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The intestinal microbiota and anorexia nervosa: cause or consequence of nutrient deprivation

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Abstract

The intestinal microbiota is a diverse microbial community that colonizes the gastrointestinal tract of animals. Abnormal changes in intestinal microbiota has been associated with multiple diseases including inflammatory bowel diseases and obesity; however, emerging evidence suggests a role for the gut microbiota in anxiety and depression via the gut-brain axis. As this microbial community is associated with weight dysregulation and host behavior it is not surprising that the intestinal microbiota may have a role to play in anorexia nervosa (AN). In this review we examine recent studies linking the gut microbiota with nutrition, psychopathology, and ultimately AN. We also review potential gut microbiota-based therapies for AN.

Etiologies of Anorexia Nervosa

Anorexia nervosa (AN) is a perplexing disorder that exhibits heterogeneous features among patients. AN is characterized by dangerously low body weight, indifference to the seriousness of the illness, and predominately affects females (DSM-5 diagnostic criteria). AN is also associated with high psychiatric comorbidities and exhibits one of the highest mortality rates of all psychiatric disorders.[1, 2] A systematic review characterized the average lifetime prevalence of AN at 1.4% for women and 0.2% for men.[3] The pathology of AN is thought to be multi-factorial, as genetic factors, early life experiences, psychosocial factors and biological changes all play role in disease development.[4] A recent genome-wide association study has shown that the genetic architecture of this illness mirrors its clinical presentation and exhibits significant genetic correlations with both psychiatric and metabolic

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traits—encouraging a reconceptualization of AN as a metabo-psychiatric disorder.[5] This finding encourages the exploration of potential contributors other than psychiatric factors, such as glycemic, lipid, and anthropometric traits, to the development or maintenance of AN and subsequent avenues for treatment approaches. Although established guidelines exist for treatments of this serious illness, renourishment can be uncomfortable for the patient, and relapse is common.[6–8] These shortcomings highlight a need for novel interventions for successful and sustained weight gain in these patients. The emerging interaction between AN-associated host genetics, host environment, and the role of the gut microbiota as an integrated facet of metabolism suggest that pairing genomic and microbiome sequencing data will increase our understanding of the pathways involved in AN pathology.[9–11]

The Intestinal Microbiota, Nutrition, and Psychopathology

The intestinal microbiota, the trillions of microorganisms that inhabit the gastrointestinal (GI) tract, encompasses a dynamic ecosystem of bacteria, virus, archaea, eukaryotes, and fungi. In healthy individuals, it has been hypothesized that a symbiotic relationship between the host and the intestinal microbiota can influence both physiological and psychological wellbeing.[12] Indeed, the intestinal microbiome (cumulative genetic material of the intestinal microbiota) is a complex network of over twenty two million unique microbial genes[13] that contribute to critical host functions such as digestion and absorption of calories from the gut.[14] The impact of short- and long-term diets on the composition of the gut microbiome has been reported,[15, 16] and the relationship between this microbial community and adiposity is well-documented;[17] however, gut microbiota-host interactions have recently become a focus of psychopathology.[12, 18] Over the past decade, gut microbiota-based studies have reported compelling evidence that this complex microbial community plays a role in regulating anxiety and stress-related behavior.[19] Additionally, consistent evidence has also identified the gut microbiota as a key regulator of pathways (neurobiological, immune, and inflammatory) associated with the gut-brain axis—a track for bidirectional communication between the central and enteric nervous systems.[20–22]

Animal models suggest that the intestinal microbiota can directly influence appetite regulation and energy homeostasis through the gut-brain axis.[23] As one of several mechanisms providing sustained communication between the GI tract and the central nervous system, the gut microbiome and its dynamic diet-responsive shifts in species can affect the production and release of various metabolites (including short-chain fatty acids, SCFA, derived from fermentation of dietary fibers) that travel to the brain to influence eating behavior.[24] Additionally, investigations have revealed that other brain functions and behaviors can be modified via intestinal microbiota.[25] Indeed, a mixture of SCFA (acetate, butyrate, and propionate) was reported to alleviate stress-related behaviors (stress-induced reward seeking and responsiveness to an acute stressor) in mice.[24] More specifically, a large population cohort study reported differences in microbial species that correlated with host quality of life and depression.[26] As technology advances, growing evidence is linking specific alterations in microbial diversity and taxa abundance to specific psychological conditions, such as eating disorders.[27] Investigating the relationship between the intestinal microbiota and eating disorders has the potential to open new avenues of intervention for mental health via targeting gut microbes.

