obesities

MDPI

Review

Gut Microbiota and Obesity: The Chicken or the Egg?

Daniele S. Tassoni [1], Rodrigo C. O. Macedo [1], Felipe M. Delpino [2] and Heitor O. Santos [3,*]

[1] Department of Health Sciences, Universidade de Santa Cruz do Sul (UNISC), Av. Independência, 2293-Universitário, Santa Cruz do Sul 96815-900, Brazil; danitassoni123@gmail.com (D.S.T.); nutricionistarodrigomacedo@gmail.com (R.C.O.M.)
[2] Postgraduate Program in Nursing, Universidade Federal de Pelotas (UFPEL), R. Gomes Carneiro, 01-Balsa, Pelotas 96010-610, Brazil; fmdsocial@outlook.com
[3] Postgraduate Program, Faculdade UNIGUAÇU, EXXA Building—Pres. Bernardes Street, 2009—2nd Floor—Center, Cascavel 85801-180, Brazil
* Correspondence: heitoroliveirasantos@gmail.com

Abstract: Although the link between gut microbiota and obesity is increasingly reported, the pathophysiological mechanisms and clinical outcomes are still under debate. This overview of human and animal data addresses several pathophysiologic mechanisms, dietary habits, exercise and probiotic and symbiotic supplementation in the fields of gut microbiota and obesity. Overall, obesity impairs gut microbiota composition due to factors that may be linked to the onset of the disease, such as excessive consumption of high-energy foods, sugars and fats, as well as a low fiber intake and physical inactivity. Conversely, low-energy diets, physical exercise, and probiotic and prebiotic supplementations can enhance gut microbiota in patients with obesity, in addition to improving cardiometabolic markers. As for perspectives, further research is warranted to ascertain proper dietary manipulation, physical exercise protocols and dosing regimens of probiotics. Regarding the latter, the effects on indicators of obesity are clinically modest, and hence skepticism must be exercised.

Keywords: overweight; microbiome; diet; physical activity; probiotic; dysbiosis

Citation: Tassoni, D.S.; Macedo, R.C.O.; Delpino, F.M.; Santos, H.O. Gut Microbiota and Obesity: The Chicken or the Egg? *Obesities* **2023**, *3*, 296–321. https://doi.org/10.3390/obesities3040024

Academic Editor: Sara Baldassano

Received: 5 November 2023
Revised: 23 November 2023
Accepted: 23 November 2023
Published: 27 November 2023

1. Introduction

Obesity is a disease characterized by excess body fat and is associated with an increased risk of developing type 2 diabetes mellitus (T2DM), dyslipidemia, cardiovascular diseases (CVD), respiratory disorders, joint diseases, gastrointestinal diseases and some types of cancer [1,2]. According to WHO data [3], more than 1.9 billion adults worldwide were classified as overweight in 2016, of which more than 650 million suffered from obesity. In the United States, the trends of obesity indicate that nearly one in two adults will develop obesity by 2030, such that the prevalence will exceed 50% in 29 states [4]. Globally, the number of subjects who are overweight and obese will be approximately 1.35 billion and 573 million individuals by 2030, respectively [5].

Obesity is a multicausal disease in which lifestyle, environment, genetics and social, cultural, economic, psychological and physiological factors are some triggering factors [6]. Furthermore, gut microbiota seems to contribute to adiposity and influences the development and progression of obesity, since patients with obesity have an altered microbiome compared to lean individuals [7,8].

In addition to participating in the digestive and absorptive processes, gut microbiota plays an important role in immune response, metabolism, gene expression, vitamin synthesis and energy harvest from food [9]. A symbiotic relationship between bacteria in the intestinal lumen and the host promotes the renewal of cells present in the villi, the maintenance of the absorption surface, an increase in the content of microorganisms, and a reduction in intestinal transit time [10].

Disorders in the composition of gut microbiota may influence many physiological aspects [11]. The integrity of the intestinal barrier is affected by high-fat diets and entails

an elevated concentration of antigens, subsequently stimulating the immune system and developing insulin resistance [12]. A high-fiber diet—mostly from plant sources—in turn, is strongly associated with stimulating the diversity of beneficial bacteria and contributing to reducing the risk of chronic diseases [13]. Moreover, physical exercise and supplementation with probiotics and/or prebiotics can enhance gut microbiota in subjects with obesity.

Despite a myriad of research studies, further attention is needed to unify the mechanistic and clinical backgrounds of non-pharmacological strategies in the circles of obesity and gut microbiota. That said, this article aims to provide an overview of the crosstalk between obesity and gut microbiota by exploring putative mechanisms and clinical environments in an attempt to elucidate the causal relationship. Taken together, pathophysiological mechanisms, dietary habits, exercise and probiotic and symbiotic supplementation are addressed in this regard.

2. Materials and Methods

An overview of human and animal studies was carried out through a search for articles in databases Pubmed (Medline), Embase and Google Scholar with the terms (and respective entry terms) "Obesity", "Gut microbiota/Gut microbiome" and "Microbiota/microbiome" published until the search period of November 2022. Studies with observational design (cross-sectional or cohort) or clinical trials, published in English and Portuguese and published in the last 20 years were included. Animal studies were included to improve the physiological background as well; however, in vitro studies, case reports and editorials were excluded.

We included articles that associated being obese or overweight with the principal themes of the present study, such as physical activity, sedentary habits, lifestyle, foods, dietary patterns, gut microbiota, probiotics and prebiotics.

3. Results

A total of 6915 results were found, of which 695 were observational studies, 509 were clinical trials and 2322 were studies with animals. The articles were first selected by reading the titles and/or abstracts. After that, the studies were filtered by reading the complete manuscript, with 40 human studies (observational and clinical trials) and 25 experimental studies on animals remaining.

A summary of several studies reporting the link between gut microbiota and obesity in humans can be seen in Tables 1 and 2, and those in animals in Table 3. Collectively, weight loss induced by low-energy diets alone or combined with physical exercise or bariatric surgery is sharply associated with improved gut microbiota. Probiotic and prebiotic supplementations can also enhance gut microbiota, but their effects on indicators of obesity are modest and cannot be overrated. Weight loss strategies alone or combined with probiotics and/or prebiotics can not only improve gut microbiota but also cardiometabolic markers. However, high-fat, high-calorie diets along with a low-complex carbohydrate (CHO) pattern can be detrimental to gut microbiota. Finally, a couple of research studies shed light on the role of fecal transplantation in modulating gut microbiota.

Further physiological and clinical backgrounds can be seen in the topics below.

Table 1. Clinical trials that evaluated gut microbiota and obesity in humans.

Author (Year)	Type of Study	Population	*N*	Intervention	Control	Time (Weeks)	Results
Crovesy, El-Bacha and Rosado [14]	Clinical trial, randomized, double-blind	Obese women	32	Hypocaloric diet + probiotic or symbiotic supplementation	Placebo supplementation	8	No differences in anthropometry between groups of intervention After the dietary intervention, all groups showed changes in the metabolic profile associated with the reduction in inflammation
Dong et al. [15]	Clinical trial, randomized	Overweight or obese adults and older adults	80	Hypoproteic diet, initially normocaloric and after with caloric reduction	Diet with normal content of PTN	8	No significant differences between weight loss in all groups Differences in microbiota composition between individuals according to higher or lower fiber consumption ↑ α diversity and abundance of 6 genera of bacteria in the intervention group
Gøbel et al. [16]	Clinical trial, randomized, double-blind	Obese adolescents	50	Probiotic supplementation with *Lactobacillus salivarius* Ls-33	Placebo supplementation	12	No changes in inflammatory markers after intervention (fasting glucose, insulin, HOMA-IR, C-peptide) ↓ fasting insulin, HOMA-IR and C-peptide in the placebo group
Gomes, Hoffmann and Mota [17]	Clinical trial, randomized, double-blind	Overweight or obese women	32	Probiotic supplementation	Placebo supplementation	12	Best lipid profile showed ↑ *Prevotella*, *Collinsella*, *Paraprevotella Enterococcus*, *Clostridiaceaee Veillonella*, while the worst lipid profile showed ↑ phylum *TM7*, *Lachnospiraceae* and *Roseburia* Alterations in microbial composition in the intervention group: ↑ Firmicutes and ↓ *Bacteroidetes*
Haro, Borrego et al. [18]	Clinical trial, randomized	Obese men	20	Mediterranean diet	Low-lipid high-complex CHO diet	48	↑ insulin sensitivity in all groups ↑ genera *Prevotella* and *F. prausnitzii* + ↓ *Roseburia* in low-lipid high-complex CHO diet ↑ genera *Roseburia* and *Oscillospira* in Mediterranean diet Both diets promoted changes in abundance of T2DM-related bacterial abundance, promoting a protective effect
Jian et al. [19]	Clinical trial, randomized	Overweight or obese individuals	38	(1) Hypocaloric high-saturated-fat diet (2) Hypocaloric high-unsaturated-fat diet (3) Hypocaloric high-sugar diet	-	3	↑ phylum *Proteobacteria* in high-saturated-fat diet ↑ *Lactococcus* and *Escherichia coli* in a high-sugar diet ↑ butyrate producers in high-unsaturated-fat diet ↑ proportion of Firmicute to *Bacteroidetes* in non-alcoholic fatty liver disease ↑ BMI in all groups No differences between the richness of microbial genes and α diversity, comparing all groups
Kanazawa et al. [20]	Clinical trial, randomized	Obese and DM2 individuals	88	Symbiotic supplementation	No type of symbiotic, probiotic or prebiotic supplementation	24	↑ fasting glucose and HbA1c in the symbiotic group, followed by normalization No differences in HbA1c, BMI, lipid profile and IL-6 between all groups at the end of the study ↑ *Bifidobacterium*, cluster *Atopobium*, total lactobacilli and *Lactobacillus*, *Lacticaseibacillus* and *Limosilactobacillus* in symbiotic group at the end of the study

Table 1. *Cont.*

Author (Year)	Type of Study	Population	*N*	Intervention	Control	Time (Weeks)	Results
Leber et al. [21]	Clinical trial, randomized	Individuals with metabolic syndrome or healthy	38	Supplementation with probiotic fermented milk (*Lactobacillus casei Shirota)*	No type of supplementation	12	Individuals with metabolic syndrome showed greater intestinal permeability in comparison to healthy individuals The probiotic showed no changes in the parameters tested in the study
Leong et al. [22]	Clinical trial, randomized, double-blind	Obese adolescents (14–18 years)	87	Fecal microbiota transplantation of eutrophic individuals by oral capsules	Placebo capsules	26	↑ microbial diversity six weeks post-intervention in women. No differences were found in men ↓ android/gnoid fat ratio, particularly in women Resolution of metabolic syndrome in most individuals after intervention
Ley et al. [23]	Clinical trial, randomized	Obese individuals	12	(1) Hypocaloric low-fat diet (2) Hypocaloric low-sugar diet	-	48	Before intervention: ↑ Firmicutes and ↓ *Bacteroidetes* After intervention: ↑ Bacteroidetes and ↓ Firmicutes ↑ *Bacteroidetes* was associated with weight loss
Marungruang et al. [24]	Clinical trial, randomized	Older individuals (50–73 years) with BMI between 25 and 33 kg/m^2	47	Diet with biomarkers related to cardiometabolic risk (foods with anti-inflammatory potential, antioxidants and anti-anti-hypercholesterolemic, like omega-3, polyphenols, dietary fiber)	Conventional diet without biomarkers	8	Weight loss in both diets Improvement in lipid profile in the intervention group No differences in diversity α and taxonomic levels of phyla and genera in the microbiome between the groups ↑ ratio *Prevotella*/*Bacteroides* after intervention in multifunctional diet
Meslier et al. [25]	Clinical trial, randomized	Overweight or obese individuals	82	Mediterranean diet without energy restriction	Habitual diet	8	↓ plasma cholesterol and HDL cholesterol ↓ fecal bile acids Changes in the composition of microbiota in the first week of intervention Greater microbial gene richnesses observed at low levels of PCR
Muralidharan et al. [26]	Clinical trial, randomized	Overweight or obese individuals	343	Mediterranean diet with energy restriction and physical activity promotion	Mediterranean diet without energy restriction	48	↓ weight, ↑ Bacteroidetes and ↓ Firmicutes in the intervention group No significant differences in α and β diversity in all groups ↓ BMI, waist circumference, TG levels, glucose and HbA1c in the intervention group
Neyrinck et al. [27]	Clinical trial, randomized, double-blind	Obese individuals	24	Inulin prebiotic supplementation + hypocaloric diet	Placebo supplementation	12	No changes between the groups in zonulin ↓ marker for intestinal inflammation after intervention ↑ SCFAs in both groups, but not significant Modification in β diversity, ↑ *Actinobacteria*, families *Bifidobacteriaceae* and *Lachnospiraceae*, *Lactobacillaceae* and genera Bifidobacterium after intervention

Table 1. *Cont.*

Author (Year)	Type of Study	Population	*N*	Intervention	Control	Time (Weeks)	Results
Nicolucci et al. [28]	Clinical trial, randomized, double-blind	Overweight or obese children (7–12 years)	38	Prebiotic supplementation with inulin enriched with oligofructose	Placebo supplementation	16	↓ weight gain and % body fat in the intervention group Four individuals with insulin resistance were no longer classified as such after prebiotic intervention ↑ fecal bile acids in the placebo group ↑ *Bifidobacterium* spp. in the intervention group
Sergeev et al. [29]	Clinical trial	Overweight or obese individual	20	Hypocaloric diet + symbiotic supplementation	Hypocaloric diet + placebo supplementation	12	No significant differences between the groups in body composition ↓ HbA1C, ↑ relative abundance of gut bacteria and ↓ microbial genera associated with inflammation in the intervention group
Van Son et al. [30]	Cohort	Overweight or obese men and post-menopause women	107	-	-	284	A positive correlation was found between PLm and diastolic BP No significant differences in Plm between insulin-resistant and -sensitive individuals
Vrieze et al. [31]	Clinical trial, randomized, double-blind	Adult men with metabolic syndrome	18	Fecal transplantation of microbiota by duodenal tube	Fecal transplantation of own feces collected and processed	6	No significant changes were found in energy expenditure at rest ↑ gut microbiota diversity ↓ fecal SCFAs ↑ peripheral insulin sensitivity Tendency to improve hepatic sensitivity
Yu et al. [32]	Clinical trial, randomized, double-blind	Obese adults with insulin resistance	24	Fecal transplantation by capsules	Placebo supplementation	12	Comparing the intervention group and the control group, no differences were found in HOMA-IR, weight, fasting lipids or energy expenditure at rest A modest reduction in HbA1c in the intervention group

BMI: body mass index; HbA1c: glycated hemoglobin; PTN: proteins; CHO: carbohydrates; LIP: lipids; SCFA: short-chain fatty acids; BP: blood pressure; PCR: C-reactive protein; T2DM: type 2 diabetes mellitus; IL-6: interleukin 6; LPS: lipopolysaccharides; TG: triglycerides; ImP: imidazole propionate; ObMH: obese metabolically healthy; ObMUH: metabolically unhealthy; EuMH: eutrophic metabolically healthy; OvMH: overweight metabolically healthy; MH: metabolically healthy; MUH: metabolically unhealthy; SIBO: small intestine bacterial overgrowth; rRNA: ribosomal RNA; qPCR: real-time quantitative PCR; Ob/Ov: obesity/overweight.

