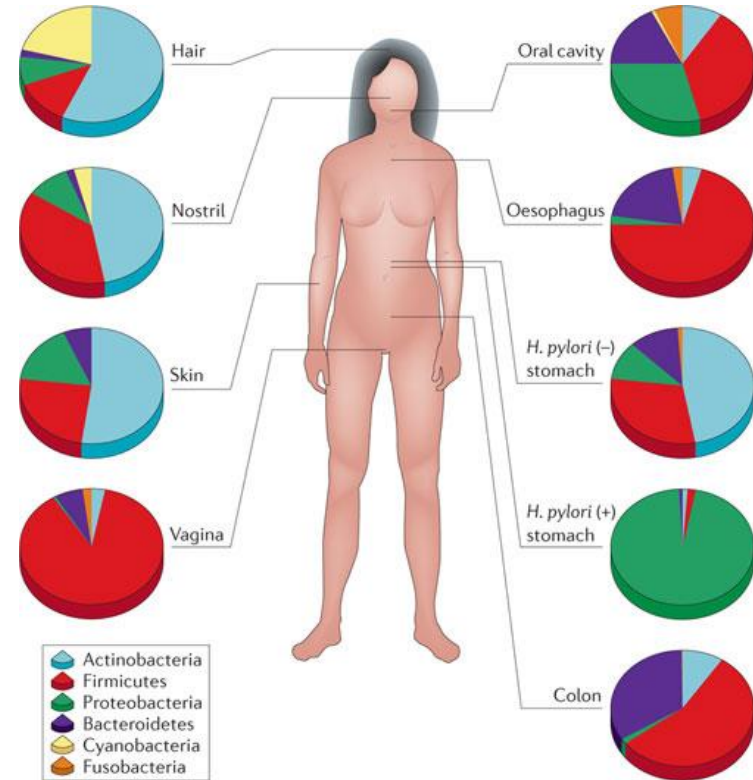
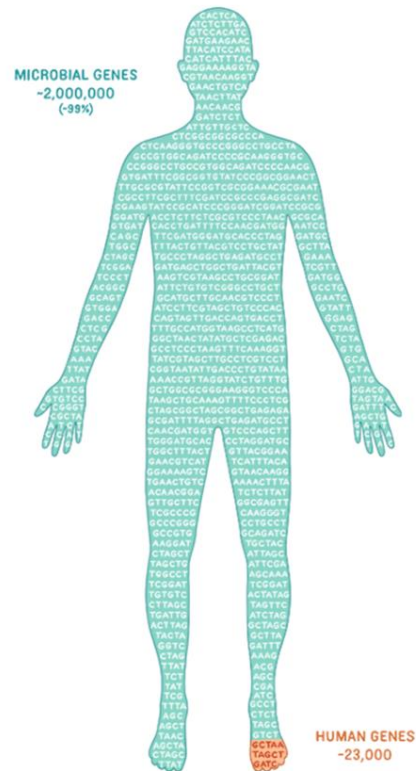
Source: WHO, Global Health Observatory

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# Oorzaken van obesitas

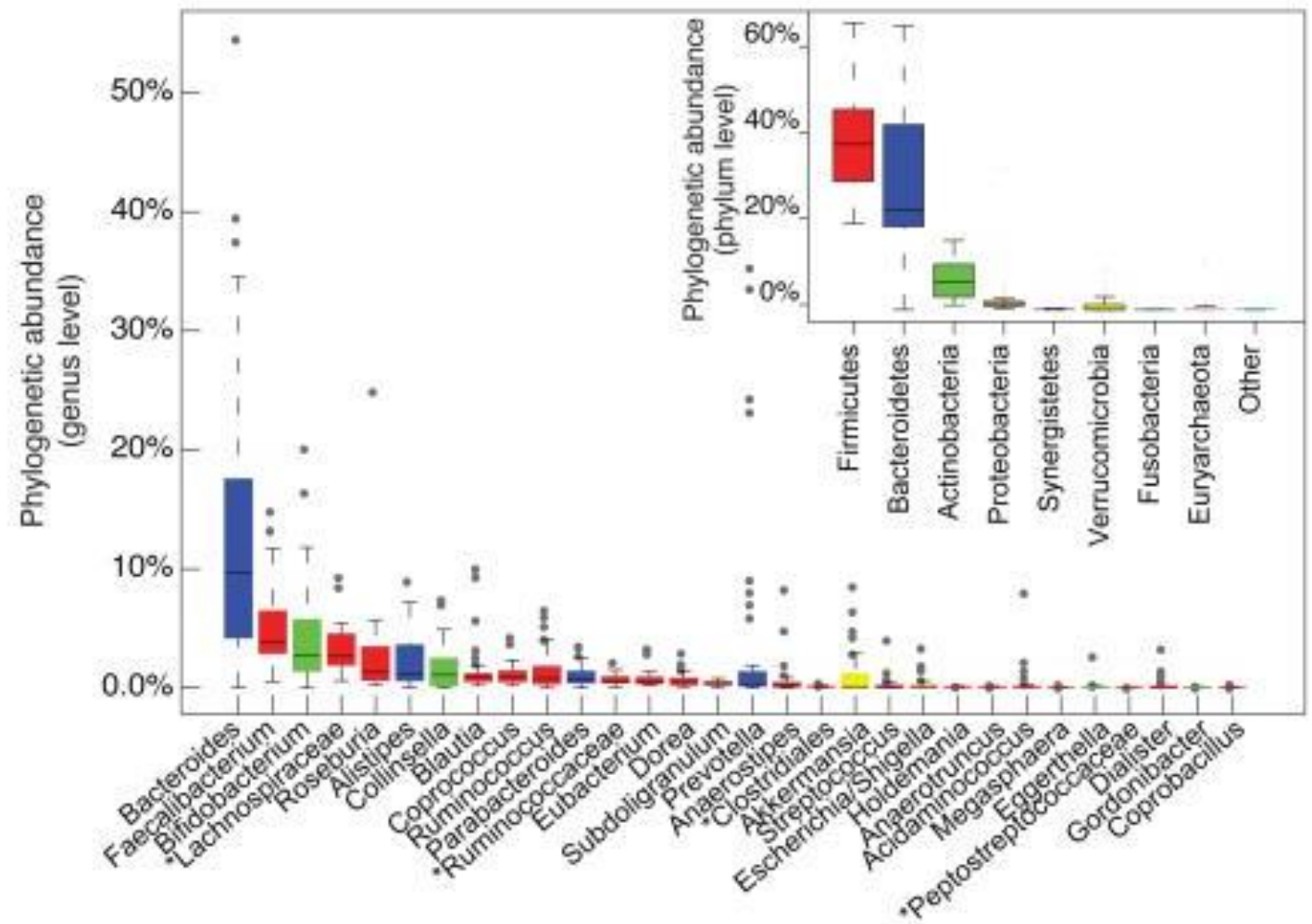
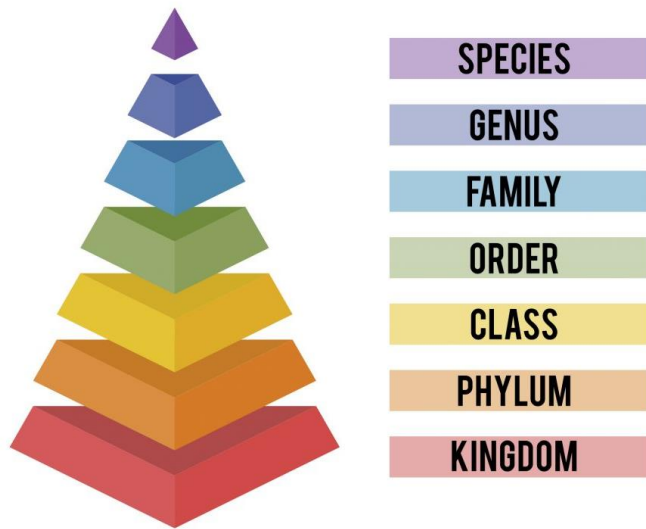


# De mens is een superorganisme



# Healthy microbiota

## HIERARCHY OF BIOLOGICAL CLASSIFICATION



# Obese muizen

obese donor (*ob/ob*)



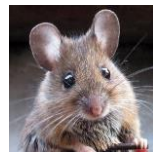
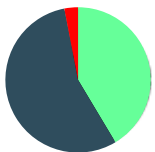
*ob/ob* donor



lean donor



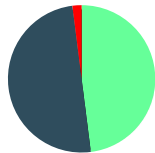
lean donor



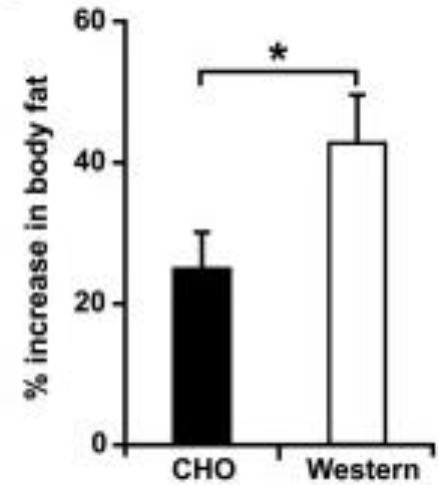
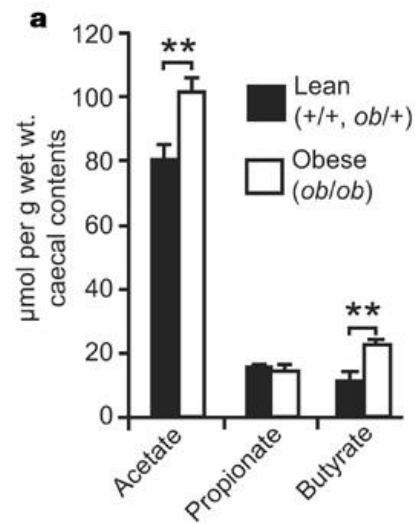
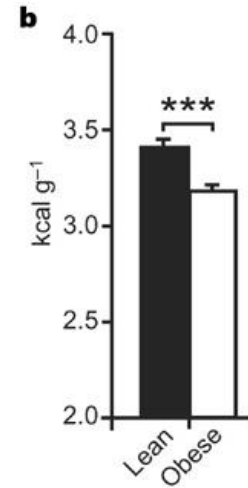
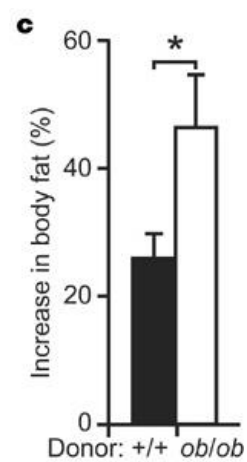
*ob/ob* recipients



lean recipients



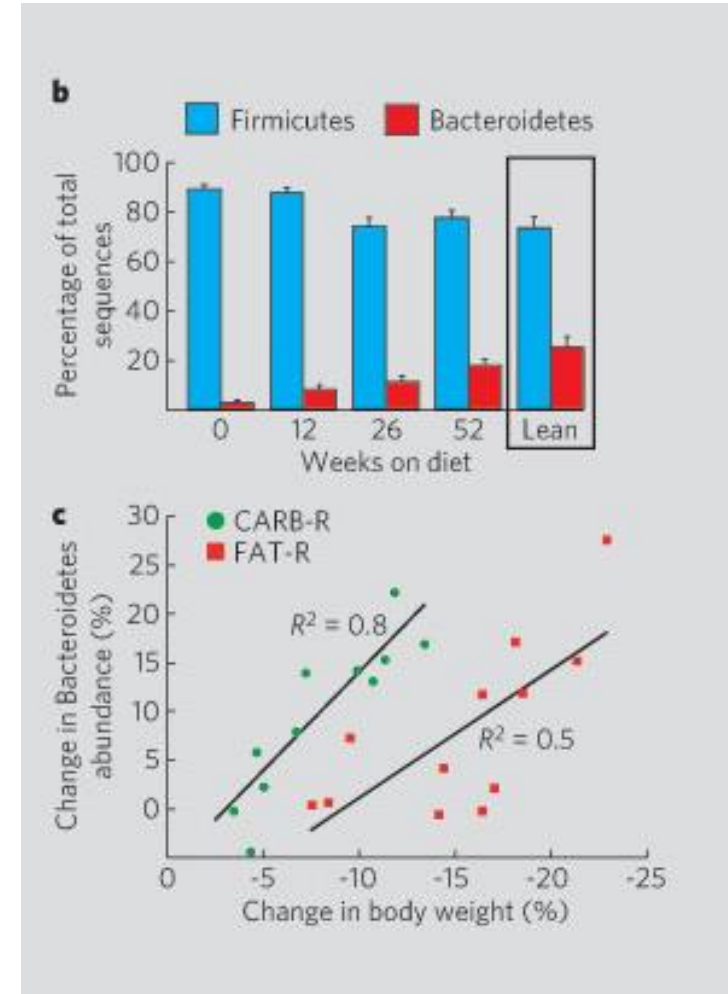
Firmicutes Bacteroidetes Other



obese microbiome possesses metabolic pathways that are highly efficient at extracting energy from food

