Examining the impact of common mental disorder symptoms, and the role of the gut-brain axis, in inflammatory bowel disease.

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The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

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My own contributions, fully and explicitly indicated in the thesis, have been:

- Design and submission of study protocol
- Data collection
- Database construction
- Statistical analysis of data
- Drafting of all manuscripts and first author of all published articles
- Design and drafting of thesis

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- Assistance in study protocol design (ACF and DJG)
- Assistance in collecting data for systematic review (JL, BB)
- Assistance in database construction (ACF and DJG)
- Assistance in analysing data (ACF, CJB, YY)
- Critical review of drafted manuscripts (ACF, DJG, PJH, CPS, CJB, EAG, BB, YY)

Abstract

Introduction

The extent to which the brain-gut axis influences the natural history of inflammatory bowel disease (IBD) is unknown. Evidence supporting the effect of common mental disorders on adverse outcomes in IBD would help to target those individuals most at risk. This thesis aims to better understand the bidirectional nature of the brain-gut axis and characterise those individuals who should have targeted psychological support.

Methods

A systematic review and meta-analysis of studies looking at the effect of common mental disorders on outcomes in IBD (brain-to-gut) and studies examining the effect of disease activity in IBD on psychological outcomes (gut-to-brain) was conducted to assess the bidirectional effect of the brain-gut axis in IBD. Longitudinal follow-up studies helped to evaluate the relationship between common mental disorders and their cumulative impact on adverse events related to disease activity. Analysis of the natural trajectory of common mental disorder symptoms over time, enabled further characterisation of this IBD cohort, to identify those most vulnerable to the influence of gut-brain interactions. Data was also collected on healthcare utilisation, including gastroenterology and nurse-led clinic appointments, as well as endoscopic, and radiological investigations.

Results

The brain-gut axis is bidirectional in its effects and influences the natural history of both IBD and psychological health. The cumulative impact of increasing psychological burden lead to a worse course of disease, in those patients in biochemical remission at baseline. During longitudinal follow-up, the burden of both disease activity and presence of symptoms of a common mental disorder significantly increased the risk of morbidity (hazard ratio (HR) 2.48; 95% confidence interval (CI) 1.38-4.46) and mortality (HR 6.26; 95% CI 2.23-17.56), with the presence of psychological co-morbidity a poor prognostic marker. Those individuals with persistently high depression and anxiety score had significantly higher healthcare utilisation with more outpatient appointments, and radiological and endoscopic investigations, for IBD-related symptoms.

Conclusions

The bidirectional effects of the gut-brain axis have an influential role in the natural progression of both physical and psychological health in IBD. Better characterisation of these patients identifies those most at risk for developing psychological co-morbidity and adverse disease outcomes from their IBD. This in turn helps target those in most need of early intervention, improves future study design, and highlights the need for a holistic, biopsychosocial care model in the management of patients with IBD.

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Glossary of Terms

5-ASA	5-aminosalicylate acid
ANOVA	Analysis of Variance
ANS	Autonomic nervous system
CAI	Clinical activity index
CBT	Cognitive behavioural therapy
CD	Crohn's disease
CDAI	Crohn’s disease activity index
CI	Confidence interval
CNS	Central nervous system
CRP	C-reactive protein
CT	Computed tomography
DAI	Disease activity index
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ENS	Enteric nervous system
ESR	Erythrocyte sedimentation rate
FC	Faecal calprotectin
FMT	Faecal microbial transplantation
GAD	Generalised anxiety disorder
GRITT	Gaining Resilience Integrated through Transitions
GWAS	Genome-wide association studies
HADS	Hospital anxiety and depression scale
HBI	Harvey Bradshaw Index
HLA	Human leukocyte antigen
HPAA	Hypothalamic-pituitary-adrenal axis
HR	Hazard Ratio
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease - unclassified
IBS	Irritable bowel syndrome

