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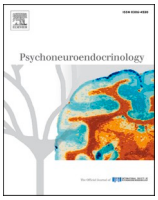

Gastrointestinal symptoms, gut microbiome, probiotics and prebiotics in anorexia nervosa: A review of mechanistic rationale and clinical evidence

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ABSTRACT

Recent research has revealed the pivotal role that the gut microbiota might play in psychiatric disorders. In anorexia nervosa (AN), the gut microbiota may be involved in pathophysiology as well as in the gastrointestinal (GI) symptoms commonly experienced. This review collates evidence for the potential role of gut microbiota in AN, including modulation of the immune system, the gut-brain axis and GI function. We examined studies comparing gut microbiota in AN with healthy controls as well as those looking at modifications in gut microbiota with nutritional treatment. Changes in energy intake and nutritional composition influence gut microbiota and may play a role in the evolution of the gut microbial picture in AN. Additionally, some evidence indicates that pre-morbid gut microbiota may influence risk of developing AN. There appear to be similarities in gut microbial composition, mechanisms of interaction and GI symptoms experienced in AN and other GI disorders such as inflammatory bowel disease and functional GI disorders. Probiotics and prebiotics have been studied in these disorders showing therapeutic effects of probiotics in some cases. Additionally, some evidence exists for the therapeutic benefits of probiotics in depression and anxiety, commonly seen as co-morbidities in AN. Moreover, preliminary evidence for the use of probiotics in AN has shown positive effects on immune modulation. Based on these findings, we discuss the potential therapeutic role for probiotics in ameliorating symptoms in AN.

1. Introduction

Eating disorders (EDs), their aetiology and maintenance, including bio-immuno-metabolic causes have come to the forefront of research attention in psychiatry. Factors within the physical and social environment, as well as biological factors such as those within the brain, endocrine, immune and gastrointestinal systems have all been found to contribute to the pathophysiology of EDs (Himmerich et al., 2019). Anorexia nervosa (AN), an eating disorder, is characterised by significantly low body weight, an intense fear of weight gain and body image disturbance. Sufferers exhibit an extreme fear of fatness and demonstrate behaviours to achieve weight loss or maintain a low weight. Their valuation of self is unduly dependent on their body weight and shape. Two subtypes of AN can be distinguished: the restrictive subtype (AN-R), in which severe food restriction is the primary means of losing weight; and the binge-eating/purging subtype (AN-BP), in which restriction is combined with episodes of consuming unusually large amounts of food followed by compensatory behaviour including self-induced vomiting, laxative or diuretic abuse, and/or excessive exercise (American Psychiatric Association, 2013). AN has one of the highest mortality rates among mental health disorders and is associated with morbidity for sufferers (van Hoeken and Hoek, 2020) and their carers (Kyriacou et al., 2008). Prevalence rates range from 0.3 % to 4 % in females and ~ 0.3 % in males (van Eeden et al., 2021).

In AN, self-starvation has physical and mental health consequences, e.g., changes in various organ systems such as the brain and the gut, and changes on cellular and molecular level, such as epigenetic changes. These consequences of self-starvation are important maintaining factors in AN (Himmerich et al., 2019). Therefore, research to identify ways to elucidate and interrupt this cycle that maintains the disorder are

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clinically warranted. The gut microbiome and its role in the gut-brain axis are being studied in relation to mental health disorders by many researchers around the world (Shoubridge et al., 2022). Thus, hypotheses and evidence have been presented for the role of the microbiome in the development and maintenance of AN (Sudo, 2021).

Gastrointestinal (GI) dysfunction in AN is at the heart of not only symptoms suffered but also in the acceptance of nutritional treatment. In this article we consider the interaction between the gut microbiome and AN especially in relation to GI symptomatology, examine available evidence for the role of the microbiome in known GI pathology and the use of modulators such as probiotics and prebiotics as a possible adjunct to current treatment modules.

2. Recent biological findings in AN

Genetic studies over the past 20–30 years have increased our understanding of the biological basis of AN. Heritability has been suggested to account for over 50 % of causality (Bulik et al., 2006). A large multi-centre Genome Wide Association Study has shown significant associations of eight loci with AN (Watson et al., 2019). It is possible that these might shape personality traits, psychological vulnerabilities and possibly interact with familial and societal factors (Himmerich et al., 2019). Recent studies have found genetic links between AN and metabolic disorders (Watson et al., 2019). Additionally, bi-directional associations between AN and auto-immune diseases have been shown (Hedman et al., 2019). Moreover, differences seen in the gut microbiome in AN compared with healthy controls (HCs) has brought the possible role of the gut-brain axis in the causation and maintenance of AN in the spotlight (Seitz et al., 2019), further raising interest in the bio-immuno-metabolic aspect of the pathogenesis model in AN.

2.1. GI symptoms and AN

Restriction of food intake and attempts to compensate for intake can result in profound effects on all the systems of the body including the GI tract. In order to continue functioning with a reduced food intake, the body metabolises energy stores including liver glycogen and visceral fat, via glycogenolysis and lipolysis (Soeters et al., 2012). A state of starvation also induces gluconeogenesis through breakdown of tissues including muscle and epithelium as a way of supplying energy (Soeters et al., 2012).

Starvation and compensatory behaviours affect the GI system in different ways. Effects may include weakened and/or dysfunctional musculature, reduced or dysfunctional absorptive surfaces, changes in secretion of digestive juices, dilatation of the stomach wall (in the AN-BP subtype) and differences in sphincter function in various parts of the GI tract (Santonicola et al., 2019). A majority of sufferers experience GI symptoms, which may be organic or functional (Salvioli et al., 2013). AN patients may complain of upper GI problems such as dysphagia, heartburn, nausea, vomiting and early satiety. Objective measures of delayed gastric emptying to both solids and liquids have been shown in AN compared with HCs (Riedlinger et al., 2020; Santonicola et al., 2019). Comparing results between AN subtypes (AN-R versus AN-BP), gastric emptying has been shown to be similarly delayed in both (Norris et al., 2016). Multiple case studies of gastric dilatation and subsequent effects such as gastric perforation have been reported in AN-BP (Norris et al., 2016; Riedlinger et al., 2020; Gibson et al., 2021). Symptoms related to functional GI disorders (FGID) are also frequently reported in AN. Functional Dyspepsia was found to be significantly higher in AN compared with HCs including postprandial distress (PDS), fullness and increased intensity and frequency of early satiety (Santonicola et al., 2012). An observational study described 83 % of patients with EDs as having at least one functional GI disorder, with postprandial distress most associated with starvation (Wang et al., 2014).

Constipation is a common lower GI complaint in AN and may be related to poor intake, weakened intestinal musculature, dysfunctional peristalsis due to electrolyte alterations and pelvic floor dysfunction (Santonicola et al., 2019). Laxative use in EDs has also been associated with pelvic floor dysfunction (Abraham and Kellow, 2013; Santonicola et al., 2019). Irritable Bowel syndrome (IBS), consisting of altered bowel habit (diarrhoea and/or constipation) in the presence of abdominal pain has been found in 32–64 % of people with EDs including AN, with a significant association related to a lower body mass index (BMI) (Kress et al., 2018).

The AN sufferer's initial presentation may be with GI symptoms. In one study, AN patients presenting at a gastroenterology service were older with a longer history of multiple GI symptoms, a substantial delay in being diagnosed with an ED, multiple investigations and admissions compared with those presenting to an ED clinic (Emmanuel et al., 2004). Data from General Practice and hospital databases have shown that in the 2 years prior to their diagnosis, patients with EDs were prescribed GI related drugs ~ 2.5 times more often compared with those who were not diagnosed with an ED (Demmler et al., 2020). Patients presenting with a Functional GI disorder and a history of disordered eating were younger, more psychologically distressed, more likely to be female, and more educated than those without a history of disordered eating (Porcelli et al., 1998).

Sufferers may report an 'intolerance' to certain foods, for example gluten, resulting in avoidance of food groups that they associate with abdominal pain or discomfort, for example starchy food. Indeed, those diagnosed with coeliac disease are at a higher risk of developing an eating disorder (Mårild et al., 2017). Reasons purported are the need to be vigilant with their food, GI symptoms causing worries around eating or weight loss from the onset of coeliac disease being a trigger for AN onset. Coeliac disease and AN may have some commonality in pathogenesis (Mostowy et al., 2016).

While nutritional rehabilitation, a cornerstone in the AN recovery process, has been shown to improve most of the GI symptoms suffered (West et al., 2021; Riedlinger et al., 2020), the process of nutritional treatment may worsen symptoms for patients. Dysfunctions of digestive processes such as secretion of enzymes & absorption (Takimoto et al., 2014; Winter et al., 2001) may worsen gut symptoms during refeeding. Previous infrequent consumption of dairy foods can result in secondary lactose intolerance (Szilagyi and Ishayek, 2018). Moreover, the anxiety of consuming feared foods may precipitate GI symptoms (Balmus et al., 2019). While recognising and acknowledging the necessity of hunger and satiety signals is an essential part of recovery, hyper-awareness of 'fullness' and discomfort may result in difficulty accepting treatment or an increase in compensatory behaviours. Additionally, some symptoms may continue beyond weight restoration. While overall upper and lower GI symptom scores decreased, most individual upper GI symptoms remained significant after nutritional treatment in one study (Mack et al., 2016). In another study, in both AN-R and AN-BP, oesophageal symptoms continued after weight restoration despite oesophageal manometry being normal (Benini et al., 2010). Furthermore, a study showed an improvement in delayed gastric emptying in AN-R with long term weight restoration but not in AN-BP (Benini et al., 2004). Functional GI symptoms persisted in 77 % of patients at a 12-month follow up in one study (Boyd et al., 2010). A study investigating symptoms in individuals who had been admitted with AN in their adolescence ~ 9 years previously, found odds ratios of 3.6 for gastralgia and 5.3 for gastro-oesophageal reflux (Chapelon et al., 2021).

With multiple possible factors influencing the presence of GI symptoms, it is useful to explore whether there is some merit in the supposition that the gut microbiome and changes within it are part of the pathophysiology of AN.

3. The gut microbiome and its variations

The gut microbiota comprises of a vast number of species of bacteria, archaea, fungi, viruses and eukaryotes, estimated to be over 100 trillion microorganisms (Rinninella et al., 2019). Table 1 provides an overview

Table 1
Overview and variations of gut microbiota.

Main microbiota phyla in the gut (Rinninella et al., 2019)	Bacteroidetes Firmicutes Actinobacteria Proteobacteria
Microbiome (Qian et al., 2020)	Microbiota, their genome and their environment
Factors affecting gut microbiota (Dąbrowska and Witkiewicz, 2016; Rinninella et al., 2019)	- Gestational age, mode of birth - Age, gender, ethnicity - Breastfeeding/complementary feeding - Habitual diet and short-term changes in diet - Antibiotics - Frequency of exercise - BMI - Host genetics - Gut disease
Microbiota diversity (Qian et al., 2020)	α diversity: diversity of species/strains within a sample (e.g within an individual) β diversity: diversity of species/strains between samples (e.g between different individuals or the same individual over time)
Enterotypes (Costea et al., 2018)	Stratification of gut microbiota into clusters by predominance of taxa Controversial as a reductionist view, but may be helpful in getting an overall sense of the microbiota in communities Enterotypes commonly described include: - Bacteroides predominant - Prevotella predominant - Firmicutes predominant

Table 2
A summary of gut microbial taxa present in health.

