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Review article

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The gut microbiota in obesity and weight management: microbes as friends or foe?

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Abstract

Obesity is caused by a long-term difference between energy intake and expenditure — an imbalance that is seemingly easily restored by increasing exercise and reducing caloric consumption. However, as simple as this solution appears, for many people, losing excess weight is difficult to achieve and even more difficult to maintain. The reason for this difficulty is that energy intake and expenditure, and by extension body weight, are regulated through complex hormonal, neural and metabolic mechanisms that are under the influence of many environmental factors and internal responses. Adding to this complexity, the microorganisms (microbes) that comprise the gut microbiota exert direct effects on the digestion, absorption and metabolism of food. Furthermore, the gut microbiota exerts a miscellany of protective, structural and metabolic effects both on the intestinal milieu and peripheral tissues, thus affecting body weight by modulating metabolism, appetite, bile acid metabolism, and the hormonal and immune systems. In this Review, we outline historical and recent advances in understanding how the gut microbiota is involved in regulating body weight homeostasis. We also discuss the opportunities, limitations and challenges of using gut microbiota-related approaches as a means to achieve and maintain a healthy body weight.

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Key points

- Two decades ago, pioneering studies showed that prebiotic-induced changes in the gut microbiota affect adipose mass in rats.
- Numerous dietary factors, such as fat, proteins and fibre, shape the gut microbiota and eventually contribute to the regulation of host energy metabolism through specific microbial metabolites.
- So far, no proof has been provided that one specific bacteria or group of bacteria can predict the onset of obesity or body weight loss in humans.
- The regulation of host energy metabolism is under the influence of many metabolites produced and/or modified by the gut microbiota, and some of these molecules might become drug candidates.
- Demonstrating whether particular microbiota compositions are beneficial or detrimental for body weight management remains a challenge and requires future studies to design personalized, targeted modulation of microbiota.

Introduction

One of the first indications that changing the gut microbiota composition has the potential to positively influence the progression of several diseases, such as obesity and type 2 diabetes mellitus (T2DM), came from studies using soluble fibre in obese rodents. These compounds were named prebiotics, as they act like fertilizers that stimulate the growth of certain bacteria that are beneficial for health[1,2]. Subsequently, mice lacking a gut microbiota (germ-free) were shown to develop less adipose mass and were less prone to obesity compared with conventional mice (that is, mice with a gut microbiota)[3,4]. Follow-up studies in humans demonstrated altered microbial compositions in individuals with obesity and proposed the ratio between two dominating phyla, Firmicutes and Bacteroidetes (or Bacillota and Bacterioidota, according to the new nomenclature), as an explanation for the phenotype[5,6]. The search for 'good' and 'bad' bacteria had begun. Today, advances in the field have made it clear that these simplistic views no longer hold up and that numerous other factors and interactions must be taken into account when considering the role of the gut microbiota on metabolic health.

In this Review, we reconstruct the progress made in the field by first summarizing its history and then reporting on the more recent literature discussing how the composition of the microbiota is implicated in obesity. We also cover several mechanisms by which either the presence of specific bacteria and/or metabolites produced by the gut microbiota could be responsible for the differential responses to weight management. We then examine the role of specific dietary regimens and how they can influence weight management by acting on the gut microbiota. Finally, we open the debate on the remaining challenges and limitations in the field.

Pioneering studies

The direct role of gut microorganisms (microbes) on the regulation of host energy metabolism has been comprehensively studied using germ-free mice. The development of germ-free animals started in the 1940s (reviewed in ref. [7]) and, by 1964, studies on germ-free and conventional rats and chicks suggested that the gut microbiota was interfering with the absorption of fats[8,9]. The earliest demonstration of specific changes in gut peptides controlling appetite being associated with gut microbes was published in 1989. Goodlad et al. observed that germ-free rats had higher circulating levels of 'enteroglucagon' and peptide tyrosine tyrosine (PYY) than conventional rats[10].

In 2000, Daubioul et al. discovered that changing the gut microbiota composition in obese *fa/fa* Zucker rats by using soluble fibre, such as the prebiotics inulin or oligofructose (that is, inulin-type fructans), was associated with decreased adipose mass, hepatic steatosis and glycaemia[11]. In 2002, in a first attempt to discover mechanisms linking microbiota and the high fermentation of inulin-type fructans compared with poorly fermented fibre such as cellulose, the same group discovered that inulin-type fructans increased the caecal content and propionate concentration in the portal vein[12]. Soon after, in 2003, propionate was shown to be one of the key short-chain fatty acids (SCFAs) able to bind and activate free fatty acid receptor 2 (FFAR2) and FFAR3 (ref. [13]). The activation of these G protein-coupled receptors (GPCRs) is dependent on the length of the SCFA chains. In humans, the order of potency for FFAR2 has acetate (C2) and propionate (C3) as equipotent, followed by butyrate (C4), valerate (C5) and formate (C1), whereas FFAR3 has a stronger affinity to the longer SCFAs (C4 = C3 = C5 > C2 = C1)[13–15].

Nowadays, SCFAs produced by the gut microbiota are commonly accepted to promote the secretion of gut peptides such as glucagon-like peptide 1 (GLP1) and PYY[16]. These hormones are produced by enteroendocrine L cells, located most abundantly in the ileum and colon, where the majority of gut microbes are present in high quantities and able to ferment fibre such as inulin-type fructans[17]. Strikingly, in 1998, Kok et al.[18] discovered that rats fed with inulin-type fructans exhibited statistically significantly higher GLP1 content in the caecum compared with rats not fed these fibres. GLP1 is a gut peptide that reduces food intake, lowers glycaemia and increases insulin sensitivity. In 2004, experiments by Cani et al.[19] in rats demonstrated that the fermentation of soluble fibre (such as inulin-type fructans) was associated with lower food intake and reduced body weight and adipose mass gain compared with rats eating a normal diet containing fibre but not enriched with inulin-type fructans. This phenotype was directly linked with specific changes in gut peptides involved in the regulation of appetite, such as statistically significantly increased production of the anorexigenic peptides GLP1 and PYY, while the orexigenic peptide ghrelin was decreased, validating the link between gut microbiota, host adiposity and food intake[11,19–22] (Fig. 1).

During the same period, in 2004, a seminal study by Bäckhed et al. unequivocally showed that gut microbes were directly involved in host energy metabolism. They found that germ-free mice gained statistically significantly less body weight and adipose mass than conventional mice[3] (Fig. 1). Conversely, the authors discovered that colonizing germ-free mice with gut microbes increased their blood levels of glucose, insulin and leptin, and stimulated lipid storage in adipose tissue while promoting triglyceride hepatic synthesis[3].

The effect of gut microbes on obesity was also demonstrated using genetically obese *ob/ob* mice. In 2005, Ley et al.[5] were the first to suggest that obesity could be characterized by a shift in the microbiota composition. Compared with lean mice, *ob/ob* mice had a 50% reduction in the abundance of Bacteroidetes (now renamed as Bacterioidota) and a proportional increase in Firmicutes (now Bacillota), introducing the concept of an obesity-related increase in the Firmicutes to Bacteroidetes ratio (F:B ratio). Ley et al. also suggested that, in *ob/ob* mice, obesity affects the diversity of the gut microbiota[5]. In 2006, Turnbaugh et al.[6] showed that the gut microbiota of *ob/ob* mice is enriched in genes

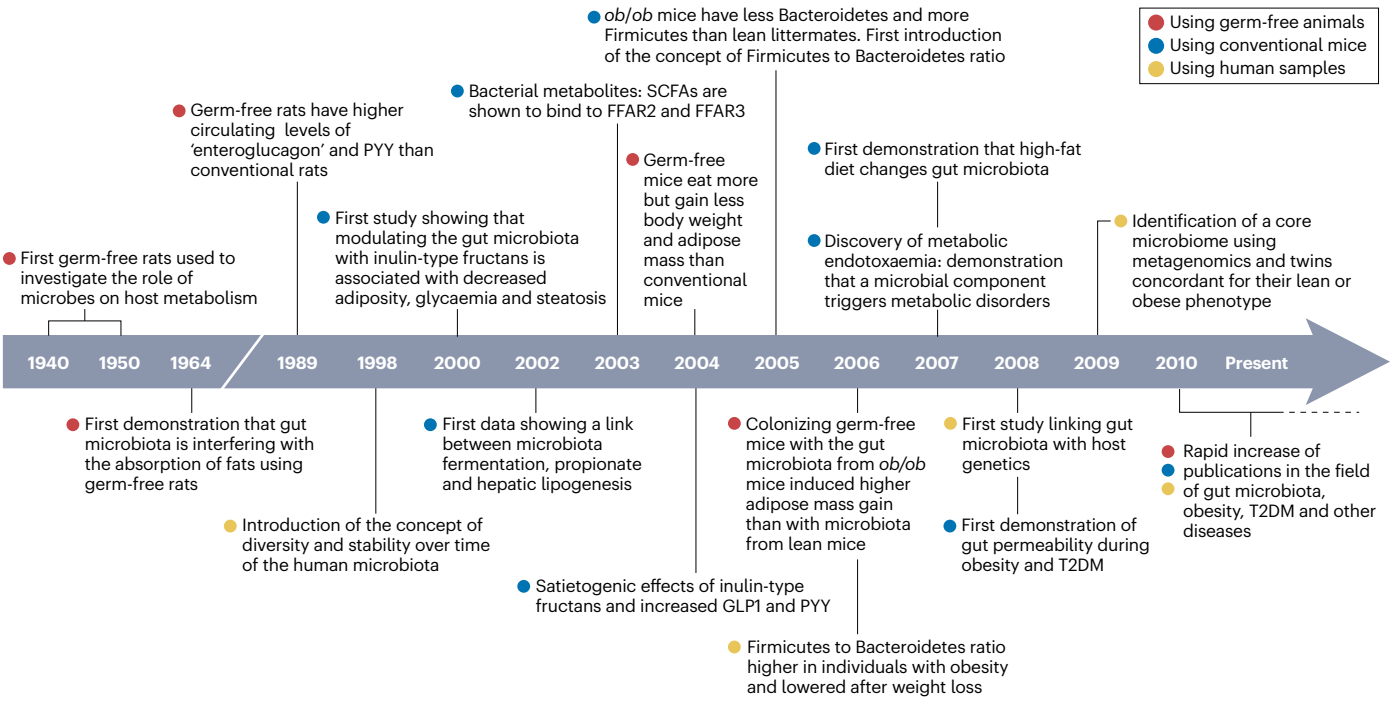


Fig. 1 | Pioneering research in the field of gut microbiota, obesity and related disorders. The figure shows a timeline that describes the history of key discoveries made in the field. Red circles show studies that used germ-free animals. Blue circles show studies that used conventional mice. Yellow circles show studies that used human samples. FFAR, free fatty acid receptor; GLP1, glucagon-like peptide 1; PYY, peptide tyrosine tyrosine; SCFAs, short-chain fatty acids; T2DM, type 2 diabetes mellitus.

involved in the absorption and conversion of non-digestible polysaccharides into available substrates for the host, leading to increased energy bioavailability. They demonstrated that colonizing germ-free mice with the gut microbiota from *ob/ob* mice induced higher adipose mass gain than the gut microbes from lean mice, and that this effect was independent of food intake[6] (Fig. 1).