Table 2. Observational studies that associated gut microbiota and obesity in humans.

Author (Year)	Type of Study	Population	*n*	Time (Weeks)	Results
Bervoets et al. [33]	Cross-sectional	Children and adolescents	53	-	↑ *Firmicutes/Bacteroidetes* ratio in obese children compared to control ↑ *Staphylococcus* spp. was associated with ↑ energy consumption ↓ *Bacteroides vulgatus* in obese subjects *Lactobacillus* spp. concentrations were associated with CRP levels
Cho [34]	Cohort	Children and adolescents	36	48	Pre-dietary intervention: ↓ Bacteroidetes in the weight-gain group, in comparison to control ↓ richness of microbial genes Post-dietary intervention: ↑ Firmicutes, ↓ *Bacteroidetes*, ↓ richness of genes in the fat-loss group ↓ Firmicutes, ↑ *Actinobacteria*, ↓ class *Clostridia* in the weight-gain group *Romboutsia*, *Ruminococcaeceae _UCG_013*, *Eubacterium coprostanollgenes-group* and *Parabacteroides* are important to microbial changes in the weight-gain group *Romboutsia* genera, *Eubacterium_halli_* group and *Clostridium_sensu_stricto* are important in microbial changes and interaction in the fat gain group
Haro, Borrego et al. [35]	Clinical trial, randomized	Obese men	20	48	↑ insulin sensitivity in all groups ↑ genera *Prevotella* and *F. prausnitzii* + ↓ *Roseburia* in low-lipid high-complex CHO diet ↑ genera *Roseburia* and *Oscillospira* in Mediterranean diet Both diets promoted changes in abundance of T2DM-related bacterial abundance, promoting a protective effect
Haro, Zúñiga et al. [18]	Cohort	Adults	75	240	Microbiota composition seems to be different according to sex and seems to be influenced by BMI ↑ Firmicutes in women independent of BMI ↑ Firmicutes in men with BMI > 33 kg/m^2 ↓ *Bacteroides* in men with a BMI of 33 kg/m^2
Jumpertz et al. [36]	Cohort	Lean or obese adults	21	-	Firmicutes → associated with increasing nutrient absorption Bacteroidetes → associated with a decrease in nutrient absorption (−150 kcal) No differences in caloric excretion in feces of eutrophic or obese with 2.400 kcal/d diet Eutrophic individuals lost less energy in feces with 3.400 kcal/d diet No differences in caloric excretion in feces of obese subjects between two diets
Kim et al. [37]	Cohort	Overweight or obese individuals	747	16	↓ diversity α in MUH No differences in α diversity between the healthy control group and MH ↑ genera *Oscillospira* and *Clostridium*, ↑ family *Coriobacteriaceae* and *Leuconostocaceae* in MH ↑ *Fusobacteria* in MUH No differences in ratio Firmicutes/Bacteroidetes between MUH and MH

Table 2. *Cont.*

Author (Year)	Type of Study	Population	*n*	Time (Weeks)	Results
Kong et al. [38]	Cross-sectional	Lean, overweight or obese individuals	45	-	↓ *Clostridia leptum*, *Clostridia coccoides* and *Bacteroides/Prevotella* in individuals that were overweight or obese ↑ richness and diversity of microbial genes in individuals with higher consumption of fruits, yogurts, soups and lower consumption of sugar and sugary drinks The worst food pattern was associated with alterations in lipid profile
Menni et al. [39]	Cross-sectional	Healthy women	1.632	-	↓ α diversity in weight-gain group Dietary fiber intake was related to microbiota diversity and lower weight gain Firmicutes were related to a lower risk of weight gain *Bacteroides* was related to an increased risk of weight gain
Navarro et al. [40]	Cross-sectional	Adults, healthy	68	336	↑ acetate concentrations, ↓ *Bacteroides* in obese subjects *Lactobacillus* was related as a risk factor for obesity
Olivares et al. [41]	Cross-sectional	Adults	109	-	↓ microbial diversity and ↓ ratio Firmicutes/Bacteroidetes in ObMUH ↑ *Bifidobacterium* in eutrophic EuMH ↑ family *Prevotellaceae* and genera *Eubacterium rectale* and *Faecalibacterium* in people ObMH and OvMH compared to EuMH ↑ *Coprococcus* and *Ruminococcus* in OvMH
Orsso et al. [42]	Cross-sectional	Obese children	21	80	Increased HOMA-IR was associated with ↓ richness of microbial genes, ↓ species richness of Firmicutes and ↓ diversity of *Proteobacteria* ↓ α diversity was associated with ↑ PCR in obese subjects
Peters et al. [43]	Cross-sectional	Lean, overweight or obese individuals	599	-	↓ richness of microbial genes in obese compared to eutrophic No differences in α diversity between overweight and eutrophic ↑ families *Streptococcaceae*, *Lactobacillaceae*, *Veillonellaceae Gemellaceae* and ↓ *Christensenellaceae*, *Clostridiaceae*, *Dehalobacteriaceae* in obese ↑ *Lactobacillaceae*, *Streptococcaceae* and ↓ *Christensenellaceae*, *Clostridiaceae*, *Dehalobacteriaceae* in overweight subjects
Roland et al. [44]	Cohort prospective	Individuals with suspicion of SIBO	30	24	Obese people showed a prevalence of SIBO ↑ small intestine transit time and ↑ gastric and small intestine pH in SIBO ↓ α diversity, ↓ genera *Parabacteriodes*, *Oscillospira* and families *Bacteroidaceae*, *Lachnospiraceae* in obese with SIBO compared to eutrophic with SIBO ↑ Firmicutes ↓ Bacteroidetes in obese
Stefura et al. [45]	Cohort prospective	Lean or grade III obese individuals	96	48	Eutrophic and obese showed phylum *Firmucutes* elevated compared *Bacteroidetes* ↑ genera *Bacteroides*, *Odoribacter*, *Blautia* in obese ↑ *Ruminococcus*, *Christensenella*, *Faecalibacterium* in eutrophic ↑ *Romboutsia*, *Lactobacillus*, *Flavonifractor* in BMI $\geq$ 50 kg/m^2

Table 2. *Cont.*

Author (Year)	Type of Study	Population	*n*	Time (Weeks)	Results
Shen et al. [46]	Cohort	Post-bariatric surgery individuals	26	48	No differences in ratio Firmicutes/Bacteroidetes pre- and post-surgery Post-bariatric surgery: ↑ α diversity, improvement in microbial metabolites and markers related to insulin resistance and DCV Several aspects of microbiota have been modified (composition, diversity) quickly (3–6 months) after the procedure. However, there was a reduction 12 m after surgery
Silva, Monteil and Davis [47]	Cohort	Children	51	-	↓ family *Bifidobacteriaceae* and phylum *Bifidobacterium*, ↑ Lactobacillus and Firmicutes in overweight/obese children compared to eutrophic ↓ phylogenetic diversity in Ob/Ov
Van Son et al. [30]	Cohort	Overweight or obese men and post-menopause women	107	284	A positive correlation was found between PLm and diastolic BP No significant differences in Plm between insulin-resistant and -sensitive individuals
Yun et al. [48]	Cross-sectional	Adults	1274	16	↓ α diversity in obese No differences in ratio Firmicutes/Bacteroidetes between obese, overweight and eutrophic Depletion in lipid metabolism, biodegradation of xenobiotics, ↑ gene-related to purine metabolism and oxidative phosphorylation, alterations in the immune response, ↓ metabolism of CHO, pyruvate and some amino acids in obese individuals In a taxonomic analysis separated by BMI, bacteria from obese individuals were not influenced by the dietary confounder
Yuan et al. [49]	Cohort	Obese children and adolescents	86	28	↑ α and β diversity in ObMH and the control group ↑ genera *Anaerostipes*, *Oscillospir*, *Odoribacter*, *Gemmiger*, *Parabacteroides*, *Alistipes* in ObMH and the control group ↑ genera *Bacteroides* in ObMH ↑ *Fusobacterium* in ObMUH
Zeng et al. [50]	Cohort retrospective	Lean, overweight or obese adults	1.914	-	↑ bacterial diversity in obese subjects without metabolic alterations compared to eutrophic Gradual changes in the microbiota with the aggravation of obesity
Zeng et al. [51]	Cohort	Obese individuals	383	-	↑ microbial diversity and gene count, ↓ ratio Firmicutes/Bacteroidetes in ObMH compared to ObMUH ↑ *Alistipes*, *Bifidobacterium*, *Eubacterium*, *Faecalibacterium*, *Ruminococcus*, *Subdoligranulum* and ↓ phylum *Fusobacteria* in ObMH ↑ *Escherichia*, *Clostridium*, *Fusobacterium* and *Megamonas* in ObMUH ↑ microbial genes associated with LPS biosynthesis in ObMUH

BMI: body mass index; HbA1c: glycated hemoglobin; PTN: proteins; CHO: carbohydrates; LIP: lipids; SCFA: short-chain fatty acids; BP: blood pressure; PCR: C-reactive protein; T2DM: type 2 diabetes mellitus; IL-6: interleukin 6; LPS: lipopolysaccharides; TG: triglycerides; ImP: imidazole propionate; ObMH: obese metabolically healthy; ObMUH: metabolically unhealthy; EuMH: eutrophic metabolically healthy; OvMH: overweight metabolically healthy; MH: metabolically healthy; MUH: metabolically unhealthy; SIBO: small intestine bacterial overgrowth; rRNA: ribosomal RNA; qPCR: real-time quantitative PCR; Ob/Ov: obesity/overweight.

Table 3. Studies that evaluated gut microbiota and obesity in animals.

Author (Year)	Type of Study	Population	*n*	Intervention	Control	Time (Weeks)	Results
Bo et al. [52]	EXP	C57BL/6J mice	36	(1) High-fat diet (HFD) (2) High-fat diet + *Bifidobacterium pseudolongum* supplementation	Standard diet	8	↓ glucose toleration and ↑ lipid profile markers in HFD ↓ visceral fat, ↑ Bacteroidetes, ↓ Firmicutes, ↑ *Butyricimonas*, *Bifidobacterium* and *Odoribacter* in obese mice using *B. pseudolongum* No differences between the groups in α and β diversity
Denou et al. [53]	EXP	Mice	16	(1) Normal diet + physical activity HIIT (2) HFD + physical activity HIIT	Without physical activity	12	↓ ratio Bacteroidetes/Firmicutes and ↓ α diversity in Ob/HFD ↑ α diversity, ↑ ratio Bacteroidetes/Firmicutes after HIIT in Ob/HFD Ob/HFD mice showed insulin and glucose intolerance No reduction in body mass or fasting glucose, but improved insulin sensitivity after HIIT in Ob/HFD
Evans et al. [54]	EXP	Male C57BL/6 mice	48	(1) Low-fat diet (LFD) sedentary (2) High-fat diet (HFD) sedentary (3) LFD + physical activity in hamster wheel (4) HFD + physical activity	-	14	↑ weight and body fat, change in glucose metabolism in group 2 ↓ *Firmicules* ↑ *Bacteroidetes*, ↑ families *Lachnospiraceae Ruminococcaceae* and *S24-7*, ↓ *Lactobacillaceae* and *Turicibacteraceae* in physical activity independent of diet ↑ *Actinobacteria* in group 1 ↑ families *Clostridiaceae*, *Lachnospiraceae* and *Ruminococcaceae*, ↓ *Turicibacteraceae* and *S24-7*, tendency ↑ *Proteobacteria* in HFD
Everard et al. [55]	EXP	C57BL/6J mice	40	(1) Control diet + PREB oligofructose (2) High-fat diet (HFD) to diet-induced obesity (3) HFD + PREB oligofructose	Control diet	8	HFD + PREB: ↓ ratio Firmicutes/Bacteroidetes, ↓ proportion of *Tenericutes*, *Cianobactérias* and *Verrucomicrobia*, ↓ *Bilophila*, *Butyrivibrio*, *LE30* and *Oribacterium*, ↑ *Allobacullum* and *Prevotella*, ↓ hepatic LBP, ↓ inflammatory markers ↑ SCFA and ↓ insulin resistance in using PREB in both diets PREB had a greater impact on HFD than the control diet
Fjære et al. [56]	EXP	Male C57BL/6J mice	70	(1) High-fat sucrose diet (HFSD) (2) Low-fat, high-protein diet (LFPD)—salmon and casein (3) Low-fat, high-protein diet (LFPD)—spare ribs and casein All animals had diet-induced obesity by HFD previously	-	16	No differences in α diversity between the groups ↑ phylum *Verrucomicrobia* and ↓ *Proteobacteria*, ↓ families *Rikenellaceae*, *Desulfovibrionaceae* and *Clostridiaceae* in LFD ↑ bacterial genes related to bile acids biosynthesis in sedentary animals in HFSD ↑ gene related to the transport of sugar in animals authorized to exercise voluntarily in HFSD
Gu et al. [57]	EXP	Male C57BL/6J mice	22	High-fat diet (HFD)	Standard diet	8	↑ Firmicutes, Bacteroidetes and Proteobacteria in the control groups and obesity-resistant mice ↑ Bacteroidetes ↓ Firmicutes in obesity-prone mice Metabolic profile and gut microbiota profile were different between obesity-resistant and obesity-prone mice

