PROSPETTIVE DI INTERVENTI TERAPEUTICI SUL MICROBIOTA NEL DIABETE TIPO 1 E TIPO 2

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CONFLITTI DI INTERESSE

il relatore dichiara che negli ultimi due anni non ha avuto rapporti di finanziamento con soggetti portatori di interessi in campo sanitario

The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities

Louise Brunkwall[1] · Marju Orho-Melander[1]

Diabetologia

Published online: 22 April 2017

Current human evidence

Dysbiotic microbiota

Slightly altered overall bacterial composition

↓ Butyrate-producing bacteria

↓ *A. muciniphila*

↑ Serum BCAAs via *P. copri* and *B. vulgatus*

Glucose-lowering medication

↑ *Lactobacillus* and *Escherichia* species with metformin

Diet

↑ *Prevotella* with high-fibre diet in some individuals

Gut microbial composition may be used to identify responders to dietary interventions

Bariatric surgery

Effects on bacterial composition may play a role in the BMI-independent effects of surgery on glucose metabolism

Future possibilities and challenges

Personalised nutrition and probiotic use

Synergistic approach: diet, probiotics and microbiota

Need for further studies of: (1) impact of habitual dietary intake on response; (2) single vs multiple probiotic strain effects; (3) use as an adjunct to glucose-lowering drugs

Targeted colonic delivery of SCFAs

No need for high intake of indigestible fibres/responsive gut microbiota

Targeted delivery of propionate decreases energy intake and improves glucose metabolism

Pasteurised probiotics

Enables production of probiotics of oxygen-sensitive anaerobic bacteria

Pasteurised *A. muciniphila* improves glucose metabolism in mice: human studies needed

Genetically modified bacteria

Recombinant bacteria can express therapeutic factors in microbiota

L. lactis modified to produce GLP-1, leading to improved glucose metabolism in mice: human studies needed

FMT

Little evidence for improved glycaemic control

Can potential risks be eliminated?

.....BIOTICI

PRE-BIOTICI: sostanze non digeribili di origine alimentare che, assunte in quantità adeguata, favoriscono selettivamente la crescita e l'attività di uno o più ceppi batterici già presenti nel tratto intestinale o assunti assieme al prebiotico. (Es: inulina, frutto-oligosaccaridi)

PRO-BIOTICI: microrganismi che si dimostrano in grado, una volta ingeriti in adeguate quantità, di esercitare funzioni benefiche per l'organismo ospite.

SIMBIOTICI: associazione di un probiotico con un prebiotico.

Probiotics and Prebiotics: Present Status and Future Perspectives on Metabolic Disorders

Nutrients **2016**, *8*, 173; doi:10.3390/nu8030173

Intervention Type	Name of Pro/Prebiotic Strains	Study Type	Pro/Prebiotic Type and Dose (Per Day)	Duration of Intervention	Outcomes	Parameter without Change	Reference
Probiotics	*Bacillus*, *Lactobacillus*, *Streptococcus*, *Clostridium*, *Saccharomyces*, *Candida*	Rats	Rice bran (10^7 CFU/g) 30 g/kg	4 weeks	Decreased serum total cholesterol Increase Δ6-desaturase activity and serum arachidonic acid		Fukushima *et al.*, 1999 [74]
Probiotics	*B. lactis* Bb-12, *B. longum* Bb-46	Rats	Buffalo milk yoghurt and soy-yoghurt	4 weeks	Decreased total cholesterol and LDL-C Increasedfecal excretions of bile acids		Abd El-Gawad *et al.*, 2005 [75]
Probiotics	*L. plantarum* PH04	Mice	Human isolate (10^7 CFU/day)	14 days	Decreased total cholesterol and TG Increased fecal lactic acid bacteria		Nguyen *et al.*, 2007 [76]
Probiotics	*L. acidophilus*, *L. casei*, *L. lactis biovar diacetylactis*	Rats	Dahi 15% (150g/kg)	8 weeks	Decreased glucose intolerance, hyperglycemia, hyperinsulinemia, dyslipidemia and oxidative stress	HDL-C	Yadav *et al.*, 2007 [70]
Probiotics	*L. acidophilus* NCDC14, *L. casei* NCDC19	Rats	Dahi (73×10^8 CFU/g)	28 days	Inhibition of insulin depletion, lipid peroxidation and nitrite formation		Yadav *et al.*, 2008 [69]
Probiotics	*B. animalis lactis* 420	Mice	(10^9 CFU/day)	6 weeks	Decreased glucose intolerance, tissue inflammation, insulin resistance and secondarily glycaemia		Amar *et al.*, 2011 [48]
Prebiotics	*Inulin*	Rats	5%	4 weeks	Decrease LDL-C, total cholesterol, Liver lipid and TG concentrations Increased HDL-C, and faecal excretions of bile acids		Kim *et al.*, 1998 [77]

Abbreviations: Bifidobacterium (B), lactobacillus (L), streptococcus (S), colony forming units (CFU), tab (tablet), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL-C), triglycerides (TG).

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Probiotics	*L. acidophilus* L1,	Human	Fermented milk 200 mL/day	4 weeks	Decreased total cholesterol		Anderson *et al.*, 1999 [78]
Probiotics	*B. longum* BL1	Human/Rats	Fermented milk 100 mL/3 ×day	4 weeks	Decreased total cholesterol, LDL-C and TG	HDL-C	Xiao *et al.*, 2003 [79]
Probiotics	*L. acidophilus* LA-1	Human	Freeze-dried Two tablet/day (3×10^3 CFU/tab)	6 weeks		Total cholesterol, HDL-C, LDL-C, TG	Lewis *et al.*, 2005 [73]
Probiotics	*L. fermentum*	Human	Freeze-dried Two tablet/2 × day (2×10^9 CFU/tab)	10 weeks		Total cholesterol, HDL-C, LDL-C, TG liver enzymes	Simons *et al.*, 2006 [80]
Probiotics	*L. casei subsp. casei.*	Human	Yogurt 100 g/day and 200 g/day	6 weeks	Decreased total cholesterol and LDL-C Increased HDL-C		Fabian *et al.*, 2006 [81]
Probiotics	*L. rhamnosus* LC705, *Propionibacterium freudenreichiissp shermaniistrain* JS	Human	Two tablet/day (2×10^{10} CFU/tab)	4 weeks		Total cholesterol, HDL-C, LDL-C, TG	Hatakka *et al.*, 2008 [82]
Probiotics	*L. acidophilus* La5, *B. lactis* Bb12	Human	Yogurt 300 g/day (2×10^6 CFU/g)	6 weeks	Decreased total cholesterol and LDL-C	HDL-C, TG	Ejtahed *et al.*, 2011 [22]
Probiotics	*L. acidophilus* La5, *B. lactis* Bb12	Human	Yogurt containing 300 g/day (2×10^6 CFU/g)	6 weeks	Decreased fasting blood glucose levels and HbA_1c, Increased erythrocyte superoxide dismutase, glutathione peroxidase activities and total antioxidantstatus	Insulin concentration	Ejtahed *et al.*, 2012 [68]
Probiotics	*L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, *S. thermophiles*	Human	Freeze-dried One tablet/day (14×10^9 CFU/tab)	8 weeks	Decreased serum hs-CRP Increased plasma total GSH Prevention of a rise in fasting plasma glucose		Asemi *et al.*, 2013 [67]

Probiotics and Prebiotics: Present Status and Future Perspectives on Metabolic Disorders

Nutrients **2016**, *8*, 173; doi:10.3390/nu8030173

Intervention Type	Name of Pro/Prebiotic Strains	Study Type	Pro/Prebiotic Type and Dose (Per Day)	Duration of Intervention	Outcomes	Parameter without Change	Reference
Probiotics Prebiotics	*L. casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, *S. thermophiles*, *Fructooligosaccharid-e*	Human	One tablet/day 500 mg/tab	8 weeks	Positive effects on systolic blood pressure	Total cholesterol, LDL-C, HDL-C TG, TG/LDL and LDL/HDL ratios	Mahboobi *et al.*, 2014 [71]
Prebiotics	*Inulin*	Human	Rice-based ready-to-eat cereal (18%)	4 weeks	Decreased total cholesterol and TG Increased breath H2 excretion and fecal lactic acid		Brighenti *et al.*, 1995 [83]
Prebiotics	*Inulin*	Human	One pint of vanilla ice cream (20 g/pint)	3 weeks	Decreased total cholesterol and TG		Causey *et al.*, 2004 [84]

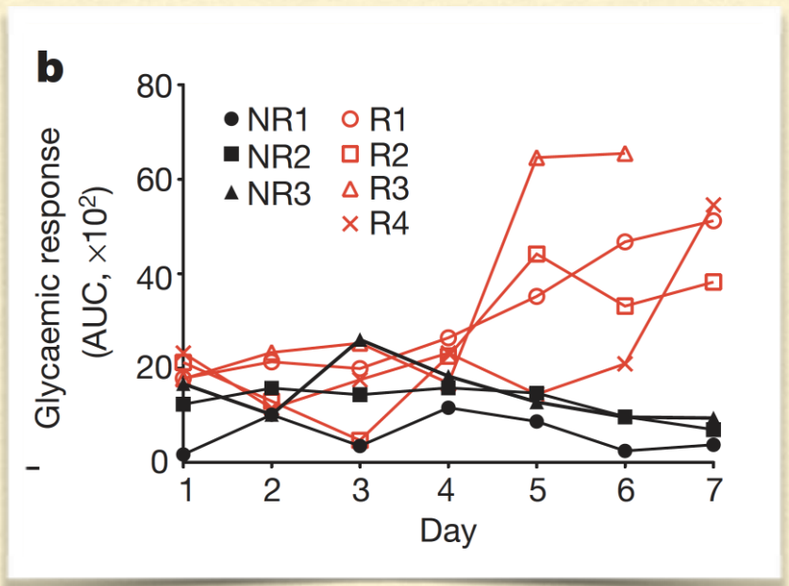
Abbreviations: Bifidobacterium (B), lactobacillus (L), streptococcus (S), colony forming units (CFU), tab (tablet), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL-C), triglycerides (TG).