Ley et al. also compared the gut microbiota of individuals who were lean or with obesity and discovered that those with obesity had lower Bacteroidetes and more Firmicutes than lean control individuals, confirming their observations in mice[23]. They found that the F:B ratio could be partially restored in individuals with obesity after 52 weeks of diet-induced weight loss using a low-calorie diet restricted in fat or carbohydrate[23]. However, the relative change in specific bacterial strains or the link with body weight were not studied. Soon after the publication of the F:B ratio as a putative characteristic of obesity, the concept was challenged as potentially not universally applicable. In 2008, a similar study by Duncan et al. was not able to support the F:B ratio hypothesis as they did not find the proportions of Bacteroidetes and Firmicutes to be different between faecal samples of individuals who were lean or with obesity, even after weight loss[24].

In 2008, Khachatryan et al. published the first study linking gut microbiota with host genetics by comparing 19 individuals with familial Mediterranean fever (a common monogenic recessively inherited autoinflammatory disorder) with 8 healthy individuals and providing convincing evidence that gut bacterial diversity was considerably distinct and depended on the allele carrier status of the host[25]. The notion that the microbiota is influenced by genetics was later solidified by other studies using twins. Furthermore, host genetics were shown to influence the composition of the human gut microbiome in ways that impact host metabolism[26]. In 2009, Turnbaugh et al. investigated the gut microbiota of a total of 154 monozygotic or dizygotic twin pairs who were concordant for their lean or obesity phenotype by using metagenomic analysis, thereby enabling the study of both taxonomic and functional changes[27] (Fig. 1). This study was the first investigating how host genotype but also environmental exposure and adiposity might be linked to both the gut microbiota composition and activity. Besides having revealed shared features of the microbiota among family members, they also found that each individual has their own microbial community signature but with an equivalent degree of co-variation between twin pairs. This study was pioneer in discovering that individuals share microbial genes, which led to the proposition of the existence of a 'core microbiome' at the gene rather than at the taxonomic level[27]. Altogether, these data supported the hypothesis that smaller changes or more specific modulation of the gut microbiota community are involved in the development of obesity rather than a simple wide change at the phylum level. Another major advance in the field derived from this study was that human obesity is associated with a different representation of bacterial genes and key metabolic pathways[27] (Fig. 1). The study also proposed that diversity (in composition and function) could be associated with different physiological states (obesity versus leanness).

Of note, the concept of microbial diversity in the gut had been introduced in 1998 by Zoetendal et al. using temperature gradient gel electrophoresis, a specific technique that, at the time, enabled the authors to propose that the microbiota from a given individual is highly stable over time (at least 6 months)[28] (Fig. 1). Nowadays, the concept of decreased microbial diversity is widely used in numerous pathological

situations, with a few exceptions. One of these exceptions is the low diversity found in the microbiota of infants, which is dominated by a single species found in high prevalence (*Bifidobacterium* spp.) but is not an indication of an unhealthy situation.

Supporting evidence for the role of the gut microbiota in the aetiology of obesity also comes from several studies that used subtherapeutic doses of antibiotics in mice during early life, showing that they moderately increase body weight and adipose mass in mice[29]. Furthermore, the effects were more pronounced when the antibiotic treatment was given to mice from birth[30]. Subtherapeutic antibiotic treatment also had a tendency to increase the effects of a high-fat diet (HFD) on obesity in mice[30]. Furthermore, transferring the gut microbiota from mice treated with a subtherapeutic dose of antibiotic to germ-free mice induced similar effects on body weight and adipose mass[30], here again arguing for a causal role of the microbiota during obesity. The use of germ-free mice remains important for the scientific community; however, a study conducted in 2022 nicely highlighted that the housing conditions of mice (specific pathogen-free versus germ-free facilities) can make a difference in the context of obesity and might eventually lead to discrepant results in the literature[31,32].

Dietary factors affecting the microbiota

Many factors can influence the gut microbiota, including lifestyle, age, host genetics, mode of birth and health status (reviewed in ref. [33]). However, the major factor shaping gut microbiota composition is the dietary habit of its host. The adoption of modern sedentary lifestyles and Westernized diets during the past several decades has undoubtedly contributed to growing health concerns. Owing to the complexity of the matter, the consequences of the different dietary components (for example, macronutrients and micronutrients, salt, and food additives) on gut microbiota modulation are still largely unknown although, since 2015, studies focusing on this have helped untangle this complex landscape (Fig. 2).

Dietary fats

A large-scale dietary trial in mice, the largest of its kind, showed that dietary fat, and not proteins or carbohydrates, regulates energy intake and causes adiposity in mice[34]. In this study, the gut microbiota was not investigated; however, a smaller, more in-depth study from 2022 confirmed that dietary fat, and not sugar, is the major determinant of body adiposity in mice and then demonstrated that diets with different sugar and fat contents induced specific changes in the abundance of certain bacterial taxa[35]. An earlier study conducted in 2007 (ref. [36]) had already found that HFD feeding in mice induced specific changes in the gut microbiota composition. These changes included a lower abundance of *Bacteroides*-like mouse intestinal bacteria, closely related to the *Bacteroides–Prevotella* group, of bacteria in the *Eubacterium rectale–Clostridium coccoides* group and of *Bifidobacterium* spp. compared with control diet-fed mice. In a series of follow-up studies, a HFD containing mostly saturated and omega-6 polyunsaturated fatty acids was confirmed to induce specific changes in the gut microbiota[37–40]. A direct link between HFD-induced changes in the gut microbiota and obesity was supported by work showing that mice treated with broad-spectrum antibiotics and fed a HFD were partially resistant to obesity, inflammation and insulin resistance[40,41]. In addition, germ-free mice were also partially resistant to HFD-induced metabolic disorders, thereby strongly suggesting an interaction between dietary fatty acids and the susceptibility to develop obesity and associated disorders[4,42,43].

Although saturated fatty acids are associated with the onset of metabolic disorders, mice fed an isocaloric HFD containing omega-3 fatty acids (that is, fish oil) were protected against low-grade inflammation, metabolic endotoxaemia, insulin resistance and obesity

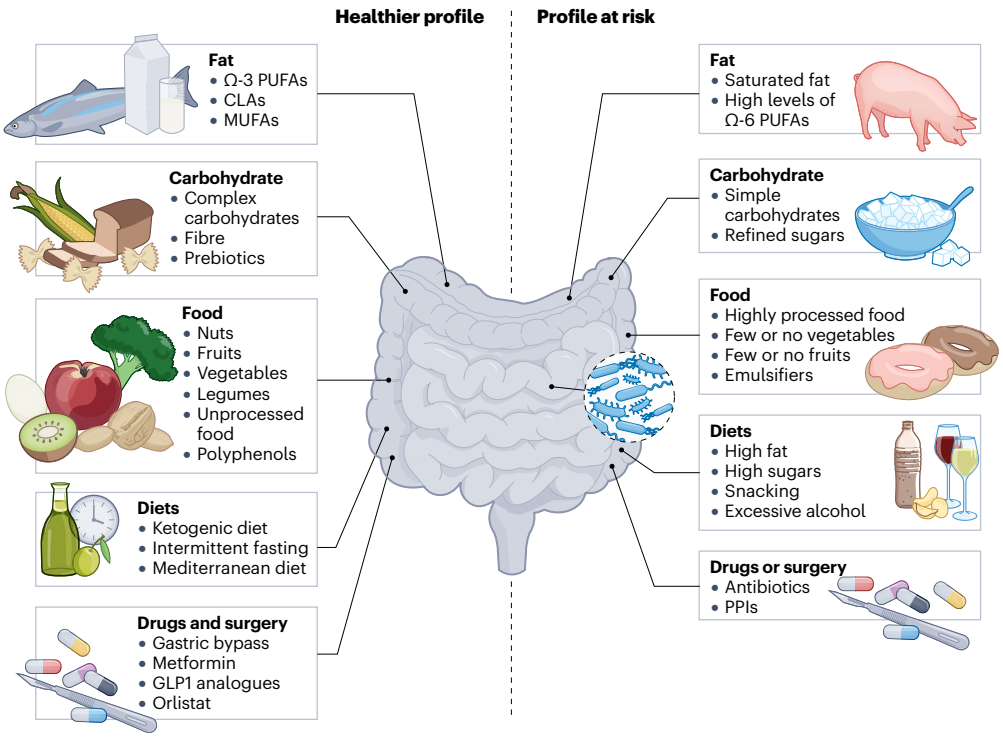


Fig. 2 | Factors influencing the gut microbiota in obesity. The left-hand side depicts factors that are mostly associated with a healthy microbiota profile and that have been linked with a specific change in the gut microbiota. The right-hand side shows factors that are more related to a microbiota profile at risk of diseases. Factors include the type of dietary macronutrient, micronutrients, fibre, diet composition, specific drugs and bariatric surgery. CLAs, conjugated linoleic acids; GLP1, glucagon-like peptide 1; MUFAs, monounsaturated fatty acids; PPIs, proton pump inhibitors; PUFAs, polyunsaturated fatty acids.

compared with mice fed the same caloric diet but containing fatty acids from lard[44] (Fig. 2). The type of dietary fat was also shown to be a major driver of the microbial community structure, affecting both the composition and diversity of the gut microbiota[44]. Furthermore, the gut microbiota of fish oil-fed mice confers protection against lard diet-induced adiposity and inflammation when transferred by faecal microbiota transplantation (FMT). Among the putative bacteria associated with a beneficial effect of the omega-3 treatment, an increased abundance of *Bifidobacterium* spp., *Lactobacillus* spp. and *Akkermansia muciniphila* were identified[44]. These three types of bacteria were also associated with the beneficial effects of prebiotics, such as inulin-type fructans, in obesity[37,45–47] (Figs. 2 and 3). In particular, *A. muciniphila* has been associated with beneficial effects in obesity (reviewed in ref. [48]).

The influence of the quantity and quality of dietary fatty acids on the gut microbiota composition and its metabolic consequences have been the subject of further investigations. An interesting systematic review from 2019 found striking results[20]; for instance, the six interventional trials analysed did not show strong effects of the quantity or quality of dietary fat on the intestinal microbiota composition or health of the study participants. Conversely, all observational studies showed that differences in dietary fat quantity and quality were associated with changes in the microbiota and health. In addition, high total fat or high saturated fatty acid ingestion negatively affected microbiota richness and diversity, and diets with increased amounts of monounsaturated fatty acids were linked with a decrease in total bacterial numbers. Surprisingly, dietary polyunsaturated fatty acids did not affect microbial richness nor diversity[49].

Dietary protein

Dietary proteins are also involved in the modulation of gut microbiota composition and activity (reviewed in ref. [50]). Although the majority of dietary proteins are absorbed in the small intestine (>90%), a fraction escapes digestion and reaches the colon, where it serves as a substrate for microbial metabolism. Diets rich in protein are often suggested for weight loss; however, the overall understanding of how increased amounts of proteins reaching the colon affect the composition and function of the microbiota is limited[51]. Even well-designed studies in humans have shown contradictory results regarding the microbiota composition upon increased dietary protein consumption, findings that are attributed to diverse factors[50]. Besides quantity, the quality of proteins should also be considered. For example, a diet representative of the complex composition of dietary protein consumed by humans in western countries directly contributed to increased weight gain and insulin resistance in mice. The detrimental effect of the protein mixture was linked with the microbial production of branched-chain fatty acids as well as with elevated plasma and hepatic levels of acylcarnitines, indicative of aberrant mitochondrial fatty acid oxidation[52].

However, the overall microbial community has been suggested to be shaped by the relative availability of nitrogen in the gut environment. This hypothesis implies that dietary protein intake should be seen as one of the many factors contributing to the host–microbiome dynamic. Exploring the interactive contributions between different protein, carbohydrate and lipid profiles will be the major challenge when developing specific dietary strategies for weight loss[53].

