ISSN 2959-409X

Influence of Gut Microflora on Eating Disorders

Xinyang Wang[1, *]

[1]University of Leeds, Leeds, LS2 9JT, United Kingdom
*Corresponding author: guoxuan@ldy.edu.rs

Abstract:

Eating disorders (EDs) have attracted extensive attention worldwide as a disease that seriously affects eating behaviour and weight control. The impact and pathogenesis of the gut microbiota in EDs remain important research directions and have sparked interest in developing treatments for these conditions. This review examines the intricate interactions between the gut microbiota and the gut-brain (GB) axis, and Eds focuses on bulimia nervosa (BN), binge eating disorder (BED), and anorexia nervosa (AN). According to the findings, the pathophysiology of AN and BED is correlated with lower levels of short-chain fatty acids (SCFAs) and beneficial bacteria in the gut microbiota. In addition, as a key mediator, the GB axis affects the neural pathways and behaviours between the brain and the gut, thereby exacerbating EDs symptoms. This review highlights the potential of gut microbiota-targeted therapies as adjunctive treatments for EDs. However, this study also has certain limitations. For example, more investigation is required to explore the clear mechanism and causal relationship between the gut microbiome and other EDs. Future studies should clarify the function of gut bacteria in EDs and advance treatment strategies.

Keywords: Gut-brain-axis; eating disorders; gut microbiota.

1. Introduction

Eating disorders (EDs) have gained considerable attention in recent years as a serious mental illness. The main characteristic of EDs is the abnormalities control behaviours for dietary or weight. Anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), avoidant/restrictive food intake disorder, pica, and rumination syndrome are the six primary types of feeding and EDs that are recognised by the Diagnostic and Statistical Manual (DSM-5) and the International Classification of Diseases (ICD-11) [1]. Women between the ages of 10 and 20 are primarily seen for the AN, BN, and BED categories of EDs [2]. EDs specifically involve atypical neural mechanisms associated with reward, behavioural regulation, and decision-making processes. Anxiety disorders and EDs have been related to damage to brain areas such as the dopamine pathway, the hippocampus, the amygdala, and the medial prefrontal cortex [3]. In addition, the neuropeptides responsible for regulating feelings of hunger and fullness, namely leptin and gastrin, are also disrupted in these conditions [4].

Emerging data highlight that the gut microbiome has a role in the emergence of neuropsychiatric conditions. The complex microorganism population of the gut elicits immense host health alteration due to the complexity of its interacting activity with host cells, which is related to different body functions, including mental health [5]. The gut microbiota-gut-brain (MGB) axis is a two-way communication pathway, and gut bacteria influence brain function and behaviour. Neurotransmitters that communicate with the central nervous system include glutamate, acetylcholine, gamma-aminobutyric acid (GABA), serotonin, and dopamine produced by gut bacteria. Variations in immune responses and appetite regulation could be created from diet-induced modifications in the microbiome diversity [6]. Dysbiosis and immune system activation stem from an imbalance in the gut microbiota, which affects the HPA axis and consequently causes behavioural changes [7-9].

Knowledge of such mechanisms is crucial in conceiving new therapeutic strategies for psychiatric disorders and emotional eating. The review will discuss the microbiota-gut-brain axis, those interrelated pathways of bidirectional communication. The focus shall be on how gut microbiota can contribute to EDs. Thereby, these interactions between the brain and gut microbes might result in their effects on emotional eating and open new therapeutic avenues.

2. Eating Disorders (EDs)

EDs are severe mental health conditions marked by irregular eating habits and an excessive focus on weight. According to the patient's body mass index, the DSM-5 classifies AN's severity into four categories: extreme (BMI

<15 kg/m^2), severe (BMI 15-15.99 kg/m^2), moderate (BMI 16-16.99 kg/m^2), and mild (BMI ≥17 kg/m^2). AN is defined by intense anxiety and a fear of gaining weight, which leads to extreme dietary restrictions. This can lead to significant weight loss and distorted appearance. The malnutrition and dramatic weight loss associated with this disease can affect all organs and systems of the body, particularly damaging the gastrointestinal tract. BN usually occurs with normal weight or weight gain, with the patient repeatedly eating large quantities of food in brief periods, subsequently countered by behaviours like vomiting, excessive physical activity, and laxative use. In contrast, BED is characterised by repeated overeating without compensating behaviour [1].The DSM-5 reflects advances in the understanding of EDs and has significantly impacted the epidemiology of EDs.Researchers are now paying more attention to diagnostic criteria, epidemiological characteristics, and the development of effective prevention and treatment strategies [10].