The Gut Microbiome in Anorexia Nervosa

Enteric microbes harbored within the GI tract have environmental preferences (i.e. substrates for energy supply) conducive to proliferation and function that can be altered by multiple factors—including diet, host genetics, and nutritional restrictions or imbalances.[15, 28] As patients with AN experience dysregulation of multiple traits that also influence the intestinal microbiota (e.g., altered dietary habits,[29, 30] genetic etiologies,[31, 32] and extreme caloric restriction), investigating the role of this complex microbial community in this disorder is warranted. Moreover, as functional bowel disorders, abnormal eating behavior, and anxious and depressive symptoms are commonly experienced by patients with AN and are associated with the intestinal microbiota, the link between eating disorders and enteric microbial communities is further strengthened.[19, 20, 33–35]

A microbial imbalance (sometimes referred to as dysbiosis) has been well-documented in patients with AN—with chronic caloric restriction, high fiber content, macronutrient imbalance, and micronutrient deficiency believed to be the primary drivers of abnormal enteric microbial communities found in individuals with AN.[36] It is therefore possible that a competitive environment exists in the intestine of patients with AN that leads to selection of specific microbes that can outcompete other members of the gut microbiota and bloom in these harsh conditions. Proliferation of gut microbes resistant to nutrient-limited conditions may be a hallmark of the AN gut microbiota.[36] A culture-based study conducted by Pfleiderer and colleagues isolated 11 new bacterial species from a stool sample of a patient with AN, suggesting that the gut microbiota of patients with AN may be substantially different than healthy individuals due to their condition.[37] A study investigating the intestinal microbiota in lean and obese individuals revealed an increase in abundance of the dominant member of gut archaea, *Methanobrevibacter smithii*, in fecal samples from individuals with BMI<25 kg/m^2 compared to individuals with BMI>25 kg/m^2.[38] Similar increases in *M. smithii* within the gut microbiota of patients with AN has been widely reported across the literature,[39, 40] but not in all studies.[41] As this archeon is an integral organism in the appropriate microbial metabolism of polysaccharides, elevated levels of *M. smithii* may increase energy efficiency leading to optimal conversion of dietary nutrients into caloric currency. Thus, the selection of specific microbes within the intestinal microbiota of AN patients (e.g. *M. smithii*) could represent a microbial adaptation that favors certain species capable of sustaining the perpetuation of AN pathology by providing the host with energy in a calorie-deprived environment.

Another study investigating the role of gut microbes in eating disorders integrated gut microbiota sequence data with clinical and anthropometric characteristics. The study reported that the gut microbial communities in 15 patients with AN were altered at every taxonomic level (Phylum to Species), with increases in the bacterial Family *Enterobacteriaceae* and the archaeon *M. smithii* (consistent with previous reports).[38] Gut microbiotas from patients with AN also displayed an enrichment in Bacteroidetes and a depletion short chain fatty acid (SCFA)-producing bacteria in Firmicutes, *Roseburia*, *Ruminococcus*, and *Clostridium*—supporting the observed reduction of specific SCFA (butyrate and propionate) in patients with AN.[39, 42, 43] A more recent study further elucidated gut microbiota-mediated changes in SCFA concentrations, differentiating

metabolite perturbations between two subtypes of AN (restrictive AN and binge-purge AN).[44] It has been suggested that SCFA and branched-chain fatty acids in patients with AN may influence appetite and metabolism.

