MICROBIOTA ED OBESITA'

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MINIREVIEWS

Gut microbiota in obesity

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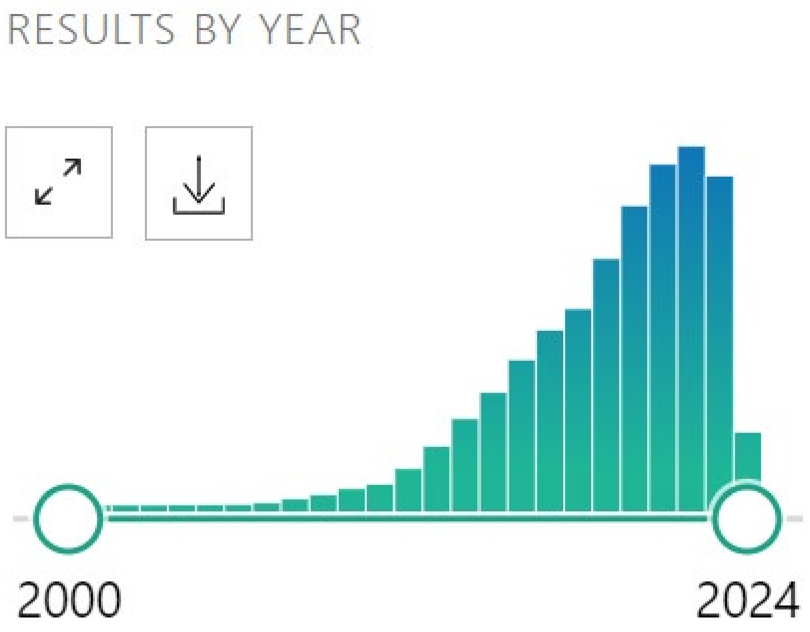
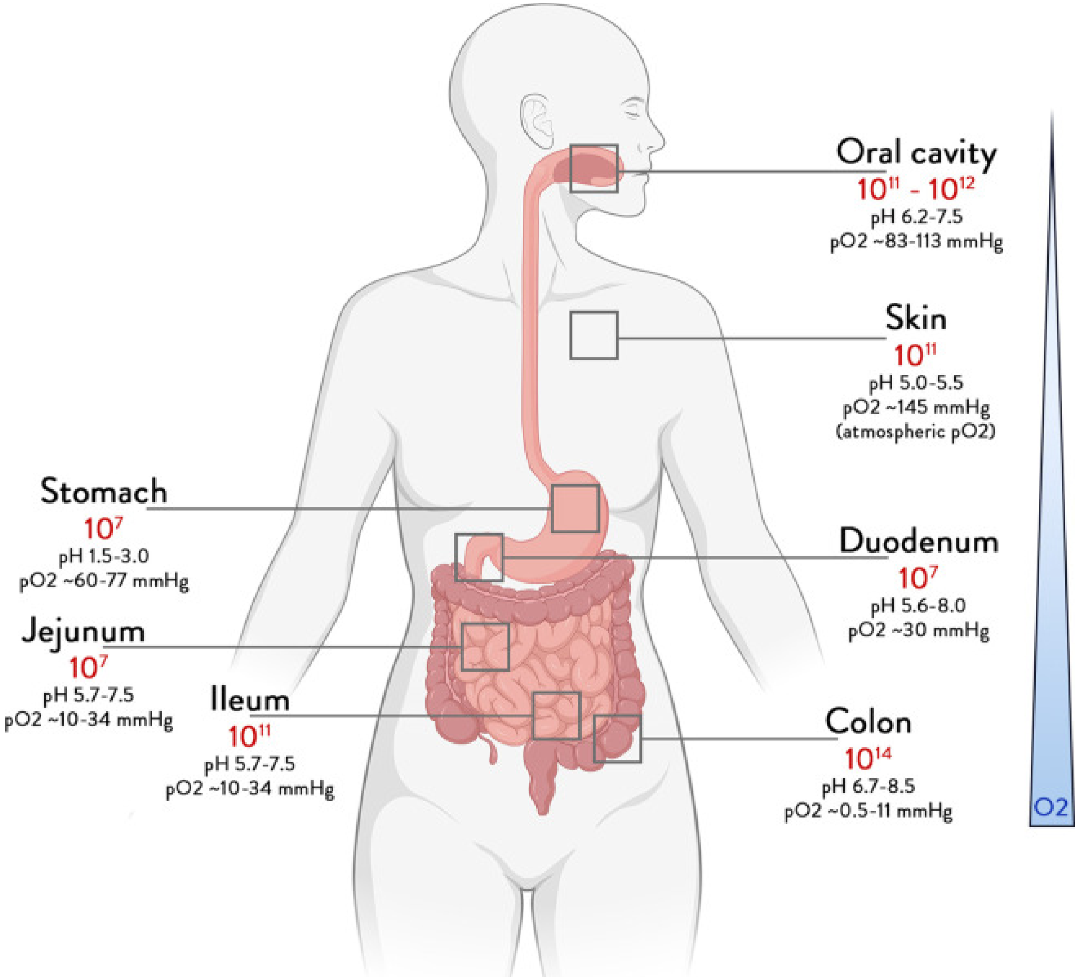
LITERATURE SEARCH

PubMed (https://pubmed.ncbi.nlm.nih.gov/) was used for search with the following keywords: Obesity, gut microbiota, dysbiosis, energy absorption, appetite, fat storage, chronic inflammation, and circadian rhythm. More than 4000 published papers including 178 clinical trial related to gut microbiota in obesity from 2000 through 2021 have been searched.



MICROBIOTA INTESTINALE: definizione e ruolo nella pratica clinica



Definizione: ampia varietà di organismi che colonizzano il tratto gastro-intestinale con specifiche funzioni nel mantenimento del benessere dell'organismo che coabitano.

Paziente adulto di 70 kg: > 10^{13}-10^{14} batteri = circa 2 kg

10 times # of cells in the body itself

Gut microbiota relies on: 1. not digested food residues
2. gut mucus
3. dead cells

microorganisms MDPI

Review

Fecal Microbiota Transplantation and Other Gut Microbiota Manipulation Strategies

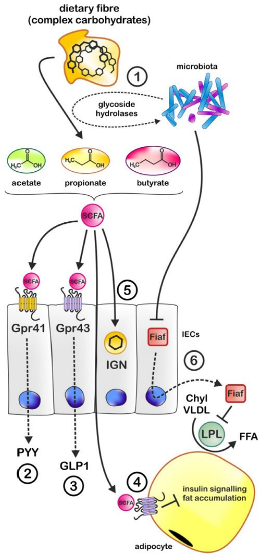
Gianluca Quaranta [1], Alessandra Guarnaccia [1,*], Giovanni Fancello [1], Chiara Agrillo [1], Federica Iannarelli [1], Maurizio Sanguinetti [1,2] and Luca Masucci [1,2]

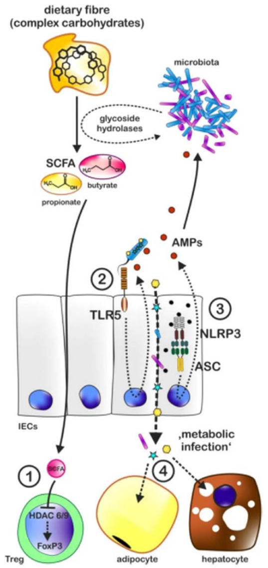
de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. Gut. 2022 May;71(5):1020-1032.

THE HEALTHY GUT MICROBIOTA

gutMEGA database[14]. The normal gut microbiota of the human body is mainly composed of *Firmicutes*, *Bacteroides*, *Proteus*, *Actinomycetes*, *Fusobacteria*, and *Verrucomicrobia*, among which *Firmicutes* and *Bacteroides* dominate[15]. The core functions of a healthy gut microbiota include the biodegradation of polysaccharides, the production

of short-chain fatty acids, the enrichment of specific lipopolysaccharides, and the production of vitamins and essential amino acids[16]. A healthy gut microbiota is





nutrients MDPI

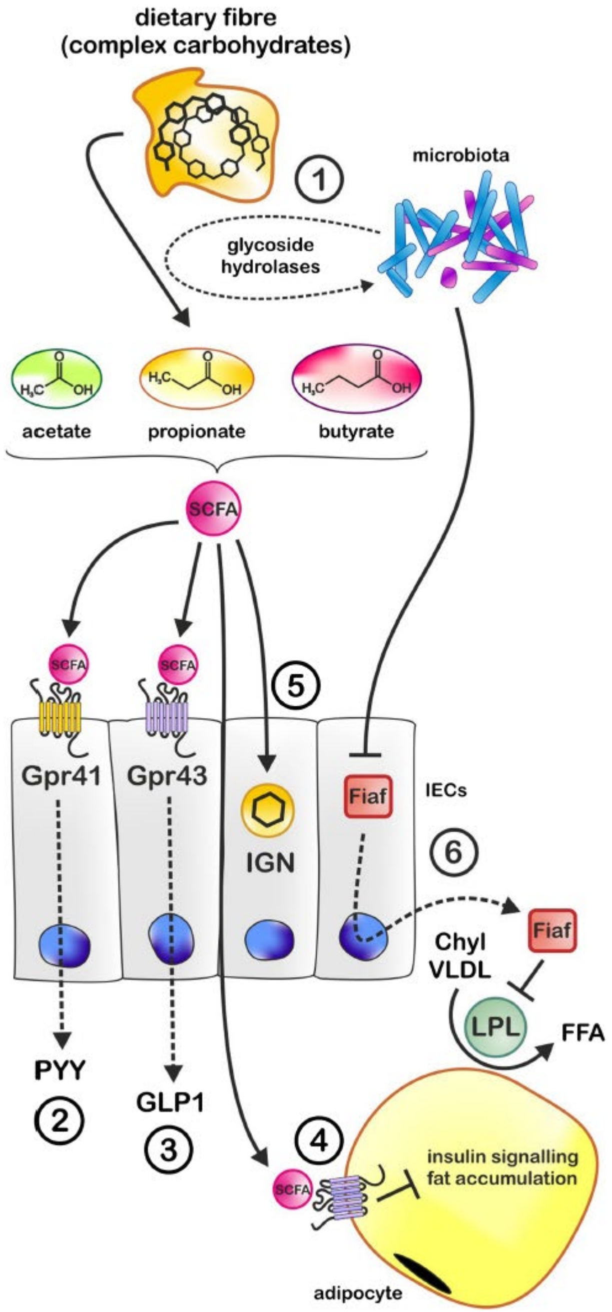
Review

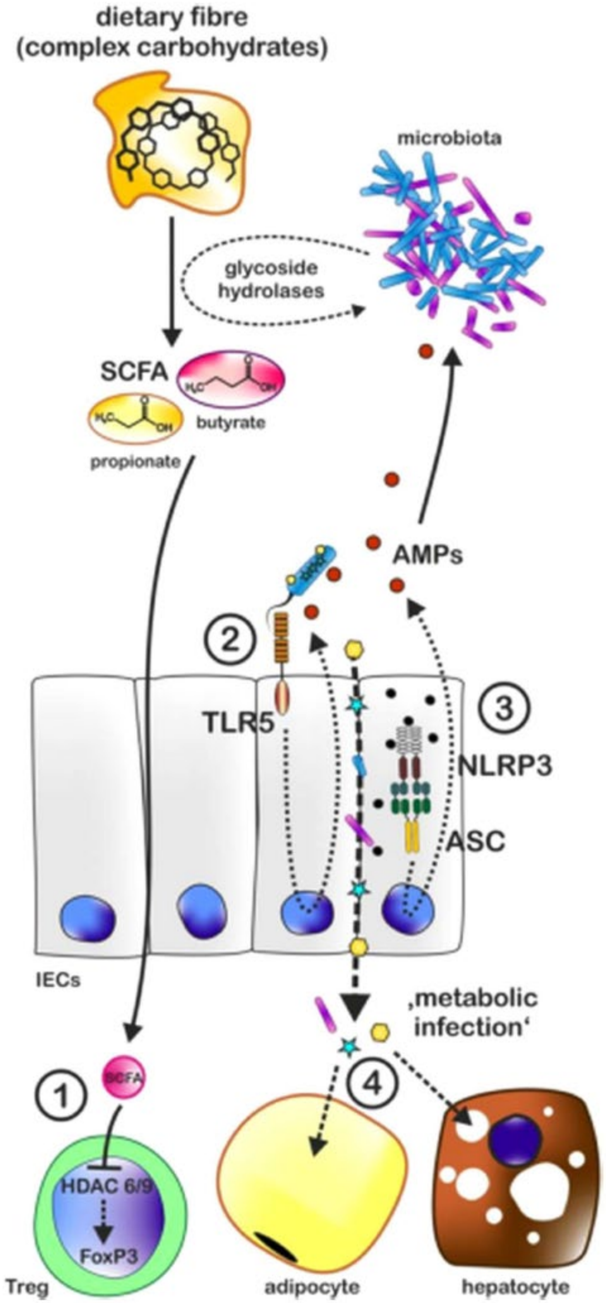
From Gut Microbiota through Low-Grade Inflammation to Obesity: Key Players and Potential Targets

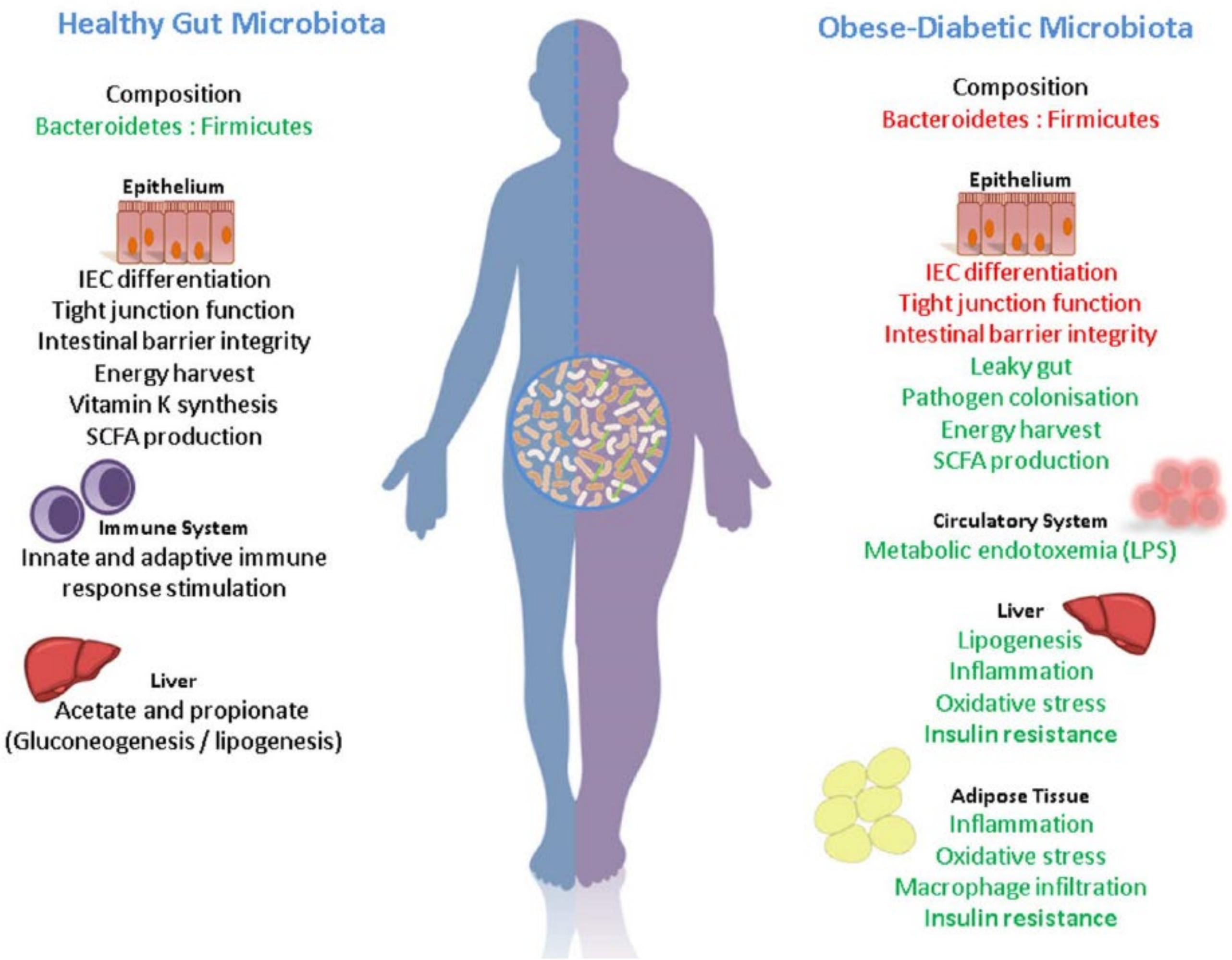
Claudia Vetrani [1], Andrea Di Nisio [2], Stavroula A. Paschou [3], Luigi Barrea [4,5], Giovanna Muscogiuri [1,5,6,*], Chiara Graziadio [1,5], Silvia Savastano [1,5], Annamaria Colao [1,5,6] and on behalf of the Obesity Programs of Nutrition, Education, Research and Assessment (OPERA) Group [†]

