Nutrition Research Reviews (2023), 36, 372–391 doi:10.1017/S0954422422000130

Microbiota in anorexia nervosa: potential for treatment

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Abstract

Anorexia nervosa (AN) is characterised by the restriction of energy intake in relation to energy needs and a significantly lowered body weight than normally expected, coupled with an intense fear of gaining weight. Treatment of AN is currently based on psychological and refeeding approaches, but their efficacy remains limited since 40% of patients after 10 years of medical care still present symptoms of AN. The intestine hosts a large community of microorganisms, called the "microbiota", which live in symbiosis with the human host. The gut microbiota of a healthy human is dominated by bacteria from two phyla: *Firmicutes* and, majorly, *Bacteroidetes*. However, the proportion in their representation differs on an individual basis and depends on many external factors including medical treatment, geographical location and hereditary, immunological and lifestyle factors. Drastic changes in dietary intake may profoundly impact the composition of the gut microbiota, and the resulting dysbiosis may play a part in the onset and/or maintenance of comorbidities associated with AN, such as gastrointestinal disorders, anxiety and depression, as well as appetite dysregulation. Furthermore, studies have reported the presence of atypical intestinal microbial composition in patients with AN compared with healthy normal-weight controls. This review addresses the current knowledge about the role of the gut microbiota in the pathogenesis and treatment of AN. The review also focuses on the bidirectional interaction between the gastrointestinal tract and the central nervous system (microbiota–gut–brain axis), considering the potential use of the gut microbiota manipulation in the prevention and treatment of AN.

Keywords: **anorexia nervosa (AN): metabolism: nutrition: diet: gut–brain interaction: eating disorder: gut microbiota: dysbiosis**

(Received 28 August 2020; revised 1 April 2022; accepted 17 June 2022; accepted manuscript published online 25 July 2022)

Introduction

Eating disorders (EDs) consist of a wide range of debilitating psychiatric diseases which are characterised by the dysregulation of weight and appetite[(1)]. Types of eating disorders include anorexia nervosa (AN) and bulimia nervosa, which also include a range of psychiatric diseases characterised by appetite dysregulation leading to abnormal feeding behaviour[(1)]. AN and BN are manifested by severe dietary restriction and/or binge eating[(2–4)]. To date, among eating disorders, AN is the most investigated one in relation to the gut microbiota[(5–9)]. Since ED are characterised by behaviour alterations, they have been classified as psychiatric diseases involving an impaired brain function[(10)]. Research done in the past two decades has shed more light on their origins, which seem to depend also on factors outside the brain, such as interactions with endocrine and immune systems as well as the gut microbiota[(11,12)]. This review seeks to address the role of the gut microbiota in the pathogenesis, recovery or relapse, and treatment of AN, mainly focusing on the microbiota–gut–brain axis, and to consider the possibility of gut microbiota manipulations as a contributing factor in facilitating weight gain, reducing gastrointestinal distress due to illness and perhaps reducing anxiety and depression.

Anorexia nervosa

Anorexia nervosais a serious psychiatric and eating disorder which is characterised by serious occurrence of underweight (body mass index (BMI) <18·5 kg/m^2), concurrent malnutrition, an intense fear of gaining weight, and alterations in an individual's perception of their weight and body image with a denial of the importance of feeding[(13)]. The prevalence of AN in the general population has been estimated to be approximately 1·4% for women and 0·2% for men, and to be steadily increasing in most countries[(14)]. AN has poor treatment outcomes and the highest mortality rate of any psychiatric disorder, with a standardised mortality ratio >5 (ratio of observed deaths in individuals with AN to expected deaths in the general population)[(15)]. AN can be classified into two subtypes: restricting type (where patients limit their food intake to decrease body weight) and binge eating/purging type (where patients use self-induced vomiting, laxatives, diuretics or enemas to counteract food intake)[(13)].

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Subjects with eating disorders such as AN often present with comorbid conditions of anxiety disorders, such as obsessive–compulsive disorder (OCD), social phobia or generalised anxiety disorder, prior to the emergence of the ED[16]. There may be individual differences especially with regards to behavioural features that go far beyond the mere classification[17]. Despite the aetiology, the pathophysiology remains unclear. AN is considered a multifactorial disease in which biological, psychological and socio-cultural factors are implicated[18]. The gut microbiota has gained a relevant role as a proposed biological factor of AN during the past two decades. In fact, the gut microbiota has been implicated to be involved in weight regulation, fat storage and energy harvest from diet, as well as in eating behaviour, anxiety and depression[19–22].

The gut microbiota

The human gut microbiota consists of trillions of microbial cells and thousands of bacterial species[23]. It encompasses millions of microorganisms belonging to the three domains of life: Bacteria, Archaea and Eukarya, which are involved in several different functions[24,25]. There is a wide diversity in the gut microbiota; some phyla such as *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia*, *Fusobacteria* and a few *Archaea*, mainly methanogens, are prevalent[26]. These microbes play important roles in the breakdown, absorption and metabolism of dietary components, including pathways associated with the microbial degradation of carbohydrates and amino acids as well as production of vitamins B and K[26]. In the large intestine, microbes digest carbohydrates, proteins and lipids left undigested by the small intestine; indigestible substances, such as the walls of plant cells, cellulose, hemicellulose, pectin and resistant starch, are subjected to microbial degradation and subsequent fermentation[25]. Dietary regimes consisting of unrefined foods and non-digestible substances have been shown to cause growth of microbes which are capable of degrading polysaccharides to short-chain fatty acids (SCFAs)[27]. SCFAs are food metabolites produced by bacterial fermentation in the colon. They include, for example, butyrate produced mainly by *Firmicutes*, propionate produced by *Bacteroidetes*, and acetate produced by some anaerobes, and they represent the greatest source of energy for intestinal cells[28]. The gut microbiota varies in the number and type of species along the intestine, and its density and composition are affected by many factors, such as the host's genetics, ethnicity, age, environmental microbial exposures, infections, medications, chronic diseases, stress, physical exercise and sleep[29,30]. Dietary composition, both long-term and short-term, may influence the gut microbiota composition[31–33]. Interestingly, the gut microbiota plays important roles in many aspects that are characteristic of AN, including regulating mood and anxiety[34], behaviour[35], appetite[36], gastrointestinal symptoms[37] and metabolism[38]. Studies have investigated the association between the gut microbiota and psychopathology in patients with AN[7,9,11]. Since changes in diet may profoundly impact the composition and function of the gut microbiota, and knowing that the diet of patients with anorexia is dramatically altered both quantitatively and qualitatively, the result could be a dysbiosis that may contribute to the onset or maintenance of disorders associated with AN.

The microbiota–gut–brain axis in anorexia nervosa

During the past decade, a growing body of evidence derived from animal models and human studies found a communication between the intestinal microbiota and the brain (i.e., the so-called microbiota–gut–brain axis)[39]. The role of the microbiota–gut–brain axis is to monitor and integrate gut functions as well as to link emotional and cognitive centres of the brain with peripheral intestinal functions and mechanisms such as immune activation, intestinal permeability, enteric reflex and entero-endocrine signalling[40]. The bidirectional communication network of microbiota–gut–brain axis includes the central nervous system (CNS), both brain and spinal cord, the autonomic nervous system, the enteric nervous system (ENS) and the hypothalamic pituitary adrenal (HPA) axis. This bidirectional communication occurs through neuronal and immunological pathways with contributions from the endocrine system, and has proven to have a relevant role, not only in normal gastrointestinal function, but also in cognitive functions. Therefore, an alteration at this level involves various types of alterations, including inflammatory and functional gastrointestinal symptoms and eating disorders[41]. The relationship between the intestinal microbiota and AN is currently receiving more research attention, but the specific mechanism through which the gut microbiota could affect the brain is still unclear. The microbiota–gut–brain axis is complex, and is carried out in several ways, which include communication through neuronal and hormonal pathways. Alterations in the microbiota–gut–brain axis may affect intestinal motility and secretion, cause visceral hypersensitivity and lead to changes in entero-endocrine and immune system function[59].