Phylum	Families	Genera *Examples:*	Species *Examples:*
Bacteroidetes (~ 70 %*)	Bacteroidaceae (~ 65 %)	*Bacteroides*	*Bacteroides fragilis* *Bacteroides vulgatus* *Bacteroides uniformis*
	Prevotellaceae	*Prevotella*	*Prevotella melaninogenica* *Prevotella copri* *Prevotella histicola*
Firmicutes (~ 25 %)	Lachnospiraceae (~ 11 %)	*Roseburia*	*Roseburia intestinalis* *Roseburia hominis*
	Ruminococcaceae (~ 8 %)	*Ruminococcus*	*Ruminococcus bicirculans* *Ruminococcus bromii* *Ruminococcus faecis*
	Clostridiaceae	*Clostridium* *Faecalibacterium*	*Clostridium difficile* *Faecalibacterium prausnitzii*
	Lactobacillaceae (< 1 %)	*Lactobacilli*	*Lactobacillus reuteri* *Lactobacillus plantarum* *Lactobacillus casei*
Actinobacteria (~ 2 %)	Bifidobacteriaceae (~ 1 %)	*Bifidobacterium*	*Bifidobacterium longum* *Bifidobacterium adolescentis* *Bifidobacterium bifidum*
	Coriobacteriaceae	*Atopobium*	
Proteobacteria (~ 2 %)	Enterobacteriaceae	*Escherichia*	*Escherichia coli*
		Shigella	*Shigella flexneri*
Verrucomicrobia (~ 1 %)	Akkermansiaceae (< 1 %)	*Akkermansia*	*Akkermansia muciniphila*
Euryarcheota (< 1 %)			*Methanobrevibacter smithii*

* Relative abundance based on a healthy urban population cohort (King et al., 2019). Individuals vary in their microbiota content – for example only ~ 40 % of this cohort had *Methanobrevibacter smithii*, while *Bacteroides* varied from 0.4 % to 98 % in individual samples.

of variations and factors influencing an individual's unique gut microbial composition while Table 2 describes the typical composition in a healthy gut, the predominant phyla being Bacteroidetes and Firmicutes representing over 90% of species isolated, with example species that may be seen in the gut.

3.1. Functional attributes of the gut microbiome

Table 3 provides a summary of some gut microbiome-host interactions, many of these identified through animal studies. Interactions that may be relevant in AN or GI symptomatology are detailed below.

3.1.1. Energy availability and tissue deposition

An interaction that may have particular significance in AN is the ability of the gut microbiome in fermenting dietary components such as dietary fibre, which are not digestible by the host. Energy availability from fibre may influence tissue deposition in the host (Delzenne et al., 2011). While differences in gut microbiota composition have been related to differences in BMI (Delzenne et al., 2011), microbial habituation may also play a part (Murphy et al., 2010). Animal studies in wild type mice have shown higher adipose tissue deposition compared with germ-free (GF) mice when exposed to high fat diets as have faecal microbial transplants (FMTs) from obese humans into GF mice (Muscogiuri et al., 2019). However, FMTs from AN individuals into GF mice have shown contradicting results, with one study showing reduced tissue deposition (Hata et al., 2019) while the other showing no difference (Glenny et al., 2021), indicating factors other than just microbiota in play.

3.1.2. Appetite and satiety cues

Another interaction of relevance is the gut microbiome's influence on appetite and satiety cues. AN has been shown to be associated with elevated levels of total and other forms of ghrelin such as the acyl and the des-acyl form (Seidel et al., 2021). Despite the orexigenic nature of ghrelin, AN patients report a reduced appetite. Raised levels of anorexigenic peptide tyrosine tyrosine (PYY) have also been associated with AN (Smitka et al., 2021). Some animal studies have shown evidence of the gut microbiome modulating these appetite and satiety cues. For instance, short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate, products of fermentation by the gut microbiota (mostly from dietary fibre fermentation), may modulate anorexigenic PYY and glucagon peptide 1 (GLP1) release peripherally. They may also affect central appetite mechanisms via glutaminergic and gamma aminobutyric acid (GABA)-ergic pathways (Smitka et al., 2021; Zhang et al., 2021a; Frost et al., 2014). Some evidence also exists on modulation of ghrelin action by the gut microbiota through inducing secretion of ghrelin or changing expression of ghrelin receptors (Schalla and Stengel, 2018). A randomised controlled trial (RCT) in overweight individuals found that ingestion of an inulin-propionate ester with resulting increased propionate production in the colon in the intervention group was associated with raised PYY and GLP1 levels post-prandially as well as significant reduction in weight gain, intra-abdominal lipid accumulation and insulin resistance in the longer term, compared with the placebo group (Chambers et al., 2015). This signifies the immediate effect of the gut microbiome and their production of SCFAs on satiety signalling together with long term effects on tissue deposition in humans. There is evidence that Enterobacteriaceae such as *E. coli* produce caseinolytic protease B (ClpB), a mimetic of anorexigenic alpha melanocyte stimulating hormone (α-MSH). ClpB has been correlated with AN symptoms (Breton et al., 2016). Such an interplay of anorexigenic and orexigenic signals may be one of the ways in which the gut microbiome influences pathogenesis or maintenance of AN.

Table 3
List of potential gut microbiome-host interactions and their relevance to AN. For further information see text and the cited literature.

Interaction with the host	*Possible effects*	*Relevance to AN*
Physical presence of a 'healthy' microbiome	- Pathogens prevented from colonising	- Potential resistance to dysbiosis
Dietary fibre and resistant starch from host used as an energy source by gut microbes, producing short chain fatty acids (SCFAs) - – acetate (50–60 %), propionate (20–25 %), butyrate (15–20 %) (Bakker et al., 2015) Acetate can also be converted to butyrate by cross-feeding microbiota metabolism	- Energy source for local cells (for example colonocytes) - Influence on adipose deposition, tissue deposition and weight gain (Delzenne et al., 2011) - Immune modulation and anti-inflammatory effect by butyrate producers - Increased mucin production enhancing barrier function - Inhibition of histone deacetylases, action as ligands to G protein coupled receptors – signalling haematopoetic and non-haematopoetic cell lines, transcription factors & modifying gene regulation - Histone deacetylase inhibition promoting an anti-inflammatory cell phenotype – epigenetic effect - Mononuclear cells and neutrophils exposed to SCFAs resulting in inactivation of pro-inflammatory NF kB and down regulation of TNF (Rooks and Garrett, 2016) - Effect on osteoclasts including inhibition of their cell differentiation, thus protective of bone mass (Lucas et al., 2018) - Butyrate can affect energy expenditure and promote thermogenesis in brown and white adipose tissue (Zhang et al., 2021a) - Maturation and differentiation of microglia in the nervous system (Rooks and Garrett, 2016) - Modulation of appetite via central mechanisms including influencing glutaminergic and GABAergic neurons (Smitka et al., 2021) as well as peripheral mechanisms, for example butyrate stimulating the anorexigenic PYY and GLP1 (Zhang et al., 2021a) acting via vagal nerve afferents	- Energy extraction from dietary intake of dietary fibre - Influencing ability to gain weight during nutritional rehabilitation - Reduction of intestinal permeability by butyrate producing bacteria – an anti-inflammatory effect - Modifying gene regulation of cell lines that are particularly affected in AN – for example the haematopoetic cell lines - Anti-inflammatory effect of SCFAs may counter the pro-inflammatory profile seen in AN - Bone loss normally seen in AN may be reduced via osteoclast inhibition - Butyrate may increase energy expenditure affecting the ability to gain weight in AN - Thermoregulation is affected in AN pre- and during nutritional rehabilitation which may be modulated by butyrate - Possible role of glial cells in food intake behaviour (Frintrop et al., 2021) - Appetite suppression peripherally and centrally may maintain reduced food intake
Dietary tryptophan used by microbes (for eg: *Lactobacilli*) producing metabolites that are ligands to aryl hydrocarbon receptor (AHR) – transcription factor expressed by immune cells and epithelial cells (Rooks and Garrett, 2016)	- AHR activation related to normal intestinal epithelial cell barrier function, normalised bacterial load in the lumen - Resistance to colonisation by pathogens via sequestration of metal ions - Reduced mucosal inflammation	- Inflammatory response reduced – likely reducing GI symptoms this can cause
Polyamines produced by microbes	- Modulation of host cell proliferation including intestinal epithelial cells - Stimulate production of intercellular tight junction proteins (occludin, zonula occludens 1, E-cadherin) - Modulation of immune function including function of macrophages, T cells, production of cytokines, anti-oxidant effects, production of mucin - Low levels related to neuro- degenerative diseases - Dysregulated metabolism related to carcinogenesis (Rooks and Garrett, 2016)	- Anti-inflammatory properties may counter the pro-inflammatory profile seen in AN as well as possible effect on reducing associated GI symptoms - Improved tight junction function may reduce gut permeability and improve gut symptoms
Gases: H_2S, H_2, CH_3 as by-products of microbial metabolism A high protein diet can result in more protein escaping digestion in the small intestine, resulting in H_2S production in the colon (Blachier et al., 2021)	- Methane can slow colonic transit (Lee et al., 2013) - H_2S acts as source of energy to colonocytes, but in excess can inhibit colonocyte respiration and increase expression of inflammatory genes (Beaumont et al., 2016) - H_2 can have an anti-oxidant, anti-inflammatory & anti-apoptotic effect - H_2 can cross the blood brain barrier and have a neuroprotective effect (Ostojic, 2018)	- Slow intestinal transit may result in constipation - Constipation and colonic gas production may cause feelings of fullness and bloating - If associated with a high protein diet, and changes in pH, H_2S production could have a deleterious effect on the colonocytes and may be associated with inflammatory changes (Blachier et al., 2021; Beaumont et al., 2016)
Neurotransmitters: - Dopamine and norepinephrine can stimulate growth of microbes such as *E. coli* - Microbes can produce or influence the release of neurotransmitters such as GABA and serotonin (Strandwitz, 2018) - Serotonin (5 hydroxy tryptamine 5HT) production by colonocytes in response to spore producing bacteria - Bacterial enzymes affecting 5HT metabolism (Rooks and Garrett, 2016)	- Potential modulation of local signalling by neurotransmitters in the intestinal lumen - GABA can inhibit lower oesophageal sphincter relaxation, affect gastric emptying and secretion, intestinal motility and nociception - GABA may have an anti-inflammatory effect by reducing release of inflammatory cytokines and promoting T-reg cells (Auteri et al., 2015) - Serotonin can affect gut motility including gastric emptying and colonic transit and visceral pain (Yano et al., 2015; Spohn and Mawe, 2017; Strandwitz, 2018) - Serotonin can have a pro- or an anti-inflammatory effect possibly dependent on luminal conditions - Serotonin associated with neurogenesis and the protection of enteric neurons (Spohn and Mawe, 2017)	- Effect of stress in changing the gut microbiome in AN - GABA inhibition of lower oesophageal sphincter relaxation may ameliorate reflux symptoms in AN - GABA may have an inhibitory effect on visceral hypersensitivity, with potential to ameliorate abdominal pain/hyperawareness experienced in AN - Anti-inflammatory effect of GABA or serotonin may counter the pro-inflammatory profile seen in AN - Serotonin could improve delayed gastric emptying and delayed colonic transit, but may exacerbate abdominal pain by increasing awareness of pain in AN

