Review

MOLECULAR METABOLISM

Microbiota and body weight control: Weight watchers within?

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ABSTRACT

Background: Despite several decades of research, managing body weight remains an unsolved clinical problem. Health problems associated with dysregulated body weight, such as obesity and cachexia, exhibit several gut microbiota alterations. There is an increased interest in utilising the gut microbiota for body weight control, as it responds to intervention and plays an important role in energy extraction from food, as well as biotransformation of nutrients.

Scope of the review: This review provides an overview of the role of the gut microbiota in the physiological and metabolic alterations observed in two body weight dysregulation-related disorders, namely obesity and cachexia. Second, we assess the available evidence for different strategies, including caloric restriction, intermittent fasting, ketogenic diet, bariatric surgery, probiotics, prebiotics, synbiotics, high-fibre diet, and fermented foods — effects on body weight and gut microbiota composition. This approach was used to give insights into the possible link between body weight control and gut microbiota configuration.

Major conclusions: Despite extensive associations between body weight and gut microbiota composition, limited success could be achieved in the translation of microbiota-related interventions for body weight control in humans. Manipulation of the gut microbiota alone is insufficient to alter body weight and future research is needed with a combination of strategies to enhance the effects of lifestyle interventions.

Keywords Body weight; Obesity; Gut microbiota; Cachexia; Dietary intervention; Metabolism

1. INTRODUCTION

The gut microbiota, defined as the trillions of microorganisms living in the gastrointestinal tract (GIT), is intricately linked with the health of the host. Several pathological conditions, including metabolic, mental, immune diseases, and cancer, have been associated with an alteration in the configuration and function of the gut microbiota [1—5]. Therefore, there is growing interest in identifying microbiota-targeted therapeutic strategies [6].

Bodyweight is the result of cumulative signals that regulate energy balance. The main factors that influence energy balance are feeding behaviour and energy intake, intestinal energy absorption, energy expenditure, and energy storage [7—9]. Long-term disruption of energy homeostasis leads to the development of several chronic disorders such as obesity (positive energy balance), cachexia and malnutrition (negative energy balance) [10,11]. Obesity is a multifactorial condition whereby the energy extracted from the food consumed is greater than what is used by the body. This leads to an expansion of adipose tissue mass and, consequently, weight gain as well as other comorbidities [12,13]. Conversely, cachexia is a multifactorial condition characterized by excessive weight loss following a severe illness such as cancer [14,15]. Alterations in the composition and functionality of gut microbiota have been observed during the pathogenesis of both obesity and cachexia [16,17]. This occurs because the gut microbiota is wholly dependent on the host organism for water and nutrients, and one of the main processes by which the gut microbiota can affect host physiology is the production of bioactive metabolites from the gastrointestinal contents. Moreover, accumulating evidence demonstrates additional mechanisms and functions of the gut microbiota that go beyond peripheral effects and span both the gut and brain [18]. For example, microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), have been shown to be involved in the control of glucose homeostasis, adipose tissue biology, secretion of gut hormones and neuroactive compounds, and the modulation of vagal nerve activity, all of which can influence metabolism, central appetite regulation, and drive eating behavior [19,20].

The current review provides an update on the effect of the microbiota on host metabolism, appetite, and eating behaviour as well as the role of the gut microbiota in the pathogenesis of obesity and cachexia. This is followed by a critical discussion on the effect of different dietary, surgical, and supplementary approaches, such as calorie restriction (CR), intermittent fasting (IF), ketogenic diet (KD), bariatric surgery,

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List of Abbreviations

16S	Subunit 16
ADF	Alternate-day fasting
AIDS	Acquired immunodeficiency syndrome
BMI	Body-mass index
CCK	Cholecystokinin
ClpB	Caseinolytic Mitochondrial Matrix Peptidase Chaperone Subunit B
CR	Calorie restriction
CRP	C-reactive protein
db/db	Leptin receptor diabetic gene deficiency
DIO	Diet-induced obesity
FA	Fatty acid
FMT	Faecal microbiota transplantation
GDF15	Growth differentiation factor 15
GF	Germ-free
GIT	Gastrointestinal tract
GLP-1	Glucagon-like peptide-1
GOS	Galacto-oligosaccharide
GPR	G-protein receptor
HDL	High-density lipoprotein
HF	High-fermentable
HFD	High-fat diet
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ICR	Intermittent caloric restriction
IF	Intermittent fasting
IL	Interleukin
ITS	Internal transcribed spacer
KD	Ketogenic diet
LDL	Low-density lipoprotein
LF	Low-fermentable
LPS	Lipopolysaccharide
ob/ob	Loss-of-function leptin gene mutation
PF	Prolonged fasting
PYY	Peptide tyrosine tyrosine
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
SCFA	Short-chain fatty acid
T2D	Type-2 diabetes
TRF	Time-restricted feeding

probiotics, prebiotics, synbiotics, high-fibre diet, and fermented foods, in shaping the gut microbiota while having an impact on the body-weight in the context of obesity and cachexia.

2. THE GUT MICROBIOTA

2.1. Introduction to the gut microbiota

Research over the past two decades has demonstrated the central role of mammalian-associated microbiota in host physiology [21] with the 'holobiont' concept proposed to encompass both the eukaryotic host and its microbiota as basic biological units [22]. The gut microbiota incorporates the bacteria, viruses, fungi, and archaea that reside within the GIT, with revised estimates of over 10 trillion total microorganisms, with a huge majority of them residing in the large intestine [23].

Metagenomic analysis of microbial composition is typically performed on faecal samples by sequencing marker genes (such as the 16S rRNA gene in bacteria and the internal transcribed spacer (ITS) in fungi) or whole metagenome sequencing approaches, allowing for both high-resolution taxonomic and functional characterization [24]. Furthermore, functional approaches such as metatranscriptomics, metaproteomics, and metabolomics are also increasingly employed to describe the behavior of these communities [25]. The developments in culture-based approaches have also significantly increased the proportion of cultivable micro-organisms available for *in vitro* analysis [26]. At the forefront of population-level microbiota research, several large studies are available, notably the National Institutes of Health (NIH)-funded Human Microbiome Project [27] in the United States and the European Commission-funded Metagenomics of the Human Intestinal Tract (MetaHIT) consortium [28], as well as national population cohorts [29–31]. These studies have documented unprecedented diversity in the human microbiota, with recently updated global estimates of about 2,500 species, extending observations beyond cohorts of largely European ancestry [32]. They have also shown large degrees of inter-individual variability in terms of composition with a more conserved functional make-up. Attempts to group individuals into categories based on their microbiota (termed 'enterotypes') have identified 3 clusters, based on enrichments in *Prevotella*, *Bacteroides,* and *Ruminococcus* [33], the generalizability, the biological and clinical relevance of which are active areas of research [34,35]. Beyond bacteria, comparatively neglected though important fungal [36] and viral [37] components are present. The gut microbiota has been implicated in a wide range of diseases, notably inflammatory and autoimmune disorders [25,38], a number of cancers [39–41], cardiometabolic [42], and neurological and psychiatric conditions [43,44]. However, many human observational microbiota studies remain underpowered, hampered by the large degree of inter-personal variability in microbiota communities and numerous confounding variables, including diet, medication use, body mass index (BMI), alcohol consumption, age, physical activity, and stool consistency [29,45].

2.2. Application of animal models and tools in the study of the microbiota

There are many ways to examine the contribution of the microbiota to host physiology (Figure 1), including experiments with germ-free (GF) or antibiotic-treated animal models. Moreover, faecal microbiota transplant (FMT) studies can be conducted to provide further proof-of-concept evidence of the association of the gut microbiota with altered disease phenotypes. The studies conducted to examine the role of the gut microbiota in body weight control began with the identification of reduced body weight in GF mice despite an increased caloric intake [46] followed by the demonstration of resistance to diet-induced obesity [47] and the transferability of this phenotype by FMT [48].

Animal models, including non-mammalian model organisms (such as *Drosophila melanogaster*), rodents, large animals (such as pigs) and non-human primates are essential tools in obesity and microbiome research (Figure 1). Several approaches are commonly employed by *in vivo* preclinical studies to investigate the role of the gut microbiota in different circumstances, for example during diet intervention, drug administration, genetic effects or disease models. The following methods aim to disturb or manipulate the gut microbiota in order to assess the consequent amelioration or worsening of the original phenotype in the animal model. These methods are used alone or in combination with the above approaches. Some common strategies employed in rodents, the model organism most commonly used in the studies reviewed in the present paper, are described below (Figure 1).

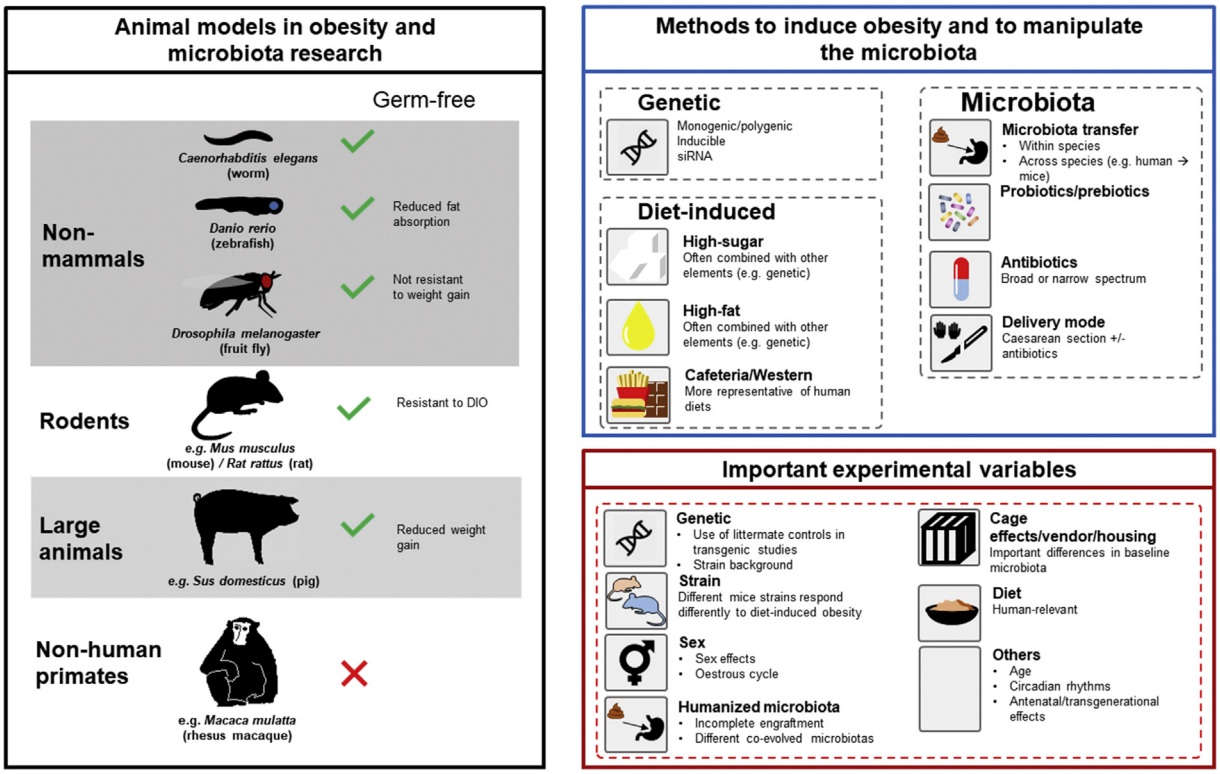

Figure 1: Animal models used as tools in obesity and microbiome research. Animal models used in obesity and microbiome research (left panel). Methods employed to induce obesity and to manipulate the gut microbiota in animal models. Also indicated are the co-factors (variables) to take into account during the preclinical experiment on obesity and microbiota analysis (right panel). Abbreviation: DIO; diet-induced obesity, siRNA; small interfering ribonucleic acid.