How the microbiota affects body weight

Although much remains unknown, important mechanistic insights into how the gut microbiota modulates host metabolism and weight status have been gained over the past decade. These studies have revealed

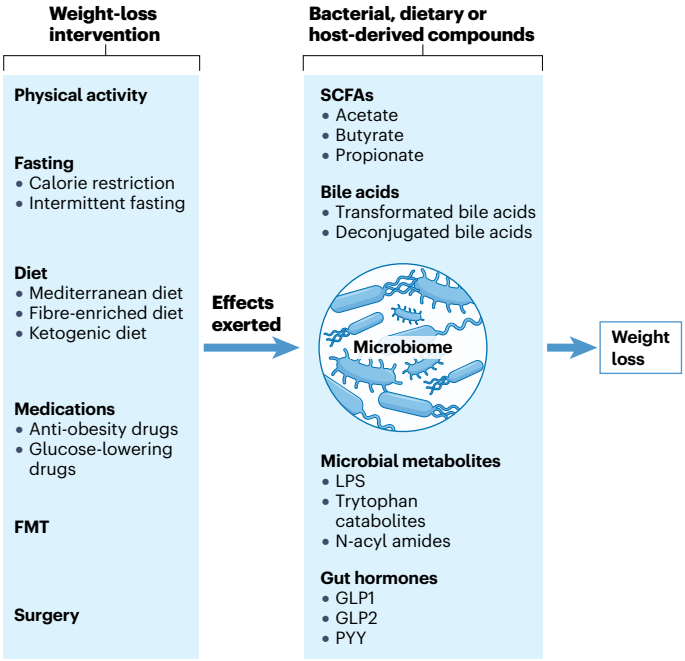


Fig. 3 | Weight-loss interventions and the microbiota. Behavioural, dietary and surgical weight-loss interventions for obesity affect the microbiota. These effects on the microbiota in turn affect host weight by producing or modulating compounds derived from bacteria, diet or host that influence the metabolic pathways of the host. FMT, faecal microbiota transplantation; GLP, glucagon-like peptide; LPS, lipopolysaccharides; PYY, peptide tyrosine tyrosine; SCFAs, short-chain fatty acids.

both direct actions (the microbiota alters the amount of calories available for absorption) and indirect mechanisms (the microbiota produces or modulates bacterial, dietary or host-derived compounds that influence host metabolic pathways). Although an exhaustive list of microbial metabolites falls outside of the scope of this Review[16], we summarize some important players in the context of host metabolism.

Another direct way for bacteria to influence host physiology has been proposed, that is, bacterial translocation to various tissues and organs (including human adipose tissue) due to increased intestinal permeability[54–57]. However, how the presence of bacteria and bacterial DNA in peripheral tissues affects host metabolism remains elusive.

Short-chain fatty acids

SCFAs are produced by certain gut bacteria as a result of carbohydrate fermentation. Acetate, propionate and butyrate are the primary SCFA products and are produced in an approximate molar ratio of 60:20:20. These SCFAs regulate the luminal pH and mucus production, provide fuel for epithelial cells, and modulate mucosal immune function. In addition, they can enter the systemic circulation and directly affect metabolism or the function of peripheral tissues[17,58,59]. Although SCFAs provide a direct source of extra calories, the elevated generation of SCFAs is thought to beneficially contribute to systemic energy regulation by decreasing hepatic glucose and lipid production[60]. As mentioned earlier, SCFAs stimulate the secretion of the anorexigenic hormones PYY and GLP1 in the colon, thereby facilitating gut–brain axis signalling by activating FFAR2 and FFAR3 to regulate immunity, intestinal transit time, inflammation and metabolism[16,17,58,59] (Fig. 4).

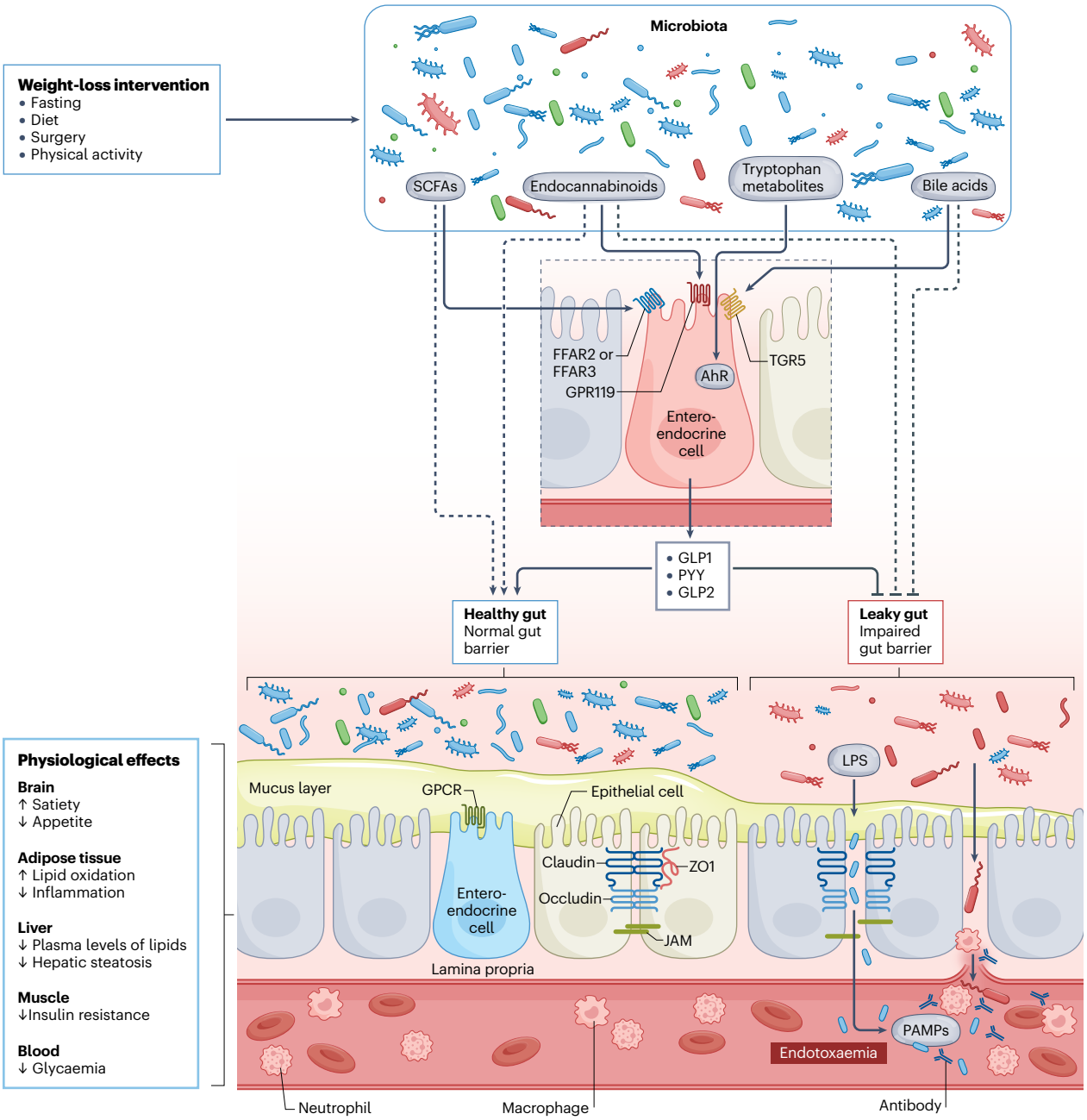


Fig. 4 | Mechanisms of actions linking activity of the gut microbiota and host metabolism in obesity. Several factors influence the gut microbiota composition and its activity (that is, metabolite production). Fasting, diet, surgery and physical activity have been shown to contribute to changes in the production of short-chain fatty acids (SCFAs), endocannabinoids, tryptophan metabolites and bile acids by the microbiota. These factors act on specific G protein-coupled receptors (GPCRs) such as free fatty acid receptor 2 (FFAR2), FFAR3, GPR119 and TGR5, causing enteroendocrine cells to produce increased amounts of gut hormones such as glucagon-like peptide 1 (GLP1), peptide tyrosine tyrosine (PYY) and GLP2. These gut hormones in turn contribute to the regulation of several host functions: reduction in appetite, glycaemia, plasma levels of lipids, inflammation, increased lipid oxidation and satiety. In addition, these changes control gut barrier function (that is, GLP2 and endocannabinoids) to reduce leaky gut and the leakage of lipopolysaccharide (LPS) to the circulation. Dashed lines show effects that might be linked to several mechanisms or have unknown mechanisms. AhR, aryl hydrocarbon receptor; PAMPs, pathogen-associated molecular patterns; TGR5, Takeda G protein-coupled receptor 5.

The current literature on SCFAs in humans focuses mainly on fibre supplementation and endogenous SCFA production, and is hampered by difficulties in measuring SCFA production, differences in mode of administration and/or site of production, variation in dietary fibres tested, differences in diet composition, and variation in metabolic phenotype between individuals[59,61]. Although acute and chronic SCFA

administration studies in rodents show beneficial effects on weight loss, weight-gain prevention or attenuation of weight gain[59], data in humans are still very limited[61]. Nevertheless, a series of studies demonstrated that increasing colonic propionate prevents weight gain and/or regulates appetite sensations in adults with overweight, suggesting that increasing SCFA production could be a valuable strategy in preventing obesity[62–64].

Bile acids

When food is ingested, primary bile acids, such as cholic acid and chenodeoxycholic acid, are released into the small intestine, where they facilitate dietary fat and fat-soluble vitamin absorption. In addition, bile acids serve as signalling molecules and are increasingly recognized as key regulators of systemic metabolism. Interactions with nuclear hormone receptors (such as farnesoid X receptor[65], vitamin D receptor[66], pregnane X receptor[67] and constitutive androstane receptor[68]) and membrane receptors (for example, Takeda G protein-coupled receptor 5)[69] can regulate the secretion of PYY, GLP1 and fibroblast growth factor 19 (FGF19, FG15 in mice), cholesterol metabolism, and systemic energy expenditure[70] (Fig. 4). Bile acids are profoundly altered by bariatric surgery, possibly contributing to the metabolic effects of the surgery[71].

In the intestinal lumen, bile acids serve as substrates for biotransformation by gut microbes. Modifications include deconjugation (the removal of amino acid residues) via bile salt hydrolase (BSH) activity and further metabolization via removal of hydroxyl groups (dehydroxylation), oxidation (dehydrogenation), or epimerization[72,73]. Modified bile acids are referred to as secondary bile acids and include deoxycholic acid, lithocholic acid and ursodeoxycholic acid (a secondary bile acid in humans, though a primary bile acid in rodents). A HFD increases faecal and circulating secondary bile acids[74–76]. Bacterial metabolism changes the bioavailability and bioactivities of bile acids, and consequently their effect on the metabolic responses they are involved in[77]. Interestingly, microbiota–bile acid crosstalk has been suggested to contribute to the rebound weight gain after calorie restriction[78]. Moreover, very-low-caloric diet-induced weight loss has been shown to increase postprandial levels of deoxycholic acid and decrease resting energy expenditure in individuals with obesity and insulin resistance[79].

