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REVIEW

The interplay of gut microbiota, obesity, and depression: insights and interventions

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Abstract
The gut microbiome, body weight, and related comorbidities are intricately linked through a complex interaction of microbial, genetic, environmental, and psychological factors. Alterations in gut microbiota can contribute to the development of weight disorders and depressive symptoms, with the potential for these relationships to be bidirectional. Effective management of these interconnected conditions often involves a combination of lifestyle modifications and psychological support. Medical interventions, including treatments for obesity, antidiabetic drugs, antidepressants, antibiotics, and probiotics, can have beneficial and detrimental effects on gut microbiota and mental health. Further research is needed to better understand their impact on gut microbiome and mental health in the context of obesity.

Keywords Obesity · Depression · Gut microbiota · Mental health · Antidepressants · Probiotics

Introduction

Genetic predispositions, socio-demographic variables, environmental conditions, psychological states, lifestyle choices, infections, and medication use influence the interplay between microbiome and health (Fig. S1a). Disruptions in the gut microbiota can lead to metabolic and psychological dysregulation, contributing to obesity and depression through mechanisms such as chronic inflammation, altered metabolism, and hormonal imbalances (Fig. S1b). Understanding these interactions is crucial for advancing our health knowledge and developing targeted prevention and treatment strategies for associated diseases [1, 2]. This review examines the interconnections between gut microbiota, obesity, and depression.

Intestinal microbiota

The gut microbiota, composed of over 1,000 species of bacteria, archaea, fungi, protozoa, and viruses significantly impacts human health [3, 4]. It plays a crucial role in immune system maturation, maintaining intestinal integrity, producing vitamins K and B, preventing infections, and regulating metabolism [5].

The bacterial genome content in the gut is 150 times larger than the human genome [4]. The main microbial phyla in the gut are *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia*, with *Bacteroidetes* and *Firmicutes* making up about 90% of the gut microbiome [6, 7]. A balanced gut microbiota, or eubiosis,

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enhances immunity, nutrient absorption, blood glucose and lipid balance, and energy metabolism, while also producing essential vitamins and protecting against pathogens. Imbalanced gut microbiota, or dysbiosis, can result from antibiotics, poor diet, stress, and other factors, leading to health issues [8, 9].

Gut microbiota composition varies across the gastrointestinal tract due to differences in environment and flow rates. Factors like age, diet, antibiotics, and exercise influence the microbiome. Gut bacteria metabolize dietary polysaccharides into short-chain fatty acids (SCFAs), providing about 70% of the energy for colon cells and contributing to glucose homeostasis, lipid metabolism, immune function, and overall health [10].

Obesity

Obesity, affecting over 650 million people globally, significantly contributes to morbidity and mortality [11]. Defined by a body mass index (BMI) over 30 kg/m2 (overweight is 25–30 kg/m2), obesity results from an imbalance between energy intake and expenditure, leading to excessive fat accumulation. It is linked to diseases like type 2 diabetes, cardiovascular diseases, certain cancers, and high blood pressure [12].

This complex disease is influenced by diet, antibiotic use, environment, genetics, lifestyle, socioeconomic factors, and gut microbiota composition. High-calorie diets contribute to obesity and alter gut microbiome function. Modern lifestyle factors, hormonal imbalances, and genetic influences drive the obesity crisis. Gut hormones communicate food intake and energy stores to the brain, regulating appetite [13].

Depression

Depression is a common chronic mental disorder characterized by symptoms such as insomnia, melancholy, lack of enjoyment in life, and low energy. Its prevalence is estimated at 11% in low- to middle-income countries and 15% in high-income countries, affecting about 280 million people globally [14, 15]. Annually, depression and anxiety cost an estimated US$ 1 trillion due to the loss of 12 billion productive workdays [16].

Depression is significantly correlated with various physical health conditions, including suicide, cancers, respiratory diseases, diabetes, and cardiovascular diseases. In the USA alone, depression-related suicides claim about 40,000 lives annually, among older men [17]. According to WHO reports from 2016, around 785,000 suicides occur worldwide each year, with up to 60% attributed to depression [18, 19].