- Germ-free rodents- GF animals are generated from founder animals that are delivered via aseptic caesarean section (C-section) and are not exposed to microorganisms since their birth and throughout the lifespan. GF rodents differ with respect to the development and physiology, relative to animals with commensal bacteria. For example, they are characterized by lower body weight, as well as impaired intestinal function, immune system, metabolism, neurodevelopment and hormone signalling regulation [49—53]. In addition to comparative studies with conventionally raised animals, GF rodents also allow for colonisation with known communities (gnotobiotic), providing exquisite control over otherwise complex communities. Relevant examples include the production of the tryptophan metabolite indole propionic acid [54,55] in *Clostridium sporogenes* and bacterial bile salt hydrolase expressed in *Escherichia coli* [56] influencing host immunity, gut permeability, and metabolism.
- Antibiotic treatment. Different antibiotics target and inhibit/interfere with a specific function essential for the bacterial cell, such as DNA replication, RNA synthesis, protein synthesis, and cell wall biosynthesis [57]. Antibiotics can be broad-spectrum, acting on different bacterial taxa, and narrow-spectrum, targeting specific taxa. Broad-spectrum antibiotic usage can have the undesirable effect of also impacting non-pathogenic bacteria [58]. A single antibiotic or an antibiotic cocktail, usually broad-spectrum, are given to the rodents dissolved in drinking water or placed directly into the GIT using oral gavage [59]. However, compared to GF rodents, antibiotic treatment offers a rapid, affordable, and achievable method to study the effects of gut microbiota depletion. The main advantages in the usage of antibiotics versus GF rodents are [59] that antibiotics can rapidly deplete gut microbiota in any rodent genotype or condition and allow for microbial depletion in rodents that were normally colonized since birth. This allows the researchers to evaluate the effects of microbial depletion independent of the numerous developmental impairments observed in GF rodents. However, this gut microbiota depletion method has some disadvantages. First, all bacteria are not killed by antibiotic treatment and antibiotic-resistant pathogens and non-bacteria, e.g., fungi, can flourish. Second, the antibiotic treatment is not always localized within the intestine, as many antibiotics exert systemic effects, influencing other organs and eukaryotic cells. This leads to antibiotic-induced side effects, such as problems with immunomodulation, metabolism, and digestion [60,61]. The use of gut-specific antibiotics such as oral vancomycin has been reported in humans though few benefits have initially been suggested for metabolic syndrome [62]. Further, a recent randomized controlled study of antibiotics in obese pre-diabetic men demonstrated no significant effect of microbiota manipulation on host metabolism, despite having significant and sustained alterations to key members of Firmicutes which have been implicated in energy harvest [63]. This study not only suggests that host metabolism and dietary energy harvest are largely resilient to gut microbiota manipulation in adult humans but also provides invaluable evidence that is not readily available from rodent studies.
- Probiotics, prebiotics, and synbiotics interventions. Probiotics are defined as a live microorganism that confers health benefits to the host when consumed in adequate amounts [64] while prebiotics are selectively fermented non-digestible food ingredients that bring about specific changes in the composition and/or activity of the gastrointestinal microbiota, thereby conferring benefits upon the host

health [65,66]. The mixtures comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confer a health benefit on the host are called synbiotics [67].

- Faecal microbiota transplant. Transfer of the gut microbiota can be achieved through co-housing of rodents or directly by FMT. FMT involves the administration of faecal material from a donor to a recipient directly into the GIT [48,68—70]. FMT is being investigated as a treatment across a huge range of conditions and has demonstrated some benefit in the induction of remission in ulcerative colitis [71—74], improving response to immune checkpoint inhibitors [75,76], and as a potential treatment in metabolic syndrome [77,78]. Through FMT, it is also possible to create the so-called humanized rodents by administering stool from a human donor into a rodent recipient [79,80]. Humanized gnotobiotic rodents, animals into which a human microbiota has been transplanted, have been used to demonstrate causality; the transfer of human disease traits has been reported across a broad spectrum of conditions, including obesity [81,82]. However, the near-universal demonstration of such 'phenotype-transfer' has raised concerns about the methodological and statistical approaches employed [83,84]. Particularly, Walter et al. noted that human microbiota-associated animal studies frequently fail to demonstrate recapitulation of disease-associated microbiota changes (or 'dysbiosis') in recipient rodents ($<$30%), while $>$80% of studies use pseudoreplication and are thus statistically underpowered to reach their conclusions [83], leading to guideline aimed at standardizing approaches to FMT in rodent models [84,85]. In addition to improving the rigor of these studies, Walter et al. suggest several approaches, including using large animal models, experimental designs aimed at addressing causality, and intervention studies in humans where the microbiota is directly manipulated.
- Mode of delivery at birth. Delivery mode is one of the most important factors that shape the gut microbiota in early life. Infants born by caesarean section have significantly different early gut microbial features compared to vaginally delivered infants [86]. Rodent models of caesarean section are used to study the effects of early life manipulations of the gut microbiota on different aspects of health and disease [87,88].

2.3. The gut microbiota depends fully on the host for its energy requirements

Microbial metabolism of undigested material in the GIT is a key mechanism by which the gut microbiota and host interact; the substances ingested or secreted into the gut lumen by the host organism provide essential nourishment for the microbes and shapes gut microbiota composition, and the products of microbial enzymes can then interact with host tissues, either locally at the gut epithelium or following absorption [89,90]. The gut microbiota depends on the host for meeting all its nutritional and water requirements. While some ingested nutrients are utilised directly by gut bacteria, most energy requirements are met by bacteria exploiting food remnants, that the host has already digested and acquired nutrients from, bacterial proteins and polysaccharides, and non-digestible fibre [91,92]. To take full advantage of the vast range of substances that make their way into the GIT, a healthy gut microbiota exhibits a substantial enzymatic repertoire [93], thus producing a wide range of metabolites and compounds capable of impacting host physiology.

In order to maintain a stable community and gut ecosystem, the gut microbiota must regulate its growth rate and population size in response to nutrient availability and population density, communicated through quorum signalling of the gut microbiota. This large contribution to bacterial growth in an organism is further modified by several host factors [94,95], such as digestive enzymes, peristalsis, and excretion. This results in a cascade of cyclical changes in gut microbiota density and diversity over the day, aligning with feeding and fasting patterns, in both rodents [96] and humans [97]. Bacterial duplication is an energy-expensive process, as $\sim$ 4 kJ is required for duplication by 1 g of gut bacteria [98]. We know that approximately 15 g of bacteria are lost daily in faeces [99], the rate of bacterial turnover in the gut remains unknown and understanding this rate is very important for understanding the daily energy requirements of the gut microbiota. GF mice exhibit 27% reduced oxygen consumption [46], which may represent the gut microbiota's energy requirements. The gut microbiota's reliance upon the host for energy implies that the gut bacteria should be able to manipulate host mechanisms of energy intake, and bacterial growth should align with feeding behaviours and interoceptive hunger and satiety [98].

2.4. The gut microbiota modifies the host metabolome and nutrient availability

Gut microbiota composition is shaped by habitual diet across mammalian species [100,101] including humans [94,102—105]. In adults, rapid, reversible shifts in the composition and function of the microbiota on an animal-based diet have been described, including switching from carbohydrate to protein fermentation, increases in the secondary bile acid deoxycholic acid, and increased abundance of bile tolerant organisms such as *Alistipes* and *Bilophila* [94]. However, microbiota resilience to dietary intervention has also been reported [106], while the beneficial effects of dietary fibre in type 2 diabetes (T2D) appear to be associated with a limited number of species (termed a 'guild') that can utilise fibre and produce SCFAs [107] and response to resistant starch is dependent on the presence of a specific species [108].

The gut microbiota itself exerts a profound effect on the mammalian host's global metabolome [55], with SCFAs [109], L-carnitine and choline derivatives [110], tryptophan metabolites [111], branched-chain amino acids [112], and transformed bile acids [56] being key classes in metabolic health that are influenced by diet (specific examples are discussed below).

The gut microbiota also contributes directly to the energy harvest of non-digestible carbohydrates from dietary fibre and this has been proposed as a mechanism by which differences in the composition of the gut microbiota can influence energy balance [113—115]. The vast majority of micro-organisms in the GIT ($>$97%) are located in the large intestine [23], where between 10 g and 60 g of carbohydrates are estimated to become available to the gut microbiota per day [116,117]. Dietary fibre is fermented in the large intestine to produce SCFAs, predominantly butyrate, propionate, and acetate, which act as fuel as well as diverse signalling molecules; SCFAs have been reported to increase in overweight individuals [118]. In addition to having anti-proliferative effects and influencing mucosal immunity [119,120], butyrate is an important energy source for the colonic epithelium. Propionate has an important role in the control and acts as a substrate for intestinal gluconeogenesis, as well as the release of the gut hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) [121,122]. Acetate circulates systemically and is important in peripheral lipid metabolism, as well as in central appetite regulation [122]. SCFA also exerts an influence on gut permeability, which has important repercussions for host inflammation and metabolism [122]. Two things remain unclear: the extent of the direct contribution of gut microbiota energy harvest to net energy balance and whether

alterations in the gut microbiota meaningfully influence this balance. A figure of up to 10% contribution to total energy gain from non-digestible carbohydrates is often cited based on a UK diet [123]. However, in revising this estimate, it was recently suggested that based on a daily fibre intake of 25 g, the contribution of bacterial-derived SCFAs to total energy absorption would be approximately 2.5% [124]. Therefore, even if gut microbiota with a high capacity for energy harvest exist [113], their maximum theoretical contribution to total energy yield would be more modest than previous estimates suggest. Furthermore, by increasing the proportion of carbohydrates from dietary fibre (and thus the influence of the gut microbiota on energy harvest), total energy gain for a fixed calorie intake is decreased [124], implying a comparatively minor role of the gut microbiota in obesogenic diets, which are associated with low levels of fibre.

These calculations may be supported by observations in patients who have had a pan-proctocolectomy (removal of the colon and rectum), an established surgical treatment for ulcerative colitis, and a prophylactic measure for patients with hereditary colorectal cancer syndromes. While most long-term follow-up focuses on quality of life (QOL), functional outcomes and specific nutritional deficiencies [125], removal of the large intestine (and thus the fermentative energy-harvesting capacity of the gut microbiota) do not appear to be associated with significant long-term weight loss [126,127]. Additionally, manipulation of the gut microbiota with antibiotics in a randomised controlled trial did not affect energy harvest (or other clinically relevant outcomes) in obese prediabetic men, following 7 days of treatment or 8 weeks after, despite showing dramatic global change in composition and diversity of the gut microbiota [63]. This finding challenges the role of variations in the energy-harvesting capacity of the gut microbiota as a key influence on host energy balance.

3. THE ROLE OF THE MICROBIOTA-GUT-BRAIN AXIS IN HOMEOSTATIC AND HEDONIC REGULATION OF APPETITE

Bodyweight control and energy homeostasis are essential for survival and health [128]. Signals from multiple organ systems are integrated into the hypothalamus and other brain regions, which then regulate food-seeking behaviour and consumption. Macronutrients and hormones released from the gut, liver, and pancreas are generated during discrete meals and act as satiation signals to halt or reduce discrete feeding bouts, while leptin and other adipokines are released proportional to total body fat and are thought to regulate long-term energy intake and expenditure [129] (For recent comprehensive reviews on the central and peripheral appetite and satiety systems please see [130–132]). In parallel and in combination with homeostatic appetite regulation, brain regions involved in reward regulate energy intake by modifying palatable food-seeking [133] and may also be modulated by the gut microbiota. A recent study found that FMT from obese mice transferred reduced preference for a high-fat high-sugar diet to recipient mice while microbial depletion with antibiotics altered intake of high-fat high-sugar diet in lean mice [134]. A number of these peripheral appetites and satiety-related molecules send a signal to the brain via the gut-brain axis, defined as a bidirectional communication between the central nervous system and the gut. In addition, the gut microbiota is an important modulator of immune system development and homeostasis [135] and can regulate cytokine production [136]; therefore, it may modify feeding behaviour indirectly through interactions with the immune system. Indeed, some pathogenic microbes have evolved mechanisms to inhibit sickness-associated anorexia to improve host health and increase transmission [137].

Accumulating evidence demonstrates a strong influence of the gut microbiota on gut-brain axis structure and function with important consequences for overall host physiology [18]. Several mechanisms of microbiota-gut-brain communication have been described. They include microbiota-mediated effects on the afferent and efferent fibres of the vagus nerve, nutrient sensing in the gut, intestinal barrier function, modulation of the immune system, microbiota-mediated changes in gut hormone secretion, fermentation of nutrients, microbial metabolite signalling, and production of neuroactive signalling molecules. Taken together, these multifaceted pathways have profound effects on host metabolism, energy balance, and different aspects of centrally regulated appetite and eating behaviour, including food reward (Figures 2 and 3) [98,138–140]. Here we focus on the effects of bacterial products on components of the gut-brain axis involved in appetite regulation.