Main Outcome	Type of Study	Main Findings
Microbiota composition	Studies in mice	- Increased *Bacteroidetes* abundance in lean mice [16] - Bacteria with increased energy-harvesting activity [20,21]
	Human studies	- Reduced diversity in overweight and obese individuals is associated with high hs-CRP levels [17] - Increased *Firmicutes* abundance in overweight and obese individuals [17–19] - Increased abundance of pro-inflammatory bacteria (e.g., *Escherichia coli*) while reduced bacteria with anti-inflammatory properties (e.g., *Fecalibacterium prausnitzii*) [22,23]
Microbial metabolites	In vitro studies	- Butyrate reduces LPS concentration and activation of macrophages [33]
	Studies in mice	- *Lactobacillus* increase the production of GABA, reducing food intake [27] - LPS infusion increases TNF-α levels [29]
	Human studies	- LPS concentration is associated with obesity, MS, and T2D [30–33] - Weight loss (bariatric surgery) decrease LPS concentrations [34,35]
Intestinal permeability	Studies in mice	- Butyrate increase the expression of mucin and tight junction proteins [43] - *Akkermansia* in lean mice increase thigh junction function [46]
	Human studies	- *Faecalibacteria* abundance is associated with reduced zonulin levels in overweight women [45]
Gut microbiota and inflammasome/cytokines interplay	Studies in mice	- Dysbiosis increases inflammation and obesity [63] - *Prevotella* abundance reduces inflammation [64,65]

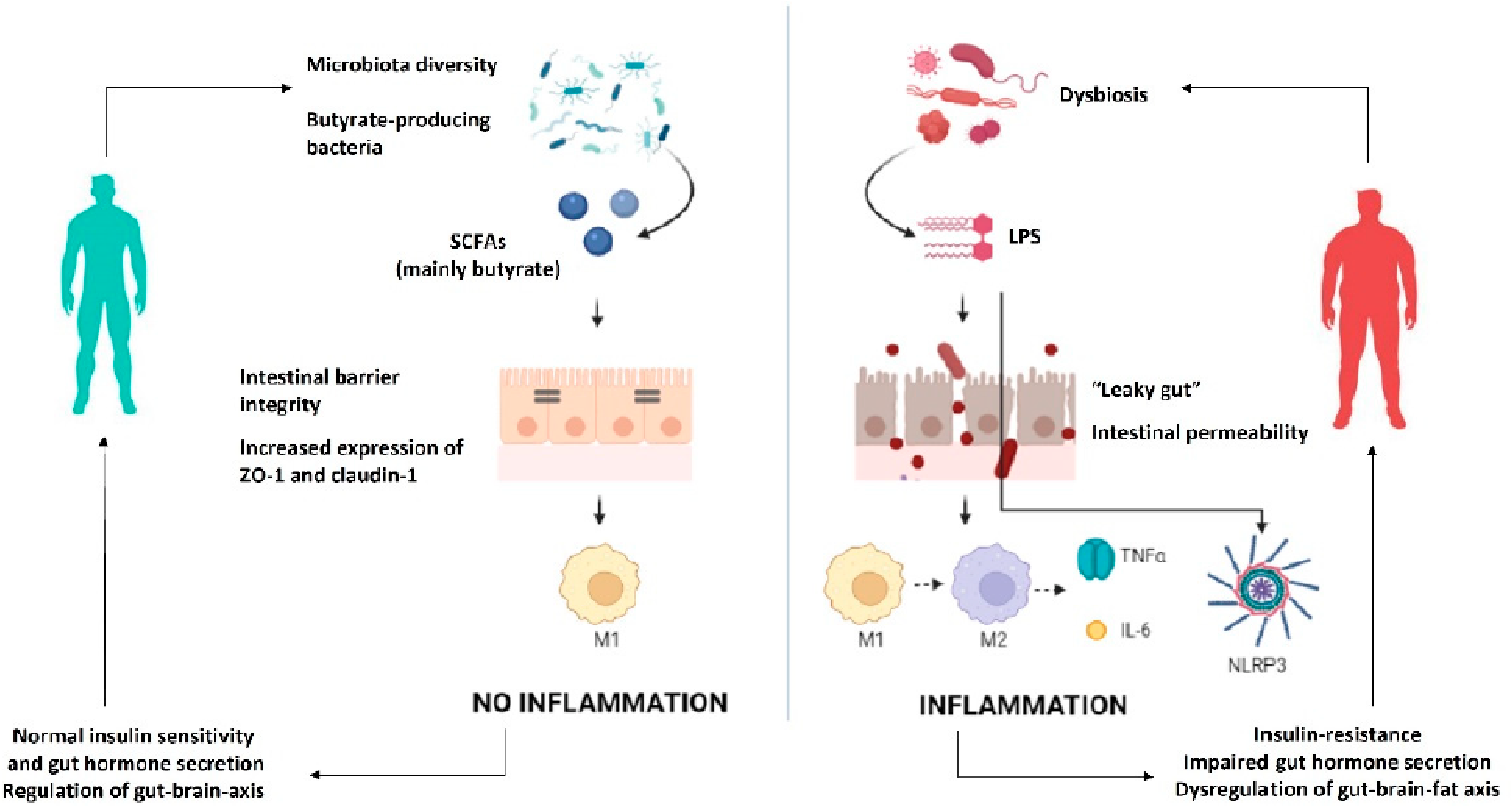
GABA—γ-aminobutyric acid; hs-CRP—high sensitivity C-reactive protein; LPS—lipopolysaccharide; MS—metabolic syndrome; T2D—type 2 diabetes.


dietary fibre
(complex carbohydrates)
1
microbiota
glycoside
hydrolases
acetate
propionate
butyrate
SCFA
Gpr41
Gpr43
5
IGN
Fiaf
IECs
6
Chyl
VLDL
LPL
FFA
PYY
2
GLP1
3
4
insulin signalling
fat accumulation
adipocyte


dietary fibre
(complex carbohydrates)
microbiota
glycoside
hydrolases
SCFA
butyrate
propionate
AMPs
2
TLR5
3
NLRP3
ASC
IECs
‚metabolic
infection‘
1
4
HDAC 6/9
FoxP3
Treg
adipocyte
hepatocyte



Patterson E, *et al*. *Postgrad Med J* 2016;**92**:286–300. doi:10.1136/postgradmedj-2015-133285



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From Gut Microbiota through Low-Grade Inflammation to Obesity: Key Players and Potential Targets

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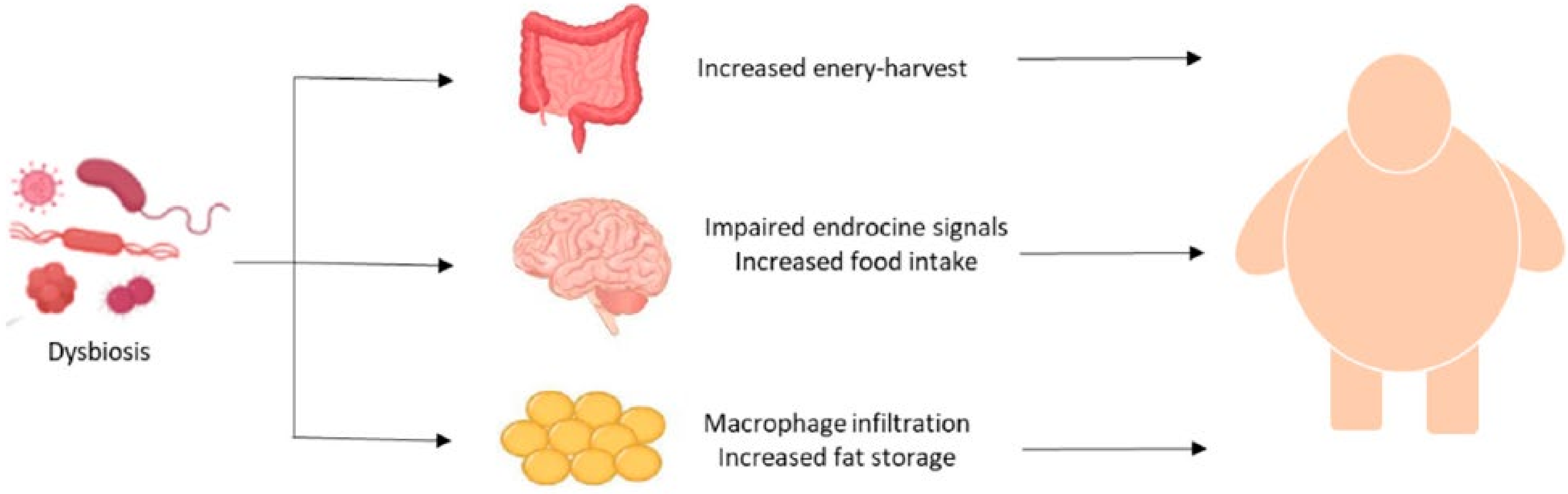

Figure 2. Main mechanisms linking dysbiosis and obesity.

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Review

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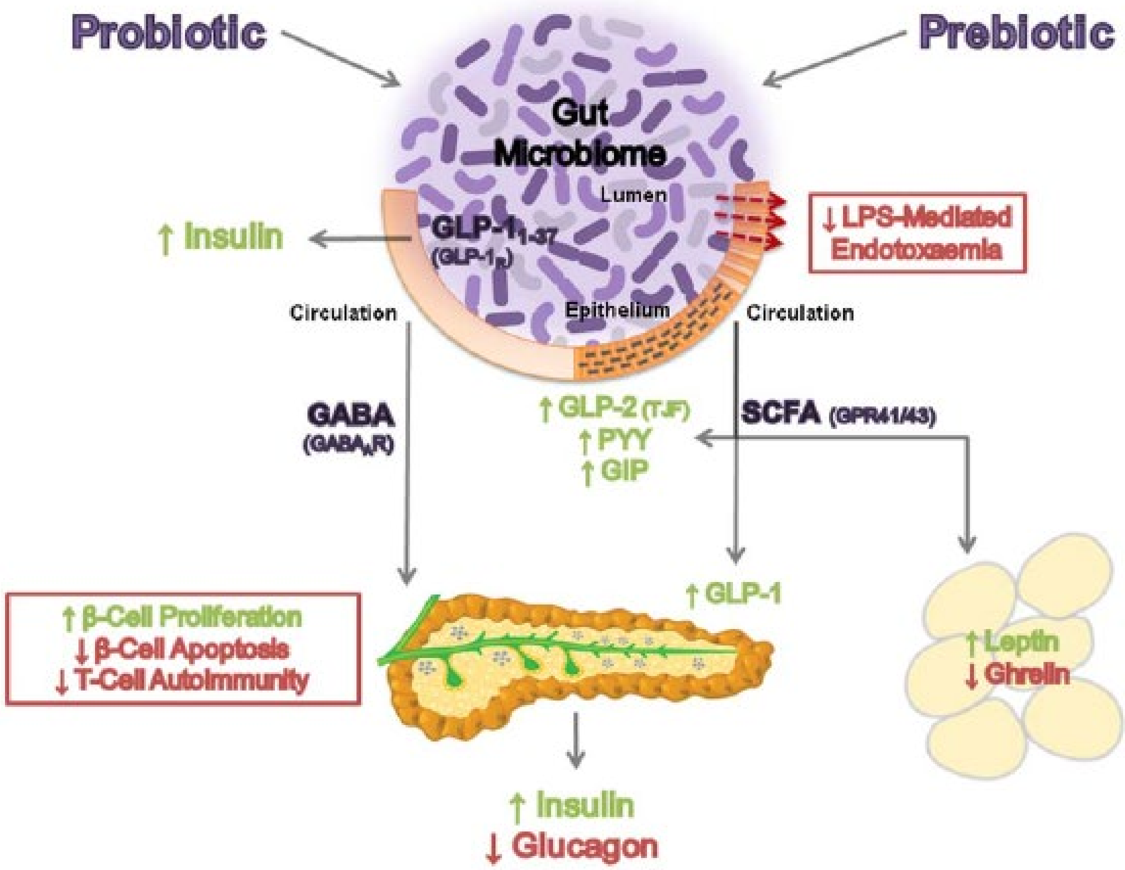

Probiotic
Prebiotic
Gut Microbiome
Lumen
↓ LPS-Mediated Endotoxaemia
↑ Insulin
GLP-1 1-37
Circulation
Epithelium
Circulation
GABA
↑ GLP-2 (TJF)
↑ PYY
↑ GIP
SCFA (GPR41/43)
↑ GLP-1
↑ β-Cell Proliferation
↓ β-Cell Apoptosis
↓ T-Cell Autoimmunity
↑ Leptin
↓ Ghrelin
↑ Insulin
↓ Glucagon

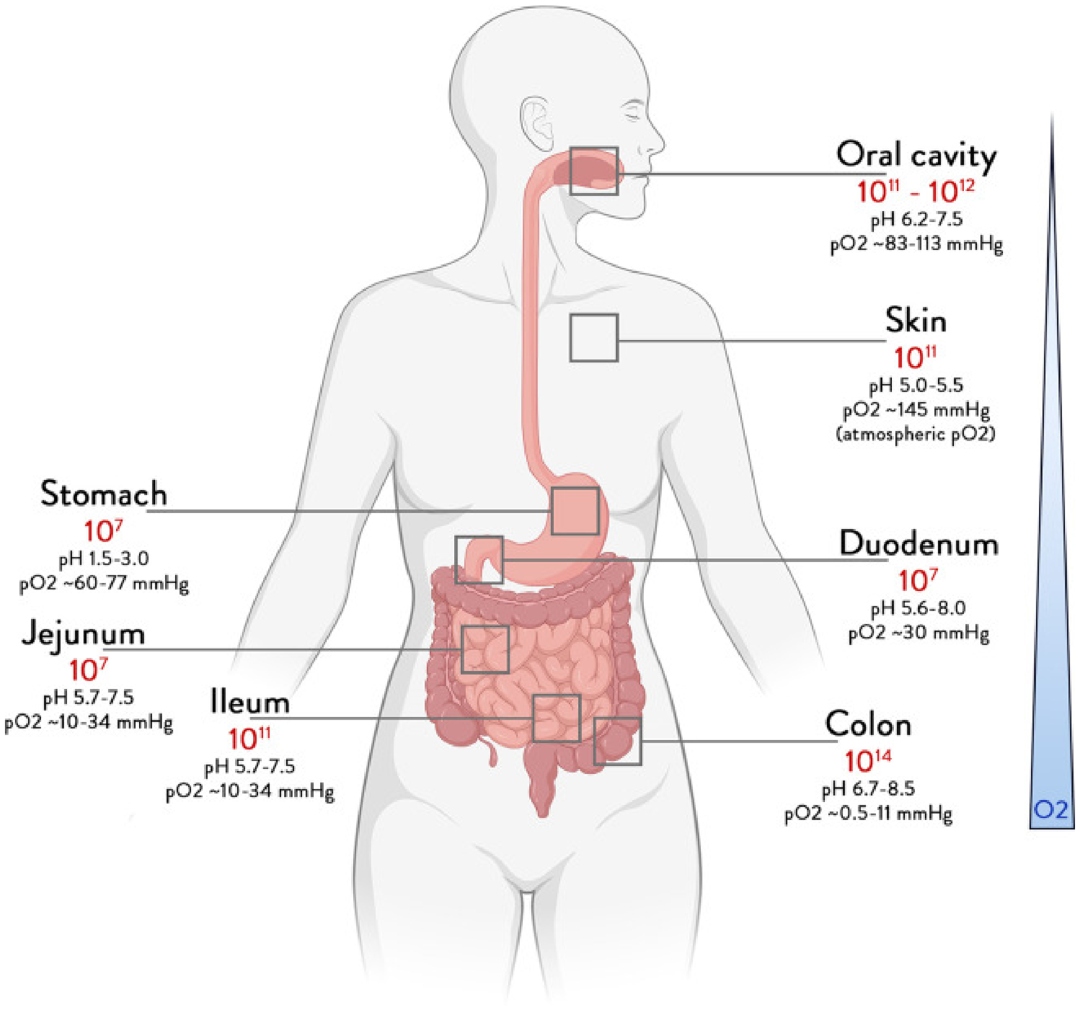
Box 1 Major findings from metagenome-wide association studies (MGWAS) in patients with T2D