Research has indicated that developing the central nervous system and regulating emotions depend on a healthy gut microbiota. Imbalances in the gut microbiota have been linked to various neuropsychiatric disorders. Specifically, alterations in the microbiota's composition are associated with anxiety and depression, both of which are prevalent in AN patients.Psychological stress can lead to microbial exacerbation and further aggravate intestinal inflammation. In contrast, anxiety ranks among the most prevalent mental health issues and often co-occurs alongside other mental disorders and EDs. Some studies have shown that stress has a genetic component and impacts gut function by weakening the gut lining. This happens through the reduction of specific tight junction proteins, which alters the bacterial composition of the gut and enhances intestinal permeability. Consequently, harmful bacteria and allergens can enter the bloodstream, triggering inflammatory and neuroinflammatory responses. When these inflammatory cytokines reach the brain, they can worsen mood disorders such as anxiety [11]. In conclusion, investigating the impact of alterations in gut microbiome on EDs using anxiety disorders proves to be beneficial.

3. Gut Microbiota and Gut-Brain Axis

3.1 Gut Microbiota

The term "human gut microbiota" describes the microorganisms and the collective genomes in a defined environment, the human body. This complex ecosystem has a significant influence on the host's health and is marked by a network of both positive and negative interactions [12]. While other microorganisms may inhabit the skin, mouth, and respiratory tract, about 90% are found in the small and large intestines [13].

Within the human body, gut microorganisms are key players in the normal functioning of the gut. These include maintenance of proper pH, control of bowel transit, participation in food absorption, and B vitamin synthesis [13,14]. Besides, an intestinal barrier is formed with the help of these microorganisms that prevents any pathogenic invasions [15]. The regulation of immune system activity and function is greatly influenced by the gut microbiota. As the largest lymphoid organ in the body, it interacts with the digestive tract lymphoid tissue to regulate immunity and cytokine levels. Moreover, gut bacteria neurotransmitters interacting with the central nervous system include glutamate, acetylcholine, gamma-aminobutyric acid (GABA), serotonin, and dopamine. Thus, alterations of diet-induced microbial diversity may influence appetite and immunity regulation, connecting diet, gut microbiota, and mental health through a complex interaction network [16].

The imbalances in the number and composition of gut microbiota—known as intestinal dysbiosis—may lead to various health-related problems such as irregular bowel habits, diminished digestive and absorptive capacity, disruptions in vitamin synthesis or metabolism, poor fat digestion, compromised intestinal barrier, and hyper-stimulated immune system.

3.2 Gut-Brain (GB) Axis

The gut-brain (GB) axis represents the bi-directional link between the gut and the brain, comprising metabolic, endocrine (particularly through the Hypothalamic-Pituitary-Adrenal (HPA) Axis), neural, and immune pathways. The vagus nerve, the HPA Axis, immunological mediators, bacterial metabolite synthesis, and enteroendocrine signalling are essential elements of the GB axis. Recent studies have demonstrated the important role that gut microbiota plays in neuropsychiatric disorders through the microbiota-gut-brain (MGB) axis. Signals are transmitted from the gut to the brain and back via neurological, immunological, endocrine, and metabolic pathways, forming a bidirectional communication axis [17].

The gut microbiota is capable of synthesising neuromodulators, such as GABA and its precursors, cytokines, brain-derived neurotrophic factor (BDNF), and short-chain fatty acids (SCFAs). The colon's rich microbiome, especially in SCFAs, prevents the activation of afferent neurons in the brainstem nuclei. This is because SCFAs increase the ileum's L-cells' synthesis of glucagon-like peptide 1 (GLP-1), the hormone with the effect of satiety [17]. Therefore, through multiple pathways, the gut microbiota plays a critical role in the so-called influencing of brain function and behaviour.

Research on the microbiome has pinpointed gut microorganisms and their metabolites as a major signalling source. Substantial preclinical evidence suggests that the microbiome can influence the GB axis homeostasis by impacting the architecture, functionality, and development from the bottom up through neuroendocrine and neuroimmune processes. The central autonomic regions, brainstem, spinal cord, and enteric nervous system (ENS) are all involved in these interactions. However, when the body's homeostasis is threatened, such as under the influence of emotional or environmental stress, it will be transformed into the regulation of the autonomic nervous system (ANS) input. This regulation is generally initiated by feelings and emotional influences [18].

The central nervous system (CNS) can receive signals derived from microbial-derived signals either directly through the systemic circulation or indirectly through interactions with receptors on enterochromaffin cells (ECCs), gut-based enteroendocrine cells, the mucosal immune system, and potentially cluster cells. These cells have the ability to release receptor molecules upon activation, which can affect how the vagus and spinal afferent nerves synaptically connect. The sympathetic and parasympathetic branches of the ANS, as well as the HPA axis, are used by the CNS to modulate activity in response to these signals. As a result, changes in the gut microbiota may upset the equilibrium of the GB axis, which may lead to EDs and affect the eating behaviour of patients [18].