ICD	International Statistical Classification of Diseases and Related Health Problems
IL	Interleukin
IQR	Interquartile range
JAK	Janus kinase
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
NF-κB	Nuclear factor-kappa-B
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NOD2	Nucleotide-binding oligomerization domain 2
OR	Odds Ratio
PCDAI	Paediatric Crohn's disease activity index
PHQ	Patient health questionnaire
PROMS	Patient-reported outcome measures
RCT	Randomised control trial
ROS	Reactive oxygen species
RR	Relative Risk
SCCAI	Simple clinical colitis activity index
SCFA	Short chain fatty acids
SF-36	36-item short form
SIBDQ	Short IBD questionnaire
SMD	Standardised Mean Difference
Th	T helper
TLR	Toll like receptor
TNF-α	Tumour necrosis factor-α
TPMT	Thiopurine methyl transferase
Treg	Regulatory T cells
UC	Ulcerative colitis
UK	United Kingdom

Chapter 1

Introduction

1.1 Introduction to IBD

Inflammatory bowel disease (IBD) is an inflammatory condition of the gastrointestinal tract, with a prevalence of over 0.3% across western countries, and rapidly increasing incidence in those areas with evolving industrial populations.[1] IBD is broadly categorised as either ulcerative colitis (UC), which is typically contiguous inflammation confined to the large bowel, or Crohn's disease (CD) which can affect anywhere along the gastrointestinal tract in a non-contiguous fashion, and more often associated with complications such as stricture, fistulae, or abscess formation. The natural history of IBD cycles through periods of remission and flare, with disease activity typically leading to symptoms of abdominal pain, increased stool frequency, and haematochezia. This, ultimately, has a substantial impact on daily life. In a meta-analysis including over 2000 patients with IBD, both adults and children reported significantly lower physical, and mental quality of life scores compared with healthy controls.[2]

The proposed links between common mental disorders, such as anxiety and depression, and IBD date back several decades, with patients diagnosed with CD described as neurotic and anxious in the 1970s.[3] Several reports since have shown a strong link between common mental disorders and IBD, with the prevalence of symptoms of anxiety or depression almost twice that compared with the general population, and affecting more than half of patients during periods of flare.[4]

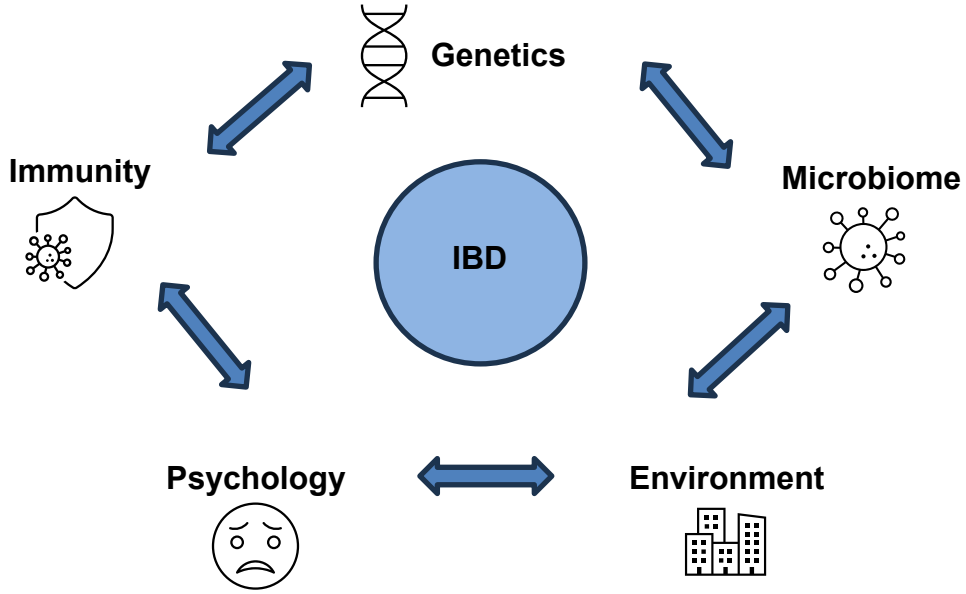
This chapter will first explore the influencing factors felt to contribute to the underlying pathophysiology of IBD, the ways in which we aim to assess and define disease activity, as well as the current medical, surgical, and psychological management of IBD. The literature evaluating gut-brain interactions, their application to IBD, and their possible bidirectional influence will be reviewed. Finally, an appraisal of current studies exploring the impact common mental disorders have on the natural history and prognosis of IBD will be undertaken.