Neural interconnection

The vagus nerve is a critical component linking biological function in the CNS and the ENS[41,42]. Signals from the ENS could either interact directly with vagus nerve or indirectly through the mediation of enteroendocrine cells and hormonal factors[43]. The vagus nerve is able to sense the metabolites of gut microbiota through its afferent fibres, transferring this gut information to the CNS where appropriate responses are generated[44]. Inappropriate activation of the vagus nerve results in excessive activation and elevation of neurotransmitters leading to the impairment of the digestive process and alterations of gastrointestinal motility[43].

The gut microbiota has been shown to affect circulating levels of various neurotransmitters. Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system, is involved in the regulation of many physiological pathways[45]. *Lactobacillus*, *Bifidobacterium*, *Bacteroides* and *Parabacteroides* are capable of synthesising GABA to reduce anxiety and stress, while *Escherichia*, *Bacillus* and *Saccharomyces* produce norepinephrine[46–48]. Accumulating evidence gathered from animal research suggests that gut microbiota influences circulating GABA levels since germ-free animals have considerably reduced luminal and serum levels of GABA[49]. In humans, preliminary

https://doi.org/10.1017/S0954422422000130 Published online by Cambridge University Press

studies suggest that manipulating the human gut microbiota may impact GABA levels[50,51], and a genetic study has provided evidence for a role of GABA in the recovery from eating disorders[52]. Serotonin has been isolated from *Candida, Streptococcus*, *Escherichia* and *Enterococcus*, and dopamine is recognised as one of the final products of the metabolism of *Bacillus* and *Serratia*[53,54]. Further, indigenous spore-forming bacteria can induce serotonin biosynthesis from colonic enterochromaffin cells[55]. In fact, dysregulation in the serotonin system at cortical and limbic levels could be associated with some features commonly affecting patients with AN such as anxiety, behavioural inhibition and body image distortions[56].

Endocrine interconnection

The HPA axis is a collection of structures that coordinates the stress response in organisms[57,58]. The mediators of the stress response are localised in paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland[57,58]. Environmental stressors and elevated levels of systemic pro-inflammatory cytokines trigger the release of corticotropin-releasing hormone from the paraventricular nucleus. The corticotropin-releasing hormone then acts on the anterior pituitary to release adrenocorticotropic hormone, which subsequently acts on the zona fasciculata of the adrenal cortex to secrete cortisol. Peak secretion of cortisol occurs in the morning and low at night. In sufficient quantities, cortisol inhibits the release of both adrenocorticotropic hormone and corticotropin-releasing hormone. Cortisol participates in blood pressure regulation, immune system modulation and metabolism of lipids, protein and carbohydrate, and also has anti-inflammatory effects[57,58]. Cortisol levels affects many organs in the human body, including the brain. Through a combination of neural and hormonal routes of communication, the brain influences activities of intestinal effectors cells (e.g. immune cells, interstitial cells of Cajal and enterochromaffin cells). These cells function under the influence of the gut microbiota[59].

Sudo *et al.*[60] showed that germ-free (GF) mice had a more aggressive HPA stress response than mice colonised by microbes. In addition, subsequent studies have shown that GF mice differ from conventional mice in their brain and neuron morphology, degree of anxiety, levels of serotonin, and brain-derived neurotropic factors[61–66]. Other endocrine systems also appeared to be affected by the gut microbiota[67]; in fact, modulation of behaviour by the gut microbiota occurs through neurohormones such as serotonin and dopamine[46]. The gut microbiota was demonstrated to produce and respond to neurohormones, such as serotonin, dopamine and norepinephrine[68]. Alcock *et al.*[69] suggests that certain microorganisms can induce effects, either positive or negative, on host feeding patterns and emotional behaviour through the release of neurohormonal molecules. By studying the faecal microbiota of patients with AN and age-matched healthy controls, Morita *et al.* found that patients with AN had significantly lower levels of the *Clostridium coccoides* group, the *Clostridium leptum* subgroup, *Bacteroides fragilis* and *Streptococcus* than the control group. Taken together, these results confirm the dysbiosis in the gut of patients with AN regarding these bacteria[8].

Immune interconnection

Gut microbiota can modulate the immune system through the release of various neuroactive substances, and also antigens mimicking host neuropeptides and neurohormones[45]. The autoantibodies for microbiota-produced antigens have been connected to neuropsychiatric disorders such as anxiety, depression, and eating and sleep disorders[45]. Gut microbiota affects mucosal immune activation. The enhanced mucosal inflammation induced in mice after treatment with oral antimicrobials increases substance P expression in ENS, an effect normalised by the administration of *Lactobacillus paracasei*, which also attenuates antibiotic-induced visceral hypersensitivity[61]. The effects of microbiota on immune activation might be in part mediated by proteases which are often upregulated in intestinal-immune mediated disorders[70]. Elevated levels of proteases have been detected in faecal samples of patients with inflammatory bowel disease associated with specific types of gut bacterial species[71]. A large Finnish case–control study showed that patients with AN have a higher risk of endocrinological or gastroenterological autoimmune disease, supporting the connection between compromised immune system and AN[72]. Similarly, in a UK record-linkage cohort study, AN was associated with increased risk of several autoimmune diseases[73]. Furthermore, meta-analyses on AN and inflammatory cytokines showed increased levels of IL6, IL1 and TNFα in patients with AN[74,75]. In general, there is a link between AN and changes in the immune system, but not much is known about the possible links between microbiota and the immune system in AN[76].

A study of circulating neuropeptide autoantibodies showed increased serum immunoglobulin (Ig) M autoantibodies in AN against α-melanocyte-stimulating hormone (α-MSH), oxytocin and vasopressin and increased IgG autoantibodies against vasopressin[77]. A-MSH autoantibody levels correlated with total score as well as with subscale dimensions on the Eating Disorder Inventory-2 score, suggesting an immune system-mediated malfunction in the melanocortin system, which is a key player in appetite control[77]. In addition, sera from patients with AN or BN were shown to bind to α-MSH-positive neurons and their hypothalamic and extrahypothalamic projections in rats[78]. The same researchers showed that IgG from patients with obesity prevented the central anorexigenic effect of α-MSH in rodents, further supporting the hypothesis that α-MSH autoantibodies can affect food intake[79]. A possible link between gut microbiota and the melanocortin system is enterobacterial caseinolytic protease B (ClpB) production. This is based on the fact that ClpB has an α-MSH-like motif which can trigger the production of α-MSH-cross-reactive antibodies[80]. Furthermore, ClpB autoantibodies were increased in patients with AN and associated with Eating Disorder Inventory-2 scores similarly to the α-MSH autoantibodies[80]. Both ClpB- and α-MSH-reactive immunoglobulin production increased in a rat model of chronic food restriction[81]. A pharmacological study identified that a fragment of ClpB with α-MSH homology is an agonist for melanocortin 1 receptor[82].

Another example of autoantibodies related to appetite-regulating hormones in AN is orexigenic hormone ghrelin. Concentrations of free active acyl ghrelin and degraded des-acyl ghrelin is shown to be increased in AN[83–88]. While acyl ghrelin is orexigenic, there is evidence that des-acyl ghrelin may have an

https://doi.org/10.1017/S0954422422000130 Published online by Cambridge University Press

opposing effect on appetite[89–91]. Binding of ghrelin to immunoglobulins protects them from degradation. IgG, IgA and IgM antibodies against acylated ghrelin were reduced in AN with ghrelin IgG autoantibodies mostly bound in immune complexes with des-acyl ghrelin[92]. Thus, if des-acyl ghrelin is anorexigenic, binding to IgG should offer some degree of protection in AN. Another study by the same researchers showed no difference between ghrelin IgG autoantibodies between AN and controls, but affinity for ghrelin binding was reduced[83]. Chronic co-administration of ghrelin and IgG from patients with AN into rats had lower orexigenic effect compared with IgG from patients with obesity[83]. Sequence homology between ghrelin and products of gut microbes could potentially link microbiota with the observed ghrelin autoantibodies[93].