4. Effects of Gut Microbiota on Eating Disorders (EDs)

4.1 Microbiota Involvement in AN

Clinical studies on patients with AN indicate a significant reduction in the total gut bacterial population, including species such as *Clostridium leptum*, *Clostridium coccoides* and *Bacteroides fragilis* [18]. In addition, the number of bacteria that produce SCFAs, such as *Roseburia*, *Ruminococcus*, and *Clostridium*, has also declined. Due to this decline, their stools now contain less butyric acid, propionic acid, and acetic acid [19-22].

Propionate levels were found to correlate positively with insulin concentrations and negatively with sadness and anxiety, possibly explaining why individuals with AN had higher anxiety and lower insulin levels [20]. Furthermore, compared to their healthy counterparts, AN patients had fewer butyrate-producing *Roseburia spp.*, which led to higher amounts of branched-chain fatty acids and protein fermentation products, which affected gut motility and physiology [23,24].

Another study shows in patients with AN, there are marked differences in certain gut microbiota compared to healthy individuals. Indeed, there was an increase in mucin-degrading bacteria and in clusters of *Clostridium* groups I, XI, and XVIII. Enter *Obacteriaceae*, methane-producing archaeon *Methanobrevibacter smithii*, and actinomycetes, which are mainly *bifidobacterium*, also increased. Patients also had higher levels of *Coronobacteriaceae* bacteria [20,23]. *Methanobrevibacter smithii* can improve microbial fermentation efficiency, thus improving the efficiency of the process of extracting calories from a low-calorie diet. Its prevalence in patients with AN may represent an adaptive mechanism to maximise the absorption of nutrients from a restricted diet [21]. A malnourished environment and delayed colon transport facilitate the growth of mucin-degrading microorganisms, leading to impaired intestinal barrier and chronic low-grade inflammation that worsens the condition [25].

While there is evidence of a correlation between certain gut bacteria and cytokine production in healthy persons, further research is needed to comprehend this relationship fully in individuals with EDs. These realisations could result in emotional eating and associated EDs being treated more successfully. The results of this study further revealed an increase in mucin-degrading bacteria and certain gram-negative bacteria, such as *Enterobacteriaceae*, in the gut of AN patients. The increase of this flora may further exacerbate the pathophysiological process of AN by promoting increased intestinal permeability and chronic low-grade inflammation. In particular, the increase in *Methanobrevibacter smithii* may be an adaptive mechanism that helps patients maximise energy absorption from a low-calorie diet.

4.2 Microbiota Involvement in BN

A study employing the Mendelian randomization (MR) method to assess the phenotypes of 196 gut microbial taxa identified nine taxa potentially causative of BN. The bacteria that caused the elevated risk of BN were *Clostridiales*, *Bilophila*, *Coprobacter*, *Holdemania*, *Ruminococcaceae* UCG009, and *Slackia*. The richness of *Clostridiales* was significantly increased in AN mice. *Bilophila* is an opportunistic pathogen whose increased abundance is closely associated with increased intestinal inflammation. *Ruminococcaceae* is positively correlated with autism and depression and is highly present in AN patients. Therefore, BN and AN have overlapping properties and the same pathological basis [26]. However, the research on BN is still insufficient so far, necessitating more comprehensive future studies on the interaction between BN and intestinal microorganisms.

4.3 Microbiota Involvement in BED

A study has revealed that binge eating behaviour in BED

patients is influenced by the gut microbiota. The quantity and variety of gut microorganisms were significantly reduced in mice given broad-spectrum antibiotics (ABX) (metronidazole, ampicillin, vancomycin, and neomycin coupled with Splenda to neutralise bitterness), which paralleled the symptoms of BED. One luminal metabolite that blocks the N-methyl-D-aspartate receptor (NMDAR) is kynurenic acid (KYNA). The study also demonstrated how, through its interaction with enteric vagus afferents, luminal KYNA regulates binge eating behaviour crucially. Peripheral KYNA affects gastrointestinal peripheral nerves, including the vagus nerve terminals, but it does not interact with NMDARs in the brain. Moreover, KYNA can boost energy metabolism by turning on Gpr35 [27].