Table 3. *Cont.*

Author (Year)	Type of Study	Population	*n*	Intervention	Control	Time (Weeks)	Results
Guirro et al. [58]	EXP	Male mice	8	(1) High-fat diet (HFD) (2) Low-fat diet (LFD)	-	14	↑ ratio Bacteroidetes/Firmicutes in HFD compared to LFD Differences were identified between the families of microorganisms that colonize the microbiome in both diets In tests with antibiotics, the cecal microbial content was reduced. In a later test with fecal microbiota transplantation, the biodiversity of the microbiome was restored
Hussain et al. [59]	EXP	Male C57BL/6J mice with diet-induced obesity	18	(1) High-fat diet (HFD) (2) HFD + simvastatin (3) HFD + *Lactobacillus plantarum* LB818 supplementation	Normal diet	16	↓ body weight using LB818 ↓ body weight in group 2, compared to group 1 ↓ TG, LDL, fasting glucose and fat deposition in the liver, ↑ HDL in groups 2 and 3 ↑ Firmicutes in HFD compared to control ↑ species *Akkermanasia* and *Bifidobacteria* and ↓ Firmicutes using LB818 ↑ ratio Bacteroidetes/Firmicutes in groups 2 and 3
Ji et al. [60]	EXP	Male C57BL/6 mice	48	High-fat diet (HFD) + coarse cereal mix (millet, corn, oats, soybeans and purple potatoes)	Feed + coarse cereal mix	8	↓ weight gain and fat accumulation, ↑ SCFA in HFD + cereal mix ↑ glucose tolerance and improvement in lipid profile, ↑ diversity and microbial richness of microbiome, ↓ liberation of pro-inflammatory cytokines using cereal mix ↑ phylum *Bacteroidetes* and *Actinobacterias*, ↑ genera *Bifidobacterium*, *Lactobacillus*, *Holdemanella*, *Barnesiella*, *Okibacterium* and *Streptophyta*, ↓ ratio Firmicutes/Bacteroidetes using cereal mix
Joung et al. [61]	EXP	Male C57BL/6J mice	40	(1) High-fat diet (HFD) (2) HFD + *Lactobacillus rhamnosus* GG (LGG) (3) HFD + *Lactobacillus plantarum* K50 (LK50)	Normal diet	12	↓ weight gain, fat accumulation, and slight improvement in intestinal permeability induced by HFD using LK50 ↓ TG, fasting glucose, ALT, AST, ↑ HDL, insulin improvement, ↓ ratio Firmicutes/Bacteroidetes, ↑ α and β diversity, ↓ liberation of pro-inflammatory cytokines using LK50 ↓ *Actinobacteria* and *Erysipelotrichia*, ↑ *Lactobacillus* using LK50
Ke et al. [62]	EXP	Germ-free male C57BL/6J mice	60	(1) Normal diet (2) High-fat diet (HFD) + PROB (*Bifidobacterium animalis subsp. lactis* and *Lactobacillus paracasei subsp. paracasei* DSM 46331) (3) HFD + PREB (oat β-glucan) (4) HFD + symbiotic (mix of 2 and 3)	(1) Normal diet + placebo (2) HFD + placebo	12	PREB/symbiotic results after changes caused by HFD: ↓ weight gain, ↓ fasting insulin and cholesterol and improvement in HOMA-IR. PROB results: ↓ fasting insulin and slight weight reduction Symbiotic results: more efficient in ↓ fasting glucose ↑ microbial richness and ↑ SFCA using supplements ↓ bile acids and improvement in functional activities of the intestinal ecosystem from symbiotics
Kiilerich et al. [63]	EXP	Females C57BL/6JBomTac mice	150	(1) Low-fat diet (LFD) (2) High-fat and sucrose diet (HFSD) (3) High-fat and protein diet (HFPD)	Low-fat diet (LFD)	72	PTN and sucrose helped reduce weight gain, but HFPD showed greater weight gain ↓ survival of animals fed with HFSD Obesity was associated with mortality ↑ *Lactobacillus* in HFSD and HFPD ↓ ratio Bacteroidetes/Firmicutes according to animals' age in HFPD and LFD

Table 3. *Cont.*

Author (Year)	Type of Study	Population	*n*	Intervention	Control	Time (Weeks)	Results
Kübeck et al. [64]	EXP	Germ-free mice (GFM) and pathogen-free male C57BL/6 mice (PFM)	60	In both types of animals: (1) High-fat diet (HFD) palm oil-based (2) HFD pork lard-based	Control diet	8	GFM on diet 2 showed no weight gain, suggesting resistance to diet-induced obesity Reduced intestinal fat absorption and higher basal metabolic rate (↑ energy expenditure) in GFM on diet 2 PFM was obese compared to GFM, suggesting that microbial composition exerts some influence on the loss of lean phenotype ↑ *Clostridiales* spp. and *Bacteroidales* in HFD Dietary cholesterol may have a protective effect against diet-induced obesity
Lai et al. [65]	EXP	Male C57BL/6JNarl mice	47	(1) High-fat diet (HFD) (2) HFD with exercise (HFDE) (3) Normal-fat diet (NFD) (4) NFD with exercise (NFDE) (5) HFD with DGE microbiota transplantation (6) HFD with NFDE microbiota transplantation (7) NFD with NFDE microbiota transplantation	-	24	Diet influenced more the composition of the microbiota and α diversity than exercise NFDE group microbiota transplantation transfers effects similar to physical exercise for weight loss and LIP on HFD diet ↑ genera *Turicibacter*, *Sutterella*, *Prevotella*, *AF12* and *Helicobacter* in NFD and NFDE ↑ *Odoribacter*, *AF12*, *Helicobacter* and *Akkermansia* in HFDE and NFDE ↑ *Odoribacter*, *Helicobacter* and *AF12* in the groups of microbiota transplantation Use of antibiotics that preceded transplantation ↑ obesity development risks
Li et al. [66]	EXP	Male Sprague Dawley mice	20	(1) Low-fat diet (LFD) followed by diet rich in FOS (2) High-fat diet (HFD) followed by diet rich in FOS	-	19	↑ weight gain, ↑ *Bacteroidetes*, ↓ *Proteobacteria*, ↑ abundance of bacterial species in lean mice in group 1 ↑ ratio Firmicutes/Bacteroidetes in lean mice compared to obese mice ↓ ratio Firmicutes/Bacteroidetes after intervention in lean mice Weight gain was associated with increase in *Bacteroidetes* Few changes in microbiome community of obese animals: ↓ *Desulfovibrionaceae* and *Lactobacillaceae*, ↑ *Ruminococcaceae*
Lu et al. [67]	EXP	Male C57BL/6J mice	60	(1) High-fat diet (HFD) for diet-induced obesity (2) HFD + acetate (3) HFD + propionate (4) HFD + butyrate (5) HFD + mixture of three SFCA	Low-fat diet (LFD)	16	The SCFA from groups 2, 3, 4 and 5 prevented weight gain, promoted a partial improvement in the composition of the microbiota and reduced the increase in TG and cholesterol caused by an HFD No differences between the groups in microbial diversity ↓ microbial richness, ↑ ratio Firmicutes/Bacteroidetes in HFD ↓ Firmicutes ↑ Bacteroidetes in groups 2 and 3
Moreira Júnior et al. [68]	EXP	Pathogen-free C57BL/6 mice	24	(1) Standard diet (2) High-sugar and butter diet	-	12	↑ weight and adiposity, development of hepatic steatosis, ↑ Firmicutes and *Actinobacteria* ↓ *Bacteroidetes* in group 2 ↑ relative abundance of *Lachnoclostridium*, *Bifidobacterium*, *Parvibacter*, *Ruminiclostridium* and *Blautia* in group 2 Diet of group 2 was associated with impulsivity and an anxiolytic effect

Table 3. *Cont.*

Author (Year)	Type of Study	Population	*n*	Intervention	Control	Time (Weeks)	Results
Moretti et al. [69]	EXP	Germ-free and conventional mice (normal microbiome)	16	Western diet	Regular diet	16	↑ weight, ↑ fat mass, ↓ lean mass, ↑ fasting glucose, adipose tissue inflammation, development of obesity in both animal groups with a western diet
Oh et al. [70]	EXP	Male mice with diet-induced obesity	36	(1) Normal diet (2) HFD + PREB *Cudrania tricuspidata* (3) HFD + PROB *Lactobacillus gasseri 505* (4) HFD + PROB *Lactobacillus gasseri 505* + PREB *Cudrania tricuspidata*	High-fat diet (HFD)	10	Less weight loss in group 4 ↑ microbial richness in group 2, but ↓ in group 3 ↑ microbial diversity in combined use or not of PROB and PREB ↑ ratio Firmicutes/Bacteroidetes in HFD and no changes using the supplement ↓ Proteobacteria and ↓ taxa associated with obesity using PROB and/or PREB Weight gain was positively associated with phylum *Verrucomicrobia* and negatively associated with Bacteroidetes and Firmicutes
Ridaura et al. [71]	EXP	Germ-free mice	12 a 16	Fecal microbiota transplantation from obese discordant human twins to germ-free mice	Mice transplanted with microbiota from lean twins	1–4	↑ body mass in obese microbiota sample ↑ fermentation of butyrate and propionate, digestion of polysaccharides in the lean microbiota sample By housing an obese microbiota mouse with a lean one, the increase in adiposity in the obese animal was reduced, and similar characteristics to the lean animal were transferred
Saiyasit et al. [72]	EXP	Male Wistar mice	140	(1) Normal diet (2) High-fat diet (HFD)	-	40	In HFD: cognitive impairment, ↑ weight, LPS, LDL, cholesterol, HOMA-IR, ↓ HDL ↑ ratio Firmicutes/Bacteroidetes and ↑ ratio *Enterobacteriaceae/Eubacteria* HFD promoted dysbiosis in animal microbiota from the first week of the study
Shang et al. [73]	EXP	Male C57BL/6J mice	12	(1) High-fat diet (HFD) (2) HFD followed by control diet	Low-fat diet (LFD)	7	Higher α diversity in groups 1 and 2 compared to control Higher metabolism capacity of LIP, CH, starch and sucrose, ↓ *S24-7*, ↑ *Lachnospiraceae* in HFD ↑ ratio Bacteroidetes/Firmicutes, ↓ *Proteobacteria* in the control group LFD partially re-established diversity and composition of gut microbiota after HFD
Turnbaugh et al. [74]	EXP	Obese and lean mice	22	-	-	-	↑ Firmicutes in Ob animals ↓ Firmicutes ↑ *Bacteroidetes* in lean animals ↑ final products of butyrate and acetate fermentation, ↓ residual energy of feces (compared to lean microbiome) in Ob mice In a fecal transplantation test of Ob and lean mice to germ-free mice, the characteristics of the obese microbiome were transmitted, promoting body fat gain

Table 3. *Cont.*

Author (Year)	Type of Study	Population	*n*	Intervention	Control	Time (Weeks)	Results
Turnbaugh et al. [75]	EXP	Germ-free male C57BL/6J mice	15	Fecal microbiota transplantation from human adults + (1) Low-fat diet (LFD) and high content of plant polysaccharides (2) Western, high-fat and high-sugar diet	Low-fat diet (LFD) and high content of plant polysaccharides	12	Fecal microbiota transplantation from human adults was successful Diet of group 1: ↑ Bacteroidetes Diet of group 2: ↑ Firmicutes (class *Erysipelotrichi* and *Bacilli*) and ↓ *Bacteroidetes* • In fecal microbiota transplantation from transplanted animals to germ-free mice, human gut microbiota were transmitted from generation to generation and hence maintained its diversity. However, the composition of the gut microbiome is directly influenced by the recipient's diet The transplanted microbiota was similar to human microbiota after 7 days, while microbiome changes were observed by 1 day of the western diet
Welly et al. [76]	EXP	Obesity-prone male mice	30	(1) HFD + hamster wheel volunteer exercise (2) HFD with weight similar to group 2	HFD and sedentary	-	↑ weight in the sedentary group No differences in α diversity, relative abundance of ratio Firmicutes/Bacteroidetes and phylum-level changes between groups ↓ *Bacteroidetes* in groups 2 and 3 compared to control Group 2: ↑ family *Streptococcaceae* and ↓ *Rikenellaceae* Group 3: ↓ *Streptococcus* compared to other groups

BMI: body mass index; HbA1c: glycated hemoglobin; PTN: proteins; CHO: carbohydrates; LIP: lipids; SCFA: short-chain fatty acids; BP: blood pressure; PCR: C-reactive protein; T2DM: type 2 diabetes mellitus; IL-6: interleukin 6; LPS: lipopolysaccharides; TG: triglycerides; ImP: imidazole propionate; ObMH: obese metabolically healthy; ObMUH: metabolically unhealthy; EuMH: eutrophic metabolically healthy; OvMH: overweight metabolically healthy; MH: metabolically healthy; MUH: metabolically unhealthy; SIBO: small intestine bacterial overgrowth; rRNA: ribosomal RNA; qPCR: real-time quantitative PCR; Ob/Ov: obesity/overweight.

4. Gut Microbiota-Derived Nutrients and Nutrient Absorption

A healthy gut microbiota is of pivotal importance in enhancing nutrient absorption. In the large intestine, bacteria interact with dietary substrates that are undigested in the upper digestive tract for survival, while bacterial fermentation can yield beneficial metabolites [77]. Gut microbiota contributes to the metabolism of CHO, proteins (PTN), lipids and short-chain fatty acids (SCFAs). Apart from macronutrients, the gut microbiota modulates the metabolism of vitamins and phytochemicals, as discussed in these subsections.

4.1. Carbohydrates

CHO metabolism and transport are major catalytic functions of the gut microbiota, with important consequences for the host. Mammals can hydrolyze starch and disaccharides to monosaccharides but have a limited ability to hydrolyze other polysaccharides [78]. Humans lack the enzymes to degrade the bulk of dietary fibers (nondigestible CHO), which are fermented by the anaerobic cecal and colonic microbiota [79]. Furthermore, gut microbiota has the ability to break down plant glycoconjugates (glycans), including cellulose, chondroitin sulfate, hyaluronic acid, mucin and heparin [80].