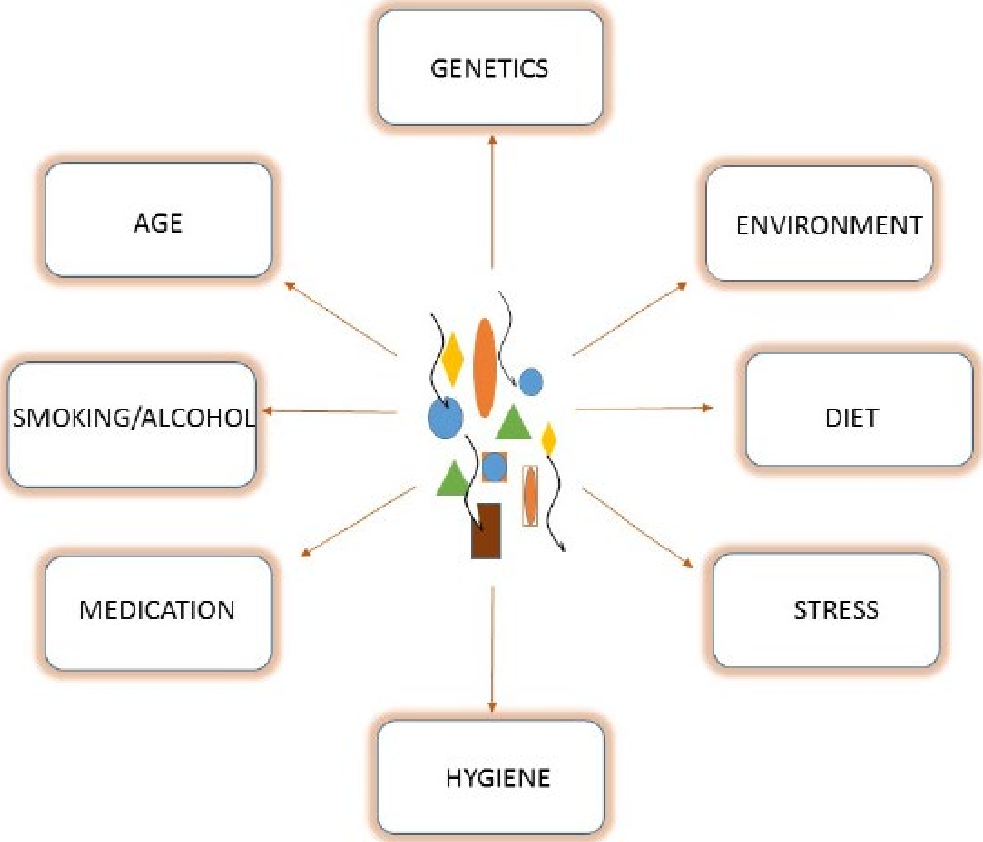
- Butyrate-producing *Roseburia intestinalis* and *Faecalibacterium prausnitzii* concentrations lower in T2D
- *Lactobacillus gasseri* and *Streptococcus mutans* and certain *Clostridiales* higher in T2D
- *Proteobacteria* higher in T2D
- Increased expression of microbiotal genes involved in oxidative stress, that is, overall a proinflammatory signature in the intestinal microbiota
- Genes involved in vitamin synthesis, for example, riboflavin lower in T2D
- Shortcomings of studies: heterogenous populations, data on diabetes medication incomplete and its role unclear, studies lack gender balance; mucosa-associated microbiota not studied

Box 2: Evidence for a beneficial effect of *Akkermansia muciniphila* on metabolic functions

- Is a mucin-degrading Gram-negative bacterium constituting 3–5% of the intestinal microbiota
- Concentrations inversely correlated with obesity and diabetes in many experimental and human studies
- Prebiotic consumption such as oligofructose is metabolically beneficial and increases *A muciniphila* concentrations
- Administration of *A muciniphila* to murines improves weight loss, metabolic control and adipose tissue inflammation
- Metformin increases *A muciniphila* concentrations
- Improves dextrane sulfate colitis
- Controversies: some animal/human studies show conflicting results; in some experimental situations rather proinflammatory.[33 36 77 78]

Microbiota diversity and richness are strongly influenced by the host and environmental factors.





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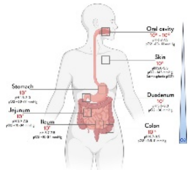

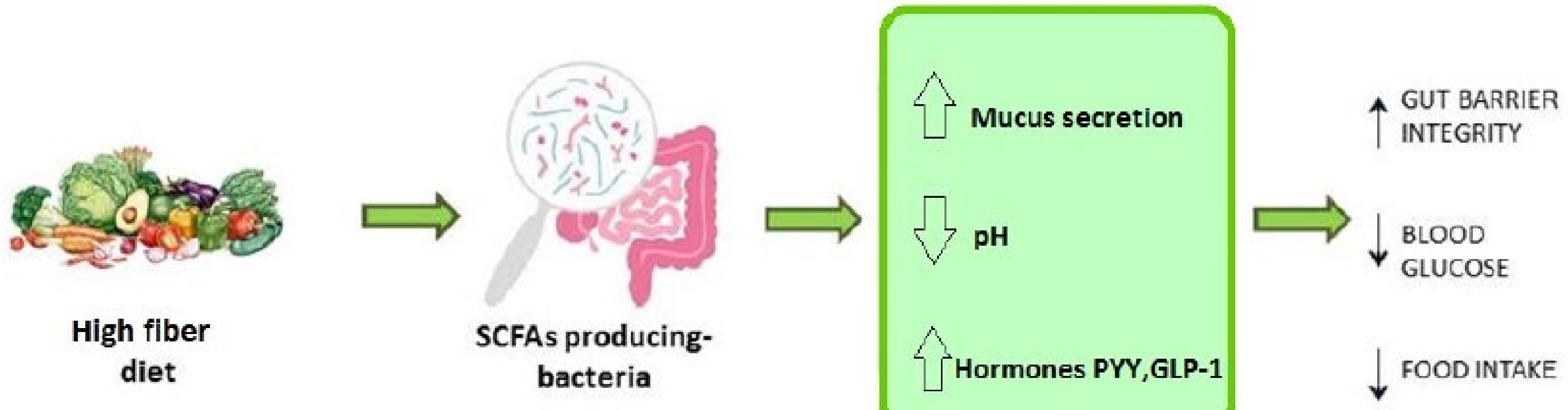

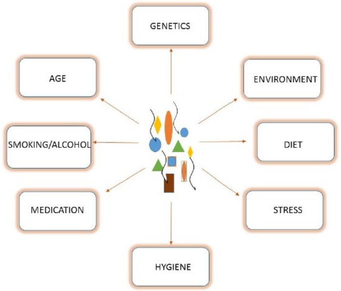

microorganisms

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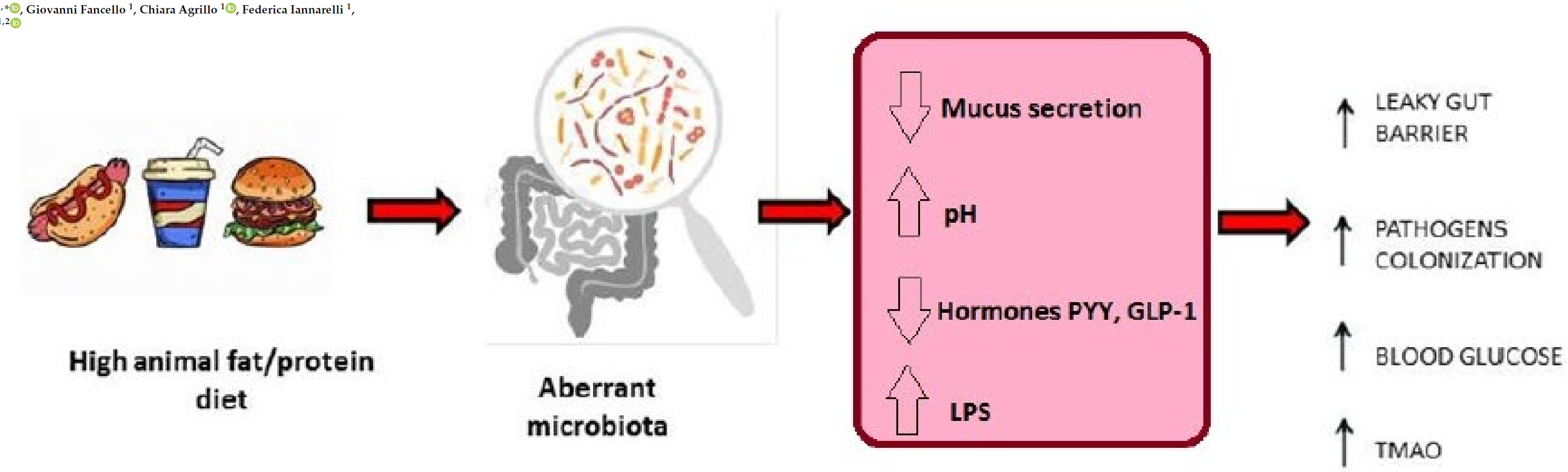


FUNZIONI del MICROBIOTA INTESTINALE nell’organismo ospite

- Modulazione e ricostituzione delle funzioni immunitarie dell’ospite
- Produzione di metaboliti coinvolti in svariate funzioni dell’organismo(SCFA, LPS, poliammine, etanolo,idrogeno solforato)
- Deidrossilazione degli acidi biliari
- Produzione di vitamine

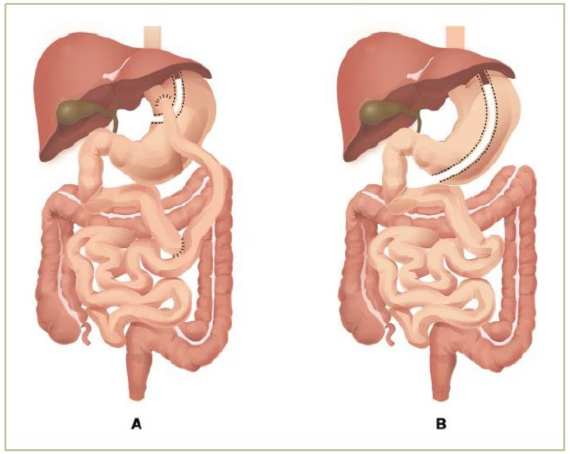


Table 2. Changes of human GM composition following BS [73].

↑/↓	RYGB	VSG
↑	*Akkermansia* (Verrucomicrobia)	*Bulleidia* (Firmicutes)
↑	*Escherichia* (Proteobacteria)	*Roseburia intestinalis* (Firmicutes)
↑	*Klebsiella* (Proteobacteria)	*Faecalibacterium prausnitzii* (Firmicutes)
↓	*Lactobacillus* (Firmicutes)	*Coprococcus comes* (Firmicutes)
↓	*Bifidobacterium* (Actinobacteria)	
↓	*Faecalibacterium prausnitzii* (Firmicutes)	
↓	*Coprococcus comes* (Firmicutes)	

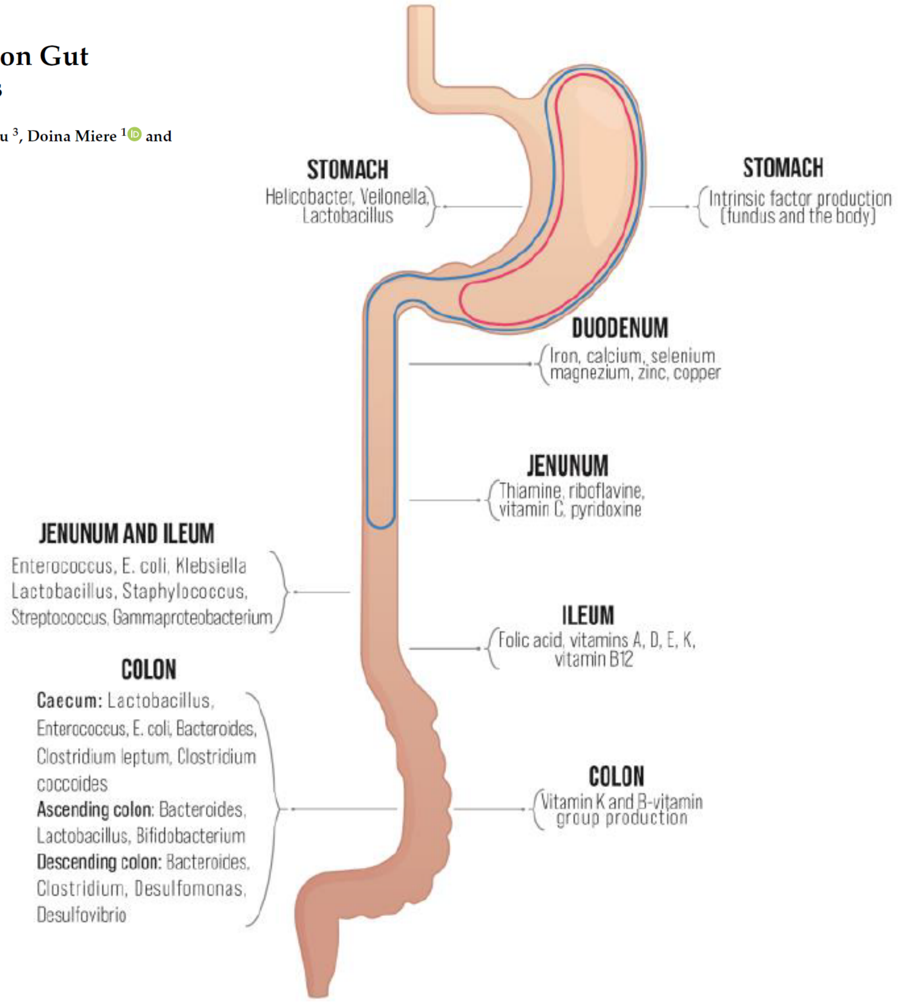
↑—increased; ↓—decreased.

nutrients

Review

Bariatric Surgery in Obesity: Effects on Gut Microbiota and Micronutrient Status

Daniela Ciobârcă [1], Adriana Florinela Cătoi [2,*], Cătălin Copăescu [3], Doina Miere [1] and Gianina Crișan [4]



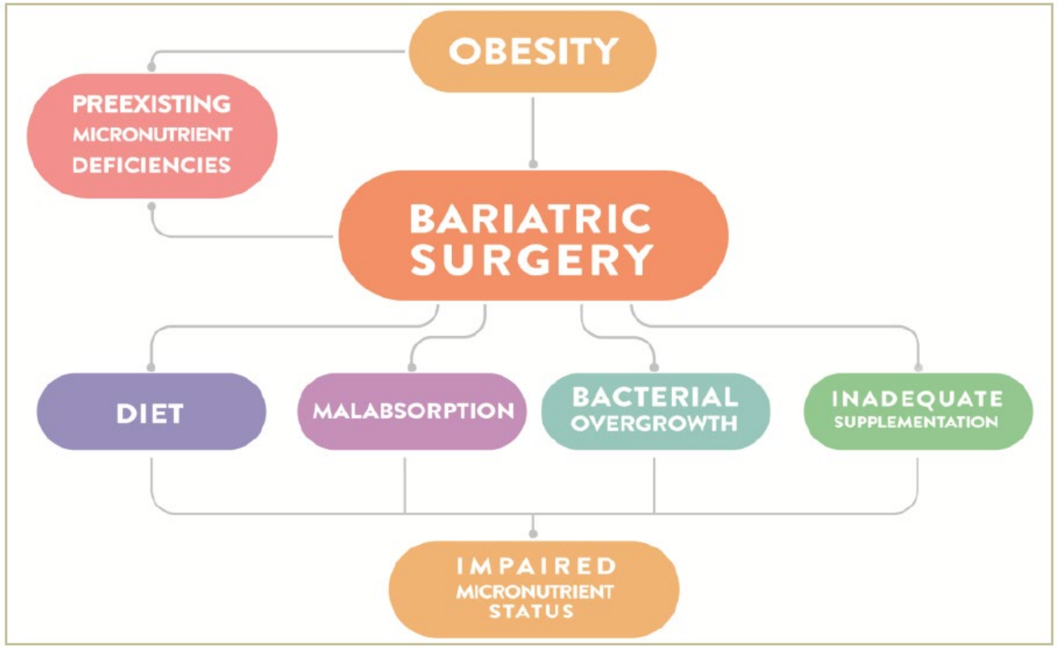


Figure 2. Distribution of micronutrient absorption/biosynthesis sites within the gut [94] and the associated microbiota [95]. Marked areas are excluded after RYGB (blue) and VSG (red).