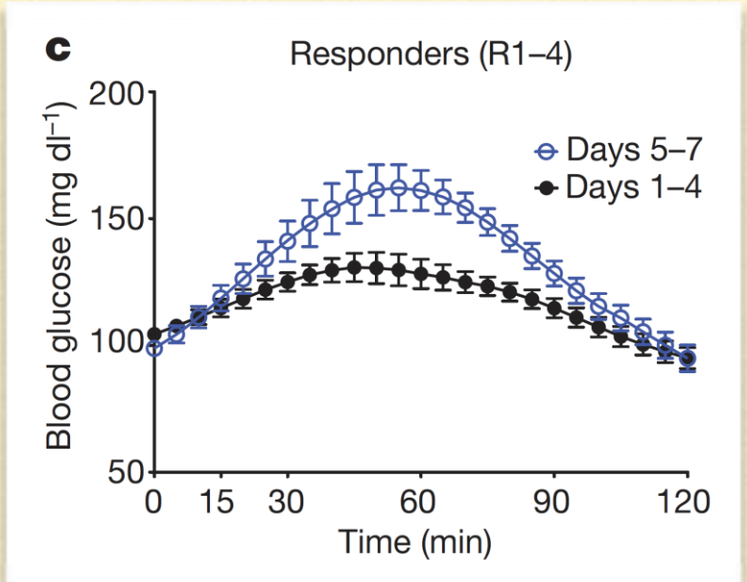
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

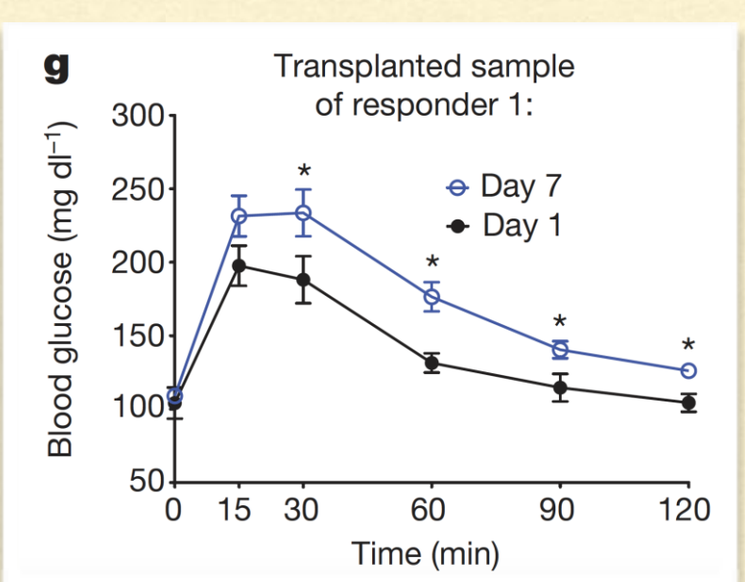
Jotham Suez[1], Tal Korem[2]*, David Zeevi[2]*, Gili Zilberman-Schapira[1]*, Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]

doi:10.1038/nature13793

- stimolano l'insulino resistenza
- effetto annullabile con la terapia antibiotica: A) gram - (ciprofloxacina e metronidazolo) e B) gram + (vancomicina)
- trasferibile con il trapianto di feci nei topi germi free





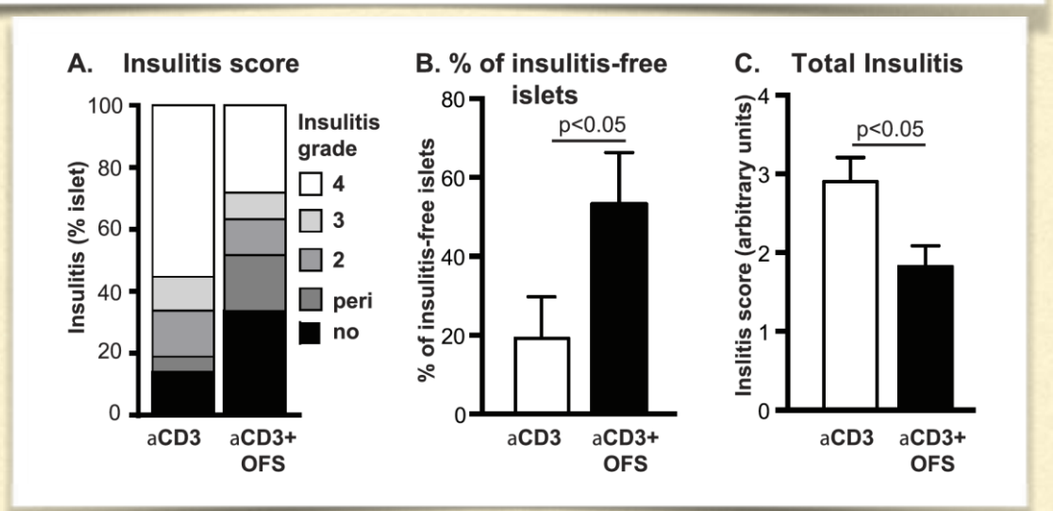


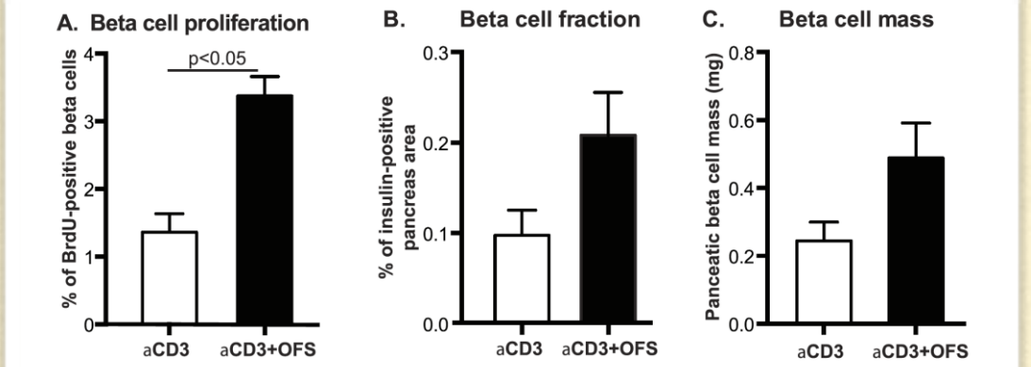
Oligofructose as an adjunct in treatment of diabetes in NOD mice

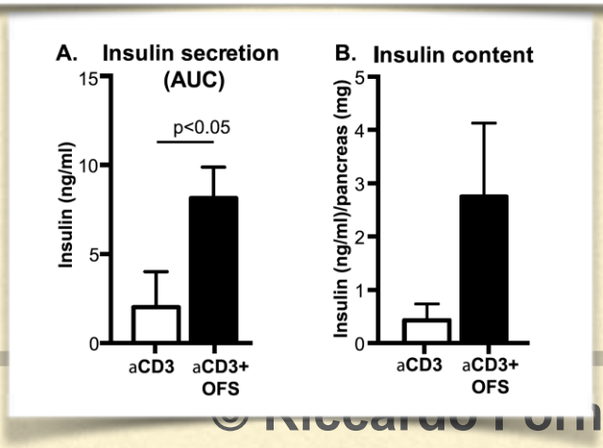
Clement Chan[1], Colin M. Hyslop[1], Vipul Shrivastava[1], Andrea Ochoa[1], Raylene A. Reimer[1,2] & Carol Huang[1,3]