Endocannabinoid-like compounds

The endocannabinoid system consists of different bioactive lipids expressed in virtually all cells and organs. They have numerous regulatory roles, including in the control of energy, glucose and lipid metabolism but also in immunity and inflammation through the activation of various receptors (reviewed in refs. [80,81]). In 2010, the endocannabinoid system and other related bioactive lipids and receptors were demonstrated, for the first time, to be regulated by the gut microbiota, thereby representing another mechanism by which gut microbes exert control over the gut barrier[82] (Fig. 4). Furthermore, germ-free mice or conventional mice, either lean or as models of obesity and T2DM, were shown to have a specific microbiota and endocannabinoid system tone[83–85]. Reciprocally, the endocannabinoid system from the host can also regulate the microbiota composition and activity, and contribute to regulating adipose tissue browning, energy expenditure and the regulation of food intake via the gut–brain axis[86–88]. Thus, these findings demonstrate an important dialogue and intertwined complex system.

In 2017, an elegant study showed that chemical mimicry of eukaryotic signalling molecules could be common among commensal bacteria as demonstrated by the finding that N-acyl amide synthase genes are enriched in gastrointestinal bacteria and the lipids that they encode interact with GPCRs[89]. For instance, commensal agonists regulate glucose homeostasis as well as gastric emptying and appetite through GPR119-dependent hormone release from enteroendocrine cells and are believed to do so as efficiently as human ligands[89]. Recently, numerous studies have pointed to the role and specific interactions between the endocannabinoidome (comprising endocannabinoids and related molecules as well as their enzymes and targets) and host metabolism (Fig. 4).

Tryptophan metabolites and AhR ligands

Microbial-derived tryptophan catabolites have been linked with appetite regulation in several models[90–92] (Fig. 4). Tryptophan is an essential amino acid, utilized for protein synthesis. In addition, tryptophan is a key player in the effects of the microbiome on weight and metabolism[93] as evidence suggests that tryptophan and relevant metabolites are able to signal both locally (to the intestinal mucosa) and to distant organs, including the brain[94]. Several microbial tryptophan catabolites, such as tryptamine, indole-3-acetic acid and 3-indolepropionic acid, are natural ligands of the aryl hydrocarbon receptor (AhR)[95], a sensor of environmental and physiological signals and a potent modulator of gut barrier integrity, immunity and metabolism[96,97]. Faecal samples of individuals with the metabolic syndrome display low levels of tryptophan-based metabolites and this phenotype is associated with reduced activity of AhR[95]. The decreased ability of the microbiota to produce AhR ligands leads to defective mucosal barrier integrity and reduced GLP1 secretion (Fig. 4), and ultimately could facilitate the development of metabolic syndrome, T2DM, increased BMI and high blood pressure[95].

Lipopolysaccharides

In 2007, in the context of obesity, specific bacterial components (such as lipopolysaccharides (LPS)) were identified as circulating inflammatory factors originating from the gut microbiota. The ability of LPS to trigger low-grade inflammation and insulin resistance induced by HFD feeding in mice[36] led to the concept of metabolic endotoxaemia. Importantly, metabolic endotoxaemia is now considered a pathological feature of a range of chronic conditions, including obesity, T2DM, non-alcoholic fatty liver disease, chronic kidney disease and atherosclerosis (Figs. 3 and 4). Subsequently, LPS from certain bacteria was found to promote a metabolically beneficial state of endotoxaemia by antagonizing Toll-like receptors, which can counteract metabolically detrimental endotoxaemia[98]. LPS from different types of bacteria can interact; therefore, these interactions should be considered when assessing the effects on host metabolism.

Microbiota modulation for weight loss

The availability of inexpensive, calorically dense foods and the reduction in physical activity in our daily lives have certainly been major contributors to the current rise in obesity rates. Lifestyle interventions combining hypoenergetic diets and regular exercise are therefore currently the primary approach to weight loss and metabolic risk reduction (Fig. 2). However, adhering to weight-loss interventions is a challenge for many people with overweight or obesity. Weight-loss success varies from person to person and depends on a complex interplay between environmental, genetic, neural and endocrine factors. The inter-individual variability in weight-loss responses could partly depend on the baseline gut microbiota composition. Human studies have proposed that an individual's microbiota composition could predict diet-induced weight-loss responses[99]. In this section, we discuss some of the approaches currently used or considered for

weight management and their link with the gut microbiota (Fig. 2). Although the emphasis of this Review is on weight management and weight loss, people with overweight or obesity might benefit from lifestyle modifications that shift microbiota composition and improve metabolic risk factors, physical functions and quality of life, regardless of their effects on body weight.

Diet

Ketogenic diet. The ketogenic diet is a dietary regimen with low carbohydrate and high fat intake. Typically, these diets are comprised of approximately 10% carbohydrates, 70% fats and 20% proteins. This balance is achieved by replacing grains, fruit, starchy vegetables, legumes and sweets with carbohydrate-free or very-low-carbohydrate foods such as non-starchy vegetables, cheese, avocados, nuts and seeds, eggs, meat, seafood, and olive or coconut oil for cooking and dressing. This diet forces the body to alter its metabolism to use fatty acids, rather than carbohydrates, as its primary energy source, producing ketone bodies as a molecular by-product and leading to a state of ketosis. However, the types of fat selected will affect the outcome; therefore, not all ketogenic diets are the same.

Ketone bodies have attracted public interest for their proposed benefits in improving metabolism, promoting weight loss, decreasing inflammation and attenuating neuropsychiatric disorders such as (epileptic) seizure activity and depression[100–102]. Although, over the years, many studies in humans have demonstrated the efficacy of a ketogenic diet in promoting weight loss, the underlying mechanisms are still not completely understood[103]. Additional research in mice showed that ketone bodies directly affect the gut microbiota[104,105].

In an inpatient crossover study published in 2020 (ref. [105]) adult men with overweight or obesity (without diabetes mellitus) were monitored while they spent 2 months in a metabolic ward, where their diets and exercise levels were controlled. For the first 4 weeks of the study, the participants were given either a standard diet consisting of 50% carbohydrates, 15% proteins and 35% fats, or a ketogenic diet comprised of 5% carbohydrates, 15% proteins and 80% fats, resulting in elevated circulating plasma levels of ketone bodies. After 4 weeks, the two groups switched diets. Shifting between standard and ketogenic diets dramatically changed the abundance of Actinobacteria, Bacteroidetes and Firmicutes phyla, and 19 genera were different between groups. Bifidobacteria, in particular *Bifidobacterium adolescentis*, decreased the most on the ketogenic diet[105]. Interestingly, these changes were probably driven by the carbohydrate restriction rather than the high fat intake as they were distinct from those observed in mice fed a high-fat and high-carbohydrate diet, which is known to promote metabolic disease in these animals[47,106,107].

Follow-up diet experiments in mice showed that supplementation of ketone bodies was sufficient to reproduce many of the specific microbial changes seen with the ketogenic diet even in mice fed a diet containing carbohydrates, and therefore not ketogenic in itself. These findings indicate that diet induces changes in the microbiota that alter the host metabolism and that these changes have downstream, reciprocal effects on the microbiota[105,108]. Of note, both monocolonization of germ-free mice with *B. adolescentis* and human FMT into germ-free mice showed that a decrease in *Bifidobacterium* was linked with a reduction of inflammation as evidenced by a marked decrease in pro-inflammatory marker T helper 17 cells both in the gut and in visceral adipose tissue[105].

One of the caveats of a ketogenic diet is the lack of beneficial fibre and polyphenols coming from fruits and cereals. Moreover, animal data also indicates that a ketogenic diet might be associated with long-term metabolic adverse effects such as glucose intolerance, dyslipidaemia and signs of hepatic steatosis[109]. Furthermore, individuals who consume a ketogenic diet are suggested to have an increased biotin requirement[110]. In an elegant study conducted in 2022, researchers performed metagenomic analyses on >1,500 individuals and linked severe obesity with a marked deficiency in microbes producing biotin and its transporters. These microbes and biotin abundances were found to correlate with numerous host metabolic parameters related to weight and adipose mass (that is, BMI, adipose mass, waist circumference and visceral adiposity) but also with glucose metabolism (that is, fasting glucose, HbA_{1c}, triglycerides and insulin resistance markers) and inflammation. In mouse experiments using germ-free or antibiotic-treated animals and HFD-fed mice, the absence or depletion of the gut microbiota altered the levels of circulating biotin. Weight loss after bariatric surgery was associated with increased bacterial biotin producers and improved host systemic biotin in both humans and mice. Finally, oral supplementation with biotin and prebiotic to HFD-fed mice improves body weight and glucose metabolism but also increased microbial diversity and the potential of bacterial production of biotin[111].

Mediterranean diet. The beneficial effects of a Mediterranean diet (MedDiet) were scientifically described over 50 years ago[112]. The MedDiet is characterized by low amounts of meat and refined cereal products, moderate amounts of fish and dairy, and high amounts of fruits, vegetables, legumes, whole grains and nuts (Figs. 2 and 3), and is linked with a decreased incidence of cardiovascular disease and related mortality[113]. Nowadays, the MedDiet is accepted to be associated with lower mortality and lower risk of obesity, T2DM, low-grade inflammation, cancer, and many other diseases than in the general population[114–116].

The interaction between diet and gut microbiota and the potential beneficial effects of MedDiet on metabolic disorders associated with obesity are reviewed in ref. [117]. One important randomized controlled study examined healthy individuals with overweight or obesity who had a sedentary lifestyle and habitually consumed low amounts of fruits and vegetables. During an 8-week follow-up, 43 individuals were assigned to the MedDiet group and received a personalized diet matched with their usual energy intake and 39 individuals were on their routine diet[118]. The MedDiet led to double the quantity of fibre ingested, reduced the ratio of animal protein to vegetables, lowered the circulating levels of saturated fatty acids and increased those of polyunsaturated fatty acids. Metabolomic analysis showed shifts in the faecal, blood and urinary metabolome after MedDiet adherence in this study population. Besides the metabolome, the gut microbiota composition after the MedDiet was characterized by more *Faecalibacterium prausnitzii* and *Roseburia* and less *Ruminococcus gnavus* and *Ruminococcus torques* than in the control group. Of note, the individuals responding to the MedDiet in terms of reduced insulin resistance had more *Bacteroides uniformis* and *Bacteroides vulgatus* and less *Prevotella copri* at baseline[118]. Strikingly, all of these effects were observed independently of energy intake, thereby strongly underlining the importance of the type of nutrients instead of their caloric content. Although the exact mechanisms are not yet fully elucidated, the available evidence suggests clear links between gut microbes, their metabolites and the efficacy of a MedDiet[119].

Fibre-enriched diets. Dietary fibre consists of a group of complex carbohydrates found mostly in vegetables, fruits and legumes, which can be found in high amounts in the MedDiet, vegetarian diet and vegan diet. The association between fibre intake and health is now

well recognized, with decades of research data supporting beneficial effects of (primarily soluble) dietary fibre. These include direct effects on gut functions and digestion but also indirect effects on blood glucose control, cardiovascular functions, diabetes mellitus and obesity[120]. Despite the many positive health associations of fibre, the average intake of the general population remains far below recommendations.

The causal relationship between fibre intake, gut microbiota changes and metabolic regulation remains elusive owing to the heterogeneity of the studies available. The effects can mostly be attributed to an increased abundance of SCFA producers and specific changes in the gut microbiota[121–124]. Indeed, the effect of fibre is directly dependent on the type and might or might not be directly related to changes in gut functions and digestion such as intestinal transit or defecation, which limit the digestion of other components (reviewed in refs. [125–127]).

Intermittent fasting. Intermittent fasting is an umbrella term for an increasingly popular dietary strategy that cycles between set periods of fasting (ranging from 12 h to several days) and periods in which eating is permitted (Fig. 3).