(*continued on next page*)

Table 3 (*continued*)

Interaction with the host	*Possible effects*	*Relevance to AN*
LPS produced by gram negative bacteria	- Activation of Toll like receptors with resulting cytokine cascades (Candelli et al., 2021) - Can cause an inflammatory reaction locally as well as systemically if absorbed through a 'leaky gut' (Candelli et al., 2021) - Potential effect on inflammation and adipose tissue deposition (Delzenne et al., 2011)	- Inflammatory reaction in the gut epithelium may cause symptoms such as abdominal pain and changes in bowel opening.
Appetite and satiety signalling	- SCFAs may stimulate GLP1 and PYY and modulate ghrelin action - Autoantibodies to various orexigenic and anorexigenic peptides including α MSH may be secreted via antigenic stimulation by gut microbes (Smitka et al., 2021)	- Stimulation of GLP1 and PYY and modulation of ghrelin may suppress appetite – this may have a role in pathogenesis or maintenance of AN - Autoantibodies may modulate appetite and satiety signalling

NF-kB: nuclear factor kappa B; TNF: Tumour necrosis factor; H_2S: hydrogen sulphide; H_2: hydrogen gas; CH_3: methane; GABA: gamma aminobutyric acid; LPS: lipopolysaccharide; GLP 1: Glucagon-like Peptide 1; PYY: peptide tyrosine tyrosine; α MSH: alpha Melanocyte Stimulating Hormone; T-reg cells: T regulator cells.

3.1.3. Gut microbiome in depression and anxiety

The gut-brain axis is said to play an important role in mood and anxiety disorders (Shoubridge et al., 2022) and is being extensively researched. While a comprehensive analysis of this topic is beyond the scope of this review (some reviews on this subject include Cryan et al., 2019, Foster and Mcvey Neufeld, 2013 and Yang et al., 2020), the following sections provide a brief overview of the interaction between the gut microbiome and these conditions given that both mood and anxiety disorders often co-exist with AN.

3.1.3.1. Evidence through animal studies in depression and anxiety. Gut dysbiosis has been associated with depression, stress and anxiety in animal studies. Some changes in microbial abundances include increased Bacteroidetes, reduced Firmicutes in depression and reduced *Bacteroides* and increased *Clostridium* species in stress (Lach et al., 2018). Exposure to gut microbiota during a critical interval in early growth can determine whether normal stress responses develop adequately (Foster and Mcvey Neufeld, 2013). FMTs from depressed mice and human participants into GF mice can induce depressive symptoms in recipients implying causality (Zheng et al., 2016; Kelly et al., 2016). Pathogens such as *Campylobacter* have been correlated to an increased anxiety response in animals while *Bifidobacteria* and *Lactobacilli* have been associated with a reduced anxiety response, reversal of depression and resilience to depression-inducing stress (Foster and Mcvey Neufeld, 2013; Cyran et al., 2019; Yang et al., 2020).

3.1.3.2. Evidence through human studies in depression and anxiety. Evidence of gut dysbiosis in human studies includes higher abundance of Enterobacteriaceae, *Alistipes* and Bacteroidales and lower numbers of Lachnospiraceae and *Faecalibacteria* in depression (Yang et al., 2020) and increased *Escherichia*, *Shigella*, *Fusobacterium* and *Ruminococcus gnavus* abundance in generalised anxiety disorder compared with HCs (Jiang et al., 2018). Healthy women with *Prevotella* predominant gut microbiome clusters showed significant negative affect and activation of emotion regulating centres in the hippocampus when exposed to negatively valanced images when compared with those with *Bacteriodes* predominant clusters implying microbiome associated vulnerability to depression (Tillisch et al., 2017). Changes in abundances seen above including increased abundance of Enterobacteriaceae and reduced Lachnospiraceae and *Faecalibacteria* have also been observed in AN (Section 5) suggesting common gut microbiome related mechanisms. *Prevotella* predominance in the gut microbiome has been associated with increased weight loss in overweight and in healthy individuals compared with *Bacteriodes* predominance (Christensen et al., 2019; Hjorth et al., 2019; Zou et al., 2020) suggesting a link between gut microbiome features and vulnerability to AN similar to the link between gut microbiome and vulnerability to depression.

3.1.3.3. Mediators between the gut microbiome and the gut-brain axis in depression and anxiety. Microbial products such as SCFAs may mediate the interaction between the gut microbiota and the gut-brain axis in depression and anxiety. Animal studies have shown anxiolytic effects, mitigation of psychological stress-induced reduction of reward seeking behaviour and restoration of innate anxiety response with SCFA supplementation (van de Wouw et al., 2018; Wu et al., 2022). Higher serum SCFA levels have been associated with attenuated cortisol levels in a human study implicating their effect on the hypothalamic-pituitary-adrenal axis as a mechanism of action (Dalile et al., 2020). Other mechanisms may be modulation of GLP1, PYY or cholecystokinin (CCK) secretion or receptor expression acting peripherally or centrally to influence anxiety-like behaviour (Lach et al., 2018) or via modifying immune responses peripherally or centrally (Fung et al., 2017).

Thus, the gut-brain axis and its interaction with the gut microbiome presents us with multiple sources of evidence, some implying causality

or vulnerability to a mental health disorder, others suggesting changes as a result of the disorder, implying potential as a maintaining factor. Reversal of or resilience to these disorders through changes in the gut microbiome also present the possibility of microbiome-based treatments as adjuncts to current management.

3.1.4. Gut microbiome and GI symptoms

Looking specifically at GI symptoms, local signalling via neurotransmitters such as serotonin or GABA produced either by microbes or by colonocytes in response to microbes may influence gut motility as well as sensation of visceral pain (Strandwitz, 2018; Yano et al., 2015). SCFAs or secondary bile acids are likely signalling molecules affecting the release of serotonin from enterochromaffin cells. Serotonin can affect GI secretion and peristalsis (Strandwitz, 2018). A recent study in mice showed that lipo-polysaccharide (LPS), a product of gram-negative bacteria, is associated with reduced serotonin selective reuptake transporters, resulting in raised mucosal serotonin, increased faecal water content and visceromotor responses in the colon (Gao et al., 2022). This indicates one of the ways in which the gut microbiota may influence gut symptoms. GABA has been shown to be secreted by a number of bacteria including some *Lactobacilli* and *Bifidobacteria*. Altered GABAergic transmission can affect intestinal motility, gastric emptying, acid secretion and nociception. An engineered strain of *Bifidobacterium* able to over-express GABA was shown to reduce visceral pain sensitivity in a rat model (Strandwitz, 2018). Thus, GI symptoms in AN may be influenced by the host gut microbial composition through the modulation of local neurotransmitters such as serotonin and GABA.

It has been hypothesised that microbes influence host behaviour including producing symptoms in order to direct the host towards ingesting food facilitating their proliferation and suppressing competitors' growth (Alcock et al., 2014). GI symptoms can also be a result of microbial metabolism. Methane, a by-product of fermentation, by slowing colonic transit can aid efficient extraction of energy from colonic content. Slow transit may then result in constipation (Lee et al., 2013).

Gut symptoms may also be affected by changes in permeability and inflammatory responses. Gut epithelial integrity and inflammatory response modulation has been associated with various gut microbes. LPS has been shown to increase permeability and the inflammatory response in the gut (Delzenne et al., 2011) as have antibiotics in mice (Feng et al., 2019). Mucin-degrading bacteria (Genus *Prevotella*) in activity-based rodent models of AN were associated with increased permeability (Achamrah et al., 2019). In contrast, *Faecalibacterium prausnitzii* and Ruminococcaceae have been associated with reduced gut permeability and an immune-protective effect (Mörkl et al., 2018) again raising the potential of microbiome-based treatment options in ameliorating GI symptoms in AN.

4. GI disorders and the gut microbiome

As there are commonalities between some GI pathologies and AN (see Table 4), exploring the gut microbiome in these conditions may give an indication of its influence on GI symptoms in AN.

4.1. Inflammatory Bowel Disease (IBD) and the gut microbiome

One hypothesis for the pathogenesis of IBD, a chronic inflammatory condition of the gut with main sub-types Crohn's disease and Ulcerative colitis, involves an aberrant immune response to an environmental stimulus, such as the gut microbiota, in genetically susceptible individuals (Xavier and Podolsky, 2007). Multiple animal studies have contributed to this hypothesis including an inability for genetically susceptible mice to develop colitis in a germ-free environment, faecal transfer from diseased mice or humans to healthy mice resulting in colitis and the transfer of CD4 lymphocytes from healthy mice to those lacking these lymphocytes transferring ability to induce colitis (Glassner et al., 2020). Studies comparing the gut microbiome in IBD and HCs have found significant differences including reduced diversity, decreased Firmicutes and increased Proteobacteria in IBD (Nishida et al., 2018). *Ruminococcus gnavus* has been positively correlated with Crohn's Disease and *Roseburia* species (Family Lachnospiraceae) and *Faecalibacterium prausnitzii* (Family Ruminococceae) have been negatively correlated with IBD presence and severity (Glassner et al., 2020). IBD is also associated with a pro-inflammatory state via cytokines such as interleukin (IL-) 6, 8, 12, 23 and tumour necrosis factor alpha (TNF-α), and a reduced regulatory response via T regulator (T-reg) cells and IL-10 (Yan et al., 2020). *Roseburia* species have been related to a positive impact on T-reg cells, the secretion of IL-10 and the upregulation of antimicrobial peptides and gut barrier function (Patterson et al., 2017). Therefore, a reduction in *Roseburia* abundance in the gut microbiome could be related to an abnormal immune response.

4.2. Functional GI disorders (FGIDs) including Functional Dyspepsia (FD) and IBS and the gut microbiome

The possible factors causing and maintaining FD such as sensorimotor abnormalities, altered epithelial barrier function and immune response abnormalities may all be influenced by the gut microbiome. Contributors may be the effects of the microbiome on GLP1, PYY and ghrelin, their ability to impact on neuronal transmission via modulating neurotransmitters such as serotonin or GABA and ability to modulate the inflammatory milieu and epithelial permeability (see Table 3). There is some evidence directly linking FD and dysbiosis such as increased Proteobacteria, reduced Bacteroidetes, *Prevotella* and *Veillonella*. *Streptococcus* abundance has been positively correlated with FD symptoms and *Prevotella* negatively correlated with symptom severity (Zhou et al., 2022).

Various causative mechanisms are proposed for IBS including abnormal intestinal transit and intraluminal stimuli (including gut microbial products) resulting in mucosal inflammation, changed permeability and increased response to stimuli resulting in visceral pain (Camilleri, 2013) all of which could be impacted on by the gut microbiome. The association of IBS symptoms with stress implies a close brain-gut connection in its pathogenesis (Qin et al., 2014) which can also be modulated by the gut microbiome. Thus, changes in the gut microbiome could affect the presentation of IBS. A review found an overall increase of Enterobacteriaceae and a decrease of genera *Faecalibacterium* and *Bifidobacterium* in IBS compared with HCs (Wang et al., 2020).