Interplay between gut microbiota, obesity and depression

There is a link between gut microbiome, obesity, and depression (Fig. 1). For example, an increased *Firmicutes/Bacteroidetes* ratio is associated with obesity. However, this ratio alone cannot fully explain obesity due to the gut microbiome's complexity [20, 21]. For instance, mutations in the leptin gene in mice have been linked to altered bacterial proportions [8, 20]. The gut microbiome affects energy intake and metabolism, influencing weight and fat storage [22, 23].

Obese individuals often have microbiomes that increase energy extraction and fat accumulation. Gut microbiome composition, such as higher *Prevotella* levels, is associated with greater weight loss compared to *Bacteroides* dominance [24, 25]. Inflammation caused by microbiota can affect leptin expression and thermogenesis, contributing to obesity. Chronic low-grade inflammation, driven by lipopolysaccharides (LPS), impairs energy expenditure (Fig. 2) [9].

The gut microbiome also impacts vitamin synthesis, xenobiotic metabolism, and obesity regulation. Studies using germ-free mice have highlighted the microbiome's role in energy metabolism and mental health. The gut-brain axis connects microbiome composition with brain function and mental disorders, such as depression [26–28]. Previous studies indicate alterations in the gut microbiota of patients with mental disorders, with the most studied phyla being *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*, and key genera including *Prevotella*, *Coprococcus*, *Parabacteroides*, *Phascolarctobacterium*, *Escherichia-Shigella*, *Bacteroides*, *Alistipes*, and *Veillonella* [29].

Specific bacteria, like *Alistipes* and *Veillonella*, are associated with depression, while others, like *Prevotella*, are less prevalent [27, 30]. Dysbiosis, including imbalances in gut microbiota, is linked to depression and systemic inflammation. Microbial lactate accumulation may also impair brain function and contribute to mental disorders [31, 32].

The link between gut microbiota and mental health, particularly depression, is increasingly recognized through the concept of the gut-brain axis. This bidirectional communication pathway allows gut bacteria to influence brain function via neurotransmitter production, immune responses, and signaling molecules. Disruptions in gut microbiota, or dysbiosis, can lead to imbalances in neurotransmitters like serotonin, increase systemic inflammation, and impair gut barrier function, all of which may contribute to depressive symptoms [28]. Dysbiosis can lead to an increase in pro-inflammatory cytokines and a disruption in the synthesis of key neurotransmitters like serotonin, dopamine, and