Similar effects after transplantation of feces of mice with diet induced obesity

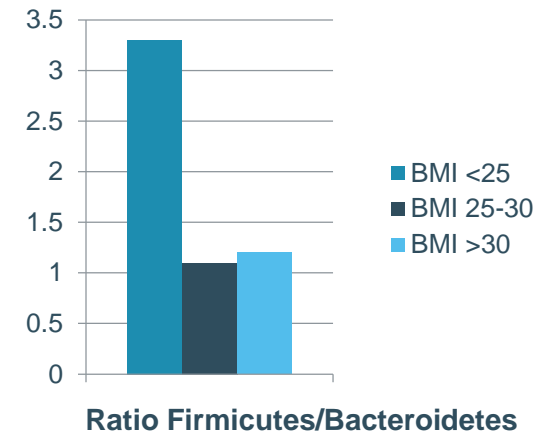
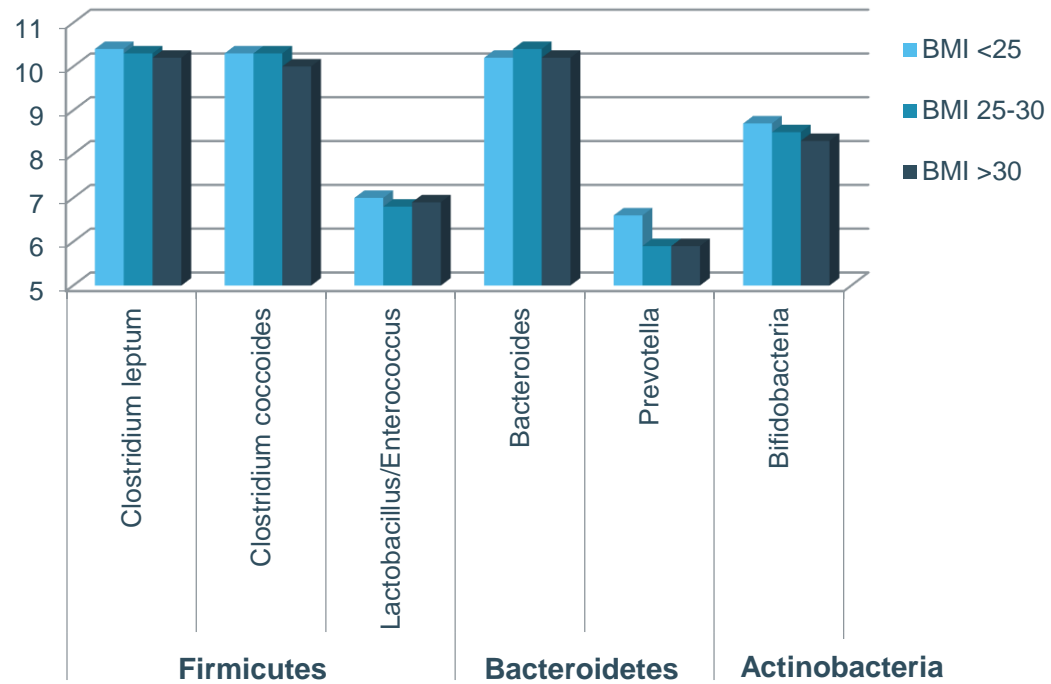
# Microbiota samenstelling in obese personen







# Or find opposite results



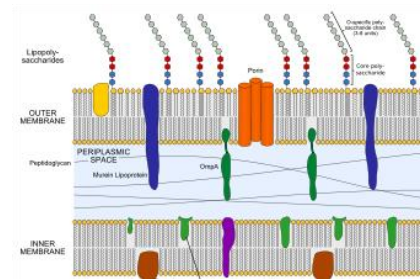
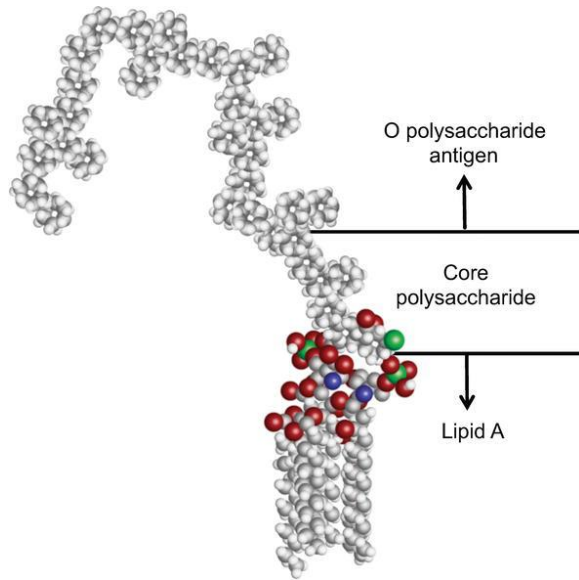
# Gut microbiota and obesity

- Phylumwide changes currently not considered as biomarker for obesity
- Changes at lower taxonomic level may better define dysbiosis
- Several genera increased or decreased in obesity – species may follow opposite trend
  - Lactobacilli ↗
  - Bifidobacteria ↘
  - Faecalibacterium prausnitzii ↘
  - Akkermansia muciniphila ↘
- Mainly association studies -> cause or consequence?

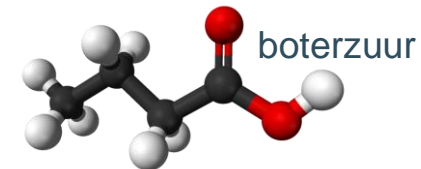
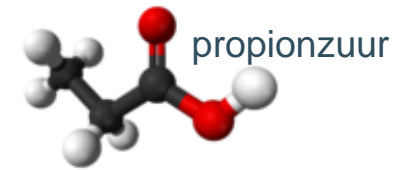
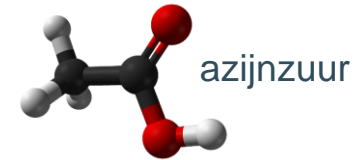
It is still impossible to define an obese microbiome

# Microbial signals linked to obesity

LPS

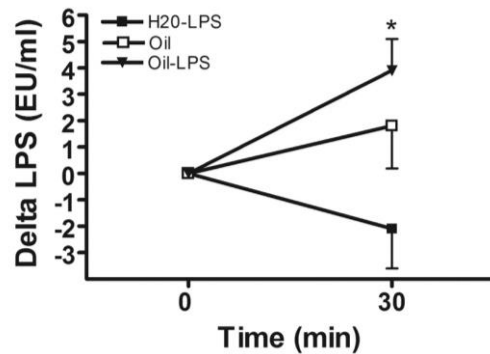
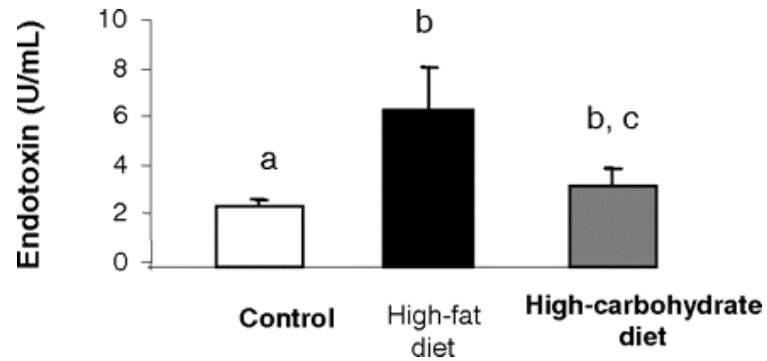


SCFA

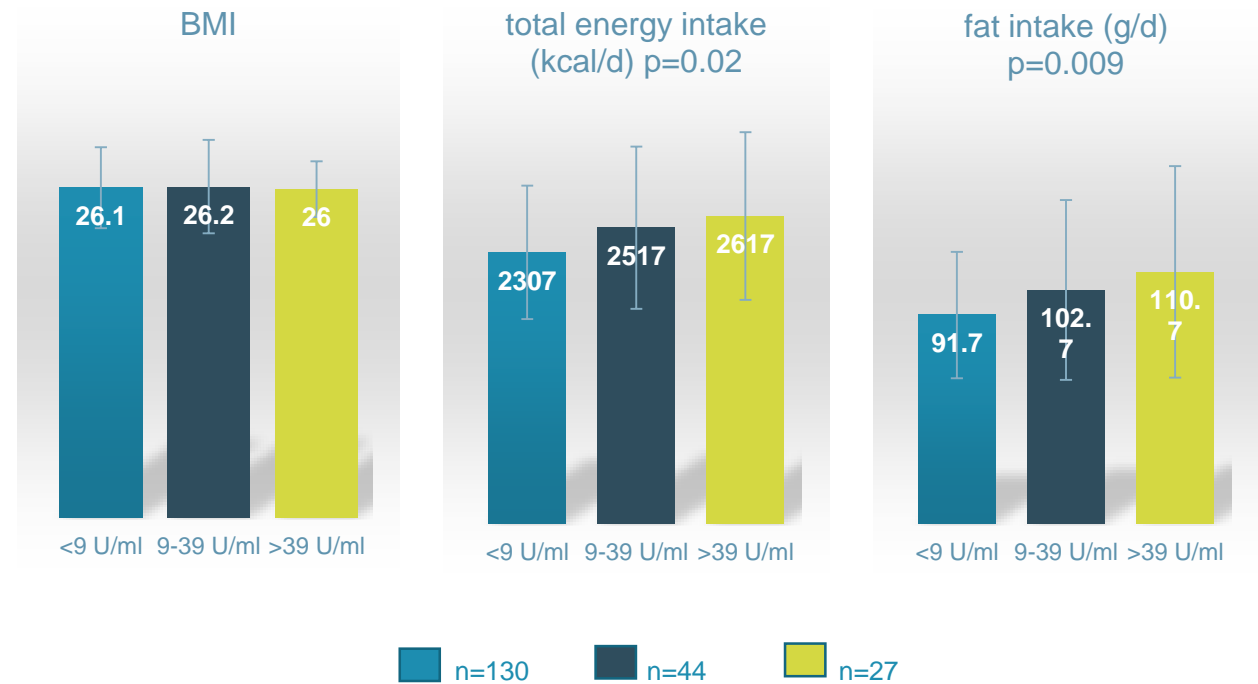


# High fat intake increases plasma LPS

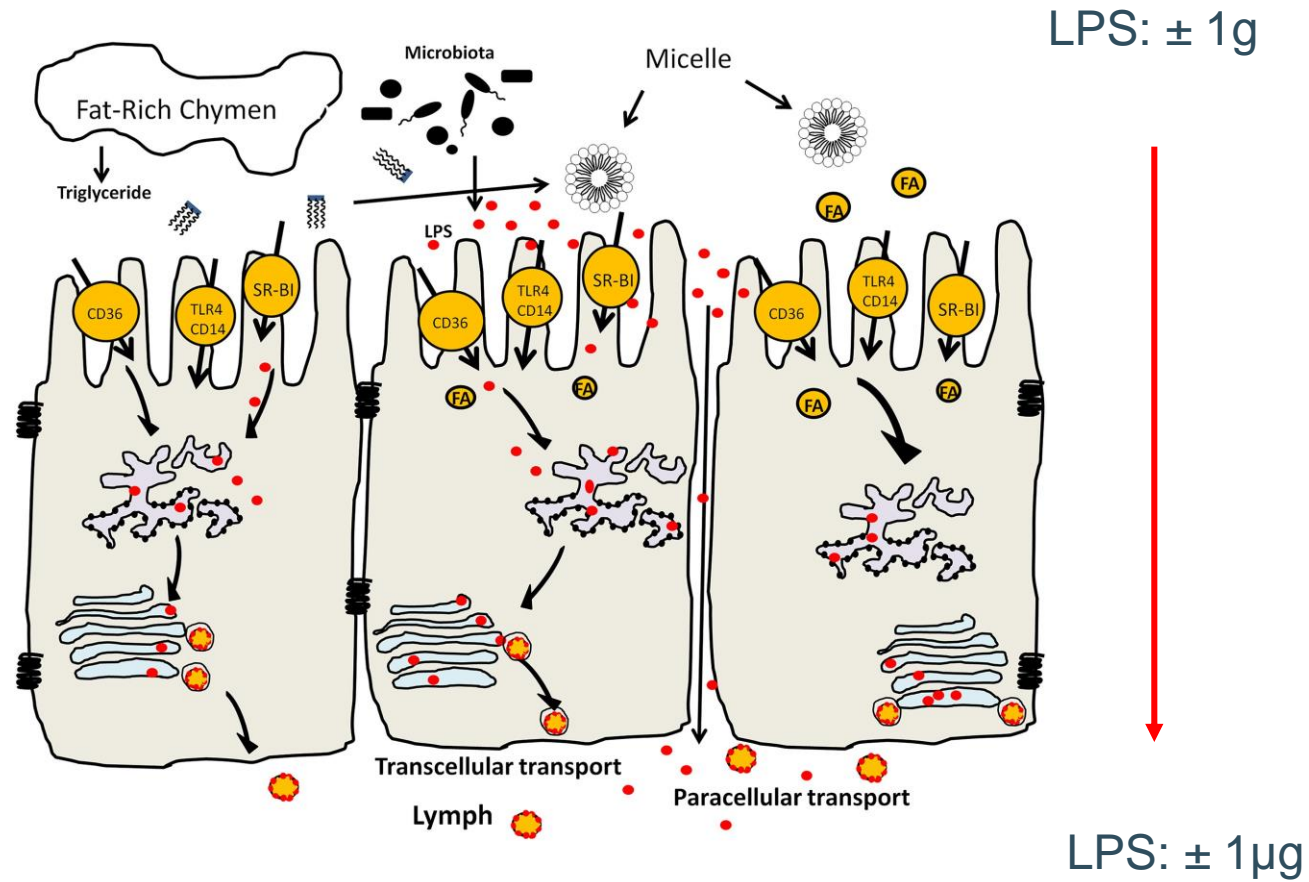
Mice  
Intervention for 4 wks



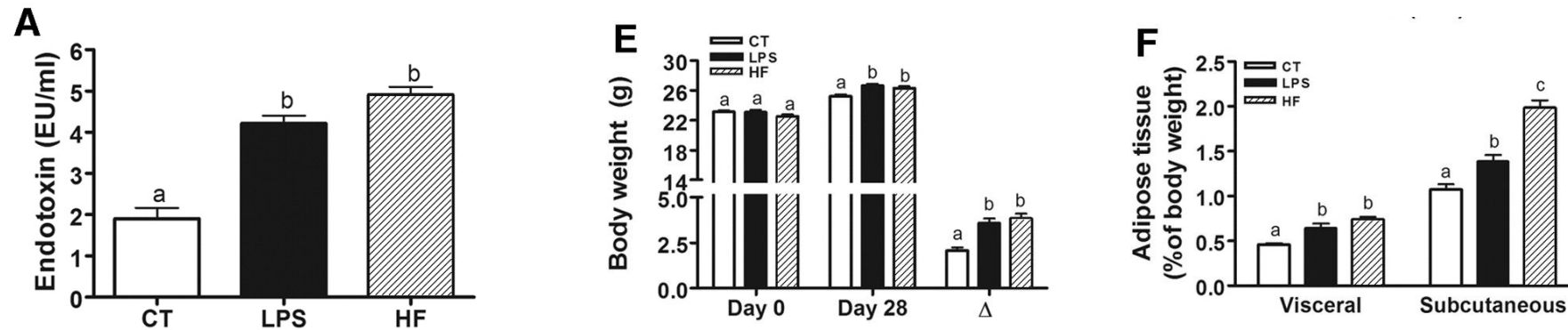
Humans  
Cross-sectional analysis, n=201