1.1.1 Pathophysiology of IBD

Despite several decades of research, the underlying pathophysiology of IBD remains incompletely understood. As the world around us continues to evolve, our knowledge surrounding the physical and psychological factors influencing chronic disease grows in both depth and complexity, and IBD is no exception. The complex genetic, environmental, microbial, epithelial, and

psychological factors are interlinked and important to acknowledge to better understand the growing number of IBD phenotypes, and their association with disease progression (Figure 1). Research such as that being undertaken by The Crohn's and Colitis Canada Genetic, Environmental, and Microbial (GEM) Project, involving prospective enrolment of first-degree relatives, is already proving insight into identifying modifiable factors related to IBD pathogenesis.[5, 6, 7]

Figure 1: Interaction of risk factors involved in the development of IBD.



1.1.1.1 Genetics

Early studies suggested that one of the strongest risk factors for developing IBD was having a family member with either UC or CD,[8] and this theory stands today, with the risk of developing IBD as high as 1 in 10 for patients reporting the condition in a first degree relative.[9, 10] The increased risk of concordant disease observed in monozygotic and dizygotic twin studies drove forward the movement of genome-wide scans in IBD,[11] and identified the first gene loci in those with CD, on chromosome 16, known as IBD1. Polymorphism within this gene, namely the nucleotide-binding oligomerization domain 2 (NOD2), leads to mishandling of intestinal Gram-positive and Gram-negative bacteria, and potential disruption of the innate immune system. However, loss of function of NOD2 is still only found in a minority of Caucasian patients with CD, usually those with isolated ileal involvement, and rarely in those of Asian

descent.[10] Advances in technology have, through genome-wide association studies (GWAS), identified more than 240 loci with susceptible features that increase the risk of immune-mediated diseases, such as UC and CD. Although the strongest genetic effect is observed in those with variants in NOD2, interleukin (IL)-23 receptor, and human leukocyte antigen (HLA) loci, the penetrance of these variants is low and the true impact on functional significance is incompletely understood.[10]

The importance of understanding genetic pathways in chronic disease is essential to being able to identify pathogenic pathways for targeted therapy. In practice, genetic testing is recommended in patients prior to the use of thiopurines, as low thiopurine methyl transferase (TPMT) enzyme activity levels can cause harm and these also help to guide clinicians with adjusted dosing.[12] With the development of biologic therapies, there is also hope that genetic testing and molecular profiling may be able to play a role in predicting natural progression of disease, help to target therapy through predicting response, potential adverse effects, and risk of loss of response to certain treatments. For example, variants in the HLA allele, highlighted through GWAS, have shown an increased association in the risk of developing renal toxicity in those prescribed 5-aminosalicylic acids (5-ASA) for UC,[13] and an increased risk of antibody formation to anti-tumour necrosis factor-α (TNF-α) therapy.[14] Genomic testing in those with infantile-onset (aged < 2 years) or very-early-onset (aged < 6 years) monogenic IBD is now recommended by the British Society of Gastroenterology, to facilitate a personalised approach to care and improve our understanding of how gene defects lead to particular phenotypic expressions, in a cohort that usually presents with treatment-refractory disease.[15]

1.1.1.2 Epithelial and immune factors

A single layer of gut epithelial cells acts as a physical barrier against the lumen of the bowel, with the primary physiological function to absorb nutrients and water. The epithelium also includes goblet cells for mucous production, and Paneth cells which secrete antimicrobial peptides. These, alongside interposed immune cells create a protective barrier against luminal microorganisms. Disruption to this barrier can lead to microbe invasion and trigger an immune response. The immune system is classified as either innate or adaptive immunity, with the innate immune response initiating a first-line, non-specific response to microorganisms. These innate immune cells tolerate the intestinal microbiota, while defending against pathogens and intestinal microbes.[16] In genetically susceptible individuals, increased permeability of the intestinal barrier disrupts

this carefully balanced equilibrium, inducing inflammation through host defence mechanisms. The production of pro-inflammatory cytokines, activation of phagocytosis, and presentation of antigens activates the adaptive immune response.[17] These mechanisms initiate and, subsequently, sustain the inflammatory response seen in IBD.

