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Gut-Brain Interactions: Implications for a Role of the Gut Microbiota in the Treatment and Prognosis of Anorexia Nervosa

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Summary

Through their effects on the intestinal epithelium and immunity, gut microbes and their fermentative byproducts can influence metabolic and psychological health parameters in patients with AN. Integrative therapies that restore gut microbial health may also benefit individuals with conditions in which gut microbial dysbiosis manifests, as in T1D, as individuals in this population experience difficulties with weight stabilization and altered metabolic traits and are vulnerable to developing symptoms of disordered eating.

Although the clinical implications of the brain-gut-microbiota axis are not yet fully understood in AN, targeted pro- and antibiotics represent two mechanisms by which augmenting the gut microbiota can serve as an ancillary therapy for lessening severity of bloating and discomfort during treatment. Specifically, antibiotics could be used to eliminate known pathogens that disrupt intestinal integrity, while targeted probiotics may help to restore beneficial species known to promote gut epithelial health. Thus, we conclude that controlled studies investigating use of such novel therapies, including FMT, should be undertaken as part of an interdisciplinary approach to address metabolic and psychological factors that influence acute and long-term health outcomes in AN and T1D. We highlight again that work on the role of the intestinal microbiota in eating disorders is both limited and confined to AN. As is commonly the case, biological research in eating disorders starts with AN before progressing to the other eating disorders presentations. Yet, in many ways, eating disorders are model conditions on in which to explore the gut-brain axis given the centrality of eating and metabolic factors to the illnesses. We encourage investigators to

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expand on this early work by conducting studies on the other eating disorders (both in youth and adults) to develop a more comprehensive picture of the role that the intestinal microbiota plays in the development and maintenance of and recovery from these debilitating illnesses.

Keywords

Anorexia nervosa; diabetes; microbiome; microbiota; metabolism

Introduction

The three most common eating disorders are anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED). Other presentations such as avoidant and restrictive food intake disorder (AFRID), purging disorder (PD), and night eating syndrome (NES) also exist and can be debilitating, yet we know virtually nothing about the role of the intestinal microbiota in these disorders. In fact, of the primary eating disorders, our understanding of the intestinal microbiota is limited to research on AN, which is the focus of this review. According to the Diagnostic Statistical Manual of Mental Disorders, 5th edition (DSM-5), AN is characterized by three diagnostic criteria:

1. restriction of energy intake relative to requirements leading to significantly low body weight,
2. fear of weight gain or becoming fat, or persistent behaviors to avoid weight gain despite low weight, and
3. disturbances in self-perceived weight and shape or persistent lack of recognition of the seriousness of the low weight.

Two subtypes—restricting AN (AN-R) and AN binge-purge (AN-BP) exist. Individuals with AN-R reach dangerous low weights primarily through restriction of food intake and/or excessive exercise or physical activity. Those with AN-BP also experience episodes of binge eating and/or purging as typical of BN.

Prevalence and etiology

The lifetime prevalence of AN has been reported to be between 1 and 4% of the population and the illness disproportionately affects women[3]. One 2007 case-control study from a cohort of Finnish women determined that the lifetime prevalence of AN according to DSM-IV criteria was 2.2%, which was higher than in previous studies that had ascertained cases of AN on the basis of hospital records alone[3]. Indeed, only about one-third of patients with eating disorders are ever detected by the healthcare system[3], demonstrating the importance of clarifying ascertainment strategy when discussing prevalence of eating disorders.