Intestinal microbiota alterations in anorexia nervosa

Differences in the gut microbiota composition have already been demonstrated between subjects with obesity and normal-weight individuals[94,95]. Likewise, an involvement of the gut microbiota in both weight gain and weight loss, as well as in energy extraction from the diet, has been demonstrated in human and animal studies[96,97]. Finally, in recent years, it has been recognised that gut microbiota not only influences gastrointestinal disorders and weight regulation in healthy individuals[37], but can also affect patients with AN. This finding has been studied by Armougom *et al.*[5], Million *et al.*[98] and Morita *et al.*[8], analysing a variety of microorganisms present in patients with AN. Armougom *et al.*[5] reported for the first time that there is an increase of *Methanobrevibacter smithii* in patients with AN. The archaeon plays a role by removing hydrogen excess from bacterial fermentation in the gut microbiota, which appears to lead to the optimisation of food transformation in very-low-energy diets. Moreover, this could also be associated with constipation, which is a common feature in AN[5]. Million *et al.*[98], analysing faecal samples from obese, overweight, lean and anorexic subjects, confirmed the increase of *M. smithii* in subjects with BMI $<25\ kg/m^2$ compared with individuals with BMI $>25\ kg/m^2$[98]. In addition, Morita *et al.*[8] found that patients with AN had significantly lower amounts of total bacteria and obligate anaerobes, including those from the *Clostridium coccoides* group, *Clostridium leptum* subgroup and *Bacteroides fragilis* group, than the age-matched healthy controls. Moreover, Pfleiderer *et al.*[6] found eleven completely new bacterial species and four new micro-eukaryote species in a faecal sample from a single patient with AN. In subsequent years, numerous other larger-scale clinical trials that investigated the composition of the gut microbiota in patients with AN, as shown in Table 1, were conducted. Finally, the gut microbiota has also been shown to have a role in anxiety, obsessive–compulsive disorder and depression[99], which are common comorbidities of eating disorders[100].

Bacterial abundance in anorexia nervosa

Few studies have investigated the abundance of the gut microbiota in AN. Both Million *et al.*[98] and Mack *et al.*[9] have demonstrated a normal abundance of the gut microbiota in AN. Million *et al.*[98] found higher levels of *Escherichia coli* and lower levels of *Lactobacillus reuteri* in patients with AN than they did in normal-weight individuals. The energy and macronutrient intake of patients with AN at baseline was low compared with those of normal-weight participants; nevertheless, both groups presented similar daily fibre intake, mainly due to the high consumption of fruit, vegetables and whole-wheat bread. This factor may perhaps have protected against the reduction in the alpha-diversity of the gut microbiota. *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* are the dominant phyla in individuals[9,11]. Interestingly, weight loss due to low carbohydrate or low-fat diets seems to lead to an increase in the *Bacteroidetes* levels[101], while high-fat diets are associated with an increase in the levels of *Firmicutes* and *Proteobacteria* and a reduction of *Bacteroidetes*[102]. However, the results of studies examining the relative abundance of *Firmicutes* and *Bacteroidetes* in patients with AN have been contradictory. Mack *et al.*[9] found that the phylum *Bacteroidetes* was significantly lower and the level of *Firmicutes* was significantly higher in patients with AN than they were in normal-weight participants. Similar results were obtained by Kleiman[103] and Armougom[5]. However, Borgo *et al.*[11] found that the gut microbiota of subjects with AN was enriched in *Bacteroidetes* and depleted in *Firmicutes*, and reduction in *Firmicutes* was in line with the lower faecal butyrate concentration in the individuals with AN. Moreover, patients with AN have shown elevated relative abundance of *Actinobacteria* (mainly *Bifidobacterium*)[9] and elevated levels of *Proteobacteria* and *Enterobacteriaceae* compared with healthy normal-weight controls[11]. Patients with AN have also demonstrated reduced abundance of *Lactobacillus*[5,98] and decreased levels of *Ruminococcus* and butyrate-producing *Roseburia*[9,11]. A previous study also demonstrated that patients with AN had increased levels of *Coriobacteriaceae*[104]. *M. smithii* was increased in patients with AN compared with normal-weight individuals in several studies[5,9,11,98]; 22% of patients with AN at baseline were found to carry *M. smithii* compared with 15% of the normal-weight controls, whereas it was observed in 100% of the AN participants in Armougom's study[5]. *M. smithii* plays a key role in improving the efficacy of microbial fermentation, and its abundance has been hypothesised to optimise energy extraction from very-low-energy diets[105]. In addition, differences have been found between restrictive and purgative AN subtypes[6–9]. These types differ in their eating behaviour in that individuals with the restrictive form eat only small amounts of food at one time, whereas persons with the purgative type control their energy intake by vomiting after a meal. Morita *et al.* provided a detailed account of there being no significant difference between the two types in terms of the abundance of individual species[8], while in Mack's study, the microbial structure was significantly explained by the AN subtype[9]. This is also supported by Alessio's study, which found distinctions between the metabolomics and the microbiome profiles of the binge eating and restrictive subtypes of AN[106]. Heterogeneity in the results from the various studies on dysbiosis in AN may be due to differences in methodology, variations in study design, or individual differences in patients with AN[107].

Most of the studies conducted on the gut microbiota in AN have examined faecal samples, which means that they mainly reflect the colorectal microbiota. However, in addition to the

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Table 1. Gut microbiota composition in patients with anorexia nervosa

Study name	Study design/type	Study population	Summary	Critique/limitation of the study
Armougom *et al.*, 2009[5]	Cross-sectional. Real-time PCR screen of *Bacteroidetes*, *Firmicutes*, *Lactobacillus* and *Methanobrevibacter smithii* from stool samples	20 obese subjects, 9 patients with anorexia nervosa, and 20 normal-weight healthy controls	No changes in *Bacteroidetes*, *Firmicutes* or *Lactobacillus*. Increase in *M. smithii*	The use of microarrays for transcriptomic data comparison of *Lactobacillus* and *M. smithii* gene pool between the different populations could have been discussed further to aid in the understanding of metabolic activities. This early study had limited coverage of microbiota. Further research is needed to understand if *M. smithii* has relevance in the pathophysiology of AN
Million *et al.*, 2013[98]	Cross-sectional. PCR screen of *Enterobacteriaceae*, *M. smithii*, *Bifidobacterium animalis* and 5 *Lactobacillus* species from stool samples	134 obese, 38 overweight, 76 lean and 15 subjects with anorexia nervosa	Higher levels of *E. coli*. Lower levels of *Lactobacillus reuteri*. Increase in *M. smithii*. *L. reuteri* was positively correlated with BMI. *B. animalis*, *M. smithii* and *E. coli* were negatively associated with BMI	Analysis of the digestive microbiota associated with obesity from the analysis of stool samples has some challenges. Roughly 95% of fat is absorbed before the caecum; the proximal gut microbiota may be critical for the analysis of factors associated with obesity and diabetes. The reported correlations have wide confidence intervals, making interpretation of the effect size difficult. Association of microbe levels with BMI are attributed to be a result from diet and drivers of weight gain, but further study is needed to determine such interactions
Pfleiderer *et al.*, 2013[6]	Case study. Stool samples analysed using culturomics and 16S rRNA pyrosequencing	21-year-old French Caucasian female who had suffered from a severe restrictive form of anorexia nervosa since the age of 12 years	133 bacterial species were identified, of which 11 new species were sequenced from a stool sample; 7 species belonged to the phylum *Firmicutes*, 2 belonged to the phylum *Bacteroidetes* and 2 belonged to the phylum *Actinobacteria*	As this was a case study, no conclusions about the possible link between the newly identified bacterial species and AN could be drawn
Kleiman *et al.*, 2015[7]	Cross-sectional. Stool samples analysed using 16S rRNA pyrosequencing	Females ($n = 16$) admitted for inpatient treatment for eating disorders. Comparison with 12 healthy controls	Lower alpha diversity, greater levels of bacilli and unspecified genera in *Coriobacteriales*, and reduced levels of *Clostridium*, anaerobes and *Faecalibacterium* in patients with AN at admission compared with healthy controls. At discharge, the difference in unspecified genus in family Coriobacteriales persisted, and there were additional differences between patients with AN and controls among the family *Ruminococcaceae* and the genus *Parabacteroides*	A limited number of microbial groups were analysed (two phyla: *Bacteroidetes* and *Firmicutes*; one genus: *Lactobacillus*; and one archaeon: *M. smithii*). Further studies are needed to evaluate the potential causal links between the observed microbe differences