# Absorptie van LPS



# Increased plasma LPS induces obesity



# Increased plasma LPS induces inflammation

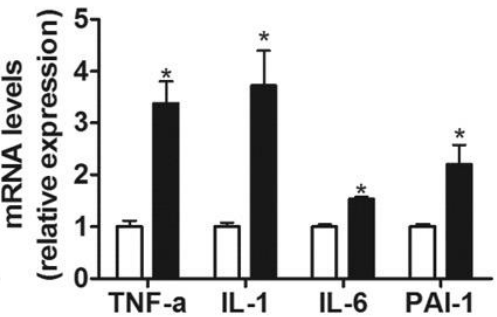
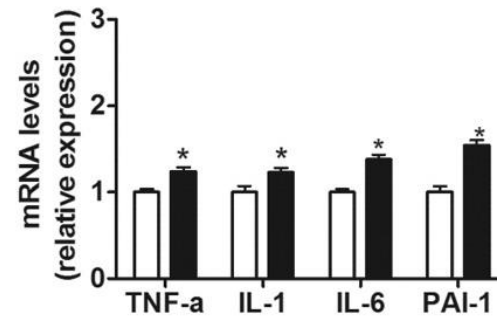
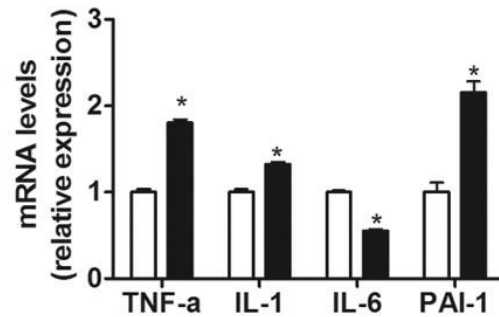
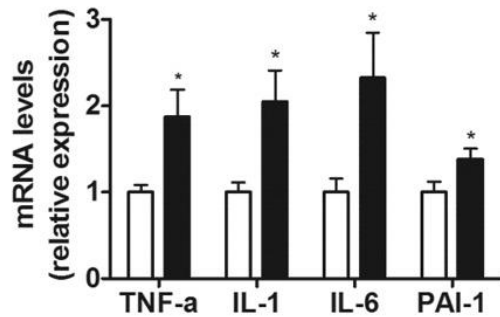
Liver

Visceral  
adipose tissue

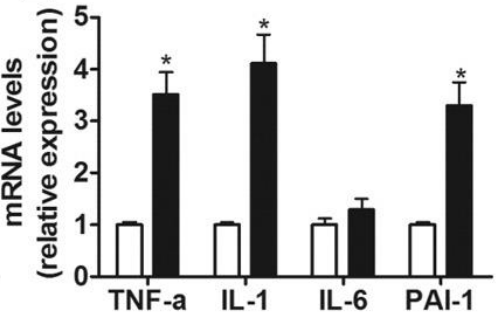
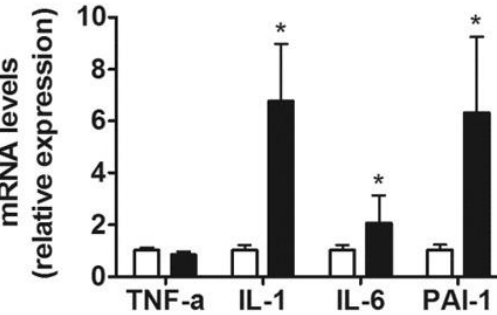
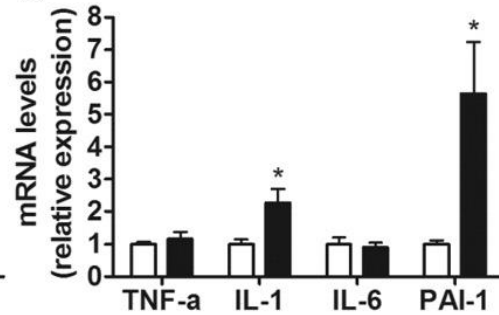
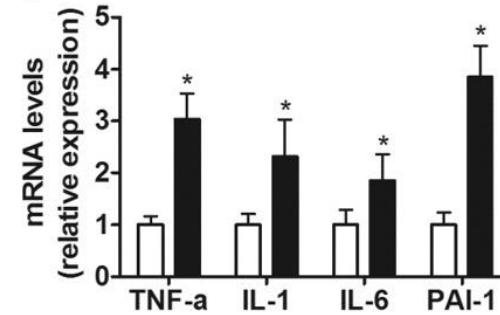
Subcutaneous  
adipose tissue

Muscle

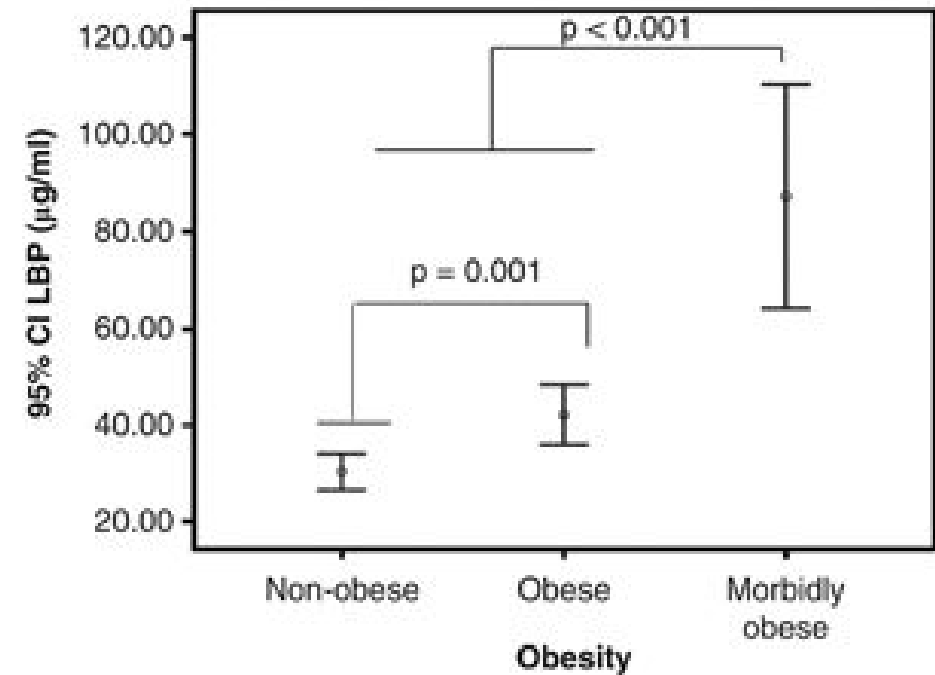
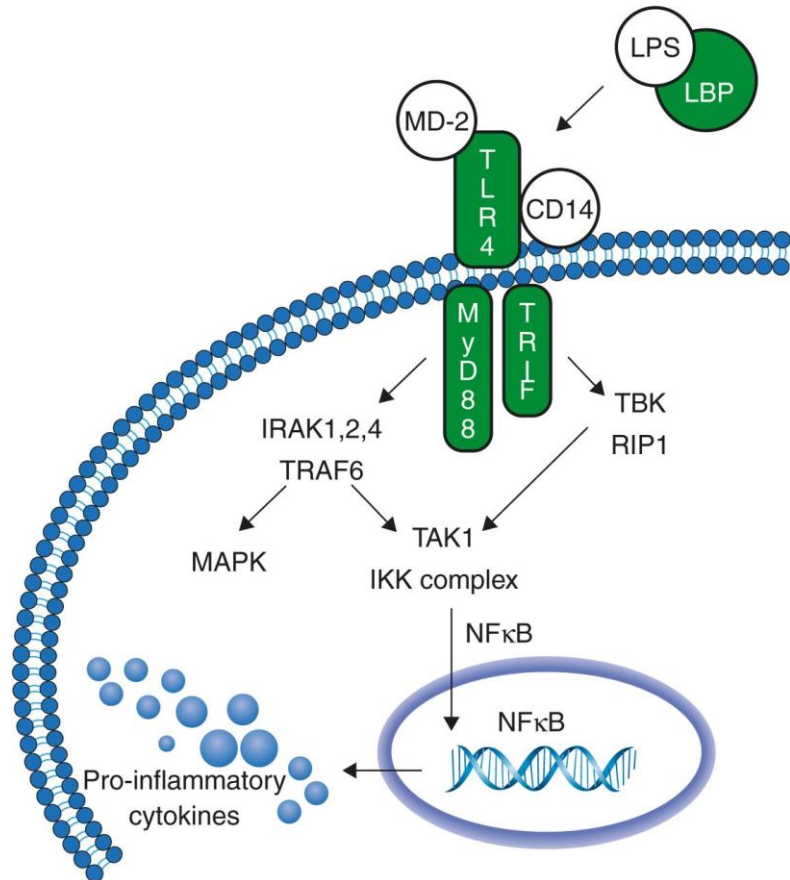
4 wks High -fat diet