The initial innate immune response actively recruits neutrophils to sites of inflammation, to eliminate invasive microorganisms. The neutrophil extracellular traps released by neutrophils limit the spread of microbes to promote healing, but also simultaneously impair the epithelial barrier and promote tissue damage and gut inflammation with the release of proteases, reactive oxygen species, and pro-inflammatory cytokines such as IL-8, TNF-α, and leukotriene B4.[18] Increased numbers of activated pro-inflammatory macrophages are also seen in IBD. These produce TNF-α, IL-6, and inducible nitric oxide synthase.[19] The release of antimicrobial peptides to protect the mucosa is co-ordinated by pattern recognition receptors, such as toll-like receptors (TLRs) and NOD. The polymorphism of NOD2 is well-recognised in ileal CD, as described above, impairing the function of these innate gut defences.[20, 21] TLRs increase the expression of TNF-α, IL-1, IL-6, and IL-8. The sustained activation of TLRs is observed in CD and UC creating a chronic inflammatory response.[20]

Antigen presentation by dendritic cells, B cells, and macrophages link the innate and adaptive immune response. IBD is strongly T cell-mediated, with an abnormal T helper (Th)1 response felt to be associated with inflammatory cytokines (IL-18, IL-12) linked to CD,[22] and Th2-induced by cytokine IL-13 is observed in those with UC.[23] The role of Th17 is also overexpressed in IBD and linked to the upregulation of IL-17, IL-21, and IL-22, as well as other pro-inflammatory cytokines driving gut inflammation.[20, 24] Th17 is markedly reduced in the presence of antibiotics, while invasive gut microbes can further drive Th17 cell differentiation.[25] Regulatory T cells (Treg) modulate proliferation of Th17 and are therefore protective. However, depleted Treg levels are observed in those with active IBD.[17] Loss of function mutations disrupt Treg differentiation and can lead to intestinal inflammation and progression of colitis. These effects were observed in murine models with increased Treg differentiation, where experimental colitis was effectively downregulated.[26]

Better understanding of the innate and adaptive immune response, particularly identifying those pro-inflammatory cytokines linked to the progression of IBD, has helped to target therapeutic intervention as discussed in more detail below (section 1.1.4).

1.1.1.3 Microbiome

The microbiome of the gut creates a symbiotic relationship with the host, enabling essential functions including regulation of immune cells, nutritional support, and synthesis of bioactive molecules such as short chain fatty acids (SCFA), tryptophan derivate and secondary bile acids.[27] It is the action of these elements that play a key role in maintaining and regulating intestinal immune homeostasis, and as well as providing an energy source to maintain the epithelial barrier. Dysbiosis and disruption in SCFA-producing bacteria, such as *Faecalibacterium prausnitzii*, creates an imbalance of pro-inflammatory cytokines and a dysfunctional mucosal layer of the epithelial barrier. This, in turn, enables bacterial penetration, promoting an inflammatory cascade that triggers further pathogenic bacteria and limits commensal growth, creating a chronic inflammatory state.[28]

The human gut microbiome is primarily comprised of Firmicutes and Bacteroidetes, as well as Proteobacteria and Actinobacteria.[29] The composition of the gut microbiome is significantly different in those with UC and CD compared with healthy controls; whether this is a cause or effect of IBD remains unclear. The dysbiosis and loss of biodiversity in CD appears to be more substantial than that observed in UC, with levels of beneficial bacterial such as *Eubacterium rectale*, *Faecalibacterium prausnitzii,* and *Roseburia intestinalis* reduced, while harmful bacteria such as *Bacteroides fragilis, Runinococcus, Clostridium hathewayi,* and *Escherichia coli* more prevalent.[29, 30] In patients with active ileal CD undergoing resection, reduced abundance of *Faecalibacterium prausnitzii* has been associated with higher rates of disease recurrence at 6 months.[31] Twin studies have demonstrated how dysbiosis has an effect on IBD disease state, suggesting its independent role in pathogenesis from environmental and genetic factors.[32]

The need for colonic bacteria in the pathogenesis of IBD has been demonstrated in murine models. Mice controlled in a germ-free environment were unable to develop colitis, despite T-cell activation following mesenteric lymph node transplantation, indicating colonic bacteria are needed to both trigger and maintain the inflammatory cascade.[33] In human studies, areas with slower transit of faecal matter and increased colonic bacteria, such as in the terminal ileum and rectum, are often sites of increased disease severity, with diversion of the faecal stream being a well-established treatment option for managing CD.[34]

Many microbiome studies in IBD are confounded by the effects of inflammation and therapeutic interventions. Murine studies have shown the ability of selectively engineered probiotics to identify inflammatory biomarkers of the gut

and release immunomodulators at these targeted sites, opening the opportunity to use the microbiome for less invasive investigations and treatments in the future.[35] Better understanding of the microbiome and dysbiosis in IBD may aid to targeting of diagnostic and therapeutic treatment.