4.3. Coeliac disease and the gut microbiome

Coeliac disease can present at any point during the lifecourse of an individual suggesting that environmental factors such as a change in gut microbiome may be involved in triggering an immune mediated enteropathy to gluten (a protein present in wheat, rye and barley). Gut microbiome changes associated with coeliac disease include increased Proteobacteria, Enterobacteriaceae, *Staphylococcus, Bacteroides, Prevotella*, and reduced *Bifidobacteria* and *Lactobacilli* (Wacklin et al., 2013; Akobeng et al., 2020). These may be a response to the pathogenic process but also may maintain the GI pathology and symptoms through effects on inflammation, visceral sensation and gut transit.

4.4. GI disorders and AN – commonalities

Table 4 compares characteristics of some GI disorders with AN. A Swedish cohort was found to have bi-directional associations between AN and IBD (Hedman et al., 2019), as has a review of case studies, finding the co-existence of AN and Crohn's disease being the most common (Ilzarbe et al., 2017). In a Danish sample aged 8–32 years, a significant risk of IBD was seen after a diagnosis of AN (Relative Risk (RR) for Crohn's disease = 1.60; RR for Ulcerative Colitis = 1.66)

Table 4
Summary of characteristics, gut microbiome findings, use of probiotics and prebiotics in some GI disorders and similarities with AN.

Gastrointestinal disorder	*Proposed mechanisms and gut microbiome evidence*	*Evidence for use of probiotics and prebiotics*	*Commonalities and associations with AN*
Inflammatory Bowel Disease (IBD) (ulcerative colitis (UC) and Crohn's disease (CD))	- Mechanism of aetiology: Genetic susceptibility + environmental trigger (such as change in the gut microbiome) = aberrant inflammatory response in the gut - Dysbiosis may maintain inflammation Gut microbiota and metabolite findings: - ↓ diversity during active disease - ↑ Proteobacteria and Enterobacteria - ↓ butyrate producing *F. praunitzii, Roseburia* species - Dysregulation of bile acid metabolism, ↓ SCFAs, change in amino acid levels, sphingolipids, polyamines in faecal samples. (Glassner et al., 2020; Nishida et al., 2018; Khan et al., 2019; Lavelle and Sokol, 2020)	Probiotics: - Most effective: 1) Multi-strain probiotics (eg: *Lactobacilli, Bifidobacteria* and *Streptococci)* 2) 12–16 week duration of intervention 3) in UC (Shen et al., 2014; Preidis et al., 2020; Oka and Sartor, 2020; Zhang et al., 2021b) Prebiotics: No effect on remission of IBD (Wedlake et al., 2014; Benjamin et al., 2011; Zhang et al., 2021b)	- Associations between IBD and AN (Hedman et al., 2019; Larsen et al., 2021) - Co-existence of AN & Crohn's disease (Ilzarbe et al., 2017) - ↑ Pro-inflammatory profile in AN (Dalton et al., 2018) - Associations between auto-immune diseases and AN (Watson et al., 2019) - Dysbiosis associated with AN may be a possible result of dietary changes, inflammatory changes, or both - Common gut microbiome changes: ↓ Bacteroidetes: Firmicutes ratio & butyrate producing bacteria such as *Roseburia* spp & *Faecalibacterium prausnitzii*
Functional Dyspepsia (FD): post-prandial distress syndrome (PDS) and epigastric pain syndrome (EPS)	- Aetiology + maintenance mechanisms include: visceral hypersensitivity, gastric sensorimotor abnormalities, immune activation, epithelial barrier permeability alteration, stress, post-infection inflammation, disordered duodeno-gastric feedback, low grade duodenal inflammation, neuronal hyperexcitability with a background of genetic susceptibility (Tziatzios et al., 2020; Zhou et al., 2022; Wauters et al., 2020) Gut microbiota and metabolite findings: - ↑ *Helicobacter pylori* - SCFAs modulate duodenal bicarbonate secretion - *E.coli* → LPS → delayed gastric emptying → ↑ symptoms of FD (Tziatzios et al., 2020) - ↑ *Streptococcus* and total bacterial load in the duodenal mucosa → ↑ symptoms (Wauters et al., 2020) - ↑ Proteobacteria, ↓ Bacteroidetes, *Prevotella, Veillonella* (Zhou et al., 2022)	Probiotics: - *Lactobacillus gasseri* → ↓ PDS symptoms (Igarashi et al., 2017). - probiotic (*Bacillus* species) vs. placebo without proton pump inhibitors → ↓FD symptoms (Wauters et al., 2021) - multistrain *Lactobacilli* → ↓ PDS symptoms (Drago et al., 2021) - *Lactobacillus rhamnosus* + hydrolysed formula → ↓ risk of developing FD symptoms compared with hydrolysed formula on its own in children with cow's milk allergy (Nocerino et al., 2019)	- FD symptoms associated with AN (Santonicola et al., 2012) - PDS associated most with starvation in EDs (Wang et al., 2014) - Upper GI symptoms persisted despite nutritional restoration (Mack et al., 2016); FGID symptoms continued at 12-month follow-up (Boyd et al., 2010) - Both FD and AN have correlations with stress and anxiety (Tziatzios et al., 2020; Guarda et al., 2015) - Dysbiosis associated with both; ↑ Proteobacteria & ↓ Bacteroidetes.
Irritable Bowel Syndrome	- Aetiology + maintenance mechanisms include: Abnormal gut transit, visceral hypersensitivity to stimuli resulting in hypervigilance of gut function, response to stress, abnormal immune response to dysbiosis (Camilleri, 2013) Gut microbiota and metabolite findings: - ↔ or ↓Diversity compared with controls - ↑ Bacteroidetes: Firmicutes ratio, ↓ *Bacteroides* - ↑ Enterobacteriaceae (phylum Proteobacteria) & ↑ or ↓ *Bifidobacteria* - ↓ *Faecalibacterium* (Wang et al., 2020; Pittayanon et al., 2019)	Probiotics: - Trend towards ↓symptoms - Multi-strain probiotic (mainly with *Lactobacilli* and *Bifidobacteria* strains ± *Streptococcus, Bacillus, Enterococcus* strains) and duration of > 8 weeks → better results (Dale et al., 2019; Sun et al., 2020; Ford et al., 2018; Fatahi et al., 2022) Prebiotics: no effect in IBS and FGID (Wilson et al., 2019). - low FODMAP diet (with low levels of prebiotics) →↓ IBS symptoms (Whelan and Staudacher, 2022)	- IBS symptoms have been associated with AN (Kress et al., 2018; Kessler et al., 2020) - Both IBS and AN have been associated with anxiety and stress (Qin et al., 2014; Zamani et al., 2019; Guarda et al., 2015) - Common gut microbiota features include: ↑ Proteobacteria, Enterobacteriaceae & ↓ *Faecalibacterium*
Coeliac disease	- Aetiology + maintenance mechanisms: genetic susceptibility + trigger (eg gut microbiome change) →immune mediated enteropathy triggered by gluten (a protein found in wheat, barley & rye). Gut microbiome and metabolite findings: - ↑Proteobacteria, Enterobacteriaceae, *Klebsiella, Staphylococcus* - ↓ Firmicutes, *Streptococcus* (Wacklin et al., 2013) - No significant difference in asymptomatic coeliac disease compared to controls (Wacklin et al., 2013) - ↑ *Bacteroides, Prevotella* and ↓ *Bifidobacteria,& Lactobacilli* (Akobeng et al., 2020) - Significantly different gut microbiota in genetically susceptible children compared with controls (Akobeng et al., 2020)	Probiotics: - inconsistent results → Some studies showed ↓ GI symptoms, changes in immune profile and gut microbiota profile, others no effect. (Akobeng et al., 2020)	- Significant bi-directional associations between coeliac disease and AN - AN after diagnosis of coeliac disease – hazard ratio: 1.46 - Coeliac disease after diagnosis of AN – odds ratio: 2.18 (Mårild et al., 2017) - Common gut microbiota changes: ↑ Proteobacteria & Enterobacteriaceae - To note, most microbiota evidence in coeliac disease is from mucosal sampling compared with faecal sampling in AN

IBD: inflammatory bowel disease; FGID: functional gastrointestinal disorders; FD: functional dyspepsia; PDS: post-prandial distress syndrome; EPS: epigastric pain syndrome; IBS: irritable bowel syndrome; SCFAs: short chain fatty acids; LPS: lipopolysaccharide; FODMAP: fermentable oligosaccharides disaccharides monosaccharides and polyols.

(Larsen et al., 2021). As discussed previously FD and IBS symptoms have been correlated with AN (Santonicola et al., 2012; Wang et al., 2014; Kress et al., 2018). A bi-directional association has been found between coeliac disease and AN (Mårild et al., 2017).

A meta-analysis of cytokine levels has found increased pro-inflammatory markers associated with AN including IL-6 and TNF α (Dalton et al., 2018). The immune profile seems to be different in AN as compared with primary undernutrition (Gibson and Mehler, 2019) indicating specific mechanisms in play in AN not merely related to starvation. AN has also been associated with other auto-immune diseases (Watson et al., 2019), so it is feasible that an immune dysfunction may be related to dysbiosis and GI symptoms in AN.

As discussed previously, AN patients often present with symptoms related to FGIDs including FD and IBS. AN is correlated to anxiety and mood disorders (Guarda et al., 2015) as is IBS to stress and anxiety and affective disorders (Qin et al., 2014; Zamani et al., 2019). FGID and AN have been related to immune function abnormalities (Camilleri, 2013; Tziatzios et al., 2020; Dalton et al., 2018). Therefore, there may be similar underlying mechanisms of GI symptoms for both AN and FGIDs.

5. AN and the gut microbiome

Studies investigating the gut microbiome in AN are described in Table 5. They indicate significant dysbiosis in AN compared with HCs. Alpha diversity in AN showed varied results. Some individual studies showed lower diversity (Kleiman et al., 2015; Monteleone et al., 2021a) or similar diversity in AN compared with HCs (Borgo et al., 2017; Mack et al., ; , 2021b) whereas others found higher alpha diversity including in an individual study (Prochazkova et al., 2021) and a pooled analysis of 4 studies (Di Lodovico et al., 2021).

Regarding abundances of individual taxa, higher abundances of *M. smithii* (Armougom et al., 2009; Borgo et al., 2017; Mack et al., 2016; Million et al., 2013), mucin-degrading bacteria (Hanachi et al., 2019; Mack et al., 2016; Monteleone et al., 2021a) and lower abundances of anaerobes including butyrate-producing *Roseburia, Eubacterium, Anaerostipes* and *Faecalibacterium* (Borgo et al., 2017; Hanachi et al., 2019; Kleiman et al., 2015; Mack et al., 2016, Prochazkova et al., 2021) were found in AN compared with HCs. Additionally, increased abundances of potential pathogens including *E. coli* (Million et al., 2013), *Salmonella* & *Klebsiella* (Hanachi et al., 2019) were also seen. In the pooled analysis, a large effect size for increased abundance of *Alistipes* & *Parabacteroides*, and decreased abundance of *Roseburia* was seen in AN compared with HCs. Furthermore, a medium size effect was also found with increased abundance of *Clostridium xvii*, *Akkermansia* & *Eisenbergiella* and reduced abundance of *Ruminococcus* in AN compared with HCs. *Roseburia* & *Anaerostipes* were significantly correlated to BMI (Di Lodovico et al., 2021).