3.1. Bacterial proteins and polysaccharides

If the strong association between bacterial growth in the gut and satiation following a meal is causally established, altered bacterial growth may be communicated to the host by a simple concentration gradient of one or many microbially-derived molecules [98]. While a limited number of experiments have been conducted to test this hypothesis, so far, the data support a role for bacterial proteins and components in satiety (Figures 2 and 3). Proteins collected from commensal *E. coli* during both exponential and stationary growth phases increased plasma GLP-1 and PYY in rats. Stationary growth phase proteins activated c-Fos expression in anorexigenic neurons in the brain and both acutely and chronically reduced food intake [141]. Numerous proteins could underlie this response, including quorum-sensing peptides, caseinolytic mitochondrial matrix peptidase chaperone subunit B (ClpB) and bacterial cell components among others. While quorum-sensing peptides have not yet been shown to interact with the peripheral and central appetite regulation, they may act on the brain to modify feeding behaviour and satiety. Numerous quorum-sensing peptides are measurable in the circulation, and some of these can cross the blood-brain barrier [142] where they might exert effects on central appetite circuitry and other brain regions. *In vitro* screening of quorum sensing peptides revealed that some peptides can alter neurite outgrowth, can induce microgliosis or astrogliosis, or exhibit neuronal and microglial toxicity [143].

Protein ClpB from commensal *E. coli* is a conformation antigen mimetic of the alpha-melanocyte stimulating hormone, a key anorexigenic neuropeptide, that has been associated with eating disorders and obesity in human populations [144,145] and is increased during the stationary growth phase of *E. coli* that express it [141]. *In vitro* experiments indicate the ClpB mRNA and protein expression is increased specifically in response to protein supplementation [146]. Mice immunized to ClpB exhibited altered food intake and body weight, and chronic oral *E. coli* K12 positive for ClpB decreased food intake in healthy mice while oral administration ClpB-deficient *E. coli* did not affect food intake [145]. ClpB is thought to act on melanocortin-4 receptors expressed on enteroendocrine L cells [147], increasing PYY production in primary rat intestinal mucosal cells *in vitro* [146,148]. This protein has recently been shown to reduce cumulative food intake when administered systemically to both healthy and ob/ob mice [149], indicating its therapeutic value in obesity.

Bacterial cell wall components, particularly lipopolysaccharide (LPS), have a long-established role in modifying food intake through activation of the host immune system via pattern recognition receptors in the context of a bacterial infection or sepsis [150]. In healthy animals, signalling from these innate immune receptors is necessary for

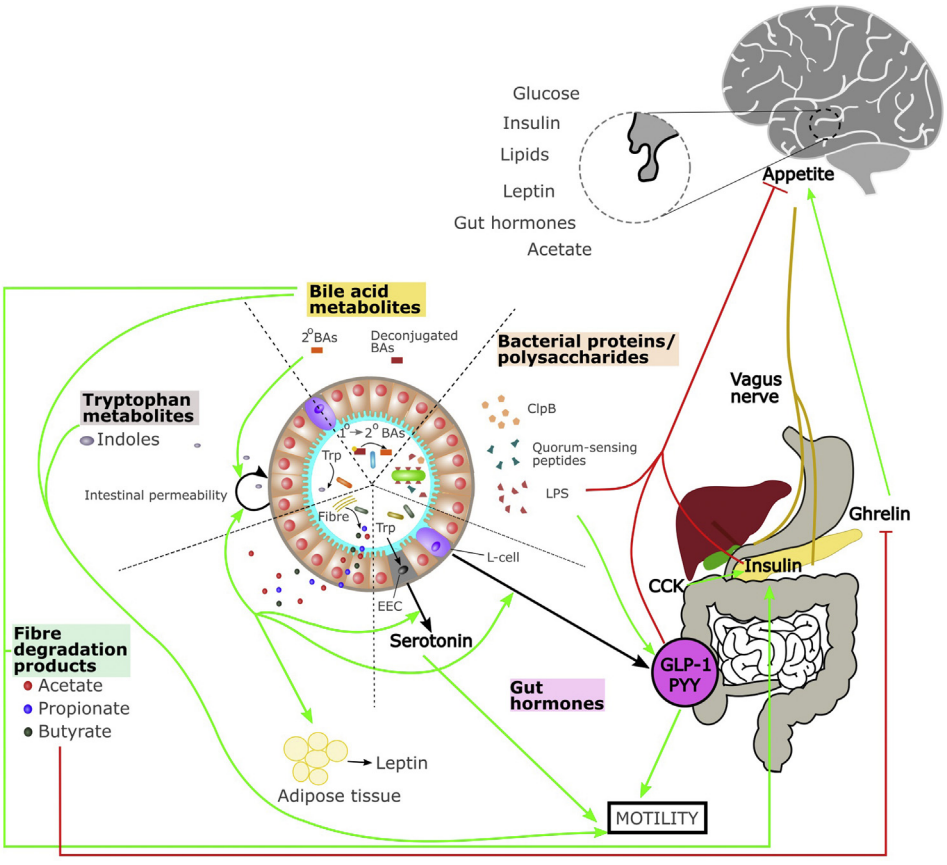

Figure 2: The gut microbiota-gut-brain axis and the control of appetite and energy metabolism. Schematic representation of the microbiota-gut-brain axis communication pathways involved in appetite control and peripheral energy metabolism. Green arrows indicate an enhancement and red arrows indicate inhibition. Abbreviation: LPS; lipopolysaccharide, PYY; peptide YY, GLP-1; glucagon-like peptide 1, CCK; cholecystokinin, 2°BAs; secondary bile acids, BAs; bile acids, ClpB; Caseinolytic Mitochondrial Matrix Peptidase Chaperone Subunit B, EEC; enteroendocrine cell.

intestinal epithelial homeostasis and contributes to intestinal epithelial circadian rhythmicity [151]. Energy intake is positively associated with circulating LPS in humans and mice [152] and a single meal rich in fat increased post-prandial plasma endotoxin in people with T2D [153]. Circulating LPS rapidly increases plasma GLP-1 in both rodents and humans prior to measurable pro-inflammatory response [154], indicating that LPS may act on host appetite independently of cytokine-induced sickness behaviour. LPS also exerts effects on the host's sweet taste receptors: seven days following oral LPS administration, mice exhibited reduced sucrose sensitivity with corresponding reductions in lingual sweet taste receptor expression which normalized after an additional seven days [155]. Both acute and chronic LPS gavage decreased licking responses to sucrose, saccharin, and sodium chloride in mice, with concomitant reductions in neural response to these compounds measured by recording from the chorda tympani [156], indicating the role of LPS in the hedonic and/or motivational aspects of palatable solutions. Muramyl dipeptide ($C_{19}H_{32}N_4O_{11}$), a cell wall component of mycobacteria, reduces feeding behaviour and inhibits gastric emptying similar to LPS and independent of vagal afferent signalling [157]. LPS transiently increases circulating growth differentiation factor 15 (GDF15) [158], a newly-identified anorexigenic protein that reduces food intake in response to metabolic and toxin-related stressors [159] including bacterial and viral inflammation [160]. However, a recent study indicates that LPS does not reduce food intake through activation of this protein as reducing GDF15 activity by both targeted monoclonal antibody administration and by genetic knockout did not impact the effect of LPS on food intake and body weight in mice [158]. However, this does not preclude other microbial proteins and components acting via this pathway. Notably, chronic inflammation caused by a high-fat diet (HFD) is associated with increased LPS (metabolic endotoxemia) which may trigger body weight gain [114,161].

Overall, several bacterial proteins and cell components can induce satiety signals and reduce food intake. Further research examining the function of other bacterial proteins produced during gut microbiota exponential growth and stationary growth phases may lead to additional pathways by which the gut microbiota can induce satiety. Furthermore, an investigation into proteins released during bacterial population decline may be of interest in determining whether the gut microbiota can elicit hunger in host organisms.

3.2. Products of fibre degradation: short-chain fatty acids, succinate, and lactate

Fibre intake is associated with reduced subjective appetite and small reductions in acute energy intake [162]. This may be through the effects of SCFAs, and other fibre-derived microbial metabolites, which reduce food intake and improve glucose homeostasis and insulin sensitivity in preclinical models [163] (Figures 2 and 3). So far acute and chronic SCFA supplementation has produced mixed effects on appetite and metabolic health in humans [122,164–167].

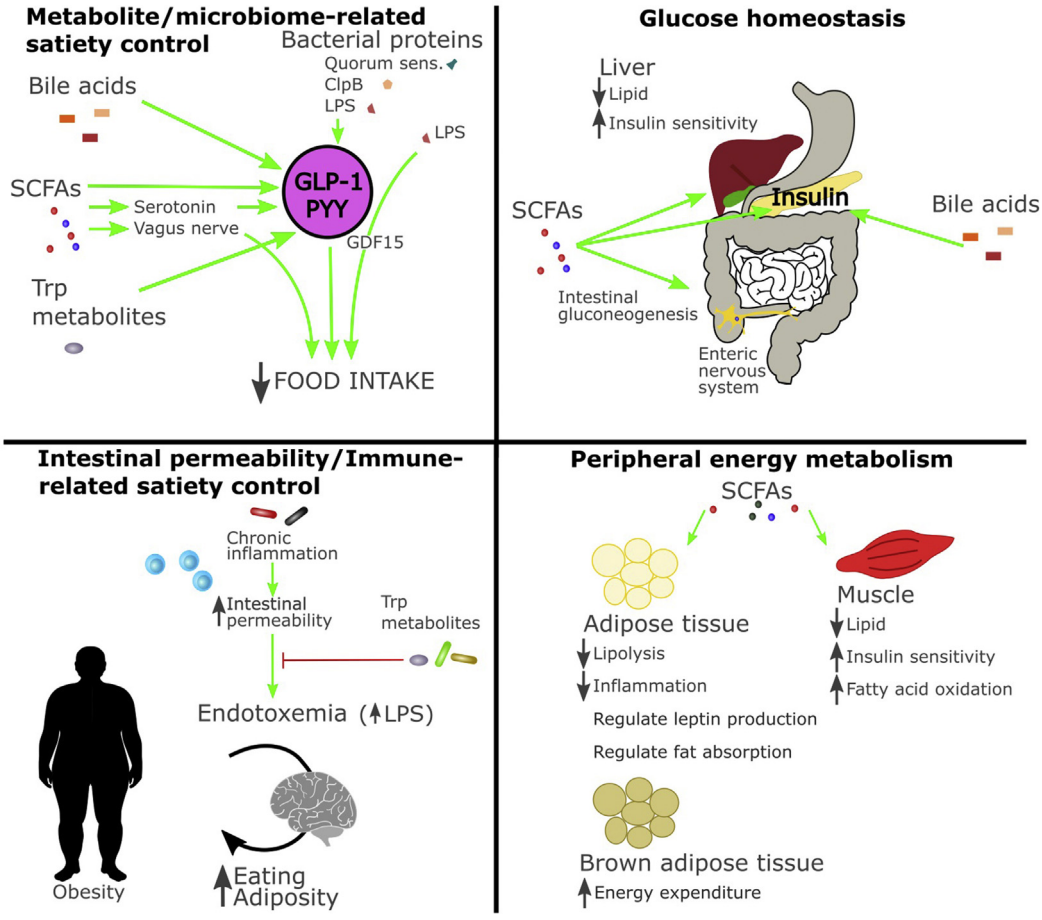

Figure 3: Influence of the gut microbiota on metabolism in regulating appetite and energy balance. Role of the gut microbiota and its metabolites in metabolite-satiety control, glucose homeostasis, immune-related satiety control, and peripheral energy metabolism. Abbreviation: SCFAs; short-chain fatty acids, Trp; tryptophan, LPS; lipopolysaccharide, C1pB; Caseinolytic Mitochondrial Matrix Peptidase Chaperone Subunit B, GDF15; growth differentiation factor 15, PYY; peptide YY, GLP-1; glucagon-like peptide 1.

Butyrate, propionate [168], and succinate [169] promote intestinal gluconeogenesis, a process known to improve glucose handling [170] and prevent hepatic steatosis, in mice fed a hypercaloric diet [171]. Of note, the metabolic benefits of administration of butyrate, propionate, or succinate on body weight and glucose handling were absent in mice that were genetically modified to prevent intestinal gluconeogenesis [168,169]. Acetate and L-lactate produced by bacteria are also able to modify intestinal fat absorption: both compounds inhibit chylomicron secretion from enterocytes while acetate promotes lipid oxidation and L-lactate promotes lipid storage [172]. Additionally, SCFAs enhance colonic secretion of serotonin in mice [173] and gut hormone, including the anorexigenic hormones (i.e., GLP-1 and PYY), from L cells in the GIT (Figure 2) [174,175]. The gut microbiota also regulates the release of ghrelin [174], an orexigenic hormone released predominantly in the stomach. Besides, SCFAs and specific microbiota strains can attenuate ghrelin receptor signalling *in vitro* [176]. Furthermore, adipocytes express specific receptors for SCFAs, which can promote the expression and release of leptin [177], potentially affecting long-term appetite regulation.