Another cross-sectional analysis involving 101 patients, utilising microbial 16S rDNA sequencing technology, revealed that levels of *Akkermansia muniphila*, which can produce SCFAs such as propionate—a critical regulator of satiety—and acetate, were reduced in the intestines of BED patients. Several acylglycerols, including 2-OG, 2-arachidonylglycerol, and 2-palmitoyl glycerol, can be elevated by *Akkermansia muniphila*. The main function of these acylglycerols in the intestine is to participate in the regulation of inflammation and immune response and affect food intake behaviour. Therefore, the reduction of microorganisms in the intestine of BED patients may be negative [17].

5. Conclusion

This review analysed relevant studies on three EDs, AN, BN, and BED, and found that alterations in microbiota composition influenced the GB axis and were inextricably linked to EDs. The impact of the intestinal flora on EDs highlights the important and intricate link between the intestinal microbiome, brain function, and dietary behaviour. In diseases, microbial imbalances result in shifts in the composition of the microbiota and its metabolites, which explains the possibility of the pathophysiology of these diseases. The GB axis is a key mediator of these effects, and signals derived from the intestine can affect neural pathways and related behaviours. Probiotics, prebiotics, and dietary interventions can help restore the number of beneficial intestinal microorganisms and restore microbial balance, which can serve as an effective adjunct to traditional therapies. The bidirectional communication of the GB axis suggests that improving intestinal health could positively influence brain function and behaviour, providing a holistic approach to the treatment of EDs.

Although this study provides new insights into the effects of alterations in gut microbes on EDs, there are some limitations. For example, the effects of the six types of EDs on the body when the gut microbiome is disturbed are not discussed, and the small sample size might restrict the applicability of the findings. In addition, the study does not explore the relevant mechanism of action and cannot determine causation. In conclusion, this study reveals the crucial role of gut microbiota in EDs, laying the groundwork for future therapeutic innovations. Understanding the relationship between gut microbiota and emotional eating can help enhance the quality of life and clinical management of individuals with EDs.

Future research should adopt longitudinal approaches to delve deeper into the causal relationship between gut microbiota and EDs and whether probiotics and dietary fibre supplementation can improve the symptoms of EDs patients. Further investigation is required into the association between gut microbiota and EDs like BN and BED. Additionally, explores how the gut microbiome influences mood and behaviour via the gut-brain axis.

References

[1] Treasure J, Duarte TA, Schmidt U. Eating disorders. Lancet. 2020;395(10227):899-911. doi:10.1016/S0140-6736(20)30059-3

[2] Preti A, Girolamo Gd, Vilagut G, et al. The epidemiology of eating disorders in six European countries: results of the ESEMeD-WMH project. J Psychiatr Res. 2009;43(14):1125-1132. doi:10.1016/j.jpsychires.2009.04.003

[3] Balodis IM, Molina ND, Kober H, et al. Divergent neural substrates of inhibitory control in binge eating disorder relative to other manifestations of obesity. Obesity (Silver Spring). 2013;21(2):367-377. doi:10.1002/oby.20068

[4] Maria Monteleone A, Monteleone P, Dalle Grave R, et al. Ghrelin response to hedonic eating in underweight and short-term weight restored patients with anorexia nervosa. Psychiatry Res. 2016;235:55-60. doi:10.1016/j.psychres.2015.12.001

[5] Gulas E, Wysiadecki G, Strzelecki D, Gawlik-Kotelnicka O, Polguj M. Can microbiology affect psychiatry? A link between gut microbiota and psychiatric disorders. Jak mikrobiologia może wpływać na psychiatrię? Powiązania między florą bakteryjną jelit a zaburzeniami psychicznymi. Psychiatr Pol. 2018;52(6):1023-1039. doi:10.12740/PP/OnlineFirst/81103

[6] Fetissov SO. Role of the gut microbiota in host appetite control: bacterial growth to animal feeding behaviour. Nat Rev Endocrinol. 2017;13(1):11-25. doi:10.1038/nrendo.2016.150

[7] Ruusunen A, Rocks T, Jacka F, Loughman A. The gut microbiome in anorexia nervosa: relevance for nutritional rehabilitation. Psychopharmacology (Berl). 2019;236(5):1545-1558. doi:10.1007/s00213-018-5159-2

[8] Zhang J, Ma L, Chang L, Pu Y, Qu Y, Hashimoto K. A key role of the subdiaphragmatic vagus nerve in the depression-like phenotype and abnormal composition of gut microbiota in mice after lipopolysaccharide administration. Transl Psychiatry. 2020;10(1):186. Published 2020 Jun 9. doi:10.1038/s41398-020-