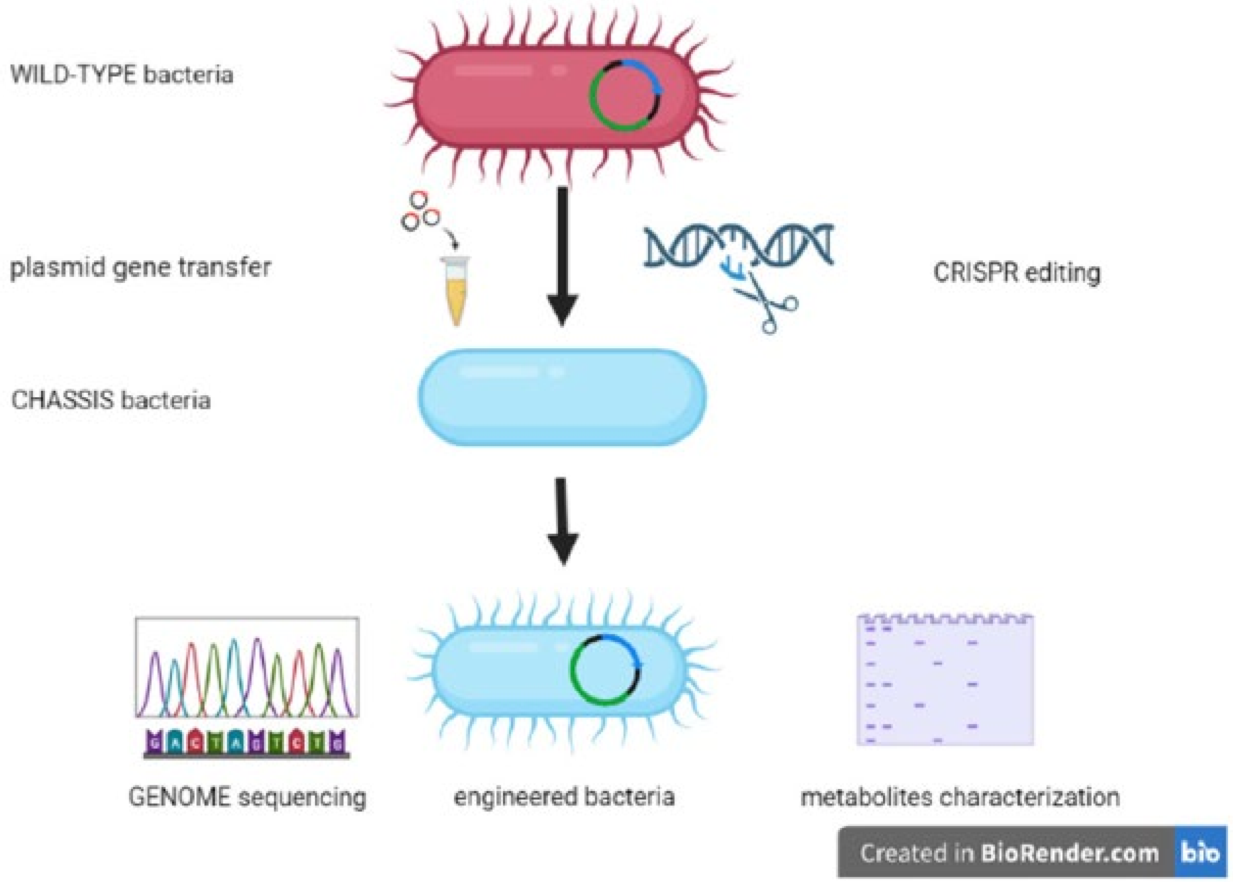


Figure 3. Engineering steps for a candidate chassis wild-type bacterium.

Table 1. A list of engineered bacteria used as potential therapeutic tools. The main target areas are metabolic pathways, the inhibition of colonization (sense–kill system), and immunity.

Biologic Target	Engineered Strain	Disorder	Reference
Metabolic pathway	*EcN SYNB1718*	PKU	[112]
	EcN SYNB1020	Hyperammonemia	[114]
	EcN1917	Obesity	[115]
	L. gasserii	Diabetes	[116]
Sense–Kill system	*EcN1917*	Opportunistic infections	[21]
	Lactococcus lactis	Opportunistic infections	[118]
Immune system	*L. lactis*	IBD	[120]
	Clostridium strain	IBD	[121]

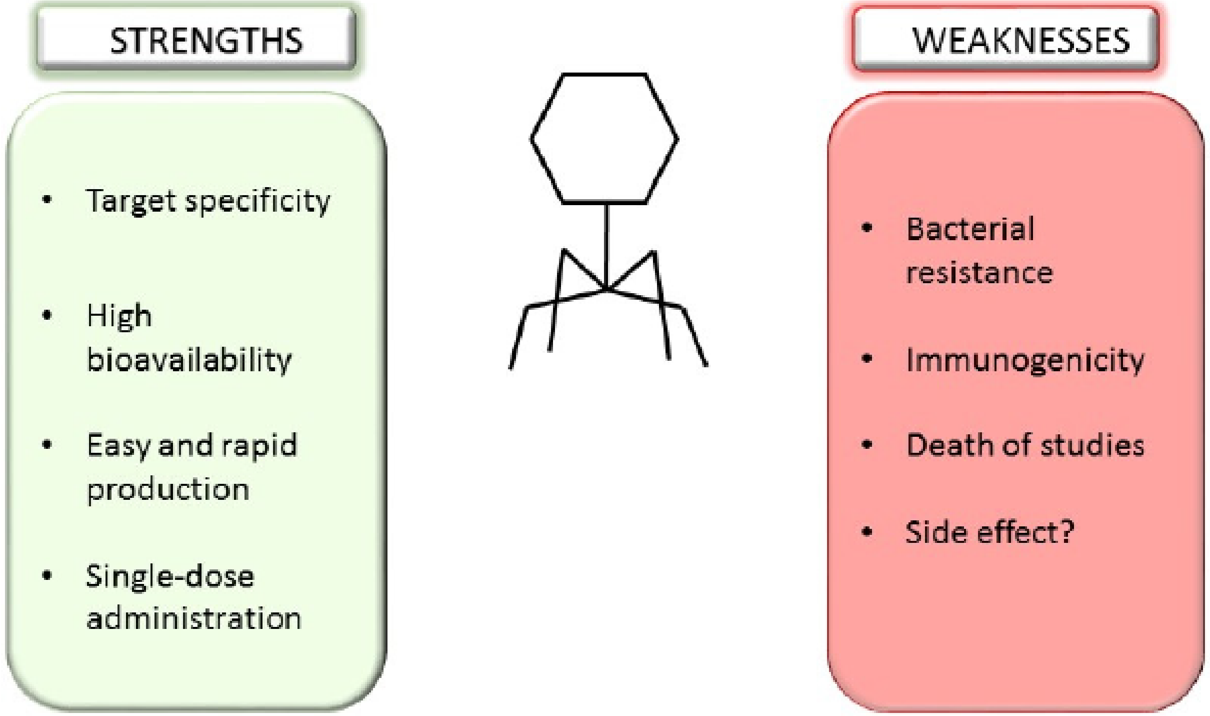
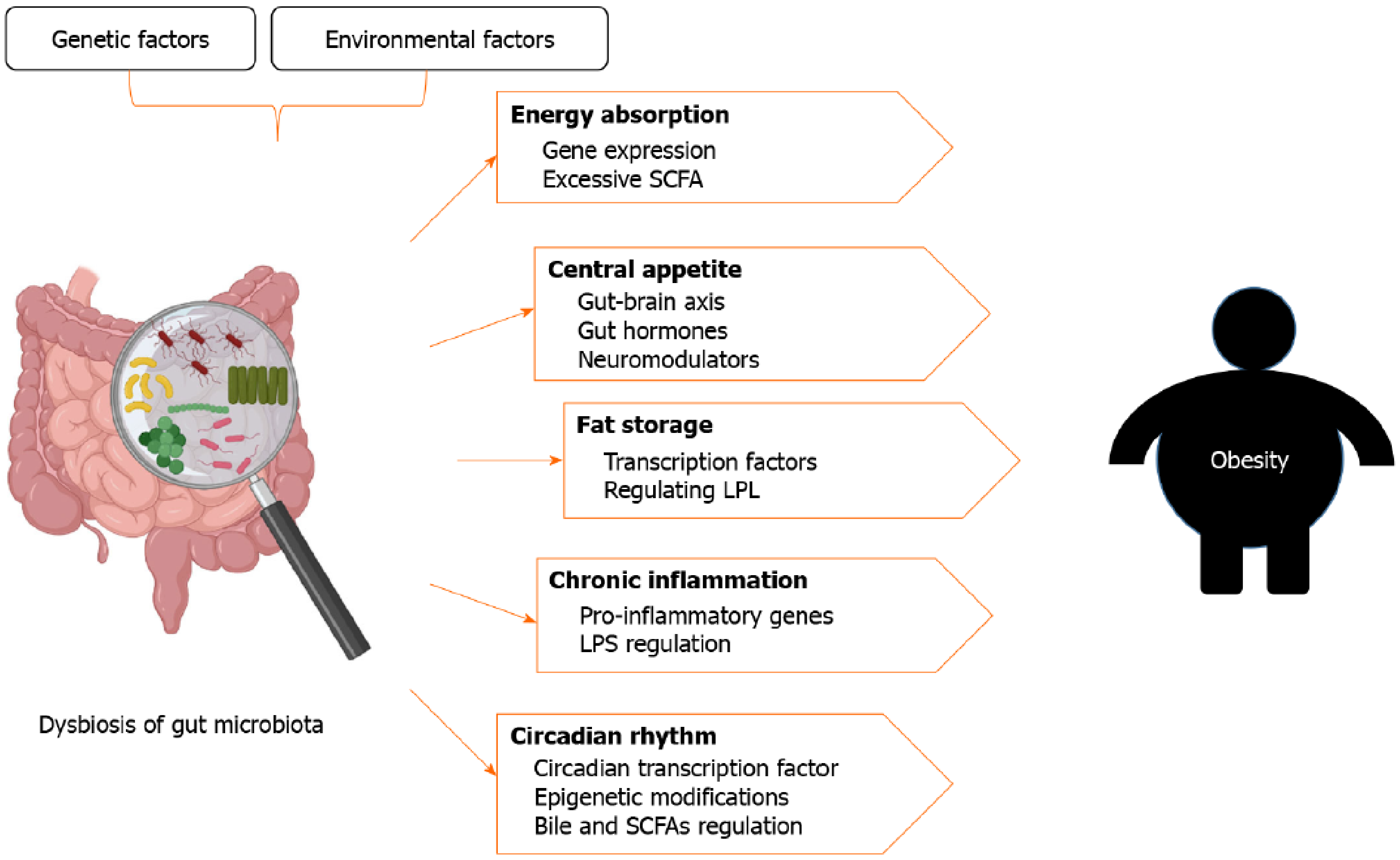
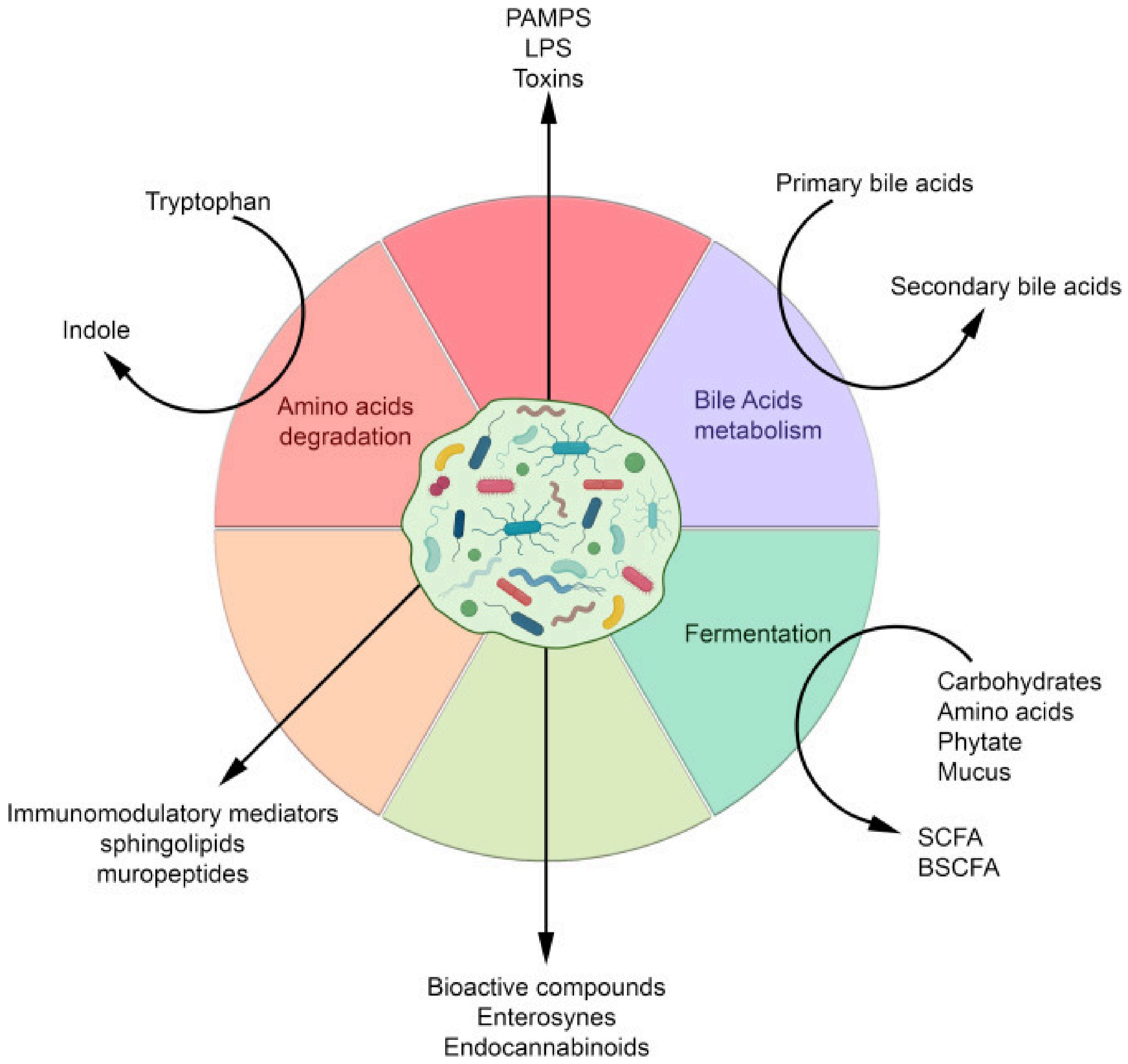


Figure 4. Strengths and weaknesses of phage therapy.



Genetic factors
Environmental factors
Energy absorption
Gene expression
Excessive SCFA
Central appetite
Gut-brain axis
Gut hormones
Neuromodulators
Fat storage
Transcription factors
Regulating LPL
Chronic inflammation
Pro-inflammatory genes
LPS regulation
Circadian rhythm
Circadian transcription factor
Epigenetic modifications
Bile and SCFAs regulation
Dysbiosis of gut microbiota
Obesity

Molecole e metaboliti prodotti dal microbiota intestinale: origine e ruolo metabolico



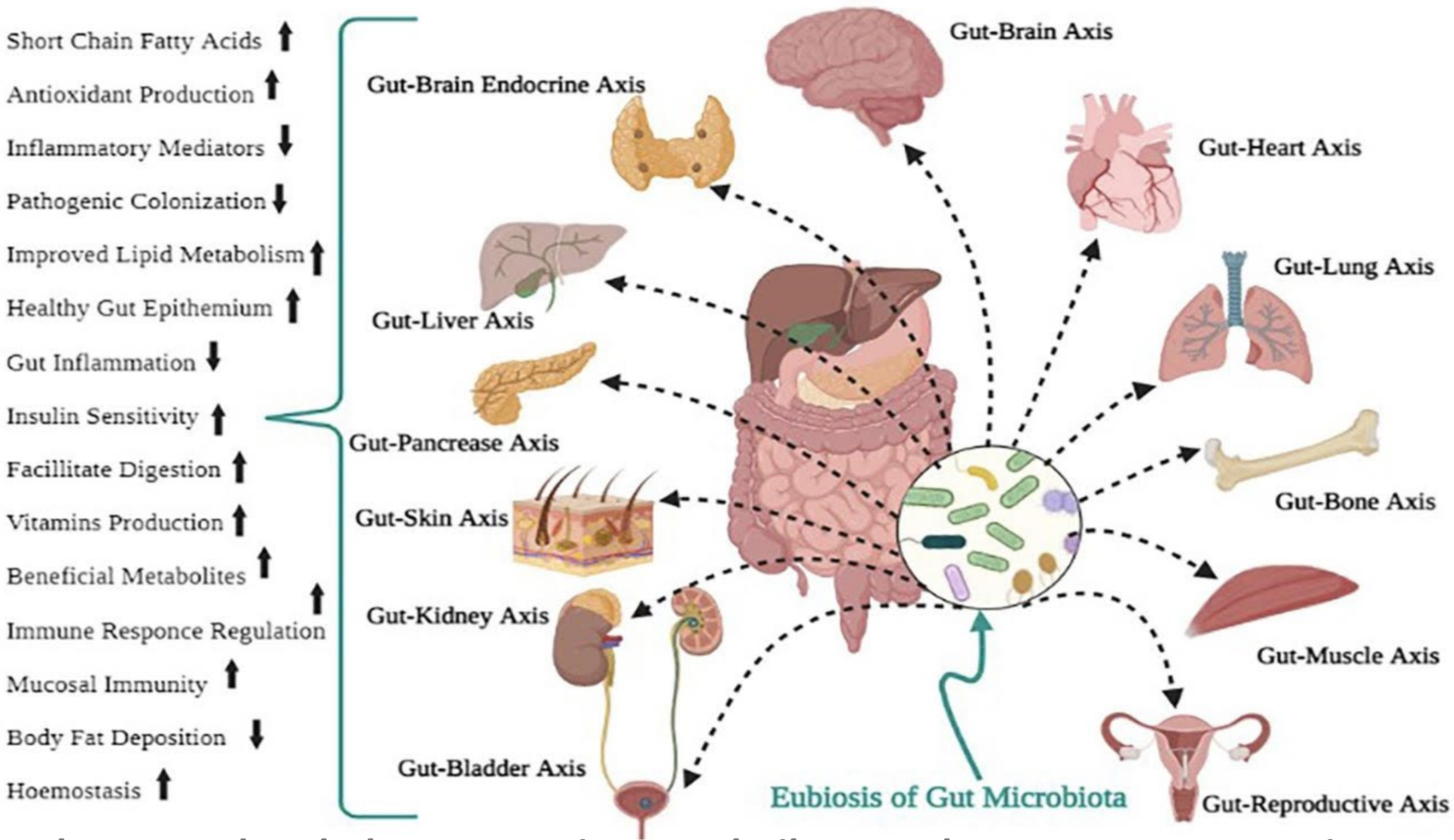
de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. Gut. 2022 May;71(5):1020-1032.