Furthermore, the new, expanded criteria for a diagnosis of AN in DSM-5 have necessitated a recalculation of prevalence. A Japanese study reported that the prevalence of lifetime AN increased by 60% in the transition to DSM-5, with evidence of somewhat lower severity associated with the DSM-5 cases[4]. A US study of 391 predominantly Caucasian (76.5%) female (91%) participants reported a jump from 14% (DSM-IV) to 20% (DSM-5) percent of

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participants classified as having AN[5]. Although compelling, the results of both studies should be interpreted with caution as they are much higher than other estimates. A 2.5% increase in AN prevalence was reported in the shift from DSM-IV to DSM-5 criteria in a Portuguese sample of female high school and university students[6]. While the increased flexibility of the new criteria are favorable for insurance reimbursement in that they will allow a greater number of individuals to be treated, those who are classified as having AN may now present as a more heterogeneous group in terms of severity and metabolic phenotype, and should therefore be evaluated at the individual level when considering novel therapies such as those that will be discussed in this review.

In terms of risk for developing AN, both genetic and environmental factors are implicated[7]. Indeed, replicated twin studies have estimated the heritability of AN to be around 50–60%[8]. Results from a recent genome-wide association study (GWAS) suggest both psychiatric and metabolic etiological factors[9]. Thus, advances in AN treatment may need to focus not only on psychiatric, but also metabolic factors.

Treatment and prognosis

Current treatments for AN are often ineffective or lead to partial recovery, with frequent relapse, especially among adults[10,11]. Adolescents generally fare better, although relapse following full recovery occurs in between 7.1% and 21% of patients[12–14]. Further, relapse has been defined inconsistently, and follow-up lengths and treatment modalities have varied. With respect to recovery rate, one study estimated that 66.8% of patients maintained normal weight and menstrual cycle while abstaining from binge-eating and purging behaviors for a minimum of one year post-treatment[15].

Therapeutic renourishment remains the cornerstone of the treatment of AN. A review describing developments in the treatment of AN recognized family based therapy (FBT) as being beneficial for youth, whereas for adults, a number of psychological approaches including cognitive behavioral therapy (CBT), specialist supportive clinical management, and interpersonal psychotherapy (IPT) have been recommended[16]. No medications have been found to be effective in the treatment of AN[11].

AN remains the deadliest of any psychiatric illness. A systematic review calculated weighted annual mortality for AN as 5.10 deaths (95% CI, 3.99–6.14) per 1000 person-years, of which 1.3 deaths were attributed to suicide[17]. In a subsequent study, suicide was verified as a leading cause of death among individuals with AN[18]. Other factors contributing to high mortality rates in AN include susceptibility to infection, dehydration, and electrolyte imbalance[19]. This highlights a pressing need for novel safe and effective treatments for AN.

Gut microbial health influences psychology and behavior

Multiple biologically plausible pathways have been proposed to explain the relationship between intestinal microbiota and neurological processes, including microbial production and modulation of neurotransmitters, short-chain fatty acids (SCFA), brain-derived neurotrophic factor (a protein with signaling properties in the central nervous system and periphery), inflammation, and the hypothalamic-pituitary axis (implicated in depression

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through secretion of hormones that stimulate cortisol production)[20]. A growing body of research—in both animals and humans—supports the concept of a brain-gut-microbiota axis[21–25], whose signals to physiologic and neurologic processes include those related to eating behavior and mood.

Associations between gut microbiota and AN

Alterations in gut microbial composition and diversity

Gut microbial diversity varies inversely with severity of disease states, including in AN[26] and T1D[27,28], among others. This is especially true when comparing patients with AN pre- and post-treatment and to normal weight (NW) healthy controls[26,29]. Interestingly, reduced enteric microbial diversity has been associated with higher depression in AN[29]. The link between gut microbial dysbiosis and depression in AN could be an important one, as a diagnosis of major depressive disorder was found to be a predictor of long-term AN-R persistence in one study (OR 5.87, P=0.01)[30].