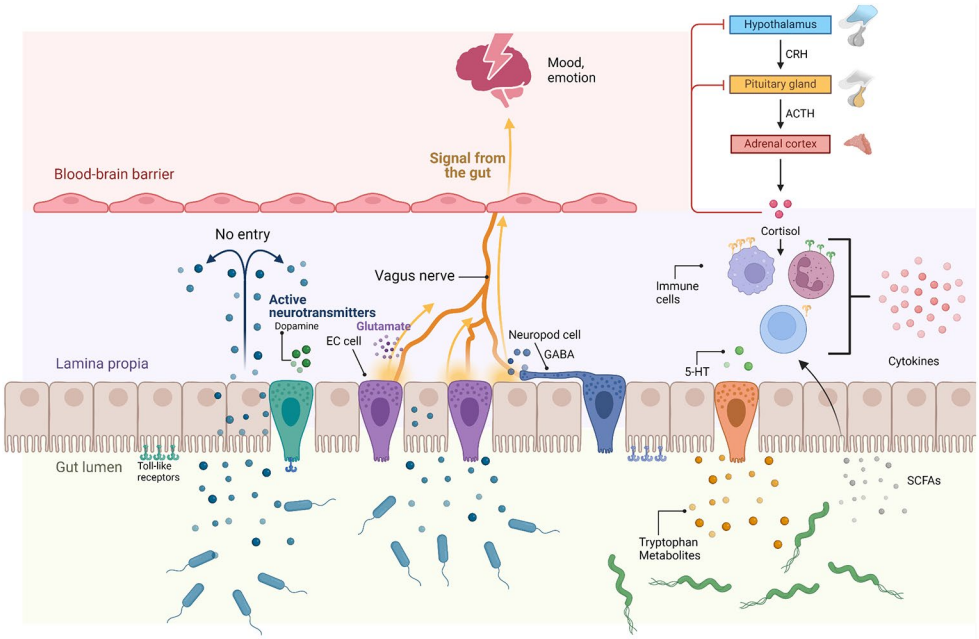

Fig. 1 Gut-brain axis signaling pathways and their influence on mood and emotion regulation. The diagram depicts the interactions between the gut lumen, gut microbiota, and the central nervous system through the vagus nerve, immune cells, and neurotransmitter signaling. Various gut-derived signals, including active neurotransmitters (dopamine, serotonin, glutamate, and gamma-aminobutyric acid (GABA)), as well as tryptophan metabolites and short-chain fatty acids (SCFAs), influence mood and emotional regulation by transmitting signals to the brain. This communication occurs through the vagus nerve, immune modulation, and the hypothalamic-pituitary-adrenal (HPA) axis, which involves the secretion of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. Dysregulation in these pathways can impact mood and emotional states, contributing to stress, depression, and anxiety

gamma-aminobutyric acid (GABA), contributing to the development of metabolic and mood disorders [33].

Obesity is often associated with mental health issues, particularly depression. High body weight is linked to poorer mental health due to systemic inflammation, hypothalamic-pituitary-adrenal axis dysregulation, and psychological stress from weight stigma and discrimination, exacerbating mental health problems and hindering weight control efforts [34].

Furthermore, imbalances in gut microbiota can impair the production of crucial metabolites like SCFAs, disrupting gut-brain signaling and leading to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. This dysregulation can result in elevated cortisol levels and altered serotonin production, which are associated with stress, anxiety, and mood disorders [35–37].

Obesity is influenced by genetics, metabolism, and environmental factors, with growing evidence highlighting the role of gut microbiota in these interactions. Dysbiosis in the gut microbiome has been linked to obesity through pathways that affect metabolism, insulin resistance, and satiety, offering potential therapeutic targets for prevention and treatment [38, 39].

Interventions of gut microbiota, obesity and depression

Lifestyle modifications, including diet, stress management, exercise, and avoiding harmful substances, are commonly recommended for managing altered gut microbiota, obesity, and depression (Table S1). While these strategies can improve quality of life, long-term results are often modest, with only 61% of individuals completing such programs successfully. In severe cases, medical interventions, surgical options, and psychotherapy may be needed to address these complex issues (Table S2, S3). Effective management can enhance health outcomes and reduce the prevalence of related conditions like type 2 diabetes, cardiovascular disease, and certain cancers, thereby improving overall public health [40].

Antibiotics and probiotics

Antibiotics like amoxicillin and ciprofloxacin can disrupt gut microbiota by killing both harmful and beneficial bacteria. This imbalance may lead to altered neurotransmitter levels, increased inflammation, and gastrointestinal issues, potentially contributing to mood disturbances and depressive symptoms.