Metaboliti prodotti dal microbiota intestinale e relative funzioni

Metabolites	Functions	References
Bile acid metabolites; including deoxycholic acid (DCA) and lithocholic acid (LCA)	Regulate bile acid, cholesterol, lipid, glucose, and energy metabolism, show antimicrobial effects, and activate host nuclear receptors and cell signaling pathways.	Ramírez-Macías et al., 2022
Short-chain fatty acids (SCFAs) metabolites such as propionate and butyrate	Regulate food intake and insulin secretion, also aid in maintaining body weight.	Psichas et al., 2015; Larraufie et al., 2018
Branched-chain fatty acids (BCFA) including isobutyrate, isovalerate	Histone deacetylase (HDAC) inhibition, increased histone acetylation.	Mischke and Plösch, 2016
Indole derivatives including indoxyl sulfate and indole-3-propionic acid (IPA)	IPA exhibits neuroprotective effects, acts as a powerful antioxidant, and regulates intestinal barrier function. Indoxyl sulfate is a uremic toxin that accumulates in the blood of individuals with impaired excretion systems.	Hendrikx and Schnabl, 2019
Lipopolysaccharide (LPS), peptidoglycan (PGN), lipoteichoic acid (LTA)	Epigenetic regulation of genes in colorectal cancer, modulation of chromatin structure and transcriptional activity.	Lightfoot et al., 2013; Mischke and Plösch, 2016
Phenolic derivatives include 4-OH phenylacetic acid, urolithins, enterodiol, and 9-prenylnaringenin	Exhibit antimicrobial effects, maintain intestinal health, and protect against oxidative stress.	Larrosa et al., 2010
Choline metabolites include choline, trimethylamine N-oxide (TMAO), and betaine	Regulating lipid metabolism, and glucose synthesis contribute to the development of cardiovascular disease.	Smallwood et al., 2016
Polyamines include putrescine, spermidine, and spermine	Sustaining the high proliferation rate of intestinal epithelial cells enhances intestinal barrier integrity and enhances the systematic adaptive immune system.	Rooks and Garrett, 2016; Tofalo et al., 2019
Vitamins including thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), pantothenic acid (B5), biotin (B7), folate (B11-B9), cobalamin (B12), and menaquinone (K2)	Help in red blood cell formation, DNA replication, and repair, work as an enzymatic co-factor, and enhance immune functioning.	Nicholson et al., 2012; Forster et al., 2017
Ethanol	Protein fermentation metabolites may be involved in NAFLD progression.	Yao et al., 2016; Wu et al., 2021
Hydrogen sulfide (H2s)	Reduction/neutralization of reactive oxygen species.	Afanas'ev, 2014; Mischke and Plösch, 2016

Afzaal M, Saeed F, Shah YA, Hussain M, Rabail R, Socol CT, Hassoun A, Pateiro M, Lorenzo JM, Rusu AV, Aadil RM. Human gut microbiota in health and disease: Unveiling the relationship. Front Microbiol. 2022 Sep 26;13:999001.

Microbiota intestinale e organismo umano: una comunicazione difficile
EUBIOSI vs DISBIOSI



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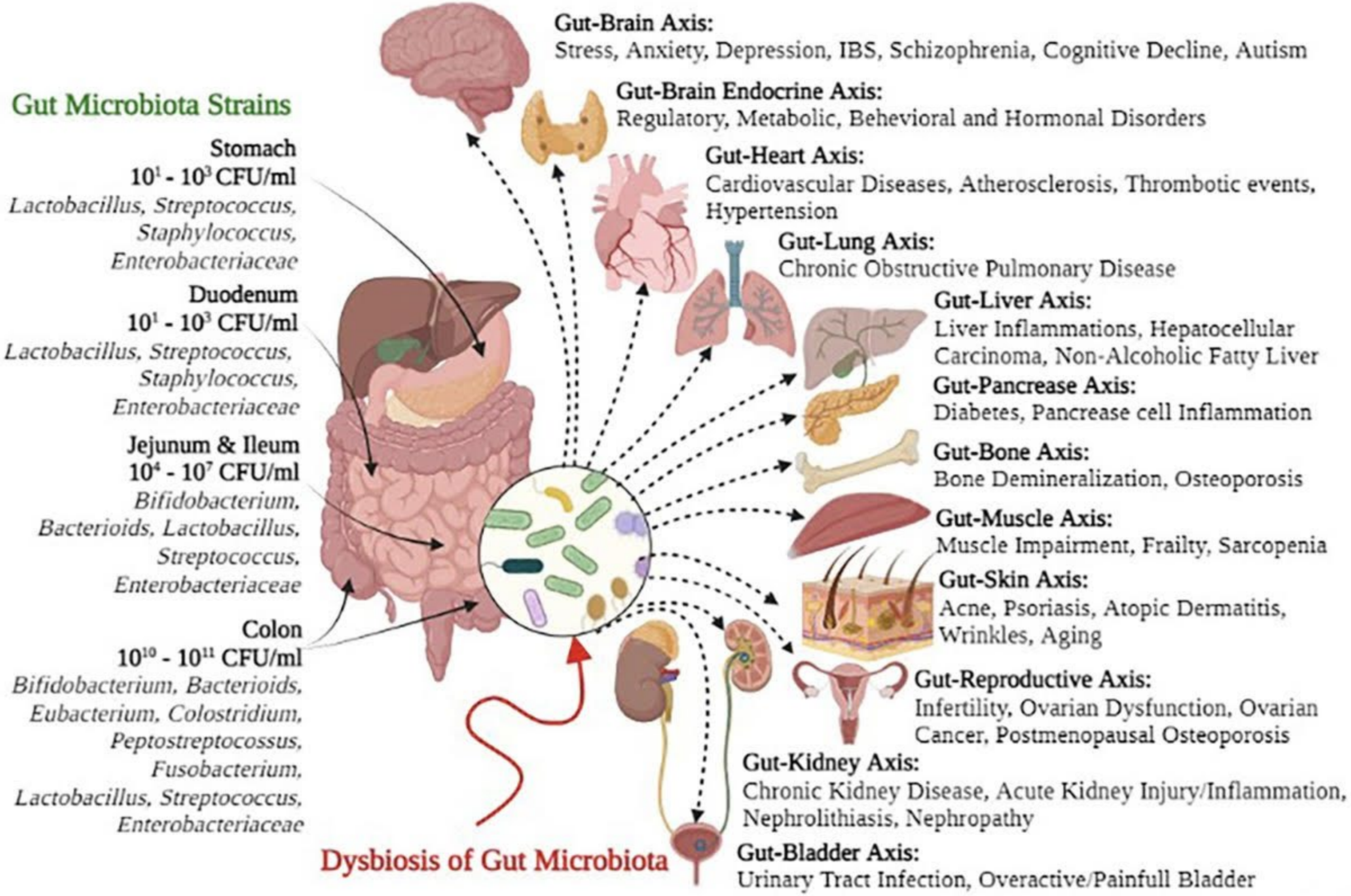

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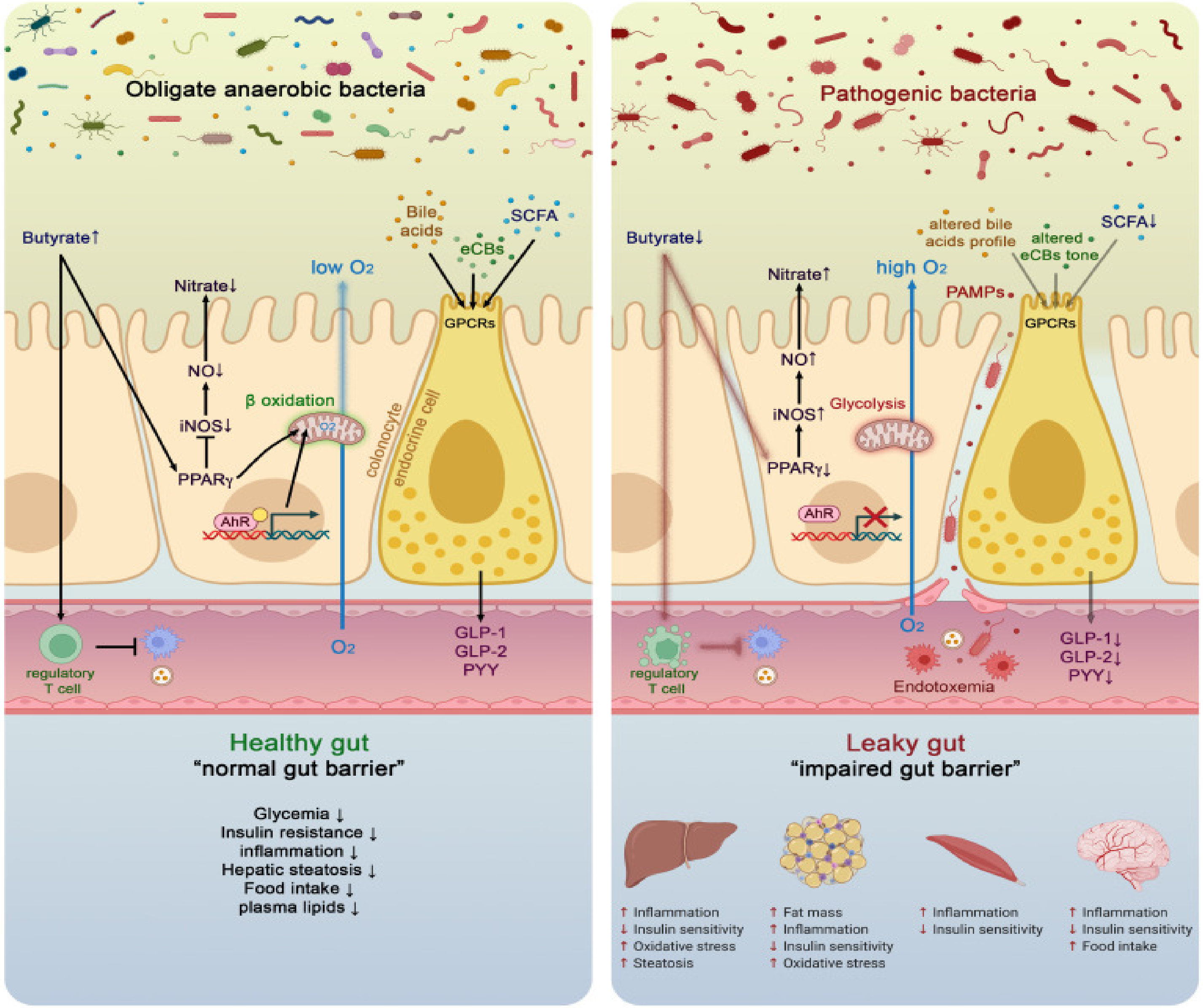
Microbiota e ospite: intestino sano vs intestino "malato"



de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome anc
health: mechanistic insights. Gut. 2022 May;71(5):1020-1032.

Obesita' e microbiota intestinale: una convivenza difficile

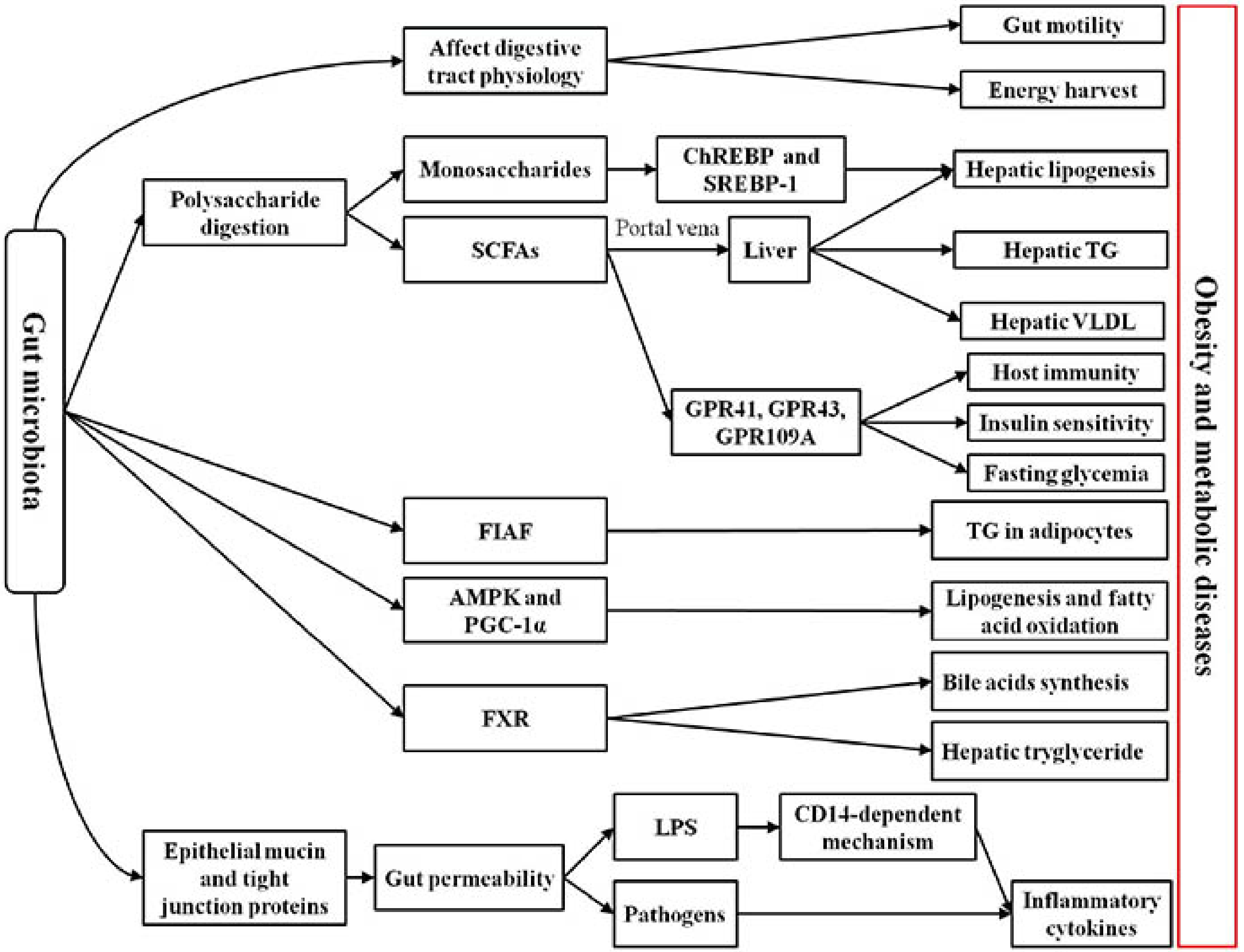
Relazione tra microbiota e obesità:

1-aumento del fabbisogno energetico

2-aumento deposito di grassi

3-effetto sul meccanismo di sazietà(gut-brain axis)

4-induzione di uno stato infiammatorio cronico



Kang Y, Cai Y. Gut microbiota and obesity: implications for fecal microbiota transplantation therapy. Hormones (Athens). 2017 Jul;16(3):223-234.