Interesting insights into fasting have been gained by studying Muslims during the holy month of Ramadan, during which individuals fast from dawn to sunset, including water avoidance. After Ramadan, individuals had increased levels of beneficial gut bacteria such as *A. muciniphila*, *F. prausnitzii* and *Roseburia*[128–131]. Fasting also increased microbial richness and diversity as well as levels of the beneficial SCFA butyrate. A review of 27 trials conducted in 2020 showed that intermittent fasting in populations of individuals with overweight or obesity reduced weight by 0.8–13% over a period of 2 weeks to 1 year, without adverse effects[132]. However, a randomized clinical trial from that same year found that time-restricted eating did not confer weight loss or cardiometabolic benefits[133].

Although this method shows promise for the treatment of obesity, the studies so far have been small and of short duration. Thus, longer-term research is still needed to understand the sustainable role that intermittent fasting can play in weight loss and if these effects are purely mediated by microbiota-dependent mechanisms.

Personalized diets. While dietary guidelines aimed at providing the general population with a standard blueprint for good nutritional practices have their merit, some studies, like the large-scale nutrition study PREDICT, indicate that this kind of one-size-fits-all approach might not be suitable for everyone. Different people, even identical twins, can respond to the same foods very differently. Thus, individuals characterized by a high *Prevotella*-to-*Bacteroides* (P:B) ratio lose more weight on diets rich in dietary fibre than individuals with low *Prevotella* abundance (low P:B ratio)[134]. The difference in weight loss between high and low P:B ratio groups was explained by interactions between the actual diet consumed and the efficacy of energy harvest by the microbiota, as the microbiota of obese mice was rich in genes encoding enzymes that break down otherwise indigestible dietary polysaccharides to SCFAs. Thus, the bacteria in obese mice seemed to assist their host in extracting extra calories from ingested food that could then be used as energy[6]. Of note, many other metabolites besides SCFAs are produced by the microbiota and could probably be affected by microbial activity. These metabolites might eventually be linked to the different metabolic responses observed in the PREDICT study but havee not yet been investigated (for instance, 3-indolepropionic acid or imidazole propionate)[135]. Although the link between intestinal SCFA concentrations and obesity is still a matter of debate[136,137], this example indicates that different people will have different levels of success on different diets and that personalized nutrition holds promise for more efficient obesity management strategies.

The role of the microbiota in the glycaemic response (not necessarily linked to body weight) was explored in another important study. Blood levels of glucose were continuously monitored over a week in a cohort of ~800 individuals who were representative of the adult Western population (without diabetes mellitus): 54% with overweight and 22% with obesity[138]. The effect of ~47,000 meals on glucose response in the volunteers was assessed and the results were integrated with many other parameters, including the gut microbiota, anthropometrics, blood parameters, dietary habits and physical activity. Machine learning was used to show that the gut microbiota could accurately predict personalized postprandial glycaemic responses to real-life meals in the cohort and this was validated in another independent cohort of 100 individuals. This study also showed that the profile of gut microbes can be used to help to design personalized interventions and dietary interventions to modify postprandial glucose and related metabolic alterations[138].

Medication

Weight loss is difficult to accomplish and even more difficult to maintain. Although lifestyle-based weight-loss strategies incorporating diet, exercise and behaviour change can be initially successful, the basal metabolic rate will gradually decrease at around 6 months in an attempt to compensate for the loss of energy. This decrease is followed by a progressive weight regain over the following months[139]. No wonder so much effort is put into finding pharmacological solutions to help achieve and maintain adequate weight loss.

To be classified as an anti-obesity drug, a product should result in at least 5% mean weight loss in >35% of patients after 1 year of treatment. The anti-obesity drugs currently approved for long-term use by the FDA and the EMA are orlistat, naltrexone–bupropion extended release, liraglutide and semaglutide. In addition, the FDA has also approved phentermine–topiramate controlled release. An interesting newcomer that is up for approval is tirzepatide, a novel once-weekly dual glucose-dependent insulinotropic peptide and GLP1 receptor agonist, the first investigational medicine to deliver more than 20% weight loss on average in a phase III study. Interestingly, this drug acts on one of the key targets of the gut microbiota, that is, GLP1, therefore suggesting that targeting the endogenous production of GLP1 by the gut should also be considered. An overview of the mechanisms of action, long-term efficacy and safety of these current anti-obesity drugs can be found in ref. [140].

Several medications affecting body weight have been demonstrated to have potential effects on the gut microbiota. For example, both mouse and human studies have shown that treatment with metformin (an anti-diabetic drug that has been linked to losing weight but is not considered a weight-loss drug as such) has a direct effect on the gut microbiota[141,142]. Furthermore, treatment with orlistat enriched bacterial taxa that were correlated with endocrine, glucose and lipid metabolism and inflammation pathways in both mouse and human studies[143–145]. In addition, liraglutide resulted in more lean-related microbial phenotypes in mice and humans[146,147].

Although data are limited and causal links still have to be investigated, these studies suggest that modulation of the gut microbiota is a potentially important component in the mechanism of action of anti-obesity drugs.

Bariatric surgery

Bariatric surgery is the most effective and long-lasting available intervention to achieve substantial and sustained weight loss as well as improved metabolic and overall health. Mechanical restriction and caloric malabsorption are generally put forward as the main mechanisms of weight loss; however, other mechanisms, such as increased blood levels of gut hormones involved in satiety, altered gut microbiota, changes in bile acid metabolism, and/or changes in energy expenditure, have also been proposed[148,149] (Fig. 3). In addition, bariatric surgery induces profound changes in gut microbiota composition that are believed to contribute to weight loss and metabolic improvement. A study conducted in 2022, in which mice were colonized with faecal samples from patients before and after bariatric surgery, showed that a subset of gut microorganisms could improve glucose tolerance independently of changes in adipose mass by mediating intestinal glucose absorption[150]. The preoperative gut microbiota has also been suggested to have an effect on bariatric surgery results, thereby explaining some of the variation in response among individuals and suggesting the potential of the microbiota as a predictor of outcome[151,152]. One interesting phenomenon observed after bariatric surgery is the increase in serum total bile acids.

At the taxa level, an increase in Bacteroidetes, Proteobacteria (including *Escherichia coli*) and Verrucomicrobia (*A. muciniphila*) and a decrease in members of the phylum Firmicutes (including *Lactobacillus*, *Clostridium*, *Faecalibacterium* and *Roseburia*) have been consistently observed in humans after gastric bypass procedures compared with the same patients preoperatively or patients with obesity who have not undergone bariatric surgery[153]. However, at the genus level, the data are much more controversial and sometimes not related to the improvement of the phenotype or showing opposite effects on the microbiota composition[154–157].

As most studies on bariatric surgery do not assess food intake before or after surgery nor adjust for changes in diet and digestion post-surgery, further research efforts will be needed to deepen the understanding of gut microbial changes after bariatric surgery[153].

Faecal microbiota transplantation

Given the evidence of potential causation between gut microbiota and obesity, FMT is often considered a potential future therapeutic strategy for the treatment of obesity and metabolic syndrome (Fig. 3). The idea is to completely replace the gut microbiota from patients with obesity with that of lean and healthy donors. A retrospective chart review of patients who underwent FMT for recurrent *Clostridium difficile* infection conducted in 2016 showed that the BMI of stool donors did not significantly affect that of the recipients[158]. In 2019, a meta-analysis of three randomized placebo-controlled studies investigating the effect of FMT from lean donors to people with obesity on the improvement of metabolic parameters reported mixed results[159]. While two studies reported improved peripheral insulin sensitivity and one study observed lower HbA_{1c} levels in patients with obesity receiving donor FMT versus patients receiving the placebo control, no differences were found in fasting plasma glucose, hepatic insulin sensitivity, BMI or cholesterol levels[159]. A meta-analysis conducted in 2020 with the inclusion of three additional trials (a total of 154 patients with obesity) could only confirm that, at 6 weeks post-FMT, HbA_{1c} levels were significantly reduced. No difference in anthropometric parameters that characterize obesity were found at 6 or 12 weeks after the procedure[160]. Overall, FMT from lean donors to those with obesity significantly increased the abundance of species such as *Roseburia intestinalis*, *A. muciniphila* and *Clostridium* spp.[159]. Weekly administration of FMT capsules in a double-blind randomized placebo-controlled study for adults with obesity resulted in gut microbiota engraftment in most recipients for at least 12 weeks[161].

To date, clear evidence of the clinical benefits of using FMT in patients with obesity and metabolic syndrome is still limited. However, a study conducted in 2020 of 24 treatment-naive individuals with metabolic syndrome showed that FMT from donors after Roux-en-Y gastric bypass increases brain expression of the dopamine transporter (DAT), whereas oral butyrate supplementation reduced DAT binding. However, no effects were observed on body weight and insulin sensitivity. The authors found a positive correlation between the levels of *B. uniformis* and DAT binding, whereas increases in *Prevotella* spp. showed an inverse association[162].

The response to FMT has been speculated to depend on the initial microbial composition of recipients or donors and on their dietary habits following the procedure[163–165]. For example, a double-blind randomized trial conducted in 2021 including patients with severe obesity and metabolic syndrome combined both FMT and daily fibre supplementation to attempt to modulate cardiometabolic outcomes. After 6 weeks, patients receiving daily low-fermentable fibre supplements (microcrystalline cellulose) had significant improvements in insulin sensitivity associated with increased bacterial richness and increased engraftment of donor microbes. Interestingly, patients supplemented with high-fermentable fibre (an equal mixture of soluble corn fibre, resistant wheat starch type 4 and acacia gum) did not show these improvements[166].

Using mouse models of weight loss and recurrent obesity, a study conducted in 2016 identified intestinal microbiome alterations after HFD feeding that persist over long periods of time and enhance the rate of weight regain during the post-dieting phase[167]. FMT experiments confirmed that the accelerated weight-regain phenotype could be transferred to germ-free mice and that the weight-gain magnitude could be predicted by the microbiome composition[167]. In humans undergoing a weight-loss intervention, autologous FMT, collected during the weight-loss phase and administered in the regain phase, might help preserve weight loss and glycaemic control as shown in a randomized controlled trial conducted in 2021 including 90 participants with abdominal obesity or dyslipidaemia (DIRECT PLUS trial)[168].

Remaining challenges and limitations

Millions of years of human–microbial coevolution have inevitably led to interdependency. The influence the microbiota exerts on its host is now recognized as a critical factor in both disease pathogenesis and health promotion. The dynamic and complex host–microorganism and microorganism–microorganism interactions have made it very difficult to determine which bacteria, or combinations of bacteria, are beneficial and which are not. While the literature is flooded with descriptive microbiota–health associations, studies enabling a transition from statistical associations to causal relationships with diseases and health are still scarce. In addition, distinguishing opportunists from real pathogens or bystanders from beneficial bacteria remains difficult.

In our opinion, these simple categorizations cannot be applied in the context of obesity. At the taxonomic level, numerous studies report changes in the relative abundance of bacteria at the phylum or family levels, but this approach has strong limitations: numerous genera and species might be affected and deeper analyses are needed to better reflect the reality of the metabolic activities of the microbes. Along the same line, we need better characterization of the microbiota composition. Identifying functional groups of microbes and metabolites is probably

the minimal requirement to obtain consistent assessments across studies and draw (partial) conclusions. Indeed, identifying functional groups instead of simply using taxa linked to different health outcomes could help explain some of the contradictory reports in the current literature and avoid them in future analyses. This topic is fairly new and merits further specific discussions. Given the complexity of this research field, we cannot restrict the role of one type of microorganism to that of a 'friend' or a 'foe'. One should always consider the other major confounding factors and interactions between microbes or microbial communities that affect why some individuals are better responders (or non-responders) to weight-loss interventions. Many studies share common general conclusions and are sometimes even in concordance in terms of which bacteria or phyla are associated with obesity; however, the number of (reported and unreported) confounding factors described earlier convey a certain caution when it comes to making statements of causality.

