Personalised nutrition for the gut microbiome: feed it, change it, swap it?

Kieran Tuohy

Fondazione Edmund Mach, San Michele all'Adige, Trento, Italy

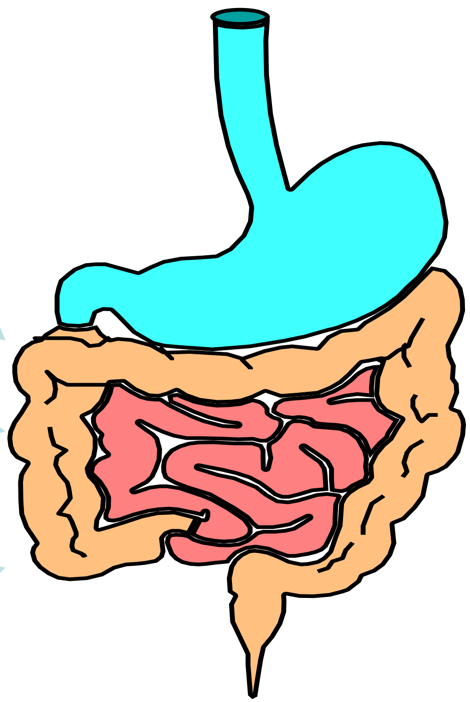
FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

The human gut microbiome

Up to 1000 species

70%
unculturable

Closely co-evolved
microbial partners



Interactions with;

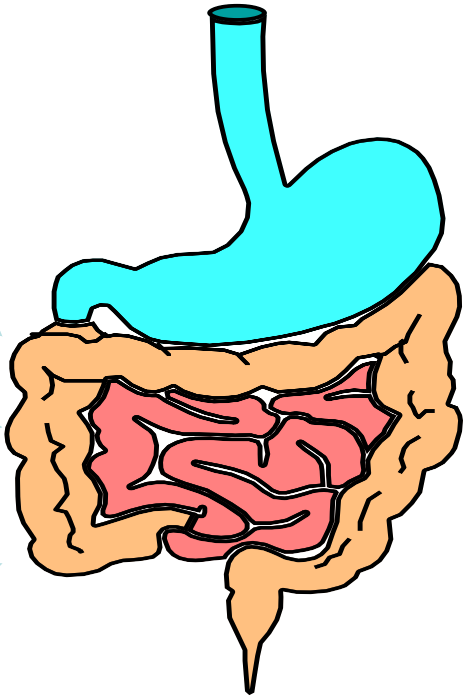
- Diet
- Drugs
- Immune system
- Gut physiology
- Bile acids/liver
- Systemic metabolism
- Adipose tissue
- Brain development & function

The human gut microbiome

Up to 1000 species

70%
unculturable

Closely co-evolved
microbial partners

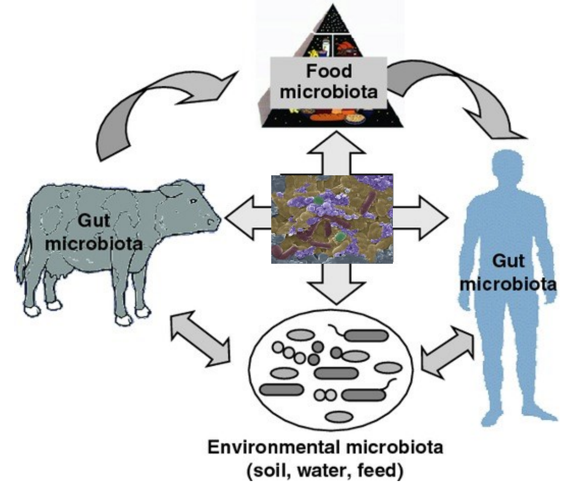


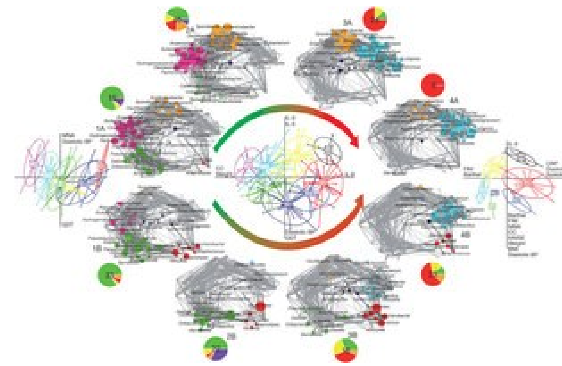
Interactions with;

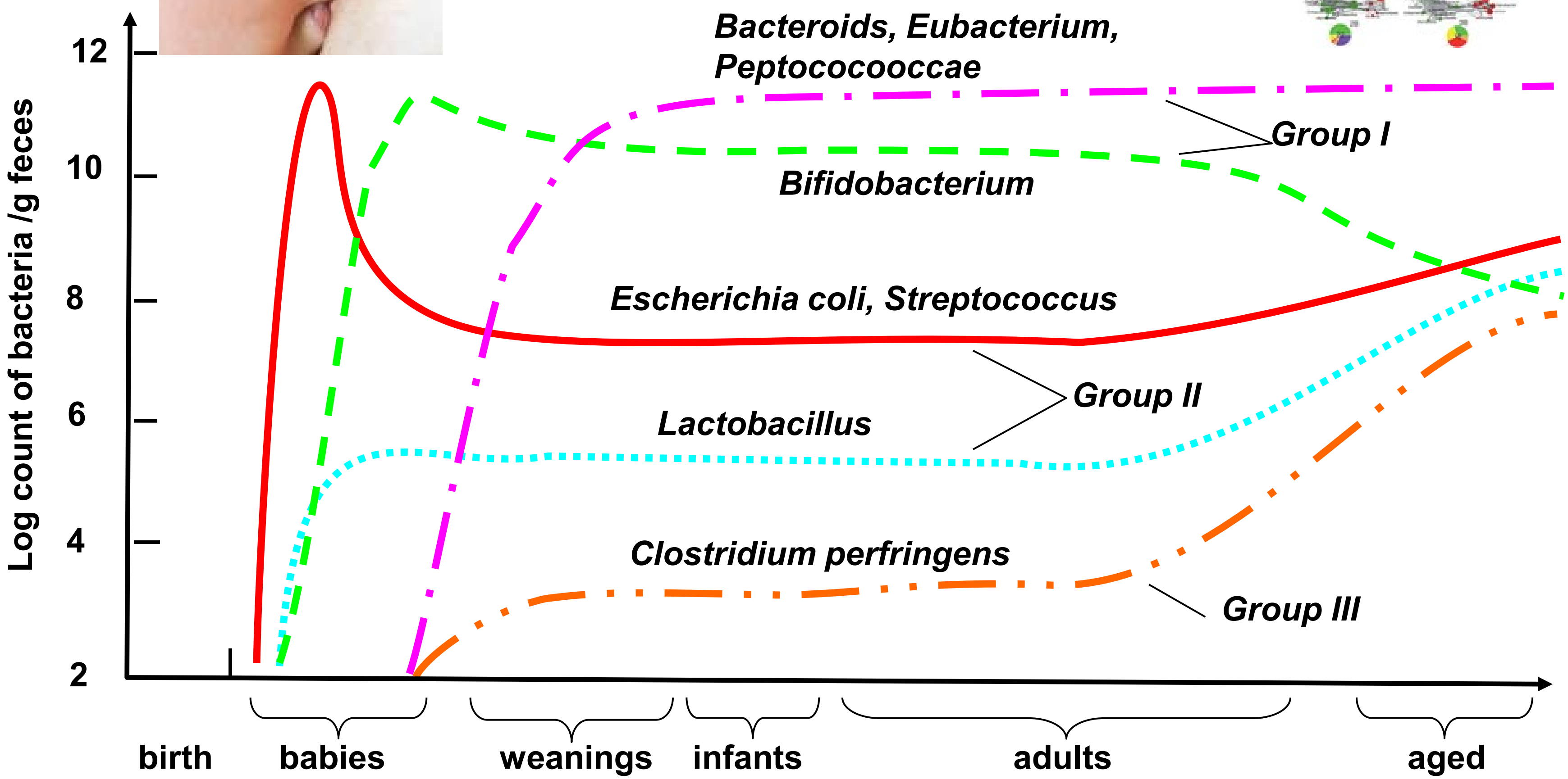
- Diet
- Drugs
- Immune system
- Gut physiology
- Bile acids/liver
- Systemic metabolism
- Adipose tissue
- Brain development & function

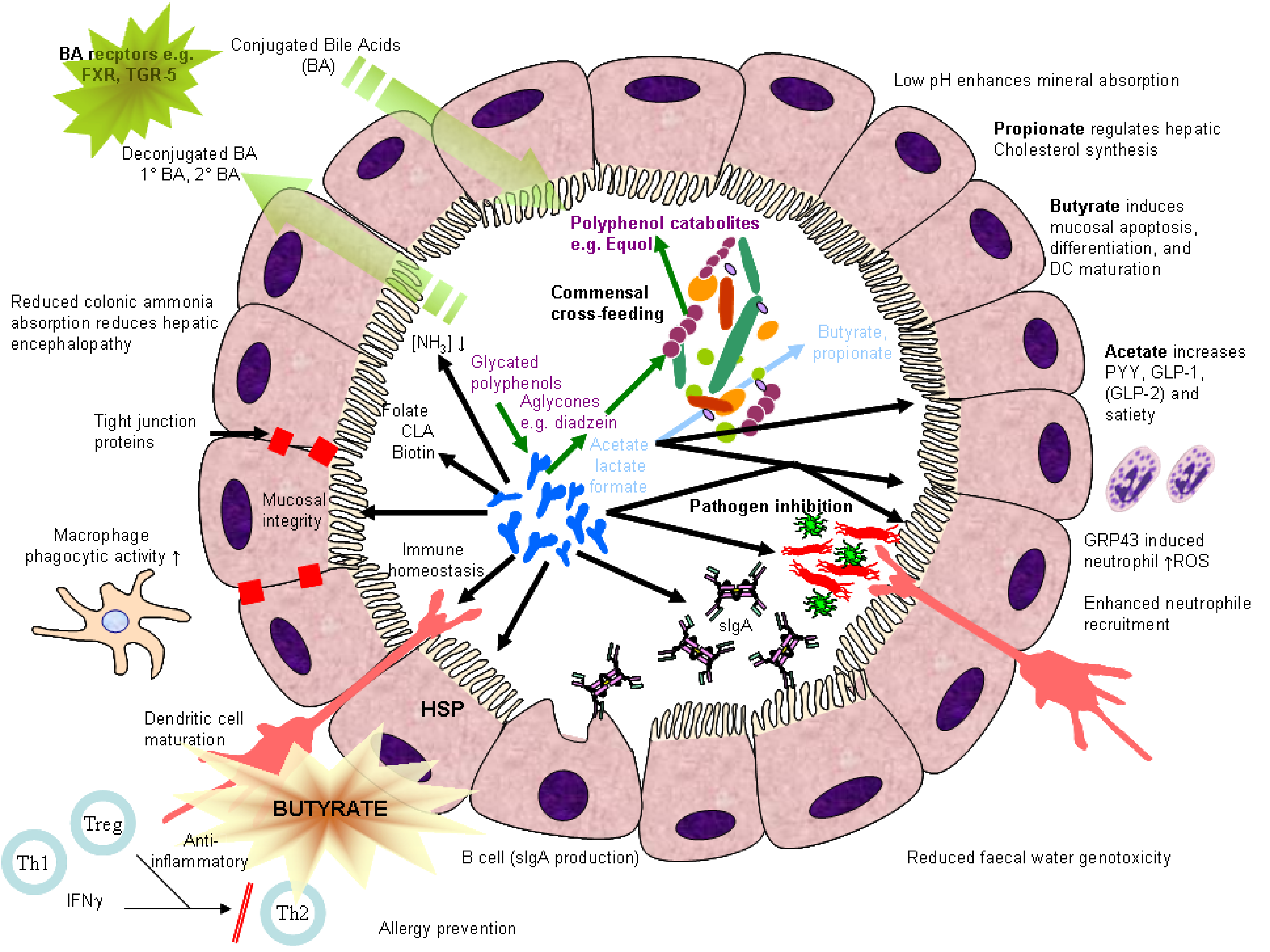
Gut microbiota and essential organ within the human system – we have become an ecosystem

FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

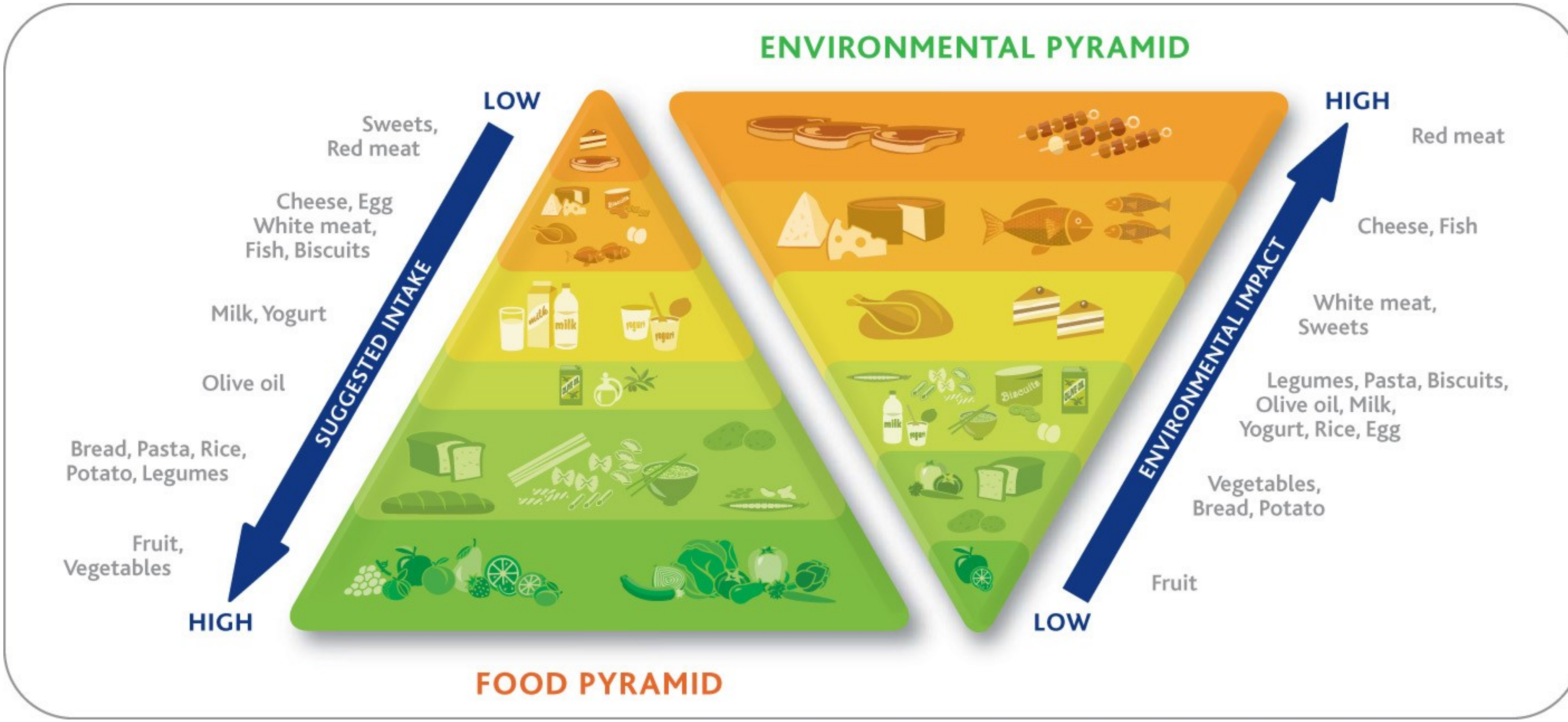







BA recptors e.g. FXR, TGR-5
Conjugated Bile Acids (BA)
Deconjugated BA 1° BA, 2° BA
Low pH enhances mineral absorption
Propionate regulates hepatic Cholesterol synthesis
Butyrate induces mucosal apoptosis, differentiation, and DC maturation
Polyphenol catabolites e.g. Equol
Commensal cross-feeding
Reduced colonic ammonia absorption reduces hepatic encephalopathy
[NH3] ↓
Glycated polyphenols
Aglycones e.g. diadzein
Butyrate, propionate
Acetate increases PYY, GLP-1, (GLP-2) and satiety
Tight junction proteins
Folate CLA Biotin
Acetate lactate formate
Mucosal integrity
Pathogen inhibition
Macrophage phagocytic activity ↑
Immune homeostasis
GRP43 induced neutrophil ↑ROS
Enhanced neutrophile recruitment
sIgA
HSP
Dendritic cell maturation
BUTYRATE
Treg
Th1
Anti-inflammatory
IFNγ
Th2
B cell (sIgA production)
Reduced faecal water genotoxicity
Allergy prevention

Dietary patterns – Mediterranean diet



INRAN, FAO Double Pyramid

Barilla Centre for Food Nutrition: Double Pyramid: healthy food for people, sustainable food for the planet

http://www.barillacfn.com/en/position-paper/pp-doppia-piramide-alimentazione/

BMJ open

FONDAZIONE EDMUND MACH CENTRO RICERCA e INNOVAZIONE

Adherence to a Mediterranean diet is associated with a better health-related quality of life: a possible role of high dietary antioxidant content

Marialaura Bonaccio,[1,2] Augusto Di Castelnuovo,[1] Americo Bonanni,[1,3] Simona Costanzo,[1] Francesca De Lucia,[1] George Pounis,[1] Francesco Zito,[1] Maria Benedetta Donati,[2] Giovanni de Gaetano,[2] Licia Iacoviello,[2,4] on behalf of the Moli-sani project Investigators*

Table 2 Multivariate regression coefficients (95% CI) for the association of Mediterranean diet scores or other dietary patterns with mental and physical component scores and further adjustment for food antioxidant content (FAC) or dietary fibre

	β*	95% CI	p Value**	β*	95% CI	p Value**	Β*	95% CI	p Value**
				Further adjusted for FAC			Further adjusted for dietary fibre		
Mental component score									
Mediterranean diet	0.33	0.18 to 0.49	<0.0001	0.08	−0.09 to 0.25	0.35	0.13	−0.04 to 0.29	0.13
Italian Mediterranean index	0.36	0.20 to 0.51	<0.0001	0.03	−0.14 to 0.22	0.67	0.15	−0.01 to 0.32	0.07
Olive oil and vegetables pattern	0.50	0.34 to 0.65	<0.0001	0.19	−0.003 to 0.38	0.05	0.32	0.15 to 0.50	0.0004
Meat and pasta pattern	0.07	−0.10 to 0.24	0.44	0.05	−0.12 to 0.21	0.59	0.14	−0.03 to 0.31	0.11
Eggs and sweets pattern	−0.33	−0.52 to −0.14	0.001	−0.18	−0.39 to 0.01	0.06	−0.16	−0.36 to 0.04	0.11
Physical component score									
Mediterranean diet	0.15	0.06 to 0.24	0.001	0.13	0.03 to 0.21	0.01	0.16	0.07 to 0.26	0.001
Italian Mediterranean index	0.08	−0.003 to 0.16	0.06	0.06	−0.04 to 0.15	0.26	0.08	−0.01 to 0.17	0.09
Olive oil and vegetables pattern	0.15	0.06 to 0.24	0.001	0.15	0.04 to 0.26	0.01	0.17	0.06 to 0.27	0.0010
Meat and pasta pattern	−0.11	−0.20 to −0.02	0.02	−0.12	−0.22 to −0.03	0.01	−0.11	−0.20 to −0.01	0.03
Eggs and sweets pattern	−0.02	−0.13 to 0.08	0.71	0.004	−0.11 to 0.12	0.94	−0.01	−0.12 to 0.10	0.90

*Regression coefficients represent the variation in mental or physical component scores for a one standard deviation change in MDS, IMI or dietary patterns.
**p for trend values obtained from fully adjusted model for age, sex, BMI, total energy intake, total physical activity, education, income, total socioeconomic status, smoking, diabetes, hypertension, hypercholesterolemia.

“**Conslusions:** Adherence to an MD pattern is associated with better HRQL. The association is stronger with mental health than with physical health. Dietary total antioxidant and fibre content independently explain this relationship”.

Calorie restricted & traditional diets increase life-span and protect against age-associated disease

FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

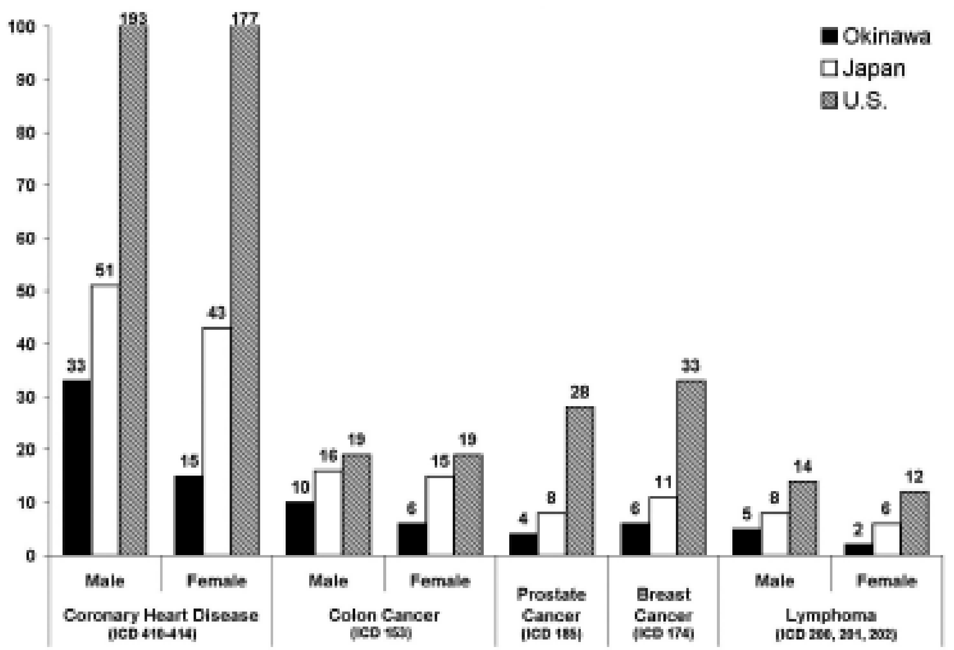


FIGURE 5. Mortality from age-associated diseases in Okinawans versus Americans. Numbers represent age-adjusted mortality rate in deaths per hundred thousand persons per year for 1995. Coding was according to ICD-9 codes; populations were age-adjusted to World Standard Population. These data show markedly lower mortality risk from age-related diseases in Okinawans versus other Japanese and Americans.