MICROBIOTA INTESTINALE ed OBESITA': quando la comunicazione fallisce

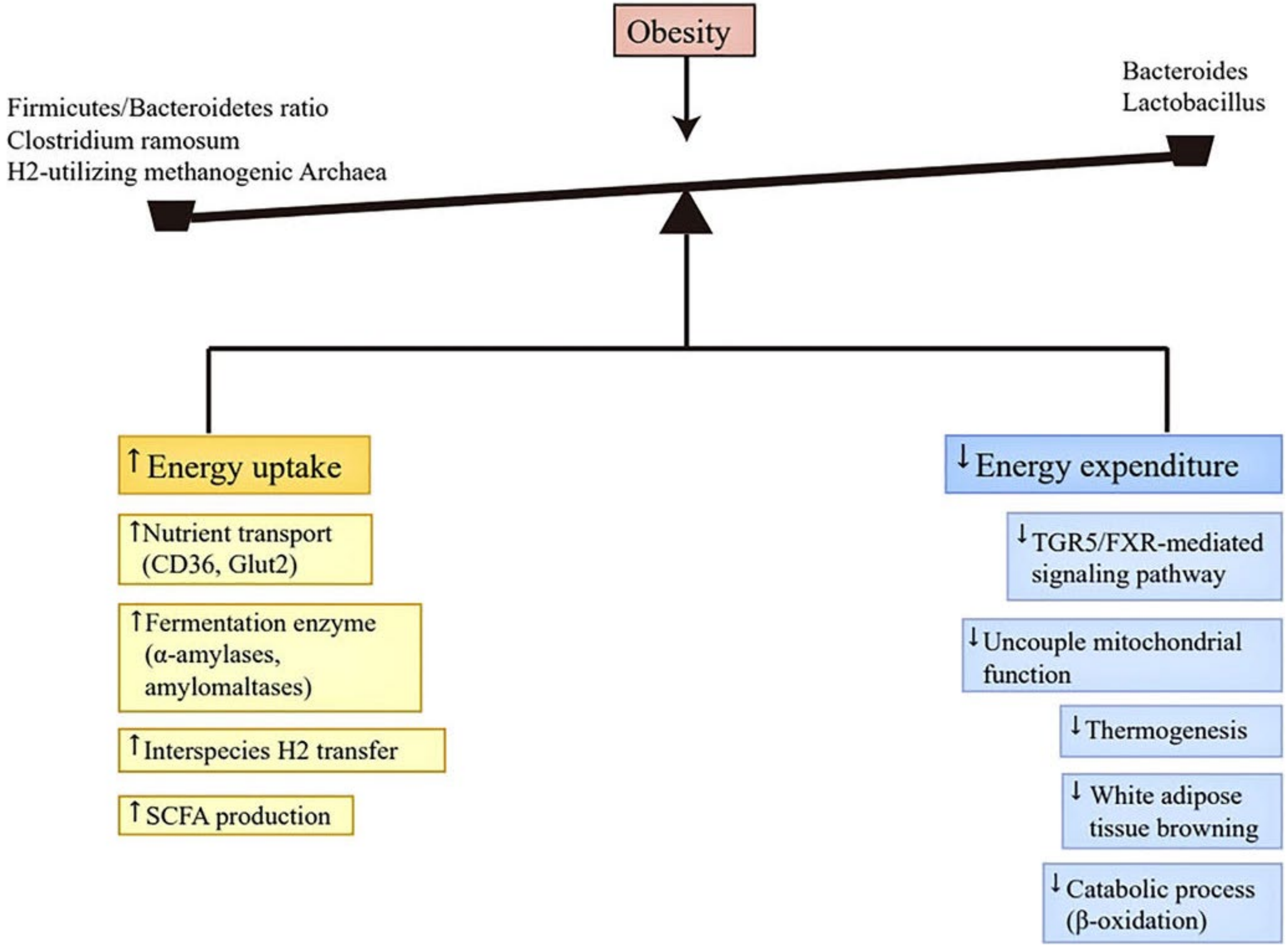
- **Disregolazione dell'omeostasi energetica**:

- ⬆ Clostridium ramosum (Firmicutes)➔ ⬆ efficienza del'uptake energetico tramite aumentata espressione di GLUT2 e CD36 (trnaslocasi di acidi grassi) .
- ⬆ Firmicutes e Firmicutes/Bacteroidetes ratio correlata con la digestione di polisaccaridi indigeribile e la successiva produzione di monosaccaridi e SCFA(short chain fatty acids) soprattuto acetato e butirrato, e estrazione di altri metaboliti che altrimenti verrebbero escreti nelle feci
- La riduzione degli acidi biliari indotta dalla disbiosi nel paziente obeso(⬇ Bacteroides e Lactobacillus) compromette processi catabolici portando ad una ulteriore progressione di malattia

- **Induzione di uno stato infiammatorio cronico**

- ⬆ gram negativin(Veillonella)➔⬆ lipopolisaccaride
- ⬇Akkermansia muciniphila ➔ translocazione batterica e alterazione della integrità della barriera immunitaria intestinale
- Attivazione LPS del TLR4 presente nei macrofagi e nel tessuto adiposo ➔produzione di citochine proinfiammatorie(TNF-α, IL-6 , MCP-1)

MICROBIOTA INTESTINALE ed OBESITA': questione di equilibrio



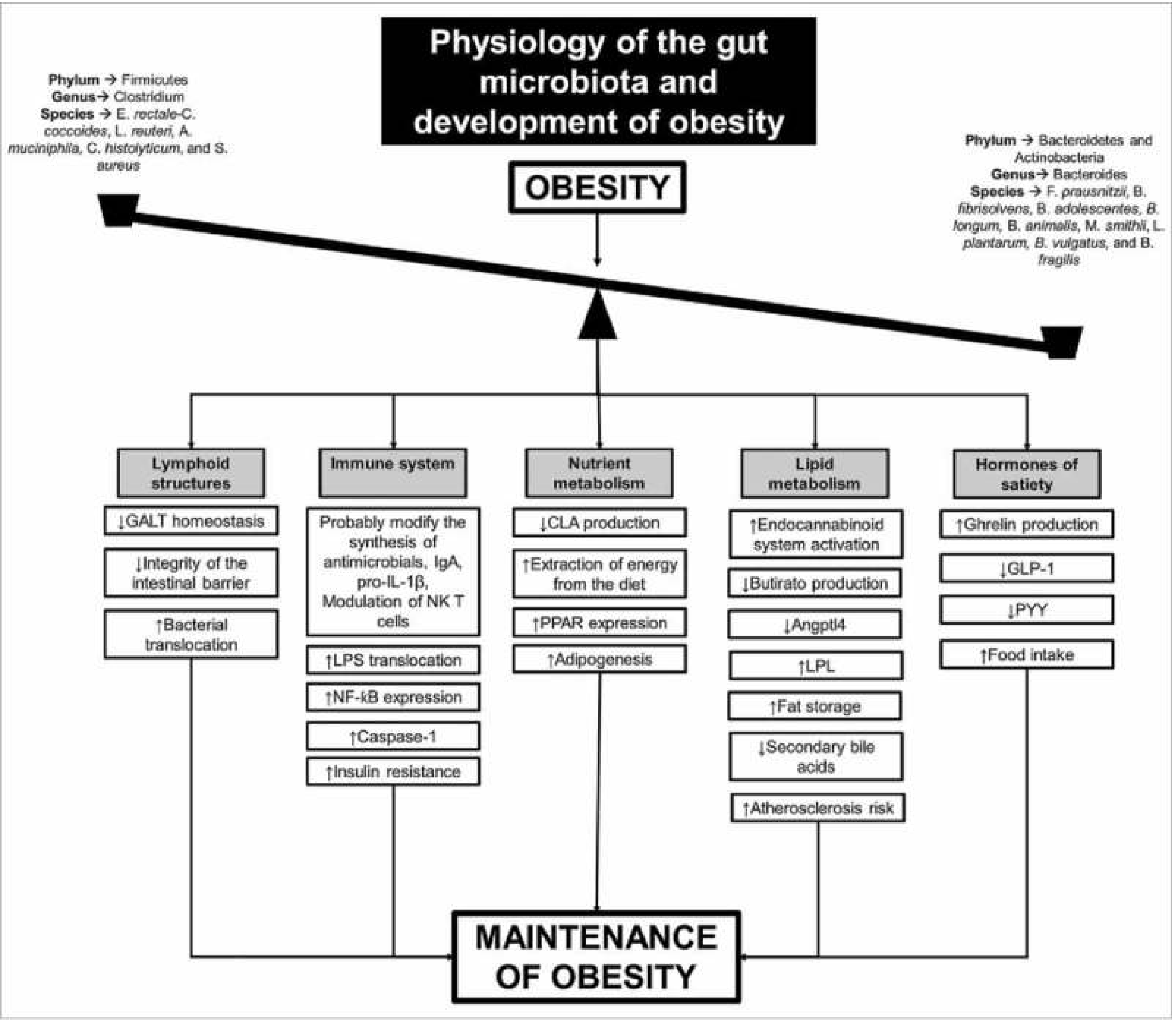
Cheng Z, Zhang L, Yang L, Chu H.. The critical role of gut microbiota in obesity. Front Endocrinol (Lausanne)2022 Oct 20;13:1025706.

MICROBIOTA INTESTINALE e OBESITA' : questione di equilibrio

Microbial taxa in obese subjects with metabolic abnormalities

	risk-increasing bacteria	risk-lowering or protective bacteria
Metabolic syndrome	*Coriobacteriaceae*	*Faecalibacterium prausnitzii, Parabacterodes, Bacteroides caccae, Parabacterodes distasonis* and *Oscillospira*
impaired glucose tolerance or Insulin resistance	*Bacteroides ovatus and Enterobacteriaceae* *Prevotellaceae and Veillonella*	*Coprococcus, Haemophilus parainfuenzae, Parabacteroides* and *Bacteroides caccae* *Oscillibacter sp, Agathobaculum butyriciproducens, Haemophilus parainfluenzae, Veillonella parvula, Dialister invisus*
High diastolic blood pressure	*Clostridium* and *Clostridiaceae*	
low high-density lipoprotein cholesterol	*Lachnospiraceae, Gemellaceae* and *Turicibacter*	
Cardiovascular risk	*Prevotellaceae and Veillonella*	*Coriobacteriaceae*

Sarmiento-Andrade Y, Suárez R, Quintero B, Garrochamba K, Chapela SP. Gut microbiota and obesity: New insights. Front Nutr. 2022 Oct 14;9:1018212.



Gomes AC, Hoffmann C, Mota JF. The human gut microbiota: Metabolism and perspective in obesity. Gut Microbes. 2018 Jul 4;9(4):308-325.

MICROBIOTA INTESTINALE e OBESITA'
NUOVE PROSPETTIVE e STRATEGIE TERAPEUTICHE

Possibili interventi sul microbiota intestinale :

- **probiotici, prebiotici, sinbiotici**
- **Trapianto di microbiota fetale(FMT, fecal microbiota transplant)**
- **Bacterial Consortium Therapy(BCT): utilizzo di composizioni predefinite di farmaci prodotte da ceppi batterici isolati al fine di indurre una risposta infiammatoria specifica.➔modulazione dello stato infiammatorio cronico intestinale al fine di ristabilire lo stato di**
- **Phage Therapy(virus batteriofaci specifici): problematica di dosaggio e di tempistiche**

PROBIOTICI

Definizione WHO: microrganismi viventi che, se amministrati in quantità sufficiente, conferiscono proprietà benefiche all'ospite.

- **se amministrato in modelli murini obesi il Bifidobacterium pseudocatenulatum CECT 7765 diminuisce notevolmente la rispostsa infiammatoria indotta dalla dieta ad alto contenuto lipidico(HFD, high fat diet) (***Moya-Pérez A, Neef A, Sanz Y. Bifidobacterium pseudocatenulatum cect 7765 reduces obesity-associated inflammation by restoring the lymphocyte-macrophage balance and gut microbiota structure in high-fat diet-fed mice. PloS One (2015) 10(7):e0126976***.**
- **Akkermansia muciniphila : meccanismo protettivo contro l'obesità migliorando la dislipidemia, l'insulino resistenza e lo sviluppo della massa (***Plovier H, Everard A, Druart C, Depommier C, Van Hul M, Geurts L, et al.. A purified membrane protein from akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nat Med (2017) 23(1):107–13)*

Cheng Z, Zhang L, Yang L, Chu H.. The critical role of gut microbiota in obesity. Front Endocrinol (Lausanne)2022 Oct 20;13:1025706.

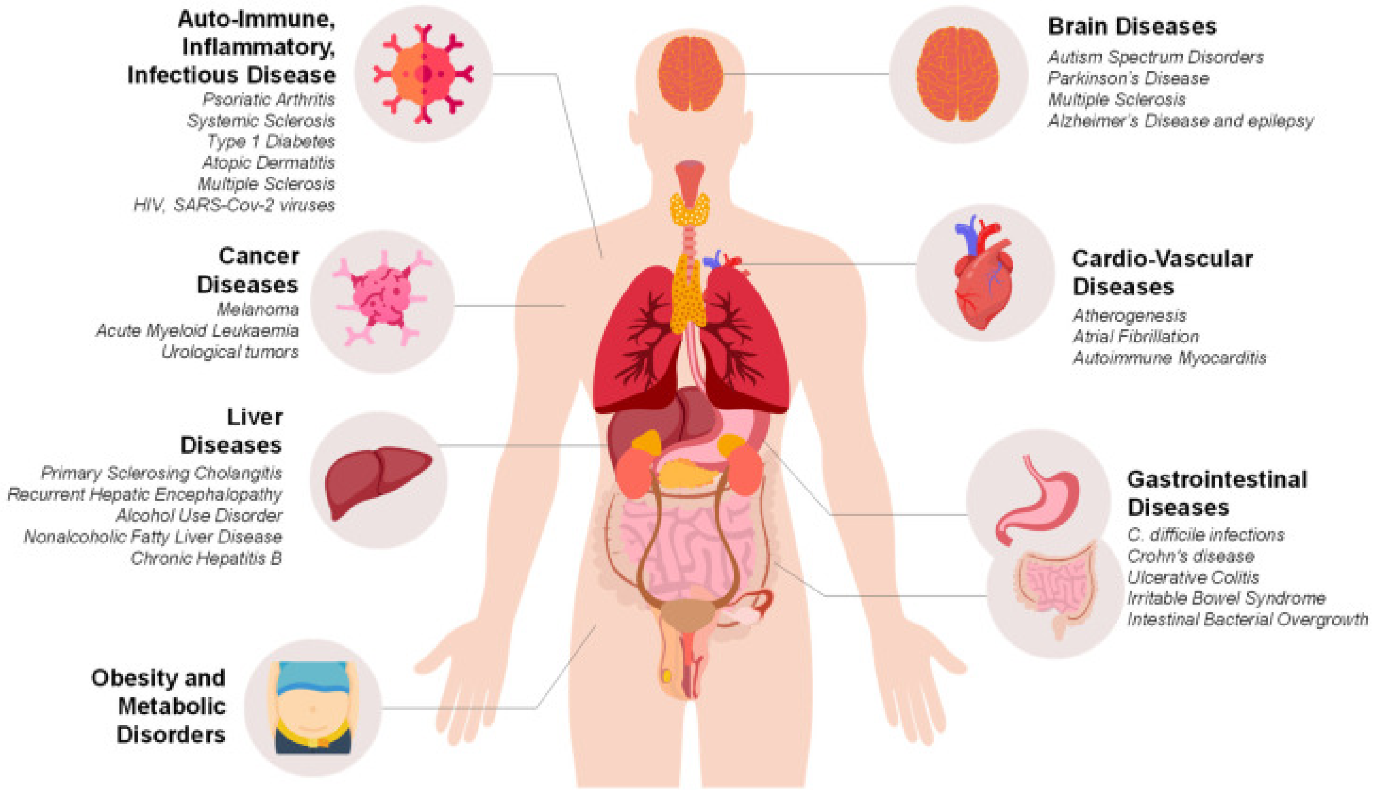
PREBIOTICI

Definizione: componenti indigeribili utilizzati selettivamente dal microbiota ospite provvedendo al mantenimento dell'eubiosi e un adeguato equilibrio tra processi anabolici e catabolici.

- Nei modelli murini di obesità, la somministrazione di prebiotici (oligofruttosio e inulina) induce la secrezione degli ormoni della sazietà(PYY e GLP-1), il ripristino del microbiota «eubiotico» (↓Firmicutes e ↑ Bacteroidetes, Lactobacillus e Bifidobacteria. ***(Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG, Neyrinck AM, et al.. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. Diabetes (2011) 60(11):2775–86.)***
- Campioni fecali estratti da pazienti obesi dopo il consumo di oligofruttosio e inulina : ↑Bacteroidetes e calprotectina fecale(***Neyrinck AM, Rodriguez J, Zhang Z, Seethaler B, Sánchez CR, Roumain M, et al.. Prebiotic dietary fibre intervention improves fecal markers related to inflammation in obese patients: Results from the Food4gut randomized placebo-controlled trial. Eur J Nutr (2021) 60(6):3159–70.)***

TRAPIANTO DI MICROBIOTA FECALE(FMT, FECAL MICROBIOTA TRANSPLANT)

Definizione: trapianto di sospensione fecale proveniente da donatore vivente sano all'interno dell'intestino di un paziente selezionato al fine di ricostituire il microbiota intestinale e trattare la malattia ad esso relata



Biazzo M, Deidda G. Fecal Microbiota Transplantation as New Therapeutic Avenue for Human Diseases. J Clin Med. 2022 Jul 15;11(14):4119.