Recent preclinical studies indicate that SCFAs are also able to regulate sympathetic and parasympathetic nervous system activation. Propionate [178] and butyrate [179] increase sympathetic tone, elevating energy expenditure in brown adipose tissue. Conversely, increased gut acetate has been shown to activate the parasympathetic nervous system, which promotes increased glucose-stimulated insulin secretion, increased ghrelin secretion, hyperphagia, and obesity [180]. The effects of SCFAs on the autonomic nervous system appear to be via vagal afferents projecting from the distal gut [181].

Optogenetic manipulation of right vagal afferent signalling from the upper GIT increases striatal dopamine and appetitive behaviour in mice [182]. This effect may be mediated by propionate which can suppress food intake through vagal afferent neurons [20] and appears to be involved in hedonic feeding. In a small study, acute colon-specific propionate delivery reduced blood oxygen level-dependent signal during food picture evaluation in brain regions involved in reward and reduced energy intake during an ad libitum meal in healthy men [164]. Overall, microbial products of dietary fibre appear to modulate several processes associated with body weight control of metabolism. Through changes to intestinal gluconeogenesis and lipid absorption, as well as altered autonomic and reward signalling, these metabolites shift body weight in preclinical models of obesity with some effects in the human experiments conducted.

3.3. Tryptophan metabolites

Tryptophan metabolites another key group of microbially-derived metabolites, exert effects on host physiology, acting on gut health and function, and the immune system [183—185] with reported effects on food intake and gut satiety hormone signalling (Figures 2 and 3).

Several bacterial taxa metabolize tryptophan, altering host tryptophan availability and metabolism, through the expression of tryptophanase and other bacterial enzymes [186]. Infusions of L-tryptophan into the gut reduce food intake in both mice [187] and humans [188], where it increases plasma cholecystokinin (CCK), glucagon, GLP-1, and PYY. The effects of tryptophan do not appear to be through conditioned taste aversion or the induction of sickness behaviour [187]. It is unclear whether these effects are via direct actions of tryptophan on the host or through the production of microbial tryptophan metabolites, which also exert effects on food intake.

Bacteria produce indole using tryptophan in response to environmental stress, improving survival of less-resistant communities members [189]. Acute administration of indole in colonic cells *in vitro* and in mice *in vivo* increases GLP-1 through activating the aryl hydrocarbon receptor and can reverse dietary- and genetic-induced metabolic impairments in mice [190]. Bacterial tryptamine activated intestinal epithelial G-protein-coupled receptor 5-HT4 to increase ionic flux and fluid secretion *in vitro*, thereby increasing GI transit in mice *in vivo* [191]. Furthermore, multiple tryptophan metabolites have been implicated in gut barrier function [192], which may impact nutrient absorption and immune signalling, indirectly affecting food intake and appetite.

3.4. Bile acids

Bile acids are enterohepatic hormones that are critical for the digestion and absorption of lipids. They are involved in glucose and lipid metabolism, energy expenditure, inflammation, cholesterol homeostasis, and enterohepatic protection. Bile acids have been implicated in cancer, cardiovascular disease (CVD), and T2D. Primary bile acids, such as cholate and chenodeoxycholate, are synthesized by the host organism in the liver and then secreted into the gut lumen, where gut microbial taxa interact with bile acids to form secondary bile acids. Bile acids exert antimicrobial actions, shape the composition of gut microbiota, and undergo extensive modification by microbes expressing bile salt hydrolase enzymes, which modifies mucosal colonization resistance, immune activity, and gut tissue physiology [193]. Bile acids increase satiety signalling in the gut, by increasing secretion of gut satiety hormones including GLP-1, PYY, glucagon, and insulin in rats [194–196] (Figures 2 and 3) and in the human intestinal mucosa [197] through activating TGR5 receptor and altering intestinal lipid sensing by modifying G protein-coupled receptor 119 (GPR119) activity in the distal intestine [198,199]. Additionally, commensal gut bacteria modulate host gut serotonin expression in part through modifying deoxycholate levels in the mouse gut, altering gastrointestinal motility in mice [200]. Specific bile acids appear to have different effects on glucose tolerance [196,201–203] and further work is required to confirm these differences and determine how different bile acids exert their effects on glucose handling. The metabolic improvements both through bariatric surgery [204] and *Parabacteroides distasonis* [201] can be simulated by targeted bile acid replacement. Finally, bile acids that reach the brain reduce food intake through activation of TGR5 receptors on agouti-related-peptide (AgRP) expressing inhibiting neurons [205].

4. OBESITY AND CACHEXIA: PATHOGENESIS AND RELATED MICROBIOTA ALTERATIONS

4.1. Obesity

Obesity is a chronic, relapsing, progressive condition, that is characterized by an abnormal or excessive accumulation of white adipose tissue [206]. It is associated with dysfunctions across several organ systems, including adipose tissue [13], gut [207], pancreas [208], and the brain [209]. Obesity contributes to premature disability and death by increasing the risk of several diseases [12], including T2D, CVD, some cancers, and neuropsychiatric disorders. Due to the rapid increase in obesity prevalence and limited evolutionary pressure in recent decades, there is a growing recognition that the current obesity epidemic is driven primarily by environmental factors, namely diet and lifestyle [12]. This simplistic view is further complicated by the discovery that diet-induced changes in gut microbiota composition may also impact body weight control and energy balance [17].

Alterations in gut microbiota composition, with a concurrent reduction in overall microbial species diversity, have repeatedly been observed in the context of obesity [210,211]. In studies conducted both in obese mice [113,212] and in humans [213], the proportion of the phylum *Firmicutes* was observed to increase with decreases in the *Bacteroidetes* in the obese condition compared to their normal-weight counterparts. These studies suggested that an increased *Firmicutes/Bacteroidetes* ratio could be used as an obesity biomarker. However, other studies have subsequently contradicted this rather simplistic reductionist view [118,214–216] and the precise taxonomic alterations that characterise obesity remain the subject of debate. However, a recent meta-analysis examining the effects of obesity and high-fat diet on microbiota composition in both mice and humans concluded that the Firmicute/Bacteroidetes ratio is reproducibly increased across 25 studies [217]. Large-scale analyses that compared lean *vs* obese humans showed no relationship between BMI and gut microbiota phylum-level composition, suggesting that a simple taxonomic signature of obesity was not detected in the gut microbiota [216]. Interpersonal variables such as dietary habits and lifestyle as well as effect size and technical differences in the analyses of the microbiota might be the causes of conflicting results between different studies [215,216]. However, a significant, but small, relationship between obesity status and microbiota diversity and richness has been observed [211,215,218]. Despite these inconsistencies in the literature, obesity has been associated with an alteration of gut microbiota. Most of the observational studies that established associations and much of the evidence of a role of the gut microbiota in body weight control comes from rodent studies [94,101–105,213].

Early work by Turnbaugh and colleagues indicated that the obesity-associated microbiota characterized by an increased capacity for energy absorption from the diet, and also that the obese phenotype can be induced in rodents through FMT of samples from obese humans, independent of diet [113]. Though this study has subsequently been criticized for overstating the effect of FMT on fat mass (for example, see analysis by Dalby [219]), it was an important catalyst for subsequent research into the role of the gut microbiota in obesity. Moreover, experiments in GF mice have illustrated the role of the gut microbiota in obesity pathogenesis and susceptibility. Bäckhed and colleagues showed that GF mice have 42% less total body fat than conventional mice, although they ingest 29% more calories than their conventionally raised littermates [46]. GF mice also gain less weight than conventional mice when exposed to an HFD and appear protected against diet-induced glucose intolerance and the development of Insulin resistance (IR) [47,220,221]. In addition, FMT from conventionally raised mice to GF mice triggered a 57% increase in the amount of body fat and a dramatic increase in hepatic triglyceride levels and IR without modifying the amount of food consumed [46]. Regarding the link between the gut microbiota and body fat, studies showed that the gut microbiota could influence the deposition of fatty acids (FAs) in the adipocytes by suppressing the intestinal fasting-induced adipocyte factor, a circulating lipoprotein lipase inhibitor [46]. Lipoprotein lipase

is a key enzyme involved in the hydrolysation of triglycerides in free FAs before their transport into the adipocytes [222].

Furthermore, rodent studies have indicated that altering microbiota composition may be sufficient to induce or reverse increased weight gain. For example, wild-derived microbiota transplanted in laboratory mice during the neonatal period protected against excessive weight gain and metabolic syndrome during a 10-week course of HFD [223]. In another study, FMT from obese and lean twin donors was performed in mice. Mice colonized with obese microbiota showed a significant increase in fat mass compared to the lean counterpart. Cohousing of the mice with donated obese and lean microbiota prevented the development of increased body mass and obesity-associated metabolic phenotypes in mice that received FMT from obese donors [81]. In addition, diet-induced obesity (DIO) promotes a microbiota composition that exacerbates weight regain in previously obese mice that can also exacerbate weight gain in naïve mice receiving FMT [224]. However, a pilot trial in people with obesity reported that FMT from lean donors did not reduce body weight while effectively shifting microbiota composition and metabolite production [225]. Another recent clinical study showed that FMT capsules from lean donors administered to adults with obesity did not cause significant changes in body weight, IR, and body composition [226]. These data indicate the insufficient role played by the gut microbiota composition in humans in improving to induce healthy weight loss.

Recent studies have further defined potential bacterial candidates underlying the effects of gut microbiota composition on body weight control and energy balance. Unexpectedly, the opportunistic pathogen, *Enterobacter cloacae* B29, isolated from the gut of an obese human, caused obesity and insulin resistance in GF mice [227]. In another study using gnotobiotic mice fed a HFD or low-fat diet, *Clostridium ramosum* was associated with the upregulation of glucose and fat transporters in the intestine, as well as increased body fat deposition [228]. Contrastively, other bacterial taxa in the gut appear to have a protective role against obesity and adiposity both in rodents and in humans. Among them, *Akkermansia muciniphila*, a mucin-degrading bacteria, is present in significantly lower levels in genetically obese *ob/ob* (leptin-deficient) and *db/db* (leptin receptor-deficient) mice [229,230] and oral administration of *A. muciniphila* reverses HFD associated metabolic disorders including fat mass gain and IR in these mice [230]. A recent pilot study in people with overweight and obesity showed that *A. muciniphila* supplementation over 3 months could not alter body weight or adiposity, but reduced plasma insulin and cholesterol levels [146]. In addition, the abundance of *A. muciniphila* within the gut microbiota is associated with the decreased risk of metabolic syndrome in a dose-dependent manner in humans [231]. Moreover, *Christensenellaceae*, a bacterial family present in lean individuals, has been shown to promote a lean host phenotype and has an impact on the diversity of the bacterial community when transplanted to mice [232].

In summary, specific gut microbiota components may underlie pathological weight gain observed in obesity, but additional work in humans is required to confirm the translatability of promising results observed in rodent studies.

4.2. Cachexia

Similar to excessive weight gain, abnormal weight loss is also associated with increased mortality [233] and reduced quality of life [234] and can result in permanent damage to several organ systems. Abnormal weight loss is primarily differentiated into four syndromes: starvation or malabsorption (caloric deficit), dehydration (fluid loss or deficit), sarcopenia (muscle atrophy in the context of aging), and cachexia. According to the most recent evidence on cachexia diagnosis, cachexia is defined as a multifactorial syndrome with involuntary progressive weight loss as a result of reduction of skeletal muscle mass with or without depletion of adipose tissue. Additionally, cachexia is characterized by loss of muscle strength, anorexia, lean tissue depletion, distinct fatigue, or abnormal metabolism (i.e., decreased albumin, increased C-reactive protein (CRP) levels [14,15]. Cachexia is observed in a subset of patients with cancer, AIDS, chronic obstructive pulmonary disease, kidney or heart failure, and during long-term care in nursing homes [235]. Overproduction of cytokines may play a role in the pathogenesis of cachexia, as well as the alterations in hormones including testosterone, insulin-like growth factor I, myostatin, and glucocorticoids [236]. However, therapeutic approaches that included the treatment with anti-cytokines and anti-inflammatory components have mainly failed to ameliorate the symptoms of cachexia in cancer patients [237–239]. While a wide range of nutritional, lifestyle and pharmacological interventions have been proposed and trialled in the treatment of cachexia, these have generally resulted in limited clinical benefit, although preliminary trials combining therapies have shown promising results [240]. The gut microbiota is known to modulate several of the systems thought to underlie cachexia, namely energy availability and absorption, and cytokine production [136], and it can interact with a number of hormone signalling pathways [241]. Subsequently, interest has been increasingly shown in the potential of the gut microbiota as a target in the treatment of cachexia.