Table 1. (*Continued*)

Study name	Study design/type	Study population	Summary	Critique/limitation of the study
Morita *et al.*, 2015[8]	Cross-sectional. Faecal microbiome assessed by 16S or 23S rRNA-targeted RT-quantitative PCR	Female patients with AN ($n=25$), and age-matched healthy female controls ($n=21$)	Lower amounts of total bacteria and decrease in *Streptococcus* genus, *Clostridium coccoides* group, *Clostridium* subgroup, *Bacteroides fragilis* group and *Lactobacillus plantarum* in AN compared with healthy controls. *Bacteroides fragilis* group in the ANR and ANBP groups and the counts of the *Clostridium coccoides* group in the ANR group were lower than those in the control group	As the study was cross-sectional, it was difficult to draw a causal link between the changes in microbe amounts and weight gain. The used YIF-SCAN technique only covers species of bacteria that can be detected with a specific primer. Lastly, the sample size was relatively small
Mack *et al.*, 2016[9]	Prospective study. 16S rRNA profiling was used to evaluate faecal microbiome. Stool SCFAs and BCFAs were measured	55 female patients with AN at baseline; from 44 of these patients, a second sample was collected at the end of their impatient stay	No differences in diversity or richness. Decrease in *Bacteroidetes* and increase in *Firmicutes*. Higher levels of mucin degraders (*Verumicrobia*, *Bifidobacterium*, *Anaerotruncus*) and members of *Clostridium* clusters I, XI and XVII. Reduced abundance of butyrate-producing bacteria (*Roseburia* spp. and *Geminger* spp.)	The study did not fully exhaust the topic on carbohydrate digestion in the large bowel, and the breakdown of proteins by gut microbiota. Microbiota-targeted intervention studies are needed to evaluate if the observed candidate bacteria could support weight recovery and alleviate psychological and gastrointestinal symptoms. 16S rRNA profiling is limited to taxonomic evaluation only
Mörkl *et al.*, 2017[104]	Cross-sectional study. 16S rRNA profiling was used to evaluate faecal microbiome	A total of 106 participants (patients with AN, ($n=18$), athletes (AT, $n=20$), normal weight (NW, $n=26$), overweight (OW, $n=22$) and obese women (OB, $n=20$))	Compared with other entities, *Coriobacteriaceae* was found to be the only enriched phylotype in AN subjects. Alpha diversity was lower in patients with AN and participants with OB compared with other groups, while athletes showed highest alpha diversity	For the study, neither patients nor controls were on any standardised diet. Dietary recalls were used, which could have been influenced by over- or underreporting. Anti-depressants are known to show antimicrobial effects. As patients with anorexia nervosa often suffer from constipation, measures for alpha diversity could have been increased. 16S rRNA profiling is limited to taxonomic evaluation only
Borgo *et al.*, 2017[11]	Cross-sectional study. 16S rRNA profiling was used to evaluate faecal microbiome. RT–PCR was used to quantify *M. smithii*. Stool and serum SCFAs were measured	15 women with AN were compared with 15 age-, sex- and ethnicity-matched healthy controls	Next-generation sequencing showed that AN intestinal microbiota was significantly affected at every taxonomic level, showing a significant increase of *Enterobacteriaceae*, and of the archaeon *Methanobrevibacter smithii* compared with healthy controls. On the contrary, the genera *Roseburia*, *Ruminococcus* and *Clostridium* were depleted, in line with the observed reduction in AN of total short-chain fatty acids, butyrate and propionate	The study did not rule out possibility that the restricted diet consumed by patients with AN, or starving of the microbiota, could have played some significant roles in the observed alteration in gut microbiota. 16S rRNA profiling is limited to taxonomic evaluation only

Table 1. (*Continued*)

Study name	Study design/type	Study population	Summary	Critique/limitation of the study
Hanachi *et al.*, 2019[193]	Cross-sectional study. 16S rRNA profiling was used to evaluate faecal microbiome	33 patients with AN and 22 healthy controls	Lower alpha diversity, decrease in *Eubacterium*, *Roseburia*, *Anaerostipes* and *Peptostreptococcaceae*, increase in *Turibacter*, *Anaerotruncus*, *Salmonella* and *Klebsiella* in AN compared with controls	Despite the noticeable alterations of the host–microbe symbiosis, a small size of the studied population was used. There were no follow-up studies after weight gain. The study would have benefited from a metagenomic analysis that would have provided potential links with the overall functions of the microbiota and their implication in the onset of AN
Monteleone *et al.*, 2021[194]	Prospective study. 16S rRNA profiling was used to evaluate faecal microbiome. GC–MS measurement of 224 endogenous metabolites involved in energy metabolism, lipid metabolism and amino acid metabolism	Women with AN in both the underweight phase ($n = 21$) and after short-term weight restoration ($n = 16$) and 20 healthy women	Lower alpha diversity in AN. *Firmicutes* and *Bacteroidetes* most abundant taxa but lower compared with control at underweight phase. Higher *Bacteroidetes* to *Firmicutes* ratio in AN than in controls. Significant increase in relative abundances of *Actinobacteria*, *Weissella* and *Coprococcus*, as well as a significant decrease in relative abundances of *Coriobacteriales*, *Parabacteroides* and *Oxalobacteraceae* in AN at underweight phase compared with controls. After weight restoration, patients with AN showed an increase in the relative abundance of *Leuconostocaceae* and a decrease in the relative abundance of the *Actinobacteria*, *Coriobacteriales*, *Catabacteriaceae* and *Collinsella*, *Parabacteroides* and *Catabacter* with respect to controls. Mainly sugars and sugar-derived metabolites were lower among AN at underweight phase	The study presented a small sample size. The study could have extended the period of follow-up for the achievement of adequate weight restoration. Further, there was lack of basic laboratory screening for the study participants. For instance, women with AN who have amenorrhea differ from normal-weight healthy women in several biochemical and hormonal parameters, and these differences may have had an influence on the study results
Monteleone *et al.*, 2021[106]	Cross-sectional study. 16S rRNA profiling was used to evaluate faecal microbiome. GC–MS measurement of 224 endogenous metabolites involved in energy metabolism, lipid metabolism and amino acid metabolism	17 women with restricting anorexia nervosa, 6 women with binge–purging anorexia nervosa and 20 healthy controls	No significant difference in alpha diversity between restrictive and binge purge subtypes as they were both reduced compared with healthy controls. Actinobacteria was less abundant in restrictive compared with binge–purge AN *Verrucomicrobia* was much higher in restrictive AN. Patients with binge–purge AN had a significant increase in relative abundance of *Bifidobacterium*, *Bifidobacteriaceae*, *Bifidobacteriales* and *Eubacteriacae* as well as a significant decrease in relative abundance of *Odoribacter*, *Haemophilus*, *Pasteurellaceae* and *Pasteurellales*	The study was a secondary analysis of an original design and the subgrouping of patients on the basis of AN subtype lead to the small number of sample size presented in the study. Thus, these findings should be considered preliminary and need confirmation by future studies with larger patient samples

Table 1. (*Continued*)