SCIENTIFIC REPORTS | 6:37627 | DOI: 10.1038/srep37627

- OFS (fibre simili all'inulina) viene fermento con produzione di SCFA con stimolazione del GLP-1, aumentano in modo dose dipendente i bifidobatteri e migliorano la tolleranza glicidica
- Trt topi NOD con AbCD3 con +/- OFS
- i topi trattati con OFS avevano minor aggressione immunitaria e un miglior funzionamento delle B cell (aumento della secrezione di insulina in risposta al carico di glucosio)







Specific inulin-type fructan fibers protect against autoimmune diabetes by modulating gut immunity, barrier function, and microbiota homeostasis

Mol. Nutr. Food Res. 0, 0, 2017,

Kang Chen[1], Hao Chen[1], Marijke M. Faas[2], Bart J. de Haan[2], Jiahong Li[1], Ping Xiao[3], Hao Zhang[1], Julien Diana[4,5], Paul de Vos[2] and Jia Sun[1,6]**

- la somministrazione di fibre inuliniche lunghe estratte da radici di cicoria in topi NOD per 24 settimane:

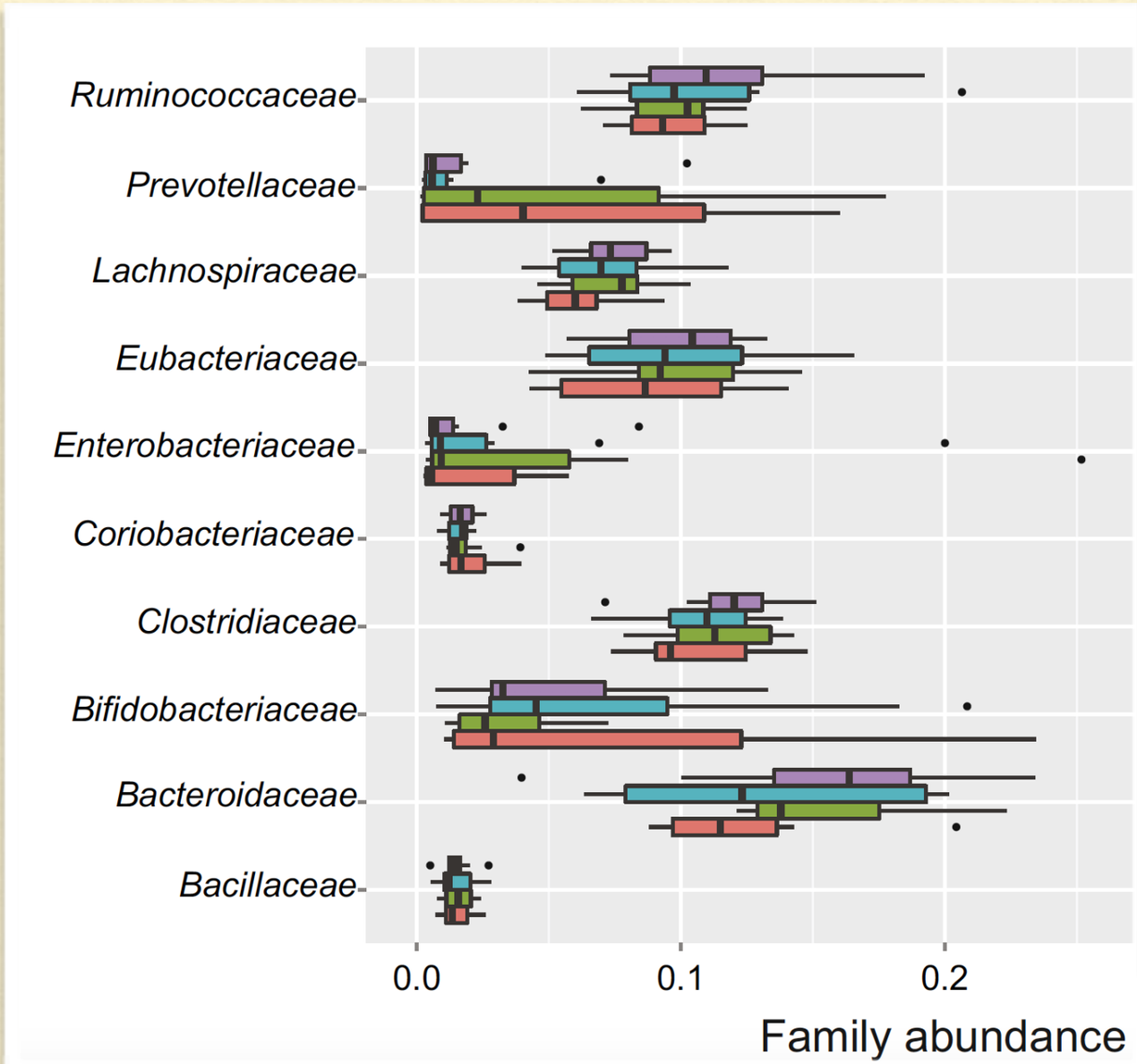
- 1) migliora l'omeostasi del microbiota (aumento della produzione di SCFA segno di migliore biodiversità e stabilità del microbiota)

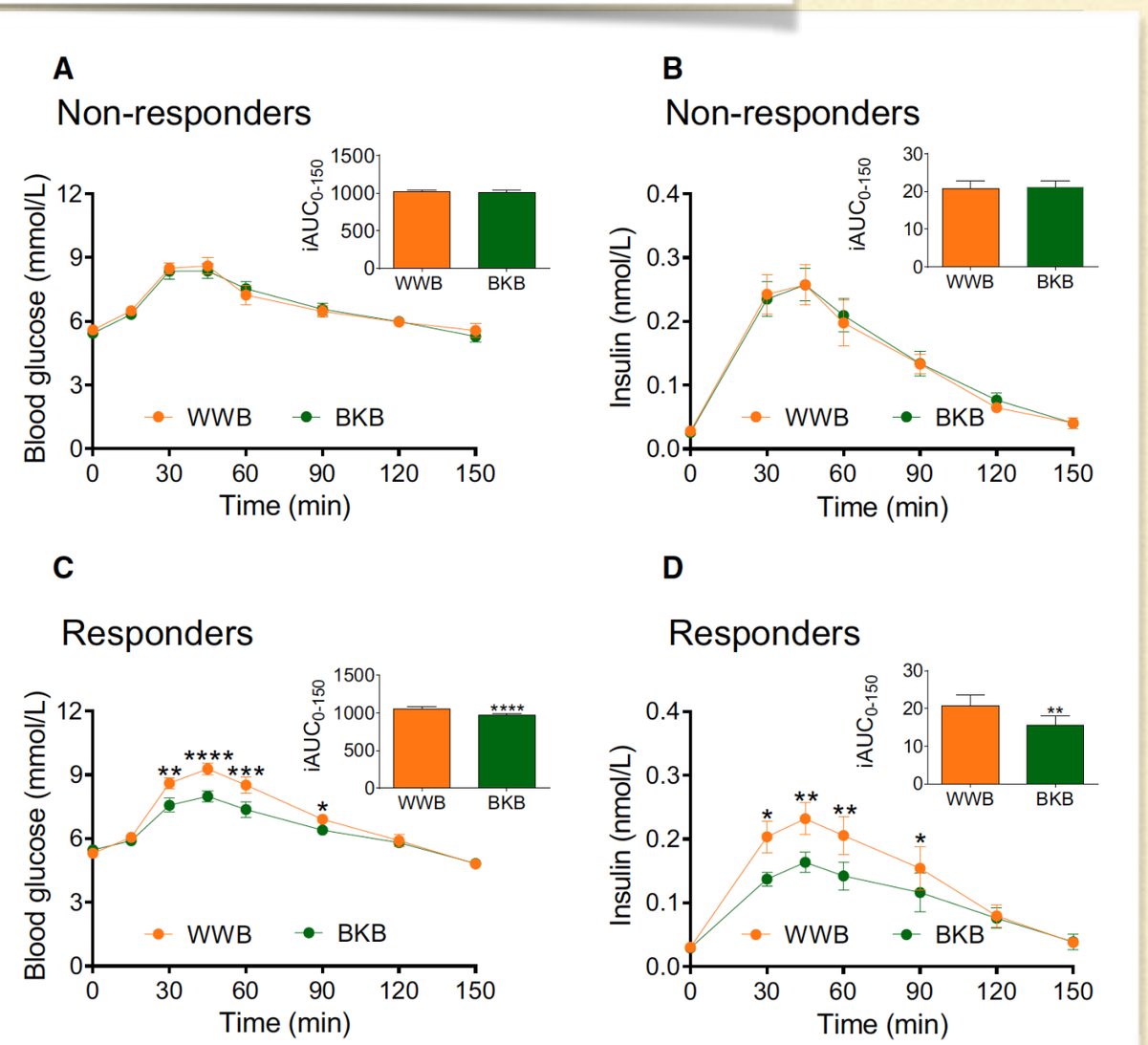
- 2) migliora le barriere funzionali intestinali (TJ)