While intentional weight loss and malnutrition are known to be associated with shifts in the gut microbiota, less is known about the effects of cachexia on gut microbiota composition and function. A recent small study in patients with lung cancer showed that patients with cachexia exhibited a significantly altered gut microbiota composition, along with differences in functional metagenomic pathways and relevant plasma metabolites. Specifically, branched-chain amino acids, vitamins, and methylhistamine were relatively reduced in the plasma of patients with cachexia, while the gut microbiota's capacity for synthesis of LPS was enriched [16]. This finding is in line with that in a separate study on colorectal and lung cancer patients where serum LPS content was shown to be an independent predictor of cachexia and survival [242]. A recent faecal transfer study showed that cachectic patients with advanced gastroesophageal cancer exhibited improved treatment response and survival following FMT from healthy obese donors relative to autologous FMT (from faeces collected prior to cancer therapy) with no improvement in any cachexia outcomes [243], indicating that the microbiota changes associated with cachexia may underlie the related differences in patient prognosis but not necessarily relate to the syndrome itself.

While there is limited human data available, rodent models of cachexia demonstrate that the condition is associated with altered gut microbiota composition and function. Preclinical models of cancer cachexia are characterized by a bloom of *Enterobacteriaceae*, particularly *Klebsiella oxytoca* [244,245], and increased gut barrier permeability [242,244,246]. In line with these microbiota compositional differences, cachectic mice exhibit altered caecal metabolomic relative to control mice, including reduced caecal acetate and butyrate levels and increased bile acid and amino acid content [247]. Furthermore, cachectic mice also exhibit an altered mycobiota with compositional changes similar to those observed in several gastrointestinal inflammatory diseases [248], which may also contribute to the local gut barrier changes as well as altered immune profile. Overall, there is strong preliminary evidence supporting further research into the role of the microbiota in cachexia in clinical populations, as well as further investigation into the therapeutic potential of bacterial strains and their products for cachexia management.

5. DIETARY INTERVENTIONS THAT ACT ON BODY WEIGHT AND THAT SHAPE THE MICROBIOTA

5.1. Calorie restriction (CR)

CR, a nutritional intervention, includes a reduced daily energy intake maintaining healthy dietary habits without malnutrition. Several studies on obesity in humans and rodents have demonstrated the multiple beneficial effects of CR. Among these, body weight loss, fat loss, reduced risk of hyperglycaemia and hyperinsulinemia, and reduced inflammation have been reported [249—251].

The involvement of the gut microbiota in the body weight loss exerted by CR has also been explored (Figure 4). Mice treated with antibiotics were resistant to the body weight loss induced by CR. In addition, mice that underwent CR showed a higher proportion of *Lactobacillus*, *Bifidobacterium, Parasutterella, Clostridiales vadinBB60* as well as a lower proportion of *Helicobacter, Lachnospiraceae* NK4A136*, Lachnoclostridium, Oscillibacter, Roseburia,* and *Gordonibacter* within the gut. FMT from CR-fed mice in HFD-fed mice prevented HFD-induced weight gain and other obesity-related metabolic features, demonstrating that CR potentially induces weight loss via gut microbiota modulation [252]. Mice fed with HFD that received FMT from CR-fed donors exhibited an increased abundance of Firmicutes and Actinobacteria, together with a decrease in the abundance of Bacteroidetes. At the genus level, these mice exhibited significant enrichment of *Faecalibaculum*, *Coriobacteriaceae* UCG-002, and *Coprococcus* [252].

Other studies performed on rodents showed that mice receiving a CR diet had a significantly higher proportion of *Lactobacillus*, frequently represented by *Lactobacillus murinus*, which is linked with an improved metabolic profile [253—256] and a lower proportion of *Lachnospiraceae* [255,257] Additionally, CR and a very-low calorie ketogenic diet enriched both *Akkermansia muciniphila* and *Christensenella minuta* [258,259]. In most of these studies, the bodyweight loss exerted by CR is linked to decrease inflammation and metabolic dysfunctions. During CR, together with the modification of the gut microbiota composition, fecal metaproteomic and the functional capacity of the microbiota changed, including the expression of propiogenic enzymes [260].

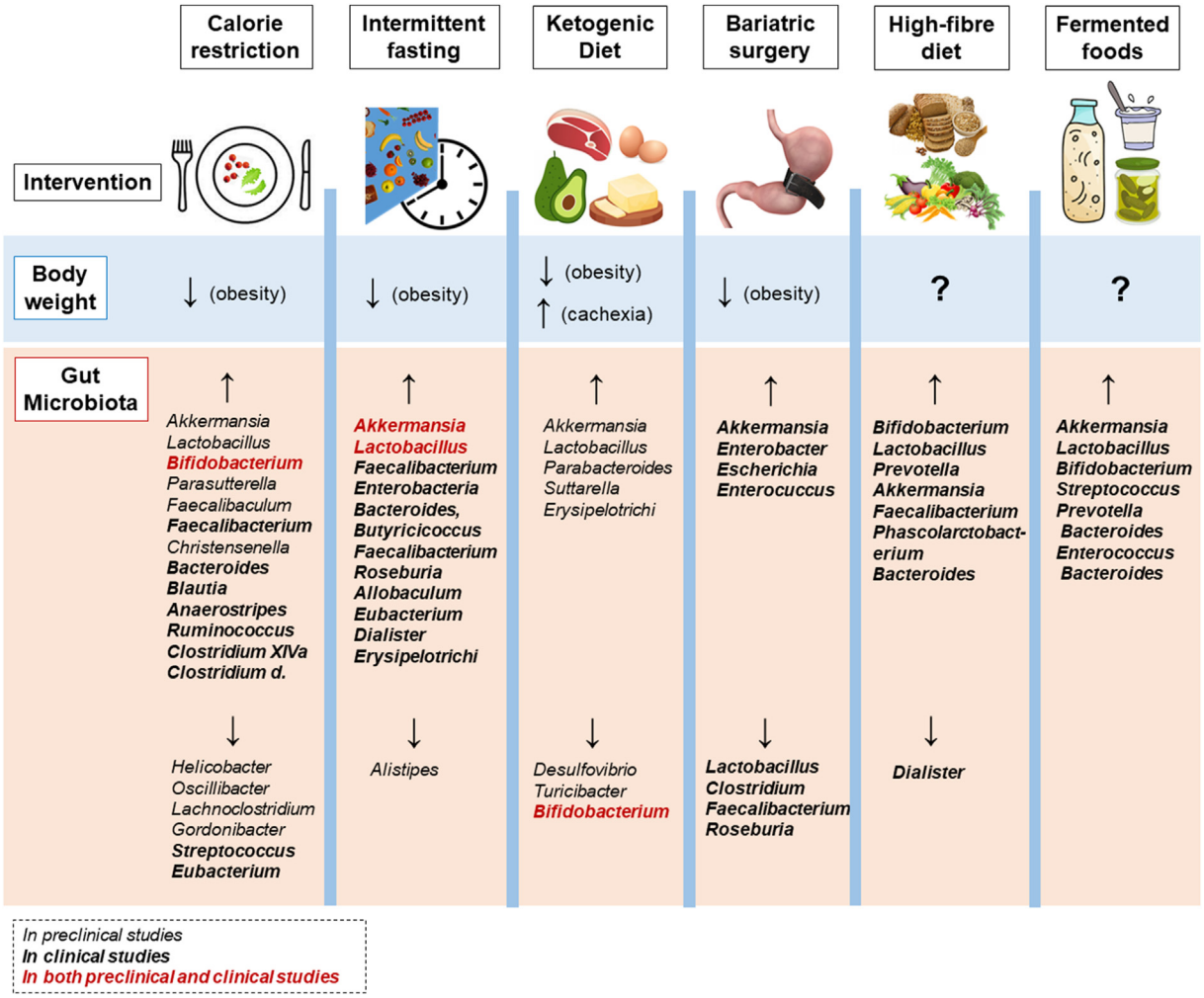

Figure 4: Body weight and gut microbiota changes following dietary and surgical interventions. The upper part of the figure summarizes the effect of calorie restriction, intermittent fasting, ketogenic diet, bariatric surgery, high-fibre diet, and fermented foods on body weight during obesity or cachexia. The question mark (?) indicates the lack of scientific evidence or contrasting endpoints. The lower part of the figure summarizes the general changes in the gut microbiota (at the genus level) upon the interventions. Terms in italics indicate the genera found in preclinical models, in bold are indicated the genera found in clinical models and terms in bold-red indicate the genera found in both preclinical and clinical models.

In non-obese adults, short-term CR intervention (40% reduction in daily calorie intake) was associated with more marked body weight loss in subjects with the *Prevotella* gut microbiota enterotype relative to *Bacteroides* enterotype subjects, indicating that CR can have different effects based on the baseline gut microbiota composition [261]. Long-term CR in obese adolescents promoted weight and adiposity loss and higher metabolic performance linked with enrichment of *Bacteroides*, *Roseburia*, *Faecalibacterium,* and *Clostridium XlVa* and with a lower abundance of *Coriobacteriaceae, Streptococcus, Clostridiales, Eubacterium,* and *Coprococcus* [262,263]. Short-term CR in obese women resulted in a significant decrease in body weight, inflammation, and gut permeability, as well as an improvement in leptin production and glucose tolerance levels. Within the gut, these obese women had a higher abundance of selected operational taxonomic units from *Lachnospiraceae* (including *Blautia* and *Anaerostripes hadrus*), as well as from *Ruminococcus* and *Bifidobacterium* [264].

A recent human study in overweight and obese women showed that a 16-week CR intervention (800 Kcal per day) reduced body weight, adiposity, hyperglycaemia, gut microbiota diversity, and SCFAs production effectively reduced body weight. Bodyweight loss and the improvement in the metabolic parameters were transmitted to the recipient via the donor microbiota in an FMT study in GF mice. Moreover, it was shown that the gut microbiota post-CR was characterized by a lower capacity in extracting energy from the diet. In addition, GF mice receiving FMT from post-CR women showed a higher abundance of the pathogenic bacteria *Clostridium difficile* in their gut, which, in part, contributed to the weight loss in a toxin-dependent manner. The authors also showed that the changes within the gut microbiota upon CR are reversible [265].

Low-calorie diets are not always a long-term solution; however, since in 80% of the cases recurrent weight gain and relapsing metabolic complications are observed after an individual resumes normal calorie intake [224,266]. This phenomenon is commonly called "weight cycling" or the "yo-yo effect". It was shown that one of the causes of this effect lies within the gut microbiota configuration. After dieting, some modifications of the microbiota do not normalize even if weight normalization after obesity is achieved. This contributes to the susceptibility to develop aggravated metabolic complications upon re-exposure to obesity-inducing conditions. The "post-obesity microbiota" seems linked with reduced production of certain flavonoids, which are important postbiotics, and energy expenditure capacity. This demonstrated that, to efficiently act to control body weight, more interventions that take into account the baseline gut microbiota composition are necessary [224,267].

5.2. Intermittent fasting (IF)

IF, a dietary pattern, include periods where energy intake is zero or extremely low. There are different ways to implement IF [298,299] including the following:

- Prolonged fasting (PF) or intermittent caloric restriction (ICR, fasting for up to 24 h once or twice a week with ad libitum food intake in the remaining days of the week),
- Time-restricted feeding (TRF, 8-hour window of eating and 16 h of fasting for most days of the week),
- Alternate-day fasting (ADF, consists of a "feed day" i.e., ad libitum food intake for 24 h, alternated with a "fast day" i.e., complete fast for 24 h).

All of these IF methods have shown efficacy in reducing body weight gain by the 2.5—9.9%, as well as reducing hyperglycaemia, energy intake, and cardiovascular disturbances (Figure 4). Conversely, a recent study in overweight/obese individuals showed no difference in body weight loss among the groups upon time-restricted feeding (TRF) [300] intervention although there were marked inter-individual differences in response. However, IF protocol, duration, and baseline characteristics of the sample population remain highly variable [299,301—303].

Recent literature reviews have summarized the effects of IF on the gut microbiota [304,305] (Figure 4). In healthy mice, one month of ADF intervention led to an increase *Lactobacillaceae*, *Bacteroidaceae*, and *Prevotellaceae* family bacteria, whereas one month of 16-hour TRF was linked with an increase in *A. muciniphila* and a decrease in *Alistipes* genus bacteria [306,307]. In addition, ketone body metabolism and glutathione metabolism-related pathways were upregulated [308]. Both short-term (4 weeks) and long-term (7 months) ADF increased the abundance of *Lactobacillus* and improved gut function and physiology in *db/db* mice [309,310]. In addition, ADF increased the browning of the white adipose tissue and counteracted the metabolic derangements induced by HFD in a gut microbiota-dependent manner [311]. Moreover, studies showed that HFD-induced obese mice exhibited reduced body weight and improved lipid metabolism linked with a higher proportion of *A. muciniphila* and *Lactobacillus* following 4 days of complete food withdrawal [312].