Chronic LPS low dose

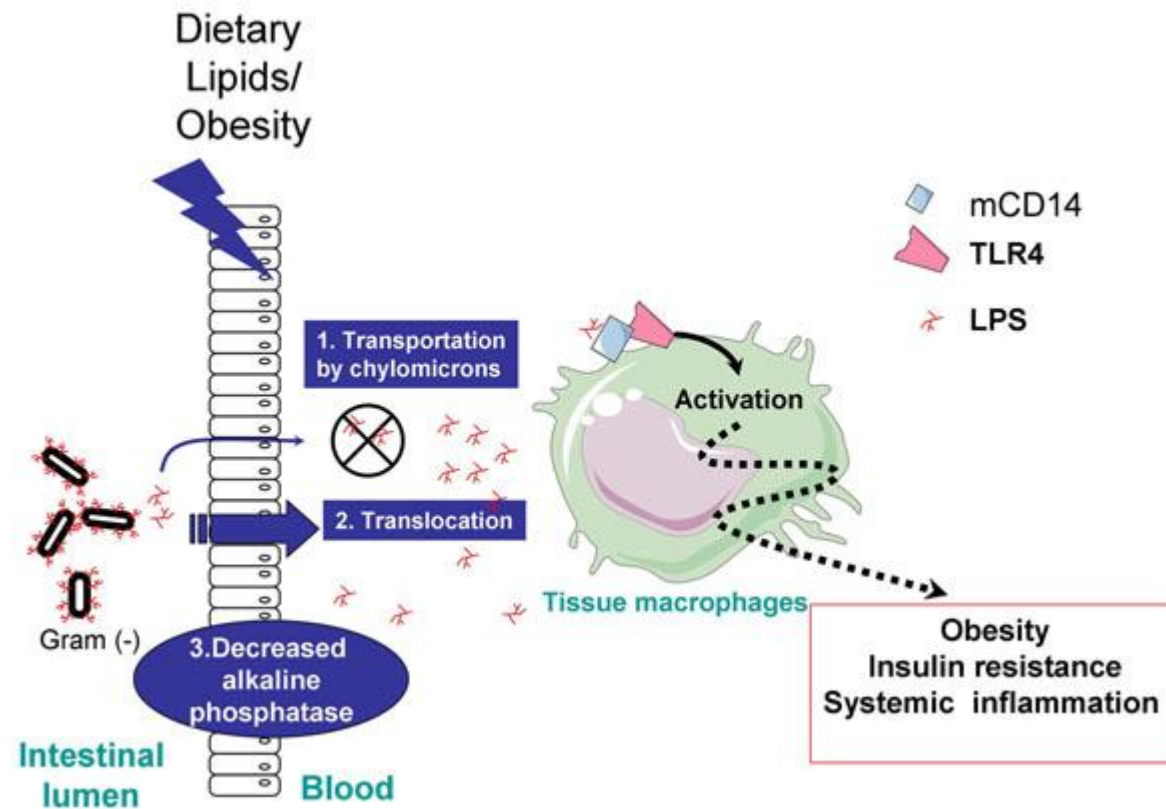


# LPS induceert laag-gradige inflammatie

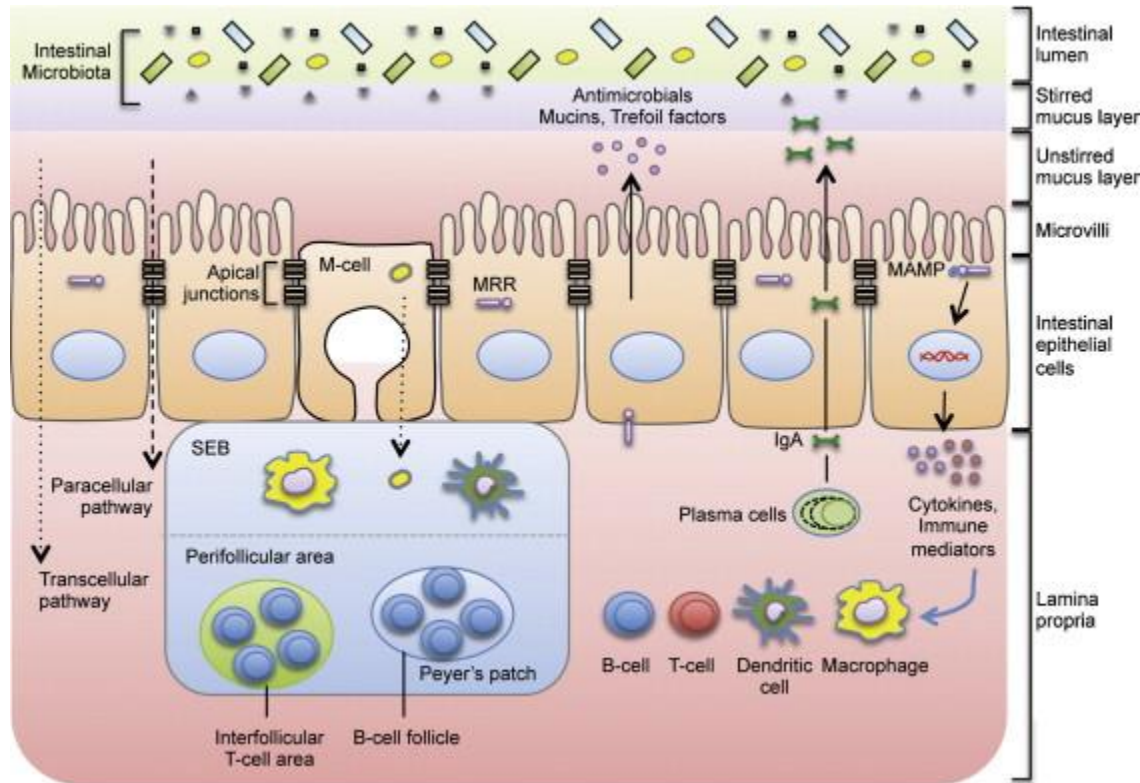




# LPS induces obesity and inflammation

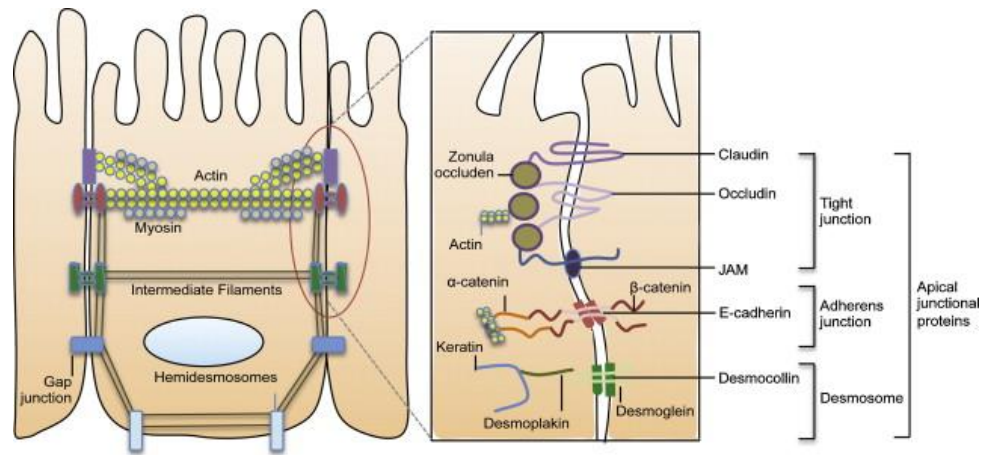


# SCFA protect against inflammation

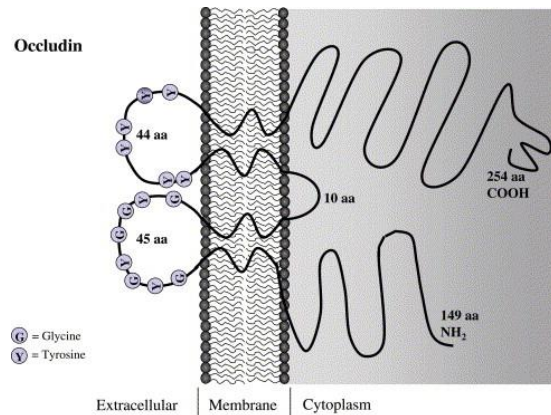
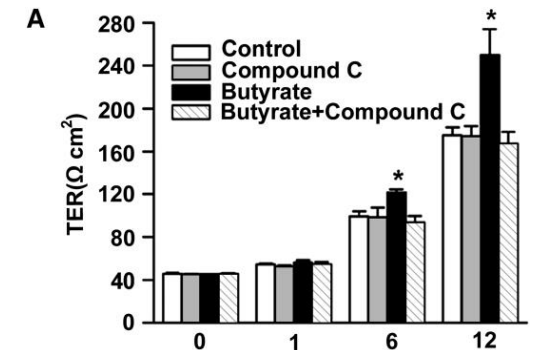
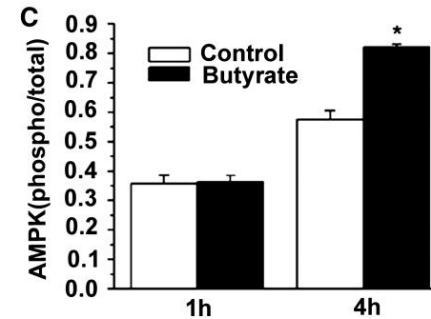


- Epithelial cells
- Mucus
- Immune system
- antimicrobials

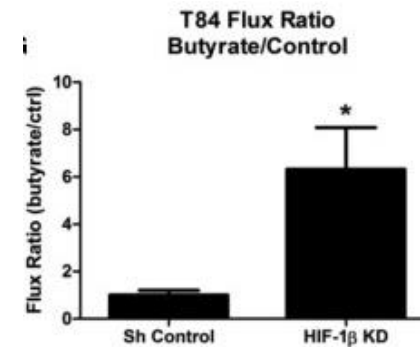
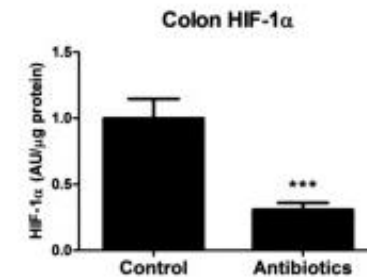
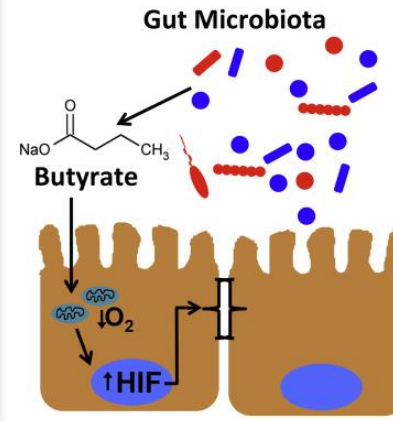
# SCFA versterken de tight junctions



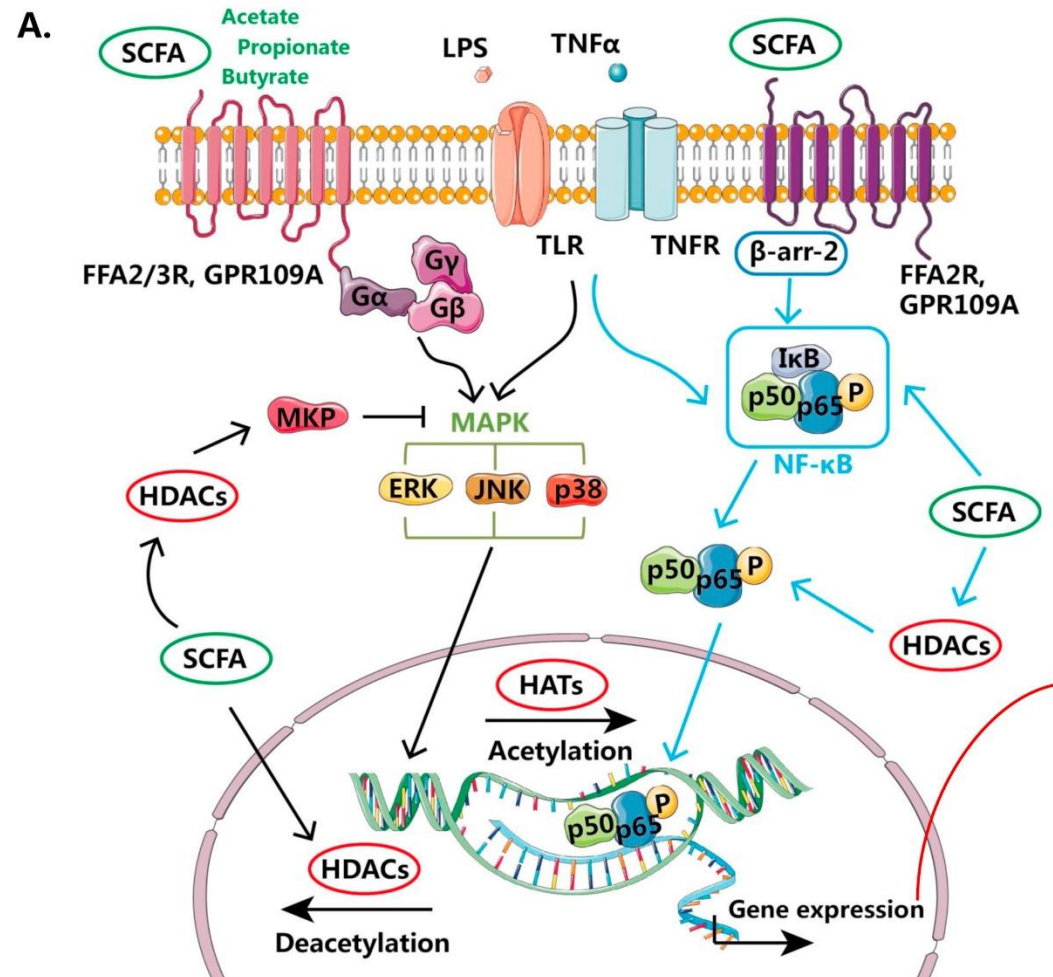
## Activatie van AMPK



## Stabilisatie van HIF

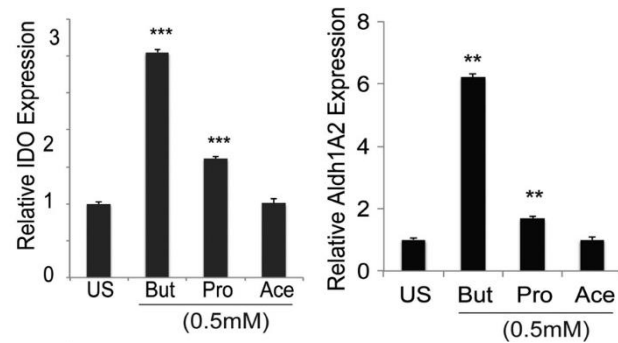


# SCFA interfereren met het immuunsysteem

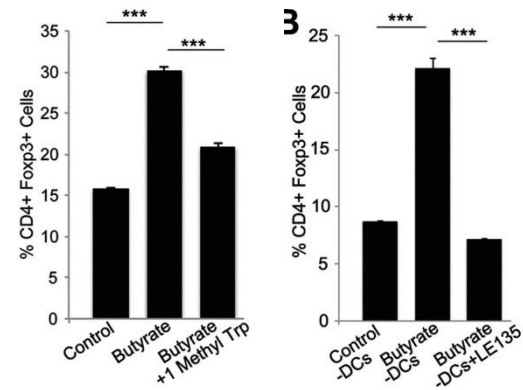


- Stimulatie van MAPK
- Inhibitie van NF- $\kappa$ -B
- Inhibitie van HDACs

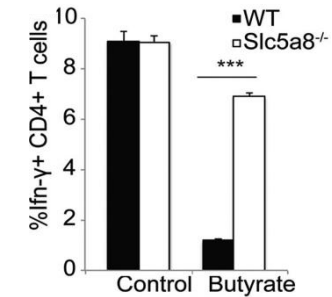
# SCFA beïnvloeden de populatie T<sub>reg</sub>-cellen in het colon



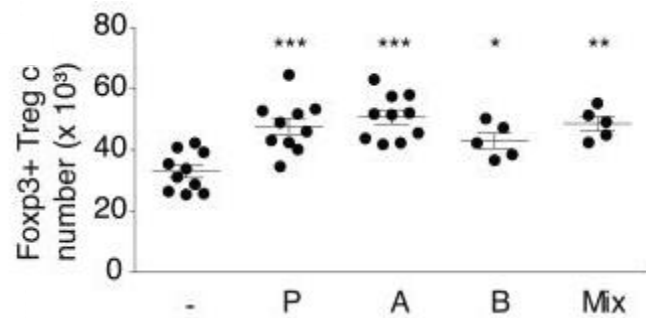
DC exposed to butyrate increases the expression of IDO and Aldh 1A2