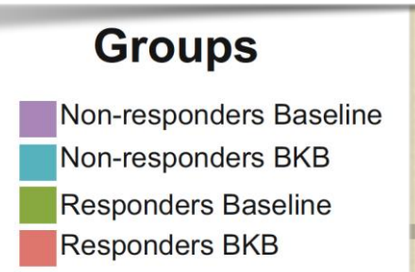
- 3) modula la risposta dei T-cell, con assenza di infiltrazione infiammatoria e ridotta infiltrazione

- 4) Riduzione dell'incidenza di DMT1 nei topi NOD

Dietary Fiber-Induced Improvement in Glucose Metabolism Is Associated with Increased Abundance of *Prevotella*







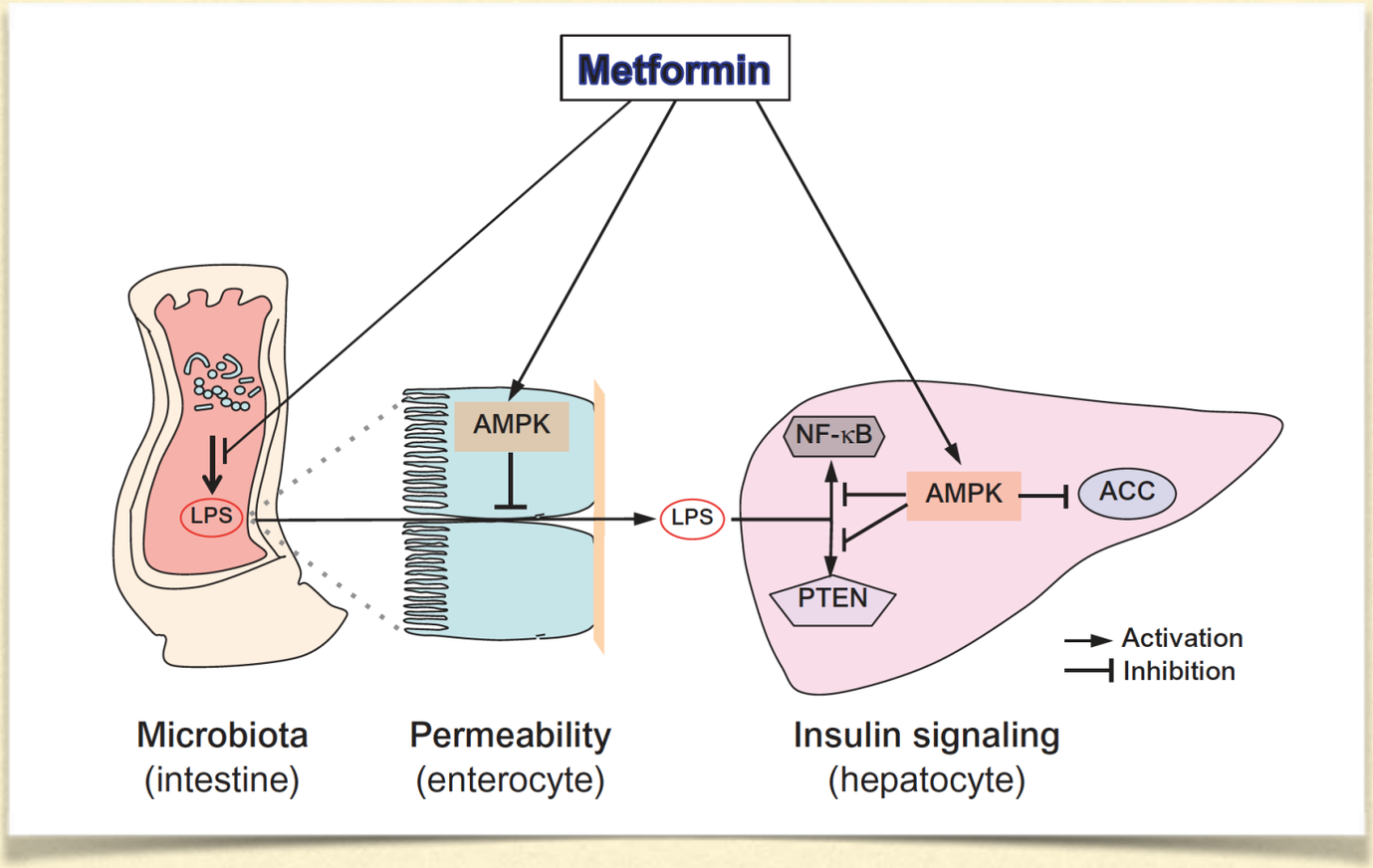
Cell Metabolism *22*, 971–982, December 1, 2015

Current understanding of metformin effect on the control of hyperglycemia in diabetes

Hongying An and Ling He

Journal of Endocrinology
(2016) **228**, R97–R106

- **INTESTINO**: riduzione della sintesi di LPS
- **PARETE**: attivazione AMPK con miglioramento dell'integrità della parete
- **FEGATO**: attivazione di AMPK con inibizione dell'infiammazione



Metformin Is Associated With Higher Relative Abundance of Mucin-Degrading *Akkermansia muciniphila* and Several Short-Chain Fatty Acid–Producing Microbiota in the Gut

Diabetes Care 2017;40:54–62

il microbiota cambia con l'uso della metformina

Aumento della Akkermansia muciniphila (ridotta nei soggetti con prediabete e nei soggetti con DMT2. Biomarker per intolleranza glucidica?)

Aumento dei batteri SCFA produttori (Es: provetella)

Aumento degli Escherichia (probabilmente implicati negli effetti collaterali GI della met: aumentano la produzione di gas)

A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice

published online 28 November 2016

- Gli effetti positivi dell'Akkermansia Muciniphila (A.M.) permangono anche se coltivata in medium sintetici adatti alla somministrazione umana

- A.M. pastorizzata induce diminuzione della massa grassa, migliora l'insulino sensibilità e la dislipidemia nei topi

- AMUC_1100 (proteina di superficie dell'A.M.) può essere pastorizzata e induce un miglioramento delle barriere intestinali e una diminuzione della massa grassa, migliora l'insulino sensibilità e la dislipidemia nei topi

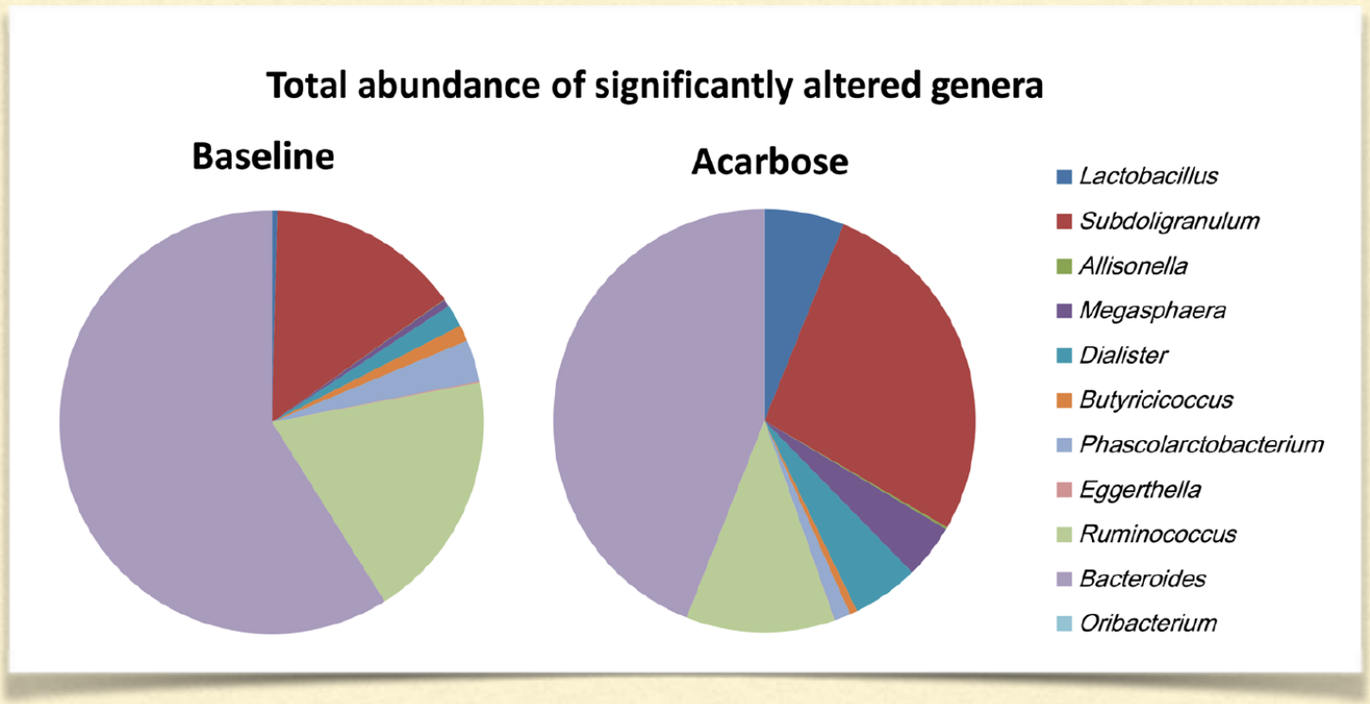
- La somministrazione di A.M. coltivata su medium sintetico viva o pastorizzata è SAFE nell'uomo