In non-obese adults, both TRF and ADF lead to an increase in the abundance of *Bacteroides* [307,313,314]. In healthy adults that underwent 29 days of TRF (Ramadan fasting regimen), an increase in *Bacteroides fragilis*, *A. muciniphila*, *Butyricicoccus*, *Faecalibacterium*, *Roseburia*, *Allobaculum*, *Eubacterium*, *Dialister,* and *Erysipelotrichi* was observed [313,314]. In overweight or obese adults, an increase in *Lactobacillus*, *A. muciniphila, Faecalibacterium prausnizii,* and *Enterobacteria* abundances was reported after a TRF intervention [315]. In contrast, no differences within the microbiota were found in a more recent study in which adults with obesity had lost weight upon TRF [316]. Further studies are needed to define the effect of long-term IF in humans and well-defined IF protocols are needed to better establish the relationship between IF benefits and the gut microbiota. Moreover, it is highly likely that the gut microbiota may play a role in the inter-individual responses to time-restricted feeding in controlled trials [300].

5.3. Ketogenic diet

The KD is a dietary strategy that includes a very low quantity of carbohydrates and a high quantity of fats. This diet accounts for approximately 10% carbohydrates, 70% fats, and 20% proteins. The objective is to minimize the dietary carbohydrates as much as possible and thus glucose and to promote the mobilization of fats directed at the liver. This facilitates the production of ketone bodies that are utilized as the main fuel by the host, rather than glucose [317]. Weight loss, optimization of metabolism, prevention/amelioration of IR syndrome and neuropsychiatric disorders (i.e., epilepsy and depression) as well as reduction of neuro-inflammation are among the advantages of a KD [318—320].

In recent years, numerous studies have demonstrated the efficacy of a KD in targeting obesity (Figure 4); however, the mechanisms underlying this effect remain unresolved. The possible causes of weight loss upon KD consumption include appetite suppression mediated by ketone bodies, as well as an improvement in fat metabolism efficiency that is secondary to consuming fats [321]. In addition, KD leads to a strong modulation of the gut microbiota (Figure 4). Healthy mice fed KD for 16 weeks showed a significant increase in the abundance of *A. muciniphila* and *Lactobacillus* and a decrease in *Desulfovibrio* and

Turicibacter [322]. These changes were coupled with a improvement in neurovascular function. Accordingly, another study performed in mice with refractory epilepsy showed an increase in *A. muciniphila*, *Parabacteroides*, *Suttarella,* and *Erysipelotrichaceae* upon KD consumption. By using gnotobiotic mice colonized with *A. muciniphila* and *Parabacteroides*, they demonstrated that the anti-seizure effect on mice was exerted by these two taxa [323].

In a recent study, 17 overweight or obese nondiabetic men were recruited and they spent two months as inpatients during which they were carefully monitored. The participants consumed a standard diet (50% carbs, 15% protein, and 35% fat) or a KD (5% carbs, 15% protein, and 80% fat) for 4 weeks and they switched the diets at the end of the 4 weeks. The abundance of Actinobacteria, Bacteroidetes, and Firmicutes phyla and in 19 genera was different between groups after KD [324]. FMT from human donors on a KD into mice could recapitulate the gut microbiota composition and the 'humanised' mice showed a decrease in pro-inflammatory marker Th17 cells both in the gut and in the AT. Thus, a decrease in *Bifidobacterium* was linked with a reduction of inflammation. In *vitro*, they demonstrated that *Bifidobacterium adolescentis* is the species that is most likely inhibited by the ketone bodies. They also observed that mice fed with classical HFD had an opposite gut microbiota configuration (i.e., higher Actinobacteria and *Firmicutes* and lower Bacteroidetes) compared to mice fed with KD, with the latter group exhibiting reduced body weight [324]. Decreased *Bifidobacterium* abundance upon KD consumption has also been observed in children with severe epilepsy [325].

KD could be a beneficial strategy to adopt in particular cases such as metabolic diseases and epilepsy. However, the same diet for a long-term period could reveal different side effects. KD, being very low in carbohydrates, is also very low in fibres which are very important for the maintenance of a healthy GIT as well as healthy gut microbiota. Accordingly, KD causes a decrease in the diversity and richness of the gut microbiota [326]. Thus, the main therapeutic approach seems to suggest increasing water and fibre intake (i.e., dietary fibre supplementation) [327].

Moreover, the kind of fats that are predominant in KD must be taken into account since the proportion of saturated FAs *vs* monounsaturated FAs content in the diet differentially affects the gut microbiota [326,328]. Thus, the use of KD should be carefully regulated and monitored based on the specific medical condition and patient response. For example, concerns in the use of KD have been raised particularly for people with GI disorders or at risk of nutritional deficiency [329,330]. In addition, it was recently shown that KD aggravates cognitive impairment in mice that underwent intermittent hypoxia, by influencing the gut microbiota and by increasing intestinal IFNg-producing Th1 cells [331].

KD was shown to exert a positive effect on cancer-associated cachexia, preventing muscular degradation and general weight loss as well as improving motor function strength (Figure 4). These beneficial outcomes were accompanied by a reduction of the tumour mass [332—334]. Whether the modulation of the gut microbiota by KD consumption could be involved in the amelioration of cachexia-related symptoms is still unexplored.

5.4. Bariatric surgery

Bariatric surgery encompasses surgical procedures that alter the GIT resulting in malabsorption, diminished food intake, and substantial weight loss [335,336] (Figure 4). Among all the weight loss strategies, bariatric surgery is the most effective and long-lasting. It causes a profound change in the production of satiety hormones, altering carbohydrate and bile acid metabolism [337]. Several recent studies and literature reviews have focused in depth on the dramatic effect of bariatric surgery on the gut microbiota in humans with obesity [338—340] (Figure 4). In summary, bariatric surgery leads to a decrease in *Firmicutes* (including *Lactobacillus*, *Clostridium*, *Faecalibacterium*, *Roseburia*) and an increase in *A. muciniphila* and Proteobacteria (including *Enterobacter*, *Escherichia*, *Enterococcus*) [338,341—343]. Additionally, a significant reduction in SCFAs, and energy and amino acid metabolism were detected post-bariatric surgery [340,344]. A longitudinal study revealed that the changes in the gut microbiota and in the faecal metabolomics were present even 4 years post surgery [344]. Furthermore, bariatric surgery response can vary among individuals and the gut microbiota configuration pre-surgery was discovered to be an important predictor of surgery outcomes [343].

Besides the beneficial effect shown against obesity, bariatric surgery can lead to some collateral effects at the GIT level such as nausea, vomiting, obstruction of the GIT, infections, neuropathies due to nutritional deficiencies and emotional disorders (e.g., depression, anxiety, drugs-alcohol abuse) [345,346]. It was shown that the post-surgery mood-related disorders are linked with changes in the production of appetite-related gut peptides as well as with the alteration of the gut microbiota composition and function (i.e., bile acids profile). However, further investigations in the context of changes in gut-brain signalling after bariatric surgery are needed to better elucidate the related mechanisms [347].

5.5. Probiotics, prebiotics, and synbiotics

5.5.1. Probiotics

Several probiotics effectively reduce body weight gain and adiposity in individuals with obesity. Specific strains or combinations of strains such as *Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *B. animalislactis*, *L. gasseri*, *L. curvatus*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum, L. fermentum, B. adolescentis*, *L. sakei*, *B. bifidum*, *B. infantis*, *B. breve*, *Enterococcus faecalis*, *L. parakefir*, *L. kefir*, *B. brevis*, *B. casei, Bacteroides vulgatus, Bacteroides dorei* and *Dysosmobacter welbionis* have been detailed elsewhere to be effective for weight loss during obesity in humans and/or rodents [139,279,348—356]. However, other probiotic strains such as *B. longum*, *L. reuteri* and *L. salivarius* cause a decrease in body weight and metabolic syndrome-related parameters in obese rodents but are mainly ineffective or partially effective in humans [349,357]. It was proposed that probiotics can be beneficial for body weight control and metabolic syndrome through the modulation of the gut microbiota, inflammation and intestinal barrier protection [139,348,357]. Table 1 details the studies on the efficacy of specific probiotics in ameliorating obesity and their effect on the gut microbiota in humans. The effect of each probiotic on the body weight, glucose tolerance, and gut microbiota is very variable. Thus, it is hard to associate the lower body weight caused by probiotics with changes in specific microbial taxa *per se*, also because several studies showed the beneficial effect of single strains of probiotics without changes in the gut microbiota [358]. Also, the positive effects of probiotics on glucose tolerance do not always translate into changes in body weight [279].

Probiotics such as *L. gasseri* and *L. reuteri* have been shown to have a positive effect in mice with cachexia, by decreasing muscle atrophy, inflammation and by increasing intestinal health as well as survival [359—361]. Upon administration of these probiotics, the level of *Lactobacillus spp.* was restored within the gut. However, bodyweight was not significantly altered or was not reported (Table 2); thus, it is still not possible to establish whether a link between probiotic consumption, cancer cachexia-induced body weight loss, and gut

Table 1 — Recent studies on the effect of probiotics/prebiotics/synbiotics on body weight and gut microbiota in obese humans.

Obesity	Dose	Model	Treatment length	Changes in the gut microbiota	Bodyweight	Other physiological and metabolic changes	Reference
Probiotics							
(a) *Lactobacillus amylovorus* or (b) *Lactobacillus fermentum* in yogurt	(a) 1.39 × 10^9 CFU, (b) 1.08 × 10^9 CFU daily	Overweight adults	3 × 43-day phases, each separated by a 6-week washout	(a) ↓ *Clostridial cluster IV,* ↑ *Lactobacillus* (b) ↑ *Lactobacillus*		(a) ↓↓ body fat mass (b) ↓ body fat mass	[268]
VSL#3 (*Bifidobacterium longum*, *B. Infantis*, *B. breve)*	112.5 × 10^9 CFU/capsule each strain	Overweight adults	6 weeks	↑ *Lactobacillus*, ↑ *Bifidobacterium*, ↑ *Bacteroides*, ↑ *Streptococcus*	Not reported	↓ total cholesterol, ↓ LDL, ↓ TAG, ↓ VLDL, ↓ CRP, ↑ insulin sensitivity, ↑ HDL	[269]
VSL#3 *(Streptococcus thermophilus* DSM24731, *L. acidophilus* DSM24735, *L. delbrueckii* ssp. *Bulgaricus* DSM24734, *L. paracasei* DSM24733, *L. plantarum* DSM24730, *B. longum* DSM24736, *B. infantis* DSM24737, *B. breve* DSM24732)	450 billion CFU/sachet	Healthy young adults that consumed HFD (55% fat)	4 weeks	↑ *L. acidophilus*, ↑ *S. thermophilus*	↓ body mass (2.47%)	↓ fat mass gain, = insulin sensitivity and fat oxidation	[270]
L. paracasei F19	9.4 × 10^9 CFU/sachet daily	Obese postmenopausal women	6 weeks	↑ *Eubacterium rectale,* ↑ *Ruminococcus torques*		= CRP,= insulin sensitivity and glucose tolerance	[271]
L. reuteri DSM 17938	10^8 or 10^{10} CFU daily	Overweight or obese adults with T2D	12 weeks	= Increased microbiota diversity at baseline predicted probiotic response	=	↑ insulin sensitivity, ↑ serum deoxycholic acid	[272]
(a) *B. adolescentis* IVS-1 and (b) *B. animalis* subsp. *Lactis* BB-12	1 × 10^9 CFU daily each	Obese adults	3 weeks	(a) ↑ *Bifidobacterium,*= ↑ *B. adolescentis* (b)=		(a) ↓ intestinal permeability during aspirin intake (b)=	[273]
B animalis subsp. *Lactis* 420™ (B420)	10^{10} CFU daily	Overweight/obese human adults	6 months	↑ *Lactobacillus*, ↑ *Akkermansia*	Trend to ↓ (∼1.5%) [274]	=SCFAs or other faecal metabolites. ↓ inflammatory markers, ↓ zonulin (intestinal permeability), ↓ CRP, ↓ body fat mass, ↓ waist circumference [274]	[275]
B. animalis subsp. *Lactis* CECT 8145	10^{10} CFU daily	Obese adults	3 months	↑ *Akkermansia*	↓ BMI (- 0.349 kg/m^2)	↓ waist circumference, ↓ visceral fat, ↓ conicity index, ↓ diastolic blood pressure, ↓ HOMA-IR index	[276]
B. pseudocatenulatum CECT 7765	10^{9-10} CFU daily	Obese children	13 weeks	↓ *Rikenellaceae*, ↑ *Alistipes*	↓ BMI (−0.38 kg/m^2)	↓ CRP, ↓ MPC-1 (inflammation), ↑ HDL, ↑ omentin-1	[277]
Akkermansia muciniphila alive (a) or pasteurized (p)	10^{10} CFU daily	Overweight/obese insulin-resistant adults	3 months	=	(p) ↓ (1.88%) (a)=	(p) ↑ insulin sensitivity, ↓ hyperinsulinemia, ↓ plasma total cholesterol, ↓ fat mass, ↓ hip circumference	[146]