Although the field has undoubtedly benefited from the many studies and interventions, as described in this Review, we can also argue that, in the literature, there are as many interventions as there are specific responses from the gut microbiota. Indeed, a ternary classification of microbes as pathogens, commensals or beneficial is not applicable in this context. Moreover, the pathogenicity of a given microorganism is highly dependent on multiple variables, not only related to the bacteria itself but also related to the host. This remark is not restricted to the context of obesity as microbiota ecological principles also apply to other non-communicable diseases. That being said, specific gut microbes have been identified for which causality and effect have been demonstrated often enough, such that they can now be considered beneficial for host health. One of the best-developed examples is *A. muciniphila* (reviewed in ref. [48]) but *F. prausnitzii* is also arising as a potentially health-promoting bacterial species. For some, like *A. muciniphila*, beneficial effects are found in different pathologies. By contrast, others are only considered potential next-generation beneficial bacteria in certain specific conditions such as *Eubacterium hallii* (renamed as *Anaerobutyricum soehngenii*), which has only been only associated with better health in obese and T2DM mice or in individuals with metabolic syndrome as compared with placebo treatment[169,170] and *E. hallii* was more abundant in individuals responding to FMT in terms of improved insulin resistance[171]. Besides these few examples, many other potential beneficial candidates, such as *Odoribacter laneus*[172], *Holdemanella biformis*[173,174] and *B. uniformis*[175], have been proposed[176] and certainly deserve a place in a more specialized review.

One of the major questions for the future use of beneficial bacteria is whether to propose a targeted approach using a single bacterium or a cocktail. Although more might seem better than less, a combination of bacteria (that is, a cocktail) could potentially have an antagonistic effect and affect the activity of individual types or compromise their potential effects in vivo. Here, again, we must not lose sight of the bigger picture and not view weight loss as the only end goal. Weight management should be part of a larger overall integrative plan that seeks to understand and treat the complex cluster of potential alterations or metabolic disorders that can occur in obesity. Such an approach should consider individual circumstances, history of treatment and, possibly, gut microbiota composition and activity. We cannot conclude the present Review without mentioning the importance of other microorganisms, which should also be investigated for their potential roles in obesity, metabolic health and health in general. Although most often used as a synonym for 'gut bacteria', the gut microbiota is much more diverse and includes archaea, fungi, viruses and protists that have important roles alongside bacteria[177–180].

Conclusions

So far, no proof has been obtained of a specific microbial culprit in the onset of obesity or the failure to resolve overweight. However, without diminishing the role of heredity and environmental factors, the gut microbiota clearly makes an important contribution to the development of metabolic disorders and obesity. Maintaining homeostasis and normal metabolism is impossible without restoring the diversity and normal functions of the gut microbiota. Dietary interventions, prebiotics, probiotics and medication can be useful to achieve this aim. However, further research is still needed to develop useful recommendations on how to effectively modulate the gut microbiota on a personalized basis.

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References

1. Gibson, G. R. & Roberfroid, M. B. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J. Nutr.* **125**, 1401–1412 (1995).
2. Gibson, G. R. et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat. Rev. Gastroenterol. Hepatol.* **14**, 491–502 (2017).
3. Bäckhed, F. et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl Acad. Sci. USA* **101**, 15718–15723 (2004).
4. Bäckhed, F., Manchester, J. K., Semenkovich, C. F. & Gordon, J. I. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc. Natl Acad. Sci. USA* **104**, 979–984 (2007).
5. Ley, R. E. et al. Obesity alters gut microbial ecology. *Proc. Natl Acad. Sci. USA* **102**, 11070–11075 (2005).
6. Turnbaugh, P. J. et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **444**, 1027–1031 (2006).
7. Kirk, R. G. "Life in a germ-free world": isolating life from the laboratory animal to the bubble boy. *Bull. Hist. Med.* **86**, 237–275 (2012).
8. Evrard, E., Hoet, P. P., Eyssen, H., Charlier, H. & Sacquet, E. Faecal lipids in germ-free and conventional rats. *Br. J. Exp. Pathol.* **45**, 409–414 (1964).
9. Hoet, P. P. & Eyssen, H. Steatorrhoea in rats with an intestinal Cul-De-Sac. *Gut* **5**, 309–314 (1964).
10. Goodlad, R. A. et al. Plasma enteroglucagon, gastrin and peptide YY in conventional and germ-free rats refed with a fibre-free or fibre-supplemented diet. *Q. J. Exp. Physiol.* **74**, 437–442 (1989).
11. Daubioul, C. A., Taper, H. S., De Wispelaere, L. D. & Delzenne, N. M. Dietary oligofructose lessens hepatic steatosis, but does not prevent hypertriglyceridemia in obese zucker rats. *J. Nutr.* **130**, 1314–1319 (2000).
12. Daubioul, C. et al. Dietary fructans, but not cellulose, decrease triglyceride accumulation in the liver of obese Zucker fa/fa rats. *J. Nutr.* **132**, 967–973 (2002).
13. Le Poul, E. et al. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J. Biol. Chem.* **278**, 25481–25489 (2003).
14. Brown, A. J. et al. The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J. Biol. Chem.* **278**, 11312–11319 (2003).
15. Nilsson, N. E., Kotarsky, K., Owman, C. & Olde, B. Identification of a free fatty acid receptor, FFA2R, expressed on leukocytes and activated by short-chain fatty acids. *Biochem. Biophys. Res. Commun.* **303**, 1047–1052 (2003).
16. de Vos, W. M., Tilg, H., Van Hul, M. & Cani, P. D. Gut microbiome and health: mechanistic insights. *Gut* **71**, 1020–1032 (2022).
17. Rastelli, M., Cani, P. D. & Knauf, C. The gut microbiome influences host endocrine functions. *Endocr. Rev.* **40**, 1271–1284 (2019).
18. Kok, N. N. et al. Insulin, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide and insulin-like growth factor I as putative mediators of the hypolipidemic effect of oligofructose in rats. *J. Nut.* **128**, 1099–1103 (1998).
19. Cani, P. D., Dewever, C. & Delzenne, N. M. Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats. *Br. J. Nutr.* **92**, 521–526 (2004).
20. Cani, P. D., Neyrinck, A. M., Maton, N. & Delzenne, N. M. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like Peptide-1. *Obes. Res* **13**, 1000–1007 (2005).
21. Cani, P. D. et al. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes* **55**, 1484–1490 (2006).
22. Delzenne, N. M., Cani, P. D., Daubioul, C. & Neyrinck, A. M. Impact of inulin and oligofructose on gastrointestinal peptides. *Br. J. Nutr.* **93**, S157–S161 (2005).
23. Ley, R. E., Turnbaugh, P. J., Klein, S. & Gordon, J. I. Microbial ecology: human gut microbes associated with obesity. *Nature* **444**, 1022–1023 (2006).
24. Duncan, S. H. et al. Human colonic microbiota associated with diet, obesity and weight loss. *Int. J. Obes.* **32**, 1720–1724 (2008).

