Diabetology & Metabolic Syndrome

REVIEW

Open Access

Understanding the complex function of gut microbiota: its impact on the pathogenesis of obesity and beyond: a comprehensive review

Aref Yarahmadi[1], Hamed Afkhami[2,3,4*], Ali Javadi[5*] and Mojtaba Kashfi[3,6*]

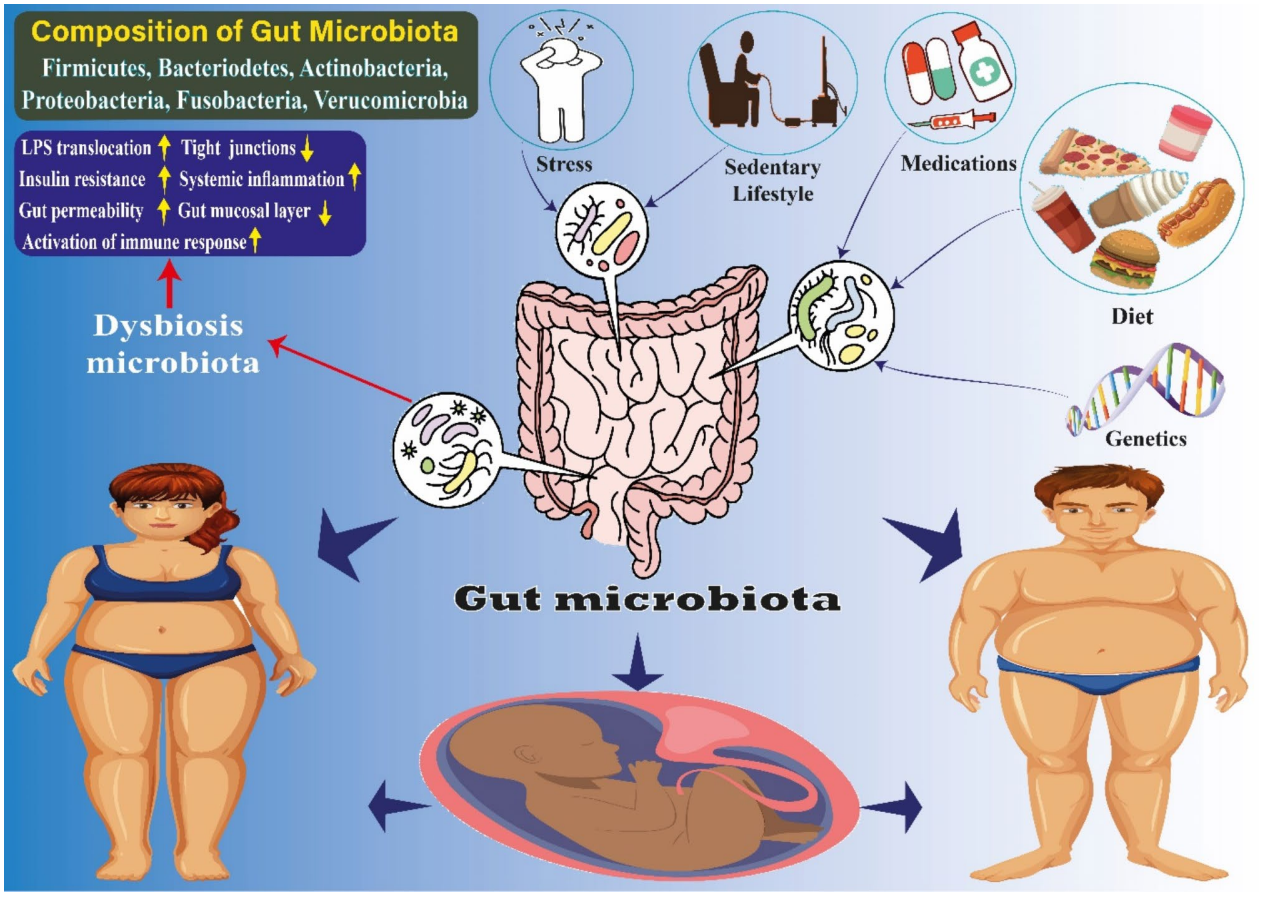
Abstract

Obesity is a multifactorial condition influenced by genetic, environmental, and microbiome-related factors. The gut microbiome plays a vital role in maintaining intestinal health, increasing mucus creation, helping the intestinal epithelium mend, and regulating short-chain fatty acid (SCFA) production. These tasks are vital for managing metabolism and maintaining energy balance. Dysbiosis—an imbalance in the microbiome—leads to increased appetite and the rise of metabolic disorders, both fuel obesity and its issues. Furthermore, childhood obesity connects with unique shifts in gut microbiota makeup. For instance, there is a surge in pro-inflammatory bacteria compared to children who are not obese. Considering the intricate nature and variety of the gut microbiota, additional investigations are necessary to clarify its exact involvement in the beginnings and advancement of obesity and related metabolic dilemmas. Currently, therapeutic methods like probiotics, prebiotics, synbiotics, fecal microbiota transplantation (FMT), dietary interventions like Mediterranean and ketogenic diets, and physical activity show potential in adjusting the gut microbiome to fight obesity and aid weight loss. Furthermore, the review underscores the integration of microbial metabolites with pharmacological agents such as orlistat and semaglutide in restoring microbial homeostasis. However, more clinical tests are essential to refine the doses, frequency, and lasting effectiveness of these treatments. This narrative overview compiles the existing knowledge on the multifaceted role of gut microbiota in obesity and much more, showcasing possible treatment strategies for addressing these health challenges.

*Correspondence:
Hamed Afkhami
hamedafkhami70@gmail.com
Ali Javadi
alijavadi1388@gmail.com
Mojtaba Kashfi
mojtabakashfi90@yahoo.com

Full list of author information is available at the end of the article

Graphical Abstract



Keywords Gut microbiota, Obesity, Pediatric obesity, Probiotic, Fecal Microbiota Transplantation

Introduction

Obesity has come out as a critical concern at present and is even rated as a cause for concern in health. The growing rate of this condition is worrisome. It has been estimated that about two billion individuals worldwide face issues with excess weight, and most of them are obese [1, 2]. In the USA, for example, nearly 100 million people in all age categories, which is about one-third of the US population, are obese. If a person has a body mass index (BMI) that is greater than or equal to 25 and less than 30 kg/m^2, the person is considered to be overweight [3]. Among various other factors, the growing obesity epidemic across the globe has also been associated with several debilitating disorders and diseases such as type 2 diabetes, visceral insulin resistance, and nonalcoholic fatty liver disease (NAFLD), among others [4–7]. Obesity has also been linked to decreased life satisfaction and the development of mental health issues, including anxiety and sadness [8]. According to research findings, the accumulation of excessive fat in individuals who are classified as obese initiates a cellular response that is associated with the body's natural defense mechanisms. This particular response leads to a chronic, mild state of inflammation [9]. As a result, obesity is the main contributor to morbidity, death, and medical spending. Additionally, people who are obese have a far higher chance of dying from coronavirus disease 2019 (COVID-19) than those who are normal weight [10]. For instance, 62% of obese hospitalized patients who needed mechanical breathing and suffered COVID-19-related problems perished [11]. Preventing the development of associated metabolic diseases is imperative to impede the growth of the obesity epidemic, as obesity has the potential to result in severe health complications [12].

The possible impact of a balanced gastrointestinal (GI) microbial community on the emergence of obesity is suggested by a growing body of evidence in recent years [13]. The intestinal microbiota, which refers to the community of microorganisms residing in the GI tract, harbors an astounding number of up to 100 trillion mutually

beneficial microorganisms. Together with their genetic material, metabolic products, and interactions with the host, these microorganisms collectively form what is known as the gut microbiome [14–16]. The bacterial compositions and concentrations per gram content vary in each section of the GI tract. To illustrate, the large intestine contains 1011–1012 cells, the small intestine contains 104–107 cells, and the stomach and duodenum contain 10–1013 cells, respectively. Additionally, the host and the gut microbiota collaborate synergistically to enhance the host's assimilation of nutrients and energy, simultaneously safeguarding it from infections [17–20]. The GI microbiota, comprising Firmicutes, Bacteroidetes, Proteus, Actinomycetes, Fusobacteria, and Verrucomicrobia, has been extensively examined [13, 21]. To uphold its elevated population quantities, the gut microbiota relies upon undigested food remnants, mucosal secretions from the GI tract, and expelled deceased cells as a source of sustenance [22]. The gut microbiome serves various purposes, including preserving intestinal integrity, producing mucus, encouraging the regeneration of the intestinal epithelium, and mediating the creation of short-chain fatty acids (SCFA) [8, 23]. Elevated concentrations of SCFA, particularly butyrate, are associated with diminished inflammation in the intestines, offering protection against the development of obesity and insulin resistance [24, 25]. Moreover, various beneficial bacterial species with anti-inflammatory properties, such as *Veillonella spp*., *Bifidobacterium* spp., *Prevotella* spp., and *Akkermansia muciniphila*, respond well to diets high in fiber, creating a favorable environment for working and immunity [26, 27]. A proficiently functioning GI microbiota is crucial in managing metabolic procedures and energy levels. Alterations in the gut microbiota can lead to an augmented appetite and metabolic disorders, both of which can be influential elements in the development of obesity [13, 28].

The focus of the study is the investigation of the gut microbiome's role in enhancing the process of losing weight fighting obesity and studying the metabolic products of the gut microbiome. Additionally, it includes looking into the sociobiology of the microbiome in obesity in children as well as the utilization of the microbiome in the integrative treatment of obesity and related disorders.

Development and composition of normal gut microbiota

The outcomes of research suggest that the commencement of the gut ecosystem is triggered during the prenatal period, thereby challenging the widely accepted belief that the development of the intestinal microbiota begins after birth. The establishment of a newborn's microbiome is still influenced by many factors, including the mother's health, mode of delivery (vaginal as opposed to cesarean section), and infant feeding practices (breastfeeding vs. formula feeding, introduction of complementary solids) and exposure to various medications (such as antacids and antibiotics) [29–32]. Babies born vaginally have a bacterial community similar to the mother's vaginal flora, mainly *Lactobacillus* spp., *Sneathia* spp., and *Prevotella* spp. Contrarily, children run through the cesarean section have bacterial communities that resemble the skin of their mothers, where *Staphylococcus* spp., *Corynebacterium* spp., and *Propionibacterium* spp. predominate [33–35]. Additionally, babies born through the cesarean section exhibit distinct gut microbiota development than those delivered vaginally [36]. Most notably, infants delivered by Cesarean section have underrepresentations of *Bacteroides* and *Bifidobacterium* and overrepresentations of pathobionts, incredibly particular strains inherited from their mother [36]. Although these discrepancies in delivery methods are most apparent during the initial year of existence, specific differences endure into the early stages of childhood [37].

Long-term health consequences result from interfering with the microbiome's development during critical formative years for immune and metabolic programming [38]. The gut microbiota keeps changing and becomes more diverse as children age, stabilizing between three and four years old and then starting to resemble the microbiota of adults [29, 39]. The quantity of microbial cells exceeds the amount of cells in the human body by a factor of ten orders of magnitude. The colon is home to the most microbiota of all the microbial habitats. A varied ecology of bacteria, fungi, protozoa, archaea, and viruses make up the gut microbiota [40, 41]. The GI tract comprises approximately 100 trillion (1014) microorganisms that belong to 12 distinguishable species [9, 40]. Firmicutes (60%), Bacteroidetes (10%), Actinobacteria (10%), and other species make up the majority of the GI microbiota, which is then followed by Proteobacteria, Verucomicrobia, Fusobacteria [40, 42]. The homeostasis and immunity of the host are significantly dependent on the gut microbiota, with which the host maintains continuous interaction [9]. The fact that the total number of genes in bacteria is between 100 and 200 times bigger than those in humans (3.3 million vs. 20,000) highlights the potential of this group [43]. The concept of the gut-brain axis refers to the interconnected and reciprocal interactions taking place between the gut microbiota and the enteric nervous system, as well as the central nervous system, via enteroendocrine and endocrine pathways [44]. Additionally, several medications like sulfasalazine and several chemotherapy treatments are processed by the gut bacteria [45]. The composition of microorganisms in the GI tract is continuously influenced by factors like antimicrobial agents and environmental elements,

including age, dietary intake, levels of physical exertion, and different pathological conditions [46–49]. The potential influence of alterations in diet, such as the incorporation of supplementary food sources, on the diversity of gut microbial composition cannot be overlooked [50]. The host's health is positively influenced by a wide range of microorganisms. When assessing this diversity, two factors are considered: richness, which refers to the number of different species present in the environment, and evenness, which pertains to the proportionate abundance of each species [29]. The differentiation observed among the different samples is commonly denoted as beta diversity. In contrast, the diversity found within a single model (or within a specific community) is recognized as alpha diversity [51]. Dysbiosis is the word for any divergence from the average microbial profile, and the imbalance may impact the resident microbial population's diversity, composition, or functionality [51]. Numerous illnesses, such as chronic inflammatory and metabolic problems, are associated with gut dysbiosis [40, 52].

The role of the gut microbiome in pediatric obesity

One of the most crucial worldwide health issues that has become more common over the past ten years is pediatric obesity. The frequency of pediatric obesity has abruptly grown since the coronavirus illness pandemic of 2019 due to the shutdown of schools during the pandemic [53]. Obesity in childhood makes other health issues, such as T2DM, hypertension, fatty liver disease, dyslipidemia, and psychosocial issues that frequently last into adulthood, worse [54]. Childhood obesity is an important target area for intervention since it reduces the risk of these illnesses if people can lose weight before they reach adulthood [55]. Obese children who subsequently became obese adults were at considerably higher risk for cardio metabolic events. If a child who was affected by obesity were able to reach adulthood while maintaining a state of optimal weight, their level of susceptibility would be equivalent to that of any other adult who had consistently upheld a healthy weight throughout their entire lifespan [55–57].

The occurrence of pediatric obesity can be attributed to a multitude of intriguing elements, encompassing environmental, behavioral, genetic, nutritional, microbiological, and biological factors [58]. There is an escalating body of proof suggesting that the intestinal microbiota exerts a substantial influence on the control of insulin resistance and obesity [59]. Children who suffer from obesity also display alterations in the constitution and operational capabilities of their intestinal microorganisms. This includes a notable rise in proinflammatory bacterial groups compared to their lean counterparts [60, 61]. Most studies conducted on the gut microbiota of childhood obesity have employed a cross-sectional approach. The microbiota makeup of obese and lean children differed significantly, according to earlier investigations of Hispanic and Mexican children [62, 63]. Additionally, cross-sectional research on Korean children revealed a link between pediatric obesity and intestinal microorganisms [64]. Research has demonstrated that the configuration of microorganisms in the GI tract, known as gut microbiota patterns, could function as an intermediary factor influencing the excessive growth of infants at an early age [65]. The composition of the microbiota, host, and nutrition may predict obesity, according to one prospective research of children that looked at microbial alterations linked to weight increase during four years [66]. Another study on kids discovered that the obese group's gut microbiota changed composition and function after a two-month weight-loss program and lifestyle adjustment [67]. The researchers employed a clinical experiment involving children genetically predisposed to obesity. They discerned that following 30 days, during which the subjects consumed a diet rich in carbohydrates that cannot be digested, the prevalence of a particular type of *Escherichia coli* experienced significant growth. In contrast, the levels of the other four strains diminished [68].

Agans et al. [69] conducted a thorough investigation into the gut microbiota of two distinct age groups: adolescents (11 to 18 years) and adults. Remarkably, their findings unveiled a remarkable discrepancy, with a noticeably greater abundance of *Bifidobacterium* spp. observed in the former cohort compared to the latter. The authors suggested that rather than rapidly dropping after toddlerhood, *Bifidobacteria* levels in children fell gradually between the ages of 2 and 18 before stabilizing at low levels in early adulthood [69]. Furthermore, Hollister and colleagues [70] the gut microbiomes of 46 pre-adolescent children (ranging from 7 to 12 years old) who were in good health were compared with those of adults in good health from the same geographical area (Houston, Texas, USA). Despite having roughly the same taxonomic and functional genes as healthy adults, children's and adults' composition and functional potential were very different. Adults showed higher levels of *Bacteroides* spp., whereas children had higher levels of *Bifidobacterium* spp., *Faecalibacterium* spp., and *Lachnospiraceae*. The relative abundance of genes linked to various biological processes such as vitamin synthesis, amino acid degradation, mucosal inflammation, and oxidative phosphorylation displayed significant differences in their functional diversity. The gut microbiota in adults, as opposed to children, was primarily linked to obesity, a heightened vulnerability to adiposity, and inflammation. Conversely, intestinal microorganisms in children displayed a more comprehensive range of functions that had the potential to support ongoing growth and development [70].