The caloric restriction characteristic of AN invites speculation that this illness allows microorganisms capable of surviving in a calorie-poor environment to thrive[31]. For instance, multiple studies suggest that the methane-producing archeon *Methanobrevibacter smithii* is more abundant in AN[26,32,33]. This increased abundance may represent an adaptive response to very low energy intake. Indeed, *M. smithii* metabolizes the hydrogen produced during bacterial fermentation, preventing the build- up of hydrogen gas and allowing increased transformation of nutrients into calories[32,33], which may benefit the host during nutrient-limited conditions. In addition, a significant decrease in the abundance of the phylum *Bacteroidetes* was reported among AN patients at baseline compared with NW controls, which persisted following weight restoration (FDR-adjusted $P < 0.15$ at baseline and $P < 0.05$ at follow-up)[26]. On the other hand, the phylum *Firmicutes* was significantly elevated in post-treated AN patients, but not at baseline, compared to NW controls (FDR-adjusted $P < 0.05$). Another bacterial phylum, *Actinobacteria*, was significantly elevated in AN patients relative to controls prior to and following weight restoration (FDR-adjusted $P < 0.05$ for both). Ultimately, there is little consistency as to which microbial phyla are associated with AN before or after clinical refeeding, most likely due to differing regional populations and treatment regimes.

Notably, Mack *et al.* found that relative abundance of several mucin degraders— whose activities may be pathological for the gut epithelium—was increased among AN patients compared to healthy controls at baseline (FDR-adjusted $P < 0.15$ for *Verrucombia* in AN group vs. controls). However, this difference was no longer statistically significant following treatment[26]. The difference in abundance of mucindegraders was also significantly reduced from baseline to follow-up among AN patients (FDR-adjusted $P < 0.05$ for *Verrucombia*)[26], suggesting that certain gut microbial changes may serve as benchmarks for recovery. (Figure 1)

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Delayed gastrointestinal motility

Methane production by *M. smithii* can contribute to constipation and slowed gastrointestinal motility, allowing more time for energy harvest from the diet[32,34]. This theory derives further support from studies demonstrating positive associations between *M. smithii* counts and either BMI or weight gain[32,35,36], as well as associations between breath methane and high BMI[34,37,38]. As mentioned previously, the abundance of this archeon is elevated in AN patients, although research is needed to clarify the role of *M. smithii* in influencing energy metabolism and weight status among individuals with or without this illness. Arguably, *M. smithii* might be an ally in weight restoration, insofar as it allows for increased fermentation of carbohydrates to SCFAs that can provide energy to the host. However, SCFA are likely not a significant source of energy, as fermentation of 32 to 42 grams of indigestible carbohydrate would produce SCFA equivalent to only two to four percent of daily energy needs[39]. *M. smithii* might also compete for utilization of SCFAs, thereby limiting any potential benefit. Moreover, as *M. smithii* contributes to slowed intestinal motility and constipation, it may discourage food intake and thereby interfere with weight restoration.

Kamal *et al.* verified that intestinal motility, or gastric transit time is delayed among AN patients by measuring whole-gut and mouth to cecum transit time. As hypothesized, whole-gut transit time was significantly delayed among AN patients compared with healthy controls ($P < 0.05$), while mouth to cecum transit time also trended towards being increased, although the difference did not reach statistical significance[40].

Implications for treatment

Delayed gastric transit time has been reported to elevate colonization of the gut by slow-growing mucin-degrading microbes, which may conceivably promote AN- associated bloating[41]. Moreover, patients may increase fiber consumption to relieve constipation-associated bloating, which can further exacerbate symptoms via gaseous byproducts of microbial fermentation[42]. Bloating symptoms may then disincentivize recovery and intensify fear of weight gain, although these byproducts of treatment can be circumvented through use of antibiotics. For instance, elimination of *M. smithii* using antibiotic rifaxamin has been shown to reduce bloating symptoms[43], while other probiotics have relieved bloating symptoms in trials of functional bowel disorders[44]. However, their influence on indigenous mucin-degrading microbes remains unknown.