(*continued on next page*)

Table 1 — (*continued*)

						(a) ↓ blood markers of liver dysfunctions and inflammation	
L. acidophilus, B. lactis, B. bifidum, B. longum	1.5×10^{10} CFU each	Overweight or obese people with prediabetes	6 months	↑ *Bacillus fragilis/E. coli* ratio ↓ F/B ration	Not reported	=food intake	[278]
B. longum APC1472	1×10^{10} CFU capsule daily	Overweight/obese human adults	12 weeks	↑ *Bifidobacterium* =		↑ fasting glucose levels, ↓ ghrelin, ↓ cortisol awakening response levels	[279]
L. plantarum Dad-13	2×10^{9} CFU/g/sachet	Overweight human adults	90 days	↓ *Coprococcus*, ↑ *Bacteroides* *L. plantarum* Dad-13 Compared to baseline	↓ (1.64%) BMI ↓ (- 0.53 kg/m^2)	=SCFAs and lipid profile	[280]
Prebiotics							
Inulin + oligofructose	8 g/day + 8 g/day	Obese adult women	3 months	↑*Bifidobacterium*, ↑*Faecalibacterium prausnitzii*, ↓*Bacteroides intestinalis*, ↓*Bacteroides vulgatus*, ↓Propionibacterium	=	A slight reduction in % fat mass	[281]
Bi2muno (mixture of *trans*-galactooligosaccharides)	5.5 g/day	Overweight adults	3 months	↑*Bifidobacterium*, ↓*Bacteroides*, ↓*C. hystolicum* ↓*Desulfovibrio*	=	↓ faecal calprotectin and secretory IgA, ↓ total cholesterol, ↓ insulin, ↓ CRP, ↓ TAG	[282]
Inulin + β-glucan + blueberry anthocyanins + blueberry polyphenols	3.79 g/day + 2.03 g/day + 162.53 mg/day + 723.99 mg/day	Overweight or obese adults	1 month	=		↓ fasting glucose and PYY levels, ↓ reported desire to eat and prospective intake, ↑ fasting plasma ghrelin levels, ↑ faecal SCFA content	[283]
Inulin, sodium butyrate, Inulin + sodium butyrate	10 g/day, 600 mg/day, 10 g/day + 600 mg/day	Overweight or obese adults with T2D	45 days	↑*Akkermansia muciniphila* in groups supplemented with inulin or sodium butyrate alone	=	↓ CRP and malondialdehyde serum levels, ↓ diastolic blood pressure in all supplemented groups	[284]
Litesse Ultra polydextrose	12 g/day	Overweight or obese adults	6 months	↑ *Christensenellaceae*	Not reported	=	[275]
Arabinoxylan	Female: 25 g/day Male: 35 g/day	Overweight or obese adults	6 weeks	↓ alpha-diversity ↑ *Bifidobacterium*, ↑ *Blautia.* ↓ *Parasutterella*, ↓ *Ruminococcus*, ↓ *Clostridium XVIII*, ↓ *Lachnospiraceae incertae sedis*	Not reported	Not reported	[285]
Synbiotics							
B. lactis Bb12 + oligofructose	20^{10} CFU + 16 g/day	Obese adults	6 weeks	↑ *Bifidobacterium*	=	=	[286]
B. adolescentis IVS-1 + galactooligosaccharide	10^{9} CFU + 5 g/day	Obese adults	3 weeks	↑ *Bifidobacterium*, ↑ *B. adolescentis*	=	=	[273]
B. animalis subsp. Lactis BB-12 + galactooligosaccharide	10^{9} CFU + 5 g/day	Overweight or obese adults	6 months	↑ *Bifidobacterium*, UP *B. animalis* subsp. *Lactis* BB-12	=	=	[273]

Bifidobacterium animalis subsp. Lactis 420 + *Litesse Ultra polydextrose*	10^{10} CFU + 12 g/day	Overweight or obese adults	3 weeks	↑ *Akkermansia*, ↑ *Christensenellaceae*, ↑ *Methanobrevibacter*, ↓ *Paraprevotella*	Not reported	↓ bile acids glycholic acid, glycoursodeoxycholic acid, taurohyodeoxycholic acid, tauroursodeoxycholic acid	[275]
Bacillus coagulans BC30, 6086 + β-glucans	5×10^8 CFU + 13 g/day	Overweight and obese adults	3 months	↑ *Faecalibacterium prausnitzii*, ↓ *Bifidobacterium spp.*	=	↑ plasma gamma-glutamyltransferase, ↓ plasma CRP, resistin and LDL/HDL cholesterol ratio	[287]
Omnibiotic Hetox: *B. bifidum* W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W37, *L. casei* W56, *L. brevis* W63, *L. salivarius* W24, *Lc. Lactis* W58 *and Lc. Lactis* W19 + Omnilogic Plus: GOS P11, FOS P6, konjac glucomannan P13 (E425), calcium carbonate (E170), zinc citrate 3-hydrate, vitamin D3 (cholecalciferol) and vitamin B2 (riboflavin) (E101) and a matrix containing maltodextrin, natural elderflower flavouring and Gum Arabic (E414)	1.5×10^{10} CFU total + 8 g/day	Obese adults with T2D	6 months	=	=	↓ hip circumference, ↓ zonulin, ↑ QoL (physical functioning), = glucose metabolism	[288]
L. acidophilus, B. lactis, B. longum, B. bifidum + GOS	15×10^9 CFU + 5.5 g/day	Overweight/obese humans that underwent weight loss program	3 months	↑ richness, ↑ *Bifidobacterium*, ↑ *Lactobacillus*, ↓ *Prevotella*, ↓ *Gardnerella*	=	=	[289]
L. acidophilus, B. lactis, B. bifidum, B. longum + inulin	1.5×10^{10} CFU each +6 g/day	Overweight or obese people with prediabetes	6 months	=	Not reported	=food intake	[278]
2 Bifidobaterium +*5 Lactobacillus strains* + FOS + inulin	1×10^9/g (total) + 9.6 g + 110.4 g	Overweight/obese humans	3 months	↑ *Lactobacillus*, ↑ *E. coli*, ↑ *Enterococcus*	=	Not measured	[290]
L. casei, *L. paracasei*, *B. breve* + GOS	3×10^8 CFU each + 7.5 g daily	Obese humans with T2D	24 weeks	↑ *Bifidobacterium*, ↑ *Lactobacillus*, ↑ *B. adolescentis*, ↑ *B. pseudocatenulatum*	=	↑ acetic and butyric acids in faeces	[291]

This table summarises recent studies, examining the unique effect of microbiota modifications on body weight and gut microbiota composition in people with overweight or obesity. Studies that involved concomitant dietary interventions or do not report gut microbiota changes are excluded. Abbreviations: CFU; colony-forming unit, LDL; low-density lipoprotein, TAG; triacylglycerol, VLDL; very-low-density lipoprotein, CRP; C-reactive protein, HDL; high-density lipoprotein, HFD; high-fat diet, T2D; type-2 diabetes, SCFAs; short-chain fatty acids, HOMA-IR; homeostatic model assessment of Insulin Resistance, MCP-1; macrophages chemoattractant protein 1, BMI; body mass index, IgA antibody; immunoglobulin A, PYY; peptide YY, QoL; quality of life.

Table 2 — Studies on the effect of probiotics/prebiotics/synbiotics on bodyweight and gut microbiota in pre-clinical and clinical models of cachexia.

Cachexia	Treatment	Dose	Model	Treatment length	Changes in the gut microbiota	Bodyweight	Other physiological and metabolic changes	References
Probiotics								
Preclinical studies	*Lactobacillus reuteri 100-23* + *Lactobacillus gasseri 311476*	2×10^8 CFU/ml of each strain	Leukemic BALB/c mice with cachexia	13 days	↑ *L. reuteri*, ↑ *L. gasseri/L. johnsonii*	=	↓ pro-inflammatory markers,↓ muscle atrophy markers	[292]
	Lactobacillus reuteri ATCC-PTA-6475	3.5×10^5 CFU daily	C57BL/6 ApcMIN mice	~ 3 months	Not measured	Not reported	↓ muscle atrophy, ↑ muscle weight, ↓ inflammation	[293]
Prebiotics								
Preclinical studies	POS	5% (w/w)	Leukemic BALB/c mice with cachexia	15 days	↑ *Bacteroides dorei*, ↑ *Bifidobacterium*, ↑ *Roseburia*	=	↓ body fat loss and β-oxidation, ↑ SCFAs acetate and propionate, ↓ isovalerate and branched SCFAs	[294]
	POS	200 mg/day	BALB/c mice with neuroblastoma	Not reported	↑ *Clostridial Family XIII*, ↓*Muribaculum*	=	No changes	[295]
Clinical studies	inulin + FOS		Elderly people with frailty syndrome	13 weeks	Not measured	Not reported	↓exhaustion, ↑ handgrip strength	[296]
Synbiotics								
Preclinical studies	*Lactobacillus reuteri 100-23* + oligofructose Orafti	6.34×10^8 CFU + 0.2 g daily	Leukemic BALB/c mice with cachexia	13 days	↑ *Lactobacillus spp (reuteri)*, ↓ *Enterobacteriaceae*, ↑ *Clostridium cluster XVIII*	Not reported	↓ muscle waste, ↑ survival, improved gut function and immunity	[245]
	Kimchi enriched with *Leuconostoc mesenteroides* + *L. plantarum*	5.1 g/kg/day	Cachectic BALB/c mice with adenocarcinoma	3 weeks	Not reported	↑ (~ 11%)	↑ survival, ↑ muscle preservation, ↓ inflammation, ↓ lipolysis	[297]

Abbreviation; CFU; colony-forming unit, POS; pectic oligosaccharides. FOS; fructo-oligosaccharides.

microbiota configuration exists. The safety of probiotic administration in cancer patients is under examination [362].

5.5.2. Prebiotics

Prebiotics can be found naturally in fruits, vegetables, milk, and unrefined cereals and grains [363]. The consumption of specific prebiotics, such as resistant starch, oligo-fructose, xylooligosaccharides, fructooligosaccharides, arabinoxylan, chitin-β-glucan, soluble corn fiber, fungus-derived (1,3)/(1,6)-β-glucan, 2′-fucosyllactose and inulin showed several beneficial effects against obesity and related comorbidities [363–371]. They resulted in a decrease of fat mass, attenuation of systemic inflammation, reduced serum LPS concentration, improved glucose tolerance and lipid metabolism in obese rodents and/or humans. These beneficial metabolic outcomes were accompanied by an increased abundance of *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium, Bacteroides, Prevotella.* and *Roseburia* [363,365,372]. It was recently demonstrated that the efficacy in ameliorating metabolic syndrome of a specific prebiotic depends on the pre-intervention microbiota configuration of the individual [371]. The studies on the effect of prebiotics on obesity and microbiota in humans are reported in Table 1.

In contrast, galacto-oligosaccharide (GOS) is not linked with modifications of the anthropometric parameters of individuals with metabolic syndrome and overweight. However, this prebiotic can modify the gut microbiota configuration, plasma lipid/biochemical, and immune profile [365,372]. Another prebiotic mixture, called GSK457, produced a strong weight loss effect in DIO and *db/db* mice but this effect was not recapitulated in overweight adults with T2D [373]. One of the possible mechanisms by which prebiotics ameliorate metabolic syndrome is through SCFAs production and signalling to the host [363,365].

Very few studies assessing the effects of prebiotics on cachexia (cancer and age-related) and gut microbiota are available (Table 2), leaving this topic mainly unexplored.

5.5.3. Synbiotics

Some synbiotics have been tested in obese rodents and humans giving contrasting outcomes. In HFD-induced obese mice, the symbiotic *B. animalis* subsp. *Lactis*, *Lactobacillus paracasei* subsp. *Paracasei* + oat β-glucan supplementation had a stronger effect in ameliorating the metabolic syndrome and in shaping the gut microbiota compared to the probiotics mix and β-glucan given separately [374].

There is evidence that synbiotics can have a beneficial impact on anthropometric measures and body composition in obese humans coupled with a weight loss intervention [375], but recent human studies showed limited improvement in metabolic syndrome dysfunctions upon synbiotic supplementation only, even if the gut microbiota was affected (Table 1). One study showed that *Bifidobacterium* strains and GOS improved gut health in obese adults without showing synergism when used together as synbiotics [273]. Therefore, further efforts are necessary to design and study novel synbiotics for the prevention/treatment of obesity.