•Average life span: Okinawa, 83.8 years; Japan 82.3 years, US 78.9 years

•Traditional Japanese diet: high in vegetables, fruit, soy, fish, fibre

•Low calorie intake, negative energy balance at young age, little weight gain with age, life-long low BMI, low risk of age associated diseases contribute to longevity in Okinawans

Wilcox et al., 2008 Ann NY Acad Sci

Bioactivity of plant based foods against CVD involves the gut microbiota

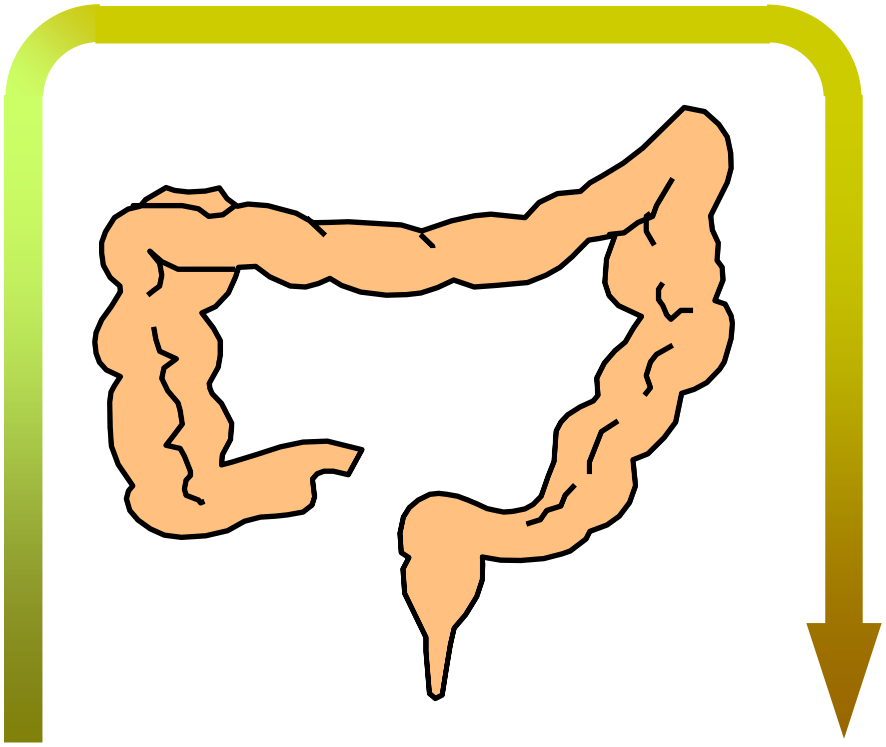
- **EPIC-elderly study:** (74,607 healthy over 60 year olds (no history of CVD, stroke, or cancer)
  - greater adherence to a plant based (**Mediterranean diet**) in elders was associated with **lower all-cause mortality** (Bamia et al., 2006 Pub Hlth Nutr.)
- **Boyd Orr cohort:** having a vegetable rich diet in childhood was associated with healthy diet in old age (Maynard et al., 2005 Eur J Pub Hlth)
- Diets rich in whole plant foods protect against the diseases of old age especially CVD and may promote longevity and healthy ageing
- Dietary fibre includes **fermentable carbohydrates and prebiotics** which can modulate the composition and activity of the gut **microbiota** and **90% of dietary plant polyphenols** reach the colon

Impact of traditional diets rich in fiber on colonic fermentation

Proximal colon
~ saccharolytic

SCFA
Acetate
Propionate
Butyrate

Energy source
Apoptosis
Differentiation
Epigenetics
Gene expression
Gut hormones
Gut permeability



Distal colon
~ proteolytic

Amines
Indoles
Ammonia
Sulphides
N-nitroso

DNA damage
Tumours
Cytotoxicity
Leaky gut
Liver disease

Modified from George Macfarlane

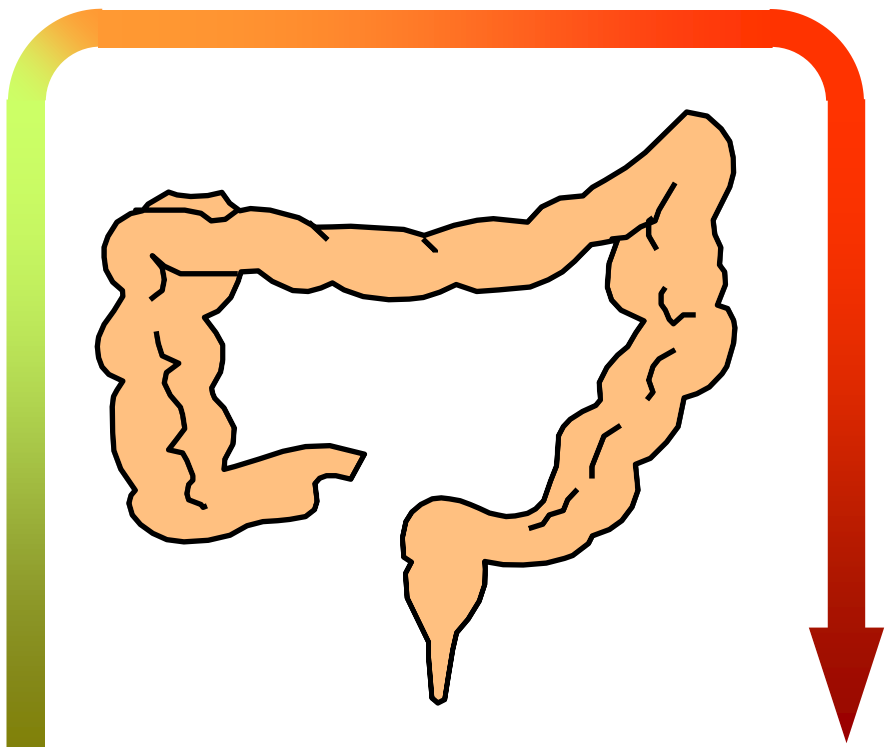
FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

Impact of Western style diet on colonic fermentation

Proximal colon
~ saccharolytic

SCFA
Acetate
Propionate
Butyrate

Energy source
Apoptosis
Differentiation
Epigenetics
Gene expression
Gut hormones
Gut permeability



Distal colon
~ proteolytic

Amines
Indoles
Ammonia
Sulphides
N-nitroso

DNA damage
Tumours
Cytotoxicity
Leaky gut
Liver disease

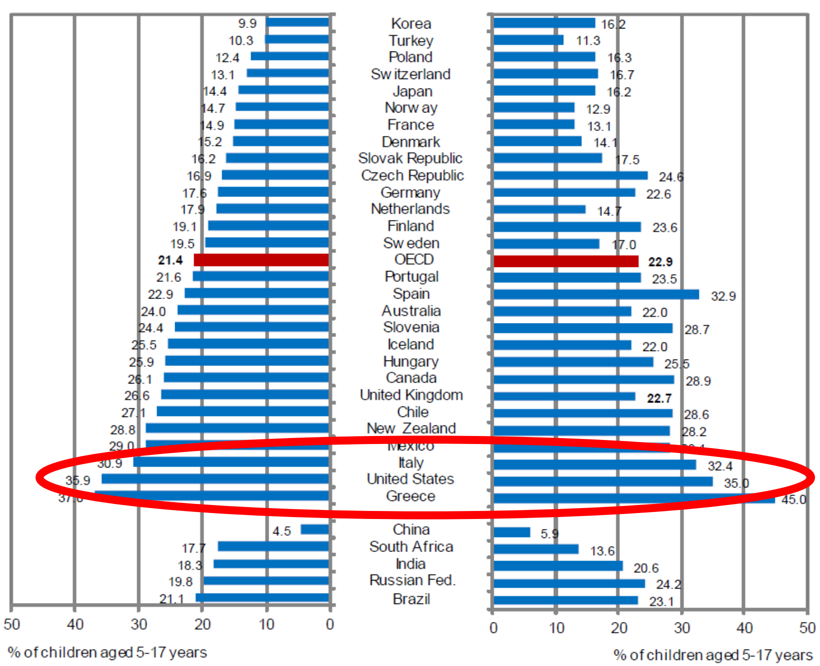
Modified from George Macfarlane

FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

OBESITY EPIDEMIC

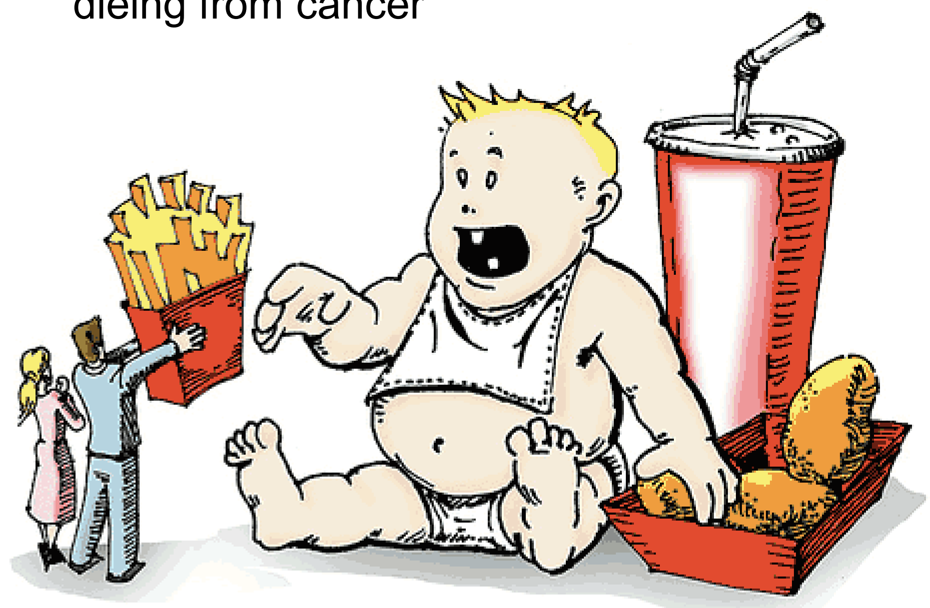
- Currently 300 million people obese world-wide
- Obese adults are up to 80 times more likely to develop type 2 diabetes than non-obese adults
- Obese adults are 2-3 times more likely to develop heart disease
- Obese adults have a 40% increased risk of dieing from cancer

Children aged 5-17 years who are overweight (including obese), latest available estimates



Source: International Association for the Study of Obesity (2011).

Statlink: http://dx.doi.org/10.1787/888932523994



FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

Vol 444 | 21/28 December 2006 nature

NEWS & VIEWS

PHYSIOLOGY

Obesity and gut flora

Matej Bajzer and Randy J. Seeley

The intestinal bacteria in obese humans and mice differ from those in lean individuals. Are these bacteria involved in how we regulate body weight, and are they a factor in the obesity epidemic?

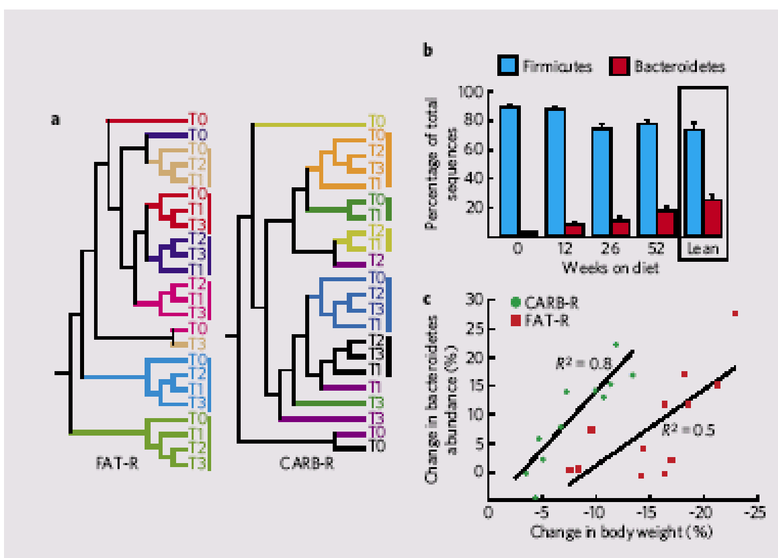
MICROBIAL ECOLOGY

Human gut microbes associated with obesity

Two groups of beneficial bacteria are dominant in the human gut, the Bacteroidetes and the Firmicutes. Here we show that the relative proportion of Bacteroidetes is decreased in obese people compared to lean people, and that this proportion increases with weight loss on two types of low-calorie diets. Our findings suggest that obesity has a microbial component, which might have potential therapeutic implications.

Trillions of microbes live in the human gut, helping to break down otherwise indigestible foods[1]. Transplanting the gut microbiota from normal mice into germ-free recipients increases their body fat without any increase in food consumption[2], raising the possibility that the composition of the microbial community in the gut affects the amount of energy extracted from the diet[2].