Study name	Study design/type	Study population	Summary	Critique/limitation of the study
Schulz *et al.*, 2021[195]	Longitudinal study. To compare gut microbiota diversity and taxon abundances in a sample of adolescent patients with AN and compare them to those of age-matched healthy controls	19 female adolescent patients with AN at admission and after short-term weight recovery compared with 20 healthy controls. DNA was extracted from stool samples and subjected to 16S rRNA gene sequencing and analysis	*Firmicutes* increased with weight gain to a significantly higher level in patients at discharge versus healthy controls. *Anaerostipes* increased in patients at admission versus health controls, while *Romboutsia* and *Enterobacteriaceae* decreased. *Fusicatenibacter*, *Lachnospiraceae*, *Ruminococcaceae*, and *Faecalibacterium* increased significantly following weight gain, while *Bacteroides* decreased between admission and discharge. *Anaerostipes* significantly contributes to differentiating patients at admission and health controls, whereas the abundance of *Lachnospiraceae*, *Enterobacteriaceae*, *Ruminococcaceae* and *Barnesiella* differentiate between patients at discharge and health controls	The sample size was relatively small. The healthy controls were not assessed at follow-up to control for a change of diet or other environmental factors. The type of diet used was not controlled. The choice of 16S rRNA gene primers may have introduced biases in some individual bacterial taxa. The time span within which the samples were obtained was relatively short
Prochazkova *et al.*, 2021[196]	A longitudinal study. The study identified hallmarks of AN microbiota, to assess their changes during re-alimentation, to determine the levels of assorted neurohormones and short-chain fatty acids at hospitalisation admission and discharge, and to identify potential correlations with various biochemical as well as anthropometric and psychometric parameters. The fungal community composition was also assessed	59 patients with restrictive AN and 67 healthy female controls were recruited for the study	Overrepresented operational taxonomic units (OTUs) in patients with AN taxonomically belonged to *Alistipes*, *Clostridiales*, *Christensenellaceae* and *Ruminococcaceae*. Underrepresented OTUs in patients with AN were *Faecalibacterium*, *Agathobacter*, *Bacteroides*, *Blautia* and *Lachnospira*. There were no significant differences in alpha diversity and fungal profile composition between patients with AN and healthy controls, nor any correlation of the fungal composition with the bacterial profile. The fungi classes included *Saccharomycetes, Eurotiomycetes, Agaricomycetes and Tremellomycetes*	The cohort was composed of only adult women, which could be a potential weakness of the study. The use of antidepressants and other medications can alter the microbiome as well as neuroactive microbial metabolites and neurotransmitters production, which may have influenced the results. The host microbiome variability, which can change in response to diet or other environmental factors may have influenced the results

colon and rectum, the small intestine – in particular the ileum – could be another potential and relevant site for sampling the gut microbiota in AN whenever sampling from the small intestine is possible. This is due to the fact that the small intestine is the region where the breakdown and absorption of nutrients occurs. It is conceivable that restrictive dietary intake, which is often present in the setting of AN, leads to dysbiosis in the small intestine or that microbial dysbiosis in this compartment could influence the brain to limit food intake via the microbiota–intestine–brain axis[108]. The bacteria and archaea from the small intestine are subjected to a harsh environment. With rapid transit times, digestive enzymes and bile acids, the conditions in the small intestine are in contrast to the more moderate environment in the colon, requiring extremely resilient inhabitants with different survival plans[109]. Furthermore, these microbes are either destroyed or rendered inactive in the digestive tract[109]. As a result, data from faecal samples may not represent the gut microbiota in the small intestine. Nevertheless, to date, faecal samples remain convenient, minimally invasive and an easy way to study the gut microbiota. In addition to faecal analysis, the introduction of small-intestine biopsy samples could be conceivable in the future.[108].

Bacterial fermentation products in anorexia nervosa

SCFAs mainly represent products of carbohydrate fermentation, whereas branched-chain fatty acids (BCFAs) (consisting mostly of isobutyrate and isovalerate) are products of protein fermentation[110]. A particularly important function of the large intestine is the fermentation process, which is the anaerobic breakdown of carbohydrates into SCFAs (C2–C6). SCFAs constitute about two-thirds of the concentration of colon anions (70–130 mmol/L), mainly as acetate, propionate and butyrate[111]. SCFAs are of great importance in understanding the physiological function of dietary fibres; their production and absorption are also associated with the nourishment of the colon mucosa and the absorption of sodium and water, as well as the mechanisms underlying diarrhoeal processes. SCFAs butyrate and propionate, along with the other gut microbiota-processed metabolites, including deoxycholate, 4-aminobenzoate and tyramine, improve gastrointestinal motility by inducing serotonin biosynthesis from colonic enterochromaffin cells[55]. In a study by Mack *et al.*[9], SCFA levels were found to be comparable among patients with AN and normal-weight participants, but were reduced in studies by both Borgo and Morita[8,11]. In Million's study[98], acetate and propionate concentrations were decreased, while in an Italian study[11], both total SCFAs and butyrate and propionate levels were reduced. In contrast to Mack's study[9], only butyrate proportions were lowered in patients with AN compared with normal-weight controls. Macfarlane[112] demonstrated significant differences in bacterial fermentation in the large gut; SCFAs, lactate and ethanol concentrations were higher in the caecum and the ascending colon. The products of protein fermentation, such as ammonia, were also increased. BCFAs progressively increased from the right to the left colon, according to the pH of the intestinal contents. BCFAs are produced during fermentation of branched-chain amino acids (BCAAs) valine, isoleucine and leucine by gut microbiota in the colon[110,112]. It has been shown that concentrations of total BCFAs, in particular isovalerate and isobutyrate, are increased in patients with AN[9,113], suggesting an increase in bacterial protein fermentation. The amount of dietary products reaching the colon in patients with AN is probably lower than normal owing to a small intake. Thus, the source of increased BCFAs may be fermentation of endogenous host and microbe-derived proteins[9]. Consequently, there is a reduced production of other SCFAs and an increase in the BCFA concentration. These alterations in the composition of the gut microbiota could have important implications for metabolic dysfunctions as well as insulin resistance conditions[114]. Moreover, Mack *et al.*[9] reported that, after nutritional rehabilitation, total BCFA and valerate concentrations were found to have increased after weight restoration, which may be due to the increased protein intake from the diet or a persistent increase in protein fermentation[9]. Surprisingly, a shift from SCFA production from carbohydrates to BCFA production by amino-acid fermentation has also been demonstrated after weight loss surgery, which was shown to be due to reduced starch intake from the diet[115].

Trace amines tyramine and β-phenylethylamine are produced by the gut microbiota from tyrosine and phenylalanine, respectively. Tyramine and β-phenylethylamine enhance gut motility by binding and signalling through trace amine-associated receptors (TAARs) lining the wall of the small intestine and colon[116,117]. Thus, these trace amines could help to reduce constipation among patients with AN. Further, activation of TAAR1 by a full agonist reduced compulsive eating in rats[118], suggesting that TAAR1 activation could have some potential in the treatment of the binge–purge subtype of AN.

Intestinal microbiota and gastrointestinal symptoms in anorexia nervosa

Several studies suggest that gastrointestinal disorders are common in patients with AN, contributing to increased anxiety, decreasing quality of life and worsening of treatment outcomes[119,120]. In fact, gastrointestinal symptoms are very common, and involve different anatomical regions, such as the oesophagus, stomach and intestine.

The connection between the intestinal microbiota and gastrointestinal symptoms has already been widely studied in other diseases, such as irritable bowel syndrome (IBS) and chronic constipation[121]. Faecal and mucosal microbiota from patients with IBS and healthy subjects has been analysed, and the intestinal microbiota profile associated with the severity of IBS symptoms has been identified[122]. On the basis of the links established between intestinal microorganisms and gastrointestinal dysfunctions, we can hypothesise that intestinal dysbiosis in patients with anorexia may contribute to the onset or maintenance of functional gastrointestinal disorders associated with AN.

Heartburn, non-cardiac chest pain, dysphagia and globus are oesophageal symptoms often present in patients with AN[123]. One of the first studies conducted on thirty patients with AN showed that a significant proportion had oesophageal motility disorders such as achalasia (23%) or other oesophageal motility abnormalities (27%)[124]. More recently, Benini *et al.*[125] showed that the presence and severity of symptoms such as dysphagia, heartburn and regurgitation were significantly higher in the

https://doi.org/10.1017/S0954422422000130 Published online by Cambridge University Press

restrictive and binge–purge types of patients with AN compared with normal-weight controls. Also, patients with AN, in contrast to healthy subjects[126], often complain of a feeling of fullness and early satiety, satisfying the criteria for the diagnosis of postprandial distress syndrome, which were introduced in the criteria of Rome III[123,127]. Occasionally, in patients with AN, dyspeptic symptoms can also be used as an excuse to refuse food[128]. Boyd *et al*. showed that IBS was the most common functional gastrointestinal disorder in patients with AN (56% of all cases) according to the Rome II criteria[129]. One study found defecatory disorders in 93% of patients with AN. According to their findings, the prevalence of defecatory disorders increased from 75% to 100% when BMI was less than 18 kg/m^2, and from 60% to 75% when illness duration was longer than 5 years[130]. Moreover, growing evidence suggests a link between constipation in AN and delayed colonic transit[131–133]. Interestingly, it seems that gastric emptying and gastrointestinal symptoms may improve following weight rehabilitation[126,131], even without reaching normal BMI[134]. Mack *et al*.[9] found that nutritional rehabilitation may decrease lower gastrointestinal symptoms (e.g. constipation) but not upper gastrointestinal symptoms (e.g. abdominal fullness, abdominal bloating and feeling of abdominal distension). Sometimes patients can suffer from delayed gastric emptying, constipation or visceral hypersensitivity. This symptomatic picture could result in poor compliance and reduced outcomes[119,120].