These collective findings suggest that the functional and compositional characteristics of the healthy gut microbiota in pediatric individuals differ from those of healthy adults with similar characteristics. Additionally, there is a proposition that the expansion velocity of the intestinal microbial community might exhibit a more gradual pace than what was previously perceived [70]. The involvement of the gut microbiome in childhood obesity brings about a differentiation in the makeup of the gut microbiome between children and grown-ups [71, 72].

Gut microbiota in obesity

Alterations in the composition of gut microbial communities have been associated with excessive weight gain and inflammation in multiple studies (Table 1). This relationship has been demonstrated in experimental animal models and observational human research [73, 74]. The investigation into the microbial community residing in the intestines of individuals afflicted with obesity is an outcome of the belief that the collection of microorganisms in the GI tract could have a substantial impact on the initiation of the condition. The acquisition of evidence that initially backed the correlation between the microbiota residing in the intestinal tract and obesity was obtained via scientific investigations performed on mice devoid of any microorganisms. The transmission of intestinal microorganisms from traditionally bred mice to microorganism-free mice demonstrated that intestinal microorganisms can amplify the production of fatty tissue in the receiving organism, leading to heightened levels of fat content and insulin resistance in the Transplantation despite a reduction in food intake [13, 28, 75–77]. Additionally, 16 S rRNA gene sequencing has exposed a plausible association between obesity and the foremost two bacterial phyla, Bacteroidetes and Firmicutes. The intestinal microbial community of overweight mice experienced a 50% decrease in the presence of Bacteroidetes, coupled with a proportional increase in the prevalence of Firmicutes [78].

Turnbaugh et al. [79] demonstrated that obese mice had a higher ability for their microbiota to extract energy from their food. They further established that the Firmicutes/Bacteroidetes ratio rose noticeably in these animals [79]. Similar occurrences also occur in people; for instance, obese children's guts have higher Firmicutes and lower Bacteroidetes concentrations [80]. Research conducted on the Ukrainian population has revealed a fascinating correlation between the rise in BMI and the corresponding increase in the ratio of Firmicutes to Bacteroidetes [81]. Other research, however, has shown the opposite findings. According to Zhang et al. [82], There was no observable distinction between individuals with normal weight and those who were obese about the amount of Bacteroidetes.

A thorough investigation was conducted, employing the publicly accessible database of the intestinal program in the United States (U.S.), to scrutinize the gut microbiota of 1655 individuals in a state of optimal well-being and 898 individuals suffering from obesity. The findings of this research have divulged that those afflicted with obesity showcased a noticeably reduced proportion of Firmicutes/Bacteroidetes [83]. According to research by Depommier et al. [84], *Akkermansia muciniphila* has demonstrated the ability to enhance energy utilization and decrease the overall weight and mass of adipose tissue in experimental subjects suffering from obesity caused by a high-calorie diet. The identical groups showcased that *Akkermansia* amplified the insulin resistance, dyslipidemia, and integrity of the gut barrier in the mice [84]. They also applied these findings to people in an exploratory trial, where they discovered that adding *Akkermansia* to the diet reduced the indicators for liver malfunction and inflammation [85]. In an intriguing investigation of individuals of average weight who possessed varying amounts of visceral fat, researchers made a captivating discovery. They observed a remarkable connection between the buildup of visceral fat and a total of 16 distinct microbial species. This correlation was determined using quantitative computed tomography, while no such connection was found with BMI or waist circumference. Low levels of visceral fat were notably associated with the presence of *Bacteroides* species [86].

A longitudinal study on individuals who underwent laparoscopic sleeve gastrectomy (LSG) revealed a tenuous inverse association between visceral fat and a limited number of microbial species. Notably, *Eubacterium eligens* emerged as the most prominent microorganism in this context. Examining various creatures before and after the LSG process exhibited a substantial surge in certain species, such as *C. citroniae*, *C. hathewayi*, *C. symbiosum*, and other members of the *Clostridiales* family [87]. The significance of this lies in the fact that *Clostridiales* are widely acknowledged as "beneficial" microorganisms and are inversely linked with metabolic disorders [88].

Other research has connected obesity to the family Christensenellaceae, the genera *Akkermansia* spp., *Lactobacillus* spp., *Bifidobacteria* spp., and *Methanobacteriales*, among others. The family Christensenellaceae has been recently connected to the phenomenon of weight reduction, and it has been observed that there exists an inverse relationship between the prevalence of this particular family and the BMI of the host [89]. 60 research were examined in a recent comprehensive analysis of gut microbiota, and the most commonly linked phylum with obesity was found to be Proteobacteria [90]. The prospective prevalence of Firmicutes may potentially result in an augmented synthesis of metabolites originating from indigestible polysaccharides, thus rendering

Table 1 Association between gut microbiomes and obesity and obesity-related disorders

Condition	Sample	Conclusion	References
Obesity	• A total of 68 college students, whose ages range from 20 to 25 years old, were included in the study.	• Intestinal microbiota, LPS, SCFA, and BMI were generally correlated in young college students. • Results may deepen our understanding of the connection between obesity and GI disorders.	Song et al. [152]
Obesity/ metabolic diseases/ Diabetes	• A meta-analysis of 248 people's samples from a total of 955 samples	• A potential remedy choice for obesity, diabetes, and other metabolic ailments could be the altered gut flora, which might assist in enhancing the levels of glucose in the blood as well as insulin resistance.	Chen et al. [153]
Obesity	• This research involves 138 newborns between 3 to 52 weeks	• High concentrations of *Bacteroides fragilis* and low concentrations of *Staphylococcus* in the GI tracts of infants ranging from 3 weeks to 1 year of age have been observed to be linked to a heightened probability of developing obesity during subsequent phases of their lifespan.	Vael et al. [154]
Obesity	• Sixty-three participants from 18 to 45 years old participated in this 12-week research.	• Supplementing with synbiotics may help overweight and obese people with their body composition, antioxidant status, and gut microbial diversity.	Oraphruek et al. [155]
Obesity	• In the present investigation, the analysis of infant fecal samples obtained at the ages of 1, 6, and 12 months was carried out employing 16 S rRNA sequencing methodology.	• The early newborn fecal microbiome of butyrate-producing bacteria and fecal butyrate is related to elevated mother BMI. The ability to predict increased adiposity in later infancy may be aided by the overall microbial richness.	Gilley et al. [156]
Obesity	• In the present investigation, 169 individuals classified as obese were included, alongside 123 subjects with a healthy weight.	• Adipose tissue was more prevalent; dyslipidemia, insulin resistance, and an inflammatory phenotype were all present in participants with reduced bacterial richness.	Le Chatelier et al. [157]
Obesity	• In this cross-sectional study, 45 kids (6 to 12 years old) were included. • Shotgun metagenomics was used for microbial analysis.	• Gut microbiome composition changes in obesity and metabolic disorders. • Microbial interactions contribute to metabolic changes in childhood.	Murga et al. [158]
Obesity	• In the KOALA Birth Cohort Study, a total of 909 infants who were one month old and presented with obesity were closely monitored for a period spanning from their first to their tenth year of life.	• The *B. fragilis* group of intestinal microbiota has a specific connection to the progression of childhood weight.	Scheepers et al. [73]
Obesity	• In this obesity study, 84 kids between the ages of 3 and 11 included 30 obese, 24 overweight, and 30 lean kids.	• The study demonstrates notable differences in the intestinal microbial ecosystems of obese and lean children, highlighting a significant correlation between BMI and the abundance of *Lactobacillus* spp. and the *B. fragilis* group. • Increasing the levels of *Lactobacillus* species and *B. fragilis* in individuals with obesity and excess weight.	Ignacio et al. [159]
Obesity	• Twenty children, ranging from nine to 11 years old, were present. • The study included 10 overweight children and 10 healthy-weight children.	• Increasing the levels of *Provotella spp.*, *Megamonas spp in obese group* • Increasing the levels of *Ruminococcus* spp. in a cohort of individuals with an average body weight. • Obese children exhibit alterations in the composition of microorganisms residing in their digestive systems compared to children who maintain a healthy weight.	Maya-Lucas et al. [74]
Obesity	• A randomized assignment was made to a cohort of 55 male and 124 female individuals, all possessing a BMI greater than 25 kg/m2, whereby they were divided into two groups. • One team was provided with a nourishment containing a moderate amount of protein (MHP), while the other received a diet consisting of a low amount of fat (LF).	• The composition of the GI microbiota and its functional characteristics exhibit variations in weight loss that are influenced by an individual's gender and dietary habits. • This implies that individuals of different sexes may exhibit varying levels of vulnerability to the advantageous effects of diets that are moderately high in protein and low in fat.	Cuevas-Sierra et al. [160]
Obesity	• In this particular investigation, nine male college students classified as obese, nine classified as overweight or lean, and ten classified as having an average weight were included as subjects.	• The proportion of Firmicutes to Bacteroidetes exhibited uniformity across the three groups. • Microbial diversity and BMI had a negative correlation.	Lv et al. [161]

Table 1 (continued)

Condition	Sample	Conclusion	References
Diabetes mellitus	• A total of 74 participants in the control group and 71 individuals with type 2 diabetes were included in this study.	• Decrease the levels of *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Clostridiales sp. SS3/4*, *Roseburia inulinivorans*, *and Roseburia intestinalis.* • Increasing the levels of opportunistic microorganisms, including *Bacteroides caccae Clostridium hathewayi*, *Clostridium symbiosum*, *Clostridium ramosum*, *Escherichia coli*, and *Eggerthella lenta*. • Butyrate-producing bacteria were reduced in type 2 diabetics.	Qin et al. [122]
type 2 diabetes/ Obesity	• Adult individuals experiencing excessive weight or obesity are placed on a 6-week weight-stabilization diet ($N=49$, including 41 women).	• In individuals who are overweight or obese, *A. muciniphila* is associated with improved clinical outcomes and a healthier metabolic state following calorie restriction.	Dao et al. [162]
Obesity	• QIIME was used to process data from nine studies derived from HFD-induced obese animal models.	• There was no observable discrepancy in the ratio of Firmicutes to Bacteroidetes or in alpha diversity when comparing animals with higher and lower adiposity. • *Oscillospira*, *Dorea*, and *Ruminococcus*, which are known for their ability to ferment polysaccharides into SCFAs, were found to be more prevalent in obese rats. • Increased inflammation in the obese condition is linked with decreased *Turicibacter* and increased *Lactococcus*.	Jiao et al. [163]
Obesity	• Forty-seven experiments involving 1,916 individuals were conducted, with 81% of the participants identifying as female. The median duration of observation was six months, with a range of 2 to 24 months.	• According to the study's findings, greater gut microbial diversity and reduced intestinal permeability are positively correlated with increased weight loss.	Koutoukidis et al. [164]

the host more vulnerable to an elevated degree of energy assimilation and consequent weight augmentation [80, 91–93]. Nevertheless, not all investigations about human obesity have reproduced this ratio between Firmicutes and Bacteroidetes [94, 95].

Alterations in the makeup of the GI microbiota possess the capacity to trigger the relocation of lipopolysaccharide (LPS), which subsequently leads to the emergence of a mild form of inflammation within the host organism [80, 92, 96]. LPS is present within the cellular membranes of bacteria that fall under the gram-negative category. Most of these bacteria are primarily categorized in the phylum Proteobacteria, in addition to the genera *Prevotella* spp. and *Bacteroides* spp. The inflammatory response is induced by LPS by using the stimulation of toll-like receptor 4 (TLR)-4, which is found in neutrophils, dendritic cells, and macrophages [97, 98]. Modifications in the transmission of TLR-4 incite the stimulation of supplementary pathways positioned more distally, encompassing the nuclear factor-κB and TNF-α and proinflammatory cytokines like interleukin IL-1, IL-6, and IL-8. Consequently, this perpetuates the sequence of heightened inflammation, thereby giving rise to insulin resistance. A direct link has been identified between the intake of a diet that contains a substantial amount of fat and an increase in the concentrations of plasma LPS [29]. The presence of increased systemic concentrations of LPS contributes to the enhancement of the permeability of the intestines through the inhibition of the production of tight junction proteins. The translocation of LPS and the development of endotoxemia arise due to this subsequent event [97–100]. The role of intestinal alkaline phosphatase is of utmost importance in the detoxification process of LPS. In the case of rats with a genetic predisposition to obesity and were furnished with a diet abundant in fats, a distinct escalation in the activation of TLR-4 was noted, thereby establishing a potential association with a decline in the levels of intestinal alkaline phosphatase [99].

The gut microbiome influences the endocannabinoid system's communication with adipose tissue via activating endothelial CB1 receptors [101]. Increased activity of the endocannabinoid system has been associated with gut dysbiosis related to obesity in mice models. The dysbiosis impacts two proteins, namely occludin and Zonula occludens (ZO)-1, that connect to the heightened levels of LPS as well as the permeability of the gut [101]. Moreover, these pathways additionally induce systemic inflammation, microbial molecular translocation, and augmented permeability of the intestines. Comparably, the occurrence of saturated fatty acids in dietary regimes that foster obesity results in an escalation of intestinal permeability, enabling the manifestation and stimulation of inborn immune receptors, along with the migration and proliferation of lymphocytes [102, 103].

Modifications in the gut microbiome can elicit alterations in generating significant compounds from bacteria and the host. These compounds include SCFA, which is the result of the fermentation process, as well as indole-3-carboxylic acid and tryptophan metabolites. Moreover, modifications in the GI microbiome have the potential to result in the production of 10-oxo-12-ocadecenoic acid.

This compound is formed from lactate, as well as bile acids, which act as regulators of thermogenesis. These molecular entities have been associated with obesity and metabolism [104–107]. The progression of NAFLD is heavily influenced by changes in the microbial population within the GI tract [108]. The gut tract is likewise a significant bodily organ in the progression of metabolic syndrome [109]. According to the research outcomes, the impact of microorganisms on obesity exhibits variation based on the particular strain, as there exist both beneficial and risky bacteria within the identical taxonomic classification. Classifying bacterial populations that are related to obesity based on taxonomic connections proves to be a challenging task. Including the term "guild" in the analysis of GI microbiota has introduced a means of identifying potential clusters linked to specific disease phenotypes and pinpointing gut microorganisms that could potentially impact human health. A guild is an assemblage of microorganisms that engage in resource-sharing or execute identical biological processes [68, 110–112].

Next, we will discuss the role of exploring the link between obesity, insulin resistance, and gut microbiome in metabolic dysfunction.

Link between obesity, insulin resistance, and gut microbiome

Global obesity rates are unavoidably causing the prevalence of Type 2 Diabetes Mellitus (T2DM) to rise. This chronic and rapidly expanding disease is caused by the body either not producing enough insulin or not using the insulin that is produced efficiently, with hyperglycemia—an elevated blood glucose level—being the primary symptom. It is one of the fastest-growing worldwide health emergencies of this century [113]. Regardless of its forms, the sharp rise in diabetes mellitus, which affects about 10.5% of the global population, is partly caused by the fast growth in obesity prevalence. The incidence of diabetes mellitus in young people is also sharply rising [113–115]. T2DM, which is primarily caused by relative insulin shortage due to pancreatic β-cell failure and insulin resistance, accounts for over 90% of diabetes mellitus globally and is closely linked to overweight and obesity, aging, ethnicity, and family history [113]. There are about 366 million individuals living with diabetes mellitus worldwide, including over 23 million Americans. By 2030, this population will reach 552 million [116, 117].

Numerous research has connected T2DM with gut microbiome [118]. Through the utilization of LEfSe analysis, it was ascertained by researchers that a noteworthy distinction existed between Chinese individuals afflicted with T2DM and their healthy counterparts. Specifically, it was revealed that 43 bacterial taxa, including *Acidaminococcales*, *Bacteroides plebeius*, and *Phascolarctobacterium* sp., exhibited substantial dissimilarities. Moreover, CAG207 is a potential candidate for T2DM biomarkers [119]. Horne and colleagues [120] discovered that the intestinal microbes in Syrian hamsters may undergo a possible modification due to a high-fat and high-sugar diet, resulting in hepatomegaly and dyslipidemia. A positive association was identified between *Tyzzerella* and *Ruminococceace* NK4A214 group about fasting triglyceride levels, while *Tyzzerella* and *Rumiclostridium* 9 exhibited a positive association with fasting cholesterol levels [120].