Intestinal permeability, autoimmunity, and effects on appetite

Alterations in gut permeability have been demonstrated in both human and mouse models of AN[45]. This may allow foreign invaders to activate the immune system and stimulate the production of autoantibodies that target neuropeptides, including anorexigenic (appetite-suppressing) α-melanocyte-stimulating hormone (α-MSH) and orexigenic (appetite-stimulating) ghrelin[46–48]. This particular phenomenon has been observed in healthy women and rats[47].

In support of the concept that autoimmunity contributes to ED, Terashi *et al.* have speculated that changes in abundance and binding availability of ghrelin autoantibodies contribute to

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the elevated plasma ghrelin and ghrelin resistance characteristic of AN[49,50]. Additionally, autoantibodies to α-MSH were found in most AN patients and a positive correlation between autoantibody levels and ED pathology was detected[51,52]. In rodents, α-MSH autoantibodies were induced by caseinolytic protease B (ClpB) – an enzyme produced by *Enterobacteriaceae*, microbes observed at higher concentrations in AN patients by multiple research groups[33,53,54]. Associations between ClpB concentration and psychopathological traits have also been detected in AN patients[53].

In contrast to other findings, reduced small intestinal permeability has also been reported among patients with AN[55]. It is possible that the effects of AN on intestinal permeability are site-specific; arguably, differential effects on the small intestine and the colon may reflect the role of gut microbiota in regulating permeability, as the highest concentrations of microbes occur in the colon[44,56]. At the same time, as Jésus *et al.*[45] used a mouse model, their findings may not translate to humans. Moreover, the level of caloric restriction in these mice—typically 30 to 40 percent of total calories—may not match the level of caloric restriction common in individuals with AN, which itself is difficult to measure accurately.

Excessive exercise alters intestinal permeability and gut microbial composition

Exercise intensity and intestinal permeability are positively correlated[57,58]. The activity-based anorexia (ABA) mouse phenotype yields hyperactivity via limited access to food. Increased colonic permeability and altered tight junction protein expression have been demonstrated in ABA mice[45]. Higher levels of mucin-degrading *Akkermansia muciniphila* have also been observed in athletes. The investigators speculated that *A. muciniphila* may improve barrier function by mechanisms still not fully understood, whereas others hypothesized that increased levels of the microbe would compromise the mucus layer of the epithelium and thereby the integrity of the intestinal barrier[59,60].

Studies of forced activity in rodents could reveal how excessive exercise could affect the gut microbiota in AN, as it may better approximate the compulsive, compensatory exercise associated with AN rather than voluntary exercise. For example, Allen *et al.* found that mice subjected to forced treadmill running (FTR) had greater microbial diversity and altered gut microbial composition relative to mice exposed to voluntary wheel running[61]. While increased gut microbial diversity is generally associated with better health, here it was related to an expansion of rare bacterial species. The FTR mouse feces also exhibited a predominance of taxa that have been linked to disease states.

SCFA

Role in human health

SCFA—dietary metabolites produced by gut microbial fermentation of indigestible dietary carbohydrates—are an emerging topic of interest in metabolic health and weight management. Butyrate is a widely studied SCFA that is known to stimulate goblet cell mucin synthesis, which promotes gut health by lubricating and protecting epithelial cells. Butyrate also serves as a salient energy source for the intestinal epithelium[62]. Interestingly, butyrate is primarily found in milk fat[63]. SCFA production could be reduced in AN due to

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avoidance of fat-containing food products (13% of calories consumed from fat have been noted in AN patients vs. 31% in controls)[64].