Current treatment of anorexia nervosa

Current treatment of AN is based on a combination of nutritional rehabilitation and psychological approaches to promote both weight recovery and reverse malnutrition and to address eating behaviours[1,135]. Nutritional rehabilitation plays a predominant role with respect to pharmacological treatment and psychotherapy[136].

The primary goal is to reverse malnutrition and its complications. Higher weight recovery rate predicts better outcome at 1 year.[137–139]. However, the weight restoration must be balanced considering the potential medical complications linked to the refeeding syndrome, such as cardiac arrhythmia, cardiac failure or arrest, haemolytic anaemia, delirium, seizures, coma and sudden death[140–142].

Treatment efficacy

As reported in the study by Zipfel *et al*.[133], only half of patients with AN recover fully in the long term. Similar results were highlighted by the study of Rigaud *et al*., which emphasises that current treatment efficacy remains limited since 40% of patients with AN still show prolonged symptoms after 10 years of medical care[143]. Both Treasure's and Zipfel's studies[133,144] have shown that the current methods of treatment for AN are not completely or are only partially effective, and may indeed cause frequent relapses, especially among adults. Unfortunately, clinical protocols for refeeding present a wide range of heterogeneity with large variations in initial energy intake, progress rates and delivery modes. Also, in recent years, there has been a shift from higher-energy-intake approaches and/or faster approaches to increasing energy in hospitalised patients with AN. Consequently, low-energy approaches with slow progress could play a role in severely malnourished and more chronic pathologies, while a higher-energy approach would be indicated for patients with moderate malnutrition who are seriously ill[145].

In patients with AN, the voluntary restriction of energy intake that lasts months or even years, could lead to a severe reduction of body mass, with a consequent reduction in total body fat as well as in total body lean mass[146–148], depending also on the subtype of AN and on behavioural features[17]. Several studies suggest that the current approaches to weight restoration predispose female patients to a central adiposity pattern, whereas very little is known about body fat distribution after weight restoration in men[149]. Despite the possible abnormal body fat distribution after weight restoration, refeeding approaches and the restoration of an optimal nutritional status are of enormous importance. It has been shown that a higher BMI correlates with a better outcome after treatment and prevents associated comorbidities, such as depression, osteoporosis and infertility[150–152]. More research needs to be conducted in this area to find weight restoration protocols which improve lean mass, prevent harmful comorbidities and do not result in central obesity.

Management of gut microbiota in treatment of anorexia nervosa

Assuming that the gut microbiota can influence metabolic and psychological health parameters in patients with AN, it would be interesting to investigate the role of integrative therapies in restoring the gut microbiota in conditions of dysbiosis in order to obtain better long-term clinical outcomes. The gut microbiota could be modulated directly by faecal microbiota transplantation (FMT) or by antibiotics or pro/prebiotics.

Faecal microbiota transplantation

FMT is the engraftment of gut microbiota from a healthy donor into a recipient, which aims to restore the normal gut microbial community. FMT has been used sporadically for over 50 years until indicated as a highly efficient treatment in epidemics of *Clostridium difficile* and associated symptoms. In recent years, FMT has been used in other pathological conditions, such as IBD, IBS, metabolic syndrome, neurological development disorders, autoimmune diseases and allergic diseases, all derived, at least in part, from dysfunction related to the gut microbiota.[153]

Case studies suggest that treatments with FMT have potential clinical applications in a wide spectrum of other conditions associated with intestinal dysbiosis. Hence, besides conventional approaches, FMT is promising as an alternative therapy for many extra-intestinal disorders which are associated with the gut microbiota[153,154]. An early study of one patient with AN showed restoration of intestinal barrier function 6 months after FMT and an increase of *Akkermansia muciniphila* and *M. smithii* at 12 months after FMT[155]. In another case study, FMT led to a 13·8% weight gain over a 36-week follow-up period in a patient with recurrent underweight following clinical recovery from AN[156]. In this study[156], resting energy expenditure was decreased after the FMT, which

https://doi.org/10.1017/S0954422422000130 Published online by Cambridge University Press

may have contributed to the observed weight gain. In addition, the levels of faecal SCFAs and SCFA producer and mucin degrader *A. muciniphila* increased, suggesting better energy harvest. Trials evaluating safety, feasibility, tolerability and acceptability (ClinicalTrials.gov: NCT03928808) of FMT and effects of FMT on gut microbiota composition, weight gain, appetite, satiety and other clinical outcomes (trialregister.nl: NL6181) in individuals with AN will shed more light on the potential of FMT in treatment of AN.

Probiotics and prebiotics supplementation

Despite that fact that the implications of the microbiota–gut–brain axis for clinical practice are still unclear, both pro-/prebiotics and antibiotics represent mechanisms to restore a healthy intestinal microbiota in patients with AN (Table 2). Antibiotics could be used to eliminate pathogens that disrupt intestinal integrity, and probiotics could help to restore beneficial species known to increase gut epithelial health. For example, Pimentel *et al.* found that the elimination of *M. smithii* using antibiotic rifaximin reduced bloating symptoms[157]. Finally, antibiotics such as erythromycin and other prokinetic agents have been used in clinical settings to accelerate gastric transit time and weight gain and to reduce gastrointestinal stress[158,159]. In light of this, it seems that a diet rich in probiotics and prebiotics or the complementation of a diet with some probiotic strain gives promising results[160].

Wallace and associates found that a significant number of *Lactobacillus* and *Bifidobacterium* strains seem to show the most beneficial effects in improving mood and reducing anxiety and cognitive symptoms[161]. Recently, it has been suggested that supplementing a diet with the probiotic strain *Lactobacillus plantarum* P8 alleviates stress and anxiety that could be related to AN[162]. Along the same lines, *L. casei* strain Shirota supplementation alleviated stress-induced cortisol release and physical symptoms in humans and animal models[163].

Furthermore, a consensus report by Gibson *et al.* showed that the use of fructans as prebiotics led to a reduction in obesity, diabetes, hepatic steatosis, inflammation and insulin resistance and promoted the secretion of YY peptide and glucagon-like peptide-1 (GLP1)[164]. Inulin is the best-known type of fructo-oligosaccharide (FOS) and has been shown to inhibit intestinal colonisation by pathogens, providing a protective effect against acute or chronic intestinal disorders. Recent evidence from research in mice shows that serial administration of FOS (an artificial sweetener) and galacto-oligosaccharides significantly alters bacterial abundances in the gut microbiota and reduces both anxiety-like and depressive behaviour[165]. In another study, SCFA supplementation in mice undergoing psychosocial stress had anti-depressant and anxiolytic effects, and it reduced anhedonia, stress responsiveness and gut permeability, which were increased by stress[166].

The communication between the brain and the gut microbiome in other mental illnesses besides AN has also been studied in the past decades. Conditions such as anxiety, obsessive–compulsive disorder and major depression are common comorbidities of AN. Data from literature have shown a link between anxiety and the gut microbiota[21,167]. Germ-free mice show reduced anxiety-like behaviour[63], although germ-free rats exhibit more anxiety-like behaviour compared with controls[168]. Moreover, it has been demonstrated that probiotic and prebiotic supplements can reduce anxiety-like behaviour in rodents[169]. These improvements were accompanied by alterations in the regional central GABA receptor expression and reduced corticosterone levels. The beneficial effects were not achieved in vagotomised mice, which shows that they were mediated by the vagus nerve.