NATURE MEDICINE ADVANCE ONLINE PUBLICATION

Effects of Acarbose on the Gut Microbiota of Prediabetic Patients: A Randomized, Double-blind, Controlled Crossover Trial

Diabetes Ther
DOI 10.1007/s13300-017-0226-y

Xiuying Zhang · Zhiwei Fang · Chunfang Zhang · Huihua Xia · Zhuye Jie · Xueyao Han · Yingli Chen · Linong Ji



pochi pazienti

dose tra i 50 e 150 die

solo popolazione cinese

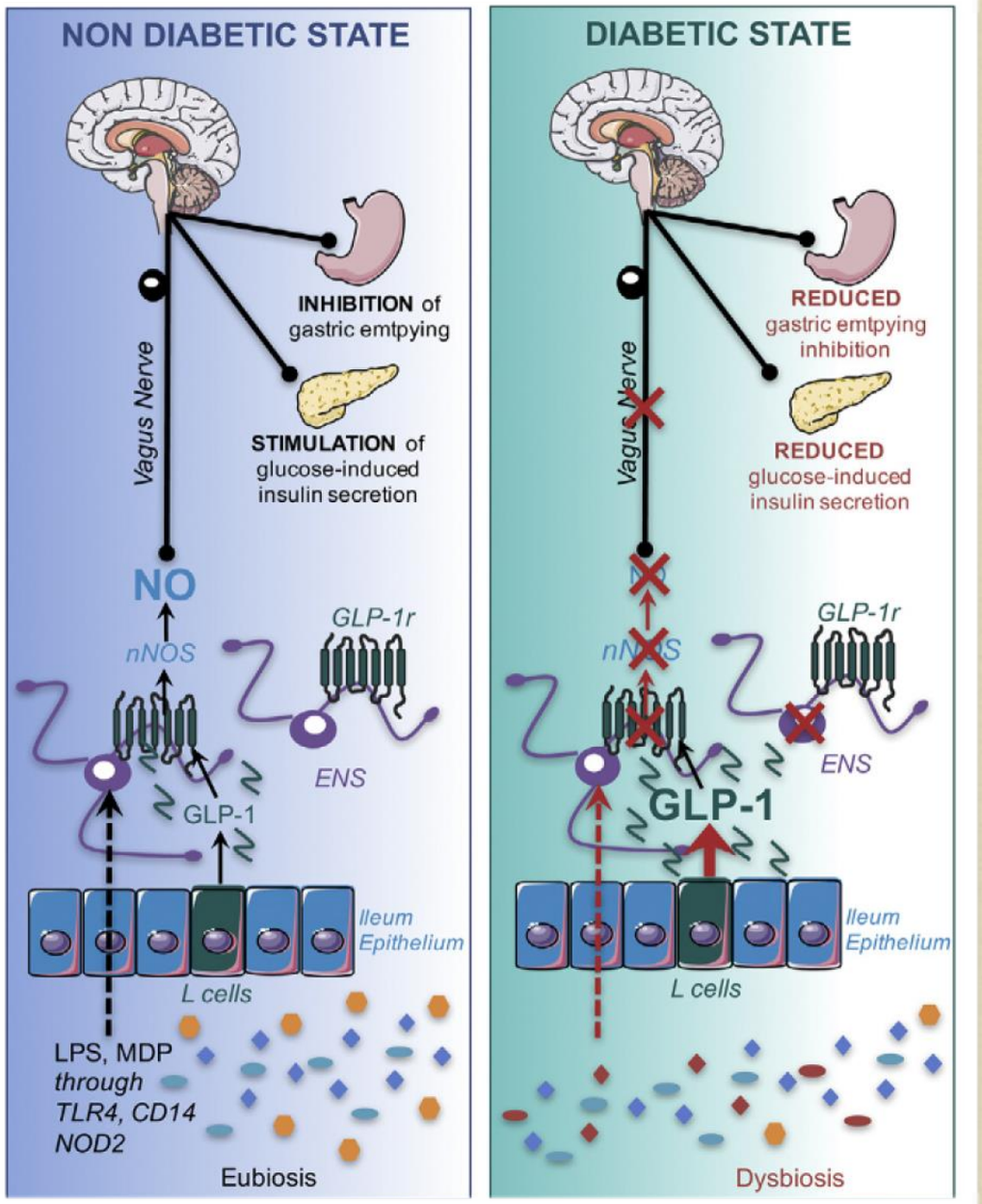
Problemi alimentazione

migliora la composizione microbiotica

Cell Metabolism *25*, 1075–1090, May 2, 2017

A Specific Gut Microbiota Dysbiosis of Type 2 Diabetic Mice Induces GLP-1 Resistance through an Enteric NO-Dependent and Gut-Brain Axis Mechanism

Estelle Grasset,[1,2] Anthony Puel,[1,2] Julie Charpentier,[1,2] Xavier Collet,[1,2] Jeffrey E. Christensen,[1,2] François Tercé,[1,2] and Rémy Burcelin[1,2,3,*]



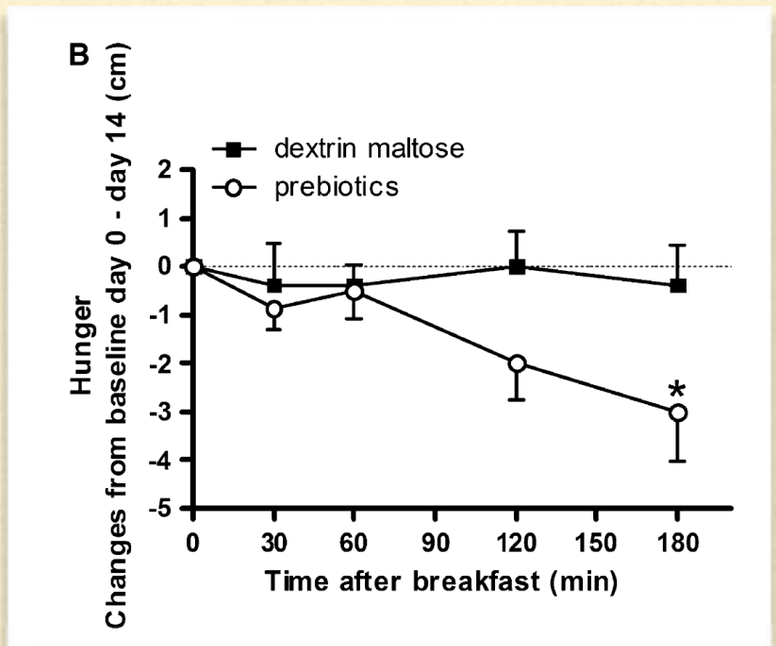
- la disbiosi del microbiota induce una resistenza all'azione del GLP-1
- questo studio potrebbe spiegare la resistenza al trattamento con GLP-1 che osserviamo in alcuni pazienti
- Alcuni pattern microbiotici sono correlati con una riduzione dei GLP-1r

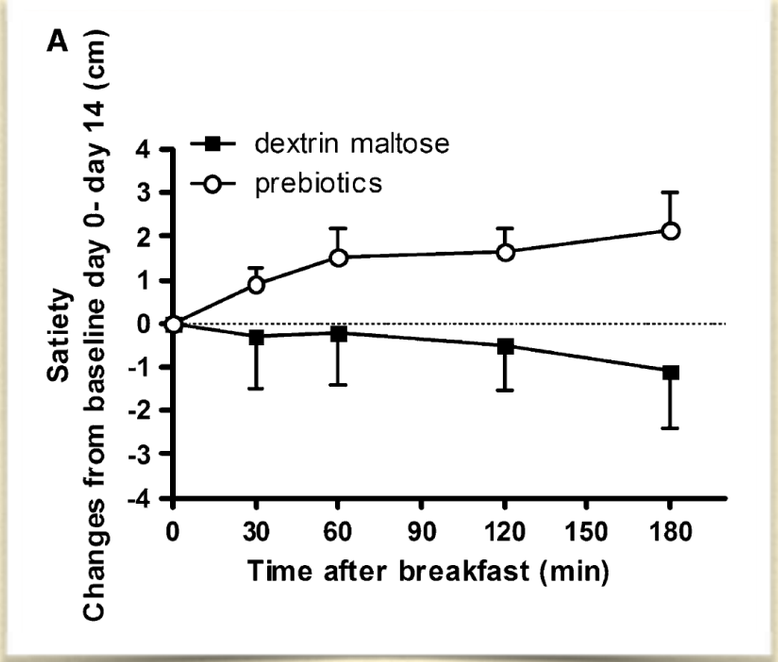
Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal[1–3]