Fecal SCFA are reduced in AN

Most studies have reported reduced fecal SCFA in AN patients compared with controls. Borgo *et al.* detected significantly lower fecal concentrations of total SCFA (P = .041), butyrate (P = .045), and propionate (P = .028); notably, their finding of decreased butyrate is consistent with decreased carbohydrate-fermenting genera *Ruminococcus* (p = .019), *Roseburia* (P = .037), and *Clostridium* (P = .031)[33]. Decreased acetate (P = .0003) and propionate (P = .001) were found in AN patients in Japan compared to healthy controls[65]. By contrast, Mack *et al.*[26] reported comparable fecal concentrations of total SCFA, acetate, butyrate, and propionate in AN patients and controls. They nevertheless detected reduced butyrate as a percentage of total SCFA among AN patients on admission, compared with discharge and with normal weight controls, which concurred with a reduced abundance of butyrate-producing *Roseburia*. Further, butyrate concentration correlated with *Roseburia* abundance in all three groups. The inconsistencies across studies may reflect compositional differences that occur across geographical regions[66,67].

To remedy reduced SCFA production in AN patients, some have proposed administering butyrate-producing *Roseburia* or supplementing directly with SCFAs[26,68]. Theoretically, increased intake of carbohydrates and prebiotic fibers would also enhance SCFA production. However, the bacterial fermentation of carbohydrates would also contribute to gas, bloating, and distention, producing physical discomfort after meals and potentially exacerbating body image concerns.

Parallels between AN and T1D

Energy dysregulation

Alterations in energy metabolism are central to both T1D and AN. Similar to the catabolic state that occurs due to starvation in AN[69], severe weight loss is a feature of untreated T1D[69,70]. Even when treated, elevated resting energy expenditure (REE) has occurs in individuals with T1D relative to prediction equations for healthy individuals[71,72]. Although reduced REE occurs in underweight AN[73], many patients experience hypermetabolism during refeeding for unknown reasons[74].

Etiology, prevalence, and complications of disordered eating in T1D

It is tempting to speculate that the increased prevalence of disordered eating among individuals with T1D is a function of constant carbohydrate counting for blood glucose control and intense attention to weight. Although this behavior is initially medically-driven, food restriction, defined as restraint, or self-imposed resistance to food consumption[75], is associated with undesirable shifts in behavior and metabolism. One such behavior includes insulin restriction[76], which can lead to uncontrolled blood glucose[77,78] and thus acute and chronic health complications. Schober et al. found that reasons most commonly reported for insulin omission included denial of the disease in situations with peers (30%), self-destructive behavior and suicidal ideation (28%), fear of severe hypoglycemia (24%), and

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intention to lose weight (15.5.%)[79]. Conversely, intentional insulin overdosing to enable binge eating has also been commonly reported among individuals with T1DM[79]. Elevated BMI may also result, as restraint can lead to uncontrolled overeating when individuals cease to limit their food intake[80,81].

Furthermore, co-occurring T1D and ED may interact to synergistically worsen health outcomes. In one study, mortality via diabetes-related metabolic complications was increased with co-occurring T1D and AN, compared with either disorder alone (standardized mortality ratio 4.06, 8.86, and 14.5 for T1D, AN, and T1D and AN combined, respectively)[82]. Peveler et al. reported that among individuals with T1D, those with EDs had a higher baseline Hemoglobin A1c (HbA1c – a three-month measure of BG) than those without an ED (11.9 vs. 9.4 , $P = 0.009$)[78]. However, HbA1c was not associated with ED status at 8 to 12 year follow-up points, suggesting that in some instances, disordered eating behaviors may normalize following adolescence[78].

A systematic review suggests that both BN and the combined presence of BN and AN are significantly elevated in patients with T1D compared with controls (both $P < 0.05$)[2]. Of 550 female patients with T1D, 1% had lifetime AN and 16.2% had lifetime BN[83]. Subthreshold disordered eating is also prevalent, with one study reporting a greater proportion of girls aged 9–14 with T1D reporting two or more unhealthy eating behaviors compared to non-diabetic controls ($P < 0.0005$)[84].