The relative abundance of the two predominant bacterial divisions (deep evolutionary lineages or superkingdoms) in mice differs between lean and obese animals: mice that are genetically obese (*ob*/*ob*) have 50% fewer Bacteroidetes, and correspondingly more



- Diets designed for reduced energy intake/slimming, with either reduced fat or reduced carbohydrate
- Microbiota approaches lean profile with weight loss – no info on diets (nutrient substitution)

Ley et al., Nature (2006)

Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

Wang et al., 2011 *Nature*

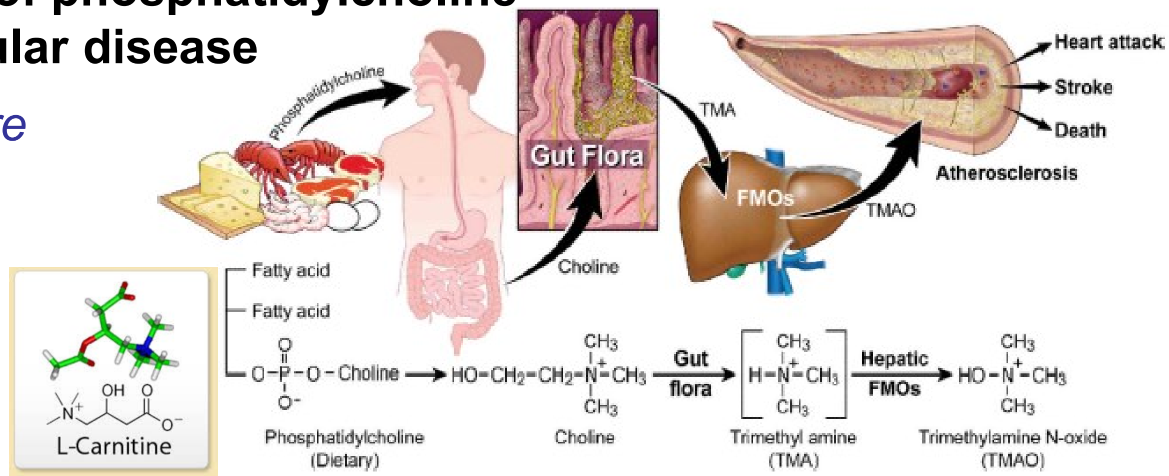


Figure 6. Gut flora dependent metabolism of dietary PC and atherosclerosis
Schematic summary illustrating newly discovered pathway for gut flora mediated generation of pro-atherosclerotic metabolite from dietary PC.

Intestinal microbiota metabolism of *L*-carnitine, a nutrient in red meat, promotes atherosclerosis

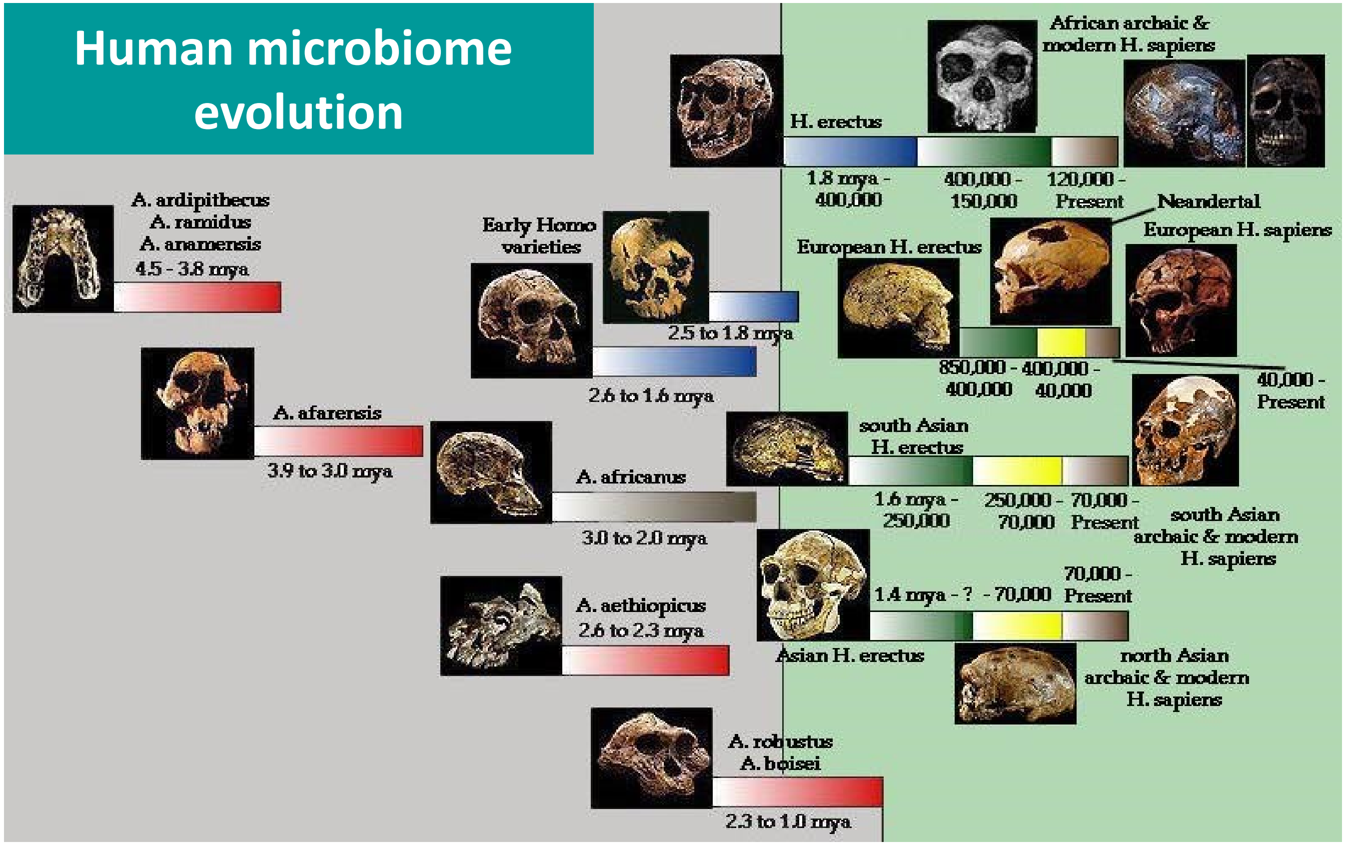
Koeth et al., 2013 *Nature Medicine*

TMA/TMAO confirmed strong link with CVD in patients

- confirmed microbiota metabolism of L-carnitine/choline → TMA→TMAO
- TMA not produced in vegans
- confirmed inflammatory activity & linked to macrophage reverse cholesterol transport
- TMAO reduced bile acid pool

Feed it!

Human diet shaped our closely co-evolved human:microbe ecosystem



Dietary evolution

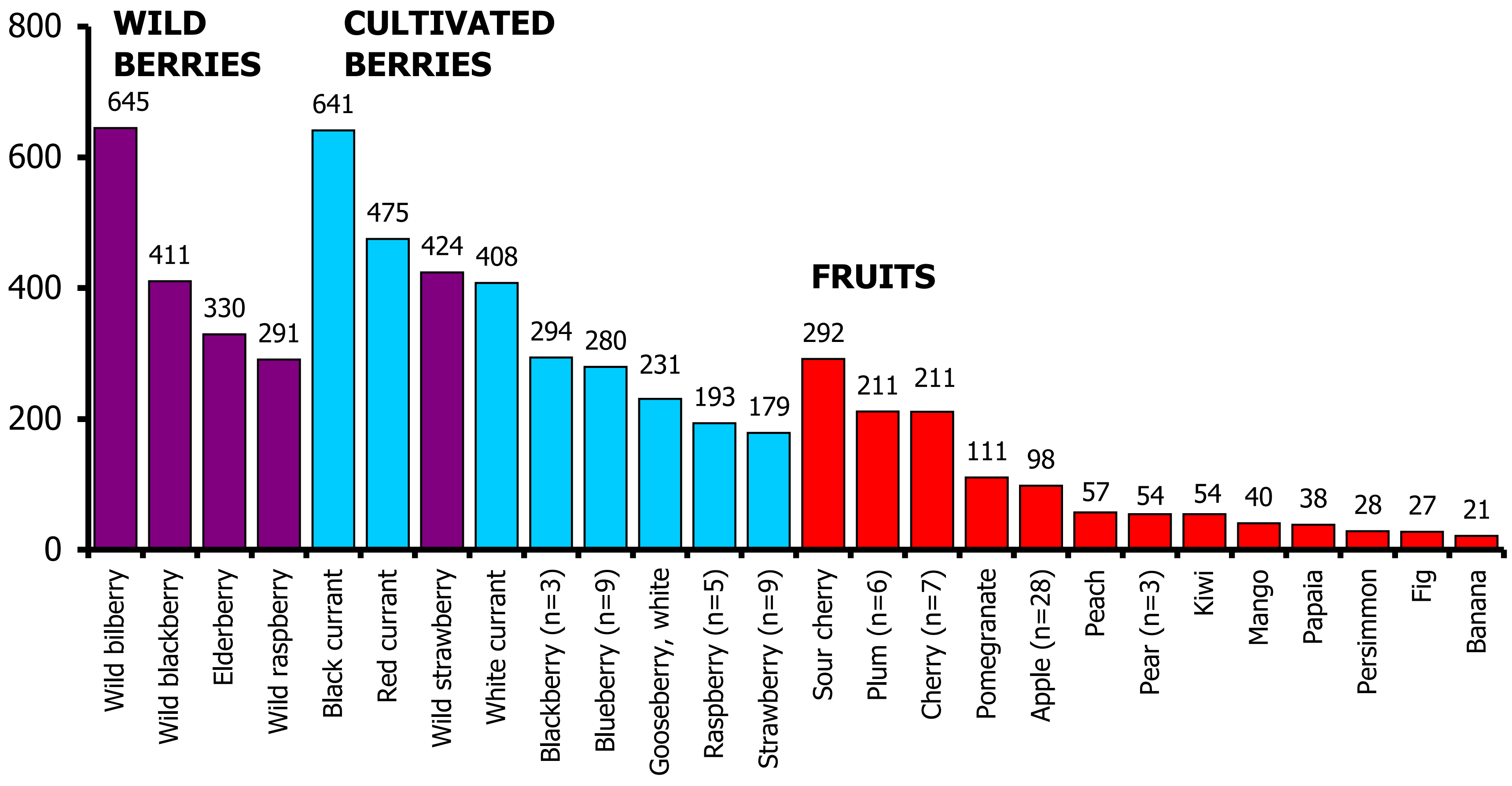
- Neolithic times: ~10,000 yrs BP (birth of agriculture)
- Agricultural/Industrial revolutions: Late 18th and early 19th century
- Green revolution: Over the last 70 yrs (Western-style diet)

Estimated daily fiber intake in Palaeolithic /Traditional diets and Modern diet

Dietary pattern	Fiber content
Palaeolithic diet first reported in 1985 (Eaton SB)	45.7g
Palaeolithic diet modified in 1990 (Eaton SB)	>100g
Palaeolithic diet reported in 1996/1997 (Eaton SB)	104g
Rural Chinese diet	77g
Rural African diet	120g
Current US diet	10-20g
Recommended fiber content in US	25-38g
Current UK diet	12g
Recommended fiber content in UK	18g

(Tuohy et al. Current Pharmaceutical Design, 2009)

Total polyphenols (catechin equivalents, mg/100 g)



Redrawn from: Mattivi F., Dietas Mediterráneas: La evidencia científica, 2004, 99-111

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Dietary Modulation of Gut Microbiota Contributes to Alleviation of Both Genetic and Simple Obesity in Children☆