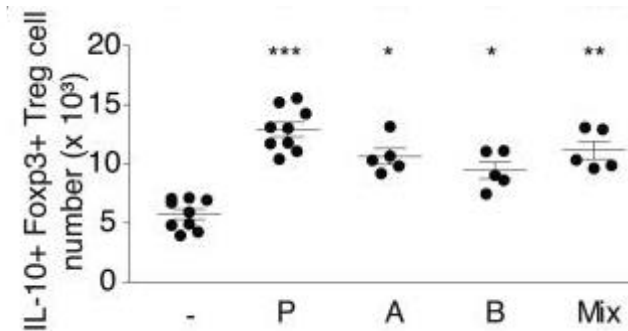
DC exposed to butyrate promote conversion to a tolerogenic phenotype in T-cells



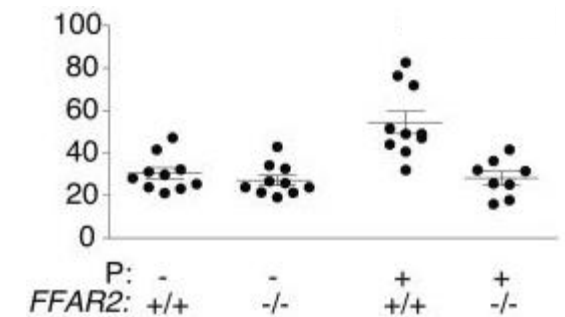
DC exposed to butyrate suppress conversion into pro-inflammatory IFN-γ<sup>+</sup> T-cells



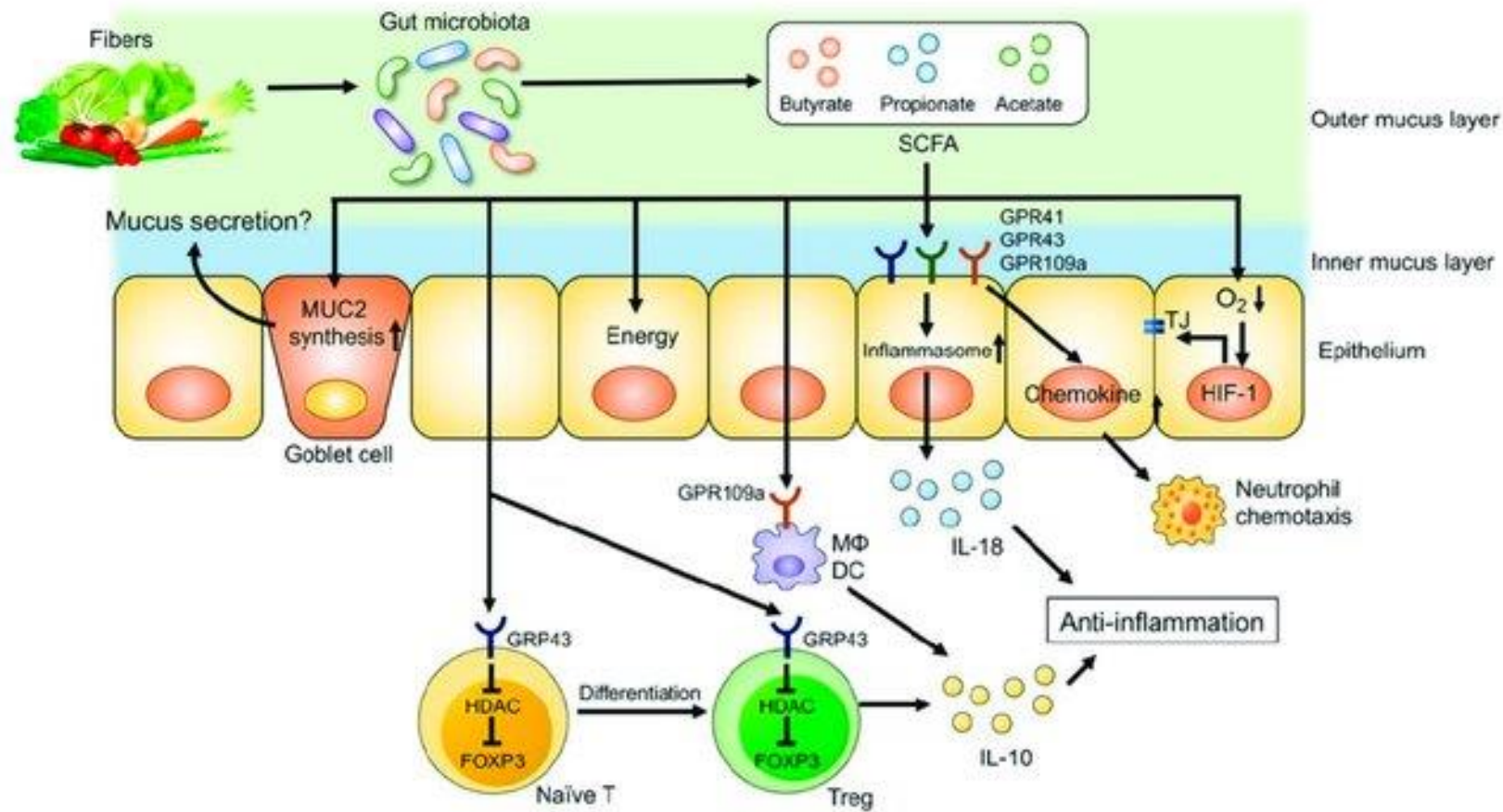
SCFA increased Treg numbers and function in colonized mice.



The effects of SCFAs on Tregs were mediated through ffar2

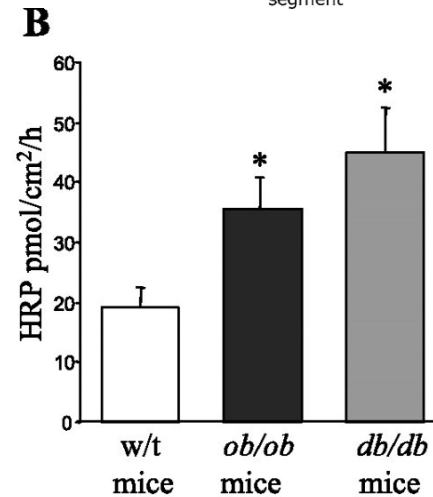
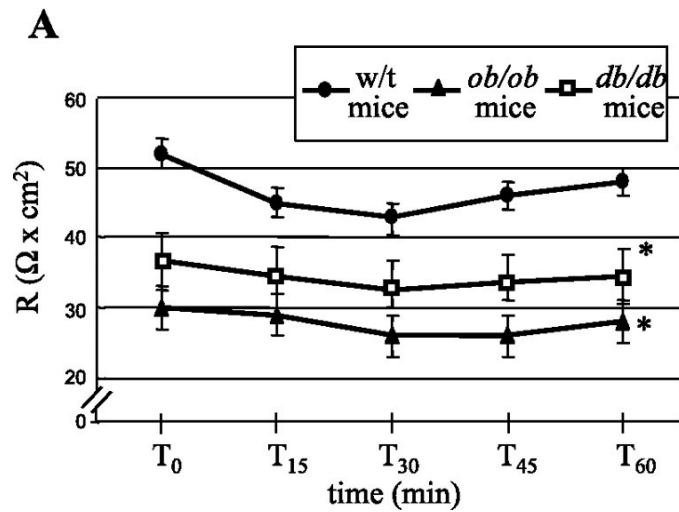
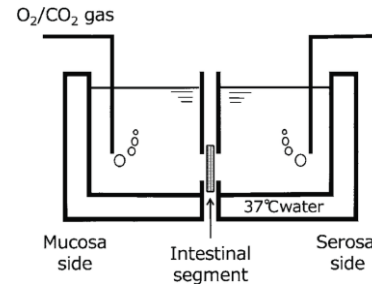


# SCFA beschermen tegen inflammatie

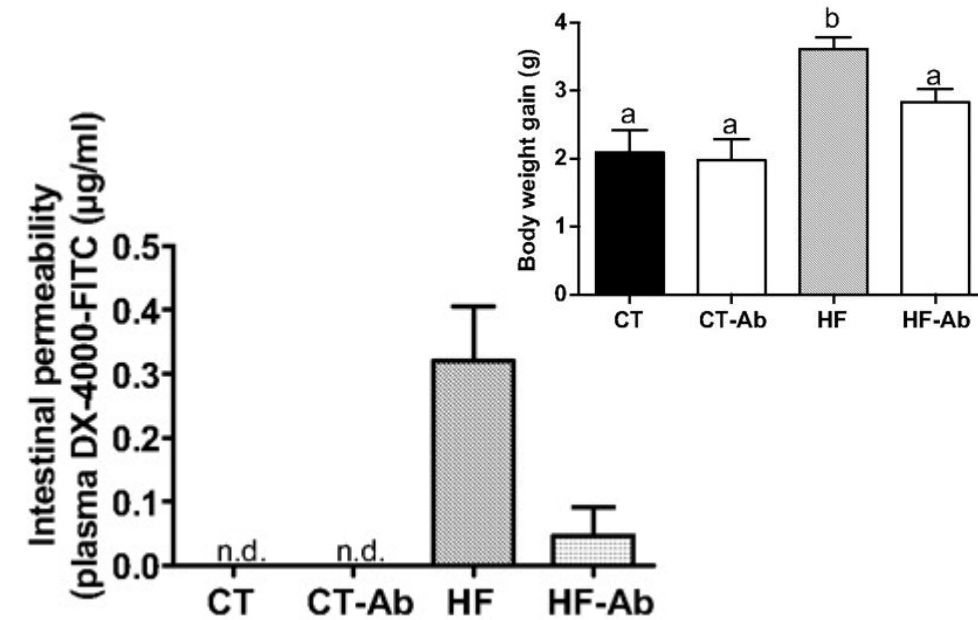


# Obese muizen hebben een verhoogde darmpermeabiliteit

## Ex vivo analyse in Ussing kamers



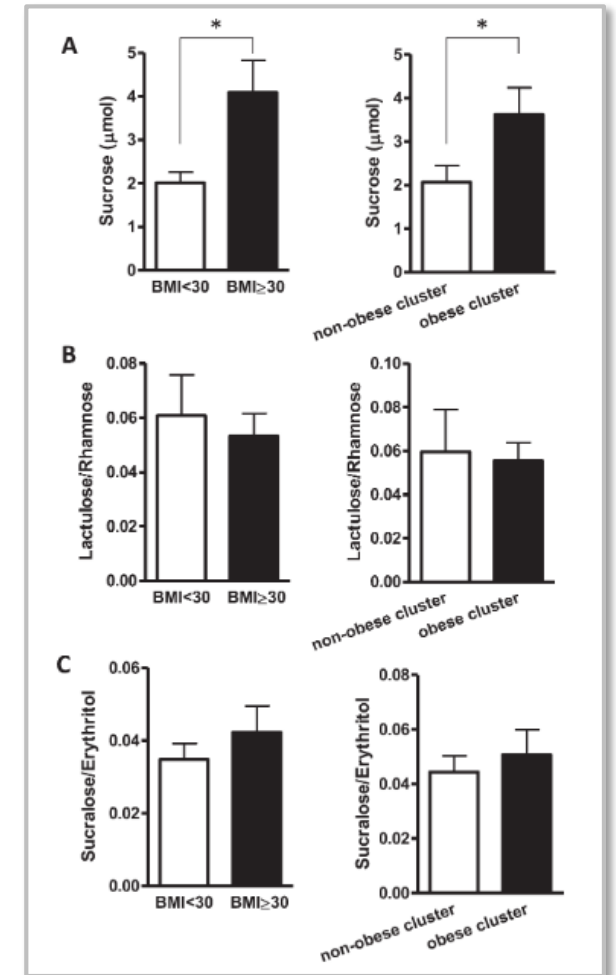
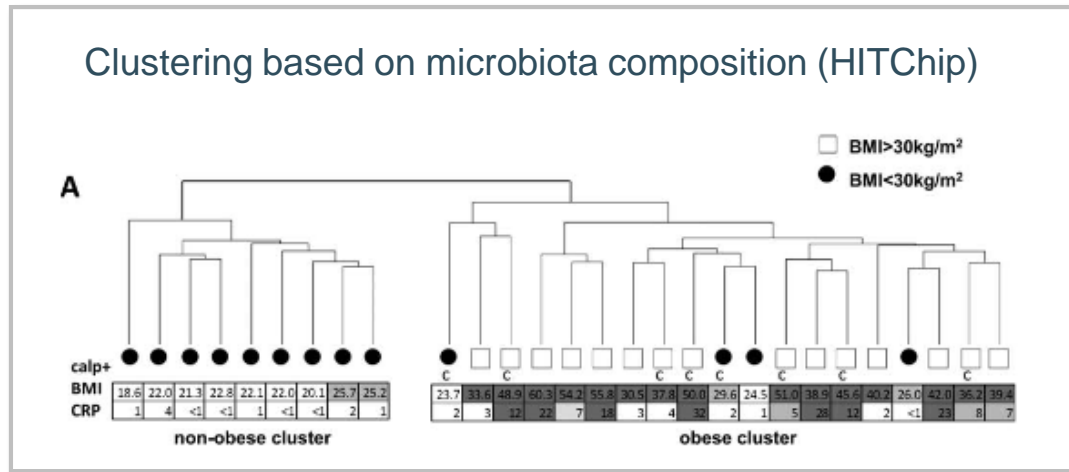
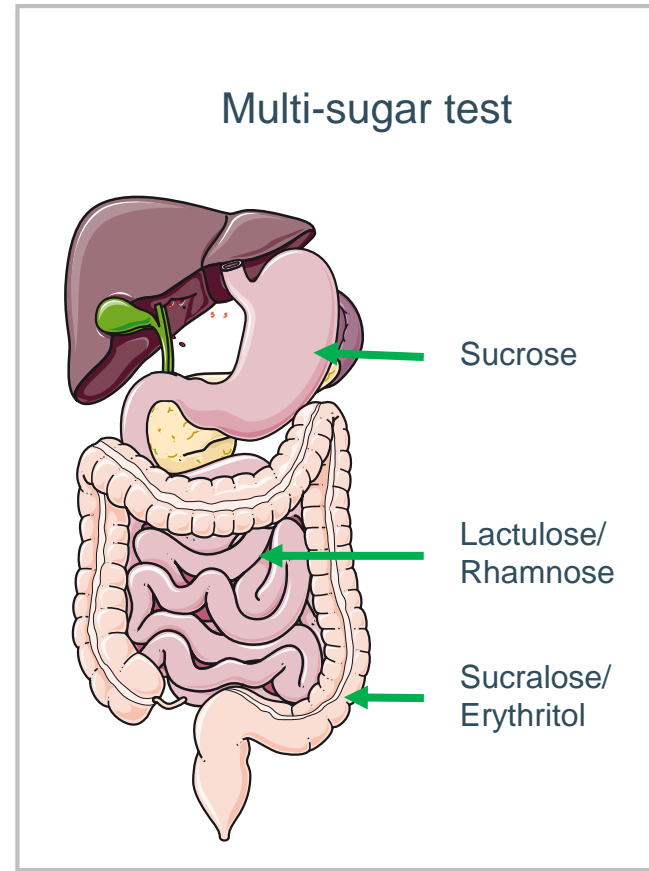
## In vivo permeabiliteit