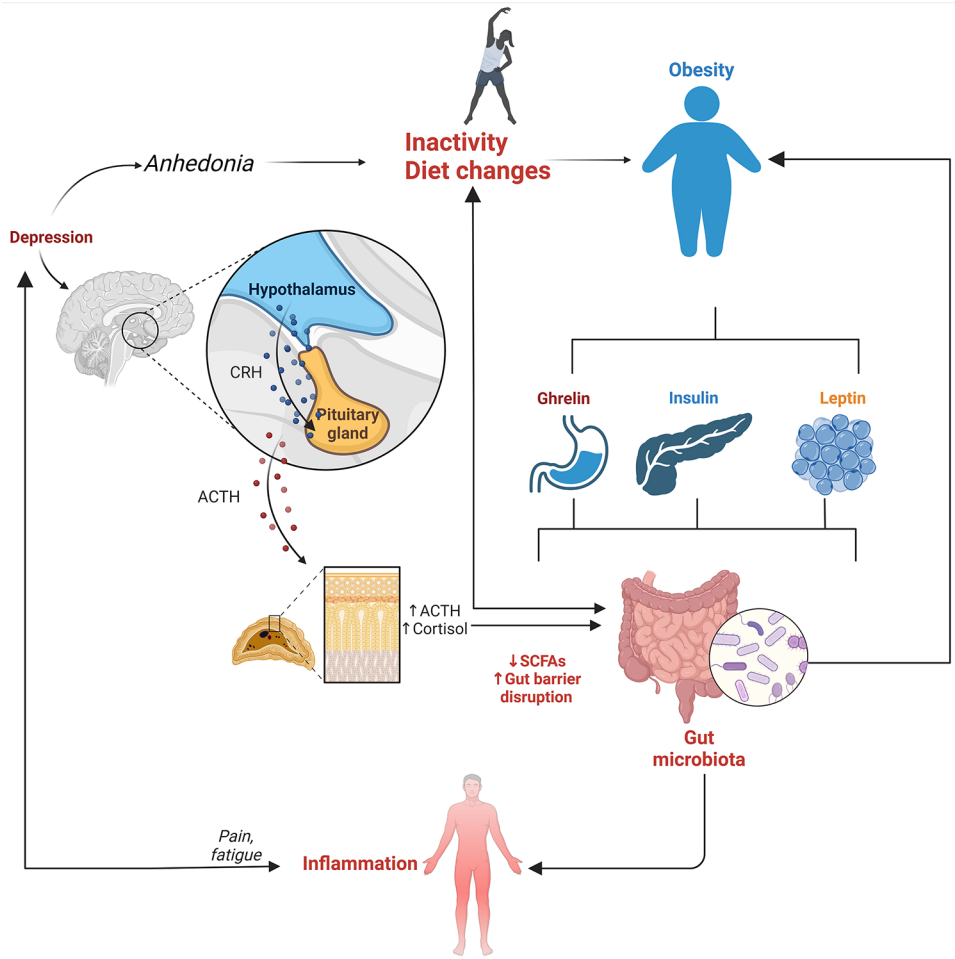

Fig. 2 Interconnection between obesity diet inactivity gut microbiota and the hypothalamic-pituitary-adrenal (HPA) axis contributing to inflammation and depression. The diagram illustrates the complex relationship between inactivity and diet changes, leading to obesity, which interacts with hormonal regulators like ghrelin, insulin, and leptin. These factors influence gut microbiota, leading to reduced short-chain fatty acids (SCFAs) and increased gut barrier disruption. Such disturbances in gut health elevate cortisol and adrenocorticotropic hormone (ACTH) levels through the activation of the HPA axis, fueling inflammation, pain, fatigue, and depressive symptoms, including anhedonia. This bidirectional feedback loop highlights the role of chronic inflammation in exacerbating psychological and metabolic health issues

Probiotics, such as *Lactobacillus rhamnosus* and *Bifidobacterium longum*, can help restore a balanced gut microbiota. They may improve mental health by enhancing gut barrier function, modulating neurotransmitter levels, and reducing stress and anxiety. These effects vary by strain and individual response, but these probiotics are commonly studied for their potential mental health benefits [41, 42].

GLP-1 receptor agonists

In 2016, the American Association of Clinical Endocrinology reviewed five anti-obesity medications (orlistat, lorcaserin, naltrexone–bupropion, liraglutide, and phentermine–topiramate) for long-term use. However, the FDA withdrew lorcaserin in 2020 due to cancer risks. In 2021, studies on semaglutide, a new weekly Glucagon-Like Peptide-1 (GLP-1) receptor agonist, showed promising results that could impact clinical practice. Other diabetes medications, such as Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors, metformin, and pramlintide, also show potential for obesity management [43, 44].

Anti-obesity drugs like liraglutide and semaglutide affect gut microbiota, enhancing bacterial diversity and influencing metabolic disorders. Semaglutide significantly alters gut microbiota, impacting mental health and metabolic pathways. Liraglutide has shown therapeutic effects on fatty liver and modifies gut bacteria linked to metabolism and inflammation (Fig. 3) [45–47].