To date, extensive proof of an imbalance in gut microorganisms has been uncovered in individuals with T2DM. Previous studies revealed that Chinese T2DM patients have a somewhat dysregulated gut microbiome [121, 122]. Patients diagnosed with T2DM displayed elevated quantities of specific detrimental microorganisms, namely *Escherichia coli*, *Clostridium symbiosum*, and *Clostridium hathewayi*, in contrast to their healthy counterparts, who possessed heightened amounts of bacteria capable of producing butyrate. Another research study validated the observation that women in Europe who have T2DM exhibit an elevated prevalence of four specific *Lactobacillus* species while simultaneously experiencing a decreased prevalence of five distinct *Clostridium* species in comparison to individuals with regular glucose tolerance [123].

Significantly, a noteworthy association was identified between glycosylated hemoglobin (HbA1c) and the levels of fasting glucose with the presence of *Lactobacillus* spp. HbA1c, fasting glucose, and plasma triglycerides were found to have a negative correlation with the presence of *Clostridium* species. The findings of this research suggest a conceivable connection between these specific groups of bacteria and the advancement of T2DM. Similar to this, patients who were recently diagnosed with T2DM exhibited significantly elevated quantities of *Lactobacillus* while simultaneously displaying markedly diminished quantities of *Clostridium leptum* and *Clostridium coccoides* [124].

Shih et al. [125], the examination of the intestinal microorganisms in individuals diagnosed with refractory T2DM (RT2D), in whom the level of HbA1c continued to increase by a minimum of 8% following treatment, deserves attention. *Veillonella denticariosi* and *Bacteroides vulgatus* were more prevalent in RT2D patients than in T2DM controls, but *Fusobacterium* and *Akkermansia muciniphila* were less prevalent. HbA1c negatively correlated with the relative levels of *A. muciniphila* among them [125]. Moreover, research has revealed that the abundance of distinct bacterial taxa within the GI microbiota can influence how glucose is metabolized. The research conducted by Larsen and his colleagues has established a favorable association between

blood glucose levels and two important ratios, namely the Firmicutes *to* Bacteroidetes ratio and the *Bacteroides Prevotella*/*Clostridium coccoides-Eubacterium* ratio [126]. Kovatcheva-Datchary and colleagues [127] revealed that after consuming a fiber-rich diet for three days, a high *Provetella*/*Bacteroides* ratio is linked to an improved response to postprandial glucose metabolism. A person with prediabetes is more likely to develop T2DM because their blood sugar levels are higher than usual but below the threshold for diabetes [128]. It's intriguing that prediabetics also have abnormal gut microbiota [129, 130]. The diminished prevalence of the *A. muciniphila* species and *Clostridium* genus stands out as the most noteworthy attribute of the intestinal microorganisms in Danish individuals with prediabetes, in contrast to those with regular glucose regulation [131].

Zhong et al. [132], there existed no identifiable disparity in the microbial gene-based diversity among individuals of Chinese descent who were afflicted with treatment-resistant T2DM and prediabetes and those who had a normal glucose tolerance. In contrast to individuals with normal glucose tolerance, prediabetic subjects displayed a reduced occurrence of metagenomic linkage groups (MLGs) derived from the *Faecalibacterium prausnitzii* class and *Clostridia*. Conversely, there was an increased abundance of such MLGs in prediabetics originating from *Streptococcus salivarius*, *Eggerthella* sp, and *Escherichia coli* [132].

Animal models such as felines, rodents, and zebrafish have regularly demonstrated a strong connection between T2DM and intestinal microbiome [133–135]. The genera *Blautia*, *Roseburia*, *Allobaculum*, *Prevotella* 1, and *Prevotella* 9 experienced a significant augmentation in their prevalence among the Goto-Kakizaki rats, which function as a genetic prototype for T2DM and were created using repetitive inbreeding of Wistar rats when compared to the conventional Wistar rats [136]. By manipulating the levels of *Bacteroides* spp., *Helicobacter* spp., *Prevotella* spp., and *Ruminococcus* spp. in mice that were administered a high-fat diet (HFD) and the antibiotic streptozotocin (STZ), the active compound genistein, belonging to the isoflavone family, demonstrated a reduction in insulin resistance and inflammation responses. The aforementioned implies that the intestinal microbiome exhibits potential as a prospective domain of focus for the management and therapy of T2DM [137]. Additionally, diabetic cats have lower levels of many butyrate-producing bacterial taxa, including *Dialister*, *Anaerotruncus*, and an unidentified *Ruminococcaceae*, than lean, healthy cats. Furthermore, in diabetic cats, there was a connection between the intestinal microbiota and particular clinical characteristics [133].

Next, we will discuss the role of the gut microbiome in the complications of diabetes and diabetes-related diseases.

Gut microbiome and diabetic complications

Several diabetic diseases, including diabetic nephropathy, diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN), and diabetes-induced cognitive impairment (DCI), are notable for having strong relationships with the gut microbiota [138–141]. One of the customary microcirculatory complications linked with diabetes mellitus is DN, a condition that advances to the ultimate stage of renal insufficiency. Previous research has demonstrated a distinct variation in the makeup of gut bacteria in people with DN, those with T2DM but without kidney dysfunction, and those in a state of optimal health [142–144]. The genera *Prevotella* 9 and *Escherichia-Shigella* spp. were discovered to successfully differentiate between patients diagnosed with DN and individuals diagnosed with T2DM but without any renal affliction. Additionally, the *Prevotella 9* genera were able to reliably distinguish between those with T2DM without renal illness and healthy controls. Furthermore, it was noted that individuals diagnosed with stage IV DN demonstrated elevated quantities of *Lachnospiraceae*_UCG-004 and *Haemophilus* compared to those with stage III DN. This discovery provides supplementary proof to fortify the notion that the GI microbial assemblage assumes an influential role in the progression of DN [145].

Further investigation has confirmed that the dysregulated microbiota in the GI tract, through the activation of G protein-coupled receptor 43 (GPR43), hampers the functioning of adenosine 5'-monophosphate-activated protein kinase (AMPK), thereby serving as the primary factor underlying the impaired response to insulin and subsequent harm to the kidney and podocyte [146]. The amelioration of glomerular impairment in diabetic rats can be accomplished by FMT or by depleting the gut microbiota using broad-spectrum antibiotics. The significant participation of the GI microbiome in the advancement of DN is emphasized [147–149]. Diabetes increases the risk of dementia in older diabetes individuals and predisposes people to cognitive impairment. The study of DCI's pathogenesis is still in its early stages, though. Patients who have cognitive impairment exhibited a unique configuration of gut microbiota when compared to T2DM patients who possess normal cognitive abilities. The special arrangement of this composition is distinguished by a lowered occurrence of *Tenericutes*, *Bifidobacterium* spp., and unrank-RF39, in addition to an increased event of unrank-*Leuconostocaceae* and *Peptococcus* [141, 150, 151].

These discoveries indicate a significant function of gut bacteria in diabetic complications. However, more

research must be done on the molecular mechanisms that underlie them.

Microbiota obesity and bile acids (BA)

The intestinal microbiota plays a significant role in the metabolism of BA by facilitating deconjugation and dehydroxylation processes within the intestinal lumen [165, 166]. The conversion of primary BA into their secondary forms involves the transformation of cholate into deoxycholate and the conversion of chenodeoxycholate into lithocholate. This phenomenon can be attributed to the presence of bile salt hydrolase enzymes, which are predominantly found within the phyla Firmicutes and Bacteroidetes, particularly in the Clostridium clusters [167].

Conversely, in the enterocytes of the colon, the BA designated for reabsorption interacts with the farnesoid X receptors. This process promotes the synthesis of fibroblast growth factor-19 (FGF19) while simultaneously reducing the hepatic production of BA. Furthermore, these BA activate the G protein-coupled bile acid receptor (TGR5) located on the plasma membrane, leading to an increase in the production of glucagon-like peptide-1 (GLP-1). This hormone regulates glucose homeostasis and energy metabolism and the synthesis, conjugation, and transport of BA [166, 168, 169]. Alterations in the enzymatic activity of the microbiota can lead to changes in the composition of BA, which in turn enhances fat absorption and contributes to the development of obesity [170]. This finding was supported by a recent investigation involving 183 participants with elevated BMI, comprising 121 individuals classified as metabolically healthy and 62 as metabolically unhealthy. The results indicated that the metabolically unhealthy obese individuals exhibited a significantly lower ratio of secondary BA in comparison to primary BA (odds ratio (OR) 1.129, 95% confidence interval (CI): 1.083–1.176, $P<0.01$). Furthermore, the altered composition of BA emerged as a predictive factor for metabolically healthy individuals with high BMI, demonstrating an area under the curve (AUC) of 0.87 (95% CI: 0.82–0.93, $P<0.01$), with a cut-off value of 66.1, sensitivity of 78.5%, and specificity of 91.9%. These findings suggest that variations in BA composition may play a role in the differing metabolic states associated with obesity [170].

Concurrently, a study was undertaken involving rodents to examine alterations in BA metabolism and its correlation with the gut microbiota. In this study, the cohort of rodents subjected to HFDs was categorized into two distinct groups: one that exhibited a predisposition to obesity and another that demonstrated resistance to obesity [170]. The analysis revealed that the microbiota composition remained relatively stable across both groups. Nonetheless, there was a notable abundance of the genera *Clostridium scindens* and *Clostridium hylemonae* in rodents predisposed to obesity. These bacteria possess a significant capacity for bioconversion, which alters BA metabolism and contributes to the development of obesity. This assertion is further supported by observations in the same cohort of rodents, which indicated a reduction in secondary bile acids alongside an increase in primary BA [165, 170].

Metabolites associated with gut microbiome

SCFAs

The intestinal microbiota can produce a substantial quantity of energy and essential nutrients for the organism through the action of anaerobic microorganisms that decompose indigestible carbohydrates in the cecum [171]. Additionally, vitamins, amino acids, and SCFAs (fatty acids with six or fewer carbons) such as isobutyric acid, acetic acid, formic acid, propionic acid, isovaleric acid, valeric acid, and butyric acid are produced during these fermentation processes [12]. Propionate, acetate, and butyrate are the SCFAs that are most common in the intestines [172, 173]. *Faecalibacterium prausnitzii* is commonly recognized as a crucial source of butyrate, while *Bacteroides thetaiotaomicron* is predominantly responsible for acetate production [12].

Obesity and metabolic diseases can be associated with the rise in plasma SCFA concentration and the corresponding decline in feces. Additionally, SCFAs can stimulate lipogenesis and boost triglyceride storage by activating the sterol regulatory element-binding transcription factor-1 (SREBP1) and the carbohydrate-responsive element-binding protein (CHREBP) through a biochemical route. By lowering the synthesis of the fasting-induced adipocyte factor (FIAF), which causes triglycerides to accumulate in adipocytes, they can also lessen the lipoprotein lipase activity [92, 174, 175]. Upon the creation of SCFAs by bacteria, they are absorbed into the bloodstream and attach themselves to G protein-coupled receptors (GPCRs). These GPCRs are integral to various cellular signaling pathways, including those related to GI inflammation, lipid and glucose metabolism, cholesterol metabolism, and neurogenesis [171, 176].

Early studies into the mechanisms of action found that the GPR41 (FFAR3) and GPR43 (FFAR2) receptors are the primary binding sites for SCFAs produced by the GI microbiota. This binding allows SCFAs to start specific cellular signal cascades. The following acute event enhances the L cells' ability to make glucagon-like peptide-1 (GLP-1). These results add to the growing body of information that suggests that regulation of host adiposity and glucose tolerance can be regulated not only by the interaction between GPCRs and SCFAs but also by the dual signaling properties of GPR43 through the Gq and

Gi pathways. In contrast, GPR41 transmits signals via the Gi pathway [177–179].

Intestinal epithelial cells possess the ability to support immune suppression and uphold intestinal balance by releasing IL-18, which is triggered by the engagement of butyric acid with GPR109A. Furthermore, butyric acid demonstrates anti-inflammatory characteristics and serves as an inhibitor of histone deacetylases (HDACs) [180]. De Vadder and colleagues [181] made an important discovery when they identified that butyrate and propionate, produced during the breakdown of soluble fiber by gut microbiota, could promote the activation of genes linked to intestinal gluconeogenesis. This activation can occur through a mechanism reliant on the second messenger cyclic adenosine monophosphate (cAMP) or through a neural pathway that connects the gut and the brain, involving the fatty acid receptor 3 (FFAR3). Furthermore, the acetate that originates from the microbiota acts as a forerunner for synthesizing lipogenic fatty acids and Acetyl-CoA, thereby playing a role in de novo lipogenesis (DNL) occurring in the liver. The ever-increasing prevalence of NAFLD and obesity can be ascribed to the excessive generation of acetate [182–185].

Zou et al. [186] discovered that the metabolic syndrome, triggered by a diet rich in fats, was remarkably ameliorated through the restoration of enterocyte function orchestrated by the microbiota, with the indispensable aid of IL-22. Furthermore, the binding of SCFAs, ingeniously generated by the microbiota and obtained from dietary fiber, to free fatty acid receptors played a pivotal role in this harmonious alleviation.

In clinical studies, individuals with NAFLD had higher abundances of the phylum Bacteroidetes and lower quantities of the SCFA-producing and 7-dehydroxylating Firmicutes [187, 188]. By secreting glucagon-like peptide-1, peptide YY, and other intestinal hormones, acetate can have positive effects on the host's energy metabolism. It can also lower systemic lipolysis and proinflammatory cytokine levels, boost lipid oxidation, and improve energy consumption [189]. Using the AMPK/LSD1 pathway, propionate promotes intestinal lipolysis and maintains energy balance in mice [190]. The primary energy source for the colon is butyrate, which is oxidized to provide most of the energy needed by intestinal epithelial cells. The gut microbiota's increased butyrate-producing bacteria improve lipid metabolism by creating more butyrate through the butyrate-SESN2/CRTC2 pathway [191].

Indole derivatives

Certain symbiotic microorganisms, such as *Lactobacillus* spp., *Escherichia coli*, and *Bacteroides* spp., produce indole and its derivatives, enabling inter-species bacterial communication and fostering symbiotic contact between the organisms and the host [192]. The enzyme tryptophanase, derived from bacteria, is crucial in producing indole and its related substances. This particular enzyme facilitates the conversion of tryptophan, obtained from the diet, into indole and its various derivatives. Familiar sources of food, such as oats, milk, cheese, chicken, and fish, are known to contain the crucial amino acid tryptophan [193]. Indole metabolites often achieve high concentrations of one-thousandth of a mole in the GI system and have the potential to elevate to 200 millionths of a mole in bodily tissues, blood, and urine after being assimilated by the host or released into the excrement. Indole undergoes hepatic metabolism via CYP2E1, resulting in the formation of 3-indoxyl sulfate (3-IS), which is subsequently eliminated through renal excretion. The presence of low levels of 3-IS in the urine serves as an indicator of dysbiosis [194, 195].

Additionally, indole, along with its various compounds, including indole-3-aldehyde (I3A), indole-3-lactic acid (ILA), indole-3-propionic acid (IPA), and indole-3-acetic acid (IAA), possess the ability to function as ligands, binding to aryl hydrocarbon receptors (AhRs). These AhRs function as vital transcription factors, assuming pivotal responsibilities in safeguarding and mitigating inflammation, notably through regulating natural lymphoids and IL-22 within the GI tract [104, 193, 196].

According to preclinical and clinical research, the potential ability of the microbiota to convert tryptophan into AhR agonists could potentially assume an influential function in the progression of metabolic syndrome [197–199]. The inactivation of the AhR pathway led to a reduction in the generation of IL-22 and GLP-1 due to the heightened permeability of the intestines and the movement of LPS. Consequently, this led to insulin resistance and liver steatosis [200]. When individuals are administered AhR agonists or *Lactobacillus reuteri*, a naturally occurring producer of AhR ligands, the incretin hormone GLP-1 is released. This hormone can treat metabolic conditions, including low-grade inflammation and impaired intestinal barriers. As a result of this release, there is an enhancement in the functionality of the intestinal wall [197]. Indole has been demonstrated to reduce liver inflammation and stop mice's aberrant cholesterol metabolism caused by LPS [201].

Natividad and colleagues [197], along with Mallmann and colleagues [202], Pharmaceutical and genetic methodologies that inhibit the activity of rate-limiting enzyme function within the kynurenine (Kyn) pathway, as well as the indoleamine 2,3-dioxygenase (IDO), have the potential to mitigate the effects of obesity and the resulting metabolic disruptions induced by a HFD [203]. Further investigation uncovered that the deactivation of IDO initiated by the combination of AhR agonists was the origin of this inhibitory mechanism [105, 204]. In addition, excessive stimulation of IDO has also been linked to

declines in the amount of tryptophan in the bloodstream and elevations in the levels of different compounds, such as 3-hydroxy anthranilic acid, kynurenic acid, 3-hydroxynurenine, and xanthurenic acid [205]. Another tryptophan metabolite, serotonin (5-HT), which influences appetite and fullness, is also used to treat obesity [206]. The observations were substantiated by empirical evidence from human subjects, which indicated that individuals suffering from metabolic disturbances displayed higher levels of the end product of serotonin metabolism, namely 5-hydroxyindole-3-acetic acid, in comparison to those individuals without any metabolic disorders [207, 208].