Gut microbial dysbiosis in T1D

Although shifts in dietary behaviors rapidly and reliably alter the enteric microbial community, much of the literature linking T1D with changes in the gut microbiota has focused on infants and children proximal to T1D onset. Most[27,28], but not all[85] studies report reduced enteric microbial diversity among patients who develop autoimmunity to pancreatic islet cells compared to controls. Compositional differences were reported in two independent cohorts of Mexican and Finnish children displaying increased *Bacteroides* among T1D cases and *Prevotella* among controls[86,87]. Another research team found that two species from the *Bacteroides* phylum were significantly increased among Finnish T1D case children months before diabetes onset[88]. Yet other studies reported reduced abundance of *Bifidobacterium* in patients compared with controls[89,90], although other compositional differences have been less consistently observed[27,85,89].

Similar to AN, reduced fecal SCFA have been observed among individuals with T1D compared to controls. Despite a trend towards increased fiber consumption among individuals with T1D compared to non-diabetic controls in one study, control participants had increased levels of plasma acetate and propionate compared to the T1D group, although total fecal SCFA were similar[91]. This may suggest enhanced utilization of SCFA metabolites by individuals with T1D before they reach the plasma, perhaps in order to fulfill functions related to gut epithelial integrity.

The gut microbiota is associated with weight status and glycemia

It is important to note that gut microbial composition has also been found to shift reliably in association with changes in weight status and metabolic parameters— including glucose

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homeostasis—in both animal and human models, which is relevant considering the increased prevalence of overweight and obesity among individuals with T1D[92]. For instance, Rabot et al. showed that germ-free mice fed a high-fat diet were able to maintain euglycemia (normal blood glucose), although conventionally-raised mice with gut microbiota that had been allowed to colonize naturally, developed glucose intolerance and had higher plasma insulin concentrations in both a fed and 6-hour unfed state[93]. In a study with human participants, Nadal et al. found that changes in blood glucose significantly correlated with changes in proportions of gut microbial groups in adolescents participating in a weight loss intervention, regardless of weight loss outcome ($P=0.006$)[94]. Of note, diagnostic crossover is common in eating disorders, meaning that during the course of an individual's illness, they may transition across diagnostic presentations (AN, BN, BED)[95], which can entail considerable fluctuations in weight. No work has yet been done to understand how the gut microbiota may be implicated in these longitudinal changes in symptom presentation.

Genetics

The association between AN and T1D may reflect shared genetic variants, including those related to metabolism. An AN GWAS detected one genome-wide significant variant for AN[9], which was previously found to be associated with T1D. Significant genetic correlations emerged between AN and multiple metabolic traits implicated in T1D, including insulin resistance, fasting insulin, fasting glucose, and cholesterol and lipid measures[9]. These findings are consistent with evidence of increased ED prevalence and disordered eating among individuals with T1D, as well as increased risk of autoimmune disorders, especially of endocrinological and gastroenterological types, among individuals with ED[48]. Considerably more work is essential to confirm and dissect the nature of this relationship. Larger sample sizes for AN GWAS are critical first steps for any more detailed analysis of the association.

Future directions

It is vital to consider genetic, metabolic, and psychological factors that influence AN and multifactorial disorders such as T1D, in which symptoms of disordered eating, energy dysregulation, gut microbial dysbiosis manifest. Fecal microbiota transplantation (FMT), or the transfer of fecal microbiota from healthy donors to diseased patients, is one potential treatment that is on the horizon for many disease states including T1D and AN[96] based on its effectiveness at treating *Clostridium difficile* infections[97]. One challenge with respect to translational application of FMT to other disease states is donor screening, as systematic assessments of donor health have yet to be established. Furthermore, no standard exists for ideal gut microbial composition, although screening out individuals with pathogenic gut microorganisms is critical. However, preliminary evidence exists that FMT can improve metabolic phenotypes, including median rate of glucose disappearance and insulin sensitivity among males with metabolic syndrome ($P < 0.05$), which is relevant in light of obesity-associated insulin resistance that can develop in T1D[98,99]. Thus, experimenting with FMT and other adjunct therapies in treating symptoms of AN and T1D may provide insight into how the gut microbiota contribute to disease pathology and prognosis.