# Gut permeability in humans

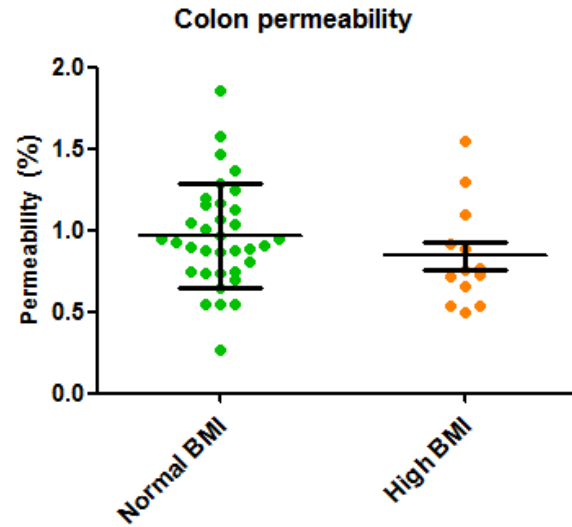
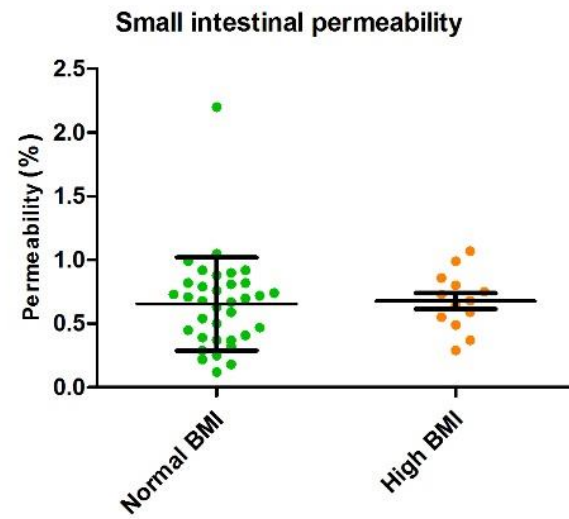
28 subjects

- 13 non-obese (BMI 18.6-29.6)
- 15 obese (BMI 30.5-60.3)

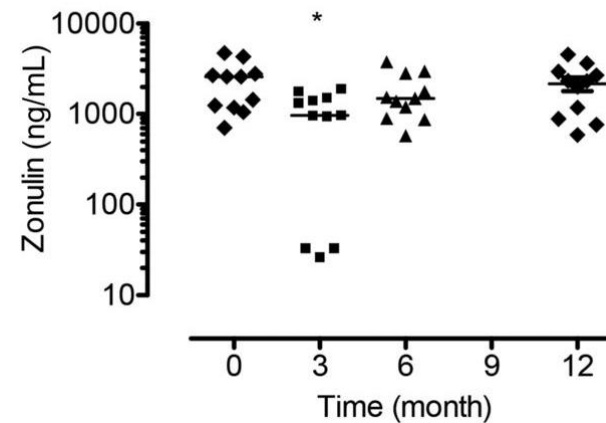
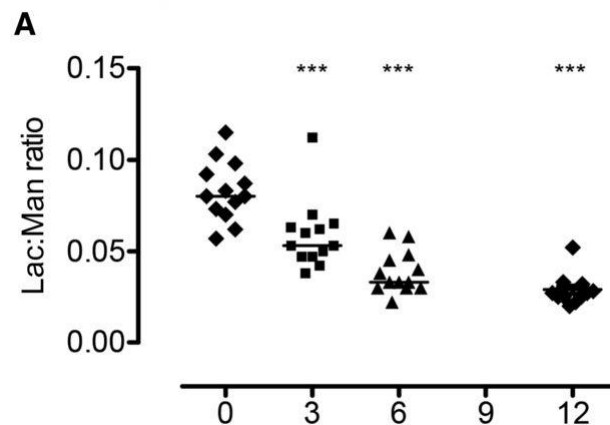




# Gut permeability in humans



Obese subjects BMI: 32 (IQR 31-34)

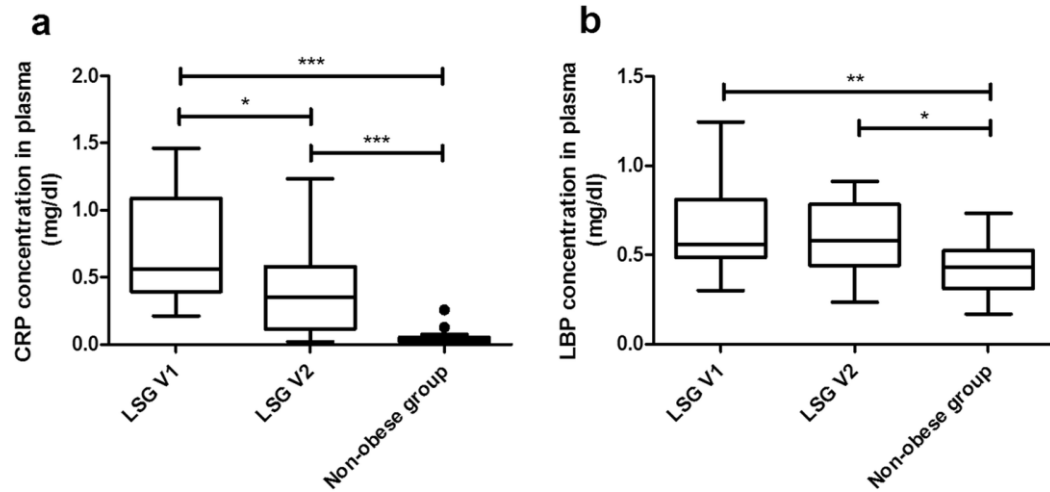


Obese subjects BMI:

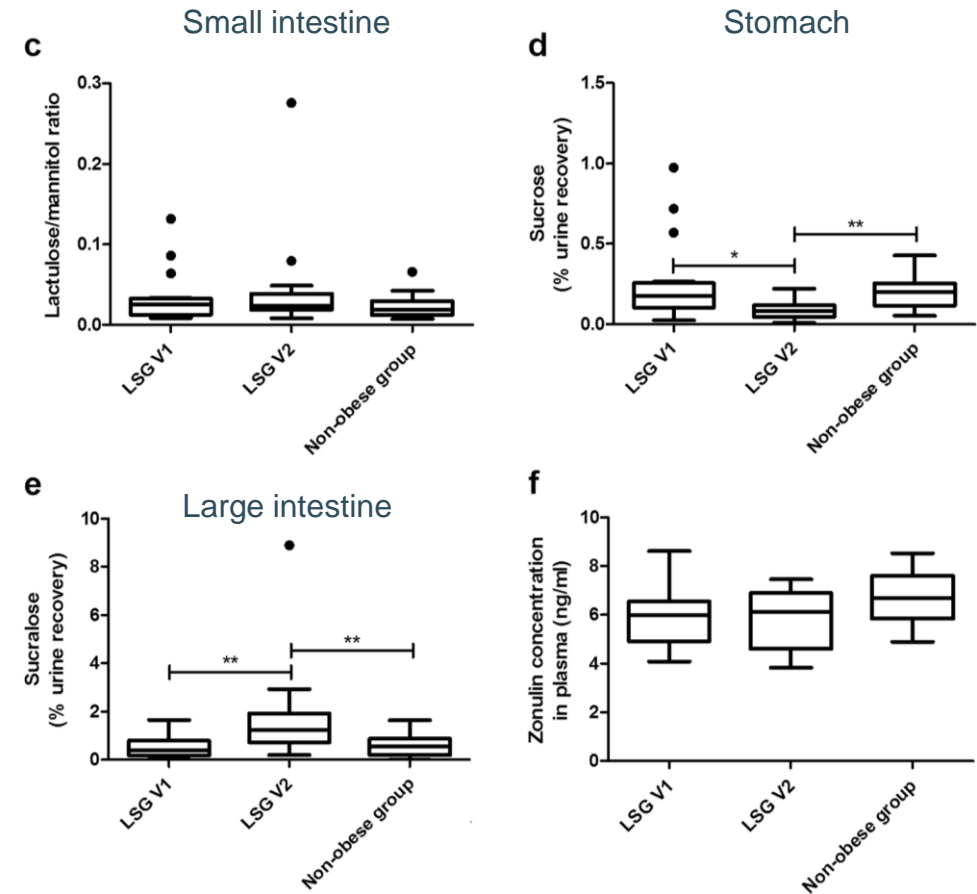
$t_{0m}$ :  $43.7 \pm 5.2$

$t_{12m}$ :  $36.4 \pm 5.1$

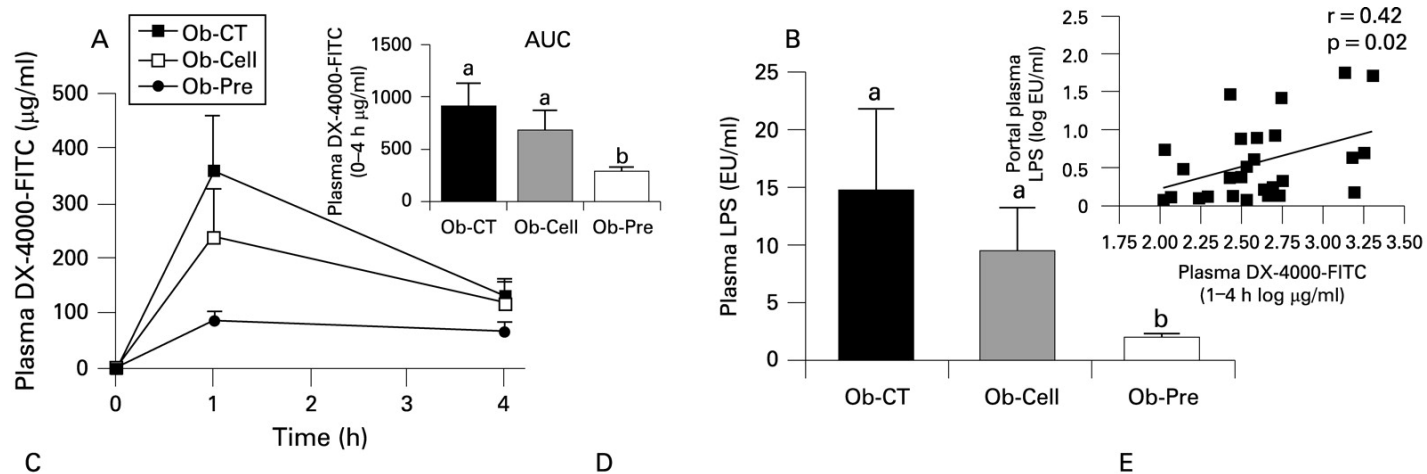
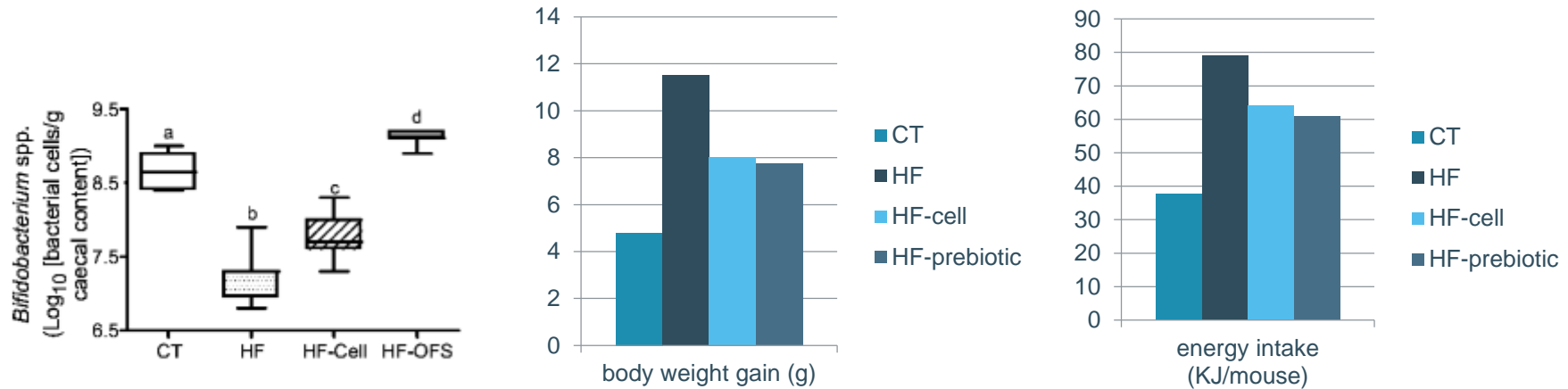
# Gut permeability in humans