Therapeutic microbiomes and their role in obesity

Probiotics

Probiotics are "live microorganisms that, when administered in sufficient amounts, confer a health benefit on the host." Studies have established a correlation between probiotics and a reduction in body weight for humans and animals (Tables 2 and 3) [209]. Probiotics are frequently made from beneficial bacteria, including *Lactobacillus* spp., *Bifidobacterium* spp., and *Streptococcus* spp [210]. Another popular probiotic used to prevent antibiotic-related diarrhea is *Saccharomyces boulardii* [211].

Probiotics work their magic on obesity by skillfully managing the delicate balance of microorganisms in the gut, mitigation of insulin resistance, and the enhancement of the perception of satiety [212, 213]. Moreover, the inclusion of probiotics leads to an increase in the number of advantageous microorganisms accountable for the synthesis of SCFAs, all the while reducing the population of harmful organisms responsible for generating LPS [214]. Several studies have shown that probiotics can reduce BMI and decrease overall body fat, with a particular emphasis on visceral fat [215]. *Bifidobacterium* and *Lactobacillus* have been utilized in animal models of obesity owing to their remarkable antibiotic resistance and minimal pathogenicity. Numerous investigations have provided evidence that these particular organisms possess the ability to cause significant decreases in body mass and the build-up of fatty tissue as a result of their formidable resistance to antibiotics and minimal pathogenic properties [216, 217].

Probiotics inclusive of *Lactobacillus* strains demonstrated notable efficacy in diminishing adipose tissue mass while concurrently augmenting lipid dispersion and regulating blood glucose equilibrium in obese mice. These outcomes were attained by stimulating the process of fatty acid oxidation or by inhibiting the activity of lipoprotein lipase [218]. Certain varieties of Lactobacillus have undergone investigation on the human population. For instance, during the earlier stages of life and the initial phase of excessive weight accumulation, the ability to manage a child's weight gain was made possible by using the probiotic *L. rhamnosus*. However, this effect was not witnessed during later stages of development in comparison to children who were subjected to an inactive substance [217]. *Lactobacillus acidophilus* increased insulin sensitivity in diabetics, according to a randomized control experiment [219]. This result could be attributable to *Lactobacillus acidophilus's* interaction with immune cells, which includes lowering LPS levels, activating TLRs, and producing cytokines [219]. Over 12 weeks, probiotics of diverse strains, including BNR17 species and *Lactobacillus gasseri* SBT2055, were administered to obese individuals. The investigation findings unveiled that the cohort subjected to *L. gasseri* SBT2055 experienced a decline in their overall mass and abdominal adiposity. Conversely, the group receiving *L. gasseri* BNR17 did not demonstrate similar effects [220, 221]. Additionally, considerable weight reduction was observed after using *Aspergillus flavus* CECT7765 in obese kids with insulin resistance [222].

Table 2 Recent animal studies on the role of probiotics, prebiotics, and synbiotics in obesity

Methods Used	Conclusion	Study subjects	References
• For a duration of 12 weeks, the mice in the obesity model were administered *Bifidobacterium lactis* 420 daily, along with a HFD. • For four weeks, mice in the diabetes model were given a high-fat diet, followed by six weeks of treatment with *B. lactis*.	• In obese and diabetic mice, *B. lactis* 420 reduces fat mass and improves glucose intolerance. • Plasma LPS levels and decreased intestinal mucosal adhesion suggest a mechanism involving reduced gut microbial translocation.	Mice	Stenman et al. [253]
• C57BL6/J mice were fed various diets for a duration of 12 weeks. • The mice were gavaged daily with either probiotic strains or a vehicle control.	• The effectiveness of probiotics is influenced by HFD. • Diet influences the reproducibility of preclinical probiotic studies.	Mice	Larsen et al. [254]
N/A	• *L. acidophilus* may be a promising candidate for probiotics in mitigating obesity and related conditions, including nonalcoholic fatty liver disease, hyperlipidemia, and insulin resistance. This potential is attributed to its anti-inflammatory properties, as well as its ability to alleviate gut dysbiosis and endothelial dysfunction.	Porcine	Kang et al. [255]

Table 3 Recent human studies on the role of probiotics, prebiotics, and synbiotics in obesity

Methods Used	Conclusion	Study subjects	References
N/A	• Probiotics possess anti-inflammatory properties and may aid in the prevention and improvement of obesity-related chronic inflammation.	Human	Tang et al. [256]
N/A	• Probiotics have emerged as a promising therapeutic approach for managing and mitigating obesity by modulating GI microbiota.	Human	Schütz et al. [257]
N/A	• Probiotics, prebiotics, and synbiotics may help prevent weight gain.	Human	Aoun et al. [258]
N/A	• Probiotics demonstrate a significant improvement in cognitive impairment and anxiety related to obesity. • Probiotics positively influence immune regulation and glycolipid metabolism.	Human	Cai et al. [259]
Ninety-seven children, aged 7 to 18 years and classified as overweight or obese (with a BMI exceeding the 85th percentile), were randomly assigned to either a placebo group (administered maltodextrin) or an experimental group (administered oligofructose). The dosage for both groups varied according to age: 8 g/d for children aged 7 to 11 years and 15 g/d for those aged 12 to 18 years. This treatment lasted for a duration of 12 weeks.	• Used oligofructose-enriched inulin as a prebiotic instead of a placebo in children with overweight and obesity, but no improvement in BMI was seen.	Human (children)	Liber et al. [260]
N/A	• The prevention and treatment of obesity represent promising applications for next-generation probiotics. • Large-scale research and experiments are essential to explore their potential.	Human	Vallianou et al. [261]
• This interventional trial will involve 30 Human (obese) who will visit the obesity unit at the Tunis Institute of Nutrition between May and August 2022.	• Probiotics may have the potential to reduce weight in obesity.	Human	Ben et al. [262]
N/A	• Probiotics have the ability to reduce obesity induced by a HFD. • Altering the composition of the intestinal microbiota presents a promising approach for the management or prevention of obesity.	Human	Zhang et al. [236]
• Search and review in databases up until May 2020 • English-language meta-analyses of controlled studies evaluating the effects of probiotics.	• High-dose probiotics can enhance indicators of overweight and obesity. • Before prescribing, a thorough risk-benefit analysis should be conducted.	Human	Shirvani et al. [263]
• The individuals were allocated into two comparable cohorts regarding age, gender, and BMI: a group that solely followed a dietary regimen and a group that consumed probiotics (specifically, one tablet of Lactibiane per day). The glycemic indicators (including fasting blood glucose levels, HbA1c levels, fasting insulin levels, and the HOMA index, which quantifies insulin resistance) were evaluated at the start of the study (T0) and again one month after the implementation of the respective interventions (T1).	• Consuming probiotics helps individuals who are obese with their glycemic parameters.	Including 30 Human (obese)	Ben et al. [264]
• The literature search utilized the PubMed, EMBASE, and MEDLINE databases. • The search for publications was conducted over the period from January 2010 to December 2019.	• Changes in intestinal microbiota in individuals with obesity. • Probiotic supplementation may be beneficial for individuals who are overweight or obese.	Human	Wiciński et al. [265]
• From the inception of the database to the start of the inquiry, scholarly articles detailing the use of probiotics in pediatric and adolescent populations affected by overweight or obesity were retrieved from seven databases using specific search terms and medical subject headings.	• Previous research on children and adolescents suffering from overweight and obesity has revealed promising therapeutic outcomes of probiotics in terms of adiposity, BMI, inflammatory markers, metabolic parameters, fatty liver, transaminase levels, and glucose metabolism.	Human (children)	Loy et al. [266]

Table 3 (continued)

Methods Used	Conclusion	Study subjects	References
• Subjects with a BMI ranging from 24.2 to 30.7 kg/m^2 and an abdominal visceral fat area between 81.2 and 178.5 cm^2 were randomly selected to participate in a study. During the study, they were administered fermented milk (FM) infused with *Lactobacillus gasseri* SBT2055 (LG2055) for a duration of 12 weeks.	• The protective effects of *Lactobacillus gasseri* SBT2055 (LG2055), a probiotic strain, are demonstrated by its capacity to reduce body weight, abdominal fat, and other parameters associated with metabolic disorders.	Human	Kadooka et al. [220]
• A study was conducted involving 128 individuals with hypertriglyceridemia who did not have diabetes. This investigation followed a design that included randomization and a placebo-controlled methodology. • During a 12-week period, the group that received probiotics consumed a daily dosage of 2 g of a powdered supplement containing *L. curvatus* HY7601 and *L. plantarum* KY1032.	• The consumption of a combination of two probiotic strains over a 12-week period led to a reduction in triglyceride levels, an increase in apolipoprotein A-V (apo A-V) levels, and an increase in the size of LDL particles in individuals with hypertriglyceridemia. • The impact of this phenomenon was more pronounced among individuals with elevated fasting triglyceride levels, regardless of their APOA5 -1131T > C genotype.	Human	Ahn et al. [267]
• Forty-eight male participants were involved in the study, with twenty-four individuals diagnosed with T2DM, and the remaining twenty-four considered healthy.	• The *Lactobacillus acidophilus* NCFM group exhibited enhanced insulin sensitivity compared to the placebo group.	Human	Andreasen et al. [219]

Rajkumar et al. [223] found With the addition of omega-3 supplements and a high-dose combination of probiotics from the *Streptococcus*, *Lactobacillus*, and *Bifidobacterium* species, overweight people's gut microbiota composition, insulin sensitivity, plasma lipids, and inflammatory indicators significantly improved [223]. Additionally, the group that got the probiotic alone only showed a favorable shift in the gut flora, whereas the group that received the omega-3 alone did not see any change [223]. The introduction of Lactobacillus paracasei F19 to 120 infants between the ages of 4 and 13 months during the weaning process did not yield any significant impact on their physical makeup or cognitive growth by the time they reached school age [224]. In a different study, the effects of fermented traditional yak yogurt's probiotic lactic acid bacteria on obese rats on a HFD were evaluated. In simulated GI fluid, the results demonstrated that the *Lactobacillus plantarum* Lp3 strain could reduce the amount of cholesterol by 73.3%. *Lactobacillus plantarum* Lp3 exhibits promising potential as a viable probiotic in combating hyperlipidemia, owing to its notable capacity in effectively diminishing the triglyceride and cholesterol concentrations in both the bloodstream and hepatic tissues of rats subjected to a high-cholesterol regimen, concurrently lessening the extent of lipid accumulation within the liver [225].

An area of research highlights the role of probiotics in the in situ production of functional bioactive compounds, such as conjugated linoleic acid (CLA), which have demonstrated significant potential in managing metabolic disorders like obesity and diabetes [226–230]. CLA comprises a collection of isomers of fatty acids synthesized from linoleic acid. These compounds are recognized for their beneficial effects, including anti-adipogenic, antidiabetic, and anti-inflammatory properties [231–233]. Cis-9, trans-11 (c9, t11), and trans-10, cis-12 (t10, c12) are the three recognized isomers of CLA that are most frequently linked to antiobesity benefits [234]. A study by Dahiya et al. [226] demonstrated the anti-obesity potential of CLA-enriched skim milk prepared with the probiotic *Lactobacillus fermentum* DDHI27 (PCLA). Five groups of C57BL/6J mice were utilized in this study to examine various metrics associated with obesity. PCLA supplementation resulted in significant reductions in body weight and epididymal and mesenteric fat deposits, alongside improvements in lipid profiles, according to the findings. Furthermore, there were notable enhancements in hepatic steatosis, blood glucose, and leptin levels, accompanied by a decrease in adipocyte size. Molecular analyses also demonstrated favorable modulation of adipogenesis-related transcription factors and key lipogenesis genes. Importantly, PCLA supplementation corrected gut microbiota dysbiosis, a critical factor in the pathogenesis of obesity [226]. Another study by Lee et al. [227] investigated the probiotic effects of *Lactobacillus rhamnosus* PL60, a human-derived bacterium known for its ability to produce the t10, c12-isomer of CLA. Using a diet-induced obesity model in mice, this study demonstrated that *Lactobacillus rhamnosus* PL60 can reduce body weight without affecting energy intake, specifically by decreasing the mass of white adipose tissue (epididymal and perirenal fat). Interestingly, the anti-obesity effects of *Lactobacillus rhamnosus* PL60 were correlated with increased apoptotic signals and elevated UCP2 mRNA levels in adipose tissue, indicating enhanced fat metabolism and regulation. The study highlights the therapeutic potential of CLA-producing probiotics, especially those derived from human origin, in managing obesity by targeting adipose tissue metabolism [227].

Probiotics are also known for improving barrier and immunomodulatory function, as well as possessing antibacterial capabilities [235]. Probiotics can thus rapidly enter the human gut, speed the burning, breakdown, and transformation of fat, boost metabolism, and efficiently eliminate the stubborn fat in the abdominal region [236].

Prebiotics

Prebiotics are dietary constituents that cannot be digested and can potentially provide advantages to the host by deliberately fostering the growth or functioning of particular bacteria in the colon. This, in turn, may contribute to improving the overall well-being of the host [218, 237]. Prebiotics must also fulfill the following three criteria: (1) resistance to digestive enzymes, and gastric acid, bile; (2) capacity for inducing commensal gut microbiota development and, or activity; and (3) capacity for fermentation by gut microbiota [238]. In the future, these substances could be used to combat obesity (Tables 2 and 3). Typical examples include lactulose, inulin, fructo-oligosaccharides, and derivatives of galactose and β-glucans. The fructo-oligosaccharides, oligosaccharides (such as inulin), galacto-oligosaccharides, and polyphenols are among the prebiotics that are commonly found. These substances can be a probiotic substrate, potentially facilitating their proliferation [239]. The observation revealed that the fermentable carbohydrate inulin significantly augmented the cell density responsible for the production of the hormone PYY, which has the potential to inhibit hunger. This discovery implies that inulin could potentially contribute to the reduction of calorie intake and enhance the management of obesity [240]. Koutnikova et al. [241] discovered that supplementing with galactooligosaccharides raised *Bifidobacterium* spp. levels while lowering *Bacteroides* spp. levels in healthy people. The composition and operational characteristics of the GI microbiota can be modified by prebiotics. Bacteria capable of producing butyrate, such as *Bifidobacterium* spp., are cultivated to increase their population. This cultivation is carried out to improve metabolic outcomes and strengthen the intestinal barrier to protect against infections [241]. Prebiotics, in addition, have been associated with enhancements in metabolic indicators, including insulin resistance, as well as the reduction of weight in individuals [242, 243].

Synbiotics

Synbiotics are an amalgamation of prebiotics and probiotics, exhibiting a synergistic impact. Prebiotics and probiotics are both made more potent and efficient by the addition of synbiotics, thereby optimizing the health advantages they provide to the host organism [244, 245]. The main benefit of creating synbiotics is that it increases probiotics' ability to survive in the GI system [246, 247]. Synbiotics have a favorable influence on health by enhancing probiotic microbe viability and providing unique health benefits [248]. Synbiotics play a crucial role in regulating metabolic activity in the GI tract through the facilitation of microbiota growth, preservation of intestinal biostructure, and suppression of potential pathogens [249]. Synbiotics decrease the number of unfavorable metabolites in the GI system, such as cancer-causing agents and inactivation of nitrosamines. Furthermore, they elevate the quantities of SCFAs, methyl acetates, ketones, and carbon disulfides, potentially bestowing advantageous effects on the well-being of the host [250]. A comprehensive examination and synthesis conducted by Mohammadi and colleagues [251] revealed that the introduction of probiotics and synbiotics for a duration of 4 to 16 weeks did not yield any noticeable alterations in fasting blood glucose levels, waist circumference, BMI, adipose tissue content, or lipid profiles when comparing the pre-and post-administration period. Nevertheless, a detailed showed that supplementing with synbiotics significantly reduced BMI [251]. A novel synbiotic composition, which comprises inulin and five distinct strains of probiotics, namely *Clostridium beijerinckii*, *Clostridium butyricum*, *Akkermansia muciniphila*, *Anaerobutyricum hallii*, and *Bifidobacterium infantis* demonstrated enhanced regulation of glycemic control in individuals with T2DM in a meticulously conducted randomized placebo-controlled trial (Fig. 1) [252].