Although these studies confirm the existence of abnormal gut microbial communities in AN, the functional influence of AN-associated gut microbiotas on the host was not determined. One study used formerly germ-free (GF) mice colonized with fecal microbiotas from patients with AN matched with healthy controls to address whether AN-associated microbiotas were merely a result of an altered GI environment due to disease pathology or could subsequently induce AN-specific pathologies in a germ-free host.[45] It was reported that mice colonized with fecal microbiotas from patients with AN consumed less food and gained less weight compared with mice colonized with fecal microbiotas from healthy controls. AN colonized mice also exhibited greater anxiety-related behavior (i.e., marble burying) compared with healthy control colonized mice. Although this study requires replication, this report suggests that dominant traits associated with AN are transmissible via the human gut microbiota and highlights this complex microbial community as a contributor to the development and maintenance of this disorder. In contrast, a more recent study using a gnotobiotic approach didn't find any influence of AN-associated gut microbiotas on adiposity in GF mice.[46] Interestingly, the authors reported that body weight, fat mass, and cecum weight were associated with human fecal microbes, but these observations were independent of whether the donor microbiota came from a patient with AN or a healthy individual. The contrasting results in these studies could potentially stem from the multiple technical differences used in each study. Ultimately, additional gnotobiotic studies with larger cohorts of human microbiota donors are needed to address whether the AN-associated gut microbiota has a negative influence on the host.

Bio-diversity within a microbial ecosystem (also known as α-diversity) is an essential component of the resilience of a microbiota, as this trait enables resistance to, recovery from, and adaption to environmental perturbations.[47] The positive association between gut microbial diversity and health was in part discovered due to known links between disease and microbial homogeneity (a hallmark of decreased diversity). Specifically, immune function and energy-harvesting capacity in the intestine are negatively impacted by declines in microbial diversity.[48]

Ruusunen and colleagues reviewed all studies characterizing the intestinal microbiota in patients with AN up to 2019 and reported decreased microbial diversity in almost all studies.[20] For example, a cross-sectional study with 106 female participants used 16S rRNA gene sequence analysis identified significantly lower α-diversity and only one significantly enriched phylotype (*Coriobacteriaceae*) in patients with AN compared with normal weight women and female athletes.[49] Interestingly, when all groups were analyzed, higher levels of depression were found to correlate with a lower number of observed species. This finding replicated the observations made by Kleiman and colleagues where greater levels of depression were negatively associated with α-diversity.[35] Changes in diversity measures may be impacted by a multitude of variables, such as AN subtype or psychosocial behaviors. Notably, two recent studies reported that gut microbiota diversity and composition were

affected by chronic food restriction but not physical activity in rodents.[41, 50] Another study reported reduced α-diversity in patients with restrictive AN but not binge-purge AN.[44]

Interestingly, the observed decline in α-diversity does not seem to be ameliorated upon inpatient discharge after a refeeding period, suggesting a resistance within the AN-associated gut microbiota to adjust to a healthy state even after renourishment.[35] This theory was contradicted by a recent study in adolescents with AN that reported increased α-diversity after short-term weight recovery. No improvements were seen in other diversity measures, and these findings have not been replicated in an older population.[51] Although there are improvements in bacterial composition and diversity after hospital-based renourishment compared to hospital admission, this persisting decreased α-diversity after renourishment relative to healthy individuals highlights a potential unaddressed element in current treatment plans for patients with AN that could contribute to relapse.[36]

Gut Microbiota-based Treatments for Anorexia Nervosa

Despite the frequency of relapse in individuals with AN, adequate therapeutic renourishment, typically in conjunction with psychotherapy, is essential for sustained wellness.[52–54] Renourishment is an essential and safe cornerstone of treatment for those with AN;[55] however, many patients hastily lose restored weight upon reentry to their typical environment.[36] Moreover, uncomfortable and even painful GI symptoms can occur during renourishment that contributes to premature discharge against medical advice and treatment drop out.[52]