4.2. Protein

Since there is a tendency for gut microbiota to ferment CHO over PTN, saccharolytic bacterial fermentation occurs predominantly in the proximal colon, while proteolytic fermentation is mainly performed in the distal colon. Moreover, gut microbiota PTN breakdown produces potentially toxic metabolites such as ammonia, sulfur-containing compounds and indoles [81,82]. Therefore, CHO and PTN fermentation results in multiple groups of metabolites, of which SCFAs substantially contribute to the host metabolic phenotype and hence to disease risk [83].

Undigested proteins have been considered potentially harmful to the gut microbiota [84,85]. Reaching the large intestine, proteinaceous fermentation substrates produce toxic metabolites, such as gaseous products (hydrogen sulfide, hydrogen, carbon dioxide and methane), ammonia, N-nitroso compounds, amines and phenolic and indolic compounds [85]. More importantly, the major concern of proteinaceous fermentation is linked to the excess of hydrogen sulfide levels, whose metabolite stimulates pro-inflammatory gene expression in colonocytes [86]. Figure 1 illustrates these concerns.

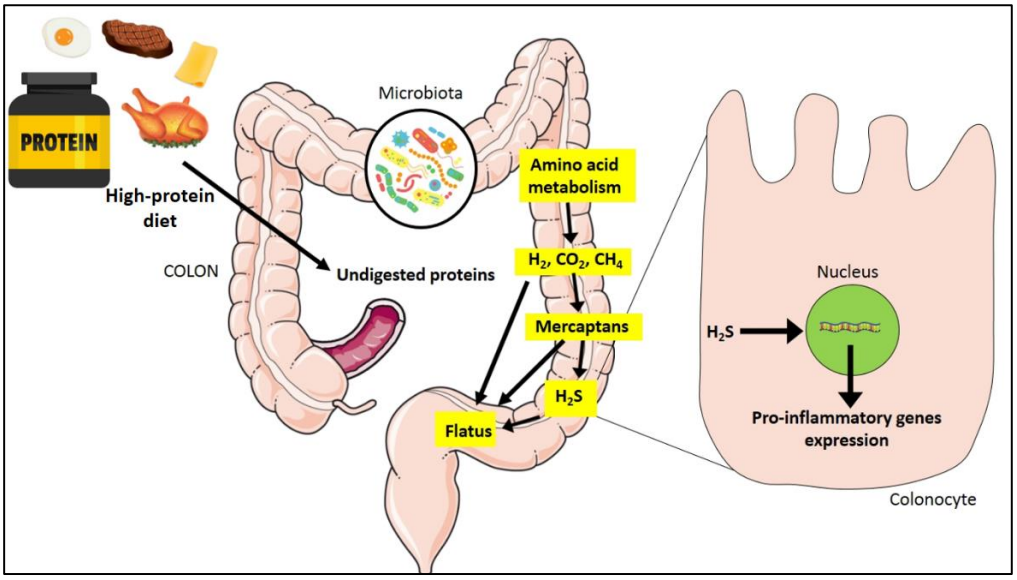

Figure 1. High-protein diets and gut microbiota imbalance. Legend: High-protein diets can increase the undigested protein amount, which, after colonic microbial protein fermentation (putrefaction)

through microbiota passage, produces several colon gases from amino acid metabolism (i.e., H_2, CO_2, CH_4, mercaptans and H_2S) [87]. These byproducts are excreted as flatus, which may lead to abdominal pain and increase the malodorous components of human flatus. A major concern is the H_2S implications in the colonocytes, where it triggers an increased expression of pro-inflammatory genes [84,86]. CO_2: carbon dioxide; CH_4: methane; H_2: hydrogen; H_2S: hydrogen sulfide.

4.3. Lipids and SCFAs

Gut microbiota is also vital to bile acid pool size and thus enhances intestinal nutrient absorption and biliary secretion of lipids [88,89]. More specifically, in the gut, primary bile acids are converted by colonic bacteria to secondary bile acids, predominantly deoxycholic acid and lithocholic acid [90]. The host, in turn, generates a large, conjugated hydrophilic bile acid pool via the positive-feedback antagonism of FXR in the gut–liver axis, which is a fundamental action insofar as decreased bile acid concentrations in the gut can lead to bacterial overgrowth and inflammation [89]. Moreover, taurine-related modulation by the gut microbiota is crucial to bile acids, as taurine is an amino acid used to conjugate bile acids [91].

SCFAs, i.e., acetate, propionate and butyrate, are organic acids produced within the intestinal lumen by bacterial fermentation of undigested dietary CHO and PTN, which can be used as energy sources either by the human colonocytes or elsewhere in the body [81,92]. In humans, fermentation of 50–60 g of CHO or ~10% of the daily energy requirement (140–180 kcal) from high-vegetable and fruit diets yields 0.5–0.6 mol of SCFAs [78]. In addition to their nutritional value, SCFAs have important effects on other aspects of human physiology. SCFAs regulate the balance between fatty acid synthesis and oxidation, glucose and cholesterol metabolism via AMP-activated protein kinase (AMPK) [79]. SCFAs broadly influence host processes, which include energy uptake, host–microbe crosstalk signaling, and colonic pH control, with ensuing effects on microbiota composition, gut motility and epithelial cell proliferation [83].

4.4. Vitamins

Gut bacteria participate in vitamin K and B synthesis. Since human neonates are born with low levels of vitamin K [93], gut microbiota is essential to provide K2 (or menaquinone) [94]. Vitamin K is necessary for several blood coagulation factors (II, VII, IX and X) and some coagulation inhibitors synthetized by the liver [95]. B-vitamins are a diverse group of molecules and biosynthetic precursors of universally essential cofactors used in numerous metabolic pathways related to energy production, protein metabolism and hemopoiesis [96]. Taking into account the bacterial patterns that synthesize B-vitamins, type 1 enterotypes participate in the synthesis of biotin, riboflavin and pantothenate, while type 2 enterotypes synthesize thiamine and folate [97]. The real contribution of microbiome-produced B-vitamins to host requirements and status are unknown [96].

4.5. Phytochemicals

Gut microbiota has an extensive capacity to metabolize phytochemicals, chiefly polyphenols [98,99]. Polyphenols are secondary metabolites of plants generally involved in defense against ultraviolet radiation or aggression by pathogens. In humans, polyphenols confer antioxidant properties and may modulate the activity of a wide range of enzymes and cell receptors [100]. Although polyphenols are common in the human diet, accounting for about 820 mg/day, mainly from fruits and vegetables, they are poorly absorbed by the intestine [77,100]. It may occur because most food polyphenols are in the form of esters, glycosides or polymers that must be hydrolyzed by intestinal enzymes or by the gut microbiota before they can be absorbed [100].

Polyphenols that are not absorbed in the small intestine reach the colon, where they are hydrolyzed by the colonic microbiota, which includes *Bacteroides distasonis*, *Bacteroides uniformis*, *Bacteroides ovatus*, *Enterococcus casseliflavus*, *Eubacterium cellulosolvens*, *Lachnospiraceae CG19-1* and *Eubacterium ramulus* [101,102]. Specific active metabolites are produced by

the gut microbiota; for instance, (a) enterolactone and enterodiol, from lignans of linseed, and (b) equol, from daidzein of soya. Both of them have antioxidant capacities as well as phytoestrogenic and potential anti-cancer properties [103,104].

5. Gut Microbiota-Derived Metabolites and Cardiovascular Disorders

Gut microbiota under unhealthy diet patterns transforms dietary nutrients into metabolically harmful substances, of which branched-chain amino acids (BCAA), imidazole propionate and trimethylamine N-oxide (TMAO) are some examples [105,106].

The microorganisms *Prevotella copri* and *Bacteroides vulgatus* increase BCAA synthesis, while *Streptococcus mutans* and *Eggerthella lenta* are producers of imidazole propionate [7]. Since high circulating levels of BCAA are an important risk factor for insulin resistance [107], BCAA-related microbial compounds (e.g., imidazole propionate) have negative effects on insulin signaling cascades [105].

TMAO, in turn, has gained much attention due to its potential role in CVD [105,108]. Trimethylamine (TMA) is synthetized by gut microbiota from phosphatidylcholine, choline, betaine and l-carnitine, which are abundant in seafood, dairy products, egg yolks and red meat. TMA enters the portal circulation and is oxidized to TMAO in the liver by flavin-containing monooxygenase 3 [7,109]. TMAO—or its dietary precursors—accelerates arteriosclerosis via inflammation, oxidative stress, platelet aggregation and thrombosis [109,110]. Accordingly, gut dysbiosis leads to high plasma TMAO levels, which are related to CVD and all-cause mortality [105,111].

Importantly, the crosstalk between gut microbiota imbalance and obesity is inherent to inflammation induced by lipopolysaccharides (LPS). LPS are glycolipid molecules that serve as important outer membrane components of Gram-negative bacteria and have a role as bacterial toxins [112], thereby favoring cardiometabolic abnormalities. High levels of LPS can induce the expression of pro-inflammatory cytokines, thus contributing to endothelial damage and increasing the oxidation of low-density cholesterol particles and foam cell formation, ultimately accelerating atherosclerosis [113].

6. Gut Microbiota Composition in Obesity

The intestinal colon is inhabited by several microorganisms that form the gut microbiota and reach nearly trillions [114]. The predominant gut bacteria belong to the following phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrumicrobia and Fusobacteria; however, Firmicutes and Bacteroidetes occur in greater quantities among bacterial cells in the gut [115]. Seemingly, *Bacteroides* and *Prevotella* appear to be the predominant bacterial genera inside the Bacteroidetes phylum. In contrast, the genera *Clostridium*, *Eubacterium* and *Ruminococcus* appear to occur in greater numbers in the Firmicutes phylum [116].

In addition to the distribution by phyla, intestinal bacteria are classified as enterotypes, i.e., groups of various microorganisms that can somehow impact the health of the host. Arumugam et al. [117] define three groups: (1) type 1 enterotypes, which are apparently rich in species of Bacteroides; (2) type 2 enterotypes, with a greater presence of the genera *Prevotella*; and (3) type 3 enterotypes, delimited by *Ruminococcus*.

Individuals with obesity have a higher prevalence of Firmicutes (Fusobacteria, Proteobacteria and Lactobacillus reuteri) and a lower prevalence of Bacteroidetes (Akkermansia muciniphila, Faecalibacterium prausnitzii, Lactobacillus plantarum and Lactobacillus paracasei) compared with normal-weight individuals [118]. Furthermore, animals and humans with obesity have a higher ratio of Firmicutes/Bacteroidetes [74,118,119].

Gut microbiota plays an important role in energy uptake (the energy harvest hypothesis). Individuals with obesity show a higher energy harvest from food compared to lean individuals. This effect seems to be associated with increased CHO degradation and, consequently, the formation of SCFAs, favoring greater energy gain. In addition, microbiota has been suggested to manipulate host behaviors by changing food preferences (e.g., altered taste receptors for fat and sweets) [120]. Since obesity is a result of energy

balance, a negative modification of gut microbiota can result in increased energy intake. The pathophysiological link between obesity and gut microbiota is depicted in Figure 2.

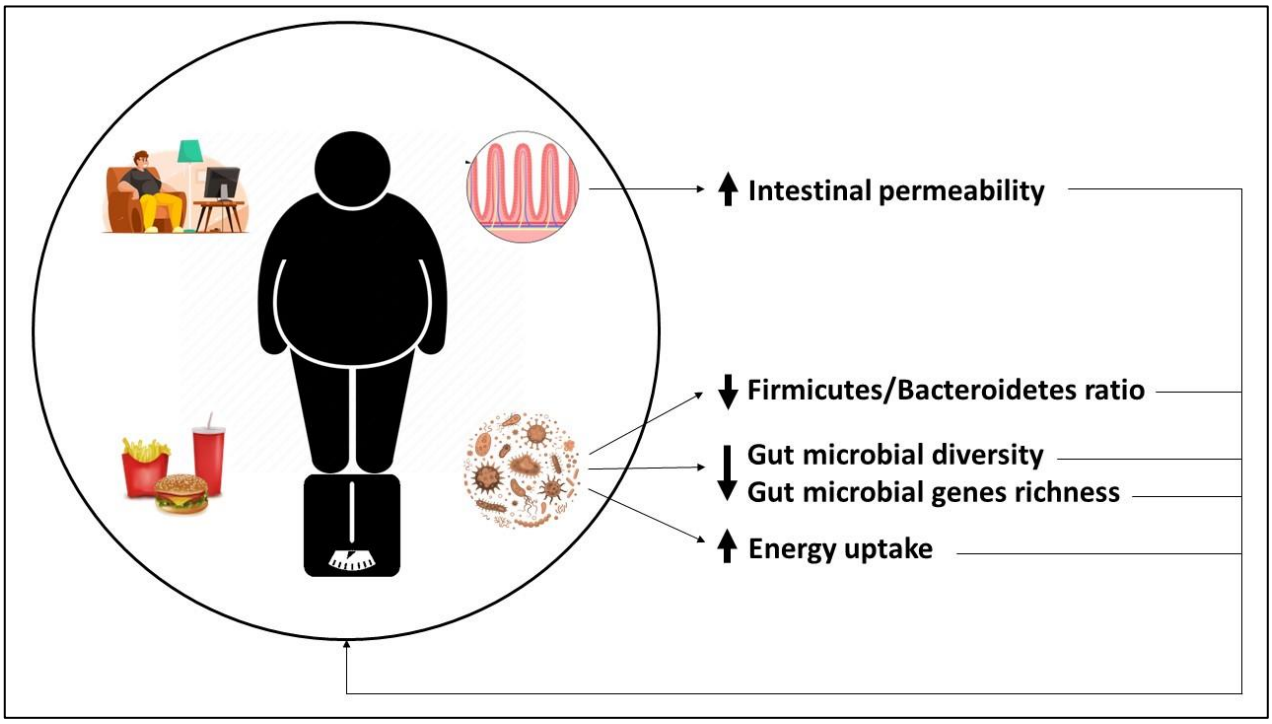

Figure 2. Pathophysiological relationship between obesity and gut microbiota. Legend: Obesity is a disease characterized by being overweight and has triggering factors such as excessive calorie consumption and a sedentary lifestyle. Individuals with obesity suffer alterations in gut microbiota and gastrointestinal tracts, such as increased energy uptake and intestinal permeability, decreased microbial diversity and gene richness, and an increased Firmicutes/Bacteroidetes ratio.