00878-3
[9] Luo Y, Zeng B, Zeng L, et al. Gut microbiota regulates mouse behaviors through glucocorticoid receptor pathway genes in the hippocampus. Transl Psychiatry. 2018;8(1):187. Published 2018 Sep 7. doi:10.1038/s41398-018-0240-5
[10] Silén Y, Keski-Rahkonen A. Worldwide prevalence of DSM-5 eating disorders among young people. Curr Opin Psychiatry. 2022;35(6):362-371. doi:10.1097/YCO.0000000000000818
[11] Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 2013;36(5):305-312. doi:10.1016/j.tins.2013.01.005
[12] E, Raoul P, Cintoni M, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms. 2019;7(1):14. Published 2019 Jan 10. doi:10.3390/microorganisms7010014
[13] Kho ZY, Lal SK. The Human Gut Microbiome - A Potential Controller of Wellness and Disease. Front Microbiol. 2018;9:1835. Published 2018 Aug 14. doi:10.3389/fmicb.2018.01835
[14] Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018;361:k2179. Published 2018 Jun 13. doi:10.1136/bmj.k2179
[15] Vancamelbeke M, Vermeire S. The intestinal barrier: a fundamental role in health and disease. Expert Rev Gastroenterol Hepatol. 2017;11(9):821-834. doi:10.1080/17474124.2017.1343143
[16] Góralczyk-Bińkowska A, Szmajda-Krygier D, Kozłowska E. The Microbiota-Gut-Brain Axis in Psychiatric Disorders. Int J Mol Sci. 2022;23(19):11245. Published 2022 Sep 24. doi:10.3390/ijms231911245
[17] Navarro-Tapia E, Almeida-Toledano L, Sebastiani G, Serra-Delgado M, García-Algar Ó, Andreu-Fernández V. Effects of Microbiota Imbalance in Anxiety and Eating Disorders: Probiotics as Novel Therapeutic Approaches. Int J Mol Sci. 2021;22(5):2351. Published 2021 Feb 26. doi:10.3390/ijms22052351
[18] Mayer EA, Nance K, Chen S. The Gut-Brain Axis. Annu Rev Med. 2022;73:439-453. doi:10.1146/annurev-med-042320-014032
[19] Morita C, Tsuji H, Hata T, et al. Gut Dysbiosis in Patients with Anorexia Nervosa. PLoS One. 2015;10(12):e0145274. Published 2015 Dec 18. doi:10.1371/journal.pone.0145274
[20] Borgo F, Riva A, Benetti A, et al. Microbiota in anorexia nervosa: The triangle between bacterial species, metabolites and psychological tests. PLoS One. 2017;12(6):e0179739. Published 2017 Jun 21. doi:10.1371/journal.pone.0179739
[21] Armougom F, Henry M, Vialettes B, Raccah D, Raoult D. Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. PLoS One. 2009;4(9):e7125. Published 2009 Sep 23. doi:10.1371/journal.pone.0007125
[22] Million M, Angelakis E, Maraninchi M, et al. Correlation between body mass index and gut concentrations of Lactobacillus reuteri, Bifidobacterium animalis, Methanobrevibacter smithii and Escherichia coli [retracted in: Int J Obes (Lond). 2024 Jun 21. doi: 10.1038/s41366-024-01557-9]. Int J Obes (Lond). 2013;37(11):1460-1466. doi:10.1038/ijo.2013.20
[23] Mack I, Cuntz U, Grämer C, et al. Weight gain in anorexia nervosa does not ameliorate the faecal microbiota, branched chain fatty acid profiles, and gastrointestinal complaints. Sci Rep. 2016;6:26752. Published 2016 May 27. doi:10.1038/srep26752
[24] Hanachi M, Manichanh C, Schoenenberger A, et al. Altered host-gut microbes symbiosis in severely malnourished anorexia nervosa (AN) patients undergoing enteral nutrition: An explicative factor of functional intestinal disorders?. Clin Nutr. 2019;38(5):2304-2310. doi:10.1016/j.clnu.2018.10.004
[25] Ghenciulescu A, Park RJ, Burnet PWJ. The Gut Microbiome in Anorexia Nervosa: Friend or Foe?. Front Psychiatry. 2021;11:611677. Published 2021 Jan 12. doi:10.3389/fpsyt.2020.611677
[26] Yu Z, Guo M, Yu B, Wang Y, Yan Z, Gao R. Anorexia nervosa and bulimia nervosa: a Mendelian randomization study of gut microbiota. Front Microbiol. 2024;15:1396932. Published 2024 May 9. doi:10.3389/fmicb.2024.1396932
[27] Fan S, Guo W, Xiao D, et al. Microbiota-gut-brain axis drives overeating disorders. Cell Metab. 2023;35(11):2011-2027.e7. doi:10.1016/j.cmet.2023.09.005