Studies comparing AN-R and AN-BP with HCs found significant differences in diversity and abundances between both subtypes and HCs, as well as some between-subtype differences (Monteleone et al., 2021a; Morita et al., 2015) indicating dysbiosis in both AN-R and AN-BP.

Studies comparing AN microbiota post-nutritional treatment with pre-treatment found increased alpha diversity (Kleiman et al., 2015; Mack et al., 2016; Schulz et al., 2021; Monteleone et al., 2021b; Prochazkova et al., 2021) and improvement in abundance of *Roseburia* (Mack et al., 2016), *Ruminococci* (Kleiman et al., 2015; Mack et al., 2016; Schulz et al., 2021) and *Faecalibacterium* (Kleiman et al., 2015; Schulz et al., 2021). Nutritional treatment was described as 'standard' or 'strict', with increased energy, fat and fibre intake, as 'assisted eating' (Kleiman et al., 2015; Mack et al., 2016; Monteleone et al., 2021b) or an incremental increase in energy intake was specified (Schulz et al., 2021). Nutritional treatment, in general, reduced dysbiosis seen in pre-treatment AN, with an increase in gut microbiota associated with anti-inflammatory properties such as *Roseburia* and *Faecalibacterium.*

Other interesting findings included improved lower GI symptoms with nutrition but no significant remission of upper GI symptoms including bloating and abdominal fullness (Mack et al., 2016) indicating the need for exploring other adjunct treatment to help mitigate these symptoms. Alpha diversity was found to be inversely associated with depression scores (Kleiman et al., 2015; Mörkl et al., 2017) and the SCFA butyrate inversely related to anxiety scores (Borgo et al., 2017) indicating a close interaction between the gut microbiome and symptoms suffered from co-morbid psychopathology such as depression and anxiety. Faecal concentrations of neurotransmitters were significantly different in AN, with GABA and dopamine lower than HCs pre-treatment, serotonin lower than HCs post-treatment, indicating an interesting dynamic between these signals pre- and post-treatment (Prochazkova et al., 2021) potentially having a local effect with GI symptoms and visceral sensation but also on inflammation. These could also be potentially related to changes in the gut microbiome with treatment.

Pre-treatment dietary analysis was compared in some studies with energy, carbohydrate (Mack et al., 2016) and fat intakes (Borgo et al., 2017) being significantly lower, while fibre intake being no different (Borgo et al., 2017; Mack et al., 2016) in AN compared with HCs. Diversity was correlated to fibre and Vitamin D intakes (Mörkl et al., 2017) indicating the effect nutritional composition and dietary patterns may have on the gut microbiome.

There is some evidence from implementing FMTs from healthy donors into AN recipients with varying results. One study involving an FMT from a related healthy donor to a AN patient with small intestinal bacterial overgrowth and multiple GI symptoms showed significant changes to the microbial composition including increased butyrate-producers such as *Roseburia* and *Faecalibacterium* and reduced *Prevotella copri* at 5–6 months post-FMT. However, microbial composition reverted towards the original state at the 12-month follow up. In addition, there were no reported changes in ED-related and GI symptoms (Prochazkova et al., 2019). Another FMT from an unrelated donor into a AN recipient resulted in significantly improved weight gain (de Clercq et al., 2019). These differing results may indicate multiple factors involved in the maintenance of symptoms in AN.

Some abundances seen pre-treatment in AN including *M.smithii* and mucin-degrading microbiota may be related to the ability of these microbes to survive the harsh environment of an undernourished gut. Reduction of butyrate-producers such as *Roseburia* may be related to carbohydrate-poor intake. Moreover, improvement in *Roseburia and Faecalibacterium* (Kleiman et al., 2015; Mack et al., 2016; Schulz et al., 2021) with nutrition signifies the role undernutrition plays in AN dysbiosis. Lachnospiraceae were correlated with carbohydrate intake (Hanachi et al., 2019) and with shorter duration of treatment (Schulz et al., 2021) again emphasising the role of nutrition. There are commonalities seen in the gut microbiome in some GI disorders as described in Table 4, which may indicate underlying common causative or perpetuating factors including a 'pro-inflammatory' gut microbiome. Moreover, changes in the gut microbiome related to depression and anxiety scores may imply their role in GI symptoms and in the gut-brain axis in AN.

Differences seen in the studies in diversity as well as specific microbiota abundances may be explained by heterogeneity of research methods and of cohorts including the location of studies, ages, BMIs and duration of illness in participants, dietary patterns prior to study, compensatory behaviours including exercise, as well as factors that generally determine the gut microbiome as listed in Table 1. Other factors that may also influence the gut microbiome are the presence of co-existing mental health disorders such as anxiety and depression as described previously. Thus, gut microbiome presentation in AN may be a result of a number of factors including those related to the history and development of the illness in an individual, co-existing factors as well as factors prior to pathogenesis. It would be useful to explore what influence some of the commonly noted dietary changes in AN have on the gut microbiome.

Table 5
Studies exploring gut microbiome changes in AN.

Study & Type	Cohort (n): mean BMI kg/m^2	Investigations and time points (T)	Relevant exclusions	Dietary information	Results/outcomes: comparing AN with controls (AN vs control), AN at different time points (for eg: AN T2 vs AN T1), AN subtypes
Pfleiderer et al. (2013) Case study	AN (1): 10.4	- Faecal analysis at a single time point before refeeding	–	Restrictive diet, with vegetables, fruit and dairy	19 new bacterial species isolated
Armougom et al. (2009) Cross-sectional study	AN (9): 12.7 HCs (20): 20.7 Obese (20): 47.1	- Faecal analysis at 1 time point - In AN – unknown time point after hospitalisation	–	No dietary information	- AN vs obese: ↑ *M. smithii*, ↓ *Lactobacillus* -AN vs HCs: Firmicutes, Bacteroidetes, *Lactobacillus* – no difference
Mörkl et al. (2017) Cross-sectional study	AN (18): 15.3 HCs (26): 21.9 Overweight (22): 27 Obese (20): 34.6 Athletes (20): 22.1	- Faecal analysis at 1 time point - In AN – near beginning of inpatient stay - Depression scores compared	IBD, IBS, use of antibiotics & pre/probiotics within 2 months	- AN – treated with a 'mixed' diet - Type of dietary recall/analysis not specified	- AN vs athletes: ↑ Coriobacteriaceae, ↓ alpha diversity - Diversity correlated with fibre and Vitamin D intake - ↓ alpha diversity - ↑depression scores
Million et al. (2013) Cross-sectional study	AN (15): 13.5 HCs (76): 22.4 Overweight (38): 27.1 Obese (134): 40	- Faecal analysis at a single timepoint from inpatients and outpatients	IBD, use of antibiotics within 6 months	No dietary information	- AN vs obese: ↑ *E.coli* - Obese vs non-obese: ↓ *M. smithii*, ↑ *L. reuteri* - *M. smithii* – trend ↑ with lower BMI
Morita et al. (2015) Cross-sectional study	AN (25): 12.8 Age matched HCs (21): 20.5	- Faecal analysis at 1 time point -Detail of when not described in relation to treatment in AN -AN-R & AN-BP compared	IBD, IBS, use of antibiotics & probiotics within 3 months	No dietary information	AN vs HCs: ↓ total bacterial count, obligate anaerobes, *Clostridium coccoides, C.leptum, Bacteroides fragilis, L. plantarum, Streptococci* ↓ acetic & propionic acid faecal levels AN-R vs AN-BP: -No difference in abundances. *C.difficile* detected in 45 % of AN-BP (not reaching significance) - Each subtype had ↓ *Bacteroides fragilis* compared with HCs
Borgo et al. (2017) Cross-sectional study	AN (15): 13.9 Age matched HCs (15): 22.1	- Faecal analysis at 1 time point - Detail of when not described in relation to treatment in AN - Depression and anxiety scores compared - Dietary intake compared	IBS, coeliac disease, use of antibiotics & probiotics within 1 month, diabetes mellitus, binge/purge behaviour, recent enteral/ parenteral nutrition	Dietary analysis based of a 3-day food diary	AN vs HCs: ↑ Gram-negative bacteria, Proteobacteria, Enterobacteriaceae, *M.smithii* ↓ Firmicutes, Ruminobacteria, *Roseburia, Ruminococcus & Clostridia* ↓ Total SCFAs, propionate & butyrate - no difference in diversity ↓ Dietary intake in total energy, fats, carbohydrates, but no difference in protein & fibre ↑ Depression & anxiety scores - *Bacteroides uniformis* inversely related to BMI
Hanachi et al. (2019) Cross-sectional study	AN (33): 11.7 HCs (22): 21	- Faecal analysis at 1 time point - Samples taken within 10 ± 5 days of commencing enteral feeding in AN - Dietary intake compared - 'Francis score' compared for functional GI symptoms	Known GI pathology, auto-immune disease, use of antibiotics within 2 months	48-h recall by experienced dietitian All AN patients started on a 1 kcal/ml low fibre enteral feed Average intake: 1850 kcal/day including < 25 % oral intake	AN vs HCs: ↓ *Eubacterium, Roseburia, Anaerostipes*, Peptostreptococcaceae ↑ *Turicibacter, Anaerotruncus, Salmonella & Klebsiella* ↑ Francis score correlated to ↓ abundance of unknown genus in family Peptostreptococcaceae & ↑ abundance of *Dialister, Robinsiella* & Ruminococcaceae - BMI inversely correlated to families

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Table 5 (*continued*)