Fecal microbiota transplantation in obesity

In the People's Republic of China, there has been a practice among the populace whereby they have employed the method of human FMT as a means of addressing various afflictions [268]. FMT has demonstrated its efficacy in effectively treating GI infections, specifically those attributed to *Clostridium difficile* and other members of the *Clostridiales* order, while also ensuring a high level of security [269]. The process of taking in capsules, performing a colonoscopy, utilizing nasogastric/nasojejunal tubes, administering an enema, conducting a sigmoidoscopy, or using a rectal tube can be employed as methods to introduce fecal matter obtained from a healthy donor into the GI system of an individual whose gut microbiota has been altered [270]. After the implementation of FMT, the microbial strains originating from the donor are actively involved in establishing themselves within the GI microbiota of the recipient and persist for a minimum period of three months [271]. However, it is crucial to note that the compatibility between the donor and recipient is of utmost importance when effectively establishing microbial strains from the donor in the recipient's gut [271].

Although there is promise demonstrated by FMTs in the realm of metabolic disorders in animals, further

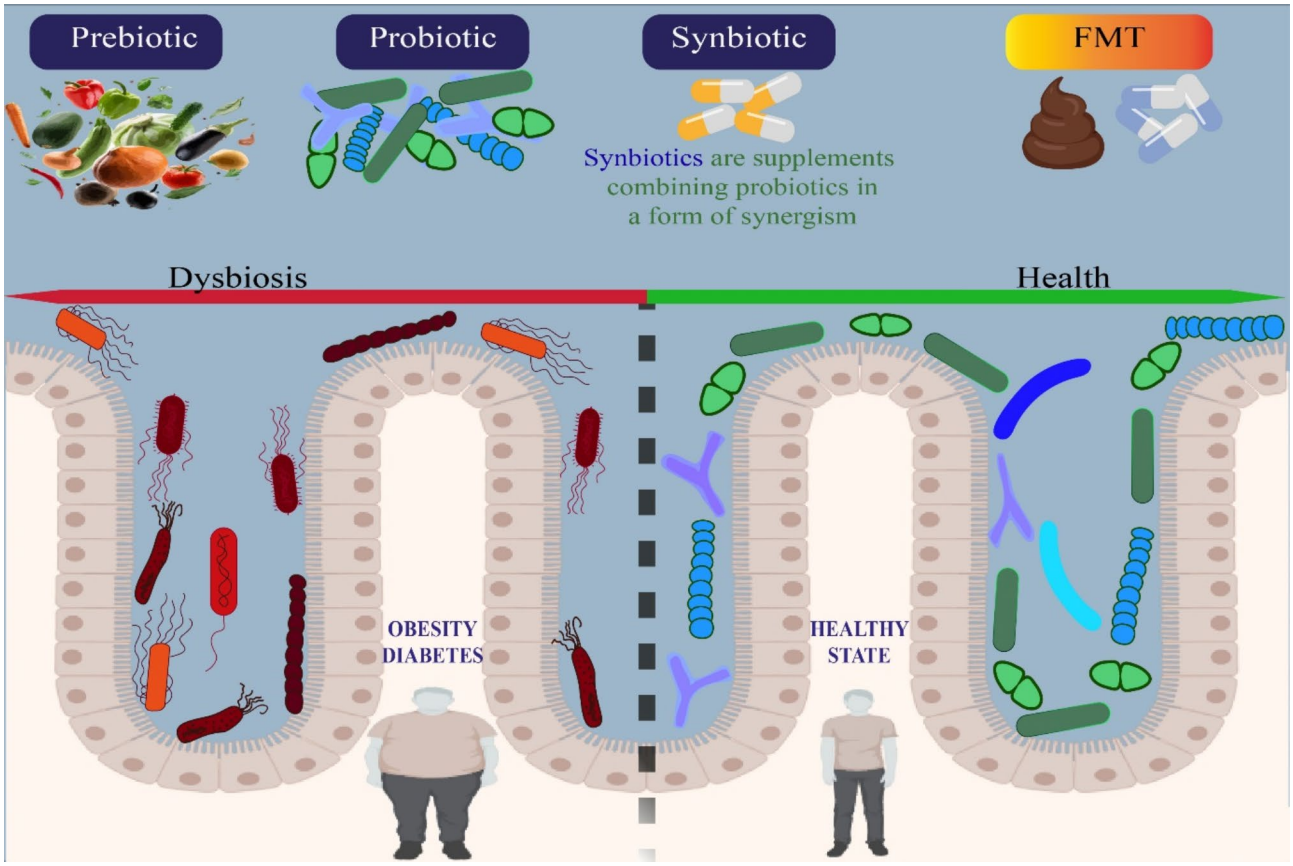


Fig. 1 An outline of the primary microbiome-based approaches that are either used or can be used to treat and prevent obesity

clinical trials are required to ascertain the effectiveness of this method for this specific indication [272]. Kootte et al. [273] documented that the administration of FMT therapy has led to a notable enhancement in the capability of individuals with metabolic syndrome to respond to insulin [273]. Allogenic FMT from lean donors failed to significantly improve clinically in two randomized control studies. However, the recipient microbiota in these experiments began to resemble the donor profile [274, 275]. In a human pilot investigation, enteral feeding tubes were used to delay enteral microflora transmission from malnourished human donors to receivers suffering from metabolic syndrome. Insulin sensitivity exhibited a notable enhancement in subjects diagnosed with metabolic syndrome six weeks following the initiation of FMT when contrasted with the individuals' insulin sensitivity levels before the commencement of FMT therapy [276].

The Gut Bugs Trial, a study conducted with randomization, double-masked methodology, and placebo control, had the objective of evaluating the effectiveness of FMT as a treatment for obesity and enhancement of metabolic function. The primary measure of interest was the variability in BMI at the six-week point following the FMT intervention [277]. A group of 87 teenagers, ranging in age from 14 to 18, who possessed a BMI below 30 kg/m2, actively took part in the study. These adolescent individuals underwent an administration of a singular treatment consisting of orally encapsulated fecal microbiota that was obtained from donors of the same biological sex. Alternatively, they were given a placebo of saline solution. A comprehensive follow-up was conducted at the 26-week mark. However, FMT reduced abdominal adiposity but did not influence insulin sensitivity, lipid profile, BMI, liver function, blood pressure, inflammatory markers, or gut health. The subjects experienced mild unfavorable effects, with loose stools being the most common occurrence, observed in 10% of individuals, but no significant adverse events were reported [277]. Of course, there are specific possible hazards associated with FMT, such as transmitting contagious diseases. No adverse effects have been observed despite occasional minor side effects, including fever and diarrhea [278]. In the figure below, treatment methods are mentioned to adjust the microbiome, reduce inflammation in the intestine, and fight obesity (Fig. 2).

Dietary and pharmacological interventions in gut microbiome modulation

Recent research has demonstrated that specific dietary patterns and pharmacological interventions can

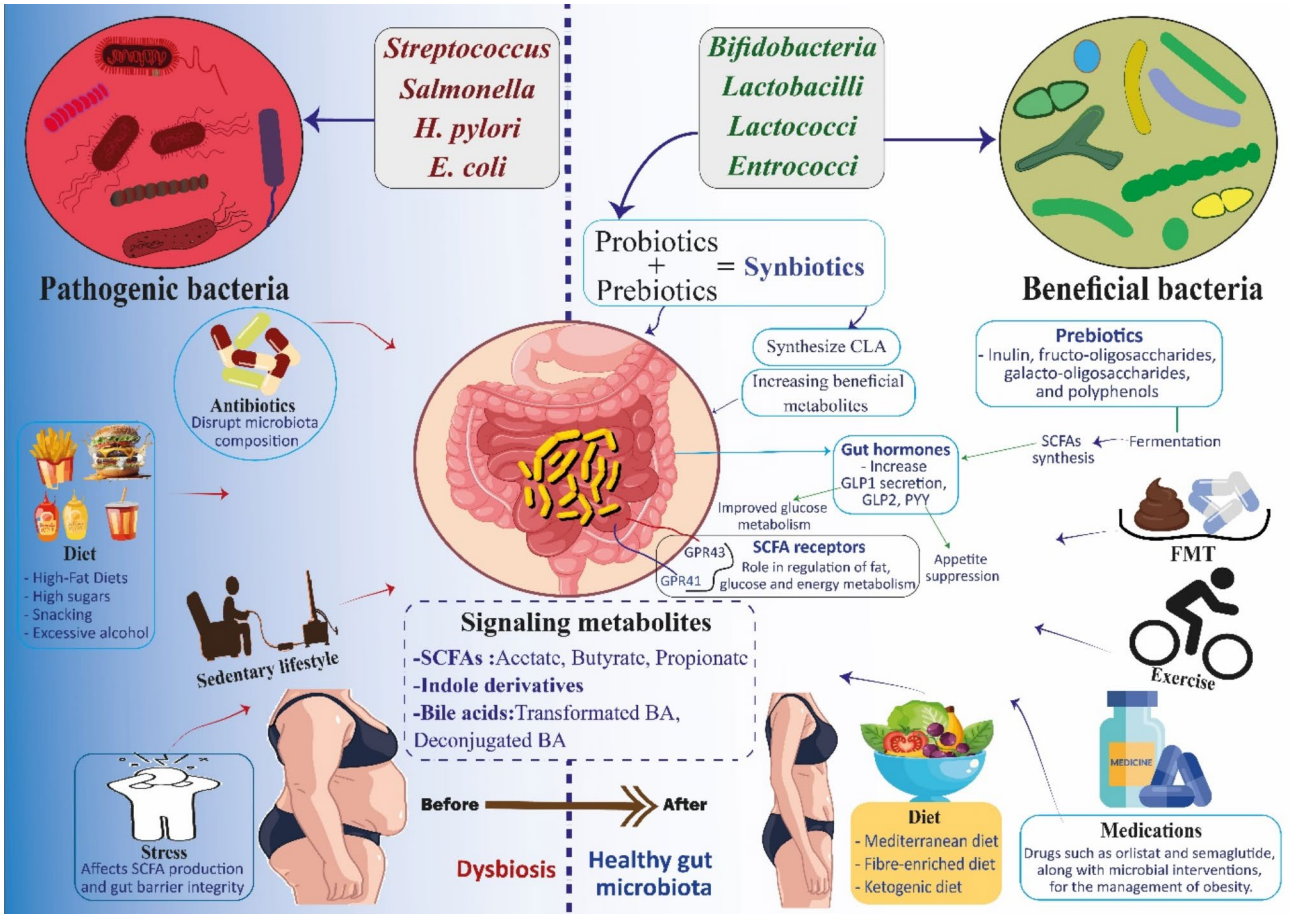


Fig. 2 This illustrates the interplay between pathogenic and beneficial gut microbiota and their impact on host metabolism and health. The figure emphasizes key factors contributing to gut dysbiosis, including antibiotics, stress, and dietary imbalances, as well as mechanisms for restoring gut health, such as probiotics, prebiotics, FMT, and dietary interventions. Beneficial gut microbiota promotes the production of SCFAs, regulates gut hormones (GLP-1, PYY), and enhances gut barrier integrity, all of which contribute to improved metabolic outcomes. In contrast, pathogenic bacteria disrupt gut homeostasis, leading to inflammation, impaired glucose metabolism, and obesity-related complications. Additionally, therapeutic approaches such as exercise, medications, and microbiota-modulating diets are illustrated for their roles in restoring microbial balance and enhancing health outcomes

significantly influence obesity, primarily through alterations in the gut microbiome [77, 279–285]. Making informed dietary choices is essential for the longevity and overall well-being of individuals with metabolic disorders. A well-balanced diet provides the necessary energy, macronutrients, and micronutrients required for growth, cell differentiation, repair, and maintenance. Conversely, metabolic imbalances can lead to serious health consequences [286, 287]. Functional foods also known as nutrient-dense foods—require a clear definition. They are primarily recommended in the following categories: fruits, vegetables, whole grains, seafood, legumes, unsalted nuts and seeds, and low-fat dairy products. Dietary fiber is the most talked-about issue in dietetics today since some diets alter the gut microbiota and provide essential health-related components. However, in addition to dietary fiber, other short- and medium-chain carbohydrates, such as oligosaccharides and inulin, also influence the etiopathophysiology of metabolic diseases by inducing the specific intestinal microbiome (SIM) and its metabolites, including SCFAs and secondary bile acids [288–291]. They interact with immune cells, hormones, metabolic processes, and the gut-organ axis [290, 292]. It is known that eating natural food produces bioactive metabolites that come from the gut microbiota. The so-called mutualism between the microbiota and the host's physiology may be mediated via aromatic amino acids like tryptophan, main bile acids, and others [279].

Soluble non-starch polysaccharides, particularly pectin, and psyllium, present significant health benefits due to their prebiotic properties, which include anti-inflammatory, antioxidant, and lipid-lowering effects [293, 294]. These fibers positively influence gut microbiota by promoting the growth of beneficial bacteria, such as *Bacteroides* spp., *Faecalibacterium* spp., and *Lachnospira eligens*, while also enhancing the production of SCFAs that play a crucial role in metabolic regulation [295–298].

Polyols, also referred to as sugar alcohols, are substances whose effects on gut microbiota are being studied. Mushrooms and several fruits and vegetables are rich sources of two common polyols, mannitol and sorbitol. Be aware that polyols are also utilized in the manufacturing of artificial sweeteners like erythritol and lactitol [299]. In a recent study, animals were given portobello or white button mushrooms for 15 weeks. Both mushrooms dramatically decreased Cyanobacteria and raised Verrucomicrobia due to their high mannitol content [300]. The impact of glycan and pectin, two polysaccharides found in mushrooms, on gut microbiota has been the subject of extensive research. In vitro simulation studies have demonstrated that mushroom polysaccharides stimulate the growth of beneficial bacteria, such as *Bacteroides* spp. and *Phascolarctobacterium* spp [300].

The Mediterranean diet (MD) is a recommended nutritional pattern that has demonstrated numerous health benefits. It has been shown to help prevent various ailments, including cancer, cardiovascular disease (CVD), type 2 diabetes, obesity, inflammatory disorders, and degenerative diseases. The MD also has demonstrated significant effects on metabolic health by reshaping microbial composition and functionality [282, 301–303]. The research conducted by Meslier et al. [282] demonstrated that transitioning from a Western dietary pattern to a Mediterranean diet, while maintaining consistent energy intake, macronutrient distribution, and levels of physical activity, significantly influences individual clinical outcomes, as well as the gut microbiome and metabolome, after a four-week intervention period in a population exhibiting cardiometabolic risk associated with an unhealthy lifestyle [282].

Similarly, pharmacological agents show promising effects in obesity management and gut microbial composition [284, 285, 304]. Liraglutide has been shown to control the gut microbiota's composition in HFD-fed mice, particularly by boosting the number of *Akkermansia* spp [305]. A research study conducted by Feng et al. [284] aimed to examine the impact of semaglutide on gut microbiota, cognitive function, and inflammation in a cohort of obese rats. The findings indicated that the HFD group experienced a substantial shift in gut microbiota composition, characterized by increased levels of *Romboutsia*, *Dubosiella*, and *Enterorhabdus* and lower levels of *Akkermansia*, *Muribaculaceae*, *Coriobacteriaceae_*UCG_002, and *Clostridia*_UCG_014. Consequently, semaglutide demonstrated distinct regulatory effects on the dysbiosis of gut microbiota induced by the HFD. Semaglutide influences the composition and structure of gut microbiota associated with inflammation and cognitive function. Therefore, modifying gut microbiota may be one mechanism by which semaglutide reduces inflammation and enhances mental function [284]. Another investigation conducted by Duan et al. [285] examined the impact of semaglutide on the gut microbiota in obese mice induced by an HFD. Male C57BL/6J mice, aged 6 weeks, were selected for the study and randomly assigned to one of four groups. These groups were administered either a normal control diet (NCD, NCD+semaglutide) or a high-fat diet (HFD, HFD+semaglutide), with the high-fat diet comprising 60% of the total caloric intake. The HFD was administered for 10 weeks to establish an obesity model, followed by an intervention period lasting 18 days. The findings demonstrated that semaglutide affected the composition of the gut microbiota, which in turn reduced the microbial dysbiosis caused by the HFD. While Lachnospiraceae and *Bacteroides* dramatically increased following the high-fat diet intervention, several strains, including *Akkermansia*, *Faecalibaculum*, and *Allobaculum*, significantly declined. Semaglutide, on the other hand, inhibited excessive bacterial abundance and restored the disrupted ecological balance. In conclusion, the research suggests that semaglutide helps treat dysbiosis of the gut microbiota and that the gut microbiota may be involved in the effects of this medication on obesity [285].