Chenhong Zhang [a,1], Aihua Yin [b,1], Hongde Li [c,1], Ruirui Wang [a,1], Guojun Wu [a,1], Jian Shen [a,1], Menghui Zhang [a], Linghua Wang [a], Yaping Hou [b], Haimei Ouyang [b], Yan Zhang [b], Yinan Zheng [b], Jicheng Wang [b], Xiaofei Lv [b], Yulan Wang [c], Feng Zhang [a], Benhua Zeng [d], Wenxia Li [d], Feiyan Yan [a], Yufeng Zhao [a], Xiaoyan Pang [a], Xiaojun Zhang [a], Huaqing Fu [a], Feng Chen [a], Naisi Zhao [a], Bruce R. Hamaker [a,i], Laura C. Bridgewater [a,j], David Weinkove [k], Karine Clement [h], Joel Dore [g], Elaine Holmes [e], Huasheng Xiao [l], Guoping Zhao [l], Shengli Yang [a], Peer Bork [f], Jeremy K. Nicholson [e], Hong Wei [d], Huiru Tang [c,*], Xiaozhuang Zhang [b,*], Liping Zhao [a,*]

- Children with Prader-Willi syndrome (PWS), n=17 and children with diet associated “standard” obesity (n=21)

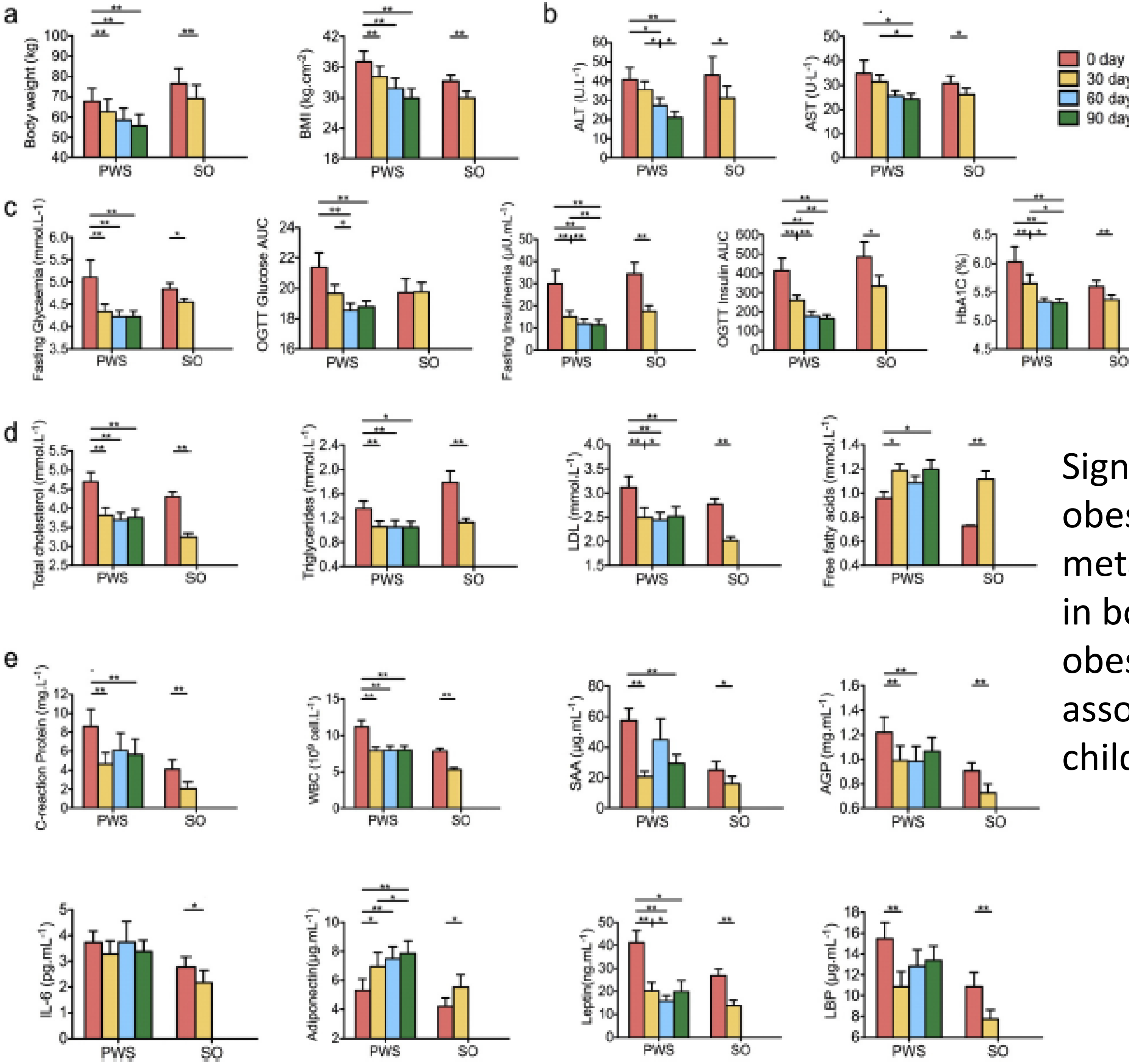
- Weight loss induced by reduced calorie intake and high fiber diet (whole grain/legume “grule”, plus 20g/prebiotic per day)

FONDAZIONE EDMUND MACH CENTRO RICERCA e INNOVAZIONE

Dietary intervention in obese children

	Before	30 day	60 day	90 day
Total Energy Intake	1559.56 (3577.4-916.2)	1232.7 (1992.4-858.3)	1167.9 (1648.8-74.2)	1169.2 (1919.3-940.7)
Protein (g)	46.9 (103.8-19.6)	46.2 (83.1-18.6)	38.2 (61.5-26.1)	36.9 (74.3-20.9)
Protein (%)	13. 6±1.1	13.7±0.5	13.0±0.5	12.7±0.5
Lipid (g)	64.6 (136.5-15.8)	26.6 (40.2-14.0)	25.2 (41.4-18.3)	24.8 (45.8-14.5)
Lipid (%)	34.0±4.0	19.7±0.4***	20.3±0.7***	19.7±0.6***
Carbohydrates (g)	218.3 (484.7-54.8)	191.9 (294.7-141.1)	189.7 (252.4-106.7)	187.1 (261.6-142.9)
Carbohydrates (%)	52.4±4.4	62.4±0.7*	62.6±0.7*	62.5±0.9*
Fiber (g)	6.2 (16.6-1.6)[a]	44.9 (58.7-30.7)[b]	48.5 (59.9-24.4)[b]	49.4 (66.9-37.3)[b]
Soluble fiber (g)	2.7 (7.2-0.7)	29.2 (40.9-10.7)	31.6 (39.3-11.1)	32.7 (45.6-23.7)

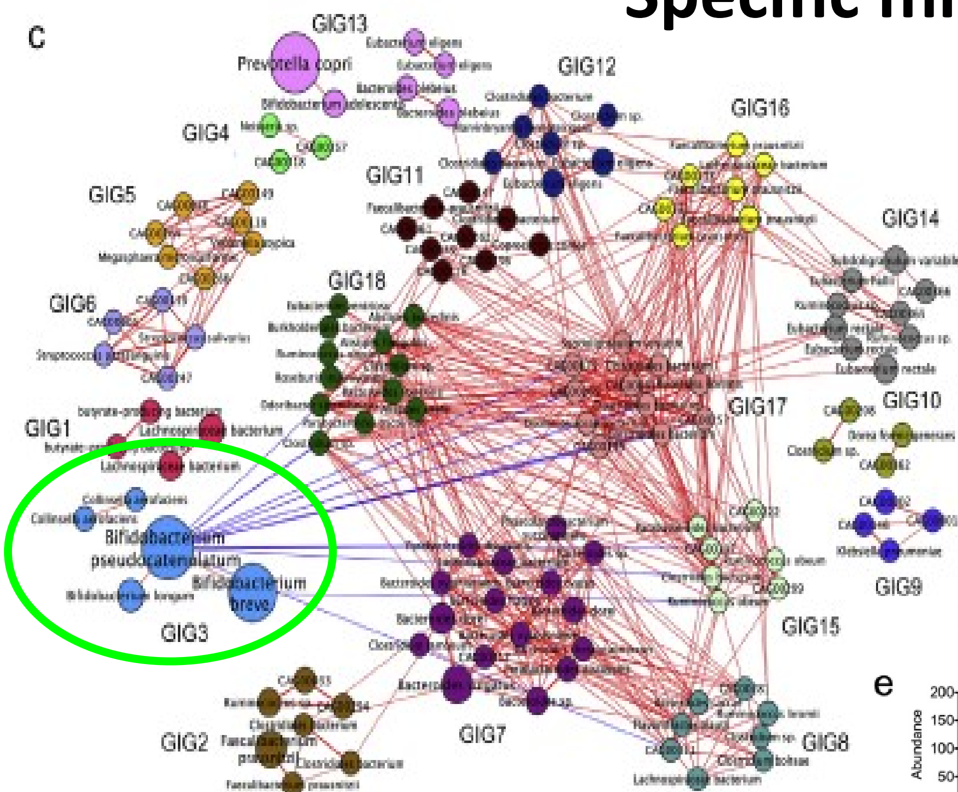
Zhang *et al.*, 2015



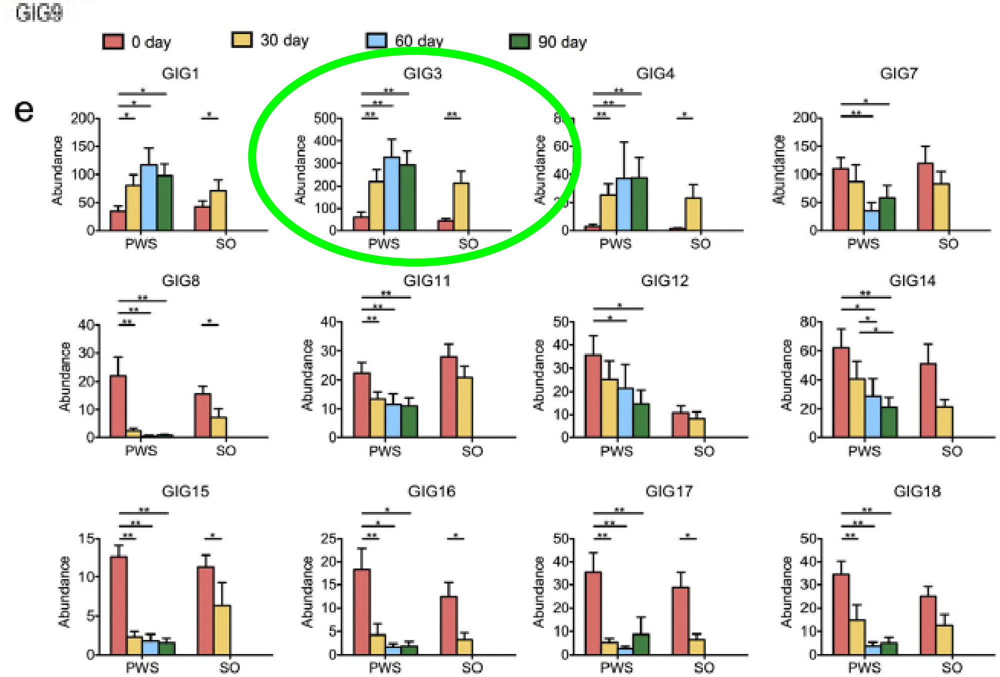
Significantly reduced obesity and improved metabolic parameters in both genetically obese and diet associated obese children.