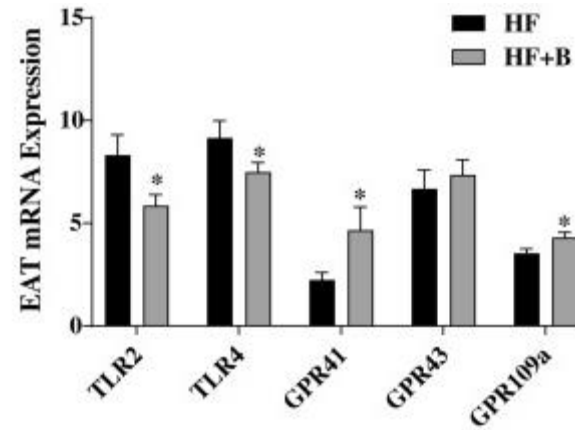
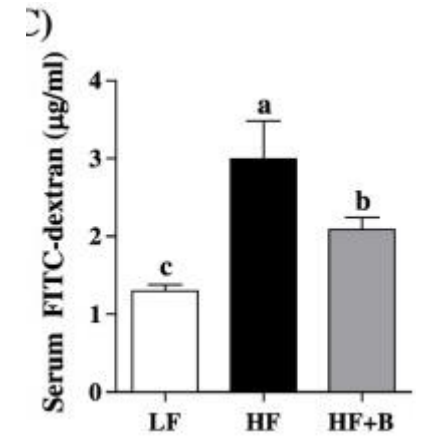
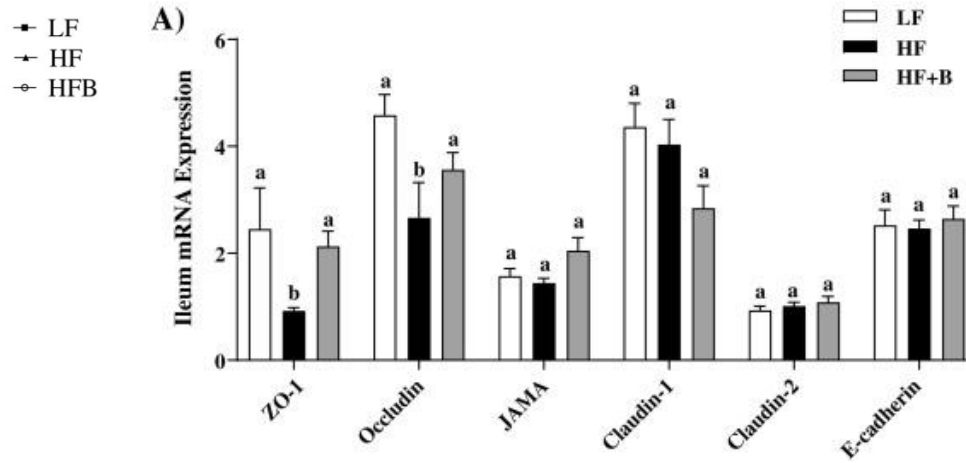
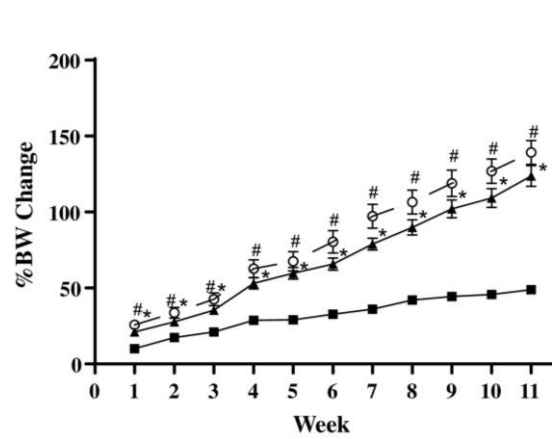
	BMI (median; IQR)
Before surgery (LSG V1)	52.5 (47.0; 56.8)
After surgery (LSG V2)	39.1 (32.6; 44.0)
Control group	21.5 (19.6; 23.3)



# Prebiotics to treat obesity: mice studies

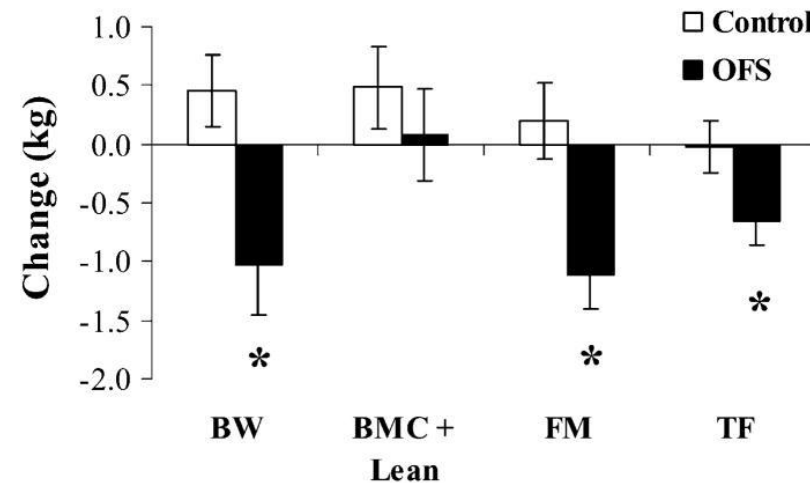
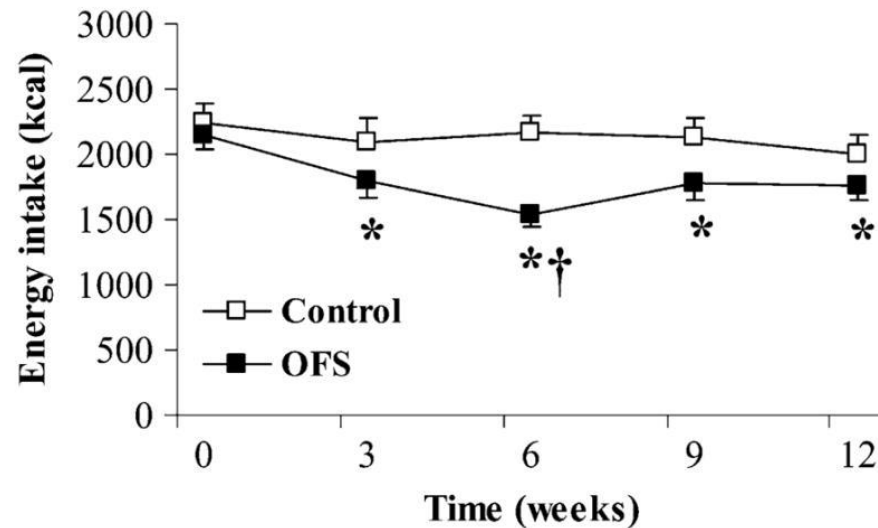


# Prebiotics to treat obesity: mice studies



# Prebiotics in humans

- 48 healthy adults with BMI > 25 kg/m<sup>2</sup>
- 21 g oligofructose or placebo for 12 weeks

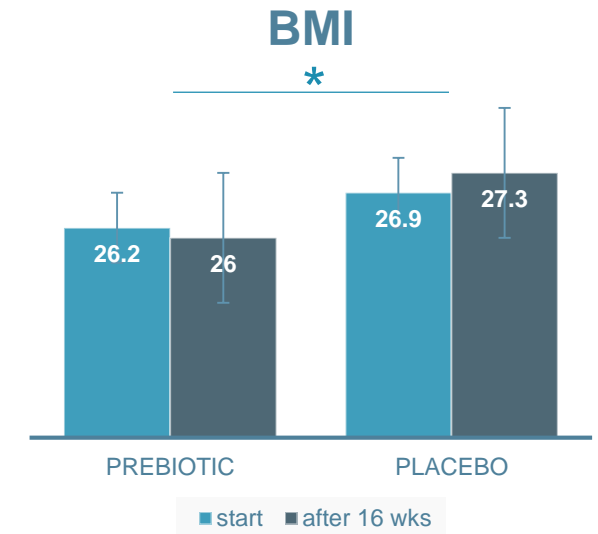
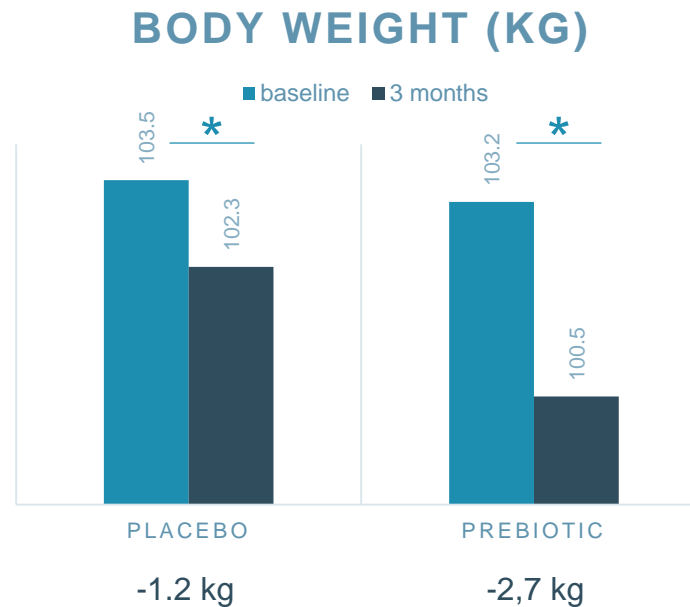
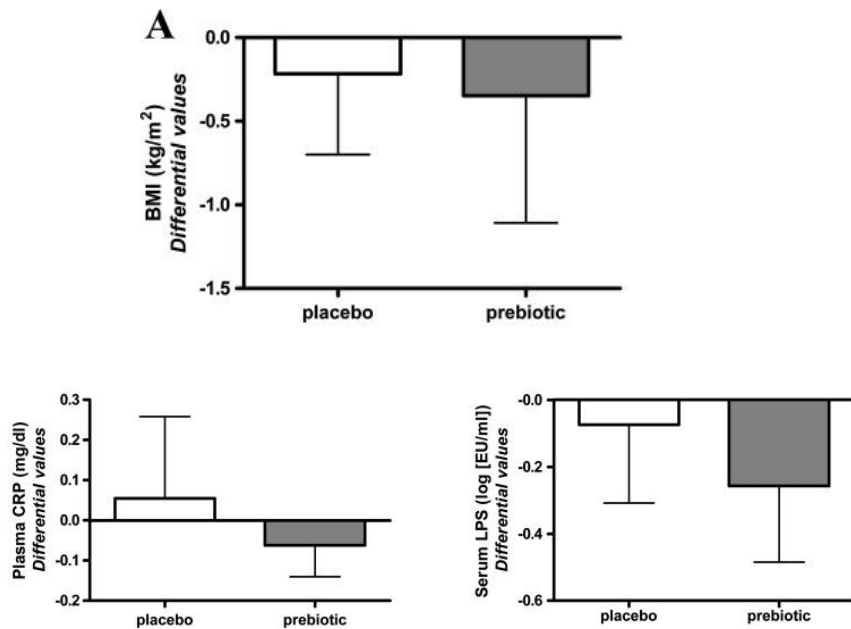


# Prebiotics in humans

- 30 obese women
- 16 g oligofructose/inulin (50/50) or placebo for 3 months

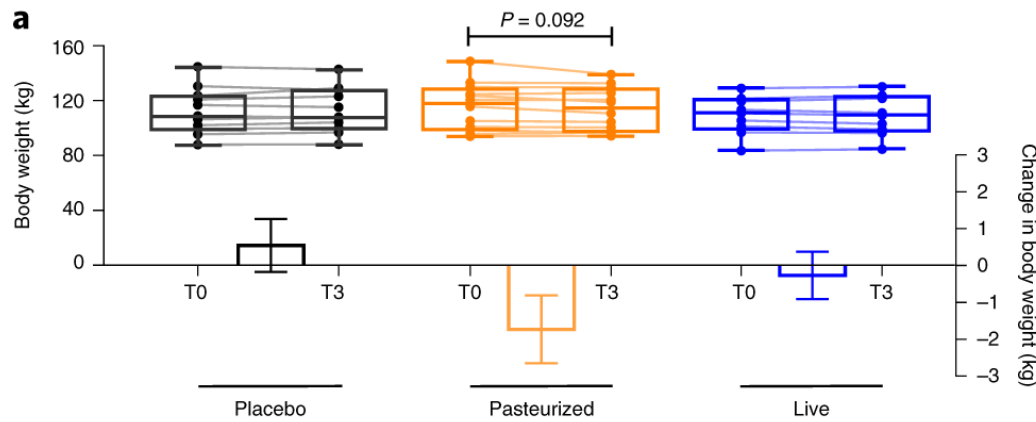
- 106 obese people (m/f)
- caloric restriction with 30% of energy intake
- 16 g inulin or placebo for 3 months

- 42 obese children 7-12y
- 8 g oligofructose/inulin (50/50) or placebo for 16 wks