Microbiota, obesity, and exercise

Research has demonstrated that physical activity can alter the microbiota, leading to enhancements in metabolic profiles and immune responses, as evidenced by studies conducted on both animal models and human subjects [306]. These temporary alterations exhibit variations between individuals of normal weight and those with obesity. This distinction was evidenced in a study involving 32 participants, comprising 18 individuals classified as thin and 14 as obese. Following engagement in physical activity, the composition of the microbiota exhibited notable variations in bacterial genera, with a predominance of *Bacteroides* observed in the obese subjects, while *Faecalibacterium* spp. and *Lachnospira* spp. were more prevalent in those of normal weight. Additionally, it was demonstrated that the composition of the microbiota varied from pre-exercise levels, with these alterations reverting following the cessation of exercise [307]. Comparable findings were reported in a study involving 27 sedentary individuals with obesity. Following participation in moderate to intense physical activity, researchers observed a reduction in the Firmicutes to Bacteroidetes (F/B) ratio, along with an increase in the abundance of *Bacteroides* and a decrease in both *Blautia* and *Clostridium* populations [308]. In another study involving 40 premenopausal women with a BMI ranging from 20 to 25 kg/m^2—comprising 19 physically active individuals and 21 sedentary individuals—no significant differences were detected in terms of alpha and beta diversity or the F/B ratio between the two groups.

However, active women tended to have a higher relative abundance of Firmicutes and a lower relative abundance of Bacteroidetes [309].

Conclusion

Obesity is one of the global problems that endangers people's health. In recent years a growing body of evidence suggests that maintaining a balanced microbial community in the GI tract may play a significant role in preventing obesity. The gut microbiome serves various functions, including preserving intestinal integrity, producing mucus, promoting the regeneration of the intestinal epithelium, and mediating the production of SCFA. A well-functioning GI microbiota is crucial for managing the body's metabolic processes and energy levels. An imbalance in the microbiome can result in increased appetite and metabolic disorders, which are influential factors in the development of obesity and its associated conditions. Children experiencing obesity exhibit alterations in the composition and functional capabilities of their intestinal microorganisms. This includes a notable increase in proinflammatory bacterial groups compared to their lean counterparts.

Based on the available evidence, therapeutic interventions aimed at modulating the intestinal microbiome—such as probiotics, prebiotics, synbiotics, and FMT, can be effective in combating obesity and promoting weight loss. Additionally, dietary interventions (e.g., low-carbohydrate and Mediterranean diets), pharmacological treatments (e.g., semaglutide), and regular physical activity can further enhance the diversity and functionality of the gut microbiota, thereby helping to restore a healthier microbial balance. These interventions work synergistically to reshape the gut microbiome, promoting metabolic health, and potentially reducing the risk of obesity. However, more clinical trials are needed to clarify the optimal dosage, frequency, and long-term effects of these therapeutic approaches. Further research is necessary to elucidate the mechanisms through which gut microbiota contribute to obesity and obesity-related disorders, given the richness and diversity of this microbial population.

Acknowledgements
None declared.

Author contributions
AY: wrote the manuscript, HA-AJ-MK: design and Supervision. All authors read and approved the final manuscript.

Funding
No Funding.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Biology, Khorramabad Branch, Islamic Azad University, Khorramabad, Iran
[2]Cellular and Molecular Research Center, Qom University of Medical Sciences, Qom, Iran
[3]Nervous System Stem Cells Research Center, Semnan University of Medical Sciences, Semnan, Iran
[4]Department of Medical Microbiology, Faculty of Medicine, Shahed University, Tehran, Iran
[5]Department of Medical Sciences, Faculty of Medicine, Qom Medical Sciences, Islamic Azad University, Qom, Iran
[6]Fellowship in Clinical Laboratory Sciences, Mashhad University of Medical Sciences, Mashhad, Iran

Received: 10 October 2024 / Accepted: 15 December 2024
Published online: 23 December 2024

References

1. Hoffman DJ, et al. Developmental origins of metabolic diseases. Physiol Rev. 2021;101(3):739–95.
2. Ridaura VK, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150):1241214.
3. Frank J, et al. Brain–gut–microbiome interactions and intermittent fasting in obesity. Nutrients. 2021;13(2):584.
4. Wu T-R, et al. Gut commensal Parabacteroides goldsteinii plays a predominant role in the anti-obesity effects of polysaccharides isolated from Hirsutella sinensis. Gut. 2019;68(2):248–62.
5. Charles-Messance H, et al. Regulating metabolic inflammation by nutritional modulation. J Allergy Clin Immunol. 2020;146(4):706–20.
6. Mongraw-Chaffin M, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2018;71(17):1857–65.
7. Howe LR, et al. Molecular pathways: adipose inflammation as a mediator of obesity-associated cancer. Clin Cancer Res. 2013;19(22):6074–83.
8. Asadi A, et al. Obesity and gut–microbiota–brain axis: A narrative review. J Clin Lab Anal. 2022;36(5):e24420.
9. Boulangé CL, et al. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016;8:1–12.
10. Petersen A, et al. The role of visceral adiposity in the severity of COVID-19: Highlights from a unicenter cross-sectional pilot study in Germany. Metabolism. 2020;110:154317.
11. Stefan N, et al. Obesity and impaired metabolic health in patients with COVID-19. Nat Reviews Endocrinol. 2020;16(7):341–2.
12. Geng J, et al. The links between gut microbiota and obesity and obesity related diseases. Volume 147. Biomedicine & Pharmacotherapy; 2022. p. 112678.
13. Liu B-N, et al. Gut microbiota in obesity. World J Gastroenterol. 2021;27(25):3837.
14. Backhed F, et al. Host-bacterial mutualism in the human intestine. Science. 2005;307(5717):1915–20.
15. Sommer F, et al. The resilience of the intestinal microbiota influences health and disease. Nat Rev Microbiol. 2017;15(10):630–8.
16. Yarahmadi A, Afkhami HJFiO. *The role of microbiomes in gastrointestinal cancers: new insights.* 2024. 13: p. 1344328.
17. Liang J, et al. Edible fungal polysaccharides, the gut microbiota, and host health. Carbohydr Polym. 2021;273:118558.
18. Tilg H, et al. The intestinal microbiota fuelling metabolic inflammation. Nat Rev Immunol. 2020;20(1):40–54.

19. Cheng H-Y, et al. Interactions between the gut microbiota and the host innate immune response against pathogens. Front Immunol. 2019;10:607.
20. Yarahmadi A et al. *Materials based on biodegradable polymers chitosan/gelatin: a review of potential applications*. 2024. 12: p. 1397668.
21. Wang AR, et al. Progress in fish gastrointestinal microbiota research. Reviews Aquaculture. 2018;10(3):626–40.
22. Gentile CL, Weir TL. The gut microbiota at the intersection of diet and human health. Science. 2018;362(6416):776–80.
23. Shanahan F, Ghosh TS, O'Toole PW. The healthy microbiome—what is the definition of a healthy gut microbiome? Gastroenterology. 2021;160(2):483–94.
24. Jiminez JA, et al. Butyrate supplementation at high concentrations alters enteric bacterial communities and reduces intestinal inflammation in mice infected with Citrobacter rodentium. MSphere. 2017;2(4):e00243–17.
25. Mollica MP, et al. Butyrate regulates liver mitochondrial function, efficiency, and dynamics in insulin-resistant obese mice. Diabetes. 2017;66(5):1405–18.
26. Velikonja A, et al. Alterations in gut microbiota composition and metabolic parameters after dietary intervention with barley beta glucans in patients with high risk for metabolic syndrome development. Anaerobe. 2019;55:67–77.
27. Yarahmadi A et al. Therapeutic bacteria and viruses to combat cancer: double-edged sword in cancer therapy: new insights for future. 2024. 22(1): p. 239.
28. Nicholson JK, et al. Host-gut microbiota metabolic interactions. Science. 2012;336(6086):1262–7.
29. Sankararaman S, et al. Gut Microbiome and Its Impact on Obesity and Obesity-Related Disorders. Curr Gastroenterol Rep. 2023;25(2):31–44.
30. Mols KL, et al. Prenatal establishment of the foal gut microbiota: A critique of the in utero colonisation hypothesis. Anim Prod Sci. 2020;60(18):2080–92.
31. Madany AM, Hughes HK, Ashwood P. Prenatal maternal antibiotics treatment alters the gut microbiota and immune function of post-weaned prepubescent offspring. Int J Mol Sci. 2022;23(21):12879.
32. Zheng J, et al. Characterization of gut microbiota in prenatal cold stress offspring rats by 16S rRNA sequencing. Animals. 2020;10(9):1619.
33. Akagbosu CO, et al. The role of the gut microbiome in pediatric obesity and bariatric surgery. Int J Mol Sci. 2022;23(23):15421.
34. Nanji JA, Carvalho B. Pain management during labor and vaginal birth. Volume 67. Best Practice & Research Clinical Obstetrics & Gynaecology; 2020. pp. 100–12.
35. Keedle H, et al. Women's experiences of planning a vaginal birth after caesarean in different models of maternity care in Australia. BMC Pregnancy Childbirth. 2020;20(1):1–15.
36. Bokulich NA, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med. 2016;8(343):pra34382–ra34382.
37. Fouhy F, et al. Perinatal factors affect the gut microbiota up to four years after birth. Nat Commun. 2019;10(1):1517.
38. Cox LM, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell. 2014;158(4):705–21.
39. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol. 2020;11:25.
40. Tanase DM et al. *Role of gut microbiota on onset and progression of microvascular complications of type 2 diabetes (T2DM)*. Nutrients, 2020. 12(12): p. 3719.
41. Pu ZCT. Microbiota profile is different for early and invasive colorectal cancer and is consistent throughout the colon. J Gastroenterol Hepatol. 2020;35(3):433–7.
42. Sircana A, et al. Altered gut microbiota in type 2 diabetes: just a coincidence? Curr Diab Rep. 2018;18:1–11.
43. Qin J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59–65.
44. Kabouridis PS, Pachnis V. Emerging roles of gut microbiota and the immune system in the development of the enteric nervous system. J Clin Investig. 2015;125(3):956–64.
45. Badgeley A, et al. Effect of probiotics and gut microbiota on anti-cancer drugs: Mechanistic perspectives. Biochim et Biophys Acta (BBA)-Reviews Cancer. 2021;1875(1):188494–p.
46. Yatsunenko T, et al. Human gut microbiome viewed across age and geography. Nature. 2012;486(7402):222–7.
47. Bisanz JE et al. *Diet induces reproducible alterations in the mouse and human gut microbiome.* bioRxiv, 2019: p. 541797.
48. Claesson MJ, et al. Gut microbiota composition correlates with diet and health in the elderly. Nature. 2012;488(7410):178–84.
49. Cho I, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature. 2012;488(7413):621–6.
50. Medina DA, et al. Simulation and modeling of dietary changes in the infant gut microbiome. FEMS Microbiol Ecol. 2018;94(9):fiy140.
51. Thavamani A, et al. Impact of altered gut microbiota and its metabolites in cystic fibrosis. Metabolites. 2021;11(2):123.
52. Sikalidis AK, Maykish A. The gut microbiome and type 2 diabetes mellitus: discussing a complex relationship. Biomedicines. 2020;8(1):8.
53. Cho KY. Association of gut microbiota with obesity in children and adolescents. Clin Experimental Pediatr. 2023;66(4):148.
54. Gurnani M, Birken C, Hamilton J. Childhood obesity: causes, consequences, and management. Pediatr Clin. 2015;62(4):821–40.
55. Juonala M, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med. 2011;365(20):1876–85.
56. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Annals translational Med, 2017. 5(7).
57. Ogden CL, et al. Trends in obesity prevalence among children and adolescents in the United States, 1988–1994 through 2013–2014. JAMA. 2016;315(21):2292–9.
58. Wyllie R, Hyams JS, Kay M. Pediatric gastrointestinal and liver disease E-Book. Elsevier Health Sciences; 2020.
59. Orsso CE, et al. Composition and functions of the gut microbiome in pediatric obesity: relationships with markers of insulin resistance. Microorganisms. 2021;9(7):1490.
60. Del Chierico F, et al. Gut microbiota markers in obese adolescent and adult patients: age-dependent differential patterns. Front Microbiol. 2018;9:1210.
61. Castaner O et al. *The gut microbiome profile in obesity: a systematic review.* International journal of endocrinology, 2018. 2018.
62. López-Contreras B, et al. Composition of gut microbiota in obese and normal-weight Mexican school-age children and its association with metabolic traits. Pediatr Obes. 2018;13(6):381–8.
63. Hollister EB, et al. Characterization of the stool microbiome in hispanic preschool children by weight status and time. Child Obes. 2018;14(2):122–30.
64. Shin S, Cho KY. *Altered gut microbiota and shift in Bacteroidetes between young obese and normal-weight Korean children: a cross-sectional observational study.* BioMed Research International, 2020. 2020.
65. Ihekweazu FD, Versalovic J. Development of the pediatric gut microbiome: impact on health and disease. Am J Med Sci. 2018;356(5):413–23.
66. Rampelli S, et al. Pre-obese children's dysbiotic gut microbiome and unhealthy diets may predict the development of obesity. Commun biology. 2018;1(1):222.
67. Cho KY. Lifestyle modifications result in alterations in the gut microbiota in obese children. BMC Microbiol. 2021;21(1):1–15.
68. Wu G, et al. Guild-based analysis for understanding gut microbiome in human health and diseases. Genome Med. 2021;13:1–12.
69. Agans R, et al. Distal gut microbiota of adolescent children is different from that of adults. FEMS Microbiol Ecol. 2011;77(2):404–12.
70. Hollister EB, et al. Structure and function of the healthy pre-adolescent pediatric gut microbiome. Microbiome. 2015;3(1):1–13.
71. Kurilshikov A, et al. Large-scale association analyses identify host factors influencing human gut microbiome composition. Nat Genet. 2021;53(2):156–65.
72. Kho ZY, Lal SK. The human gut microbiome–a potential controller of wellness and disease. Front Microbiol. 2018;9:1835.
73. Scheepers L, et al. The intestinal microbiota composition and weight development in children: the KOALA Birth Cohort Study. Int J Obes. 2015;39(1):16–25.
74. Maya-Lucas O, et al. The gut microbiome of Mexican children affected by obesity. Anaerobe. 2019;55:11–23.
75. Vázquez-Baeza Y, et al. EMPeror: a tool for visualizing high-throughput microbial community data. Gigascience. 2013;2(1):2047–217. X-2-16.
76. Caporaso JG, et al. Ultra-high-throughput microbial community analysis on the Illumina HiSeq and MiSeq platforms. ISME J. 2012;6(8):1621–4.
77. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol. 2014;12(10):661–72.
78. Ley RE, et al. Obesity alters gut microbial ecology. Proc Natl Acad Sci. 2005;102(31):11070–5.
79. Turnbaugh PJ, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027–31.
80. Indiani CM, et al. Childhood obesity and Firmicutes/Bacteroidetes ratio in the gut microbiota: a systematic review. Child Obes. 2018;14(8):501–9.