7. Unhealthy Dietary Patterns

An excessive intake of alcohol, sugars, and saturated fatty acids (SFAs) is associated with a reduction in bacterial abundance, diversity and richness in the gut and, by virtue of an augmentation of Gram-negative bacteria (dysbiosis), can raise the production of LPS and disrupt intestinal barrier integrity [121–125].

That said, the crosstalk between gut microbiota imbalance and obesity is related to a dietary cluster of high-energy food, fat and sugar intake, suggesting that an "obese microbiota" may not be triggered by obesity itself [126]. In this regard, the high intake of ultra-processed foods with a low nutritional profile is an unhealthy dietary pattern that plays a negative role in gut microbiota [127,128].

The triad of a high content of sodium, SFAs and sugars across ultra-processed foods leads to a higher calorie intake, as observed in a clinical trial in which participants received an ultra-processed diet for two weeks and then a healthy food-based diet for the same period [129]. In the period of the ultra-processed diet, there was an increase of 500 calories ingested daily from CHO and fats, accompanied by a body mass gain of 900 g. Conversely, in the healthy eating phase, the participants lost an average of 900 g. Thus, a diet rich in ultra-processed foods is not only harmful to the gut microbiota but also results in a higher energy intake that, in turn, can cause obesity in the long term.

Reduced microbial gene diversity is observed in low-complex CHO diets, suggesting that this type of CHO acts as a prebiotic and promotes the diversity of gut bacteria [130]. Overall, the benefits of high-complex CHO diets and gut microbiota modulation are thoroughly discussed in the topic below.

8. Healthy Dietary Patterns

A dietary pattern based on fruits, vegetables, seeds, whole grains and mono- and polyunsaturated fatty acids has been shown to result in gut microbiota diversity, mainly because of the large supply of dietary fiber [131]. Such an eating pattern improves cardiometabolic markers mediated by the gut microbiota, as shown in Figure 3. More specifically, the low-energy, high-fiber pattern is the cornerstone of increasing microbial gene diversity, thus affording reductions in serum cholesterol levels, adiposity and inflammation in patients with obesity [132].

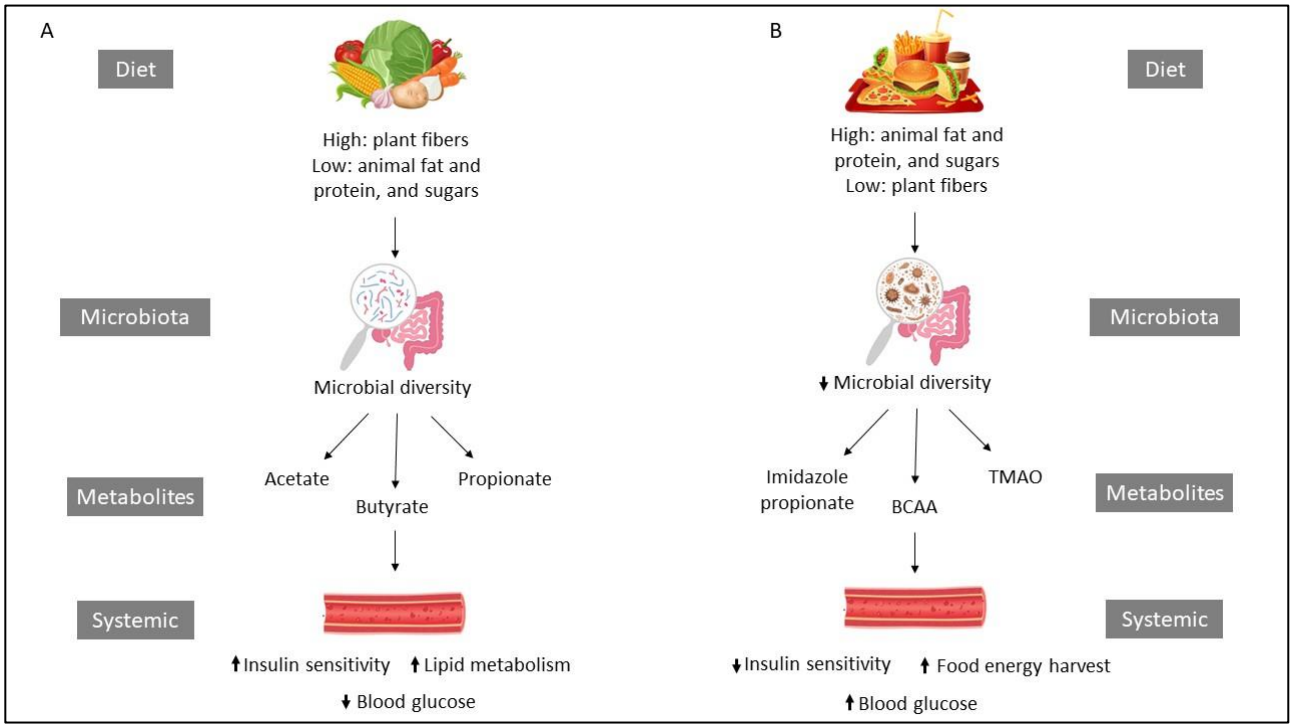

Figure 3. Influence of diet on gut microbiota and accompanied systemic consequences. Legend: (**A**) A metabolically healthy microbiota may be achieved through a diet high in fiber and low in animal fat and protein, as well as a low sugar intake. Fermentation of nondigestible CHO results in short-chain fatty acids (acetate, butyrate and propionate), whose elements improve cardiometabolism. (**B**) Gut dysbiosis may be induced by a diet low in fiber and high in animal fat and protein, as well as by high intake of sugar and alcohol. An unhealthy diet is associated with a reduction in bacterial abundance, diversity and richness in the gut, transforming dietary nutrients into metabolically harmful metabolites, i.e., branched-chain amino acids (BCAA), imidazole propionate and trimethylamine N-oxide (TMAO), and thus increasing the production of lipopolysaccharides (LPS) and/or disrupting the intestinal barrier integrity. Finally, such a background can induce the expression of pro-inflammatory cytokines and hence contribute to insulin resistance and related cardiometabolic disorders (e.g., atherosclerosis).

Both low-fat and low-CHO diets with energy restriction increase Bacteroidetes, while reducing body weight, as observed in a one-year intervention of individuals with obesity [23]. In light of this, energy restriction is imperative for modulating the gut microbiota of patients with obesity.

Lastly, public policies encouraging greater consumption of fresh or minimally processed foods and taxation of ultra-processed foods may reflect healthier habits, contributing to obesity reduction [133].

9. Probiotics and Synbiotics in Weight Loss

It is recognized that supplementation with products containing live microorganisms, known as probiotics, improves intestinal epithelial barrier function and increases mucus production [134], thereby partially reducing gastrointestinal problems such as diarrhea, abdominal pain, lactose intolerance, etc. [135]. More interestingly, probiotic supplementation has emerged as a weight loss [136] strategy by virtue of its putative anorexigenic effect by increasing SCFA production, which plays a role in fatty acid oxidation as well as the secretion of gut hormones (YY peptide and glucagon-like peptide 1) and leptin in adipocytes.

The potential effects of probiotic supplementation on weight loss could be enhanced when combined with prebiotics, a specific group of non-digestible and fermentable foods that confer more gastric volume during the meal and are substrates for microorganisms in the gut lumen [137]. Thus, the combination of probiotics and prebiotics, named synbiotics ("live microorganisms that, after ingestion in specific numbers, exert benefits for the health of the host") [138], merits attention as to their potential in improving indicators of obesity.

Species from the *Lactobacillus* and *Bifidobacterium* genera are the components of probiotic supplements in the field of weight loss [139]; however, optimal dosing regimens and plausible clinical effects are far from discernible. A meta-analysis of randomized clinical trials (15 studies, 957 patients) of patients who were overweight or obese revealed that probiotic supplementation alone for 3 to 12 weeks significantly reduced body weight by ~0.60 kg and BMI by ~0.27 kg/m^2 compared to placebos, along with a non-statistical decrease of ~0.42 kg in fat mass [140]. In addition to obesity, such a modest effect is similar in patients suffering from both obesity and its metabolic-related diseases [141]. Not only probiotics but also supplementation with symbiotics portrays a small clinical magnitude in improving anthropometric indicators of obesity [142].

10. Exercise

Exercise significantly contributes to the increased biodiversity of microbial species, modulation of the immune system, improved motility and decreased intestinal permeability. Changes in gut microbiota seem to be intensity- and volume-dependent with exercise [143]. Furthermore, exercise increases microbiota-induced SCFA synthesis in the intestinal lumen, which is related to fat oxidation and the preservation of muscle mass [144].

Aerobic exercise training improved gut microbiota and microbial-derived SCFA in previously sedentary patients with obesity without dietary modification, whereas those benefits were reversed after exercise training cessation [145].

In a recent study [26] whereby individuals who were overweight or obese underwent a Mediterranean diet with caloric restriction associated with physical activity promotion for one year, the Bacteroidetes/Firmicutes ratio increased at the end of the intervention, such that there were improvements in the indicators of obesity as well as glycemic and lipid profiles.

Regarding high-intensity interval training, it can counteract high-fat diet-induced changes in the gut by increasing the alpha diversity and Bacteroidetes/Firmicutes in rats with obesity; however, further research using this type of exercise ought to be performed in humans [53].

11. Microbiota Transplantation

Mice receiving obese microbiota transplantation increase in body mass as a result of an increase in the energy harvest without changing energy intake or expenditure, suggesting that the microbiome may favor weight gain [9]. Ridaura et al. [71] tested if gut microbiota may promote body fat increase by performing a microbiota transplant from obese discordant twins (one obese and one lean) to germ-free mice. The animals were fed a low-fat diet and a high-plant polysaccharide diet. The fecal material from mice was analyzed to identify differences between their microbial communities and the relevance of these results to metabolism and host body composition. Gut microbiota composition was modified

according to the characteristics of the transplanted microbiota. Comparing results from the transplant, mice that received obese microbiota samples gained more weight than animals that received lean microbiota samples.

In humans, Vrieze et al. [31] implanted lean feces in men with metabolic syndrome and, after six weeks, identified an improvement in gut microbiota composition and insulin sensitivity. However, Yu et al. [32] performed a fecal microbiota transplant by capsules in individuals with obesity and did not find significant changes between the two groups in microbial diversity, body mass, insulin sensitivity, energy expenditure, HOMA-IR or fasting lipid profile.

There are severe limitations when comparing trials in animals and humans due to physiological, food, and microbial differences. Mice that received obese microbiota transplantation showed weight gain as a result of an increase in energy harvest without changing energy intake or expenditure, suggesting that the microbiome may favor weight gain [9].

Collectively, gut microbiota transplantation is promising; however, there are several limitations between animals and humans due to physiological, food, and microbial differences, such that there is no uniform evidence for humans.

12. Conclusions and Perspectives

A common obesity pattern can be a cause of dysbiosis due to the accumulative effects of a high intake of high-energy foods, sugars and SFAs, as well as a reduced consumption of fiber and physical inactivity.

Conversely, low-energy diets, high fiber intake and physical exercise are crucial to enhancing gut microbiota of patients with obesity. Moreover, advice to reduce the intake of ultra-processed foods with a low nutritional profile, along with increasing the intake of natural or minimally processed foods, are reasonable strategies to afford a better status of gut microbiota.

Regarding perspectives, although supplementing probiotics and synbiotics (mainly those containing *Lactobacillus* and/or species from the *Bifidobacterium genus*) can aid in the management of obesity, skepticism must be exercised due to modest clinical effects, such that more investigation is needed to better understand proper bacterial strains and dosing regimens.

Finally, microbiota transplantation is a field that deserves substantial elucidation in terms of clinical recommendations.

Author Contributions: D.S.T. and R.C.O.M. were responsible for conceiving the review. D.S.T. and F.M.D. searched and organized the results. All authors participated in the analysis and interpretation of the data and manuscript writing. H.O.S. wrote and contributed to the revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research did not receive any specific grants from funding agencies in the public, commercial or not-for-profit sectors.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Upadhyay, J.; Farr, O.; Perakakis, N.; Ghaly, W.; Mantzoros, C. Obesity as a Disease. *Med. Clin. N. Am.* **2018**, *102*, 13–33. [CrossRef]
2. Fruh, S. Obesity: Risk factors, complications, and strategies for sustainable long-term weight management. *J. Am. Assoc. Nurse Pract.* **2019**, *29*, 3–14. [CrossRef]
3. World Health Organization. *Presents Technical Data and Information about Obesity in the World*; World Health Organization: Geneva, Switzerland, 2021.
4. Ward, Z.; Bleich, S.; Cradock, A.; Barrett, J.; Giles, C.; Flax, C.; Long, M.; Gortmaker, S. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. *N. Engl. J. Med.* **2019**, *381*, 2440–2450. [CrossRef]
5. Kelly, T.; Yang, W.; Chen, C.-S.; Reynolds, K.; He, J. Global burden of obesity in 2005 and projections to 2030. *Int. J. Obes.* **2008**, *32*, 1431–1437. [CrossRef]
6. Wright, S.M.; Aronne, L.J. Causes of obesity. *Abdom. Radiol.* **2012**, *37*, 730–732. [CrossRef] [PubMed]
7. Fan, Y.; Pedersen, O. Gut microbiota in human metabolic health and disease. *Nat. Rev. Microbiol.* **2021**, *19*, 55–71. [CrossRef] [PubMed]