Zhang *et al.*, 2015

Specific microbiota modulation



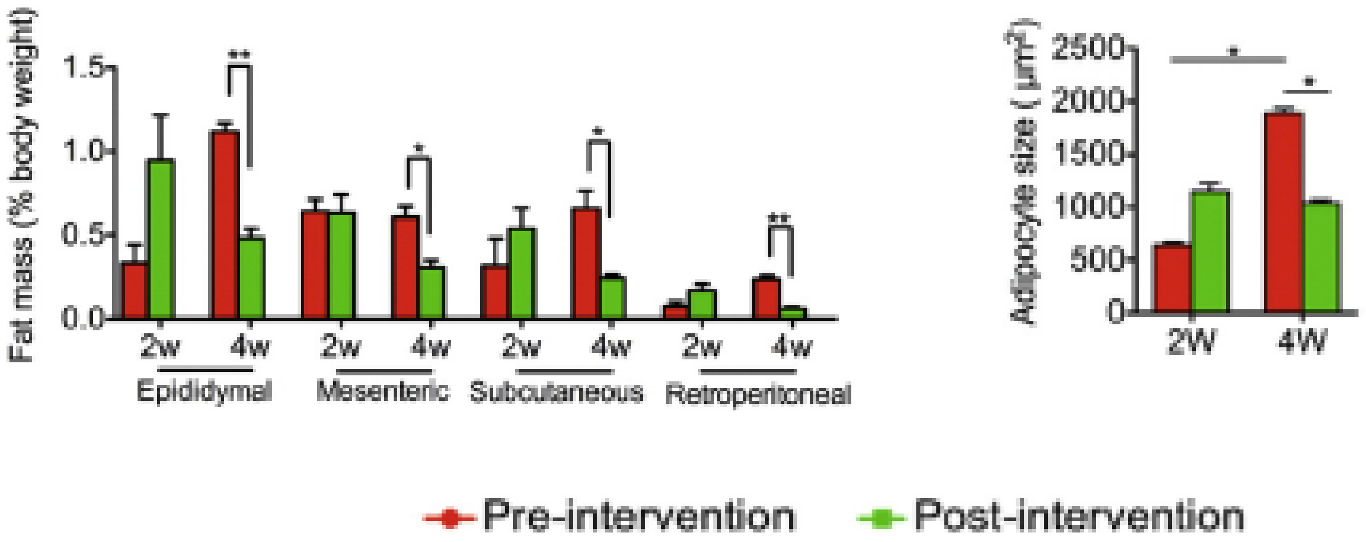
•Dietary interventions reduced relative abundance of organisms involved in TMAO, TRP and choline metabolism



•Dietary interventions modulate gut microbiota (increased relative abundance of *Bifidobacterium* and other fiber degraders.

Zhang *et al.*, 2015

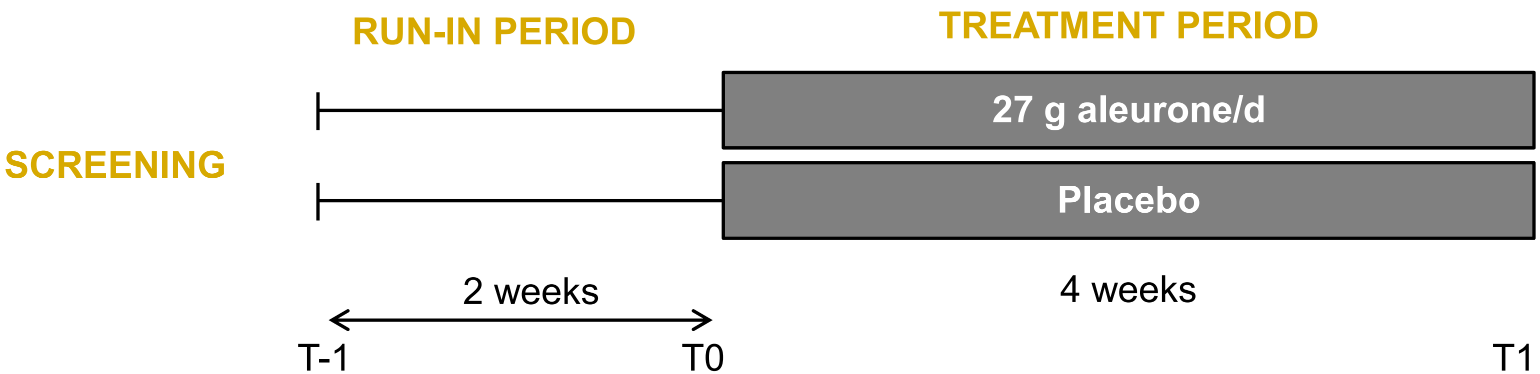
Fat distribution in obese mice after faecal transplant from human donor pre- or post- intervention



Zhang *et al.*, 2015

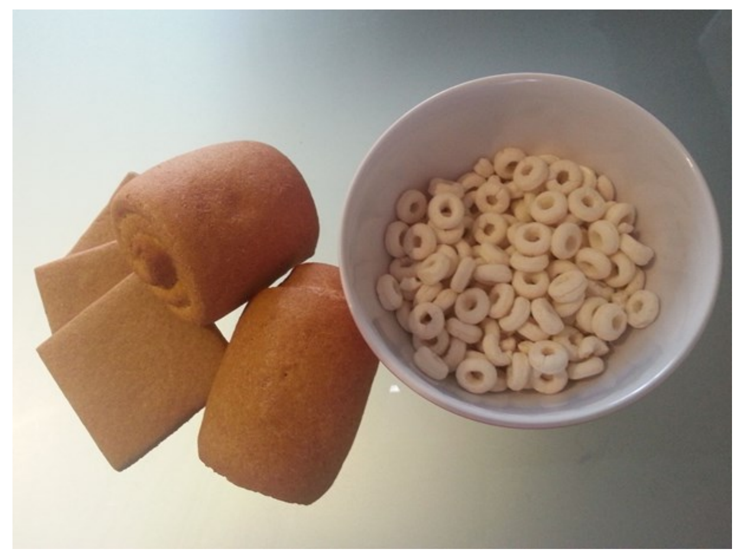
FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

Impact of wheat bran fibre (WBF) on gut microbiota & markers of CVD in overweight adults



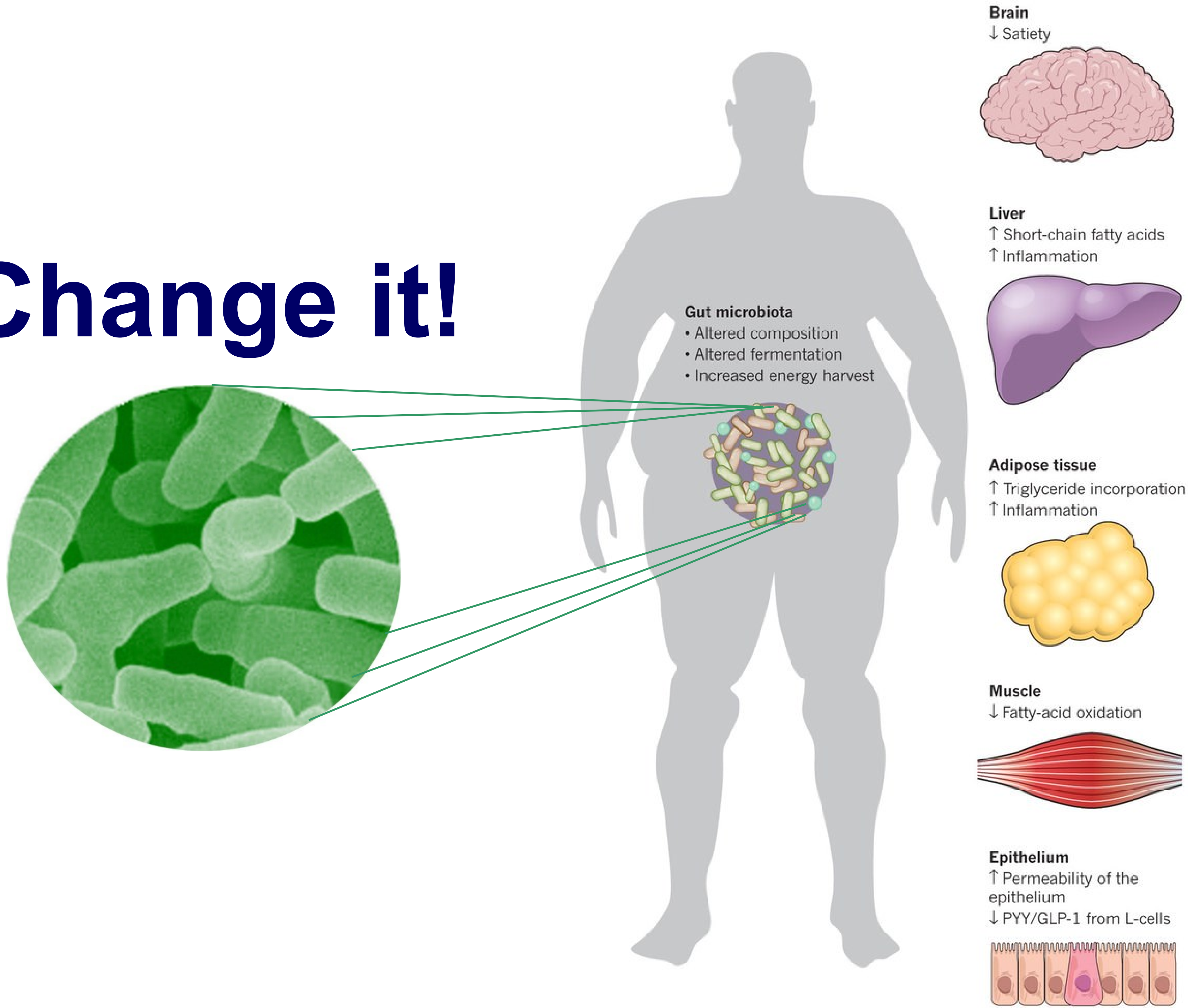
- Subjects: n=34/gp, age 18-65 yrs, BMI > 27
- FEM & Santa Chiara Hospital, TN (Dr Carlo Pedrolli), APSS, Trento
- Biomarkers of CVD risk
- Gut microbiota (Illumina 16S rRNA, FISH)
- MS based metabolomics (targeted and untargeted)

(Supported by Cargill)



ClinicalTrials.gov CFIS-13-001
NCT02067026

Change it!


Gut microbiota
• Altered composition
• Altered fermentation
• Increased energy harvest
Brain
↓ Satiety
Liver
↑ Short-chain fatty acids
↑ Inflammation
Adipose tissue
↑ Triglyceride incorporation
↑ Inflammation
Muscle
↓ Fatty-acid oxidation
Epithelium
↑ Permeability of the epithelium
↓ PYY/GLP-1 from L-cells

European Journal of Clinical Nutrition (2012) 66, 1234–1241

www.nature.com/ejcn

FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

ORIGINAL ARTICLE

Cholesterol lowering and inhibition of sterol absorption by *Lactobacillus reuteri* NCIMB 30242: a randomized controlled trial

ML Jones[1,2], CJ Martoni[2] and S Prakash[1,2]