Both liraglutide and semaglutide impact the gut microbiota in conditions like Polycystic Ovary Syndrome (PCOS). They influence the abundance of various bacterial species and promote beneficial bacteria, altering the gut microbiome's diversity and composition. These changes may optimize obesity treatment outcomes [46].

Studies on GLP-1 receptor agonists reveal mixed effects on mental health. Semaglutide and liraglutide have been associated with depressive symptoms, anxiety, and, in some cases, suicidal thoughts. However, there's no clear causal link between GLP-1R agonism and severe depression or suicide. Monitoring for mood changes is advised for patients using these medications [48–50].

Recent social media discussions also reflect concerns about GLP-1 receptor agonists affecting mood and mental

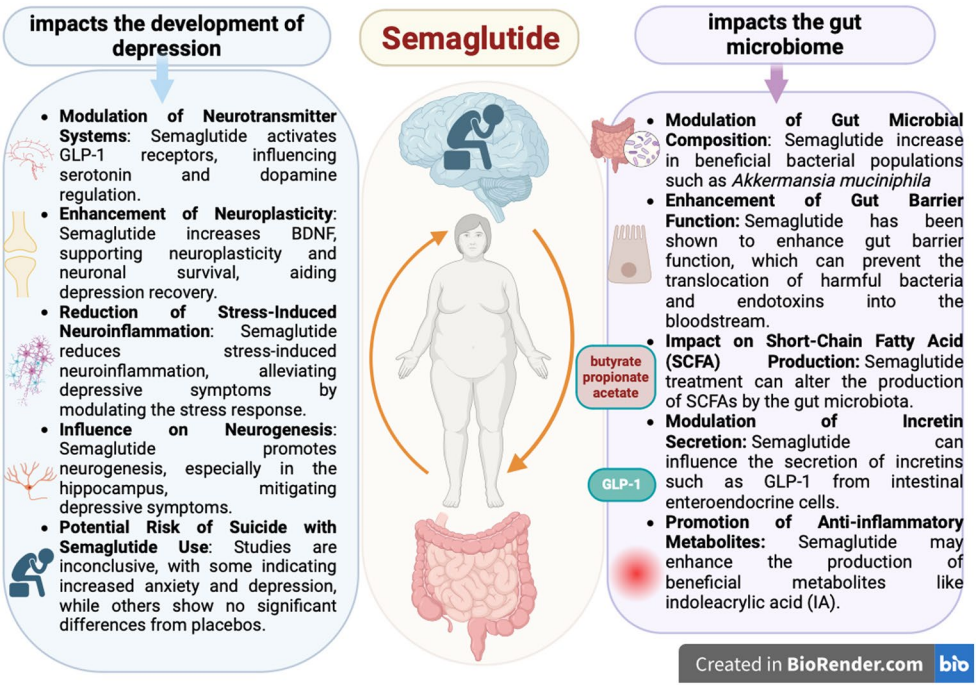

Fig. 3 Effect of semaglutide on mental health and gut microbiome. This diagram illustrates how Semaglutide influences mental health and changes the gut microbiota, showing its combined effects on managing obesity and related conditions

health, indicating the need for ongoing vigilance and assessment [51].

Antidiabetic drugs

Metformin affects gut microbiota by altering its composition, enhancing SCFA-producing bacteria like *Butyricimonas* and beneficial probiotics such as *Lactobacillus*, while reducing harmful pathogens like *Prevotella* [52, 53]. It improves glucose control in obese mice and enhances SCFA-producing bacteria, and in T2DM and COVID-19 patients, it boosts beneficial bacteria like *Bacteroides* while lowering harmful ones [54]. Metformin might also impact mental health and depressive symptoms, potentially offering benefits for treatment-resistant depression. However, the exact mechanisms of its effects on mental health need further research [55, 56].