There is evidence indicating that OCD-like behaviour in rodents can be modified by microbial treatments, including germ-free environments and probiotic supplements[170,171]. Specifically, supplementation with *L. casei* Shirota in a rat model of OCD reduced OCD-like behaviour, which was accompanied by an increase in brain-derived neurotrophic factor (BDNF) and a reduction in 5-hydroxytryptamine receptor type 2A[172]. Similarly, in a mouse study, the induction of OCD-like behaviour with 5-$HT_{1A/1B}$ receptor agonist was blocked using a *L. rhamnosus* GG pre-treatment[171]. This protective effect was similarly achieved by pre-treatment with fluoxetine.

Both probiotic and prebiotic treatments have been shown to reduce depressive-like behaviour in rodent models[173]. In a rat study[174], supplementation with *L. helveticus* NS8 reduced chronic restraint stress-induced anxiety and depression and cognitive dysfunction to a similar or higher extent compared with citalopram. The behavioural improvements were accompanied by reduced plasma corticosterone and adrenocorticotropic hormone levels as well as higher plasma interleukin-10 levels. Hippocampal serotonin and norepinephrine levels and BDNF gene expression were improved. A recent meta-analysis of human studies suggests that probiotics reduce depressive symptoms in patients with major depression, and that using multiple strains is more effective than using a single strain[175].

Nutritional rehabilitation

The growing evidence in favour of poor outcomes due to undernourishment in AN has led to a change in clinical practice towards higher energy intake. Higher-energy diets produced rapid weight gain compared with lower-energy diets[145], and it also appears that they are associated with a shorter length of hospital stay[176]. Similar results have been found by both Peebles and Smith[177,178]. Thus, the high-energy-intake approach represents the current AN standard of care, beginning with consuming at least 1400 kcal/d or more through meals alone[176,179–182] or combined naso-gastric and oral feeding[183]. However, to date, none of the published high energy nutritional refeeding protocols has been tested for possible effects on the intestinal microbiome. Overall, energy intake and proportions of macronutrients may alter the composition of the intestinal microbiota[184]. In particular, a diet rich in fats and proteins and low in non-digestible carbohydrates and other fibres can lead to an altered microbial diversity and potential dysbiosis[29,185,186]. Furthermore, recent evidence[5] illustrates

https://doi.org/10.1017/S0954422422000130 Published online by Cambridge University Press

Table 2. Probiotics and prebiotics supplementation

Study name	Agents	Setting	Effects	Comments
Foster *et al.*, 2013[21]	*Lactobacillus farciminis*, *Bifidobacterium infantis*, enteropathogenic *E. coli*, *Lactobacillus rhamnosus*	Mice and rats	Reduced the intestinal permeability that typically results from restraint stress and prevented associated HPA hyper-reactivity cFOS activation of neurons in the paraventricular nucleus of the hypothalamus has been shown in GF mice following oral feeding with probiotic	There are still some unanswered questions regarding the role of microbiota in normal healthy CNS development of cognition and in childhood learning disorders
Diaz Heijtz *et al.*, 2011[46]	Non-pathogenic gut microbiota was used unlike *Campylobacter jejuni* infection, which tends increase anxiety-like behaviour	Animal study. Comparison of germ-free (GF) mice with specific pathogen-free (SPF) mice having normal microbiota and GF mice with early introduction of normal microbiota (CON)	GF mice display increased motor activity and reduced anxiety-like behaviour compared with SPF and CON. Higher noradrenaline, dopamine and serotonin turnover in the striatum of GF mice compared with SPF. Nerve growth factor-inducible clone A (NGFI-A) mRNA expression was lower in various subregions of the prefrontal cortex in GF compared with SPF mice. GF mice show alterations in genes involved in four canonical pathways in brain regions implicated in motor control and anxiety-like behaviour. The expression of both synaptophysin and PSD-95 in the striatum was lower in SPF and CON mice compared with GF mice	Only male mice used. The study needed to provide more information on the suggestion that, during evolution, the colonisation of gut microbiota has become integrated into the programming of brain development, affecting motor control and anxiety-like behaviour. The differences that were observe between GF and SPF mice are mediated by signalling initiated soon after birth at a time when the newborn mice become exposed to gut microbiota
Lew *et al.*, 2019[133]	*Lactobacillus plantarum* P8	Human study. A 12-week randomised, double-blind and placebo-controlled study investigating the effects of *Lactobacillus plantarum* P8 on psychological, memory and cognition parameters in stressed adults (P8 $n = 52$, placebo $n = 51$)	*L. plantarum* P8 reduced stress, anxiety and total scores in DASS-42 questionnaire at 12 weeks but no significant effect on depression compared with placebo in DASS-42 or stress in PSS-10 at 12 months. *L. plantarum* P8 group had higher reduction in IFN-γ and TNF-α than placebo group at 12 weeks	More information is needed to determine ideal duration of treatment and dosage. Considerable dropout rate was attributed solely to the patients' mental state, but treatment side effects were not described
Takada *et al.*, 2016[134]	*Lactobacillus casei* Shirota	Human and animal studies. Healthy medical students under academic examination stress received *L. casei* Shirota fermented milk or placebo daily for 8 weeks prior to taking a national standardised examination. In the animal study, rats were given feed with or without *L. casei* Shirota for 2 weeks, then submitted to water avoidance stress (WAS). In an electrophysiological study, gastric vagal afferent nerve activity was monitored after intragastric administration of *L. casei* Shirota to urethane-anaesthetised rats	Increases in salivary cortisol levels and the incidence rate of physical symptoms were suppressed in the *L. casei* Shirota group compared with the placebo group in students at the end of the intervention period, but there was no difference between the groups in perceived anxiety measured by STAI. WAS-induced increases in plasma corticosterone were reduced in rats pre-treated with *L. casei* Shirota. Intragastric administration of *L. casei* Shirota stimulated gastric vagal afferent activity in a dose-dependent manner	Stress-relieving effects of *L. casei* Shirota were not compared with other anxiolytics or probiotics. No significant correlation was established between reduced salivary cortisol levels by *L. casei* Shirota and decrease in gastrointestinal symptoms. Measurement of bacterial fermentation products could have shed more light on potential mechanisms

Table 2. (*Continued*)