1.1.1.4 Environmental factors

The geographic distribution of IBD suggests that environmental triggers play a major role in the evolution of IBD. Throughout the 20th century, IBD was known as a disease of The West. However, with increased industrialisation of The East the geographical distribution of IBD is changing, with a rising prevalence across areas of South America, Africa, Eastern Europe, and Asia.[36] Urbanisation creates an environment of increased and chronic exposure to air pollutants. In murine models this has been shown to increase the permeability of the gut, alter composition of microbiota, and increase pro-inflammatory cytokine expression, inducing an inflammatory response.[37] Associations between increased levels of pollutants such as nitrogen dioxide, sulphur dioxide, and carbon dioxide have been associated with both increased rates of adult hospitalisations related to IBD exacerbations and overall incidence of both UC and CD.[38, 39]

Individual patient factors also contribute to the natural progression of disease. The toxic and carcinogenic effects of tobacco are linked to a wide range of chronic inflammatory conditions, cancers, and circulatory disorders; exacerbating the pro-inflammatory response of both the respiratory and the gastrointestinal tracts, and remains one of the strongest risk factors for CD.[40] The underlying mechanism is a combination of altered luminal microbiota, activation of intestinal inflammation, gene expression, and reduction in innate and acquired immunity.[41] Cigarette smoking is associated with a more aggressive course of disease, with higher rates of relapse, fistulae, and strictures, and ultimately increasing the need for intestinal surgery.[41] The link between cigarette smoking and post operative morbidity is also shown to be significant, with higher rates of surgical site infections, anastomotic leaks, and readmission to hospital.[42]

Malnutrition is not uncommon within the IBD population and is associated with increased morbidity and mortality.[43] The potential to use dietary measures to reduce inflammation during periods of active disease has been an area of interest for many years. There is strong evidence for use of exclusive enteral nutrition in children with IBD, with efficacy comparable to the use of glucocorticosteroids in inducing remission in CD.[44, 45] Data from adult

populations are more limited due to intolerance and the perceived impracticalities. However, the improvement in nutritional indices, mucosal healing, and the potential to downstage the need for surgical intervention in those with IBD-related complications, such as strictures or fistulae, is notable.[46, 47] A randomised control trial (RCT) investigating the benefits of a CD exclusion diet, with partial enteral nutrition, was also shown to be effective in inducing and maintaining remission, in a selected adult cohort, with mild to moderate CD activity.[48] Similarly, a Mediterranean diet of healthy unsaturated fats, vegetables, and fish has been shown to be effective in a selected cohort of patients in both improving nutritional indices and reducing biochemical inflammation.[7, 49] Irritable bowel syndrome (IBS)-type symptoms are common in those with IBD, affecting almost a quarter of patients, despite evidence of endoscopic remission.[50] A number of small trials support a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which significantly improved quality of life and reduced clinically active IBD symptoms.[51] Despite this, adherence to specific diets, despite improvement in symptom-reporting, remains low in adult populations.[52]

1.1.1.5 Psychological factors

Depression and anxiety are common in patients with IBD. A systematic review and meta-analysis including over 30,000 patients reported an increased risk of common mental disorders in those with CD compared with UC, (odds ratio (OR) = 1.2; 95% confidence interval (CI) 1.1-1.4), with over a quarter of women reporting symptoms in keeping with anxiety or depression.[4] Significant mood disturbances, such as that observed in schizophrenia, bipolar disorder, and major depressive disorder (MDD), are linked to the activation of a systemic immune response and release of several pro-inflammatory cytokines including TNF-α, IL-6, and C-reactive protein (CRP).[53] In murine models, induced depression through cerebrovascular injection of reserpine impaired the parasympathetic function of the vagal nerve and, thus, increased the susceptibility of intestinal inflammation. This same study showed that the reinstatement of parasympathetic function and inhibition of pro-inflammatory macrophage activity, via administration of tricyclic antidepressants, ameliorated the inflammatory response in the gut.[54] Conversely the induction of experimental colitis increases circulating pro-inflammatory cytokines and nitric oxide to the hippocampus, influencing the regulation of emotions, with murine models displaying features of depression and anxiety.[55] The intricacies of the brain-gut axis and its bidirectional nature are described in more detail later in this chapter.