81. Koliada A, et al. Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukrainian population. BMC Microbiol. 2017;17(1):1–6.
82. Zhang H, et al. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci. 2009;106(7):2365–70.
83. Wu T, et al. Characteristics of gut microbiota of obese people and machine learning model. Microbiol China. 2020;47:4328–37.
84. Depommier C, et al. Pasteurized Akkermansia muciniphila increases whole-body energy expenditure and fecal energy excretion in diet-induced obese mice. Gut Microbes. 2020;11(5):1231–45.
85. Depommier C, et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med. 2019;25(7):1096–103.
86. Yan H, et al. Gut microbiome alterations in patients with visceral obesity based on quantitative computed tomography. Front Cell Infect Microbiol. 2022;11:823262.
87. Voruganti VS. Precision nutrition: Recent advances in obesity. Physiology. 2023;38(1):42–50.
88. Palmas V, et al. Gut microbiota markers associated with obesity and overweight in Italian adults. Sci Rep. 2021;11(1):5532.
89. Waters JL, Ley RE. The human gut bacteria Christensenellaceae are widespread, heritable, and associated with health. BMC Biol. 2019;17(1):1–11.
90. Xu Z, et al. Gut microbiota in patients with obesity and metabolic disorders—A systematic review. Genes Nutr. 2022;17(1):1–18.
91. Tsukumo DM, et al. Translational research into gut microbiota: new horizons on obesity treatment: updated 2014. Archives Endocrinol metabolism. 2015;59:154–60.
92. Khan MJ et al. *Role of gut microbiota in the aetiology of obesity: proposed mechanisms and review of the literature.* Journal of obesity, 2016. 2016.
93. Ley RE, et al. Human gut microbes associated with obesity. Nature. 2006;444(7122):1022–3.
94. Bisanz JE, et al. Meta-analysis reveals reproducible gut microbiome alterations in response to a high-fat diet. Cell Host Microbe. 2019;26(2):265–72. e4.
95. Duncan SH, et al. Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes. 2008;32(11):1720–4.
96. Castro A, Macedo-De la L, Concha, Pantoja-Meléndez C. Low-grade inflammation and its relation to obesity and chronic degenerative diseases. Revista Médica del Hosp Gen de México. 2017;80(2):101–5.
97. Saad M, Santos A, Prada P. Linking gut microbiota and inflammation to obesity and insulin resistance. Physiology. 2016;31(4):283–93.
98. Cani PD, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761–72.
99. de La Serre CB, et al. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. American Journal of Physiology-Gastrointestinal and Liver Physiology; 2010.
100. Kobyliak N, Virchenko O, Falalyeyeva T. Pathophysiological role of host microbiota in the development of obesity. Nutr J. 2015;15:1–12.
101. Muccioli GG, et al. The endocannabinoid system links gut microbiota to adipogenesis. Mol Syst Biol. 2010;6(1):392.
102. Kim K-A et al. *High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway.* 2012.
103. Romero LO, et al. Dietary fatty acids fine-tune Piezo1 mechanical response. Nat Commun. 2019;10(1):1200.
104. Agus A, Planchais J, Sokol H. Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe. 2018;23(6):716–24.
105. Laurans L, et al. Genetic deficiency of indoleamine 2, 3-dioxygenase promotes gut microbiota-mediated metabolic health. Nat Med. 2018;24(8):1113–20.
106. Xiao H, Kang S. The role of the gut microbiome in energy balance with a focus on the gut-adipose tissue axis. Front Genet. 2020;11:297.
107. Gill SR, et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006;312(5778):1355–9.
108. Boursier J, et al. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. Hepatology. 2016;63(3):764–75.
109. Fändriks L. Roles of the gut in the metabolic syndrome: an overview. J Intern Med. 2017;281(4):319–36.
110. Kalayu G. Phosphate solubilizing microorganisms: promising approach as biofertilizers. Int J Agron. 2019;2019:1–7.
111. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13(10):701–12.
112. Nguyen NH, et al. FUNGuild: an open annotation tool for parsing fungal community datasets by ecological guild. Fungal Ecol. 2016;20:241–8.
113. Ruze R et al. *Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments.* 2023. 14: p. 1161521.
114. Lancet NRFCJ. *Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants.* 2016. 387(10026): p. 1377.
115. Mayer-Davis EJ et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. 2017. 376(15): pp. 1419–29.
116. Damanik J, Yunir E. Type 2 Diabetes Mellitus and Cognitive Impairment. Acta Med Indones. 2021;53(2):213–20.
117. Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996–2016. BMJ Open Diabetes Res Care. 2020;8(1):e001071.
118. Takagi T, et al. Changes in the gut microbiota are associated with hypertension, hyperlipidemia, and type 2 diabetes mellitus in Japanese subjects. Nutrients. 2020;12(10):2996.
119. Wang T-Y, et al. A comparative study of microbial community and functions of type 2 diabetes mellitus patients with obesity and healthy people. Appl Microbiol Biotechnol. 2020;104:7143–53.
120. Horne RG, et al. High fat-high fructose diet-induced changes in the gut microbiota associated with dyslipidemia in Syrian hamsters. Nutrients. 2020;12(11):3557.
121. Zhou Z, et al. Gut microbiota: an important player in type 2 diabetes mellitus. Front Cell Infect Microbiol. 2022;12:112.
122. Qin J, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55–60.
123. Karlsson FH, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature. 2013;498(7452):99–103.
124. Chen P-C, Chien Y-W, Yang S-C. The alteration of gut microbiota in newly diagnosed type 2 diabetic patients. Nutrition. 2019;63:51–6.
125. Shih C-T, et al. Akkermansia muciniphila is negatively correlated with hemoglobin A1c in refractory diabetes. Microorganisms. 2020;8(9):1360.
126. Larsen N, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS ONE. 2010;5(2):e9085.
127. Kovatcheva-Datchary P, et al. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of Prevotella. Cell Metabol. 2015;22(6):971–82.
128. Tabák AG, et al. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279–90.
129. Zhou W, et al. Longitudinal multi-omics of host–microbe dynamics in prediabetes. Nature. 2019;569(7758):663–71.
130. Chávez-Carbajal A, et al. Characterization of the gut microbiota of individuals at different T2D stages reveals a complex relationship with the host. Microorganisms. 2020;8(1):94.
131. Allin KH, et al. Aberrant intestinal microbiota in individuals with prediabetes. Diabetologia. 2018;61:810–20.
132. Zhong H, et al. Distinct gut metagenomics and metaproteomics signatures in prediabetics and treatment-naïve type 2 diabetics. EBioMedicine. 2019;47:373–83.
133. Kieler IN, et al. Diabetic cats have decreased gut microbial diversity and a lack of butyrate producing bacteria. Sci Rep. 2019;9(1):4822.
134. Okazaki F, et al. Microbiome alteration in type 2 diabetes mellitus model of zebrafish. Sci Rep. 2019;9(1):867.
135. Wang Y et al. *Phocea, Pseudoflavonifractor and Lactobacillus intestinalis: three potential biomarkers of gut microbiota that affect progression and complications of obesity-induced type 2 diabetes mellitus.* Diabetes, Metabolic Syndrome and Obesity, 2020: pp. 835–850.
136. Peng W, et al. Integrated 16S rRNA sequencing, metagenomics, and metabolomics to characterize gut microbial composition, function, and fecal metabolic phenotype in non-obese type 2 diabetic Goto-Kakizaki rats. Front Microbiol. 2020;10:3141.
137. Yang R, et al. Genistein ameliorates inflammation and insulin resistance through mediation of gut microbiota composition in type 2 diabetic mice. Eur J Nutr. 2021;60:2155–68.
138. Salguero MV, et al. Dysbiosis of Gram–negative gut microbiota and the associated serum lipopolysaccharide exacerbates inflammation in type 2 diabetic patients with chronic kidney disease. Experimental therapeutic Med. 2019;18(5):3461–9.
139. Jayasudha R, et al. Gut mycobiomes are altered in people with type 2 Diabetes Mellitus and Diabetic Retinopathy. PLoS ONE. 2020;15(12):e0243077.

140. Xie J, et al. Protective effect of quercetin on streptozotocin-induced diabetic peripheral neuropathy rats through modulating gut microbiota and reactive oxygen species level. Volume 127. Biomedicine & Pharmacotherapy; 2020. p. 110147.
141. Zhang Y, et al. The diversity of gut microbiota in type 2 diabetes with or without cognitive impairment. Aging Clin Exp Res. 2021;33:589–601.
142. Tao S, et al. Understanding the gut–kidney axis among biopsy-proven diabetic nephropathy, type 2 diabetes mellitus and healthy controls: an analysis of the gut microbiota composition. Acta Diabetol. 2019;56:581–92.
143. Chaudhury A, et al. Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Front Endocrinol. 2017;8:6.
144. Bäumler AJ, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. Nature. 2016;535(7610):85–93.
145. Du X, et al. Alteration of gut microbial profile in patients with diabetic nephropathy. Endocrine. 2021;73(1):71–84.
146. Lu J, et al. GPR43 deficiency protects against podocyte insulin resistance in diabetic nephropathy through the restoration of AMPKα activity. Theranostics. 2021;11(10):4728.
147. Al-Obaide MA, et al. Gut microbiota-dependent trimethylamine-N-oxide and serum biomarkers in patients with T2DM and advanced CKD. J Clin Med. 2017;6(9):86.
148. Kikuchi K, et al. Gut microbiome-derived phenyl sulfate contributes to albuminuria in diabetic kidney disease. Nat Commun. 2019;10(1):1835.
149. Zhao L, et al. Comprehensive relationships between gut microbiome and faecal metabolome in individuals with type 2 diabetes and its complications. Endocrine. 2019;66:526–37.
150. Evert AB, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care. 2019;42(5):731.
151. Association AD. Standards of medical care in diabetes—2022 abridged for primary care providers. Clin Diabetes. 2022;40(1):10–38.
152. Song B, et al. Association of the gut microbiome with fecal short-chain fatty acids, lipopolysaccharides, and obesity in young Chinese college students. Front Nutr. 2023;10:1057759.
153. Chen R, et al. Meta-analysis reveals gut microbiome and functional pathway alterations in response to resistant starch. Food & Function; 2023.
154. Vael C, et al. Intestinal microflora and body mass index during the first three years of life: an observational study. Gut pathogens. 2011;3(1):1–7.
155. Oraphruek P, et al. Effect of a Multispecies Synbiotic Supplementation on Body Composition, Antioxidant Status, and Gut Microbiomes in Overweight and Obese Subjects: A Randomized, Double-Blind, Placebo-Controlled Study. Nutrients. 2023;15(8):1863.
156. Gilley SP, et al. Associations between maternal obesity and offspring gut microbiome in the first year of life. Pediatr Obes. 2022;17(9):e12921.
157. Le Chatelier E, et al. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013;500(7464):541–6.
158. Murga-Garrido S, et al. Virulence Factors of the Gut Microbiome Are Associated with BMI and Metabolic Blood Parameters in Children with Obesity. Microbiol Spectr. 2023;11(2):e03382–22.
159. Ignacio A, et al. Correlation between body mass index and faecal microbiota from children. Clin Microbiol Infect. 2016;22(3):258. e1-258. e8.
160. Cuevas-Sierra A, et al. Diet-and sex-related changes of gut microbiota composition and functional profiles after 4 months of weight loss intervention. Eur J Nutr. 2021;60:3279–301.
161. Lv Y, et al. The association between gut microbiota composition and BMI in Chinese male college students, as analysed by next-generation sequencing. Br J Nutr. 2019;122(9):986–95.
162. Dao MC, et al. Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. Gut. 2016;65(3):426–36.
163. Jiao N, et al. Gut microbiome may contribute to insulin resistance and systemic inflammation in obese rodents: a meta-analysis. Physiol Genom. 2018;50(4):244–54.
164. Koutoukidis DA, et al. The association of weight loss with changes in the gut microbiota diversity, composition, and intestinal permeability: A systematic review and meta-analysis. Gut Microbes. 2022;14(1):2020068.
165. Sarmiento-Andrade Y et al. *Gut microbiota and obesity: New insights.* 2022. 9: p. 1018212.
166. Calderon G et al. Ileo-colonic delivery of conjugated bile acids improves glucose homeostasis via colonic GLP-1-producing enteroendocrine cells in human obesity and diabetes. 2020. 55.
167. Mullish BH et al. *Functional microbiomics: evaluation of gut microbiota-bile acid metabolism interactions in health and disease.* 2018. 149: pp. 49–58.
168. Thomas C et al. *TGR5-mediated bile acid sensing controls glucose homeostasis.* 2009. 10(3): pp. 167–177.
169. Sayin SI et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. 2013. 17(2): pp. 225–35.
170. Wei M et al. *A dysregulated bile acid-gut microbiota axis contributes to obesity susceptibility.* 2020. 55.
171. Den Besten G, et al. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013;54(9):2325–40.
172. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes. 2016;7(3):189–200.
173. Yousefi B, et al. Gastrointestinal Tract, Microbiota and Multiple Sclerosis (MS) and the Link Between Gut Microbiota and CNS. Curr Microbiol. 2023;80(1):38.
174. Rahat-Rozenbloom S, et al. Evidence for greater production of colonic short-chain fatty acids in overweight than lean humans. Int J Obes. 2014;38(12):1525–31.
175. Murugesan S, et al. Study of the diversity and short-chain fatty acids production by the bacterial community in overweight and obese Mexican children. Eur J Clin Microbiol Infect Dis. 2015;34:1337–46.
176. Koh A, et al. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016;165(6):1332–45.
177. Adak A, Khan MR. An insight into gut microbiota and its functionalities. Cell Mol Life Sci. 2019;76:473–93.
178. Man AW, et al. Involvement of gut microbiota, microbial metabolites and interaction with polyphenol in host immunometabolism. Nutrients. 2020;12(10):3054.
179. Tolhurst G, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein–coupled receptor FFAR2. Diabetes. 2012;61(2):364–71.
180. Priyadarshini M, et al. Role of short chain fatty acid receptors in intestinal physiology and pathophysiology. Compr Physiol. 2018;8(3):1091.
181. De Vadder F, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014;156(1):84–96.
182. Zhao S, et al. Dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate. Nature. 2020;579(7800):586–91.
183. Jensen T, et al. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. J Hepatol. 2018;68(5):1063–75.
184. Hannou SA, et al. Fructose metabolism and metabolic disease. J Clin Investig. 2018;128(2):545–55.
185. Softic S, Cohen DE, Kahn CR. Role of dietary fructose and hepatic de novo lipogenesis in fatty liver disease. Dig Dis Sci. 2016;61:1282–93.
186. Zou J, et al. Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health. Cell Host Microbe. 2018;23(1):41–53. e4.
187. Wang B, et al. Altered fecal microbiota correlates with liver biochemistry in nonobese patients with non-alcoholic fatty liver disease. Sci Rep. 2016;6(1):32002.
188. Da Silva HE, et al. Nonalcoholic fatty liver disease is associated with dysbiosis independent of body mass index and insulin resistance. Sci Rep. 2018;8(1):1466.
189. González Hernández MA et al. *The short-chain fatty acid acetate in body weight control and insulin sensitivity.* 2019. 11(8): p. 1943.
190. Wang D et al. Propionate promotes intestinal lipolysis and metabolic benefits via AMPK/LSD1 pathway in mice. 2019. 243(3): pp. 187–97.
191. Yu C et al. Effect of exercise and butyrate supplementation on microbiota composition and lipid metabolism. 2019. 243(2): pp. 125–35.
192. Sonowal R, et al. Indoles from commensal bacteria extend healthspan. Proc Natl Acad Sci. 2017;114(36):pE7506–E7515.
193. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat reviews Gastroenterol Hepatol. 2020;17(4):223–37.
194. Weber D, et al. *Low urinary indoxyl sulfate levels early after transplantation reflect a disrupted microbiome and are associated with poor outcome.* Blood. J Am Soc Hematol. 2015;126(14):1723–8.
195. Yang J, et al. Biphasic chemotaxis of Escherichia coli to the microbiota metabolite indole. Proc Natl Acad Sci. 2020;117(11):6114–20.
196. Liu J-R, et al. Gut microbiota-derived tryptophan metabolism mediates renal fibrosis by aryl hydrocarbon receptor signaling activation. Cell Mol Life Sci. 2021;78:909–22.