8. Greiner, T.; Bäckhed, F. Effects of the gut microbiota on obesity and glucose homeostasis. *Trends Endocrinol. Metab.* **2011**, *22*, 117–123. [CrossRef] [PubMed]
9. Tsai, F.; Coyle, W.J. The microbiome and obesity: Is obesity linked to our gut flora? *Curr. Gastroenterol. Rep.* **2009**, *11*, 307–313. [CrossRef]
10. Cornejo-Pareja, I.; Muñoz-Garach, A.; Clemente-Postigo, M.; Tinahones, F.J. Importance of gut microbiota in obesity. *Eur. J. Clin. Nutr.* **2019**, *72*, 26–37. [CrossRef]
11. Lynch, S.V.; Pedersen, O. The Human Intestinal Microbiome in Health and Disease. *N. Engl. J. Med.* **2016**, *375*, 2369–2379. [CrossRef]
12. Kau, A.L.; Ahern, P.P.; Griffin, N.W.; Goodman, A.L.; Gordon, J.I. Human nutrition, the gut microbiome and the immune system. *Nature* **2011**, *474*, 327–336. [CrossRef]
13. Deehan, E.C.; Yang, C.; Perez-Muñoz, M.E.; Nguyen, N.K.; Cheng, C.C.; Triador, L.; Zhang, Z.; Bakal, J.A.; Walter, J. Precision Microbiome Modulation with Discrete Dietary Fiber Structures Directs Short-Chain Fatty Acid Production. *Cell Host Microbe* **2020**, *27*, 389–404.e6. [CrossRef] [PubMed]
14. Crovesy, L.; El-Bacha, T.; Rosado, E.L. Modulation of the gut microbiota by probiotics and symbiotics is associated with changes in serum metabolite profile related to a decrease in inflammation and overall benefits to metabolic health: A double-blind randomized controlled clinical trial in women with obesity. *Food Funct.* **2021**, *12*, 2161–2170. [CrossRef] [PubMed]
15. Dong, T.S.; Luu, K.; Lagishetty, V.; Sedighian, F.; Woo, S.-L.; Dreskin, B.W.; Katzka, W.; Chang, C.; Zhou, Y.; Arias-Jayo, N.; et al. A High Protein Calorie Restriction Diet Alters the Gut Microbiome in Obesity. *Nutrients* **2020**, *12*, 3221. [CrossRef]
16. Gøbel, R.J.; Larsen, N.; Jakobsen, M.; Mølgaard, C.; Michaelsen, K.F. Probiotics to Adolescents With Obesity: Effects on Inflammation and Metabolic Syndrome. *J. Pediatr. Gastroenterol. Nutr.* **2012**, *55*, 673–678. [CrossRef]
17. Gomes, A.C.; Hoffmann, C.; Mota, J.F. Gut microbiota is associated with adiposity markers and probiotics may impact specific genera. *Eur. J. Nutr.* **2020**, *59*, 1751–1762. [CrossRef]
18. Haro, C.; Rangel-Zúñiga, O.A.; Alcalá-Díaz, J.F.; Gómez-Delgado, F.; Pérez-Martínez, P.; Delgado-Lista, J.; Quintana-Navarro, G.M.; Landa, B.B.; Navas-Cortés, J.A.; Tena-Sempere, M.; et al. Intestinal Microbiota Is Influenced by Gender and Body Mass Index. *PLoS ONE* **2016**, *11*, e0154090. [CrossRef] [PubMed]
19. Jian, C.; Luukkonen, P.; Sädevirta, S.; Yki-Järvinen, H.; Salonen, A. Impact of short-term overfeeding of saturated or unsaturated fat or sugars on the gut microbiota in relation to liver fat in obese and overweight adults. *Clin. Nutr.* **2021**, *40*, 207–216. [CrossRef]
20. Kanazawa, A.; Aida, M.; Yoshida, Y.; Kaga, H.; Katahira, T.; Suzuki, L.; Tamaki, S.; Sato, J.; Goto, H.; Azuma, K.; et al. Effects of Synbiotic Supplementation on Chronic Inflammation and the Gut Microbiota in Obese Patients with Type 2 Diabetes Mellitus: A Randomized Controlled Study. *Nutrients* **2021**, *13*, 558. [CrossRef]
21. Leber, B.; Tripolt, N.J.; Blattl, D.; Eder, M.; Wascher, T.C.; Pieber, T.R.; Stauber, R.; Sourij, H.; Oettl, K.; Stadlbauer, V. The influence of probiotic supplementation on gut permeability in patients with metabolic syndrome: An open label, randomized pilot study. *Eur. J. Clin. Nutr.* **2012**, *66*, 1110–1115. [CrossRef]
22. Leong, K.S.W.; Jayasinghe, T.N.; Wilson, B.C.; Derraik, J.G.B.; Albert, B.B.; Chiavaroli, V.; Svirskis, D.M.; Beck, K.L.; Conlon, C.A.; Jiang, Y.; et al. Effects of Fecal Microbiome Transfer in Adolescents With Obesity: The Gut Bugs Randomized Controlled Trial. *JAMA Netw. Open* **2020**, *3*, e2030415. [CrossRef] [PubMed]
23. Ley, R.E.; Turnbaugh, P.J.; Klein, S.; Gordon, J.I. Human gut microbes associated with obesity. *Nature* **2006**, *444*, 1022–1023. [CrossRef] [PubMed]
24. Marungruang, N.; Tovar, J.; Björck, I.; Hållenius, F.F. Improvement in cardiometabolic risk markers following a multifunctional diet is associated with gut microbial taxa in healthy overweight and obese subjects. *Eur. J. Nutr.* **2018**, *57*, 2927–2936. [CrossRef] [PubMed]
25. Meslier, V.; Laiola, M.; Roager, H.M.; De Filippis, F.; Roume, H.; Quinquis, B.; Giacco, R.; Mennella, I.; Ferracane, R.; Pons, N.; et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut* **2020**, *69*, 1258–1268. [CrossRef] [PubMed]
26. Muralidharan, J.; Moreno-Indias, I.; Bulló, M.; Lopez, J.V.; Corella, D.; Castañer, O.; Vidal, J.; Atzeni, A.; Fernandez-García, J.C.; Torres-Collado, L.; et al. Effect on gut microbiota of a 1-y lifestyle intervention with Mediterranean diet compared with energy-reduced Mediterranean diet and physical activity promotion: PREDIMED-Plus Study. *Am. J. Clin. Nutr.* **2021**, *114*, 1148–1158. [CrossRef]
27. Neyrinck, A.M.; Rodriguez, J.; Zhang, Z.; Seethaler, B.; Sánchez, C.R.; Roumain, M.; Hiel, S.; Bindels, L.B.; Cani, P.D.; Paquot, N.; 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*, 3159–3170. [CrossRef]
28. Nicolucci, A.C.; Hume, M.P.; Martínez, I.; Mayengbam, S.; Walter, J.; Reimer, R.A. Prebiotics Reduce Body Fat and Alter Intestinal Microbiota in Children Who Are Overweight or With Obesity. *Gastroenterology* **2017**, *153*, 711–722. [CrossRef] [PubMed]
29. Sergeev, I.N.; Aljutaily, T.; Walton, G.; Huarte, E. Effects of Synbiotic Supplement on Human Gut Microbiota, Body Composition and Weight Loss in Obesity. *Nutrients* **2020**, *12*, 222. [CrossRef]
30. Van Son, J.; Serlie, M.J.; Ståhlman, M.; Bäckhed, F.; Nieuwdorp, M.; Aron-Wisnewsky, J. Plasma Imidazole Propionate Is Positively Correlated with Blood Pressure in Overweight and Obese Humans. *Nutrients* **2021**, *13*, 2706. [CrossRef]

31. Vrieze, A.; Van Nood, E.; Holleman, F.; Salojärvi, J.; Kootte, R.S.; Bartelsman, J.F.W.M.; Dallinga–Thie, G.M.; Ackermans, M.T.; Serlie, M.J.; Oozeer, R.; et al. Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome. *Gastroenterology* **2012**, *143*, 913–916.e7. [CrossRef]
32. Yu, E.W.; Gao, L.; Stastka, P.; Cheney, M.C.; Mahabamunuge, J.; Torres Soto, M.; Ford, C.B.; Bryant, J.A.; Henn, M.R.; Hohmann, E.L. Fecal microbiota transplantation for the improvement of metabolism in obesity: The FMT-TRIM double-blind placebo-controlled pilot trial. *PLoS Med.* **2020**, *17*, e1003051. [CrossRef]
33. Bervoets, L.; Van Hoorenbeeck, K.; Kortleven, I.; Van Noten, C.; Hens, N.; Vael, C.; Goossens, H.; Desager, K.N.; Vankerckhoven, V. Differences in gut microbiota composition between obese and lean children: A cross-sectional study. *Gut Pathog.* **2013**, *5*, 10. [CrossRef] [PubMed]
34. Cho, K.Y. Lifestyle modifications result in alterations in the gut microbiota in obese children. *BMC Microbiol.* **2021**, *21*, 10. [CrossRef]
35. Haro, C.; Montes-Borrego, M.; Rangel-Zúñiga, O.A.; Alcalá-Díaz, J.F.; Gómez-Delgado, F.; Pérez-Martínez, P.; Delgado-Lista, J.; Quintana-Navarro, G.M.; Tinahones, F.J.; Landa, B.B.; et al. Two Healthy Diets Modulate Gut Microbial Community Improving Insulin Sensitivity in a Human Obese Population. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 233–242. [CrossRef] [PubMed]
36. Jumpertz, R.; Le, D.S.; Turnbaugh, P.J.; Trinidad, C.; Bogardus, C.; Gordon, J.I.; Krakoff, J. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am. J. Clin. Nutr.* **2011**, *94*, 58–65. [CrossRef] [PubMed]
37. Kim, M.-H.; Yun, K.E.; Kim, J.; Park, E.; Chang, Y.; Ryu, S.; Kim, H.-L.; Kim, H.-N. Gut microbiota and metabolic health among overweight and obese individuals. *Sci. Rep.* **2020**, *10*, 19417. [CrossRef] [PubMed]
38. Kong, L.C.; Holmes, B.A.; Cotillard, A.; Habi-Rachedi, F.; Brazeilles, R.; Gougis, S.; Gausserès, N.; Cani, P.D.; Fellahi, S.; Bastard, J.-P.; et al. Dietary Patterns Differently Associate with Inflammation and Gut Microbiota in Overweight and Obese Subjects. *PLoS ONE* **2014**, *9*, e109434. [CrossRef] [PubMed]
39. Menni, C.; Jackson, M.A.; Pallister, T.; Steves, C.J.; Spector, T.D.; Valdes, A.M. Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain. *Int. J. Obes.* **2017**, *41*, 1099–1105. [CrossRef] [PubMed]
40. Fernández-Navarro, T.; Salazar, N.; Gutiérrez-Díaz, I.; De Los Reyes-Gavilán, C.; Gueimonde, M.; González, S. Different Intestinal Microbial Profile in Over-Weight and Obese Subjects Consuming a Diet with Low Content of Fiber and Antioxidants. *Nutrients* **2017**, *9*, 551. [CrossRef] [PubMed]
41. Olivares, P.D.S.G.; Pacheco, A.B.F.; Aranha, L.N.; Oliveira, B.D.S.; Santos, A.A.; Santos, P.C.M.D.; Neto, J.F.N.; Rosa, G.; Oliveira, G.M.M. Gut microbiota of adults with different metabolic phenotypes. *Nutrition* **2021**, *90*, 111293. [CrossRef]
42. Orsso, C.E.; Peng, Y.; Deehan, E.C.; Tan, Q.; Field, C.J.; Madsen, K.L.; Walter, J.; Prado, C.M.; Tun, H.M.; Haqq, A.M. Composition and Functions of the Gut Microbiome in Pediatric Obesity: Relationships with Markers of Insulin Resistance. *Microorganisms* **2021**, *9*, 1490. [CrossRef]
43. Peters, B.A.; Shapiro, J.A.; Church, T.R.; Miller, G.; Trinh-Shevrin, C.; Yuen, E.; Friedlander, C.; Hayes, R.B.; Ahn, J. A taxonomic signature of obesity in a large study of American adults. *Sci. Rep.* **2018**, *8*, 9749. [CrossRef]
44. Roland, B.C.; Lee, D.; Miller, L.S.; Vegesna, A.; Yolken, R.; Severance, E.; Prandovszky, E.; Zheng, X.E.; Mullin, G.E. Obesity increases the risk of small intestinal bacterial overgrowth (SIBO). *Neurogastroenterol. Motil.* **2018**, *30*, e13199. [CrossRef] [PubMed]
45. Stefura, T.; Zapała, B.; Gosiewski, T.; Skomarovska, O.; Dudek, A.; Pędziwiatr, M.; Major, P. Differences in Compositions of Oral and Fecal Microbiota between Patients with Obesity and Controls. *Medicina* **2021**, *57*, 678. [CrossRef] [PubMed]
46. Shen, N.; Caixàs, A.; Ahlers, M.; Patel, K.; Gao, Z.; Dutia, R.; Blaser, M.J.; Clemente, J.C.; Laferrère, B. Longitudinal changes of microbiome composition and microbial metabolomics after surgical weight loss in individuals with obesity. *Surg. Obes. Relat. Dis.* **2019**, *15*, 1367–1373. [CrossRef] [PubMed]
47. Da Silva, C.C.; Monteil, M.A.; Davis, E.M. Overweight and Obesity in Children Are Associated with an Abundance of Firmicutes and Reduction of Bifidobacterium in Their Gastrointestinal Microbiota. *Child. Obes.* **2020**, *16*, 204–210. [CrossRef] [PubMed]
48. Yun, Y.; Kim, H.-N.; Kim, S.E.; Heo, S.G.; Chang, Y.; Ryu, S.; Shin, H.; Kim, H.-L. Comparative analysis of gut microbiota associated with body mass index in a large Korean cohort. *BMC Microbiol.* **2017**, *17*, 151. [CrossRef] [PubMed]
49. Yuan, X.; Chen, R.; McCormick, K.L.; Zhang, Y.; Lin, X.; Yang, X. The role of the gut microbiota on the metabolic status of obese children. *Microb. Cell Factories* **2021**, *20*, 53. [CrossRef]
50. Zeng, Q.; Li, D.; He, Y.; Li, Y.; Yang, Z.; Zhao, X.; Liu, Y.; Wang, Y.; Sun, J.; Feng, X.; et al. Discrepant gut microbiota markers for the classification of obesity-related metabolic abnormalities. *Sci. Rep.* **2019**, *9*, 13424. [CrossRef]
51. Zeng, Q.; Yang, Z.; Wang, F.; Li, D.; Liu, Y.; Wang, D.; Zhao, X.; Li, Y.; Wang, Y.; Feng, X.; et al. Association between metabolic status and gut microbiome in obese populations. *Microb. Genom.* **2021**, *7*, 000639. [CrossRef]
52. Bo, T.; Wen, J.; Zhao, Y.; Tian, S.; Zhang, X.; Wang, D. Bifidobacterium pseudolongum reduces triglycerides by modulating gut microbiota in mice fed high-fat food. *J. Steroid Biochem. Mol. Biol.* **2020**, *198*, 105602. [CrossRef]
53. Denou, E.; Marcinko, K.; Surette, M.G.; Steinberg, G.R.; Schertzer, J.D. High-intensity exercise training increases the diversity and metabolic capacity of the mouse distal gut microbiota during diet-induced obesity. *Am. J. Physiol.-Endocrinol. Metab.* **2016**, *310*, E982–E993. [CrossRef]
54. Evans, C.C.; LePard, K.J.; Kwak, J.W.; Stancukas, M.C.; Laskowski, S.; Dougherty, J.; Moulton, L.; Glawe, A.; Wang, Y.; Leone, V.; et al. Exercise Prevents Weight Gain and Alters the Gut Microbiota in a Mouse Model of High Fat Diet-Induced Obesity. *PLoS ONE* **2014**, *9*, e92193. [CrossRef]