FMT e OBESITA’

- health-promoting bacteria (*Lactobacillus, Bifidobacterium, Akkermansia)* :
- opportunistic pathogens (*Enterobacteriaceae, Desulfovibrionaceae*, and *Streptococcaceae*):

- **Effetto del FMT su diabete e sindrome metabolica**

-pazienti diabetici: ↓*Akkermansia muciniphila* rispetto ai controlli sani. *Akkermansia muciniphila* è un batterio Gram-negative che migliora la tolleranza glucidica e la insulino resistenza. Se trapiantato nei soggetti diabetici➔ ↓ LPS e ↑ barriera immunitaria (***Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med. (2019) 25:1096–103. 10.1038/s41591-019-0495-2***)

- ↑ colonie di batteri produttori di butirrato(Clostridium, Roseburia, Faecalibacterium prausnitzii). Il Butirrato è un SCFA associato con migliorata sensibilità all’insulina e rallentamento della progrssione del ***(Liu F, Li P, Chen M, Luo Y, Prabhakar M, Zheng H, et al. Fructooligosaccharide (FOS) and Galactooligosaccharide (GOS) Increase Bifidobacterium but reduce butyrate producing bacteria with adverse glycemic metabolism in healthy young population. Sci Rep. (2017) 7:11789. 10.1038/s41598-017-10722-2)***

FMT e OBESITA’

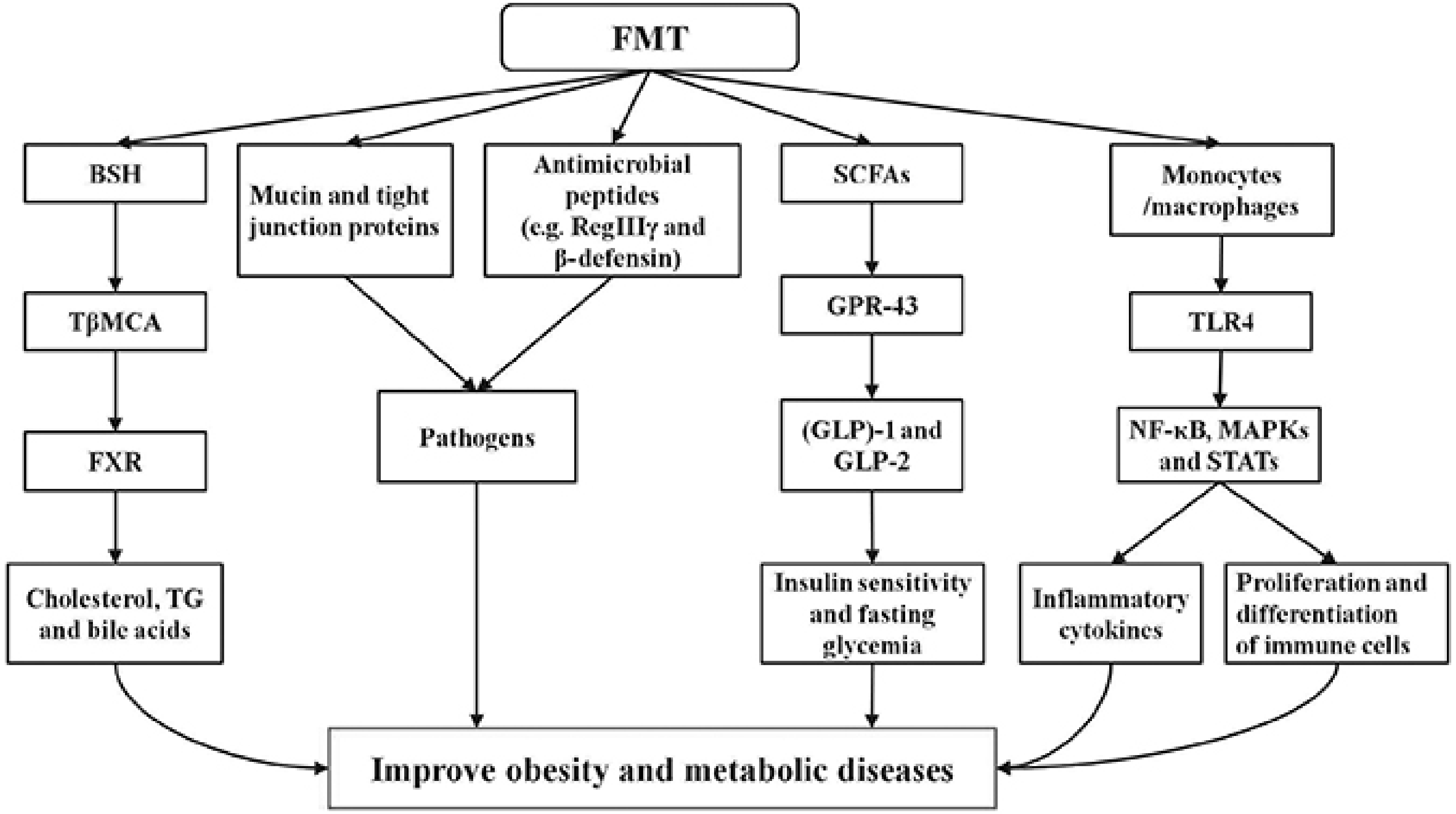
Table 2. Changes in microbiota composition associated with obesity and FMT therapeutic strategies

Models	Disease	Implicated microbiota	New therapeutic strategies	Implicated microbiota	Reference
Mice	Obesity	*Bacteroidetes* ↓, *Firmicutes* ↑	FMT	*Bacteroidetes* ↑, *Firmicutes* ↓	31
Human	Metabolic syndrome	NO	FMT	Butyrate-producing microbiota (e.g. *Roseburia intestinalis* or *Eubacterium hallii*)	56
Mice	Obesity	NO	FMT	NO	61
Mice	Obesity	*Gammaproteobacteria (Escherichia)* ↓, *Verrucomicrobia (Akkermansia)* ↓ and *Bacteroidales* ↓	FMT	*Verrucomicrobiales* ↑, *Akkermansia* ↑, *Alistipes* (*Bacteroidetes* phylum) ↑	65
Mice	Obesity	NO	FMT	NO	66

NO refers to no test or no research.

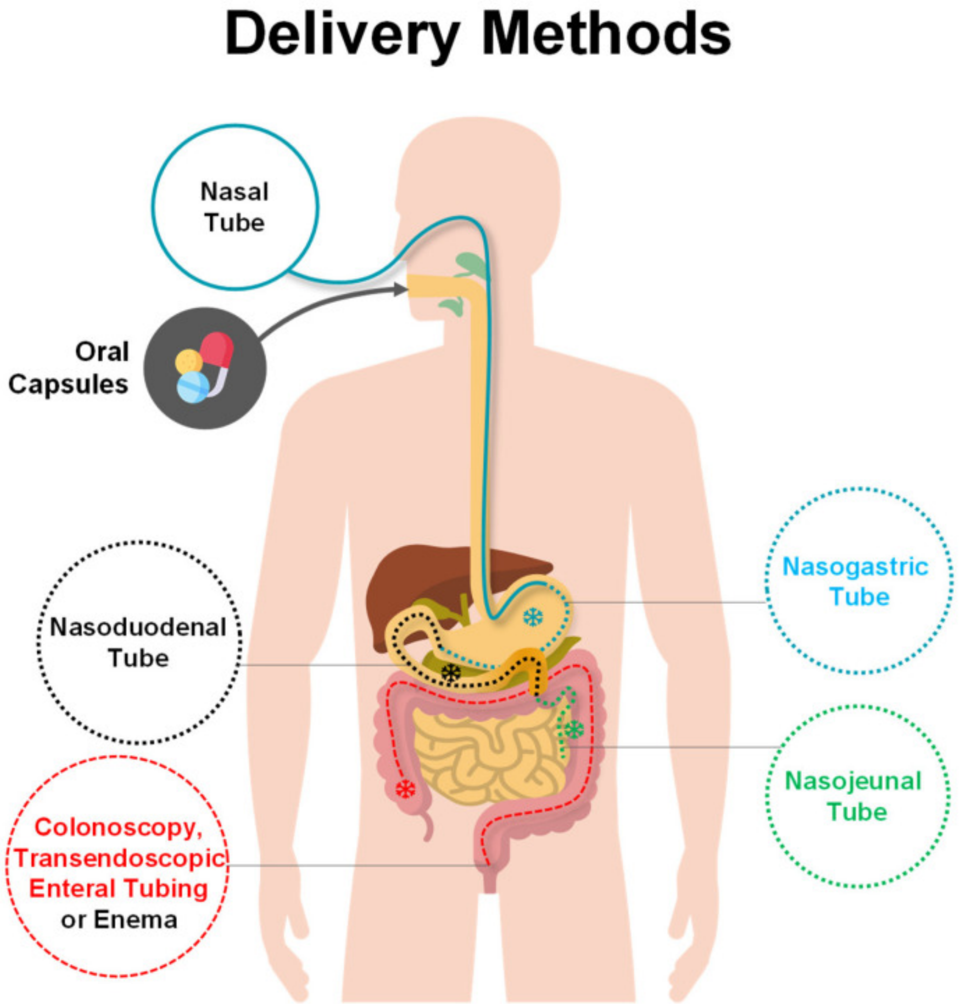
Kang Y, Cai Y. Gut microbiota and obesity: implications for fecal microbiota transplantation therapy. Hormones (Athens). 2017 Jul;16(3):223-234.

FMT e OBESITA'



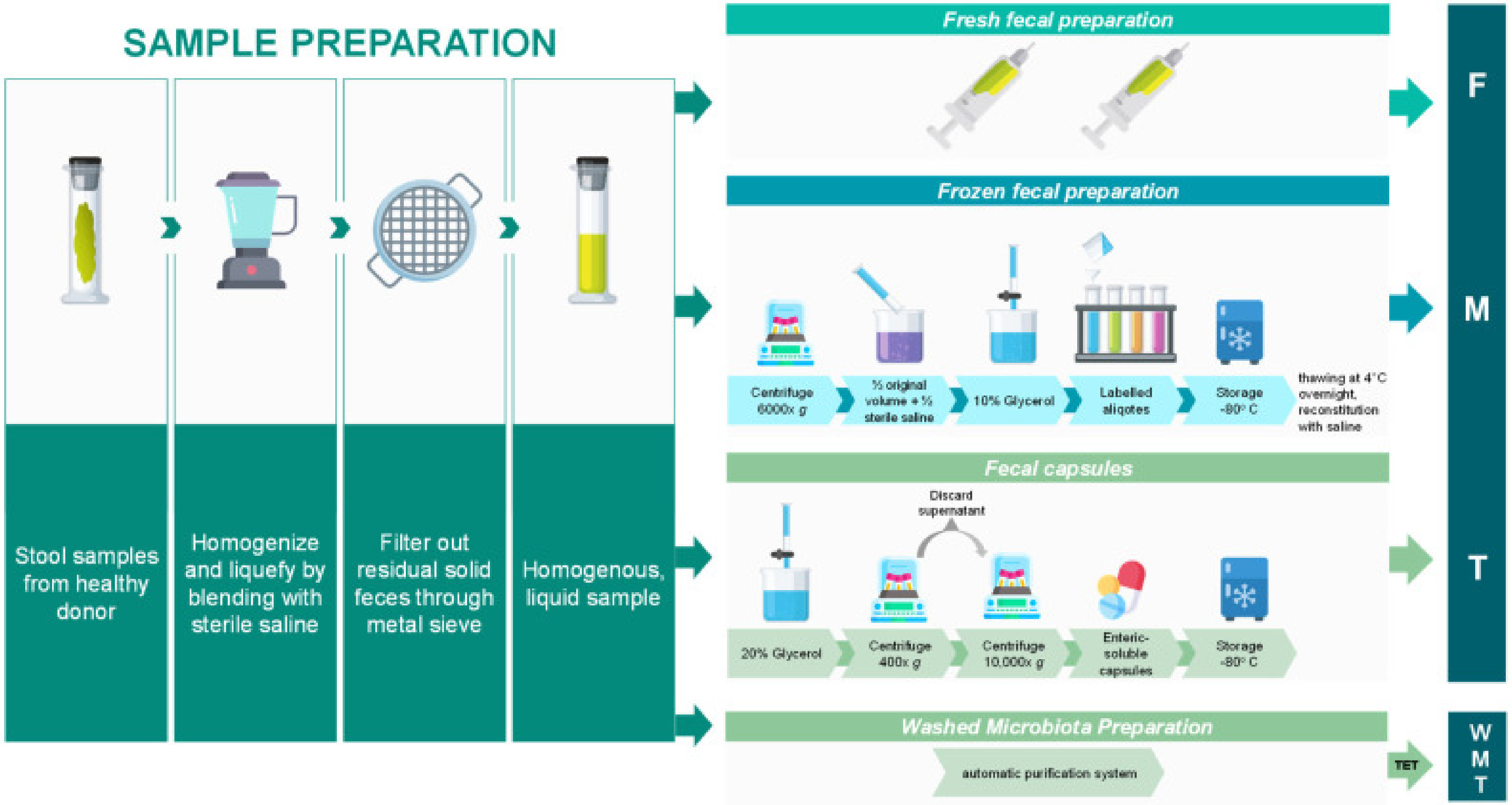
Kang Y, Cai Y. Gut microbiota and obesity: implications for fecal microbiota transplantation therapy. Hormones (Athens). 2017 Jul;16(3):223-234.

FMT: METODICA E SELEZIONE DEI PAZIENTI CANDIDATI



Biazzo M, Deidda G. Fecal Microbiota Transplantation as New Therapeutic Avenue for Human Diseases. J Clin Med. 2022 Jul 15;11(14):4119.

FMT: METODICA E SELEZIONE DEI PAZIENTI CANDIDATI



Biazzo M, Deidda G. Fecal Microbiota Transplantation as New Therapeutic Avenue for Human Diseases. J Clin Med. 2022 Jul 15;11(14):4119.

FMT: METODICA E SELEZIONE DEI PAZIENTI CANDIDATI

Inclusion criteria
Age: 18–50 ani (Children under 18 can only donate with parental consent)
BMI 18.5–30 kg/m^2
Should feel good at the time of donation and are similar to age as recipient, if possible

Hamamah S, Gheorghita R, Lobiuc A, Sirbu IO, Covasa M. Fecal microbiota transplantation in non-communicable diseases: Recent advances and protocols. Front Med (Lausanne). 2022 Dec 8;9:1060581

Exclusion criteria

High risk behavior

- Use of drugs or other injections without a prescription
- Exposure to HIV, HBV, or HCV in the last 12 months
- Unprotected sexual contact or prostitution in the last 12 months
- Tattoos and piercings made in the last 6 months
- Incarceration
- Risk factors for Creutzfeldt-Jakob disease
- Chronically poor diet
- Homelessness
- Pregnancy
- Frequent activities involving animal (to exclude the risk of transmission of zoonotic infections)
- Diarrhea (more than three stools per day) among close contacts members (including children) within 4 weeks before donation
- Person is in a vulnerable group, unable to take care of him/her or unable to protect him/her from significant harm or exploitation

Current contagious diseases

- Fever, vomiting, diarrhea, or other symptoms of infection in the last 4 weeks
- Vaccinations or injections in the last 8 weeks
- Blood transfusion, accidental sting with needles exposed to another person's blood or biological fluids in the last 12 months
- International travel to countries with poor hygiene, in the last 6 months

Other conditions

- Family members with active gastrointestinal infections
- Antibiotic treatment in the last 3 months
- Organ/tissue transplantation
- *Helicobacter pylori* induced ulcers
- Gastrointestinal diseases, celiac disease, irritable bowel syndrome, chronic constipation, gastrointestinal tumors, or major gastrointestinal tract surgery
- Family history of colorectal cancer (more than 2 grade two relatives have/have had the disease)
- Autoimmune disease
- Treatment with immunomodulatory drugs
- Other cancers and active chemotherapy for other diseases
- History of metabolic syndrome, obesity (BMI > 30 kg/m^2) or malabsorption
- Chronic pain syndrome or other neurodegenerative diseases
- Diabetes
- Autism
- Cardiovascular disease, stroke
- Active or history of mental illness; depression requiring treatment
- Systemic autoimmunity or atopic diseases
- Anterior prosthetic implant (e.g., metal heart valve, joint replacement, ventricular-peritoneal shunt, cardiac stent)
- Allergy to tested antibiotics
- Known contagious disease or at least 2 weeks after complete recovery from infectious diseases (e.g., chickenpox)

Hamamah S, Gheorghita R, Lobiuc A, Sirbu IO, Covasa M. Fecal microbiota transplantation in non-communicable diseases: Recent advances and protocols. Front Med (Lausanne). 2022 Dec 8;9:1060581

FMT: applicazione nella pratica clinica

Clinical application	Study model	Effects in host related to obesity	Reference
Akkermansia muciniphila	Obese adults	Insulin sensitivity ↑ Insulinemia and total plasma cholesterol ↓	5
SCFAs mixtures	Normoglycemic men	Fasting fat oxidation, resting energy expenditure ↑ PYY ↑	152
Propionate	Overweight adult humans	PYY, GLP-1 ↑ Energy intake and weight gain ↓	30
BAs	Participants with obesity and diabetes	Glucose, fructosamine, insulin, LDL, FGF19 ↓ GLP-1, C-peptide ↑	153
FMT	Obese adolescent	No effect of FMT on weight loss in adolescents with obesity	154
FMT	Adults with obesity and mild–moderate insulin resistance	No clinically significant metabolic effects during the study	155
FMT	Obese patients	Taurocholic acid levels↓ BAs profiles began to resemble No significant changes in mean BMI	156
FMT	Male with the metabolic syndrome	Not observe metabolic change insulin sensitivity ↑	157
FMT	Patients with severe obesity and metabolic syndrome	Improvements in HOMA2-IR	158
FMT	Obese subjects with T2D	*Bifidobacterium* and *Lactobacillus* ↑ LDL cholesterol, liver stiffness ↓	159
Green-Mediterranean dieters and FMT	Obese or dyslipidemic participants	Prevents weight gain and improves glucose tolerance	160