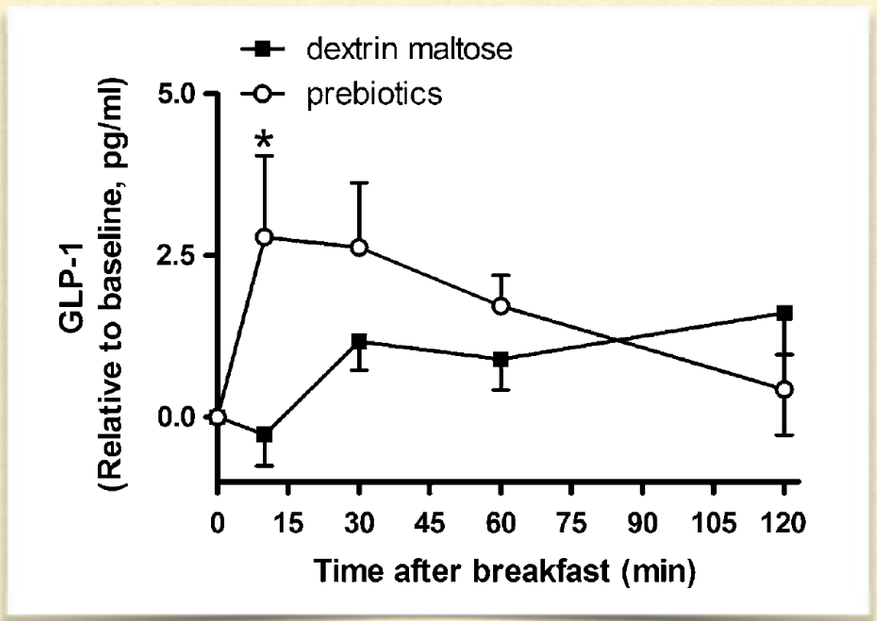
Am J Clin Nutr 2009;90:1236–43.

Patrice D Cani, Elodie Lecourt, Evelyne M Dewulf, Florence M Sohet, Barbara D Pachikian, Damien Naslain, Fabienne De Backer, Audrey M Neyrinck, and Nathalie M Delzenne

- la somministrazione di PREBIOTICI diminuiva la fame, aumentava la sazietà e aumentava la sintesi di GLP-1







What Bariatric Surgery Can Teach Us About Endoluminal Treatment of Obesity and Metabolic Disorders

Lee M. Kaplan, MD, PhD

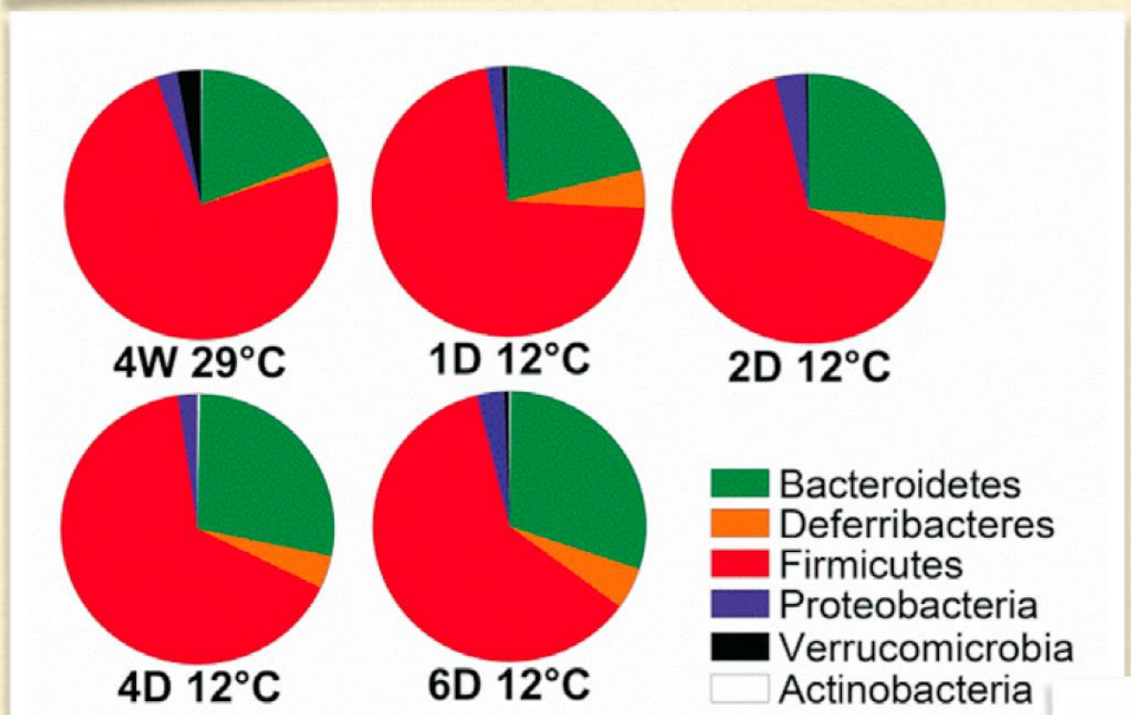
Gastrointest Endoscopy Clin N Am 27 (2017) 213–231

- remissione parziale o totale del diabete
- Importante calo ponderale
- calo ponderale non è collegato solo con la riduzione dell'introduzione del cibo o con il malassorbimento
- induce alterazione del microbiota (aumento di Akkermansia muciniphila e Roseburia, etc) netto miglioramento del metabolismo, aumento della sintesi e secrezione di GLP-1 e della sintesi e secrezione di insulina
- Trapianto di microbiota da persone sottoposte a ch Bariatrica in topi germ free induce A) incremento del consumo energetico come si vede nel post intervento e B) decremento del grasso come si osserva nei soggetti sottoposti a CH Bariatrica
- solo lo 0,25% degli obesi in USA si sottopone a chirurgia bariatrica ogni anno

Altered Microbiota Contributes to Reduced Diet-Induced Obesity upon Cold Exposure

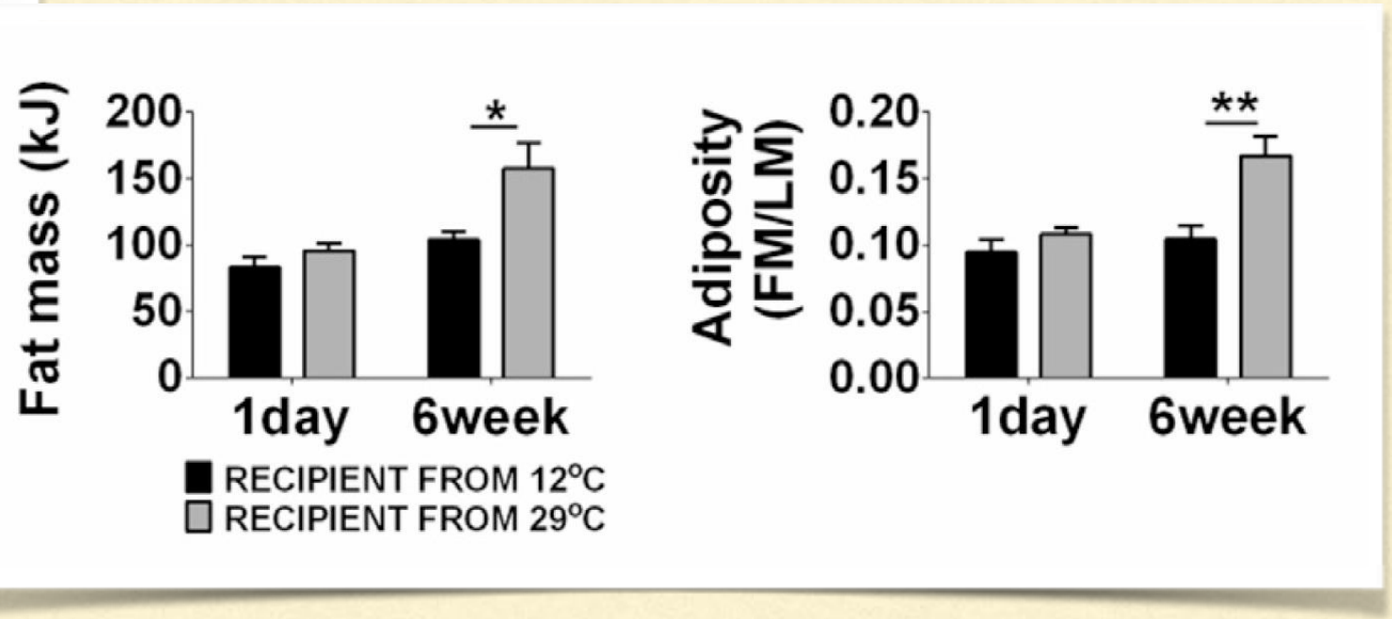
Cell Metabolism 23, 1216–1223, June 14, 2016