Although identifying the gut microbiota as a causative factor of AN has not yet been credibly reported,[18] the current science suggests that when patients with AN severely restrict nutrition, they also starve their microbes; thus, it is important to consider the refeeding of microbes when undergoing nutritional rehabilitation. Despite this knowledge, investigative work regarding possible microbiota-focused treatments in the context of AN is lacking. Probiotic (consuming live beneficial microbes) and prebiotic (non-digestible food that selectively increases beneficial microbes in the gut) supplementation and fecal microbiota transplantation (FMT) are common approaches to reestablish a healthy gut microbiota—with FMT typically used for recurrent *Clostridium difficile* infections. Human clinical trials have reported probiotic treatments reduced anxiety and depression compared to placebo[56] and protected against intestinal barrier abnormalities,[57, 58] suggesting supplementation may provide a multifactorial mechanism to impact several components of AN pathology. Understanding microbial-level changes within the intestinal microbiota of patients with AN is a crucial first step for the generation of pro- and prebiotic treatments, and the fate of future clinical trials relies on the development of a more complete understanding of the role of the microbiota in AN pathophysiology.

FMT may bear higher risks of adverse events than probiotic and prebiotic supplementations; however, FMT may induce more direct and immediate improvements to the fecal metabolome. Of these approaches, only FMT has been attempted as a treatment for patients with AN.[59, 60] Specifically, a healthy stool microbiota from an unrelated relative with a BMI of 25 kg/m^2 was infused into the GI tract of an AN patient who had had multiple

unsuccessful attempts at maintaining a normal body weight. A 55% increase in body weight (mostly due to body fat) in addition to the establishment of certain taxa associated with a normal, healthy return of a normal gut microbiota was reported in this patient 36 weeks following FMT despite no increase in caloric consumption. Another study focused on FMT as a mechanism to restore normal GI function in an AN patient.[60] Following FMT, the AN patient exhibited increased GI barrier function and normalized gut microbiota and metabolites. Although FMT needs to be assessed for safety and efficacy in a larger number of patients with AN, these studies support the concept that reestablishing a normal gut microbiota via FMT may have a role in the treatment of some individuals with AN.

Conclusions

Many questions have yet to be addressed regarding the role of the gut microbiota in AN; however, growing evidence supports this complex microbial community in the emergence and maintenance of AN. A more comprehensive characterization of the intestinal microbiota in patients with AN through well-phenotyped studies enriched with thorough clinical and dietary metadata is necessary to advance knowledge in regard to how both the current pathology and treatment of AN impacts the gut microbiota, and how gut microbial communities may, in turn, influence expression of the illness. Future research should further seek to establish whether the gut microbiota is a cause or consequence of AN pathophysiology by utilizing the aforementioned approach to translate the characterization of the intestinal microbiota to clinical outcomes. As the body of research rapidly evolves the identification of specific microbes associated with weight gain,[46] and anxiety-like behaviors,[45] in patients with AN may imply a more causative role for an AN-associated microbial dysbiosis. Performing studies both in human and in preclinical models, and investigating the functional alterations in addition to taxonomic changes of the intestinal microbiome, will enhance our knowledge of AN pathology beyond associations. Moreover, gut microbiome research in eating disorders have been mainly focused on AN so far. Given the relevance of the intestinal microbiota to the traits (altered dietary habits and disordered eating behaviors) and comorbidities (anxiety, depression, and GI disorders) observed in other eating disorders such as bulimia nervosa and binge-eating disorder, investigating the role of the intestinal microbes in these disorders may enhance our understanding of their biology.

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References

1. O'Brien KM, Vincent NK. Psychiatric comorbidity in anorexia and bulimia nervosa: nature, prevalence, and causal relationships. Clin Psychol Rev2003;23:57–74. [PubMed: 12559994]
2. Pisetsky EM, Thornton LM, Lichtenstein P, et al.Suicide attempts in women with eating disorders. J Abnorm Psychol2013;122:1042–56. [PubMed: 24364606]