Study & Type	Cohort (n): mean BMI kg/m^2	Investigations and time points (T)	Relevant exclusions	Dietary information	Results/outcomes: comparing AN with controls (AN vs control), AN at different time points (for eg: AN T2 vs AN T1), AN subtypes
					Verrucomicrobeaceae & Ruminococcaceae - Mean carbohydrate intake correlated to Lachnospiraceae
Monteleone et al. (2021a) Cross-sectional study comparing AN-R and AN-BP with HCs	AN-R (17): 15 AN-BP (6): 14.7 HCs (20): 20.3	Faecal analysis 1 week after standardised diet in AN and in HCs	IBD, malabsorption, coeliac disease, diarrhoea within a month, use of antibiotics within 3 months, probiotics within 2 months	Standardised diets for a week before sampling: AN diet: 1500 kcal/day – 54 % carb, 17 % protein, 29 % fat HC diet: 2000 kcal/day – 45 % carb, 18 % protein, 35 % fat	AN-BP vs AN-R: ↑ Actinobacteria, *Bifidobacteria*, Eubacteriaceae ↓ *Odoribacter, Haemophilus* AN-R vs HCs: ↓ alpha diversity ↑ Verrucomicrobia AN-BP vs HCs: -Trend towards ↓ alpha diversity
Kleiman et al. (2015) Longitudinal study comparing admission (T1) and discharge (T2) data in AN with HCs Nutritional rehabilitation of AN patients during inpatient stay	T1: AN (16): 16.2 T2: AN (10): 17.4 HCs (12): 21.5	- Faecal analysis at 2 time points for AN: T1- near admission T2- near discharge - Analysis at 1 time point for HCs - Depression scores compared	IBD, IBS, coeliac disease, gut symptoms & use of antibiotics or probiotics within 2 months	- During nutritional rehab of AN patients: 'standard diet' as per recommendations -No detail on nutritional composition	AN vs HCs: ↓ *Clostridia, Faecalibacterium, Anaerostipes* at T1, becoming non-significant at T2 ↓ Alpha diversity at T1, becoming non-significant at T2 AN T2 vs AN T1 ↑ Alpha diversity & *Ruminococcus* - Alpha diversity inversely related to depression scores
Mack et al. (2016) Longitudinal study comparing admission (T1) and discharge (T2) data in AN with HCs Nutritional rehabilitation of AN patients between admission and discharge	T1: AN (55): 15.3 T2 AN (44): 17.7 HCs (55): 21.6	- Faecal analysis at 2 time points for AN: T1- near admission T2- near discharge - Analysis at 1 time point for HCs - GI symptoms analysed - Dietary intake compared	GI pathology/symptoms not excluded	During nutritional rehab of AN patients: 'strict' diet plans and increased energy, fat and fibre intake	AN vs HCs: ↓ Bacteroidetes: Firmicutes at T1, ↓ further at T2, ↑ Firmicutes at T2 - Alpha diversity not different at T1, ↑ at T2 ↑ Mucin-degrading bacteria & *M.smithii* at T1 ↓ *Roseburia* at T1, becoming non-significant at T2 ↑ *Ruminococcus* at T2 ↑ Branched chain fatty acids, markers of protein fermentation, at T1 ↓ Energy & macronutrient intake at T1, but fibre intake comparable ↓ Lower GI symptoms at T2
Monteleone et al. (2021b) Longitudinal study comparing admission (T0) and discharge (T1) data in AN with HCs Nutritional rehabilitation of AN patients between admission and discharge- 20 week rehab	T0: AN (21): 14.6 T1: AN (16): 20.5 HCs (20): 20.3	- Faecal analysis at 2 time points for AN: T0 – near admission T1 – near discharge 4–6 weeks after reaching BMI 18.5. - analysis at 1 point for HCs after having a standard diet of 2000 kcal/day for 1 week -metabolomics also analysed	- diarrhoea in the past month - history of coeliac disease, GI surgery, IBD, bowel tumors, malabsorption, chemo/radiotherapy, endocrine/ metabolic disorders, - antibiotics in last 3 months - probiotics, enemas, laxatives, psychotropic drugs in past 2 months	T0: standardised diet of 1500 kcal/day for 5–7 days prior – 54 % carb, 17 % pro, 29 % fat intake T1: Dietary intake at that point – 2000–2250 kcal/day for 7–10 days prior – 44–51 % carb, 19 % pro, 30–36 % fat intake HC standardised diet: 2000 kcal/day for 1 week prior – 45 % carb, 18 % pro, 35 % fat intake Nutritional rehab via assisted eating Discharge 4–6 weeks after reaching BMI 18.5	AN T0 vs HCs: ↓ Alpha diversity ↑ Bacteroidetes: Firmicutes ratio ↑ Actinobacteria, genera *Weissella, Coprococcus* ↓ Coriobacteriales, Oxalobacteraceae, *Parabacteroides* AN T1 vs HCs: Alpha diversity not significantly different ↑ Bacteroidetes: Firmicutes ratio ↓ Actinobacteria, Catabacteriaceae, *Collinsella, Parabacteroides, Catabacter* Leuconostocaceae ↑ Trend towards increasing beta diversity with nutrition Faecal metabolomics at specific time points: AN T0: ↓ sugar/ sugar metabolites AN T1: ↓ amino acid and gut microbe derived metabolites HCs: ↓ faecal metabolites of fatty acids and SCFAs At AN T0 - *Coprococcus, Clostridium_iv,*

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Table 5 (*continued*)

Study & Type	Cohort (n): mean BMI kg/m^2	Investigations and time points (T)	Relevant exclusions	Dietary information	Results/outcomes: comparing AN with controls (AN vs control), AN at different time points (for eg: AN T2 vs AN T1), AN subtypes
					Roseburia, Termosporobacter, Lachnospiraceae, *Ruminococcus* negatively associated with EDE score
Prochazkova et al. (2021) Longitudinal study comparing admission (AN1) to discharge (AN2) in AN compared with HCs Nutritional rehabilitation in patients with AN	AN 1 (52): 14.4 AN 2 (52): 17.1 HCs (67): 21.9	- Faecal analysis at 2 time points in AN – admission and discharge. No info on how far into admission or before discharge samples were taken. - faecal analysis for HCs at 1 time point	Diabetes, other chronic disease, severe infection Participants asked to not consume probiotics or aspirin 2 days prior to faecal sampling	No indication of the type of nutritional treatment. Average duration of inpatient stay 51 days in AN.	Core microbiota different in AN compared with HCs. More inter-individual variation in AN compared with HCs. AN1 vs HCs: ↑ *Alistipes*, Clostridiales, Christensenellaceae, Ruminococcaceae ↓ *Faecalibacterium, Agathobater, Bacteroides, Blautia, Lachnospira* ↑ Alpha diversity AN2 vs AN1: ↑*Megapshaera* ↑ Alpha diversity No significant correlations between EDE-Q, BMI, hyperactivity, disease duration and gut microbiome composition Faecal concentration of neurotransmitters & SCFAs: AN1 vs HCs: ↓ GABA, dopamine, butyrate AN2 vs HCs: ↓ serotonin AN2 vs AN1: ↑ butyrate, ↓ propionate
Schulz et al. (2021) Longitudinal study comparing gut microbiota from admission through short term refeeding in adolescents	T1 AN (19): % EBW: 75.1 T2 AN (19): % EBW: 79.8 HCs (20): % EBW: 94.8	- Faecal analysis at 2 time points for AN: T1- near admission T2- near discharge	GI pathology, coeliac disease, diabetes mellitus, use of antibiotics & probiotics within 4 weeks	AN nutritional treatment: started at 1200 kcal/day increasing in increments of 200 kcal every 2nd day until achieving weight gain of 0.5–1 kg/week	AN vs HCs: ↑ *Anaerostipes* AN T2 vs AN T1: ↑ Alpha diversity, Firmicutes, Lachnospiraceae, Ruminococceae & *Faecalibacterium* - Beta diversity significantly different at T1 and remained so at T2 ↑ Abundance of Lachnospiraceae at admission predicted shorter duration of treatment

BMI: body mass index; EBW: expected body weight; IBD: inflammatory bowel disease; IBS: irritable bowel disease; AN-R: anorexia nervosa, restrictive subtype; AN-BP: anorexia nervosa, binge/purge subtype; HC: healthy control; EDE Q score: Eating Disorder Examination Questionnaire score; GI: gastro intestinal.

6. AN, dietary intake and the gut microbiota

As AN is characterised by change of habitual dietary intake, exploring this may help us interpret typical gut microbiota found in AN. While energy restriction is a fundamental part of AN, studies investigating the nutritional composition of patients' typical diets have shown a reduction in carbohydrate and fat intakes in restrictive AN, but no significant difference in fibre and protein intake compared to HCs (Mack et al., 2016). It would be useful to examine if this reduction in intake and change in nutritional composition modulates the gut microbiome.

6.1. Energy restriction and effect on the gut microbiota

Murine models have shown a significant change in the gut microbiota with energy restriction (Wang et al., 2018) for example, increases in the abundance of *Lactobacillus* and *Bifidobacterium*. In a recent study looking at the gut microbiota in overweight/ obese subjects having undergone a very low-calorie diet (VCLD) for 8 weeks, showed an increase in microbes associated with digestion of host-glycans (*Akkermansia*) and decrease in species that specialised in digestion of plant polysaccharides (*Roseburia, Ruminococcus, Eubacterium*) (von Schwartzenberg et al., 2021). Microbial species tended to revert back to baseline when the VCLD was changed back to a 'maintenance diet'. A high protein but energy restricted diet in an obese cohort resulted in a similar increase in *Akkermansia* and decrease in carbohydrate digestors such as *Roseburia* (Dong et al., 2020). Increased *Akkermansia* species and reduced carbohydrate digestors seen in AN may thus be related to energy restriction, particularly reduction in carbohydrate intake.

Existence of a particular cluster of gut microbiota may increase the host's susceptibility for weight loss. An interesting study investigating a 40 % reduction in energy intake for 3 weeks in 41 subjects with a healthy BMI (mean 23 kg/m^2) found that those with a *Prevotella* predominant enterotype had a significantly higher BMI loss than those with a *Bacteroides* predominant enterotype (Zou et al., 2020). There was no significant change in enterotype between the baseline and 3 weeks post-intervention.

Similar results have been found in studies with overweight subjects. *Prevotella* abundance has been associated with a significantly higher weight loss in overweight individuals on a 6-week wholegrain ad-libitum diet compared with those with a Bacteroides abundance (Christensen et al., 2019). A higher fibre diet and a 500 kcal/day energy deficit intervention in overweight subjects, stratified based on their *Prevotella/Bacteroides* (P/B) ratio, found that those with a high P/B ratio had a significantly higher weight loss than those with a low P/B ratio (Hjorth et al., 2019).

Dietary restriction is one of the factors said to contribute to the establishment of AN (Stice et al., 2010). A monozygotic (MZ) twin discordant study exploring environmental/epigenetic factors by examining the differences between MZ twins affected by AN and co-twins not affected by AN, found that affected twins had a higher likelihood of having started dieting at an earlier age and of GI symptoms than the unaffected co-twins (Thornton et al., 2017). It is conceivable that, in those with a genetic susceptibility to AN and a pre-morbid gut microbiome making them vulnerable to significant weight loss (for example *Prevotella* predominance), energy restriction and high fibre intake as part of 'dieting' could help establish the eating disorder.

Thus, evidence indicates that not only is the gut microbiome influenced by energy restriction and nutritional compositional changes while 'dieting', but also that the pre-existence of a particular cluster of gut microbiota may make the host more susceptible to weight loss while dieting.

6.2. Dietary changes and the microbiome in AN

AN often present with dietary changes including becoming a vegetarian or a vegan. A systematic review found correlations between vegetarianism and eating disorders, especially AN (Sergentanis et al., 2020). Here we explore the impact habitual dietary pattern may have on the gut microbiome as well as modulation through changes in these patterns while developing AN.

Habitual dietary intake can have a major impact on the type of gut microbiota in an individual. 'Westernised diets' high in protein and fat have been related to the Bacteroides predominant enterotype while carbohydrate/ fibre rich diets related to vegetarianism/veganism have been associated with the *Prevotella* predominant enterotype (Glick-Bauer and Yeh, 2014). Examining changes over time within the gut microbiome, there seems to be a resilience within its 'structure' often retaining the core microbes over years (Faith et al., 2013).