The inflammatory drive associated with common mental disorders may influence the progression of IBD in susceptible individuals, with several observational studies supporting this correlation.[56, 57, 58, 59, 60, 61] A large, nested case-control study including over 15,000 patients with IBD showed a significantly higher percentage of individuals developed IBD who had reported gastrointestinal and depressive symptoms up to 5 years prior to their diagnosis compared with healthy controls (CD: 3.7% vs. 2.9%, OR = 1.36; 95% CI 0.94-1.99; UC: 3.7% vs. 2.7%, OR = 1.58; 95% CI 1.24-2.02) with a divergence from the general population noted 9 years before diagnosis.[62] Higher levels of perceived psychological stress are associated with both anxiety and depression in IBD.[63] Everyday stressors are strongly associated with the reporting of gastrointestinal symptoms, although not necessarily with active disease.[64] However, the impact of chronic psychological stress may be more profound, as the increase in cortisol and pro-inflammatory cytokines have been shown to alter the microbiome, increase gut permeability, and increase the risk of microbial translocation activating an immune response.[65]

The influence of common mental disorders on the progression of IBD is likely multifactorial. Anxiety and depression lead to poor adherence with treatment and lack of service engagement, and are associated with lower health-related quality of life scores.[66] The need to recognise common mental disorders as both a manifestation of IBD, but also as a potential factor in the pathogenesis of this pro-inflammatory condition, is important in the management and risk reduction of IBD-related complications. These complex, bidirectional interactions between the gut and brain are discussed throughout this chapter.

1.1.2 The natural progression of IBD

The lifelong relapsing-remitting course of IBD varies greatly between patients but undoubtedly has a significant impact both physically and mentally. These episodic relapses of flare often present with new gastrointestinal symptoms, representing luminal inflammation. As chronic gastrointestinal diseases, both CD and UC result in the need for long-term medical surveillance, with progressive disease often resulting in escalation of immunosuppressive medical therapies or surgical intervention, with the aim to preserve bowel and limit gastrointestinal injury. Progression of disease requiring escalation in management, hospitalisation, or surgery does not denote a failure in management, and early intervention is increasingly supported to prevent complications.[67] The penetrating and stricturing phenotypes of CD are common and debilitating, affecting around 20% within the first 3 months of diagnosis,[68]

with 50% undergoing surgery within the first 10 years, and with a high risk of postoperative disease recurrence.[69] The number of new biologic therapies has grown exponentially over the last few years, paving the way for medical management of severe disease and reducing the requirement for surgical intervention. The management of IBD is discussed in detail later in this chapter.

1.1.3 Measures of IBD activity

There is no single 'gold standard' test for the diagnosis or monitoring of IBD. Assessment of disease activity is traditionally based upon subjective markers of patient-reported symptoms, that are a consequence of gastrointestinal inflammation. Objective markers of disease progression, such as ileocolonoscopy, radiological investigations, or biochemical indicators of inflammation are measured to quantify disease severity and extent. A physician will aim to consider all elements to guide treatment, and the need for escalation of medical therapy or consideration of surgery. It is important to aim for both clinical and endoscopic remission if we are to achieve a biopsychosocial model of care. This is widely acknowledged with many clinical trials investigating novel therapies often using both clinical and endoscopic remission as target endpoints. The role of both objective and subjective markers of disease activity are explored below.