Few studies have investigated the potential benefits of synbiotics on excessive weight loss, muscle waste, inflammation, and intestinal health in individuals with cachexia [376] (Table 2). Since just one study in rodents includes the analysis of the gut microbiota, further studies that test the involvement of the gut microbiota in the amelioration of cachexia upon synbiotics supplementation are required.

5.6. High-fibre diet

Dietary fibres are classified as soluble (i.e. able to dissolve in water and to be digested) and insoluble (i.e., indigestible fibres that reach the colon and are fermented through several gut bacteria) [377].

Table 3 — Several candidate taxa involved in the control of body weight.

Phylum	Family	Genus (Species)	How might it affect body weight?
Firmicutes	*Lactobacillaceae*	*Lactobacillus (plantarum, rhamnosus, gasseri, curvatus, sakei, kefir, parakefir)*	↑ after CR, IF, KD, FF. • Aero-tolerant anaerobe. • Protective effect on the tight junctions, decreasing gut permeability and inflammation [406—408]. The inflammation decreases also in the hypothalamus, increasing insulin and satiety hormones sensitivity [409,410]. This leads to reduced food intake, increased satiety, and fat accumulation [411,412]. • Production of antimicrobial peptides, able to eliminate pathogenic bacteria, • Production of linoleic acid, which modulates the FAs composition of liver and adipose tissue (increases lipolysis) and reduces leptin levels [349,413,414].
	Lachnospiraceae	*Roseburia (hominis, intestinalis, inulinivorans, faecis)*	↑ after CR, IF. • Obligate anaerobes. • Production of SCFAs, especially butyrate, upon fibres consumption. Butyrate is the main energy source for colonic cells and inhibits the production of pro-inflammatory cytokines by blocking NF-kB and by activating pro-inflammatory T-cells [415,416]. This has a protective effect on the intestinal epithelium. In addition, butyrate is an important regulator of thermogenesis, lipid and glucose metabolism and appetite [417].
	Ruminococcaceae	*Faecalibacterium (prausnitzii)*	↑ after CR, IF. • Obligate anaerobe. • Butyrate-producer (see the benefits of butyrate in *Roseburia*) [418]. • Production of salicylic acid, which has anti-inflammatory properties (decreases IL8) [419,420].
	Christensenellaceae	*Christensenella (minuta)*	↑ after CR, HFi. • Obligate anaerobe. • Linked with low adiposity, lean phenotype, healthy diet consumption, and intestinal health and motility [421,422]. • Moderate production of butyrate and acetic acid. • Linked with an increase in energy expenditure pathways in the liver and adipose tissue as well as an improved expression of intestinal tight junctions [423].
Bacteroidetes	*Bacteroidaceae*	*Bacteroides (uniformis, thetaiotaomicron)*	↑ after CR, IF, HFi, FF. • Obligate anaerobe. • Production of SCFAs (acetate, succinate, lactate, and propionate) [424]. I • Regulation glutamate metabolism in epithelial cells [425] and insulin-dependent routes in the adipose tissue and the liver. • Improvement immunity function and lipid metabolism [425].
Actinobacteria	*Bifidobacteriaceae*	*Bifidobacterium (lactis, animalis, adolescentis, bifidum, infantis, breve, brevis, casei)*	↑ after CR, FF; ↓ KD • Obligate anaerobe. • Production of butyrate (see the benefits of butyrate in *Roseburia*). • Most abundant genera present in a healthy gut early in life as well as in the intestine of healthy breastfed infants. It plays an important role in gut homeostasis and immune system development [426,427]. • Important immuno-regulatory role in the adults [427]. • It promotes insulin sensitivity, glucose tolerance, liver and adipose tissue functions, mitochondrial biogenesis, and body fat loss [412,428,429].
Verrucomicrobia	*Akkermansiaceae*	*Akkermansia (muciniphila)*	↑ after CR, IF, KD, BS, HFi, FF. • Strict anaerobe. • Utilization of mucin as the sole source of carbon and nitrogen elements. • Its abundance is inversely proportional to the body weight in mice and humans. It is associated with an improvement of intestinal health (gut permeability, tight junctions), immune system function, glucose tolerance, adipose tissue metabolism, and insulin sensitivity [430,431]. • Linked with an increased level of satiety hormones (GPL-1 and PYY), suppression of appetite, increased energy expenditure, and decreased adipocytes size [432]. • Its inactivation (pasteurization) enhances more, even the beneficial effects [433].

Abbreviation; CR; calorie restriction, IF; intermittent fasting. KD; ketogenic diet, BS; bariatric surgery, FF; fermented foods, HFi; high-fibre diet, NF-kB; nuclear factor kappa B, GLP-1; glucagon-like peptide, PYY; peptide tyrosine tyrosine.

Different proportions of fibres are contained in fruits, vegetables, legumes, cereals, nuts, and seeds [377]. The Mediterranean, vegetarian and vegan diets include a high amount of these foods [378,379]. High-fibre intake has been associated with intestinal health, improved bowel motility, low risk of intestinal inflammation and colorectal cancer, low cholesterol absorption and improvement in cognitive functions [379—381].

Numerous clinical trials have tested the effect of a high-fibre diet in obese individuals, which revealed positive effects in lowering body weight gain and adiposity, improving satiety and glucose tolerance [380]. In addition, high-fibre diets are associated with a modulation in the gut microbiota, in particular an increase in *Bifidobacterium*, *Lactobacillus*, *Prevotella*, *A. muciniphila*, *F. prausnitzii,* and *Ruminococcus* [378,382] (Figure 4). In most of the studies, the changes in the gut microbiota are linked with an increase in SCFAs [383]. Indeed, it was shown that dietary fibres intake promoted a greater gut microbiota diversity and the growth of a select group of SCFA-producing strains within the gut in diabetic humans. These changes were accompanied by improvements in GLP-1 production and glucose tolerance [107]. However, in some studies, fibre consumption significantly changed the gut microbiota configuration without affecting glucose tolerance, IR, and other metabolic parameters [382,384]. This is due to the high variability of the diets tested as well as the different proportions of fibre within the diets and the baseline fibre intake of the participants. In a recent study, people with severe obesity were selected and underwent FMT from healthy donors. Following FMT, the participants consumed high-fermentable (HF) or low-fermentable (LF) fibre supplements for 6 weeks. Unlike HF fibre, LF fibre significantly improved insulin

sensitivity and satiety hormones production. However, the cessation of LF fibre consumption reversed the beneficial effects on insulin sensitivity. There were no differences in body weight gain among the groups. Moreover, the FMT-LF group showed an increase in bacterial richness, an increase in the abundance of *Phascolarcobacterium*, *Christensenellaceae*, *Bacteroides,* and *A. muciniphila,* and a decrease in *Dialister* and *Ruminococcus torques*. In addition, the abundance of *Phascolarctobacterium*, *Bacteroides stercoris,* and *Bacteroides caccae* was significantly associated with HOMA-IR and insulin sensitivity [368].

Deeper and long-term investigations on the consumption of different kinds of fibre as well as more knowledge on the effect of soluble *vs* non-soluble fibres on metabolism and gut microbiota are needed. This would help to design specific high-fibre diets for defined pathological conditions.

5.7. Fermented foods

Fermented foods are foods enriched in live microorganisms, bacterial-derived molecules and compounds, and micronutrients that are potentially good for human health. Fruit, vegetables, and legumes, can be spontaneously fermented by promoting the growth of bacteria that naturally colonize the food (i.e., sauerkrauts and kimchi). Other foods, such as milk, tea, and soybeans, can be fermented with starter cultures (i.e., yogurt, kefir, kombucha, and natto) [385].

Few studies have investigated the effect of certain fermented foods on health, even if most of them are largely undocumented (Figure 4). It was shown that some fermented foods such as *kefir, natto, miso,* and k*imchi* are linked with the increase of *Lactobacillus* and *Bifidobacterium spp.* within the gut [386]. In another study, the gut microbiota of a large cohort of fermented foods consumers was assessed. Higher proportions of *Streptococcus*, *Prevotella*, *Bacteroides*, *Enterococcus spp*. were also observed as well as a different metabolomics profile compared to non-consumers [387]. Recently, it was shown that 17 weeks of high-fermented food consumption (i.e., 6 servings per day) increased gut microbiota diversity and decreased inflammatory markers in a small cohort of healthy volunteers [388].

Products derived from the fermentation of milk have shown positive effects in people with T2D and CVDs, by improving glucose metabolism [389]. Kefir showed a beneficial effect on GIT health both in healthy individuals and in people with inflammatory bowel disease [386]. In addition, fermented foods consumption exerts anti-inflammatory properties and could prevent cancer development [390—393]. Recently, it was observed that kefir consumption can regulate the microbiota-gut-brain axis by influencing mood and behaviour [394,395].

Limited studies aiming to look at the effects of fermented foods on body weight control and gut microbiota have been carried out. In rodents with HFD-induced obesity, some fermented foods such as Chinese fermented dark tea and fermented ginger showed positive effects by reducing body weight gain and improving obesity-related metabolic markers [396,397]. In humans, Chungkookjang (Korean fermented soybeans, similar to natto) and kimchi significantly improved body fat mass and metabolic parameters [398,399]. However, the composition of the gut microbiota was not assessed in these studies. In another study, HFD-fed mice were supplemented with fermented rice enriched in *Bifidobacterium sp.* MKK4. After 8 weeks of intervention, a reduction in body weight was observed, as well as an improvement of metabolic parameters, glucose tolerance, and lipolysis. These changes were associated with increased proportions of *Lactobacillus*, *Bifidobacterium* and *Bacteroides* within the gut [400]. In a recent clinical study, the improvements in LDL/HDL ratio and CRP levels, a higher abundance of *Akkermansia*, *Bacteroides* and acetate within the gut were reported upon yogurt consumption. Here, the changes in body weight were not significant [401].

With all their beneficial properties and excellent nutritional values, fermented foods could also be a helpful dietary solution for people with cachexia. Only one study in mice has been performed. Here, kimchi consumption suppressed IL-6 levels and ameliorated body weight loss, muscle atrophy, and lipolysis in mice with cancer cachexia [297]. More pre-clinical and clinical studies are needed to better explore the potential of fermented foods in cachexia improvement.

6. CONCLUSIONS & FUTURE PERSPECTIVES

Substantial work has demonstrated strong associational relationships between gut microbiota composition and function and body weight regulation. Preclinical evidence in both obesity and cachexia supports a role of the gut microbiota in associated body weight and metabolic dysfunction. However, these encouraging results have had limited translatability when assessed in clinical populations. In addition, associations and causality of human diseases and gut microbiota are better explored in rodents than humans but gaps remain for many conditions [82,402]. A key challenge for researchers investigating the role of the microbiota in body weight control is determining whether specific taxa or microbial functions can underlie bodyweight dysregulation in these pathologies.

The strategies investigated to rebalance the body weight lead to the modification in the proportion of different taxa and current research implicates several bacterial taxa in body weight control (detailed in Table 3). It remains unclear whether these taxa exert effects directly on body weight, or if their benefits depend on modifications to other metabolic processes, such as changes in glycaemic control, IR, intestinal health, and immune function. Furthermore, bodyweight control may depend on a specific bacterial function or product that may be redundant across multiple strains.

Currently, the literature is highly variable in terms of intervention length, formulation, and dose, making comparison difficult. Thus, more consistency in the intervention protocols might help to reduce variability in the results. Furthermore, there is a lack of long-term experiments and follow-up. Since in many clinical studies, the response to a certain bodyweight control intervention is not the same for each individual, in the future it is essential to always include baseline gut microbiota assessment and focus on individual response to intervention longitudinally [6]. This could help understand the temporal relationship between gut microbiota and metabolic changes, and is key for determining causality in human studies. Accordingly, a recent human study showed that the baseline microbiota composition can determine the efficacy of responses to weight loss interventions [403]. In addition, we now need to go deeper into the analysis of bacterial strains by using more precise methods such as the shotgun metagenomics [24] and to investigate more about the function, combined with metabolomics, of the candidate strains [404,405]. These deeper analyses, rather than superficial classification at the genus level, are essential for determining the underlying mechanisms by which potential probiotics exert effects in body weight control.

In summary, while there are strong relationships between body weight and gut microbiota composition both in preclinical and clinical studies, so far there is limited evidence for a causal role of the gut microbiota in body weight control in both healthy people, and people suffering from bodyweight dysregulation. Addressing dysregulated body weight remains a key clinical challenge and manipulation of the gut microbiota alone may not be sufficient to exert beneficial effects in this context

and future research should focus on combining strategies to potentiate the benefits of lifestyle interventions.

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CONFLICT OF INTEREST

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