Studies investigating vegetarian/ vegan diets in the short term and their effects on the gut microbiota have found contradictory results, for example, some showing reduced *Bacteroides*, increased *Prevotella*, others showing an increase in both *Bacteroides* and *Prevotella*, but many have found a significant shift in microbial composition in the short term (Glick-Bauer and Yeh, 2014). Interestingly, a study based in a western urban environment comparing long term vegans (at least 6 months) versus omnivores, found only modest differences in the microbiome between the groups (Wu et al., 2016). Another study based in Italy compared intake and the microbiome of vegans, vegetarians (at least 12 months) and omnivores, all within the normal range for BMI. They also did not find significant differences in the vegan microbiota except for an increase in Bacteroidetes compared with omnivores (Losasso et al., 2018). They attributed this to a similar fat intake in all their groups. A recent study found butyrate producing species such as *Roseburia hominis*, *F. prausnitzii* and *Anaerostipes hadrus* associated with dietary intake of unprocessed plant-based foods (Asnicar et al., 2021).

Thus, in AN, it may be a combination of dietary factors including their habitual intake, changes in quantity and composition of their diet and duration of these dietary changes that modulates their gut microbiome. For instance, a patient following a low-fat vegan diet long term may have a very different microbiome composition compared with someone with a reduced intake of their regular omnivore diet short-term. It is also interesting that although butyrate producing species seem associated with unprocessed plant foods, a food group that is often eaten in normal quantities by patients with AN, yet the gut microbiome of AN seems to be associated with a low abundance of these bacteria. This may point to other mechanisms in play including the effect of overall energy restriction and inflammatory processes.

6.3. AN, artificial sweeteners and the gut microbiome

Patients with AN are known to regularly use artificial sweeteners (Schebendach et al., 2017) possibly as a non-calorific sweet-tasting reward system. Animal studies have shown a significantly different microbiome and worsened glucose tolerance with intake of sweeteners. A study in healthy weight human volunteers showed a similar change in the gut microbiome and glucose tolerance in those subjects whose gut microbiome was found to be 'responsive' to sweetener consumption. Changes seen were an increased Bacteroides: Firmicutes ratio, increase in *Bacteroides vulgatus, B. fragilis*, decrease in *Akkermansia muciniphila* & *Lactobacillus reuteri*. Interestingly, the initial microbial composition of the 'responders' was significantly different from the 'non-responders' (Suez et al., 2014).

6.4. Influences on the gut microbiome in AN

In summary, the gut microbiome in AN is likely a result of the gut microbial composition prior to onset of illness modulated by the changes in pattern and types of food that the individual follows as part of AN, periods of fasting, whether using exercise, laxatives, vomiting as compensation and biological responses in the gut as well as co-existing conditions such as anxiety and depression. The microbiome by its very nature may influence the type of symptoms that the individual

experiences, for example changes in transit times or production of gases as by-products increasing bloating or inflammatory responses causing symptoms. Nutritional rehabilitation as treatment will modulate the gut microbiome and may eventually support the return of normal gut function including gut microbiome function. However, as nutritional rehabilitation may be associated with symptomatic worsening, it may also be helpful to think of other ways to facilitate normalisation of symptoms and the gut microbiome.

7. Probiotics, prebiotics, their place and rationale for use

From the intense interest in the role of the gut microbiome in host health, it stands to reason that there would be an equal interest in modifying the gut microbiome in promoting health or correcting 'dysbiosis' with the introduction of live organisms into the gut or promoting the proliferation of the 'probiotic' organisms in the gut. The idea of gut microbial resilience - the tendency of the gut microbiota composition to remain stable or in a state of homeostasis - lends itself to the possibilities of a 'healthy resilience' or a 'dysbiotic resilience' based on the effects of the microbiota on their host (Coyte et al., 2015; Sommer et al., 2017). The use of probiotics, prebiotics and synbiotics then are attractive propositions for moving the dysbiotic resilience towards a healthy one.

Probiotics are defined as 'live organisms that, when administered in adequate amounts, confer a health benefit on the host' (Hill et al., 2014). They may be delivered in foods, for example yoghurts, or as supplements. Currently available probiotics often have microbial strains from the genera *Bifidobacterium, Lactobacillus, Streptococcus* and the yeast *Saccharomyces*. With probiotics intended for the gut, they need to survive the acidic and alkaline environments while transiting through the various parts of the GI tract, to reach and survive in sufficient numbers at the target site as evidenced by controlled scientific studies.

A prebiotic is defined as 'a substrate that is selectively utilised by host microorganisms conferring a health benefit' (Gibson et al., 2017). It not only includes those stimulating proliferation of healthful microbes but also benefits conferred by their products and metabolites on health markers. Commonly studied prebiotics include inulin, fructooligosaccharides (FOS) and galactooligosaccharides (GOS). Although often thought of as synonymous, not all dietary fibres are prebiotics.

7.1. Probiotics and prebiotics in GI disorders

As listed in Table 4, probiotics have been studied in relation to many GI disorders including IBD and functional GI disorders such as FD and IBS. There is some evidence related to probiotic use in coeliac disease.

A systematic review on the use of probiotics in induction and maintenance of remission in IBD found significantly increased remission rates in active ulcerative colitis (UC) with probiotics compared with placebo (RR:1.51), especially related to a multi-strain probiotic VSL#3 (RR: 1.74) (Shen et al., 2014). Moreover, maintenance of remission of pouchitis was found to be significantly increased with this probiotic (Shen et al., 2014). However, no significant difference was found for Crohn's disease (Preidis et al., 2020; Shen et al., 2014). Another recent meta-analysis found a trend towards remission with probiotic use, reaching significance when 2 or more probiotic strains were used and when they contained 10^{10}–10^{12} colony forming units. Duration of intervention of 12–16 weeks in UC had a greater effect on disease activity (Zhang et al., 2021b). A recent technical review by the American Gastroenterology Association while pointing out the heterogeneity of studies, also found a trend towards improvement in mild/moderate UC with multi-strain probiotic containing *Lactobacilli, Bifidobacteria* and *Streptococci* in adults. Although based on fewer studies, there appeared more promise with evidence in UC in children (Preidis et al., 2020).

Proposed mechanisms of action of probiotics in IBD include preventing harmful bacterial adherence to intestinal luminal cells, promoting an 'anaerobic' atmosphere therefore preventing Enterobacteria from thriving, promoting an anti-inflammatory effect and improving the intestinal barrier function (Oka and Sartor, 2020).

Overall, indications are that probiotics have the potential to improve GI symptoms in IBD by reducing the pro-inflammatory atmosphere in the gut. The differences in results of the studies may be due to various factors including the starting point of the microbiome and receptiveness to the probiotic, aspects of IBD being different in individuals, their dietary intake/restriction modulating effects and differences in probiotic strains, dosage and duration of intervention.

There are far fewer studies on the effect of prebiotics in IBD. A systematic review of 23 RCTs of fibre intake in IBD identified only 6 trials pertaining to interventions fulfilling the criteria for prebiotics (Wedlake et al., 2014). The largest study to date investigated the use of inulin-type fructans in treatment of active Crohn's disease ($n = 103$), which showed no impact on response or remission rates, indeed there was increased abdominal pain in those receiving the prebiotic intervention, although the dose was relatively high (15 g/day) (Benjamin et al., 2011).

Regarding the effects of probiotics in functional GI disorders, there are some indications of benefit with use of a probiotic (*Bacillus* strains or *Lactobacilli* strains) in FD (Drago et al., 2021; Wauters et al., 2021; Igarashi et al., 2017). A study also showed promising results in infants with cow's milk protein allergy given a probiotic alongside hydrolysed formula in preventing development of FD symptoms (Nocerino et al., 2019).

Many studies have examined the effects of probiotics in IBS. Recent systematic reviews and meta-analyses have found some trends towards improvement in symptoms (for example, bloating, flatulence, abdominal pain) and symptom scores with multi-strain probiotics (including *Lactobacilli, Bifidobacterium* strains and *Streptococci*) (Ford et al., 2018; Sun et al., 2020) although mostly not reaching significance. They also pointed out the heterogeneity among the studies. Another systematic review showed similar trends indicating that a duration of intervention lasting greater than 8 weeks had better results. Interestingly, many studies reported improvement in symptoms with the placebo as well as the intervention, pointing towards support, in general, being helpful (Dale et al., 2019). Promising results were also seen in children with single and multi-strain probiotics in IBS with a duration of intervention $>$ 4weeks especially in children below age 10 years (Fatahi et al., 2022).

Mechanism of action of probiotics in FGID may include their anti-inflammatory effect, their modulation of visceral hypersensitivity, their effect on gut transit and their effect on mood and anxiety. Effect on GI symptoms may in turn have an effect on their well-being and quality of life, reducing the effects of stress and anxiety further. Differing results may be due to heterogeneity of cohorts and probiotic administration.

With the use of prebiotics in IBS and functional bowel disease, a systematic review did not find a significant difference in symptomatic relief when comparing prebiotics with placebo. The intervention was however associated with an increase in *Bifidobacteria* abundance, strains of which have been associated with mood improvement. Despite this, there was no significant difference in anxiety and depression scores. (Wilson et al., 2019). It is useful to note that a low 'FODMAP' (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet which is low in natural prebiotics has substantial evidence in reducing symptoms in IBS (Whelan and Staudacher, 2022).

A review looking at the use of probiotics, *Bifidobacteria* or *Lactobacilli*, in coeliac disease found inconsistent results, with some positive associations with reduction in GI symptoms, changed gut microbiota and improved immune profile, while others found no difference (Akobeng et al., 2020).

7.2. Probiotics and prebiotics in mental health conditions

A systematic review and meta-analysis on the effects of probiotics and prebiotics in depression and anxiety found significant effects of probiotics compared with placebo in depression and anxiety (Liu et al., 2019). In depression, the effect was larger with samples in the clinical/medical settings compared with those in the community. Use of

probiotics for 4 weeks or more and multi-strain probiotics were found to be more effective. With anxiety as an outcome measure, there was a modest effect of the use of probiotics. As all the included samples were from the community, this review could not comment on clinical anxiety. In contrast, prebiotics did not have a significant effect on depression or anxiety (Liu et al., 2019). The mechanisms proposed by which probiotics affect anxiety and depression include their effect on the vagus nerve and afferent signals via microbial molecules (Dalton et al., 2019), reducing inflammatory response and the modulation of GABA and 5HT signalling (Foster and McVey Neufeld, 2013).

7.3. Probiotics in AN

Currently there is only preliminary evidence on the use of probiotics in AN. An early study compared the use of milk with probiotic yoghurt containing *Lactobacillus. bulgaris & Streptococcus. thermophilus* in 22 malnourished children (70–80 % weight for height) and 12 controls (100 % weight for height) in Morocco, while also examining the effect of these interventions in 27 adolescent females (mean BMI 15.5 kg/m^2) with AN. These AN patients received either yoghurt or milk for 10 weeks followed by a crossover period for 10 weeks of the opposite intervention alongside standard refeeding. While malnourished children in both the milk and yoghurt groups and controls having yoghurt had significant increases in γ interferon, in AN, probiotic yoghurt was associated with a significantly higher increase in γ interferon compared with milk (Solis et al., 2002) indicating an effect of the probiotic on immune modulation. Another study with 30 AN patients and 35 controls, both groups randomised to having either probiotic yoghurt (*L. bulgaris & S. thermophilus* containing) or milk for 10 weeks showed an increased γ interferon and an increased CD4:CD8 ratio in the yoghurt group (Nova et al., 2006). Such immune modulations may also have a positive effect on the GI tract potentially reducing GI symptoms in AN.