Marika Ziętak,[1] Petia Kovatcheva-Datchary,[2] Lidia H. Markiewicz,[1] Marcus Ståhlman,[2] Leslie P. Kozak,[1,4,*] and Fredrik Bäckhed[2,3,4,*]



Cambiamento del microbiota dei topi a seconda dell'esposizione al freddo

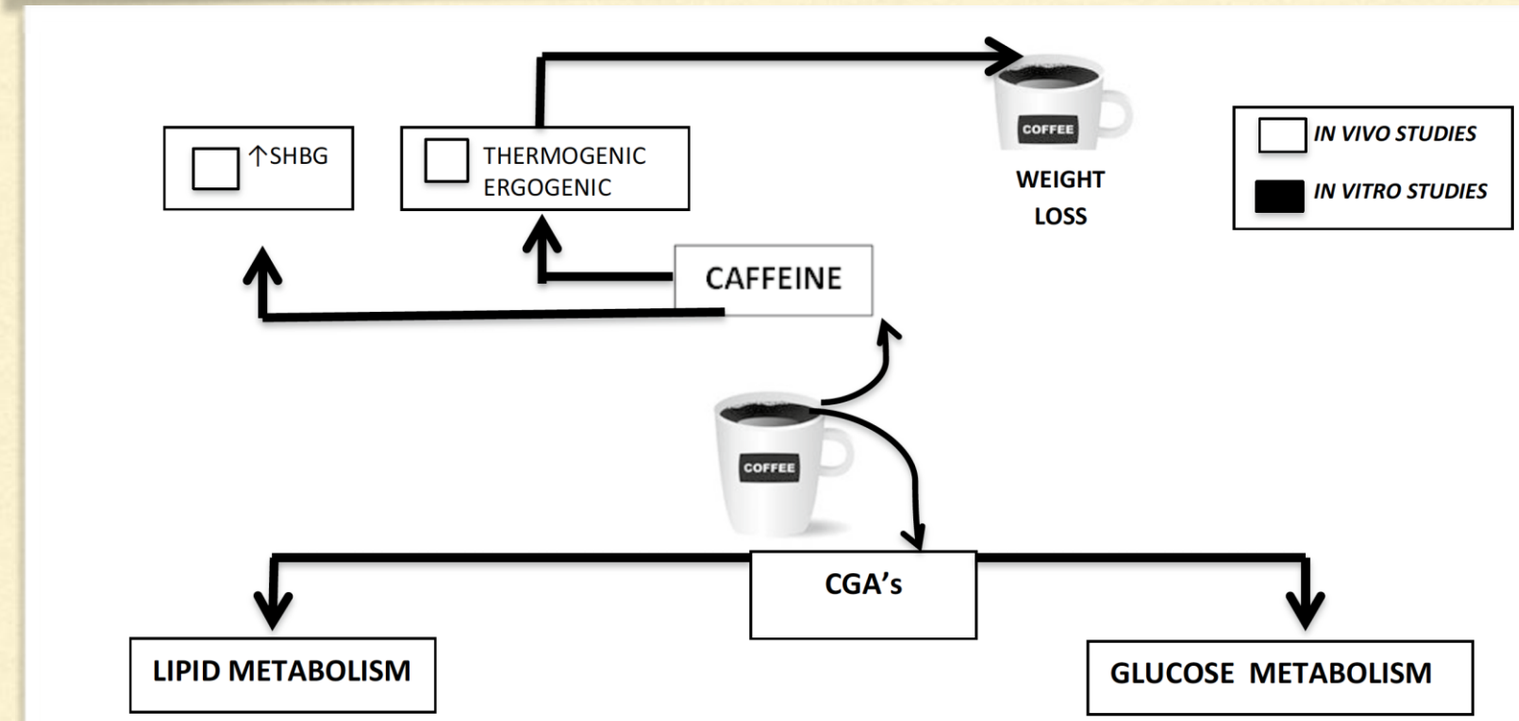
- Trapianto di microbiota in topi germ free



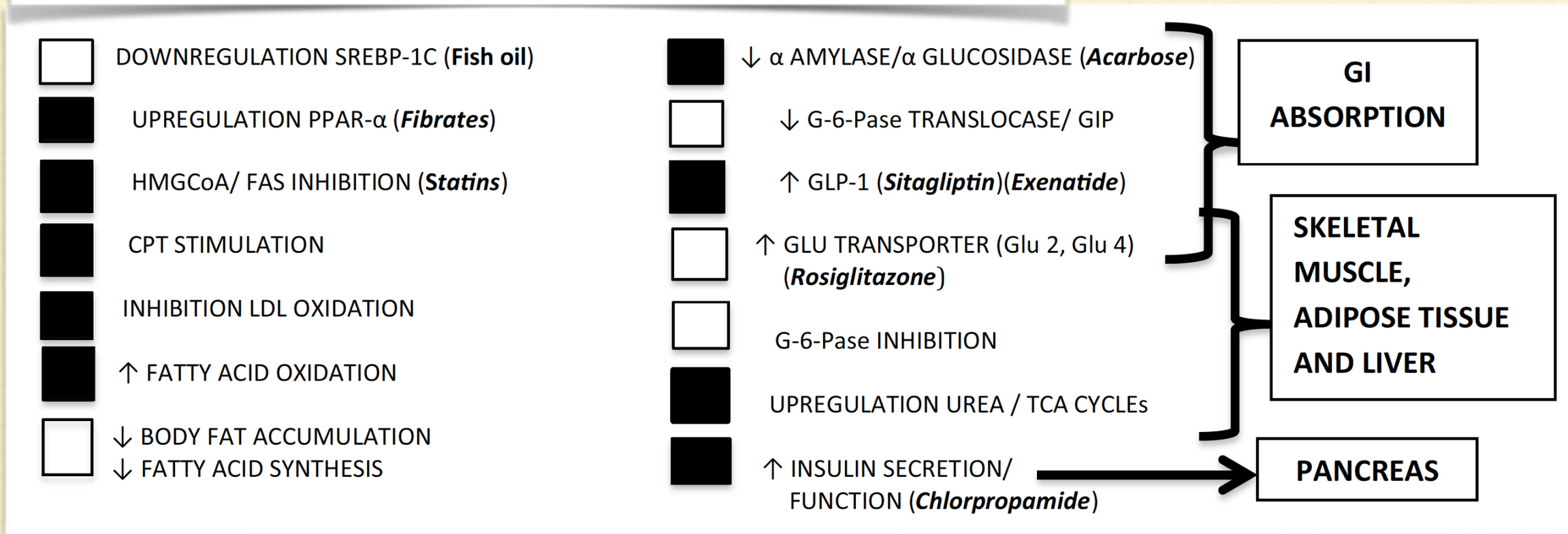
Coffee consumption, obesity and type 2 diabetes: a mini-review

Roseane Maria Maia Santos[1] · **Darcy Roberto Andrade Lima**[2]

Eur J Nutr (2016) 55:1345–1358
DOI 10.1007/s00394-016-1206-0



- CGA: ac clorogenico, derivato dalla caffeina
- Parte assorbito e parte metabolizzato dal microbiota