3. Galmiche M, Déchelotte P, Lambert G, et al.Prevalence of eating disorders over the 2000–2018 period: a systematic literature review. Am J Clin Nutr2019;109:1402–1413. [PubMed: 31051507]
4. Gorwood P, Blanchet-Collet C, Chartrel N, et al.New Insights in Anorexia Nervosa. Front Neurosci2016;10:256. [PubMed: 27445651]
5. Watson HJ, Yilmaz Z, Thornton LM, et al.Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet2019;51:1207–1214. [PubMed: 31308545]
6. Khalsa SS, Portnoff LC, McCurdy-McKinnon D, et al.What happens after treatment? A systematic review of relapse, remission, and recovery in anorexia nervosa. J Eat Disord2017;5:20. [PubMed: 28630708]
7. Kaye WH, Gwirtsman HE, Obarzanek E, et al.Caloric intake necessary for weight maintenance in anorexia nervosa: nonbulimics require greater caloric intake than bulimics. Am J Clin Nutr1986;44:435–43. [PubMed: 3766430]
8. Kaplan AS, Walsh BT, Olmsted M, et al.The slippery slope: prediction of successful weight maintenance in anorexia nervosa. Psychological medicine2009;39:1037–45. [PubMed: 18845008]
9. Goodrich JK, Waters JL, Poole AC, et al.Human genetics shape the gut microbiome. Cell2014;159:789–99. [PubMed: 25417156]
10. Nicholson JK, Holmes E, Kinross J, et al.Host-gut microbiota metabolic interactions. Science2012;336:1262–7. [PubMed: 22674330]
11. Goodrich JK, Davenport ER, Clark AG, et al.The Relationship Between the Human Genome and Microbiome Comes into View. Annu Rev Genet2017;51:413–433. [PubMed: 28934590]
12. Dinan TG, Cryan JF. The impact of gut microbiota on brain and behaviour: implications for psychiatry. Curr Opin Clin Nutr Metab Care2015;18:552–8. [PubMed: 26372511]
13. Tierney BT, Yang Z, Luber JM, et al.The Landscape of Genetic Content in the Gut and Oral Human Microbiome. Cell Host Microbe2019;26:283–295.e8. [PubMed: 31415755]
14. Basolo A, Hohenadel M, Ang QY, et al.Effects of underfeeding and oral vancomycin on gut microbiome and nutrient absorption in humans. Nat Med2020;26:589–598. [PubMed: 32235930]
15. David LA, Maurice CF, Carmody RN, et al.Diet rapidly and reproducibly alters the human gut microbiome. Nature2014;505:559–63. [PubMed: 24336217]
16. Wu GD, Chen J, Hoffmann C, et al.Linking long-term dietary patterns with gut microbial enterotypes. Science2011;334:105–8. [PubMed: 21885731]
17. Ridaura VK, Faith JJ, Rey FE, et al.Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science2013;341:1241214. [PubMed: 24009397] This is a seminal study where the authors transplanted unculutred feces from lean and obese twins into germ-free mice. Mice consumed the same type and amount of food, yet mice the received a fecal transplant from obese twins gained more mass and adiposity. Co-housing mice (a situation where mice consume eath others' feces) that received an "obese" microbiota with mice that received a "lean" microbiota prevented increased adiposity in mice receiving an "obese" microbiota. This study was the first to suggest that specific parameters associated with obesity was transmissible via the intestinal microbiota, and set the stage for the wealth of subsequent studies investigating this phenomenon.
18. Di Lodovico L, Mondot S, Doré J, et al.Anorexia nervosa and gut microbiota: A systematic review and quantitative synthesis of pooled microbiological data. Prog Neuropsychopharmacol Biol Psychiatry2021;106:110114. [PubMed: 32971217] This article gathers high throughput sequencing data from multiple studies investigating the intestinal microbiota in AN. The authors re-analyze the combined data and find specific taxa (namely Alistipes, Parabacterioides, and Roseburia) associated with BMI in AN patients. The authors also highlight a decrease in butyrate producing microbes and an increase in mucin degrading microbes as hallmarks of the AN gut microbiota.
19. Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci2013;36:305–12. [PubMed: 23384445]
20. Ruusunen A, Rocks T, Jacka F, et al.The gut microbiome in anorexia nervosa: relevance for nutritional rehabilitation. Psychopharmacology(Berl)2019;236:1545–1558. [PubMed: 30612189]