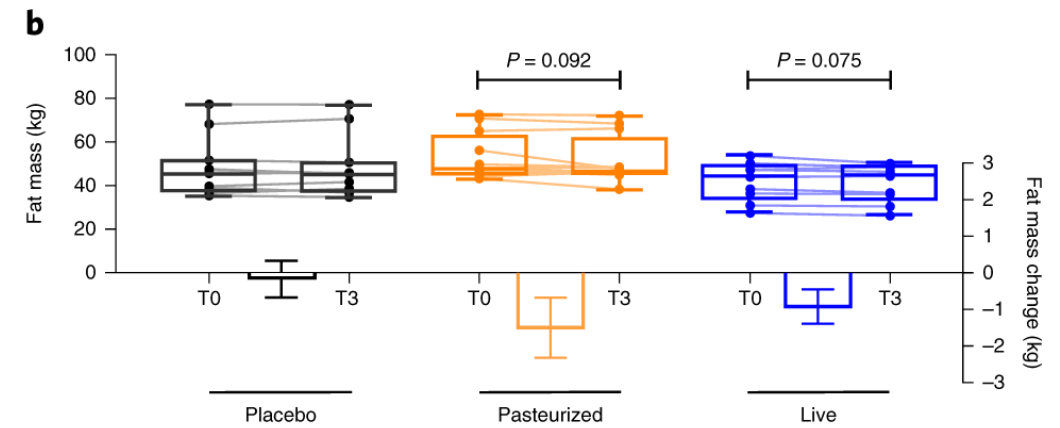


# Impact of probiotics

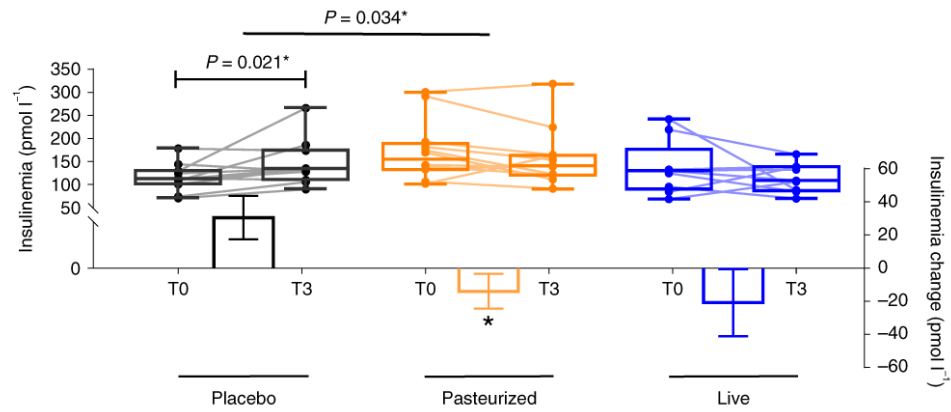
- $10^{10}$  *A. muciniphila* bacteria either live or pasteurized for 3 months
- 32 overweight/obese insulin-resistant subjects



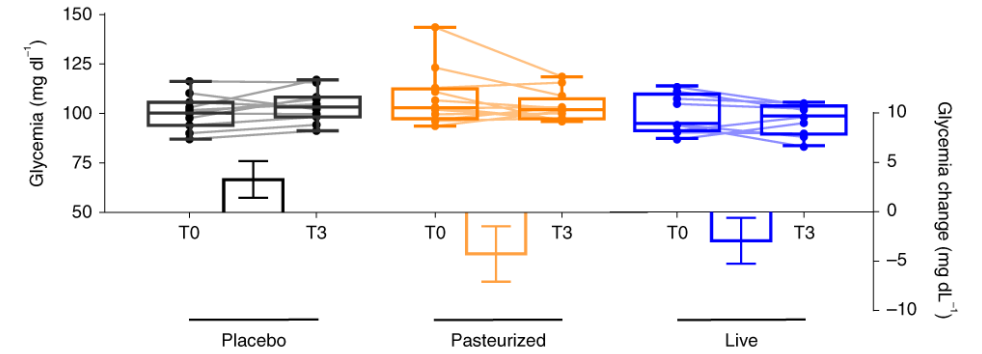
Mean difference	$0.54 \pm 0.72$	$-1.73 \pm 0.92$	$-0.27 \pm 0.64$
<i>P</i> value (Mann–Whitney <i>U</i> -test)		0.091	0.46
Mean difference from placebo (kg)	--	$-2.27 \pm 0.92$	$-0.81 \pm 0.64$
Mean difference from placebo (%)	--	$-1.88 \pm 0.68\%$	$-0.84 \pm 0.58\%$



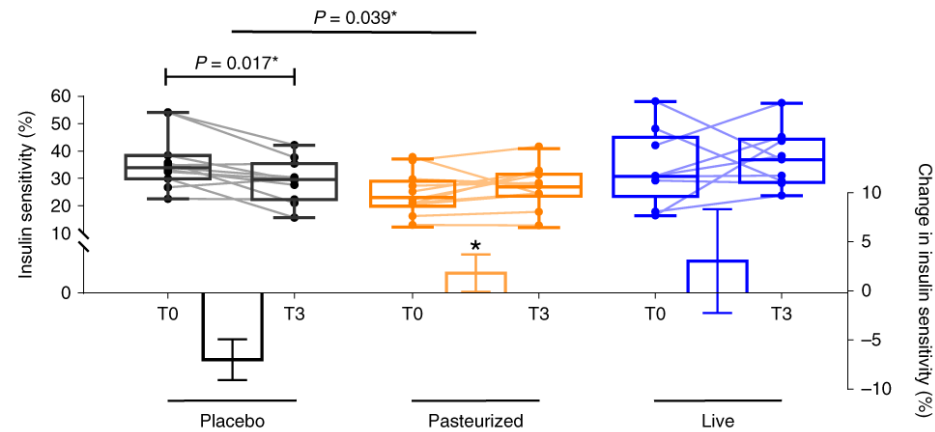
Mean difference	$-0.13 \pm 0.50$	$-1.50 \pm 0.82$	$-0.92 \pm 0.47$
<i>P</i> value (Mann–Whitney <i>U</i> -test)		0.32	0.33
Mean difference from placebo (kg)	--	$-1.37 \pm 0.82$	$-0.79 \pm 0.47$
Mean difference from placebo (%)	--	$-2.53 \pm 1.60\%$	$-1.89 \pm 0.99\%$



	Placebo	Pasteurized	Live
Mean difference	29.65 ± 13.06	-14.81 ± 10.41	-21.70 ± 20.23
P value (Mann-Whitney U-test)		0.006*	0.056
Mean difference from placebo (pmol l <sup>-1</sup> )	--	-44.46 ± 10.41	-51.35 ± 20.33
Mean difference from placebo (%)	--	-34.08 ± 7.12%	-32.38 ± 13.97%



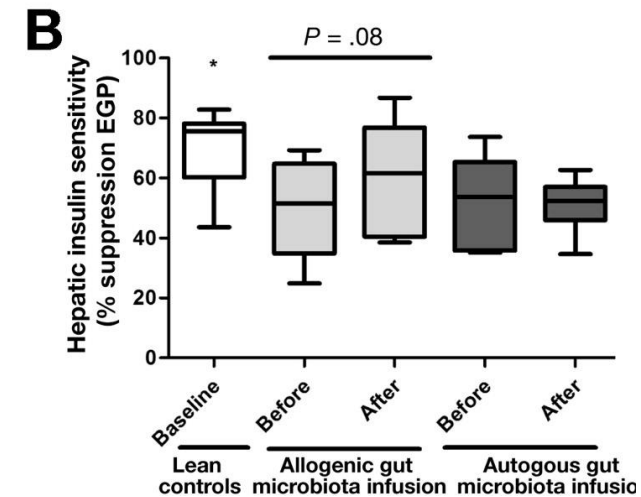
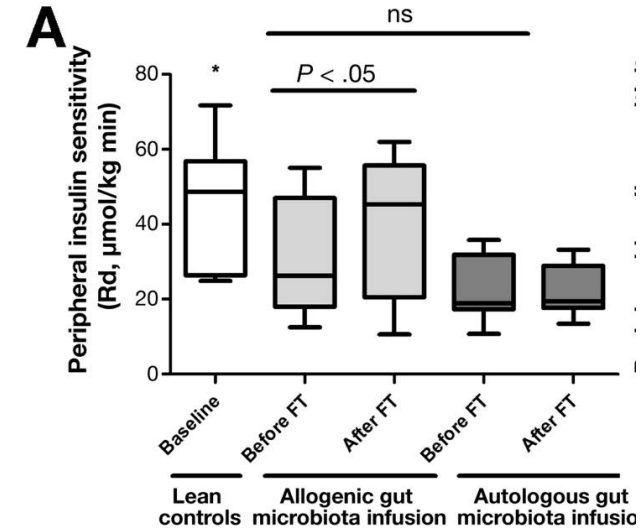
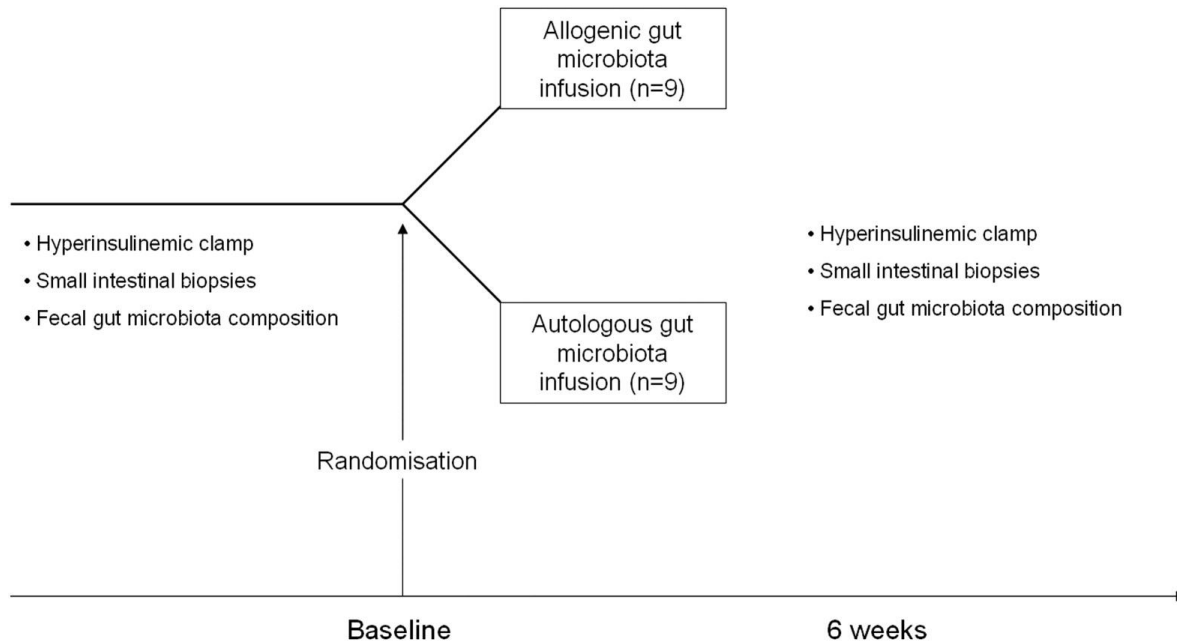
	Placebo	Pasteurized	Live
Mean difference	3.28 ± 1.86	-4.17 ± 2.80	-2.89 ± 2.33
P value (Mann-Whitney U-test)		0.069	0.056
Mean difference from placebo (mg dl <sup>-1</sup> )	--	-7.45 ± 2.80	-6.17 ± 2.33
Mean difference from placebo (%)	--	-6.58 ± 2.30%	-6.02 ± 2.43%



	Placebo	Pasteurized	Live
Mean difference	-6.79 ± 2.07	2.13 ± 1.89	3.24 ± 5.28
P value (Mann-Whitney U-test)		0.002*	0.095
Mean difference from placebo	--	8.92 ± 1.89	10.03 ± 5.28
Mean difference from placebo (%)	--	28.62 ± 7.02%	42.42 ± 20.44%

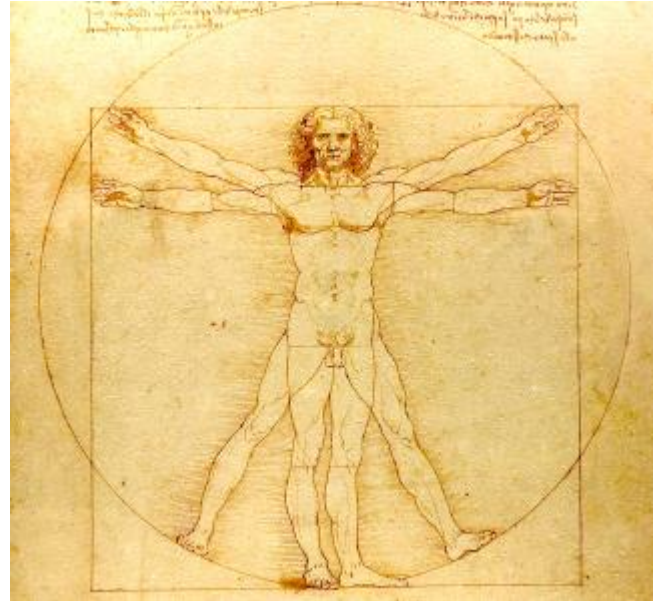


# Fecal microbiota transplantation



# Take home messages

- Er zijn meer en meer aanwijzingen dat de microbiota betrokken is in het ontstaan van obesitas
- Microbiële componenten/metabolieten kunnen fungeren als signaalmoleculen
  - In combinatie met een hoog-vet dieet wordt meer LPS opgenomen dat obesitas en inflammatie induceert
  - SCFA verhinderen inflammatie
- De rol van darmpermeabiliteit bij de mens is niet duidelijk
- Interventies bij proefdieren die de microbiota moduleren leveren veelbelovende resultaten
- De effecten van dergelijke interventies bij de mens zijn eerder bescheiden



Een gezonde geest in een gezond lichaam (Juvenalis)

~~Calam~~

Bedankt voor uw aandacht!