Anti-obesity pharmacological agents

Naltrexone-Bupropion has been shown to influence gut microbiome diversity [57]. Orlistat treatment results in a reduction of *Firmicutes* and an increase in *Bacteroidetes*, with associated improvements in the diversity indices and elevated levels of *Lactobacillus*, particularly *Lactobacillus gasseri* [58]. Topiramate increases *Lactobacillus johnsonii* but significantly reduces the overall abundance of *Lactobacillus* [59]. SGLT2 Inhibitors alter the prevalence of specific bacteria, including the LPS-producing *Oscillibacter* and SCFA-producing *Bacteroides* and *Odoribacter*, while boosting *Ruminococci*, which are beneficial for SCFA production [60].

Regarding mental health outcomes, behavioral weight loss (BWL) and Naltrexone-Bupropion have demonstrated efficacy in treating binge-eating disorder, with BWL showing superior results compared to no intervention [61]. Orlistat has been linked to increased physical activity and reduced depression in Latinx patients with obesity, although these effects were not directly associated with weight loss [62]. Phentermine-Topiramate has been shown to alleviate depressive symptoms in obese patients and improve quality of life, though it poses risks such as hypomania in bipolar patients and potential psychosis when combined with venlafaxine [63].

SGLT2 inhibitors have improved quality of life in diabetes patients and show promise for adjunctive treatment of major depressive disorder (MDD) [64]. These findings highlight the complex relationship between weight loss medications, gut microbiota changes, and psychiatric outcomes.

Antidepressants

Antidepressants are pharmacological agents used primarily to treat major depressive disorder (MDD) and other mood disorders by modulating neurotransmitter systems in the brain. The most widely prescribed antidepressants include Selective Serotonin Reuptake Inhibitors (SSRIs), such as fluoxetine and sertraline, which enhance serotonergic neurotransmission by inhibiting the reuptake of serotonin. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), including venlafaxine and duloxetine, act on both serotonin

and norepinephrine, aiming to alleviate depressive symptoms through dual neurotransmitter modulation. Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs), though less commonly used as first-line treatments due to their broader side effect profiles, remain effective for treatment-resistant cases and specific mood disorders. TCAs, such as amitriptyline, affect multiple neurotransmitter systems, while MAOIs, such as phenelzine, inhibit monoamine oxidase, leading to increased levels of serotonin, norepinephrine, and dopamine [65, 66].

Atypical antidepressants, including bupropion and mirtazapine, exhibit diverse mechanisms and are employed based on individual patient profiles and specific clinical needs. Bupropion, for instance, primarily affects norepinephrine and dopamine systems, while mirtazapine enhances neurotransmitter release through its antagonistic effects on certain receptors. The therapeutic efficacy of antidepressants is often accompanied by a range of side effects, which vary by drug class and individual patient response. Monitoring and managing these effects are crucial, as abrupt discontinuation of antidepressants can precipitate withdrawal symptoms. Overall, the choice of antidepressant and treatment regimen should be tailored to the patient's specific condition and response to therapy, with ongoing assessment to optimize outcomes and minimize adverse effects [65, 66].

The studies demonstrate that fluoxetine significantly affected the growth of *E. coli*, *E. faecalis*, and *S. aureus*, with minimal impact on *C. albicans*. In contrast, escitalopram notably influenced the growth of *E. coli*, *E. faecalis*, *B. bifidum*, *L. rhamnosus*, and *C. albicans*, while mirtazapine exhibited the greatest activity against *L. rhamnosus* and *C. albicans* [67]. Antidepressants can modify the abundance and composition of intestinal microbiota, which in turn affects treatment outcomes for depression by influencing drug metabolism, absorption, and blood-brain barrier permeability [68].

Conclusions

Changes in gut microbiota and the presence of depressive disorders are commonly noted in obesity, with these conditions potentially aggravating each other. The influence of different treatments—such as antibiotics, probiotics, anti-obesity medications, antidiabetic agents, and antidepressants—on gut microbiota and mental health is often intricate and multifaceted. These interventions can produce conflicting effects and may differ considerably among individuals. Consequently, thorough research is required to clarify how these treatments affect gut microbiota and mental health.

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Data availability All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethical approval Not applicable.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

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