Coffee consumption, obesity and type 2 diabetes: a mini-review

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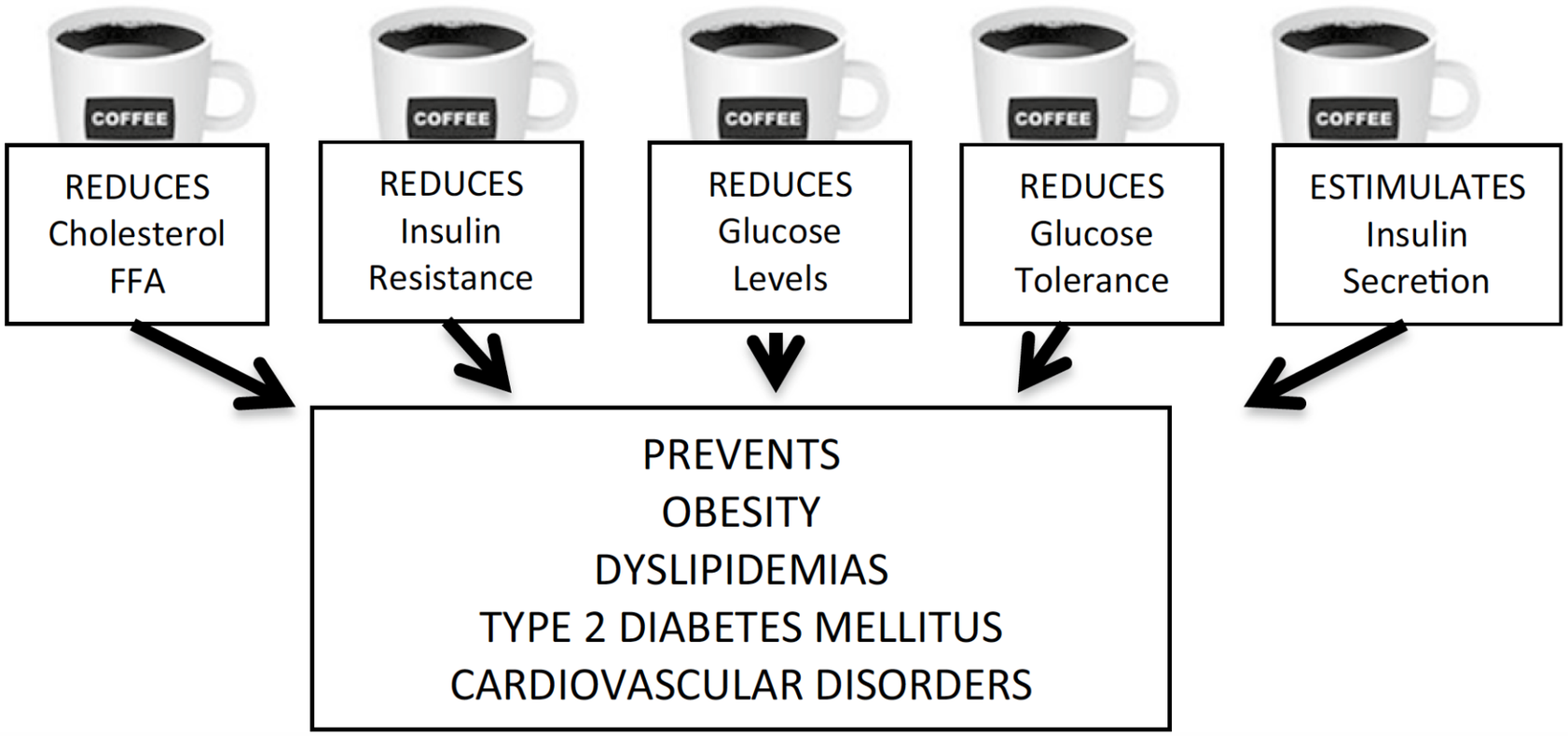

(Cell Metabolism *24*, 63–74; July 12, 2016)

Effects of Gut Microbiota Manipulation by Antibiotics on Host Metabolism in Obese Humans: A Randomized Double-Blind Placebo-Controlled Trial

Dorien Reijnders, Gijs H. Goossens, Gerben D.A. Hermes, Evelien P.J.G. Neis, Christina M. van der Beek, Jasper Most, Jens J. Holst, Kaatje Lenaerts, Ruud S. Kootte, Max Nieuwdorp, Albert K. Groen, Steven W.M. Olde Damink, Mark V. Boekschoten, Hauke Smidt, Erwin G. Zoetendal, Cornelis H.C. Dejong, and Ellen E. Blaak*

Trattamento con vancomicina, o amoxicillina o placebo per 7 giorni in s

Vancomicina (no amoxicillina) riduzione di firmicutes implicati nella sintesi di SCFA e nel metabolismo dei Ac biliari

nessun effetto sull'insulino sensibilità, sulla grandezza degli adipociti del sottocutaneo addominale durante i 7 die di terapia e nelle 8 settimane di follow up

Resilienza del microbiota? Trattamento troppo breve?

Improved Glucose Homeostasis in Obese Mice Treated With Resveratrol Is Associated With Alterations in the Gut Microbiome

Diabetes 2017;66:418–425

Miranda M. Sung,[1] Ty T. Kim,[1] Emmanuel Denou,[2] Carrie-Lynn M. Soltys,[1] Shereen M. Hamza,[1] Nikole J. Byrne,[1] Grant Masson,[1] Heekuk Park,[3] David S. Wishart,[4] Karen L. Madsen,[3] Jonathan D. Schertzer,[2] and Jason R.B. Dyck[1]

- la somministrazione di polifenoli come il Resveratrolo comporta un incremento dei bacteroides e dei parabacteroides, inoltre riduce l'akkermansia muciniphila (correlata in altri studi con il miglioramento della tolleranza glucidica)
- Riduce l'infiammazione tissutale e la endotossiemia
- il trapianto di microbiota da topi trattati con Resveratrolo in topi obesi comporta una miglioramento della tolleranza glucidica

Grazie per l'attenzione

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Gut microbiome-based medical methodologies for early-stage disease prevention

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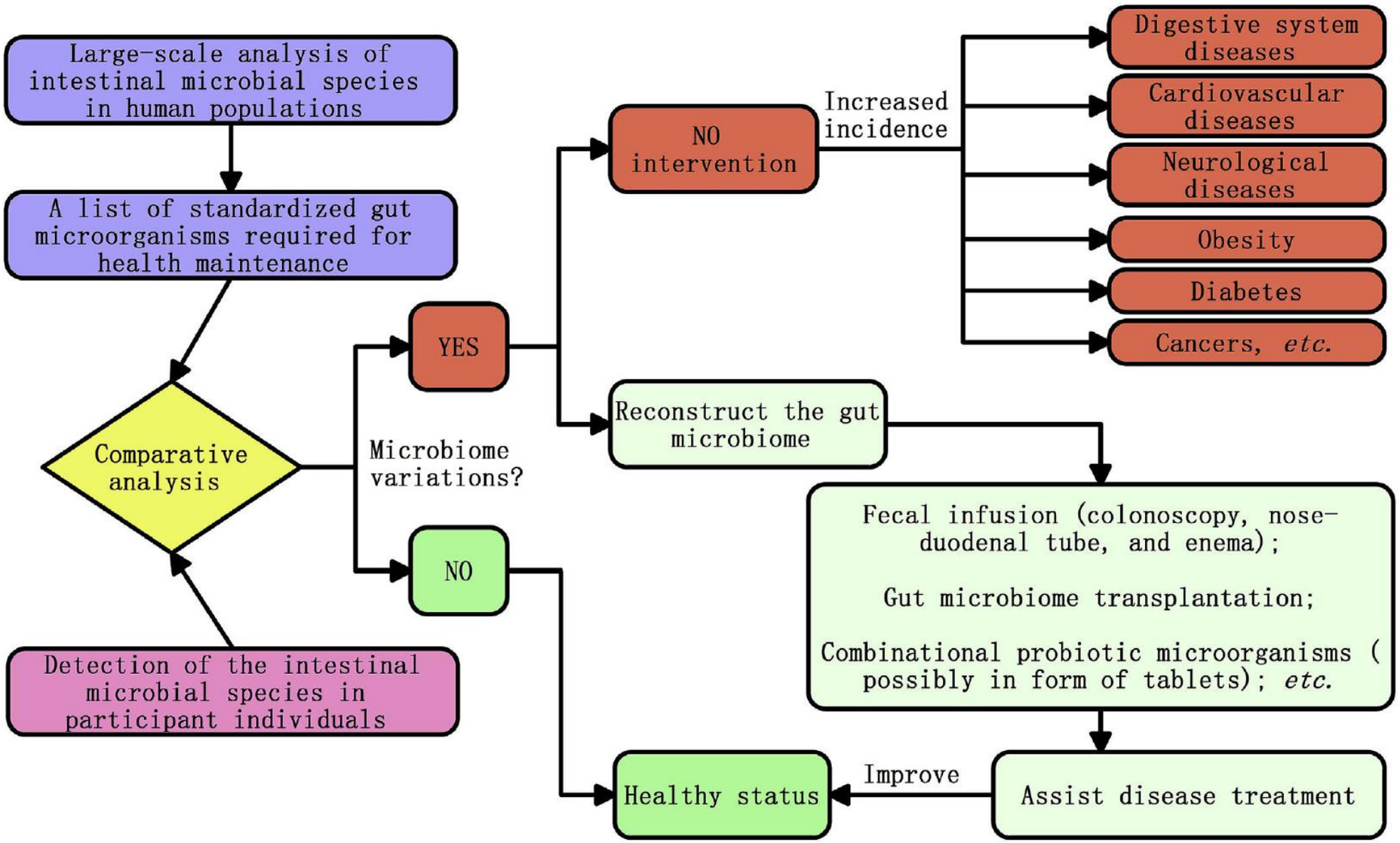

Fig. 1. A flowchart of the perspectives on health maintenance (or disease prevention) *via* monitoring bacterial variations in the gut microbiome and *via* reconstructing a regular and balanced micro-ecosystem in the intestines.