21. Slyepchenko A, Maes M, Jacka FN, et al.Gut Microbiota, Bacterial Translocation, and Interactions with Diet: Pathophysiological Links between Major Depressive Disorder and Non-Communicable Medical Comorbidities. Psychother Psychosom2017;86:31–46. [PubMed: 27884012]
22. Carabotti M, Scirocco A, Maselli MA, et al.The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol2015;28:203–209. [PubMed: 25830558]
23. van de Wouw M, Schellekens H, Dinan TG, et al.Microbiota-Gut-Brain Axis: Modulator of Host Metabolism and Appetite. J Nutr2017;147:727–745. [PubMed: 28356427]
24. van de Wouw M, Boehme M, Lyte JM, et al.Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. J Physiol2018;596:4923–4944. [PubMed: 30066368]
25. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci2012;13:701–12. [PubMed: 22968153]
26. Valles-Colomer M, Falony G, Darzi Y, et al.The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol2019;4:623–632. [PubMed: 30718848]
27. Seitz J, Belheouane M, Schulz N, et al.The Impact of Starvation on the Microbiome and Gut-Brain Interaction in Anorexia Nervosa. Front Endocrinol(Lausanne)2019;10:41.
28. Hasan N, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. PeerJ2019;7:e7502. [PubMed: 31440436]
29. Segura-García C, De Fazio P, Sinopoli F, et al.Food choice in disorders of eating behavior: correlations with the psychopathological aspects of the diseases. Compr Psychiatry2014;55:1203–11. [PubMed: 24703769]
30. Gwirtsman HE, Kaye WH, Curtis SR, et al.Energy intake and dietary macronutrient content in women with anorexia nervosa and volunteers. J Am Diet Assoc1989;89:54–7. [PubMed: 2909592]
31. Klump KL, Miller KB, Keel PK, et al.Genetic and environmental influences on anorexia nervosa syndromes in a population-based twin sample. Psychological medicine2001;31:737–40. [PubMed: 11352375]
32. Wade TD, Bulik CM, Neale M, et al.Anorexia nervosa and major depression: shared genetic and environmental risk factors. The American journal of psychiatry2000;157:469–71. [PubMed: 10698830]
33. Riedlinger C, Schmidt G, Weiland A, et al.Which Symptoms, Complaints and Complications of the Gastrointestinal Tract Occur in Patients With Eating Disorders? A Systematic Review and Quantitative Analysis. Front Psychiatry2020;11:195. [PubMed: 32425816]
34. Fetissov SO, Hökfelt T. On the origin of eating disorders: altered signaling between gut microbiota, adaptive immunity and the brain melanocortin system regulating feeding behavior. Curr Opin Pharmacol2019;48:82–91. [PubMed: 31430598]
35. Kleiman SC, Watson HJ, Bulik-Sullivan EC, et al.The Intestinal Microbiota in Acute Anorexia Nervosa and During Renourishment: Relationship to Depression, Anxiety, and Eating Disorder Psychopathology. Psychosom Med2015;77:969–81. [PubMed: 26428446]
36. Bulik CM, Flatt R, Abbaspour A, et al.Reconceptualizing anorexia nervosa. Psychiatry Clin Neurosci2019;73:518-525. [PubMed: 31056797] -This review investigates AN research related to genetics. Specifically, the authors investigate emerging research identifying significant negative genetic correlations between AN and obesity suggests that the conditions may represent ‘metabolic bookends’
37. Pfleiderer A, Lagier JC, Armougom F, et al.Culturomics identified 11 new bacterial species from a single anorexia nervosa stool sample.European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology2013;32:1471–81.
38. 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. Int J Obes (Lond)2013;37:1460–6. [PubMed: 23459324]
39. Borgo F, Riva A, Benetti A, et al.Microbiota in anorexia nervosa: The triangle between bacterial species, metabolites and psychological tests. PLoS One2017;12:e0179739. [PubMed: 28636668]