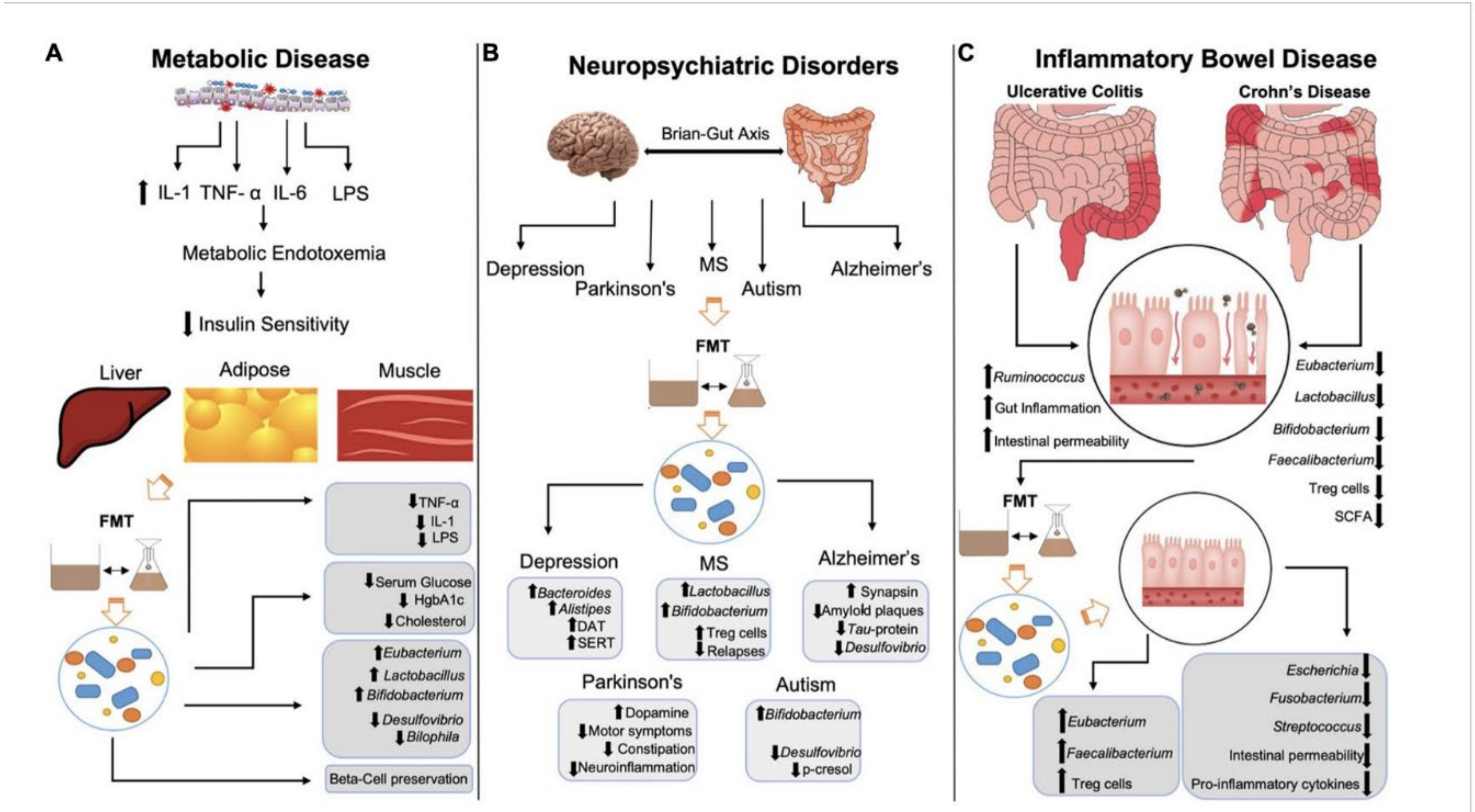
Abbreviations: BA, bile acid; BMI, body mass index; FGF, fibroblast growth factor; FMT, fecal microbiome transplantation; GLP-1, glucagon-like peptide 1; LDL, low-density lipoprotein; SCFA, short-chain fatty acid; T2D, type 2 diabetes.

Lin K, Zhu L, Yang L. Gut and obesity/metabolic disease: Focus on microbiota metabolites. MedComm (2020). 2022 Sep 1;3(3):e171.

FMT: applicazione nella pratica clinica

Disease studied	Study description	Observed effect	Adverse effects	Gut microbiota alterations
Obesity	Oral capsule FMT to obese adolescents ($n = 42$) vs. sham treatment ($n = 45$)	No effect on BMI. Reduced abdominal adiposity observed at 12 weeks	Loose stools, abdominal pain, nausea, vomiting, bloody stools	↑*Faecalibacterium prausnitzii, Alistipes, Bacteroides* ↓ *Escherichia coli*
	Endoscopic FMT on obese patients. FMT ($n = 20$) vs. FMT + lifestyle intervention (LSI) ($n = 21$) vs. sham FMT treatment ($n = 20$)	No significant weight loss in FMT only and sham FMT groups. Reduced liver stiffness, total and LDL cholesterol with weight loss in the FMT + LSI group at 24 weeks	Nausea, vomiting, abdominal pain No FMT related serious adverse effects	FMT alone: ↑ *Faecalibacterium, Roseburia, Eubacterium* FMT + LSI: ↑ *Bifidobacterium, Lactobacillus*
Type 2 diabetes mellitus (T2DM)	Transendoscopic enteric tube FMT treatment ($n = 17$) on T2DM patients	64% with significant decrease in HgbA1c, blood glucose and uric acid with elevated C-peptide at 12 weeks	none	↑ *Anaerotruncus, Rikenenellaceae*
	Diet only ($n = 8$) vs. Diet + Oral capsule FMT group ($n = 8$) on T2DM patients	Both groups showed decreased blood glucose and weight loss after 90 days with FMT accelerating the effect	None	↑ *Bifidobacterium, Lactobacillus* ↓ *Desulfovibrio, Bilophila*
Type 1 diabetes mellitus (T1DM)	Allogenic FMT ($n = 11$) vs. Autologous FMT ($n = 10$) in T1DM patients	Preserved C-peptide levels and beta-cell function at 12 months	None	*Desulfovibrio piger* concentrations predicted beta-cell function
	Nasojejunal FMT on a 24-year-old patient with T1DM and depression	Improved blood glucose, HgbA1c, constipation, nutritional status Depression symptoms resolved	None	↑ *Bifidobacterium, Blautia, Faecalibacterium, Bacteroides, Eubacterium, Streptococcus* ↓*Alistipes, Escherichia, Parabacteroides*
Diabetic kidney disease (DKD)	Rectal probe FMT into a mouse model with T2DM and DKD	No weight gain Reduced insulin resistance, TNF-α and albuminuria		↑ *Odoribacteraceae*
Metabolic syndrome	Oral gavage FMT in metabolic syndrome induced rodent model	Decreased LPS, TNF-α and oxidative stress post-FMT		↓ *Ruminococcus, Coprococcus*

Hamamah S, Gheorghita R, Lobiuc A, Sirbu IO, Covasa M. Fecal microbiota transplantation in non-communicable diseases: Recent advances and protocols. Front Med (Lausanne). 2022 Dec 8;9:1060581.



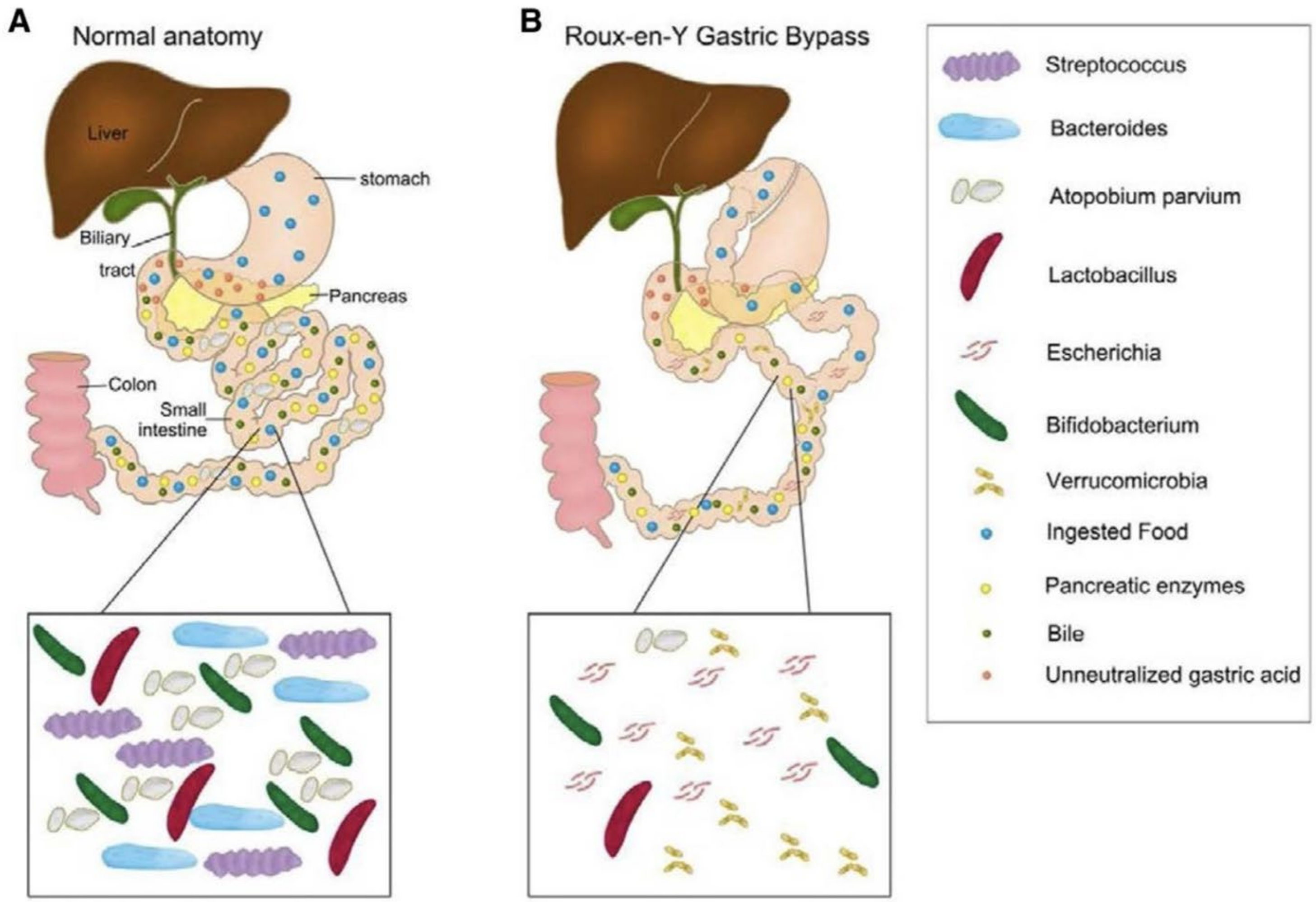
Hamamah S, Gheorghita R, Lobiuc A, Sirbu IO, Covasa M. Fecal microbiota transplantation in non-communicable diseases: Recent advances and protocols. Front Med (Lausanne). 2022 Dec 8;9:1060581

	Increase	Decrease
RYGB	Bacteroidetes[71] Firmicutes[81] Fusobacteria[73,75] Proteobacteria[73,75,78] *Akkermansia*[79,80] *Alistipes*[82] *Bacteroides*[82] *Citrobacter*[78,80] *Fusobacterium*[73] *Granulicatella*[73,80] *Klebsiella*[79,80] *Streptococcus*[76,79,80,83] *Veillonella*[73,76,78,80] *Alistipes shahii*[75,79] *Streptococcus parasanguinis*[75,79] *Streptococcus salivarius*[75] *Streptococcus thermophilus*[75,79] *Veillonella dispar*[75,78] *Veillonella parvula*[75,78]	Bacteroidetes[81] Firmicutes[78] Bifidobacteriaceae[73] *Anaerostipes*[78] *Bacteroides*[79] *Bifidobacterium*[73,82] *Blautia*[76,80,82] *Faecalibacterium*[78,83] *Coprococcus comes*[78] *Faecalibacterium prausnitzii*[75,78] *Streptococcus salivarius*[83]
SG	Bacteroidetes[81] Fusobacteria[74] *Akkermansia*[73,79] *Alistipes*[83] *Fusobacterium*[74] *Klebsiella*[79] *Streptococcus*[79,83] *Alistipes shahii*[79] *Faecalibacterium prausnitzii*[84] *Streptococcus parasanguinis*[79] *Streptococcus salivarius*[83] *Streptococcus thermophilus*[79]	Firmicutes[74] Bifidobacteriaceae[73,74] *Anaerostipes*[73] *Bacteroides*[79] *Bifidobacterium*[73] *Coprococcus comes*[84]

La chirurgia bariatrica induce un cambiamento nel microbiota intestinale se comparato con quello pre-operatorio

Obesity (Silver Spring). 2021 Apr;29(4):636-644

Obesità e microbiota



**Nell'obesità e in alcune condizioni ad essa associate si osserva una predominanza dei Firmicutes rispetto ai Bacteroides,
mentre il rapporto Firmicutes/Bacteroides diminuisce significativamente dopo RYBG**

Shi Y, et al. Medicine (Baltimore). 2022 Jul 22;101(29)

Microbiota e complicanze post-chirurgia bariatrica

- ⇨ ↑ impatto delle **complicanze** dopo RYGB o LSG (esofagite da reflusso, diarrea, dumping syndrome, anemia, malassorbimento) sul metabolismo attraverso il microbiota
- ⇨ ↑ ***Gammaproteobacteria*** correlata a **malassorbimento post-RYGB**
- ⇨ ***Faecalibacterium prausnitzii*:** strettamente correlato alla **diminuzione dei marker di infiammazione sistemica**, alla **diminuzione dell'insulino resistenza,** all'instaurarsi di uno **stato di infiammazione** di basso grado dopo chirurgia bariatrica. Numerosi studi hanno dimostrato che i suoi metaboliti possono prevenire la produzione di mediatori della flogosi sistemica e l'attivazione del fattore nucleare-kB
- ⇨ ↑ **batteri produttori di collagenasi** (*P. Aeruginosa e E.Faecalis)* associati ad un maggior tasso di fistole anastomotiche post-RYBG

Microbiota and diabetes: an evolving relationship

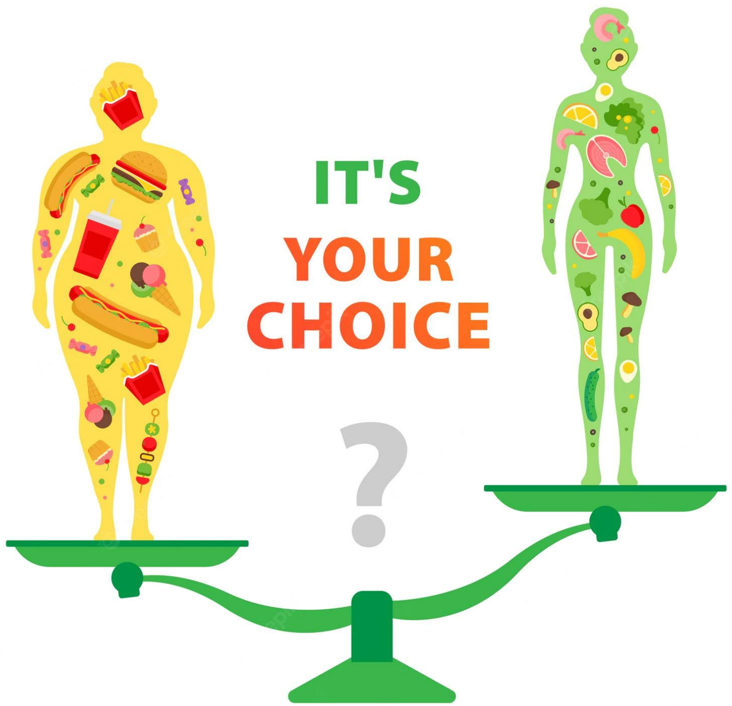
Herbert Tilg, Alexander R Moschen

An altered microbiota in metabolic disease might allow to initiate inflammatory processes. Such an altered microbiota might act 'locally' and via an impaired mucosal barrier act systemically. In support of such a concept, it has been recently demonstrated that patients with metabolic syndrome and T2D exhibit a remarkable endotoxaemia.[15 16] This is in accordance with the recently proposed concept of 'metabolic infection', where parts of the intestinal microbiota might affect systemic including adipose tissue inflammation.[17 18] In various disorders such as IBD or obesity a 'microbiotal signature' has been identified.[19 20] In this article we will discuss the

Tilg H, *et al*. *Gut* 2014;**63**:1513–1521. doi:10.1136/gutjnl-2014-306928

Ippocrate: la morte risiede nell'intestino …

Siate voi gli artefici del vostro intestino !!!!



ACCADEMIA SICOB II EDIZIONE

IL MANAGEMENT DELL'OBESITÀ

Grazie