25. Khachatryan, Z. A. et al. Predominant role of host genetics in controlling the composition of gut microbiota. *PLoS One* **3**, e3064 (2008).
26. Goodrich, J. K. et al. Human genetics shape the gut microbiome. *Cell* **159**, 789–799 (2014).
27. Turnbaugh, P. J. et al. A core gut microbiome in obese and lean twins. *Nature* **457**, 480–484 (2009).
28. Zoetendal, E. G., Akkermans, A. D. & De Vos, W. M. Temperature gradient gel electrophoresis analysis of 16S rRNA from human fecal samples reveals stable and host-specific communities of active bacteria. *Appl. Environ. Microbiol.* **64**, 3854–3859 (1998).
29. Cho, I. et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature* **488**, 621–626 (2012).
30. Cox, L. M. et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* **158**, 705–721 (2014).
31. Daoust, L. et al. Gnotobiotic mice housing conditions critically influence the phenotype associated with transfer of faecal microbiota in a context of obesity. *Gut* https://doi.org/10.1136/gutjnl-2021-326475 (2022).
32. Cani, P. D. & Knauf, C. Gnotobiotic mice housing conditions makes the difference in the context of obesity! *Gut* https://doi.org/10.1136/gutjnl-2022-328532 (2022).
33. Hasan, N. & Yang, H. Factors affecting the composition of the gut microbiota, and its modulation. *PeerJ* **7**, e7502 (2019).
34. Hu, S. et al. Dietary fat, but not protein or carbohydrate, regulates energy intake and causes adiposity in mice. *Cell Metab.* **28**, 415–431.e4 (2018).
35. Suriano, F. et al. Fat and not sugar as the determining factor for gut microbiota changes, obesity and related metabolic disorders in mice. *Am. J. Physiol. Endocrinol. Metab.* https://doi.org/10.1152/ajpendo.00141.2022 (2022).
36. Cani, P. D. et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **56**, 1761–1772 (2007).
37. Cani, P. D. et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* **50**, 2374–2383 (2007).
38. Turnbaugh, P. J. et al. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci. Transl. Med* **1**, 6ra14 (2009).
39. Hildebrandt, M. A. et al. High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology* **137**, 1716–1724 (2009).
40. Cani, P. D. et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* **57**, 1470–1481 (2008).
41. Carvalho, B. M. et al. Modulation of gut microbiota by antibiotics improves insulin signalling in high-fat fed mice. *Diabetologia* **55**, 2823–2834 (2012).
42. Ding, S. et al. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS One* **5**, e12191 (2010).
43. Rabot, S. et al. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. *FASEB J.* **24**, 4948–4959 (2010).
44. Caesar, R., Tremaroli, V., Kovatcheva-Datchary, P., Cani, P. D. & Bäckhed, F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. *Cell Metab.* **22**, 658–668 (2015).
45. Cani, P. D. et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* **58**, 1091–1103 (2009).
46. Dewulf, E. M. et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut* **62**, 1112–1121 (2013).
47. Everard, A. et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* **60**, 2775–2786 (2011).
48. Cani, P. D., Depommier, C., Derrien, M., Everard, A. & de Vos, W. M. Akkermansia muciniphila: paradigm for next-generation beneficial microorganisms. *Nat. Rev. Gastroenterol. Hepatol.* **19**, 625–637 (2022).
49. Wolters, M. et al. Dietary fat, the gut microbiota, and metabolic health — a systematic review conducted within the MyNewGut project. *Clin. Nutr.* **38**, 2504–2520 (2019).
50. Bartlett, A. & Kleiner, M. Dietary protein and the intestinal microbiota: an understudied relationship. *iScience* **25**, 105313 (2022).
51. Beaumont, M. et al. Quantity and source of dietary protein influence metabolite production by gut microbiota and rectal mucosa gene expression: a randomized, parallel, double-blind trial in overweight humans. *Am. J. Clin. Nutr.* **106**, 1005–1019 (2017).
52. Choi, B. S. et al. Feeding diversified protein sources exacerbates hepatic insulin resistance via increased gut microbial branched-chain fatty acids and mTORC1 signaling in obese mice. *Nat. Commun.* **12**, 3377 (2021).
53. Holmes, A. J. et al. Diet-microbiome interactions in health are controlled by intestinal nitrogen source constraints. *Cell Metab.* **25**, 140–151 (2017).
54. Anhe, F. F. et al. Type 2 diabetes influences bacterial tissue compartmentalisation in human obesity. *Nat. Metab.* **2**, 233–242 (2020).
55. Massier, L. et al. Adipose tissue derived bacteria are associated with inflammation in obesity and type 2 diabetes. *Gut* **69**, 1796–1806 (2020).
56. Velmurugan, G., Dinakaran, V., Rajendhran, J. & Swaminathan, K. Blood microbiota and circulating microbial metabolites in diabetes and cardiovascular disease. *Trends Endocrinol. Metab.* **31**, 835–847 (2020).
57. Cani, P. D. & Van Hul, M. Microbial signatures in metabolic tissues: a novel paradigm for obesity and diabetes? *Nat. Metab.* **2**, 211–212 (2020).
58. Regnier, M., Van Hul, M., Knauf, C. & Cani, P. D. Gut microbiome, endocrine control of gut barrier function and metabolic diseases. *J. Endocrinol.* **248**, R67–R82 (2021).
59. Blaak, E. E. et al. Short chain fatty acids in human gut and metabolic health. *Benef. Microbes* **11**, 411–455 (2020).
60. Canfora, E. E., Jocken, J. W. & Blaak, E. E. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat. Rev. Endocrinol.* **11**, 577–591 (2015).
61. van Deuren, T., Blaak, E. E. & Canfora, E. E. Butyrate to combat obesity and obesity-associated metabolic disorders: Current status and future implications for therapeutic use. *Obes. Rev.* **23**, e13498 (2022).
62. Chambers, E. S. et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. *Gut* **68**, 1430–1438 (2019).
63. Byrne, C. S. et al. Effects of inulin propionate ester incorporated into palatable food products on appetite and resting energy expenditure: a randomised crossover study. *Nutrients* **11**, 861 (2019).
64. Chambers, E. S. et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut* **64**, 1744–1754 (2015).
65. Makishima, M. et al. Identification of a nuclear receptor for bile acids. *Science* **284**, 1362–1365 (1999).
66. Makishima, M. et al. Vitamin D receptor as an intestinal bile acid sensor. *Science* **296**, 1313–1316 (2002).
67. Ihunnah, C. A., Jiang, M. & Xie, W. Nuclear receptor PXR, transcriptional circuits and metabolic relevance. *Biochim. Biophys. Acta* **1812**, 956–963 (2011).
68. Wagner, M. et al. CAR and PXR agonists stimulate hepatic bile acid and bilirubin detoxification and elimination pathways in mice. *Hepatology* **42**, 420–430 (2005).
69. Kawamata, Y. et al. A G protein-coupled receptor responsive to bile acids. *J. Biol. Chem.* **278**, 9435–9440 (2003).
70. McGlone, E. R. & Bloom, S. R. Bile acids and the metabolic syndrome. *Ann. Clin. Biochem.* **56**, 326–337 (2019).
71. Tu, J., Wang, Y., Jin, L. & Huang, W. Bile acids, gut microbiota and metabolic surgery. *Front. Endocrinol.* **13**, 929530 (2022).
72. Ridlon, J. M., Kang, D. J. & Hylemon, P. B. Bile salt biotransformations by human intestinal bacteria. *J. Lipid Res.* **47**, 241–259 (2006).
73. Ridlon, J. M., Harris, S. C., Bhowmik, S., Kang, D. J. & Hylemon, P. B. Consequences of bile salt biotransformations by intestinal bacteria. *Gut Microbes* **7**, 22–39 (2016).
74. Duparc, T. et al. Hepatocyte MyD88 affects bile acids, gut microbiota and metabolome contributing to regulate glucose and lipid metabolism. *Gut* **66**, 620–632 (2017).
75. Lin, H., An, Y., Tang, H. & Wang, Y. Alterations of bile acids and gut microbiota in obesity induced by high fat diet in rat model. *J. Agric. Food Chem.* **67**, 3624–3632 (2019).
76. Li, J. Y. et al. Secondary bile acids mediate high-fat diet-induced upregulation of R-spondin 3 and intestinal epithelial proliferation. *JCI Insight* **7**, e148309 (2022).
77. de Aguiar Vallim, T. Q., Tarling, E. J. & Edwards, P. A. Pleiotropic roles of bile acids in metabolism. *Cell Metab.* **17**, 657–669 (2013).
78. Li, M. et al. Gut microbiota-bile acid crosstalk contributes to the rebound weight gain after calorie restriction in mice. *Nat. Commun.* **13**, 2060 (2022).
79. van Nierop, F. S. et al. Effects of acute dietary weight loss on postprandial plasma bile acid responses in obese insulin resistant subjects. *Clin. Nutr.* **36**, 1615–1620 (2017).
80. Cani, P. D. et al. Endocannabinoids–at the crossroads between the gut microbiota and host metabolism. *Nat. Rev. Endocrinol.* **12**, 133–143 (2016).
81. Busquets-Garcia, A., Bolanos, J. P. & Marsicano, G. Metabolic messengers: endocannabinoids. *Nat. Metab.* **4**, 848–855 (2022).
82. Muccioli, G. G. et al. The endocannabinoid system links gut microbiota to adipogenesis. *Mol. Syst. Biol.* **6**, 392 (2010).
83. Suriano, F. et al. Exploring the endocannabinoidome in genetically obese (ob/ob) and diabetic (db/db) mice: links with inflammation and gut microbiota. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **1867**, 159056 (2022).
84. Manca, C. et al. Germ-free mice exhibit profound gut microbiota-dependent alterations of intestinal endocannabinoidome signaling. *J. Lipid Res.* **61**, 70–85 (2020).
85. Suriano, F. et al. Novel insights into the genetically obese (ob/ob) and diabetic (db/db) mice: two sides of the same coin. *Microbiome* **9**, 147 (2021).
86. Geurts, L. et al. Adipose tissue NAPE-PLD controls fat mass development by altering the browning process and gut microbiota. *Nat. Commun.* **6**, 6495 (2015).
87. Everard, A. et al. Intestinal epithelial N-acylphosphatidylethanolamine phospholipase D links dietary fat to metabolic adaptations in obesity and steatosis. *Nat. Commun.* **10**, 457 (2019).
88. Rastelli, M. et al. Intestinal NAPE-PLD contributes to short-term regulation of food intake via gut-to-brain axis. *Am. J. Physiol. Endocrinol. Metab.* **319**, E647–E657 (2020).
89. Cohen, L. J. et al. Commensal bacteria make GPCR ligands that mimic human signalling molecules. *Nature* **549**, 48–53 (2017).
90. Ye, L. et al. Enteroendocrine cells sense bacterial tryptophan catabolites to activate enteric and vagal neuronal pathways. *Cell Host Microbe* **29**, 179–196.e9 (2021).
91. Bhattarai, Y. et al. Gut microbiota-produced tryptamine activates an epithelial G-protein-coupled receptor to increase colonic secretion. *Cell Host Microbe* **23**, 775–785.e5 (2018).
92. Chimerel, C. et al. Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells. *Cell Rep.* **9**, 1202–1208 (2014).