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Synopsis

Anorexia nervosa has poor prognosis and treatment outcomes, and is influenced by genetic, metabolic, and psychological factors. Gut microbes interact with gut physiology to influence metabolism and neurology, although potential therapeutic benefits remain unknown. Type 1 diabetes is linked to anorexia through energy dysregulation, which in both disease states is related to the gut microbiota, disordered eating, and genetics.

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Key points

- Anorexia nervosa is highly refractory, and novel treatments are needed to improve prognosis.
- The gut microbiota is dysregulated in anorexia nervosa, and may be a new avenue for research in reducing discomfort during refeeding.
- Metabolism is often dysregulated in anorexia nervosa and type 1 diabetes, which share common genetic alterations, disordered eating patterns, and features of gut microbial dysbiosis.

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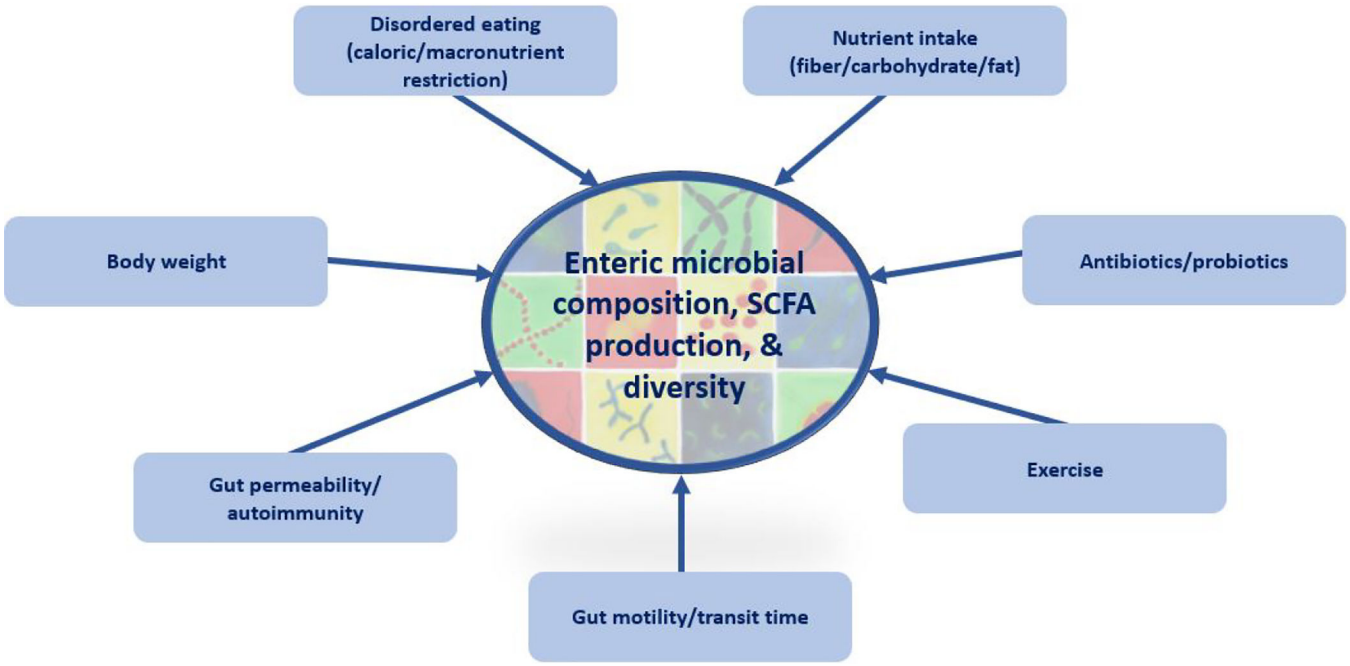

Figure 1:
Factors that influence gut microbial composition, SCFA production, and diversity in anorexia nervosa.