Study name	Agents	Setting	Effects	Comments
Burokas *et al.*, 2017[136]	Prebiotics; fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS)	Animal study. C57BL/6J male mice were administered FOS, GOS, a combination of FOS + GOS, or water for 3 weeks. FOS-, GOS- or water-treated mice were also exposed to 6 weeks of psychosocial stress, and behaviour, immune and microbiota parameters were assessed	FOS + GOS treatment had both anti-depressant and anxiolytic effects. GOS and FOS + GOS reduced stress-induced corticosterone release. Prebiotics modified specific gene expression in the hippocampus and hypothalamus. Prebiotic administration increased caecal acetate and propionate and reduced isobutyrate concentrations, which correlated with the positive effects on behaviour. FOS + GOS reduced chronic stress-induced elevations in corticosterone and pro-inflammatory cytokine levels as well as depression- and anxiety-like behaviour, and normalised the effects of stress on the microbiota	Mechanisms by which FOS and GOS support behaviour were not elucidated. Only male mice were studied
van de Wouw *et al.*, 2018[36]	SCFAs (acetate, propionate and butyrate)	Animal study. A mix of sodium acetate, propionate and butyrate was administered to male C57Bl/6J mice via drinking-water *ad libitum*	SCFA treatment alleviated psychosocial stress-induced alterations in reward-seeking behaviour, and increased responsiveness to an acute stressor and *in vivo* intestinal permeability SCFAs exhibited behavioural test-specific antidepressant and anxiolytic effects, which were not present when mice had also undergone psychosocial stress. SCFA supplementation had no effect on caecal microbiota composition, stress-induced body weight gain, or gene expression of colonic free fatty acid receptors 2 and 3	The previously reported effects of chronic stress on cognition, anxiety- and depressive-like behaviour, and alterations in gut microbiota composition were not repeated in this study. This is attributed to dissipation of stress effects over time, but this remains unconfirmed Increased intake of sodium may have modified the findings
Crumeyrolle-Arias *et al.*, 2014[139]	Gut microbiota	Animal study. Comparison GF rat with SPF stress-sensitive F344 rats	GF rats showed a greater anxiety-like behaviour in the open field test and corticosterone levels after the test as well as higher levels of corticotropin-releasing factor mRNA in hypothalamus and lower levels of glucocorticoid receptor mRNA in hippocampus. GF rats had higher dopamine turnover rates in frontal cortex, striatum and hippocampus	In contrast to these results, some GF mice strains (Swiss, NMRI) have shown reduced anxiety-like behaviour compared with their SPF counterparts. This may result from yet-unexplained interactions between the genetic background of the animal strains and microbiome, differences in the "normal" microbiome and/or different tasks used for measurement
Bravo *et al.*, 2011[140]	*Lactobacillus rhamnosus* JB-1	Animal study. Adult male BALB/c mice were orally gavaged with *L. rhamnosus* JB-1 or broth without bacteria for 28 d. The role of vagal nerve on mediating the effects of probiotic supplementation was studied in groups of vagotomised mice with or without *L. rhamnosus* JB-1 supplementation	*L. rhamnosus* JB-1 increased GABAB1b mRNA in cortical regions (cingulate and prelimbic) and reduced the expression in the hippocampus, amygdala and locus coeruleus compared with control-fed mice. *L. rhamnosus* JB-1 reduced GABAAα2 mRNA expression in the prefrontal cortex and amygdala, but increased GABAAα2 in the hippocampus. *L. rhamnosus* JB-1 reduced stress-induced corticosterone and anxiety- and depression-related behaviour. The neurochemical and psychological effects of *L. rhamnosus* were not present in vagotomised mice	Further investigation is required to be conducted to investigate the molecular mechanisms at a microbiome level and possible roles of other neurotransmitter systems on the observed effects

Table 2. (*Continued*)

Study name	Agents	Setting	Effects	Comments
Nishino *et al.*, 2013[141]	Commensal microbiota	Animal study. Comparison of GF BALB/c mice with GF mice exposed to gut microbiota from stool of SPF mice	GF mice exposed to microbiota from stool showed reduced anxiety-like behaviour and locomotor activity. The norepinephrine, dopamine, and serotonin turnover rates were higher in the GF mice exposed to microbiota than in the GF mice in most regions of the brain	Bacterial examination was done on only a limited number of culturable bacteria. Use of culture-based approaches predisposes susceptibility to false-negative results owing to possible effects from non-culturable bacteria. Further study is needed to identify bacterial strains and mechanisms behind the findings
Kantak *et al.*, 2014[142]	*Lactobacillus rhamnosus* GG	Animal study. OCD-like behaviours were induced using RU 24 969, a 5-HT1A/1B receptor agonist in male Balb/cJ mice. Pre-treatment with *L. rhamnosus* GG in prevention of OCD-like symptoms was compared with fluoxetine and saline	2 and 4 weeks of pre-treatment with *L. rhamnosus* GG attenuated the induction of OCD-like behaviours in mice	*Lactobacillus rhamnosus* could have produced non-specific effects in mice such as sedation. Only male mice studied
Sanikhani *et al.*, 2020[143]	*Lactobacillus casei* Shirota	Animal study. OCD induced in rats by using quinpirole hydrochloride, a D2/D3 dopamine agonist. Treatment with *L. casei* Shirota, fluoxetine (10 mg/kg, combination of *L. casei* Shirota and fluoxetine, saline (positive control group)	Improvement of OCD signs in rats treated with *L. casei* Shirota, fluoxetine, and a combination of drugs. *L. casei* Shirota reversed the decrease in the expression of Bdnf and the increase in the Htr2a in orbitofrontal cortex in quinpirole-treated rats	Lack of assessment of protein expression and no gene expression assessment of other regions in the brain. The animal model was selected on the basis of a very specific intervention using a D2/D3 dopamine agonist. The study addresses only one chemically induced disorder
Desbonnet *et al.*, 2010[144]	*Bifidobacterium infantis*	Animal study. Maternal separation rat offspring chronically treated with *Bifidobacterium infantis* or citalopram	Probiotic supplementation corrected the separation-induced increased immobility and reduced swimming time in forced swimming test and amygdala corticotrophin-releasing factor mRNA levels although to a lesser extent than citalopram. In addition, probiotic supplementation decreased noradrenaline content in amygdala and prevented concanavalin-induced IL-6 hypersecretion	No definitive conclusion was made regarding the specific mechanisms involved in the central effects of the probiotic bacteria. No control treatment groups in rats without separation
Liang *et al.*, 2015[145]	*Lactobacillus helveticus* NS8	Animal study	Results showed that *L. helveticus* NS8 improved chronic restraint stress-induced behavioural (anxiety and depression) and cognitive dysfunction, showing an effect similar to and better than that of citalopram	The experimental groups were relatively small. Only male rats were studied. Cognition trials and open field test with longer duration may provide more detailed information about the effects of *L. helveticus* NS8 *L. helveticus* was stated to have a different mechanism of action than citalopram with which it was compared
Goh *et al.*, 2019[146]	Various probiotics	Systematic review: 9 double-blind, randomised, placebo-controlled trials with a total of 1901 participants	Altering the gut–brain axis with probiotics may be an approach to ameliorate depression severity	Studies with a larger sample size are needed to verify the efficacy of specific combinations or strains of probiotics for depressive symptoms

that micronutrient deficiencies disrupt the gut microbiota composition and function, dictating microbial–microbial as well as microbial–environmental interactions throughout the gut[187].

According to literature, a diet favourable to the gut microbiota should include non-digestible carbohydrates, different types of fibre, especially prebiotics, proteins mainly based on plants, mono- and polyunsaturated fatty acids, micronutrients and phytochemicals[29,188,189].

Non-digestible carbohydrates and prebiotic foods could have a beneficial effect by increasing the levels of beneficial intestinal *Bifidobacterium* and lactic acid bacteria and play a role in the generation of SCFA[29,185,190]. Fermented foods, such as kefir, yogurt, sauerkraut and tempeh, have also been noted as important sources of probiotics, and may provide energy and nutrients for weight restoration as well as aid nutritional recovery[191]. Furthermore, evidence indicates that the way food is processed determines the amount and type of nutrients that reach the gut bacteria and influence growth and production of the gut microbiota metabolites[192].

Conclusion

The mechanisms underlying the development of AN often involve a complex interplay of the microbiota–gut–brain axis. There is mounting evidence linking the dysbiosis of gut microbiota in AN and psychiatric disorders. To date, although limited changes have been observed in the gut microbiota composition in the post-nutritional rehabilitation state, nutritional treatment has proven useful in weight restoration in patients with AN. Appropriate consideration should therefore be given to structuring nutritional treatment strategies aimed at improving the gut microbiota composition and optimising the treatment for AN. Results thus far obtained highlight the importance of modulating the gut microbiota in order to influence the nutritional status and improve long-term results, whilst maintaining limited side effects. Recent studies provide evidence to the effect that incorporation of microbiome data into dietary planning will help design novel foods aimed at combating specific health issues, thus potentially ushering us into an era of personalised nutrition. Large randomised controlled trials involving faecal microbiota transplantation, pre-/probiotics and personalised refeeding protocols combined with multidisciplinary approach are needed to address the metabolic and psychological factors that contribute to and maintain AN.

Acknowledgments

The authors thank Professor S.G. Sukkar and Dr. Stefano Pinelli for the support given. The authors thank Jussi Heinonen, M.A., LL.B., for the language review of this article.

Author Contribution

L.L. wrote first version of the manuscript; P.D. and M.J.H. drafted and revised the manuscript; C.H. and F.G. were involved in the critical reading and reviewing of the manuscript. L.L. is the corresponding author and thus takes responsibility for the integrity of the data and the accuracy of information presented in this review.

Conflict of Interest

The authors declare no conflicts of interest within the contents of this article.

Funding

None.

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