197. Natividad JM, et al. Impaired aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome. Cell Metabol. 2018;28(5):737–49. e4.
198. Kowalski K, Mulak A. Brain-gut-microbiota axis in Alzheimer's disease. J Neurogastroenterol Motil. 2019;25(1):48.
199. Milani C, et al. The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. Microbiol Mol Biol Rev. 2017;81(4). https://doi.org/10.1128/mmbr. 00036 – 17.
200. Taleb S. Tryptophan dietary impacts gut barrier and metabolic diseases. Front Immunol. 2019;10:2113.
201. Beaumont M, et al. The gut microbiota metabolite indole alleviates liver inflammation in mice. FASEB J. 2018;32(12):6681.
202. Mallmann NH, Lima ES, Lalwani P. Dysregulation of tryptophan catabolism in metabolic syndrome. Metab Syndr Relat Disord. 2018;16(3):135–42.
203. Moyer BJ, et al. Inhibition of the aryl hydrocarbon receptor prevents Western diet-induced obesity. Model for AHR activation by kynurenine via oxidized-LDL, TLR2/4, TGFβ, and IDO1. Toxicol Appl Pharmcol. 2016;300:13–24.
204. Zhou C, et al. Exosome-derived miR-142-5p remodels lymphatic vessels and induces IDO to promote immune privilege in the tumour microenvironment. Cell Death Differ. 2021;28(2):715–29.
205. Liu J-J, Movassat J, Portha B. Emerging role for kynurenines in metabolic pathologies. Curr Opin Clin Nutr Metabolic Care. 2019;22(1):82–90.
206. Young RL, Lumsden AL, Keating DJ. Gut serotonin is a regulator of obesity and metabolism. Gastroenterology. 2015;149(1):253–5.
207. Crane JD, et al. Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis. Nat Med. 2015;21(2):166–72.
208. Fukui M, et al. High plasma 5-hydroxyindole-3-acetic acid concentrations in subjects with metabolic syndrome. Diabetes Care. 2012;35(1):163–7.
209. So D, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. Am J Clin Nutr. 2018;107(6):965–83.
210. Johnson CL, Versalovic J. The human microbiome and its potential importance to pediatrics. Pediatrics. 2012;129(5):950–60.
211. Pais P, et al. Saccharomyces boulardii: what makes it tick as successful probiotic? J Fungi. 2020;6(2):78.
212. Li H-Y, et al. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: A narrative review. Nutrients. 2021;13(9):3211.
213. Khanna S, et al. Administration of indigenous probiotics modulate high-fat diet-induced metabolic syndrome in Sprague Dawley rats. Antonie Van Leeuwenhoek. 2020;113:1345–59.
214. Okeke F, Roland BC, Mullin GE. The role of the gut microbiome in the pathogenesis and treatment of obesity. Global Adv health Med. 2014;3(3):44–57.
215. Mazloom K, Siddiqi I, Covasa M. Probiotics: how effective are they in the fight against obesity? Nutrients. 2019;11(2):258.
216. Cerdó T, et al. The role of probiotics and prebiotics in the prevention and treatment of obesity. Nutrients. 2019;11(3):635.
217. Luoto R, et al. The impact of perinatal probiotic intervention on the development of overweight and obesity: follow-up study from birth to 10 years. Int J Obes. 2010;34(10):1531–7.
218. Gérard P. Gut microbiota and obesity. Cell Mol Life Sci. 2016;73(1):147–62.
219. Andreasen AS, et al. Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. Br J Nutr. 2010;104(12):1831–8.
220. Kadooka Y, et al. Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial. Eur J Clin Nutr. 2010;64(6):636–43.
221. Jung S-P, et al. Effect of Lactobacillus gasseri BNR17 on overweight and obese adults: a randomized, double-blind clinical trial. Korean J family Med. 2013;34(2):80.
222. Sanchis-Chordà J, et al. Bifidobacterium pseudocatenulatum CECT 7765 supplementation improves inflammatory status in insulin-resistant obese children. Eur J Nutr. 2019;58:2789–800.
223. Rajkumar H et al. *Effect of probiotic (VSL# 3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial.* Mediators of inflammation, 2014. 2014.
224. Karlsson Videhult F, et al. Impact of probiotics during weaning on the metabolic and inflammatory profile: follow-up at school age. Int J Food Sci Nutr. 2015;66(6):686–91.
225. Won S-M, et al. Lactobacillus sakei ADM14 induces anti-obesity effects and changes in gut microbiome in high-fat diet-induced obese mice. Nutrients. 2020;12(12):3703.
226. Dahiya DK, Renuka, Puniya AKJFM. Conjugated linoleic acid enriched skim milk prepared with Lactobacillus fermentum DDHI27 endorsed antiobesity in mice. 2018. 13(9): pp. 1007–20.
227. Lee H-Y et al. Human originated bacteria, Lactobacillus rhamnosus PL60, produce conjugated linoleic acid and show anti-obesity effects in diet-induced obese mice. 2006. 1761(7): pp. 736–44.
228. Li JJ et al. Anti-obesity effects of conjugated linoleic acid, docosahexaenoic acid, and eicosapentaenoic acid. 2008. 52(6): pp. 631–45.
229. Ibrahim KS. and E.M.J.J.o.B. El-Sayed, *Dietary conjugated linoleic acid and medium-chain triglycerides for obesity management*. 2021. 46(1): p. 12.
230. Mao B et al. Production of conjugated fatty acids in probiotic-fermented walnut milk with the addition of lipase. 2022. 172: p. 114204.
231. Badawy S et al. *Conjugated linoleic acid (CLA) as a functional food: Is it beneficial or not?* 2023: p. 113158.
232. Hsu C-Y et al. Facile adipocyte uptake and liver/adipose tissue delivery of conjugated linoleic acid-loaded tocol nanocarriers for a synergistic anti-adipogenesis effect. 2024. 22(1): p. 50.
233. Du M et al. *Metabolic, structure-activity characteristics of conjugated linolenic acids and their mediated health benefits.* 2024. 64(23): pp. 8203–8217.
234. Dahiya DK. A.K.J.J.o.f.s. Puniya, and technology, *Isolation, molecular characterization and screening of indigenous lactobacilli for their abilities to produce bioactive conjugated linoleic acid (CLA)*. 2017. 54: pp. 792–801.
235. Abenavoli L, et al. Gut microbiota and obesity: a role for probiotics. Nutrients. 2019;11(11):2690.
236. Zhang J, et al. Relationship between probiotics and obesity: a review of recent research. Food Sci Technol. 2022;42:e30322.
237. Yadav MK, et al. Probiotics, prebiotics and synbiotics: Safe options for next-generation therapeutics. Appl Microbiol Biotechnol. 2022;106(2):505–21.
238. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr. 1995;125(6):1401–12.
239. Geurts L, et al. Gut microbiota controls adipose tissue expansion, gut barrier and glucose metabolism: novel insights into molecular targets and interventions using prebiotics. Beneficial microbes. 2014;5(1):3–17.
240. He M, Shi B. Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics. Cell bioscience. 2017;7(1):1–14.
241. Koutnikova H, et al. Impact of bacterial probiotics on obesity, diabetes and non-alcoholic fatty liver disease related variables: a systematic review and meta-analysis of randomised controlled trials. BMJ open. 2019;9(3):e017995.
242. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am J Clin Nutr. 2009;89(6):1751–9.
243. Guarino MPL, et al. Mechanisms of action of prebiotics and their effects on gastro-intestinal disorders in adults. Nutrients. 2020;12(4):1037.
244. Cencic A, Chingwaru W. The role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutrients. 2010;2(6):611–25.
245. Darb Emamie A, et al. The effects of probiotics, prebiotics and synbiotics on the reduction of IBD complications, a periodic review during 2009–2020. J Appl Microbiol. 2021;130(6):1823–38.
246. Rioux KP, Madsen KL, Fedorak RN. The role of enteric microflora in inflammatory bowel disease: human and animal studies with probiotics and prebiotics. Gastroenterol Clin. 2005;34(3):465–82.
247. Cruz BC, et al. Preclinical and clinical relevance of probiotics and synbiotics in colorectal carcinogenesis: a systematic review. Nutr Rev. 2020;78(8):667–87.
248. Panesar PS et al. *Synbiotics: potential dietary supplements in functional foods.* IFIS: Berkshire, UK, 2009. 2009.
249. De Vrese M, Schrezenmeir. *Probiotics, prebiotics, and synbiotics.* Food biotechnology, 2008: pp. 1–66.
250. Manigandan T, et al. Probiotics, prebiotics and synbiotics-a review. Biomedical Pharmacol J. 2012;5(2):295.
251. Mohammadi H, et al. Effects of pro-/synbiotic supplementation on anthropometric and metabolic indices in overweight or obese children and adolescents: A systematic review and meta-analysis. Complement Ther Med. 2019;44:269–76.
252. Perraudeau F, et al. Improvements to postprandial glucose control in subjects with type 2 diabetes: a multicenter, double blind, randomized placebo-controlled trial of a novel probiotic formulation. BMJ Open Diabetes Res Care. 2020;8(1):e001319.

253. Stenman L, et al. Potential probiotic Bifidobacterium animalis ssp. lactis 420 prevents weight gain and glucose intolerance in diet-induced obese mice. Beneficial microbes. 2014;5(4):437–45.
254. Larsen IS, et al. Experimental diets dictate the metabolic benefits of probiotics in obesity. Gut Microbes. 2023;15(1):2192547.
255. Kang Y, et al. Lactobacillus acidophilus ameliorates obesity in mice through modulation of gut microbiota dysbiosis and intestinal permeability. Pharmacol Res. 2022;175:106020.
256. Tang C, et al. Protective and ameliorating effects of probiotics against diet-induced obesity: A review. Food Res Int. 2021;147:110490.
257. Schütz F et al. Obesity and gut microbiome: review of potential role of probiotics. Porto biomedical J, 2021. 6(1).
258. Aoun A, Darwish F, Hamod N. The influence of the gut microbiome on obesity in adults and the role of probiotics, prebiotics, and synbiotics for weight loss. Prev Nutr food Sci. 2020;25(2):113.
259. Cai Y, et al. Probiotics therapy show significant improvement in obesity and neurobehavioral disorders symptoms. Front Cell Infect Microbiol. 2023;13:533.
260. Liber A, Szajewska H. Effect of oligofructose supplementation on body weight in overweight and obese children: a randomised, double-blind, placebo-controlled trial. Br J Nutr. 2014;112(12):2068–74.
261. Vallianou NG, et al. The Role of Next-Generation Probiotics in Obesity and Obesity-Associated Disorders: Current Knowledge and Future Perspectives. Int J Mol Sci. 2023;24(7):6755.
262. Ben OR, et al. Can probiotics improve weight loss in patients with obesity? Endocrine Abstracts. Bioscientifica; 2023.
263. Shirvani-Rad S et al. *Probiotics as a complementary therapy for management of obesity: a systematic review.* Evidence-Based Complementary and Alternative Medicine, 2021. 2021.
264. Ben OR, et al. Does probiotics consumption improve glycemic parameters in adults with obesity? Endocrine Abstracts. Bioscientifica; 2023.
265. Wiciński M, et al. Probiotics for the treatment of overweight and obesity in humans—a review of clinical trials. Microorganisms. 2020;8(8):1148.
266. Loy MH, et al. Probiotic use in children and adolescents with overweight or obesity: A scoping review. Child Obes. 2023;19(3):145–59.
267. Ahn HY, et al. Supplementation with two probiotic strains, Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032, reduces fasting triglycerides and enhances apolipoprotein AV levels in non-diabetic subjects with hypertriglyceridemia. Atherosclerosis. 2015;241(2):649–56.
268. Wang Y, et al. Encyclopedia of fecal microbiota transplantation: A review of effectiveness in the treatment of 85 diseases. Chin Med J. 2022;135(16):1927–39.
269. Rakotonirina A, Galperine T, Allémann E. Fecal microbiota transplantation: a review on current formulations in Clostridioides difficile infection and future outlooks. Expert Opin Biol Ther. 2022;22(7):929–44.
270. Kelly CR, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. Gastroenterology. 2015;149(1):223–37.
271. Li SS, et al. Durable coexistence of donor and recipient strains after fecal microbiota transplantation. Science. 2016;352(6285):586–9.
272. Zhang F, et al. Microbiota transplantation: concept, methodology and strategy for its modernization. Protein Cell. 2018;9(5):462–73.
273. Kootte RS, et al. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. Cell Metabol. 2017;26(4):611–9. e6.
274. Smits LP, et al. Effect of vegan fecal microbiota transplantation on carnitine- and choline-derived trimethylamine-N-oxide production and vascular inflammation in patients with metabolic syndrome. J Am Heart Association. 2018;7(7):e008342.
275. Allegretti JR, et al. Effects of fecal microbiota transplantation with oral capsules in obese patients. Clin Gastroenterol Hepatol. 2020;18(4):855–63. e2.
276. Vrieze A, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012;143(4):913–6. e7.
277. Leong KS, et al. Effects of fecal microbiome transfer in adolescents with obesity: the gut bugs randomized controlled trial. JAMA Netw open. 2020;3(12):e2030415–2030415.
278. Marotz CA, Zarrinpar A. Focus: microbiome: treating obesity and metabolic syndrome with fecal microbiota transplantation. Yale J Biol Med. 2016;89(3):383.
279. Chu NH, Chow E, Chan JCJB. *The Therapeutic Potential of the Specific Intestinal Microbiome (SIM) Diet on Metabolic Diseases.* 2024. 13(7).
280. Goldsmith JR. and R.B.J.J.o.g. Sartor, *The role of diet on intestinal microbiota metabolism: downstream impacts on host immune function and health, and therapeutic implications*. 2014. 49: pp. 785–98.
281. Santos-Marcos JA, Perez-Jimenez F. J.T.J.o.n.b. Camargo. role diet intestinal microbiota Dev metabolic syndrome. 2019;70:1–27.
282. Meslier V, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes. gut microbiome metabolome independently energy intake. 2020;69(7):1258–68.
283. Chu N, Chan JC, Chow EJFiE. *Pharmacomicrobiomics in Western medicine and traditional Chinese medicine in type 2 diabetes.* 2022. 13: p. 857090.
284. Feng J et al. Effects of semaglutide on gut microbiota, cognitive function and inflammation in obese mice. 2024. 12: p. e17891.
285. Duan X et al. Semaglutide alleviates gut microbiota dysbiosis induced by a high-fat diet. 2024. 969: p. 176440.
286. Schoeneck M, Iggman DJN, Metabolism, Diseases C. The effects of foods on LDL cholesterol levels: A systematic review of the accumulated evidence from systematic reviews and meta-analyses of randomized controlled trials. 2021. 31(5): pp. 1325–38.
287. Rodríguez-Monforte M et al. Metabolic syndrome and dietary patterns: a systematic review and meta-analysis of observational studies. 2017. 56: pp. 925–47.
288. Chu N, Chan JC, Chow EJCN. A diet high in FODMAPs as a novel dietary strategy in diabetes? 2022. 41(10): pp. 2103–12.
289. Rao M et al. Effect of inulin-type carbohydrates on insulin resistance in patients with type 2 diabetes and obesity: a systematic review and meta-analysis. 2019. 2019(1): p. 5101423.
290. Hills RD et al. Gut microbiome: profound implications for diet and disease. 2019. 11(7): p. 1613.
291. Ratajczak W et al. Immunomodulatory potential of gut microbiome-derived short-chain fatty acids (SCFAs). 2019. 66(1): pp. 1–12.
292. Sun L-J, Li J-N, Y.-Z. J.C.m.j. Nie, *Gut hormones in microbiota-gut-brain cross-talk.* 2020. 133(7): pp. 826–833.
293. Yu K et al. The impact of soluble dietary fibre on gastric emptying, postprandial blood glucose and insulin in patients with type 2 diabetes. 2014. 23(2): pp. 210–8.
294. Hu W, Cassard A-M, Ciocan DJN. Pectin metabolic liver disease. 2022;15(1):157.
295. Pascale N et al. The potential of pectins to modulate the human gut microbiota evaluated by in vitro fermentation: A systematic review. 2022. 14(17): p. 3629.
296. Deng Z et al. The different effects of psyllium husk and orlistat on weight control, the amelioration of hypercholesterolemia and non-alcohol fatty liver disease in obese mice induced by a high-fat diet. 2022. 13(17): pp. 8829–49.
297. Bacha AA et al. *Effect of Psyllium husk fiber and lifestyle modification on human body insulin resistance.* 2022. 15: p. 11786388221107797.
298. Ziai SA et al. Psyllium decreased serum glucose and glycosylated hemoglobin significantly in diabetic outpatients. 2005. 102(2): pp. 202–7.
299. Msomi NZ et al. Suitability of sugar alcohols as antidiabetic supplements: A review. 2021. 29(1): p. 1.
300. García-Sanmartín J et al. Agaricus mushroom-enriched diets modulate the microbiota-gut-brain axis and reduce brain oxidative stress in mice. 2022. 11(4): p. 695.
301. Martínez-González MA, Gea A. .r. Ruiz-Canela. Mediterranean diet Cardiovasc health: Crit Rev. 2019;124(5):779–98.
302. Bendall C et al. Central obesity and the Mediterranean diet: A systematic review of intervention trials. 2018. 58(18): pp. 3070–84.
303. Eleftheriou D et al. *Mediterranean diet and its components in relation to all-cause mortality: Meta-analysis.* 2018. 120(10): pp. 1081–1097.
304. Mao T et al. *Semaglutide alters gut microbiota and improves NAFLD in db/db mice.* 2024. 710: p. 149882.
305. Zhao L et al. Gut microbiota mediates positive effects of liraglutide on dyslipidemia in mice fed a high-fat diet. 2022. 9: p. 1048693.
306. Moreno-Pérez D et al. Effect of a protein supplement on the gut microbiota of endurance athletes: a randomized, controlled, double-blind pilot study. 2018. 10(3): p. 337.
307. Allen JM et al. Exercise alters gut microbiota composition and function in lean and obese humans. 2018. 50(4): pp. 747–57.

308. Motiani KK et al. Exercise training modulates gut microbiota profile and improves endotoxemia. 2020. 52(1): p. 94.
309. Bressa C et al. Differences in gut microbiota profile between women with active lifestyle and sedentary women. 2017. 12(2): p. e0171352.

Publisher's note