55. Everard, A.; Lazarevic, V.; Gaïa, N.; Johansson, M.; Ståhlman, M.; Backhed, F.; Delzenne, N.M.; Schrenzel, J.; François, P.; Cani, P.D. Microbiome of prebiotic-treated mice reveals novel targets involved in host response during obesity. *ISME J.* **2014**, *8*, 2116–2130. [CrossRef]
56. Fjære, E.; Myrmel, L.S.; Lützhøft, D.O.; Andersen, H.; Holm, J.B.; Kiilerich, P.; Hannisdal, R.; Liaset, B.; Kristiansen, K.; Madsen, L. Effects of exercise and dietary protein sources on adiposity and insulin sensitivity in obese mice. *J. Nutr. Biochem.* **2019**, *66*, 98–109. [CrossRef]
57. Gu, Y.; Liu, C.; Zheng, N.; Jia, W.; Zhang, W.; Li, H. Metabolic and Gut Microbial Characterization of Obesity-Prone Mice under a High-Fat Diet. *J. Proteome Res.* **2019**, *18*, 1703–1714. [CrossRef] [PubMed]
58. Guirro, M.; Costa, A.; Gual-Grau, A.; Herrero, P.; Torrell, H.; Canela, N.; Arola, L. Effects from diet-induced gut microbiota dysbiosis and obesity can be ameliorated by fecal microbiota transplantation: A multiomics approach. *PLoS ONE* **2019**, *14*, e0218143. [CrossRef] [PubMed]
59. Hussain, A.; Kwon, M.H.; Kim, H.K.; Lee, H.S.; Cho, J.S.; Lee, Y.I. Anti-Obesity Effect of *Lactobacillus plantarum* LB818 Is Associated with Regulation of Gut Microbiota in High-Fat Diet-Fed Obese Mice. *J. Med. Food* **2020**, *23*, 750–759. [CrossRef] [PubMed]
60. Ji, Y.; Ma, N.; Zhang, J.; Wang, H.; Tao, T.; Pei, F.; Hu, Q. Dietary intake of mixture coarse cereals prevents obesity by altering the gut microbiota in high-fat diet fed mice. *Food Chem. Toxicol.* **2021**, *147*, 111901. [CrossRef] [PubMed]
61. Joung, H.; Chu, J.; Kim, B.-K.; Choi, I.-S.; Kim, W.; Park, T.-S. Probiotics ameliorate chronic low-grade inflammation and fat accumulation with gut microbiota composition change in diet-induced obese mice models. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 1203–1213. [CrossRef] [PubMed]
62. Ke, X.; Walker, A.; Haange, S.-B.; Lagkouvardos, I.; Liu, Y.; Schmitt-Kopplin, P.; Von Bergen, M.; Jehmlich, N.; He, X.; Clavel, T.; et al. Synbiotic-driven improvement of metabolic disturbances is associated with changes in the gut microbiome in diet-induced obese mice. *Mol. Metab.* **2019**, *22*, 96–109. [CrossRef] [PubMed]
63. Kiilerich, P.; Myrmel, L.S.; Fjære, E.; Hao, Q.; Hugenholtz, F.; Sonne, S.B.; Derrien, M.; Pedersen, L.M.; Petersen, R.K.; Mortensen, A.; et al. Effect of a long-term high-protein diet on survival, obesity development, and gut microbiota in mice. *Am. J. Physiol.-Endocrinol. Metab.* **2016**, *310*, E886–E899. [CrossRef] [PubMed]
64. Kübeck, R.; Bonet-Ripoll, C.; Hoffmann, C.; Walker, A.; Müller, V.M.; Schüppel, V.L.; Lagkouvardos, I.; Scholz, B.; Engel, K.-H.; Daniel, H.; et al. Dietary fat and gut microbiota interactions determine diet-induced obesity in mice. *Mol. Metab.* **2016**, *5*, 1162–1174. [CrossRef] [PubMed]
65. Lai, Z.-L.; Tseng, C.-H.; Ho, H.J.; Cheung, C.K.Y.; Lin, J.-Y.; Chen, Y.-J.; Cheng, F.-C.; Hsu, Y.-C.; Lin, J.-T.; El-Omar, E.M.; et al. Fecal microbiota transplantation confers beneficial metabolic effects of diet and exercise on diet-induced obese mice. *Sci. Rep.* **2018**, *8*, 15625. [CrossRef]
66. Li, S.; Yingyi, G.; Chen, L.; Lijuan, G.; Ou, S.; Peng, X. Lean rats gained more body weight from a high-fructooligosaccharide diet. *Food Funct.* **2015**, *6*, 2315–2321. [CrossRef]
67. Lu, Y.; Fan, C.; Li, P.; Lu, Y.; Chang, X.; Qi, K. Short Chain Fatty Acids Prevent High-fat-diet-induced Obesity in Mice by Regulating G Protein-coupled Receptors and Gut Microbiota. *Sci. Rep.* **2016**, *6*, 37589. [CrossRef]
68. Moreira Júnior, R.E.; De Carvalho, L.M.; Dos Reis, D.C.; Cassali, G.D.; Faria, A.M.C.; Maioli, T.U.; Brunialti-Godard, A.L. Diet-induced obesity leads to alterations in behavior and gut microbiota composition in mice. *J. Nutr. Biochem.* **2021**, *92*, 108622. [CrossRef]
69. Moretti, C.H.; Schiffer, T.A.; Li, X.; Weitzberg, E.; Carlström, M.; Lundberg, J.O. Germ-free mice are not protected against diet-induced obesity and metabolic dysfunction. *Acta Physiol.* **2021**, *231*, e13581. [CrossRef]
70. Oh, J.K.; Amoranto, M.B.C.; Oh, N.S.; Kim, S.; Lee, J.Y.; Oh, Y.N.; Shin, Y.K.; Yoon, Y.; Kang, D.-K. Synergistic effect of Lactobacillus gasseri and Cudrania tricuspidata on the modulation of body weight and gut microbiota structure in diet-induced obese mice. *Appl. Microbiol. Biotechnol.* **2020**, *104*, 6273–6285. [CrossRef]
71. Ridaura, V.K.; Faith, J.J.; Rey, F.E.; Cheng, J.; Duncan, A.E.; Kau, A.L.; Griffin, N.W.; Lombard, V.; Henrissat, B.; Bain, J.R.; et al. Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice. *Science* **2013**, *341*, 1241214. [CrossRef]
72. Saiyasit, N.; Chunchai, T.; Prus, D.; Suparan, K.; Pittayapong, P.; Apaijai, N.; Pratchayasakul, W.; Sripetchwandee, J.; Chattipakorn, N.; Chattipakorn, S.C. Gut dysbiosis develops before metabolic disturbance and cognitive decline in high-fat diet–induced obese condition. *Nutrition* **2020**, *69*, 110576. [CrossRef]
73. Shang, Y.; Khafipour, E.; Derakhshani, H.; Sarna, L.K.; Woo, C.W.; Siow, Y.L.; O, K. Short Term High Fat Diet Induces Obesity-Enhancing Changes in Mouse Gut Microbiota That are Partially Reversed by Cessation of the High Fat Diet. *Lipids* **2017**, *52*, 499–511. [CrossRef] [PubMed]
74. Turnbaugh, P.J.; Ley, R.E.; Mahowald, M.A.; Magrini, V.; Mardis, E.R.; Gordon, J.I. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **2006**, *444*, 1027–1031. [CrossRef] [PubMed]
75. Turnbaugh, P.J.; Ridaura, V.K.; Faith, J.J.; Rey, F.E.; Knight, R.; Gordon, J.I. The Effect of Diet on the Human Gut Microbiome: A Metagenomic Analysis in Humanized Gnotobiotic Mice. *Sci. Transl. Med.* **2009**, *1*, 6ra14. [CrossRef] [PubMed]
76. Welly, R.J.; Liu, T.-W.; Zidon, T.M.; Rowles, J.L.; Park, Y.-M.; Smith, T.N.; Swanson, K.S.; Padilla, J.; Vieira-Potter, V.J. Comparison of Diet versus Exercise on Metabolic Function and Gut Microbiota in Obese Rats. *Med. Sci. Sports Exerc.* **2016**, *48*, 1688–1698. [CrossRef]
77. Rowland, I.; Gibson, G.; Heinken, A.; Scott, K.; Swann, J.; Thiele, I.; Tuohy, K. Gut microbiota functions: Metabolism of nutrients and other food components. *Eur. J. Nutr.* **2018**, *57*, 1–24. [CrossRef]

78. Musso, G.; Gambino, R.; Cassader, M. Interactions Between Gut Microbiota and Host Metabolism Predisposing to Obesity and Diabetes. *Annu. Rev. Med.* **2011**, *62*, 361–380. [CrossRef]
79. Den Besten, G.; Van Eunen, K.; Groen, A.K.; Venema, K.; Reijngoud, D.-J.; Bakker, B.M. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J. Lipid Res.* **2013**, *54*, 2325–2340. [CrossRef]
80. Devaraj, S.; Hemarajata, P.; Versalovic, J. The Human Gut Microbiome and Body Metabolism: Implications for Obesity and Diabetes. *Clin. Chem.* **2013**, *59*, 617–628. [CrossRef]
81. Hamer, H.M.; Jonkers, D.; Venema, K.; Vanhoutvin, S.; Troost, F.J.; Brummer, R.-J. Review article: The role of butyrate on colonic function: REVIEW: ROLE OF BUTYRATE ON COLONIC FUNCTION. *Aliment. Pharmacol. Ther.* **2007**, *27*, 104–119. [CrossRef]
82. Cummings, J.; Hill, M.; Bone, E.; Branch, W.; Jenkins, D.J.A. The effect of meat protein and dietary fiber on colonic function and metabolism II. Bacterial metabolites in feces and urine. *Am. J. Clin. Nutr.* **1979**, *32*, 2094–2101. [CrossRef]
83. Nicholson, J.K.; Holmes, E.; Kinross, J.; Burcelin, R.; Gibson, G.; Jia, W.; Pettersson, S. Host-Gut Microbiota Metabolic Interactions. *Science* **2012**, *336*, 1262–1267. [CrossRef] [PubMed]
84. Blachier, F.; Beaumont, M.; Portune, K.J.; Steuer, N.; Lan, A.; Audebert, M.; Khodorova, N.; Andriamihaja, M.; Airinei, G.; Benamouzig, R.; et al. High-protein diets for weight management: Interactions with the intestinal microbiota and consequences for gut health. A position paper by the my new gut study group. *Clin. Nutr.* **2019**, *38*, 1012–1022. [CrossRef] [PubMed]
85. Yao, C.K.; Muir, J.G.; Gibson, P.R. Review article: Insights into colonic protein fermentation, its modulation and potential health implications. *Aliment. Pharmacol. Ther.* **2016**, *43*, 181–196. [CrossRef]
86. Blachier, F.; Beaumont, M.; Andriamihaja, M.; Davila, A.-M.; Lan, A.; Grauso, M.; Armand, L.; Benamouzig, R.; Tomé, D. Changes in the Luminal Environment of the Colonic Epithelial Cells and Physiopathological Consequences. *Am. J. Pathol.* **2017**, *187*, 476–486. [CrossRef] [PubMed]
87. Dallas, D.C.; Sanctuary, M.R.; Qu, Y.; Khajavi, S.H.; Van Zandt, A.E.; Dyandra, M.; Frese, S.A.; Barile, D.; German, J.B. Personalizing protein nourishment. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 3313–3331. [CrossRef]
88. Chiang, J.Y.L. Bile Acid Metabolism and Signaling. In *Comprehensive Physiology*, 1st ed.; Terjung, R., Ed.; Wiley: Hoboken, NJ, USA, 2013; pp. 1191–1212, ISBN 978-0-470-65071-4.
89. Ridlon, J.M.; Kang, D.J.; Hylemon, P.B.; Bajaj, J.S. Bile acids and the gut microbiome. *Curr. Opin. Gastroenterol.* **2014**, *30*, 332–338. [CrossRef]
90. *Clinical and Research Information on Drug-Induced Liver Injury [Internet]*; National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, USA, 2012.
91. Duszka, K. Versatile Triad Alliance: Bile Acid, Taurine and Microbiota. *Cells* **2022**, *11*, 2337. [CrossRef]
92. Venema, K. Role of gut microbiota in the control of energy and carbohydrate metabolism. *Curr. Opin. Clin. Nutr. Metab. Care* **2010**, *13*, 432–438. [CrossRef]
93. Van Winckel, M.; De Bruyne, R.; Van De Velde, S.; Van Biervliet, S. Vitamin K, an update for the paediatrician. *Eur. J. Pediatr.* **2009**, *168*, 127–134. [CrossRef]
94. Dominguez-Bello, M.G.; Godoy-Vitorino, F.; Knight, R.; Blaser, M.J. Role of the microbiome in human development. *Gut* **2019**, *68*, 1108–1114. [CrossRef]
95. Shearer, M.J. Vitamin K metabolism and nutriture. *Blood Rev.* **1992**, *6*, 92–104. [CrossRef] [PubMed]
96. Pham, V.T.; Dold, S.; Rehman, A.; Bird, J.K.; Steinert, R.E. Vitamins, the gut microbiome and gastrointestinal health in humans. *Nutr. Res.* **2021**, *95*, 35–53. [CrossRef] [PubMed]
97. Magnúsdóttir, S.; Ravcheev, D.; De Crécy-Lagard, V.; Thiele, I. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. *Front. Genet.* **2015**, *6*, 148. [CrossRef] [PubMed]
98. Wan, M.L.Y.; Co, V.A.; El-Nezami, H. Dietary polyphenol impact on gut health and microbiota. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 690–711. [CrossRef] [PubMed]
99. Santos, H.O.; Genario, R.; Gomes, G.K.; Schoenfeld, B.J. Cherry intake as a dietary strategy in sport and diseases: A review of clinical applicability and mechanisms of action. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 417–430. [CrossRef] [PubMed]
100. Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C.; Jiménez, L. Polyphenols: Food sources and bioavailability. *Am. J. Clin. Nutr.* **2004**, *79*, 727–747. [CrossRef]
101. Braune, A.; Engst, W.; Blaut, M. Identification and functional expression of genes encoding flavonoid *O*- and *C*-glycosidases in intestinal bacteria: Bacterial flavonoid *O*- and *C*-glycosidase genes. *Environ. Microbiol.* **2016**, *18*, 2117–2129. [CrossRef]
102. Rechner, A. Colonic metabolism of dietary polyphenols: Influence of structure on microbial fermentation products. *Free Radic. Biol. Med.* **2004**, *36*, 212–225. [CrossRef]
103. Carreau, C.; Flouriot, G.; Bennetau-Pelissero, C.; Potier, M. Enterodiol and enterolactone, two major diet-derived polyphenol metabolites have different impact on ERα transcriptional activation in human breast cancer cells. *J. Steroid Biochem. Mol. Biol.* **2008**, *110*, 176–185. [CrossRef]
104. Lampe, J.W. Is equol the key to the efficacy of soy foods? *Am. J. Clin. Nutr.* **2009**, *89*, 1664S–1667S. [CrossRef] [PubMed]
105. Koh, A.; Molinaro, A.; Ståhlman, M.; Khan, M.T.; Schmidt, C.; Mannerås-Holm, L.; Wu, H.; Carreras, A.; Jeong, H.; Olofsson, L.E.; et al. Microbially Produced Imidazole Propionate Impairs Insulin Signaling through mTORC1. *Cell* **2018**, *175*, 947–961.e17. [CrossRef] [PubMed]