93. Gao, K., Mu, C. L., Farzi, A. & Zhu, W. Y. Tryptophan metabolism: a link between the gut microbiota and brain. *Adv. Nutr.* **11**, 709–723 (2020).
94. Agus, A., Planchais, J. & Sokol, H. Gut microbiota regulation of tryptophan metabolism in health and disease. *Cell Host Microbe* **23**, 716–724 (2018).
95. Natividad, J. M. et al. Impaired Aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome. *Cell Metab.* **28**, 737–749.e4 (2018).
96. Zelante, T. et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity* **39**, 372–385 (2013).
97. Postal, B. G. et al. AhR activation defends gut barrier integrity against damage occurring in obesity. *Mol. Metab.* **39**, 101007 (2020).
98. Anhe, F. F., Barra, N. G., Cavallari, J. F., Henriksbo, B. D. & Schertzer, J. D. Metabolic endotoxemia is dictated by the type of lipopolysaccharide. *Cell Rep.* **36**, 109691 (2021).
99. Roager, H. M. & Christensen, L. H. Personal diet-microbiota interactions and weight loss. *Proc. Nutr. Soc.* **81**, 243–254 (2022).
100. Puchalska, P. & Crawford, P. A. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab.* **25**, 262–284 (2017).
101. Kolb, H. et al. Ketone bodies: from enemy to friend and guardian angel. *BMC Med.* **19**, 313 (2021).
102. Hersant, H. & Grossberg, G. The ketogenic diet and Alzheimer's disease. *J. Nutr. Health Aging* **26**, 606–614 (2022).
103. Dilliraj, L. N. et al. The evolution of ketosis: potential impact on clinical conditions. *Nutrients* **14**, 3613 (2022).
104. Qi, J. et al. Metagenomics reveals that intravenous injection of beta-hydroxybutyric acid (BHBA) disturbs the nasopharynx microflora and increases the risk of respiratory diseases. *Front. Microbiol.* **11**, 630280 (2020).
105. Ang, Q. Y. et al. Ketogenic diets alter the gut microbiome resulting in decreased intestinal Th17 cells. *Cell* **181**, 1263–1275.e16 (2020).
106. Van Hul, M. et al. Comparison of the effects of soluble corn fiber and fructooligosaccharides on metabolism, inflammation and gut microbiome of high-fat diet fed mice. *Am. J. Physiol. Endocrinol. Metab.* **319**, E779–E791 (2020).
107. Anhe, F. F. et al. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. *Gut* **64**, 872–883 (2015).
108. Leclercq, S. et al. Gut microbiota-induced changes in beta-hydroxybutyrate metabolism are linked to altered sociability and depression in alcohol use disorder. *Cell Rep.* **33**, 108238 (2020).
109. Ellenbroek, J. H. et al. Long-term ketogenic diet causes glucose intolerance and reduced beta- and alpha-cell mass but no weight loss in mice. *Am. J. Physiol. Endocrinol. Metab.* **306**, E552–E558 (2014).
110. Yuasa, M. et al. Consumption of a low-carbohydrate and high-fat diet (the ketogenic diet) exaggerates biotin deficiency in mice. *Nutrition* **29**, 1266–1270 (2013).
111. Belda, E. et al. Impairment of gut microbial biotin metabolism and host biotin status in severe obesity: effect of biotin and prebiotic supplementation on improved metabolism. *Gut* **71**, 2463–2480 (2022).
112. Menotti, A. & Puddu, P. E. How the Seven Countries Study contributed to the definition and development of the Mediterranean diet concept: a 50-year journey. *Nutr. Metab. Cardiovasc. Dis.* **25**, 245–252 (2015).
113. Hidalgo-Mora, J. J. et al. The Mediterranean diet: a historical perspective on food for health. *Maturitas* **132**, 65–69 (2020).
114. Sofi, F., Cesari, F., Abbate, R., Gensini, G. F. & Casini, A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* **337**, a1344 (2008).
115. De Filippis, F. et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut* **65**, 1812–1821 (2016).
116. Khalili, H. et al. Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from two large prospective cohort studies. *Gut* **69**, 1637–1644 (2020).
117. Tsigalou, C. et al. Gut microbiome and Mediterranean diet in the context of obesity. Current knowledge, perspectives and potential therapeutic targets. *Metab. Open* **9**, 100081 (2021).
118. Meslier, V. et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut* **69**, 1258–1268 (2020).
119. Cani, P. D. & Van Hul, M. Mediterranean diet, gut microbiota and health: when age and calories do not add up! *Gut* **69**, 1167–1168 (2020).
120. Reynolds, A. et al. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet* **393**, 434–445 (2019).
121. Hiel, S. et al. Link between gut microbiota and health outcomes in inulin -treated obese patients: lessons from the Food4Gut multicenter randomized placebo-controlled trial. *Clin. Nutr.* **39**, 3618–3628 (2020).
122. Rodriguez, J. et al. Discovery of the gut microbial signature driving the efficacy of prebiotic intervention in obese patients. *Gut* **69**, 1975–1987 (2020).
123. Rodriguez, J. et al. Metabolite profiling reveals the interaction of chitin-glucan with the gut microbiota. *Gut Microbes* **12**, 1810530 (2020).
124. Myhrstad, M. C. W., Tunsjo, H., Charnock, C. & Telle-Hansen, V. H. Dietary fiber, gut microbiota, and metabolic regulation-current status in human randomized trials. *Nutrients* **12**, 859 (2020).
125. Makki, K., Deehan, E. C., Walter, J. & Bäckhed, F. The impact of dietary fiber on gut microbiota in host health and disease. *Cell Host Microbe* **23**, 705–715 (2018).
126. Vinelli, V. et al. Effects of dietary fibers on short-chain fatty acids and gut microbiota composition in healthy adults: a systematic review. *Nutrients* **14**, 2559 (2022).
127. Rastall, R. A. et al. Structure and function of non-digestible carbohydrates in the gut microbiome. *Benef. Microbes* **13**, 95–168 (2022).
128. Ozkul, C., Yalinay, M. & Karakan, T. Structural changes in gut microbiome after Ramadan fasting: a pilot study. *Benef. Microbes* **11**, 227–233 (2020).
129. Ozkul, C., Yalinay, M. & Karakan, T. Islamic fasting leads to an increased abundance of Akkermansia muciniphila and Bacteroides fragilis group: a preliminary study on intermittent fasting. *Turk. J. Gastroenterol.* **30**, 1030–1035 (2019).
130. Su, J. et al. Remodeling of the gut microbiome during Ramadan-associated intermittent fasting. *Am. J. Clin. Nutr.* **113**, 1332–1342 (2021).
131. Ali, I. et al. Ramadan fasting leads to shifts in human gut microbiota structured by dietary composition. *Front. Microbiol.* **12**, 642999 (2021).
132. Welton, S. et al. Intermittent fasting and weight loss: systematic review. *Can. Fam. Physician* **66**, 117–125 (2020).
133. Lowe, D. A. et al. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: the TREAT randomized clinical trial. *JAMA Intern. Med.* **180**, 1491–1499 (2020).
134. Hjorth, M. F. et al. Prevotella-to-Bacteroides ratio predicts body weight and fat loss success on 24-week diets varying in macronutrient composition and dietary fiber: results from a post-hoc analysis. *Int. J. Obes.* **43**, 149–157 (2019).
135. Cani, P. D. & Van Hul, M. Do diet and microbes really 'PREDICT' cardiometabolic risks? *Nat. Rev. Endocrinol.* **17**, 259–260 (2021).
136. Ridaura, V. K. et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* **341**, 1241214 (2013).
137. Murphy, E. F. et al. Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. *Gut* **59**, 1635–1642 (2010).
138. Zeevi, D. et al. Personalized nutrition by prediction of glycemic responses. *Cell* **163**, 1079–1094 (2015).
139. Franz, M. J. et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J. Am. Diet. Assoc.* **107**, 1755–1767 (2007).
140. Son, J. W. & Kim, S. Comprehensive review of current and upcoming anti-obesity drugs. *Diabetes Metab. J.* **44**, 802–818 (2020).
141. Wu, H. et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. *Nat. Med.* **23**, 850–858 (2017).
142. de la Cuesta-Zuluaga, J. et al. Metformin is associated with higher relative abundance of mucin-degrading akkermansia muciniphila and several short-chain fatty acid-producing microbiota in the gut. *Diabetes Care* **40**, 54–62 (2017).
143. Jin, J. et al. Distinctive gut microbiota in patients with overweight and obesity with dyslipidemia and its responses to long-term orlistat and ezetimibe intervention: a randomized controlled open-label trial. *Front. Pharm.* **12**, 732541 (2021).
144. Jin, J. et al. Orlistat and ezetimibe could differently alleviate the high-fat diet-induced obesity phenotype by modulating the gut microbiota. *Front. Microbiol.* **13**, 908327 (2022).
145. Ke, J. et al. Orlistat-induced gut microbiota modification in obese mice. *Evid. Based Complement. Altern. Med.* **2020**, 9818349 (2020).
146. Wang, L., Li, P., Tang, Z., Yan, X. & Feng, B. Structural modulation of the gut microbiota and the relationship with body weight: compared evaluation of liraglutide and saxagliptin treatment. *Sci. Rep.* **6**, 33251 (2016).
147. Wang, Z. et al. Gut microbiome differences between metformin- and liraglutide-treated T2DM subjects. *Endocrinol. Diabetes Metab.* **1**, e00009 (2018).
148. Mulla, C. M., Middelbeek, R. J. W. & Patti, M. E. Mechanisms of weight loss and improved metabolism following bariatric surgery. *Ann. N. Y. Acad. Sci.* **1411**, 53–64 (2018).
149. Valenti, V., Cienfuegos, J. A., Becerril Manas, S. & Fruhbeck, G. Mechanism of bariatric and metabolic surgery: beyond surgeons, gastroenterologists and endocrinologists. *Rev. Esp. Enferm. Dig.* **112**, 229–233 (2020).
150. Anhe, F. F. et al. Human gut microbiota after bariatric surgery alters intestinal morphology and glucose absorption in mice independently of obesity. *Gut* https://doi.org/10.1136/gutjnl-2022-328185 (2022).
151. Gutierrez-Repiso, C. et al. Predictive role of gut microbiota in weight loss achievement after bariatric surgery. *J. Am. Coll. Surg.* **234**, 861–871 (2022).
152. Ben Izhak, M. et al. Projection of gut microbiome pre- and post-bariatric surgery to predict surgery outcome. *mSystems* **6**, e0136720 (2021).
153. Crommen, S., Mattes, A. & Simon, M. C. Microbial adaptation due to gastric bypass surgery: the nutritional impact. *Nutrients* **12**, 1199 (2020).
154. Debedat, J., Clement, K. & Aron-Wisnewsky, J. Gut microbiota dysbiosis in human obesity: impact of bariatric surgery. *Curr. Obes. Rep.* **8**, 229–242 (2019).
155. Tremaroli, V. et al. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. *Cell Metab.* **22**, 228–238 (2015).
156. Dao, M. C. et al. Akkermansia muciniphila abundance is lower in severe obesity, but its increased level after bariatric surgery is not associated with metabolic health improvement. *Am. J. Physiol. Endocrinol. Metab.* **317**, E446–E459 (2019).
157. Lau, E. et al. Gut microbiota changes after metabolic surgery in adult diabetic patients with mild obesity: a randomised controlled trial. *Diabetol. Metab. Syndr.* **13**, 56 (2021).
158. Saffouri, G., Pardi, D., Kashyap, P. & Khanna, S. Body mass index changes after fecal microbiota transplant for recurrent Clostridium difficile infection: 216. *Am. J. Gastroenterol.* **111**, S103 (2016).
159. Zhang, Z. et al. Impact of fecal microbiota transplantation on obesity and metabolic syndrome — a systematic review. *Nutrients* **11**, 2291 (2019).

160. Proenca, I. M. et al. Fecal microbiota transplantation improves metabolic syndrome parameters: systematic review with meta-analysis based on randomized clinical trials. *Nutr. Res.* **83**, 1–14 (2020).
161. Yu, E. W. et al. Fecal microbiota transplantation for the improvement of metabolism in obesity: the FMT-TRIM double-blind placebo-controlled pilot trial. *PLoS Med* **17**, e1003051 (2020).
162. Hartstra, A. V. et al. Infusion of donor feces affects the gut-brain axis in humans with metabolic syndrome. *Mol. Metab.* **42**, 101076 (2020).
163. Benitez-Paez, A., Hartstra, A. V., Nieuwdorp, M. & Sanz, Y. Species- and strain-level assessment using rrn long-amplicons suggests donor's influence on gut microbial transference via fecal transplants in metabolic syndrome subjects. *Gut Microbes* **14**, 2078621 (2022).
164. Wilson, B. C. et al. Strain engraftment competition and functional augmentation in a multi-donor fecal microbiota transplantation trial for obesity. *Microbiome* **9**, 107 (2021).
165. Ng, S. C. et al. Microbiota engraftment after faecal microbiota transplantation in obese subjects with type 2 diabetes: a 24-week, double-blind, randomised controlled trial. *Gut* **71**, 716–723 (2022).
166. Mocanu, V. et al. Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial. *Nat. Med.* **27**, 1272–1279 (2021).
167. Thaiss, C. A. et al. Persistent microbiome alterations modulate the rate of post-dieting weight regain. *Nature* **540**, 544–551 (2016).
168. Rinott, E. et al. Effects of diet-modulated autologous fecal microbiota transplantation on weight regain. *Gastroenterology* **160**, 158–173.e10 (2021).
169. Udayappan, S. et al. Oral treatment with Eubacterium hallii improves insulin sensitivity in db/db mice. *NPJ Biofilms Microbiomes* **2**, 16009 (2016).
170. Koopen, A. et al. Duodenal Anaerobutyricum soehngenii infusion stimulates GLP-1 production, ameliorates glycaemic control and beneficially shapes the duodenal transcriptome in metabolic syndrome subjects: a randomised double-blind placebo-controlled cross-over study. *Gut* **71**, 1577–1587 (2022).
171. Vrieze, A. et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* **143**, 913–916.e7 (2012).
172. Huber-Ruano, I. et al. Orally administered Odoribacter laneus improves glucose control and inflammatory profile in obese mice by depleting circulating succinate. *Microbiome* **10**, 135 (2022).
173. Pujo, J. et al. Bacteria-derived long chain fatty acid exhibits anti-inflammatory properties in colitis. *Gut* **70**, 1088–1097 (2021).
174. Romani-Perez, M. et al. Holdemanella biformis improves glucose tolerance and regulates GLP-1 signaling in obese mice. *FASEB J.* **35**, e21734 (2021).
175. Gomez Del Pulgar, E. M., Benitez-Paez, A. & Sanz, Y. Safety assessment of bacteroides uniformis CECT 7771, a symbiont of the gut microbiota in infants. *Nutrients* **12**, 551 (2020).
176. Romani-Perez, M., Agusti, A. & Sanz, Y. Innovation in microbiome-based strategies for promoting metabolic health. *Curr. Opin. Clin. Nutr. Metab. Care* **20**, 484–491 (2017).
177. Rasmussen, T. S. et al. Faecal virome transplantation decreases symptoms of type 2 diabetes and obesity in a murine model. *Gut* **69**, 2122–2130 (2020).
178. Shkoporov, A. N. et al. Reproducible protocols for metagenomic analysis of human faecal phageomes. *Microbiome* **6**, 68 (2018).
179. Yang, K. et al. Alterations in the gut virome in obesity and type 2 diabetes mellitus. *Gastroenterology* **161**, 1257–1269.e13 (2021).
180. Shareefdeen, H. & Hill, C. The gut virome in health and disease: new insights and associations. *Curr. Opin. Gastroenterol.* **38**, 549–554 (2022).

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Competing interests
P.D.C. is an inventor on patent applications dealing with the use of specific bacteria and components in the treatment of different diseases. P.D.C. was co-founder of The Akkermansia Company SA and Enterosys. M.V.H. declares no competing interests.

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