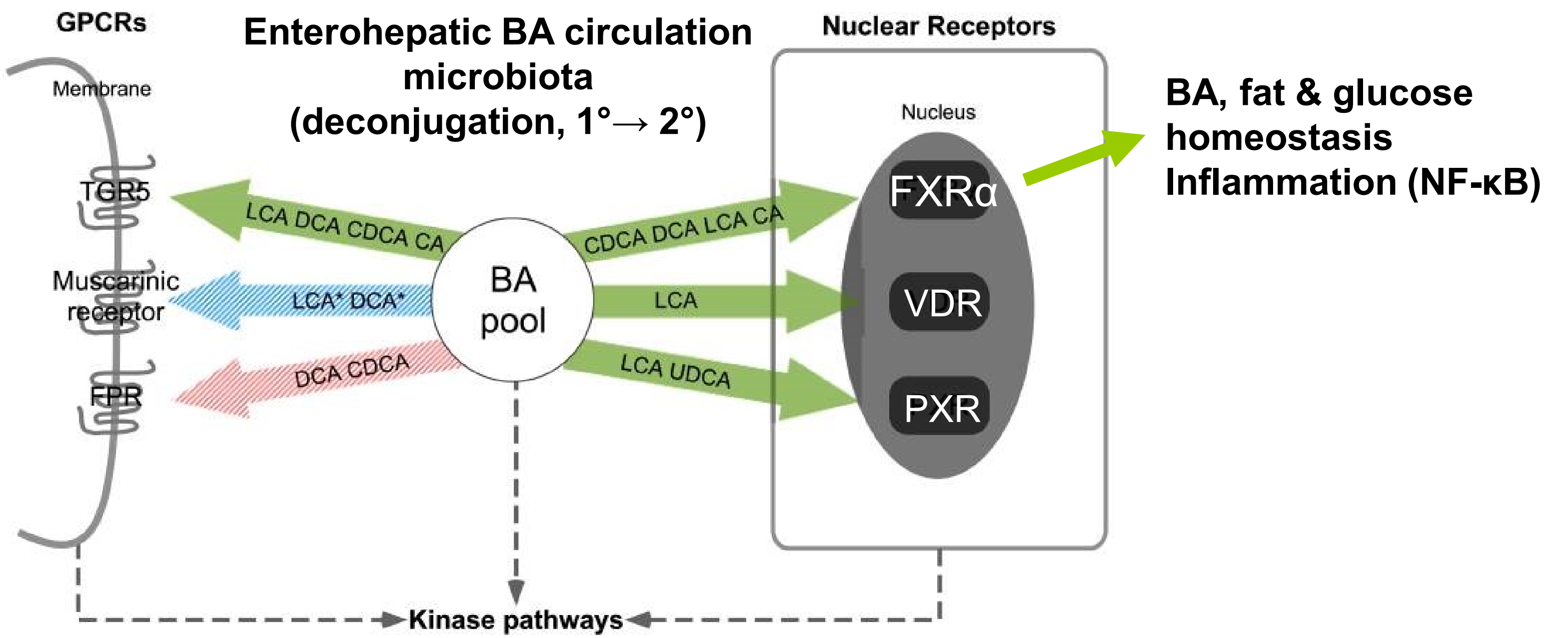
- *Lb. reuteri* selected for Bile Salt Hydrolase activity (2 capsules/day at 2 x 10^9 CFU/capsule) for 9 weeks
- Randomized, double-blind, placebo-controlled, parallel-arm, multicenter study
- N=127 hypercholesterolemic patients
- Probiotic reduced plasma
  - TC by 9.14%
  - LDL-C by 11.64%
  - LDL-C/HDL-C ratio by 13.39%
  - Non-cholesterol plant sterols
  - Increased circulating deconjugated bile acids
- Proposed new cholesterol lowering activity of probiotics via modified absorption of lipids from the gut

The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation

Thijs W.H. Pols, Lilia G. Noriega, Mitsunori Nomura, Johan Auwerx, Kristina Schoonjans*

Laboratory of Integrative and Systems Physiology (LISP), Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

Journal of Hepatology (2011)

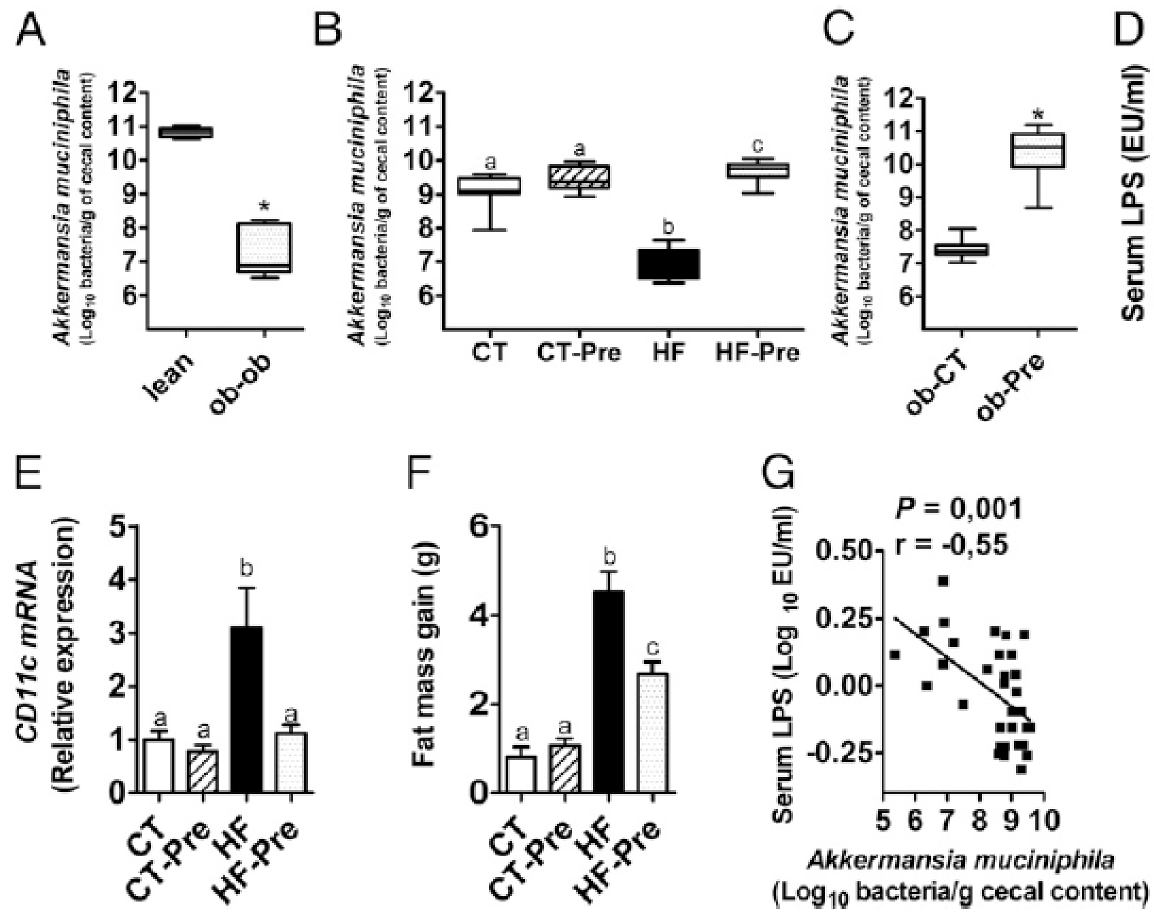


Cell type	Species	Cellular action	References
Macrophages*	Human / Rabbit / Rat	Inhibition of cytokine production	[62, 68]
Enteroendocrine cells	Human / Mouse	Secretion of GLP-1	[71, 79]
Brown adipocytes	Mouse	Increase in energy expenditure	[69]
Sketelal muscle cells	Human	Increase in energy expenditure	[69]
Sinusoidal endothelial cells	Rat	Regulation of endothelial NO synthase	[67]
Biliary epithelial cells	Mouse	Promotion of chloride secretion	[65]
Astrocytes	Rat	Generation of ROS	[101]
Enteric neurons	Mouse	Release of NO and suppression of intestinal motility	[70]
Gallbladder smooth muscle cells	Mouse	Decrease of gallbladder smooth muscle cell function	[73]

Table 1. Cellular actions described for TGR5 in different cell types. ∗Macrophages include alveolar macrophages, Kupffer cells and THP-1 cells.

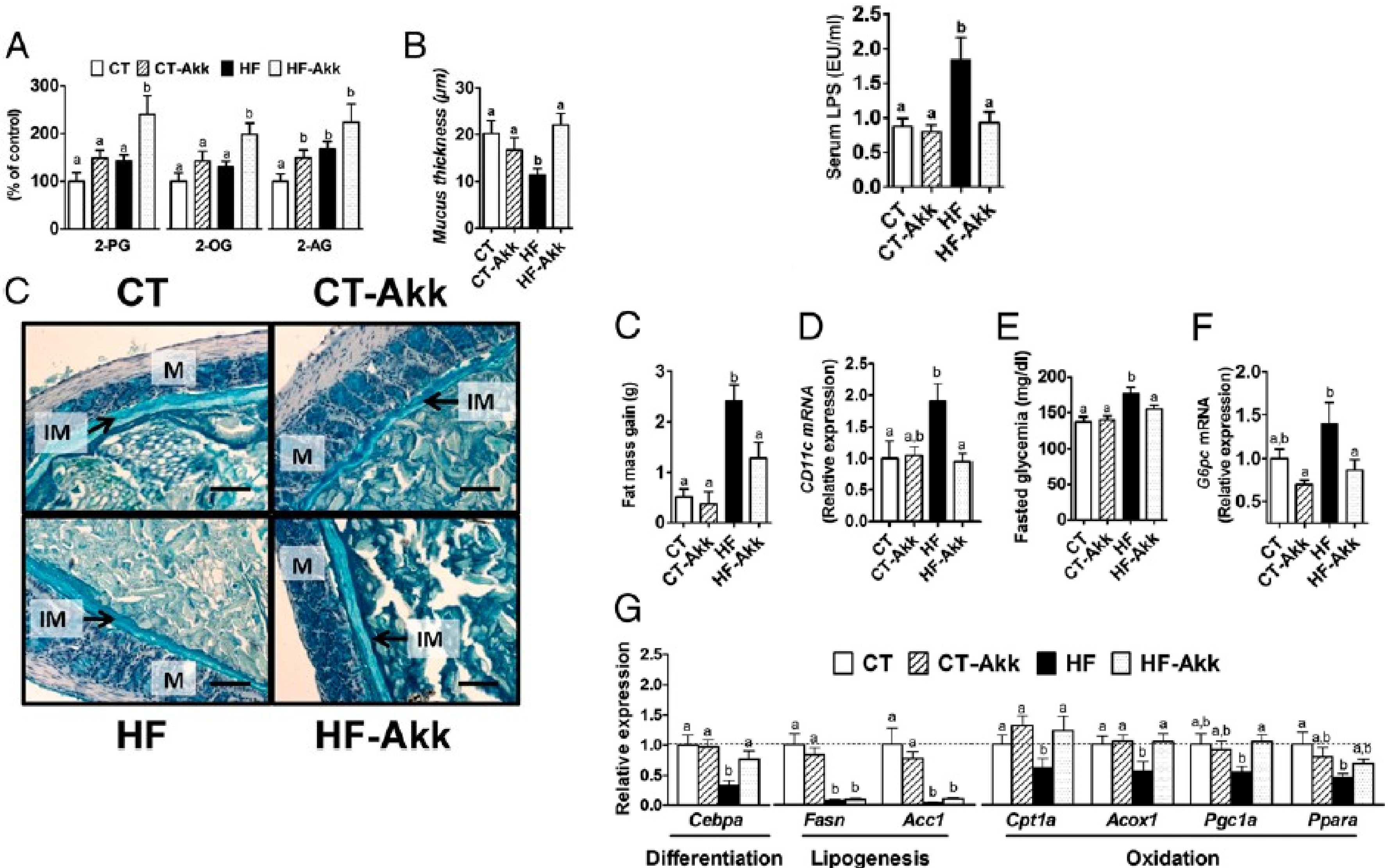
Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity

Amandine Everard[a], Clara Belzer[b], Lucie Geurts[a], Janneke P. Ouwerkerk[b], Céline Druart[a], Laure B. Bindels[a], Yves Guiot[c], Muriel Derrien[b], Giulio G. Muccioli[d], Nathalie M. Delzenne[a], Willem M. de Vos[b,e], and Patrice D. Cani[a,1]