Results are awaited from a study comparing the use of a multi-strain probiotic (*Lactobacilli & Bifidobacteria* strains) with a placebo for 6 months alongside treatment as usual in 60 adolescents with AN and 60 HCs (Gröbner et al., 2022). Outcomes examined will be changes in weight, ED psychopathology, GI symptoms and the gut microbiome over 12 months. This study should add crucial evidence about the suitability of this adjunct treatment as well as its effects on GI symptoms.

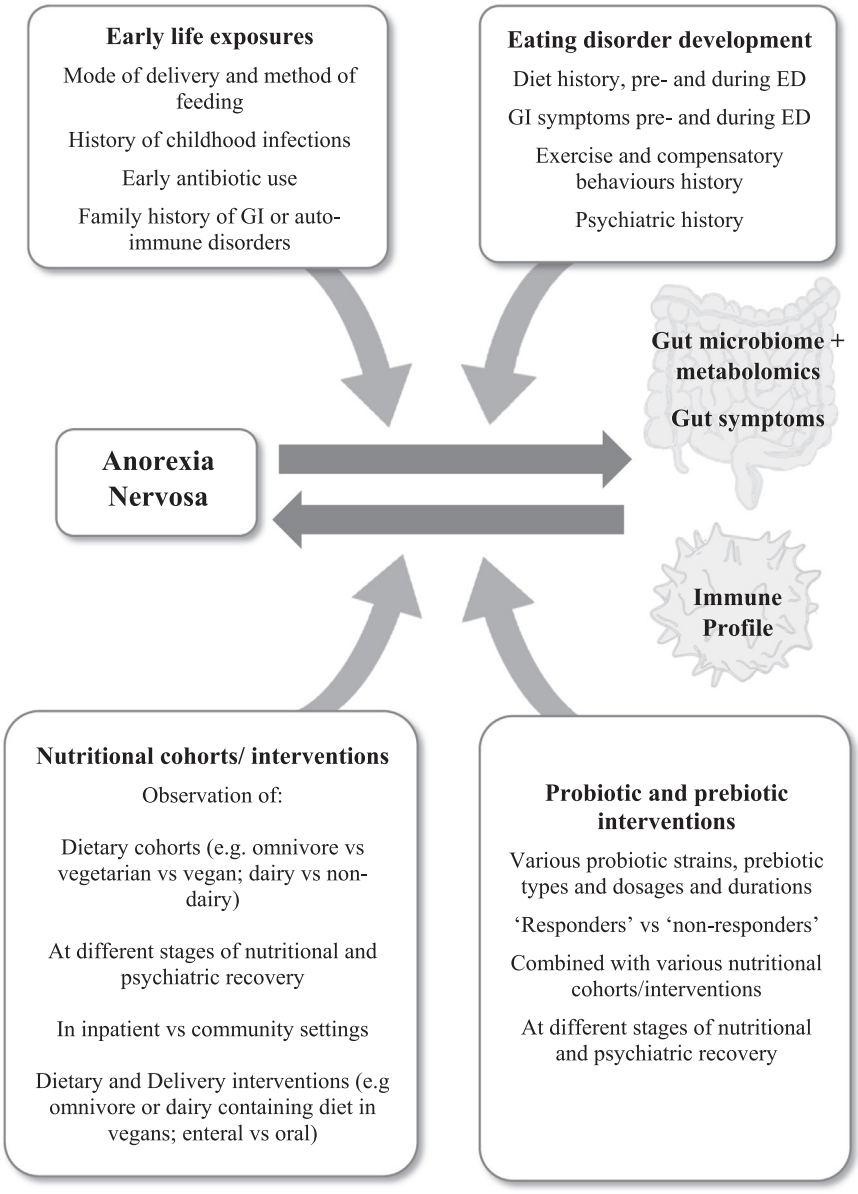

Fig. 1. Potential research avenues relating AN, the gut microbiome and metabolomics.

8. Discussion

GI symptoms in AN seem to mainly resolve with standard nutritional rehabilitation (West et al., 2021). However, increasing GI symptoms during the course of treatment and persistence of symptoms beyond nutritional recovery are also seen (Boyd et al., 2010; Chapelon et al., 2021; Mack et al., 2016). There is evidence of gut dysbiosis in AN with some similarities of microbiota seen in AN and IBD. Both conditions are associated with aberrant immune responses. Initial studies in AN with probiotics have shown improvement in immune responses (Nova et al., 2006; Solis et al., 2002). Probiotics have been used in IBD, FGID and in mental health illnesses such as depression and anxiety with some indication of improvement in symptoms. Therefore, the use of probiotics in AN should theoretically be a helpful adjunct to nutritional rehabilitation with the potential to mitigate GI symptoms and improve immune responses. However, the use of prebiotics for amelioration of GI symptoms has scant evidence so far.

Multi-strain probiotics with *Lactobacilli* and *Bifidobacteria* seem to have the most evidence with IBD and IBS as well as in depression and anxiety. Bacterial strains that are in direct competition with each other appear to have a stabilising effect in models, attributed to reducing excessive positive feedback loops, in turn preventing one microbe dominating (Coyte et al., 2015). It is possible that a similar mechanism is in play when multi-strain probiotics from similar genera are used in vivo helping establishment of these microbes in the gut. Treatment duration greater than 4 weeks seems to be most effective with IBS, depression and anxiety. Preliminary studies of probiotic use in AN have shown some immune modulatory effects with a 10-week intervention (Nova et al., 2006; Solis et al., 2002). Durations of treatment were much longer with UC mainly used for maintenance of remission. It may be that effects on anxiety and low mood occur earlier but changing dysbiosis and the immune system response require longer treatment. As both anxiety related GI symptoms and functional and immunological GI symptoms may be a part of AN, it seems feasible that probiotics, shorter and longer term, may be helpful in reduction of symptoms.

There exists an argument that experiencing GI discomfort during recovery in AN is of therapeutic value, perhaps as a way of modulating the gut-brain axis feedback and fear de-conditioning. While it is important for AN sufferers to acknowledge and accept appetite and satiety cues as being normal and necessary (Treasure and Alexander, 2013), our premise of supporting them manage their GI symptoms should not be a counter-argument. Evidence from gut microbiome research so far indicates its potential role in magnifying GI symptoms suffered and so support with ameliorating these is in keeping with 'normalising' appetite and satiety cues. Moreover, evidence also indicates that gut microbiome changes have a role beyond their effect on GI symptoms, including modifying signalling through the gut-brain axis and immune-modulation making further exploratory research in this field all the more important.

8.1. Limitations in the literature and directions for future research

The few studies so far in AN have been on the impact of probiotics on the immune system. While the gut microbiome as a target for treatment is a theoretical possibility, more research is needed in being able to recommend this as adjunct to current treatment. The planned study by Gröbner et al. (2022) is a starting point in examining the use of probiotics in AN and GI symptom recovery. Fig. 1 includes our thoughts on research avenues exploring gut microbiome and metabolomics in AN and the potential for initiating change in the microbiome towards health.

While there are indications that standard nutritional treatment in AN has positive effects on the gut microbiome and on GI symptoms, it was beyond the scope of this article to explore the particulars of nutritional treatment including nutritional composition that may be beneficial towards the microbiome and GI symptoms. It would be important to examine these further to pinpoint nuances in nutritional rehabilitation that may enhance the recovery process and also mitigate GI symptoms. Current evidence in AN is based on nutritional treatment in an inpatient setting. It would be useful to also explore whether treatment in an individual's own environment results in differences in the microbiome compared with an inpatient setting.

Studies investigating the current resident microbiota in AN and their associations with various factors would be important to explore: the duration and type of AN, the current and previous dietary patterns, previous history and current GI symptoms, use of antibiotics and the use of exercise and other compensatory behaviours. Correlations between resident microbiome and previous history may eventually produce insights into the pathogenesis of AN and/or reveal microbiome-related biomarkers for early detection and possibly prevention of AN. There is some evidence of *in-utero* infections, history of hospitalisations and use of anti-microbial agents in childhood and history of viral/bacterial infections immediately preceding onset in AN (Galmiche et al., 2022). Exploring their relationship with AN microbiota may add to our understanding of cause and effect. 48 % of patients with an eating disorder had a family history of GI symptoms (Salvioli et al., 2013). It would therefore be interesting to explore family history of GI symptoms, IBD, FGID and other GI disorders in AN. Relating AN more closely with immune disorders or functional GI disorders may again reveal other potential effective treatments.

Measuring the diversity and composition of microbiota pre-, during and post-nutritional treatment and when probiotics or prebiotics are used would be interesting data to gather. Correlating these with the occurrence and/or remittance of GI symptoms as well as investigating their immune profile during this process would give us important information on the effects and chronology of effects during treatment. Additionally, it would be important to see if there are specific differences between the 'responders' and 'non-responders'. A study looking at colonisation of the gut with probiotic bacteria found that while 60 % of the participants had these bacteria in their stools, 40 % had none of these microbes in their stool attributed to a pre-existing 'colonisation resistance microbiome' (Suez et al., 2019).

While it would be useful to investigate the current available multi-strain combinations in AN as they have been trialled in other GI conditions and may therefore be helpful in reducing symptoms, use of strains that may be specifically beneficial in AN would be a worthwhile avenue to explore. For instance, *Faecalibacterium prausnitzii*, an anti-inflammatory butyrate producing commensal bacterial species has been suggested as a future probiotic in IBD. As *F. prausnitzii* is reduced in abundance in AN, it may be similarly beneficial. However, as this is an extremely oxygen sensitive microbe, manufacturing and commercial production of an off-the-shelf probiotic would be challenging. Another avenue may be long term studies examining the microbiota profile in recovering patients indicating which changes may be associated with recovery and point towards AN-specific probiotics.

9. Conclusions

AN appears to have similarities to other GI disorders and to mental health disorders where the mechanism of action of gut microbiota has been postulated in relation to pathology and gut symptoms and the use of probiotics have been shown to have some effect. It is therefore possible that the use of probiotics in AN may be a helpful adjunct to current treatment. However more studies are needed to prove efficacy.

CRediT authorship contribution statement

N.D: Conceptualization, Funding acquisition, Methodology, Project administration, Visualization, Writing – original draft. **J.K:** Methodology, Supervision, Visualization, Writing – review & editing. **H.M:** Writing – review & editing. **K.W:** Supervision, Writing – review & editing. **J.T:** Conceptualization, Methodology, Supervision, Writing –

review & editing. **H.H:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Conflict of interest

KW has received research funding from charities including Helmsley Charitable Trust, Crohn's & Colitis UK, and industry including Almond Board of California, Clasado Biosciences, Danone, International Dried Fruit & Nut Council. KW has received lecturing fees from Yakult and Bromatech. KW is the co-inventor of VOC in the diagnosis and dietary management of IBS. All other authors have no conflict of interest to declare.

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