40. Armougom F, Henry M, Vialettes B, et al.Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. PloS One2009;4:e7125. [PubMed: 19774074]
41. Breton J, Tirelle P, Hasanat S, et al.Gut microbiota alteration in a mouse model of Anorexia Nervosa. Clin Nutr 2021;40:181–189.
42. 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 Rep2016;6:26752. [PubMed: 27229737]
43. Morita C, Tsuji H, Hata T, et al.Gut Dysbiosis in Patients with Anorexia Nervosa. PLoS One2015;10:e0145274. [PubMed: 26682545]
44. Monteleone AM, Troisi J, Serena G, et al.The Gut Microbiome and Metabolomics Profiles of Restricting and Binge-Purging Type Anorexia Nervosa. Nutrients2021;13:507. [PubMed: 33557302]
45. Hata T, Miyata N, Takakura S, et al.The Gut Microbiome Derived From Anorexia Nervosa Patients Impairs Weight Gain and Behavioral Performance in Female Mice. Endocrinology2019;160:2441–2452. [PubMed: 31504398]
46. Glenny EM, Fouladi F, Thomas SA, et al.Gut microbial communities from patients with anorexia nervosa do not influence body weight in recipient germ-free mice. Gut Microbes 2021;13:1–15.
47. Heiman ML, Greenway FL. A healthy gastrointestinal microbiome is dependent on dietary diversity. Mol Metab2016;5:317–320. [PubMed: 27110483]
48. Lippert K, Kedenko L, Antonielli L, et al.Gut microbiota dysbiosis associated with glucose metabolism disorders and the metabolic syndrome in older adults. Benef Microbes2017;8:545–556. [PubMed: 28701081]
49. Mörkl S, Lackner S, Müller W, et al.Gut microbiota and body composition in anorexia nervosa inpatients in comparison to athletes, overweight, obese, and normal weight controls. Int J Eat Disord2017;50:1421–1431. [PubMed: 29131365]
50. Trinh S, Kogel V, Voelz C, et al.Gut microbiota and brain alterations in a translational anorexia nervosa rat model. J Psychiatr Res2021;133:156–165. [PubMed: 33341454]
51. Schulz N, Belheouane M, Dahmen B, et al.Gut microbiota alteration in adolescent anorexia nervosa does not normalize with short-term weight restoration. Int J Eat Disord 2020;1:1–12.
52. Bulik CM, Berkman ND, Brownley KA, et al.Anorexia nervosa treatment: a systematic review of randomized controlled trials. Int J Eat Disord2007;40:310–20. [PubMed: 17370290]
53. Sullivan PF. Mortality in anorexia nervosa. The American journal of psychiatry1995;152:1073–4. [PubMed: 7793446]
54. Watson HJ, Bulik CM. Update on the treatment of anorexia nervosa: review of clinical trials, practice guidelines and emerging interventions. Psychol Med2013;43:2477–500. [PubMed: 23217606]
55. Peebles R, Lesser A, Park CC, et al.Outcomes of an inpatient medical nutritional rehabilitation protocol in children and adolescents with eating disorders. J Eat Disord2017;5:7. [PubMed: 28265411]
56. Liu RT, Walsh RFL, Sheehan AE. Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. Neurosci Biobehav Rev2019;102:13–23. [PubMed: 31004628]
57. Plaza-Diaz J, Gomez-Llorente C, Fontana L, et al.Modulation of immunity and inflammatory gene expression in the gut, in inflammatory diseases of the gut and in the liver by probiotics. World J Gastroenterol2014;20:15632–49. [PubMed: 25400447]
58. Dudek-Wicher R, Junka A, Paleczny J, et al.Clinical Trials of Probiotic Strains in Selected Disease Entities. Int J Microbiol2020;2020:8854119. [PubMed: 32565816]
59. de Clercq NC, Frissen MN, Davids M, et al.Weight Gain after Fecal Microbiota Transplantation in a Patient with Recurrent Underweight following Clinical Recovery from Anorexia Nervosa. Psychother Psychosom2019;88:58-60. [PubMed: 30625497] -Although this study is limited in the number of AN patients investigated, it provides a foundation for research regarding the use of fecal microbiota transplantion from an healthy individual into an AN patients to help with healthy weight gain.

60. Prochazkova P, Roubalova R, Dvorak J, et al.Microbiota, Microbial Metabolites, and Barrier Function in A Patient with Anorexia Nervosa after Fecal Microbiota Transplantation. Microorganisms2019;7:338.