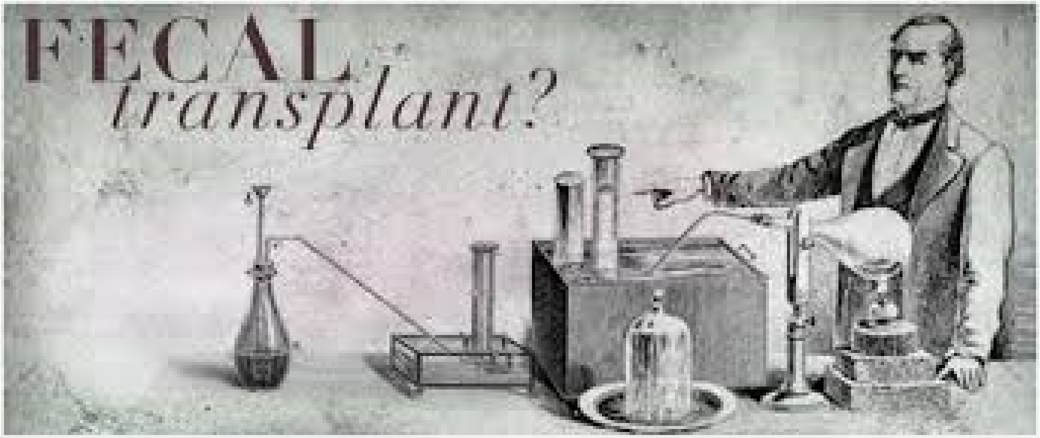


Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity

Amandine Everard[a], Clara Belzer[b], Lucie Geurts[a], Janneke P. Ouwerkerk[b], Céline Druart[a], Laure B. Bindels[a], Yves Guiot[c], Muriel Derrien[b], Giulio G. Muccioli[d], Nathalie M. Delzenne[a], Willem M. de Vos[b,e], and Patrice D. Cani[a,1]



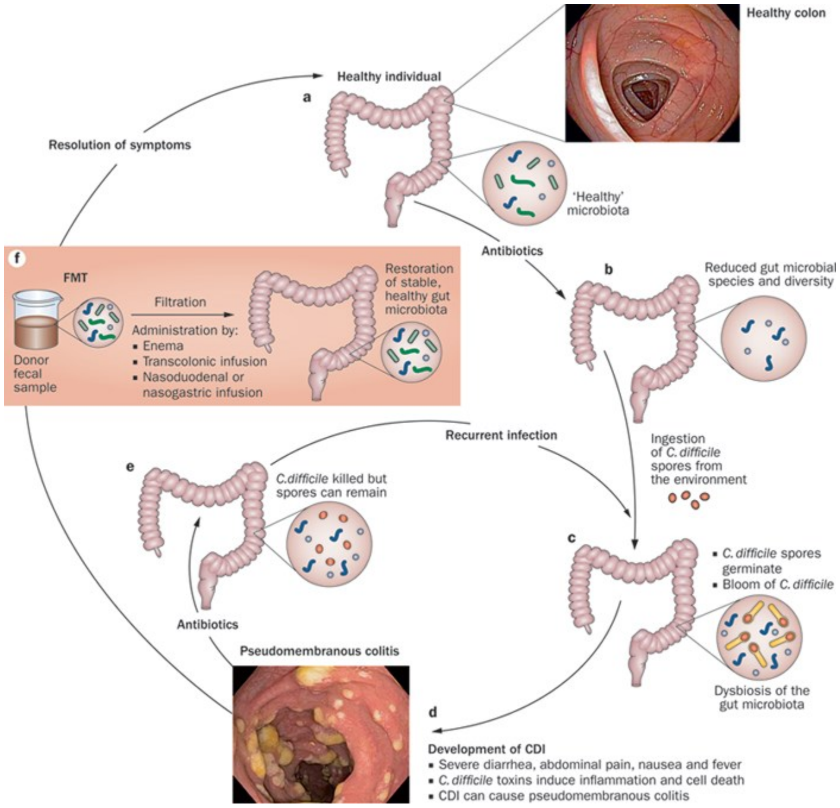
Swap it!



http://www.openbiome.org/about-fmt

FONDAZIONE EDMUND MACH
CENTRO RICERCA e INNOVAZIONE

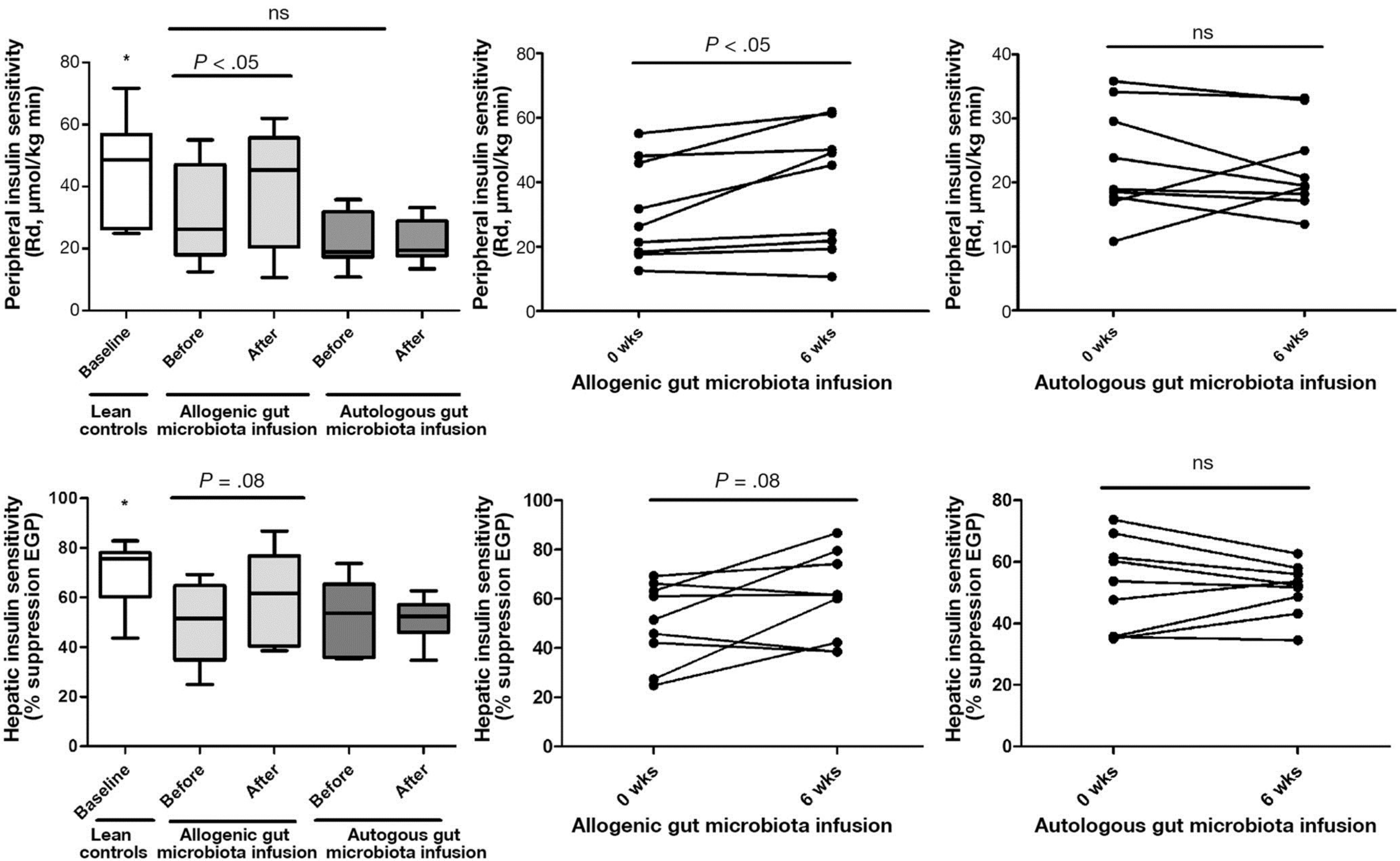
Figure 1 FMT for patients with recalcitrant CDI



Borody, T. J. & Khoruts, A. (2011) Fecal microbiota transplantation and emerging applications
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2011.244

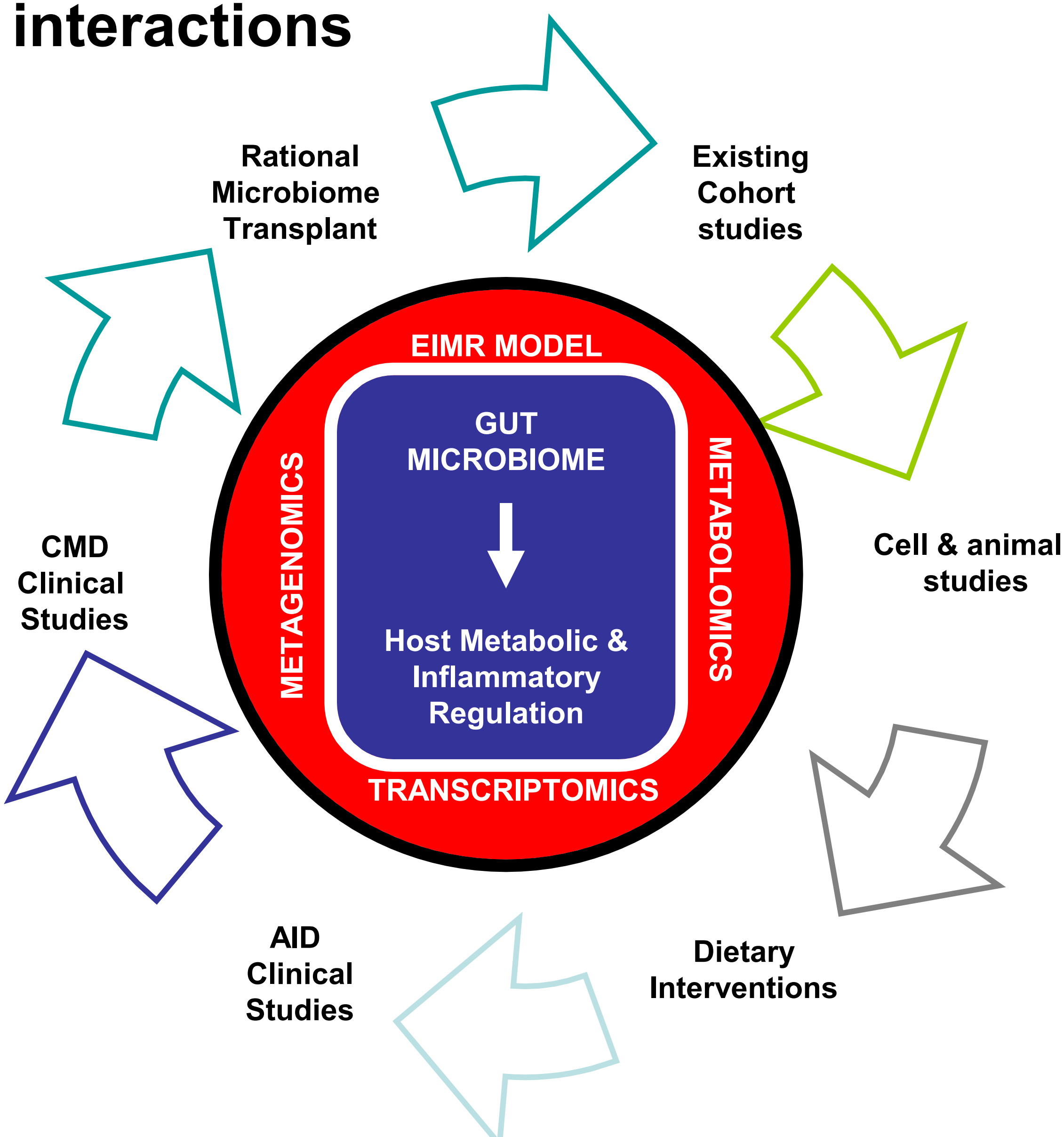
nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome.



Vrieze et al. 2012 Gastroenterology143(4):913-6.e7.

Ecosystem level immune and metabolic regulatory (EIMR) model of diet:microbe:host interactions



- Rational faecal microbiome transplant
- Mechanistically driven probiotics & prebiotics
- Mechanisms of effect for diet in health & disease
  - how fiber and polyphenols work
- Personalised nutrition
  – me and my bugs!

Fondazione Edmund Mach

- Thank you

- Fulvio Mattivi, Davide Albanese, Claudio Donati, and Roberto Viola, FEM-IASMA

- NN Group: Lorenza Conterno, Francesca Fava, Elena Franciosi, Carlotta de Filippo, Maria Lima, Athanasios Koutsos, Ilaria Caraffa, Andrea Machini