106. Li, D.; Lu, Y.; Yuan, S.; Cai, X.; He, Y.; Chen, J.; Wu, Q.; He, D.; Fang, A.; Bo, Y.; et al. Gut microbiota–derived metabolite trimethylamine-N-oxide and multiple health outcomes: An umbrella review and updated meta-analysis. *Am. J. Clin. Nutr.* **2022**, *116*, 230–243. [CrossRef]
107. Karusheva, Y.; Koessler, T.; Strassburger, K.; Markgraf, D.; Mastrototaro, L.; Jelenik, T.; Simon, M.-C.; Pesta, D.; Zaharia, O.-P.; Bódis, K.; et al. Short-term dietary reduction of branched-chain amino acids reduces meal-induced insulin secretion and modifies microbiome composition in type 2 diabetes: A randomized controlled crossover trial. *Am. J. Clin. Nutr.* **2019**, *110*, 1098–1107. [CrossRef] [PubMed]
108. Li, J.; Li, Y.; Ivey, K.L.; Wang, D.D.; Wilkinson, J.E.; Franke, A.; Lee, K.H.; Chan, A.; Huttenhower, C.; Hu, F.B.; et al. Interplay between diet and gut microbiome, and circulating concentrations of trimethylamine N-oxide: Findings from a longitudinal cohort of US men. *Gut* **2022**, *71*, 724–733. [CrossRef] [PubMed]
109. Liu, Y.; Dai, M. Trimethylamine N-Oxide Generated by the Gut Microbiota Is Associated with Vascular Inflammation: New Insights into Atherosclerosis. *Mediat. Inflamm.* **2020**, *2020*, 4634172. [CrossRef] [PubMed]
110. Naghipour, S.; Cox, A.J.; Peart, J.N.; Du Toit, E.F.; Headrick, J.P. Trimethylamine *N*-oxide: Heart of the microbiota–CVD nexus? *Nutr. Res. Rev.* **2021**, *34*, 125–146. [CrossRef]
111. Schiattarella, G.G.; Sannino, A.; Toscano, E.; Giugliano, G.; Gargiulo, G.; Franzone, A.; Trimarco, B.; Esposito, G.; Perrino, C. Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: A systematic review and dose-response meta-analysis. *Eur. Heart J.* **2017**, *38*, 2948–2956. [CrossRef]
112. Farhana, A.; Khan, Y. Biochemistry, Lipopolysaccharide. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
113. Schicho, R.; Marsche, G.; Storr, M. Cardiovascular Complications in Inflammatory Bowel Disease. *Curr. Drug Targets* **2015**, *16*, 181–188. [CrossRef]
114. Al-Assal, K.; Martinez, A.C.; Torrinhas, R.S.; Cardinelli, C.; Waitzberg, D. Gut microbiota and obesity. *Clin. Nutr. Exp.* **2018**, *20*, 60–64. [CrossRef]
115. Blaut, M. Gut microbiota and energy balance: Role in obesity. *Proc. Nutr. Soc.* **2015**, *74*, 227–234. [CrossRef]
116. Adak, A.; Khan, M.R. An insight into gut microbiota and its functionalities. *Cell. Mol. Life Sci.* **2019**, *76*, 473–493. [CrossRef]
117. MetaHIT Consortium (additional members); Arumugam, M.; Raes, J.; Pelletier, E.; Le Paslier, D.; Yamada, T.; Mende, D.R.; Fernandes, G.R.; Tap, J.; Bruls, T.; et al. Enterotypes of the human gut microbiome. *Nature* **2011**, *473*, 174–180. [CrossRef] [PubMed]
118. Crovesy, L.; Masterson, D.; Rosado, E.L. Profile of the gut microbiota of adults with obesity: A systematic review. *Eur. J. Clin. Nutr.* **2020**, *74*, 1251–1262. [CrossRef] [PubMed]
119. Flint, H.J. Obesity and the Gut Microbiota. *J. Clin. Gastroenterol.* **2011**, *45*, S128–S132. [CrossRef]
120. Delzenne, N.M.; Neyrinck, A.M.; Bäckhed, F.; Cani, P.D. Targeting gut microbiota in obesity: Effects of prebiotics and probiotics. *Nat. Rev. Endocrinol.* **2011**, *7*, 639–646. [CrossRef] [PubMed]
121. Sanmiguel, C.; Gupta, A.; Mayer, E.A. Gut Microbiome and Obesity: A Plausible Explanation for Obesity. *Curr. Obes. Rep.* **2015**, *4*, 250–261. [CrossRef] [PubMed]
122. Wolters, M.; Ahrens, J.; Romaní-Pérez, M.; Watkins, C.; Sanz, Y.; Benítez-Páez, A.; Stanton, C.; Günther, K. Dietary fat, the gut microbiota, and metabolic health—A systematic review conducted within the MyNewGut project. *Clin. Nutr.* **2019**, *38*, 2504–2520. [CrossRef]
123. Redondo-Useros, N.; Nova, E.; González-Zancada, N.; Díaz, L.E.; Gómez-Martínez, S.; Marcos, A. Microbiota and Lifestyle: A Special Focus on Diet. *Nutrients* **2020**, *12*, 1776. [CrossRef]
124. Patel, S.; Behara, R.; Swanson, G.; Forsyth, C.; Voigt, R.; Keshavarzian, A. Alcohol and the Intestine. *Biomolecules* **2015**, *5*, 2573–2588. [CrossRef]
125. Lee, E.; Lee, J.-E. Impact of drinking alcohol on gut microbiota: Recent perspectives on ethanol and alcoholic beverage. *Curr. Opin. Food Sci.* **2021**, *37*, 91–97. [CrossRef]
126. Bell, D.S.H. Changes seen in gut bacteria content and distribution with obesity: Causation or association? *Postgrad. Med.* **2015**, *127*, 863–868. [CrossRef] [PubMed]
127. Martínez Leo, E.E.; Segura Campos, M.R. Effect of ultra-processed diet on gut microbiota and thus its role in neurodegenerative diseases. *Nutrition* **2020**, *71*, 110609. [CrossRef] [PubMed]
128. Cuevas-Sierra, A.; Milagro, F.I.; Aranaz, P.; Martínez, J.A.; Riezu-Boj, J.I. Gut Microbiota Differences According to Ultra-Processed Food Consumption in a Spanish Population. *Nutrients* **2021**, *13*, 2710. [CrossRef] [PubMed]
129. Hall, K.D.; Ayuketah, A.; Brychta, R.; Cai, H.; Cassimatis, T.; Chen, K.Y.; Chung, S.T.; Costa, E.; Courville, A.; Darcey, V.; et al. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. *Cell Metab.* **2019**, *30*, 67–77.e3. [CrossRef]
130. Seganfredo, F.B.; Blume, C.A.; Moehlecke, M.; Giongo, A.; Casagrande, D.S.; Spolidoro, J.V.N.; Padoin, A.V.; Schaan, B.D.; Mottin, C.C. Weight-loss interventions and gut microbiota changes in overweight and obese patients: A systematic review: Weight-loss impact on gut microbiota. *Obes. Rev.* **2017**, *18*, 832–851. [CrossRef]
131. Koponen, K.K.; Salosensaari, A.; Ruuskanen, M.O.; Havulinna, A.S.; Männistö, S.; Jousilahti, P.; Palmu, J.; Salido, R.; Sanders, K.; Brennan, C.; et al. Associations of healthy food choices with gut microbiota profiles. *Am. J. Clin. Nutr.* **2021**, *114*, 605–616. [CrossRef]

132. Cotillard, A.; Kennedy, S.P.; Kong, L.C.; Prifti, E.; Pons, N.; Le Chatelier, E.; Almeida, M.; Quinquis, B.; Levenez, F.; Galleron, N.; et al. Dietary intervention impact on gut microbial gene richness. *Nature* **2013**, *500*, 585–588. [CrossRef]
133. Boysen, O.; Boysen-Urban, K.; Bradford, H.; Balié, J. Taxing highly processed foods: What could be the impacts on obesity and underweight in sub-Saharan Africa? *World Dev.* **2019**, *119*, 55–67. [CrossRef]
134. La Fata, G.; Weber, P.; Mohajeri, M.H. Probiotics and the Gut Immune System: Indirect Regulation. *Probiotics Antimicrob. Proteins* **2018**, *10*, 11–21. [CrossRef]
135. Kechagia, M.; Basoulis, D.; Konstantopoulou, S.; Dimitriadi, D.; Gyftopoulou, K.; Skarmoutsou, N.; Fakiri, E.M. Health Benefits of Probiotics: A Review. *Int. Sch. Res. Not.* **2013**, *2013*, 481651. [CrossRef] [PubMed]
136. Gomes, A.C.; De Sousa, R.G.M.; Botelho, P.B.; Gomes, T.L.N.; Prada, P.O.; Mota, J.F. The additional effects of a probiotic mix on abdominal adiposity and antioxidant Status: A double-blind, randomized trial: Probiotic Mix and Abdominal Adiposity. *Obesity* **2017**, *25*, 30–38. [CrossRef] [PubMed]
137. Mohajeri, M.H.; Brummer, R.J.M.; Rastall, R.A.; Weersma, R.K.; Harmsen, H.J.M.; Faas, M.; Eggersdorfer, M. The role of the microbiome for human health: From basic science to clinical applications. *Eur. J. Nutr.* **2018**, *57*, 1–14. [CrossRef] [PubMed]
138. Swanson, K.S.; Gibson, G.R.; Hutkins, R.; Reimer, R.A.; Reid, G.; Verbeke, K.; Scott, K.P.; Holscher, H.D.; Azad, M.B.; Delzenne, N.M.; et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat. Rev. Gastroenterol. Hepatol.* **2020**, *17*, 687–701. [CrossRef] [PubMed]
139. Álvarez-Arraño, V.; Martín-Peláez, S. Effects of Probiotics and Synbiotics on Weight Loss in Subjects with Overweight or Obesity: A Systematic Review. *Nutrients* **2021**, *13*, 3627. [CrossRef]
140. Borgeraas, H.; Johnson, L.K.; Skattebu, J.; Hertel, J.K.; Hjelmesaeth, J. Effects of probiotics on body weight, body mass index, fat mass and fat percentage in subjects with overweight or obesity: A systematic review and meta-analysis of randomized controlled trials: Effects of probiotics on anthropometrics. *Obes. Rev.* **2018**, *19*, 219–232. [CrossRef] [PubMed]
141. Perna, S.; Ilyas, Z.; Giacosa, A.; Gasparri, C.; Peroni, G.; Faliva, M.A.; Rigon, C.; Naso, M.; Riva, A.; Petrangolini, G.; et al. Is Probiotic Supplementation Useful for the Management of Body Weight and Other Anthropometric Measures in Adults Affected by Overweight and Obesity with Metabolic Related Diseases? A Systematic Review and Meta-Analysis. *Nutrients* **2021**, *13*, 666. [CrossRef]
142. Suzumura, E.A.; Bersch-Ferreira, Â.C.; Torreglosa, C.R.; Da Silva, J.T.; Coqueiro, A.Y.; Kuntz, M.G.F.; Chrispim, P.P.; Weber, B.; Cavalcanti, A.B. Effects of oral supplementation with probiotics or synbiotics in overweight and obese adults: A systematic review and meta-analyses of randomized trials. *Nutr. Rev.* **2019**, *77*, 430–450. [CrossRef]
143. Pedersini, P.; Turroni, S.; Villafañe, J.H. Gut microbiota and physical activity: Is there an evidence-based link? *Sci. Total Environ.* **2020**, *727*, 138648. [CrossRef]
144. Ortiz-Alvarez, L.; Xu, H.; Martinez-Tellez, B. Influence of Exercise on the Human Gut Microbiota of Healthy Adults: A Systematic Review. *Clin. Transl. Gastroenterol.* **2020**, *11*, e00126. [CrossRef]
145. Allen, J.M.; Mailing, L.J.; Niemiro, G.M.; Moore, R.; Cook, M.D.; White, B.A.; Holscher, H.D.; Woods, J.A. Exercise Alters Gut Microbiota Composition and Function in Lean and Obese Humans. *Med. Sci. Sports Exerc.* **2018**, *50*, 747–757. [CrossRef]