1.1.3.1 Endoscopic and radiological measures of disease activity in IBD

Endoscopy plays an important role in IBD from diagnosis, to monitoring of disease progression, response to treatment, surveillance for dysplasia or neoplasia, through to intervention such as stricture dilatation. The advantage of colonoscopy is direct visualisation of the bowel mucosa and the ability to take mucosal biopsies for histology. It is widely accepted that ileocolonoscopy should be performed on all patients with a new diagnosis of IBD to exclude differential causes of mucosal inflammation.[70, 71] It is a relatively safe and objective measure for evaluating acute severe colitis, with early endoscopic features of active disease often apparent prior to the onset of clinical symptoms. An early trial examining the recurrence of CD post ileocolic resection observed 73% of patients had endoscopic disease recurrence at 1 year, although less than 50% reported any clinical features of disease activity.[72] With the goal of IBD management to achieve both endoscopic and clinical remission, pharmaceutical trials of new drugs recognise the role of endoscopy as a desired outcome measure.[73, 74] Capsule endoscopy allows visualisation of the small bowel

mucosa with minimal invasion. For the diagnosis, or evaluation of CD, capsule endoscopy can be particularly useful with an increased yield for the detection of small bowel disease (sensitivity 83% vs. 74% for ileocolonoscopy vs. 65% for small bowel follow-through imaging), although specificity is lower than other modalities.[75]

Radiological imaging is increasingly used alongside endoscopy, providing a non-invasive method of disease monitoring. Small bowel magnetic resonance imaging (MRI) is the 'gold standard' imaging for small bowel CD, but, is rarely available out of routine working hours and requires some preparation with oral water-based contrast agents to achieve the desired weighted images. Small bowel ultrasound is well-tolerated, quick, and inexpensive in comparison to MRI with comparable sensitivity and specificity (sensitivity 92% vs. 97% for MRI; specificity 84% vs. 96% for MRI).[76] Small bowel ultrasound is user-dependent and a recent survey demonstrated few National Health Service (NHS) trusts within the United Kingdom (UK) offer this service compared with MRI, limiting its use in clinical practice.[77] Computed tomography (CT) is readily available and a non-invasive imaging technique. However, risks of radiation exposure and nephrotoxicity should be considered. CT is often used in an acute setting to investigate the cause of abdominal pain, primarily to exclude those complications of acute severe colitis that require urgent intervention, such as perforation or collection.[78]

Endoscopic and radiological investigations come with varying degrees of risk, time, and financial burden. In practice it is recognised that the benefits of these investigations outweigh the risks in those patients who are symptomatic and may require changes to management. In large population-based studies, lower-risk investigations and clinical measures of disease activity are more acceptable to both clinicians and patients, as discussed below.

1.1.3.2 Biochemical measures of disease activity in IBD

Although there is no single biomarker that is specific to IBD, several serum and faecal biomarkers are used in practice and present a quick, cost-effective and relatively non-invasive measure of disease activity in most patients. Common serum biomarkers such as CRP or erythrocyte sedimentation rate (ESR), as acute phase reactants, represent non-specific, systemic inflammation. In practice, the poor sensitivity of CRP requires careful interpretation; a meta-analysis including 2499 patients gave a pooled sensitivity of 0.49 (95% CI 0.34-0.64), yet CRP remains an integral component in the management and monitoring of disease activity.[79] For decades CRP has remained integral in the

acute setting, with a 19 hour half-life its daily readings, in combination with clinical features, have been shown to predict outcomes, with stool frequency >8 stools a day and CRP >45mg/l predictive of colectomy in acute severe UC.[80] Substantial advances in medical management over the last 10 years would likely paint a different picture in modern times, but these markers continue to guide us on the predicted severity of disease and need for more intensive management.

The same meta-analysis by Mosli *et al.* suggested faecal calprotectin (FC) is more sensitive than CRP (0.88; 95% CI 0.84-0.90), but with lower specificity when using endoscopic inflammation as the gold standard.[79] FC is a protein released by neutrophils, macrophages, and monocytes during the inflammatory process. Higher concentrations are associated with more active disease. In 59 patients with UC significantly higher concentrations of FC were observed in those with active histological inflammation (278 µg/g; interquartile range (IQR); 136-696) compared with those in remission (68 µg/g; IQR 20-172).[81] Similar values were seen in those with CD (median value for patients with relapse in disease activity = 220.1 µg/g; 95% CI 21.7-418.5). However, in CD there was no significant difference from values observed in non-relapsing patients. Overall, there was a 14-fold increased risk of relapse in both UC and CD with FC concentration >150 µg/g.[82, 83] FC correlates well with endoscopic disease activity, and has the capability to distinguish between mild, moderate, and severe activity.[84]

The normalisation of CRP and FC are recognised short-term treatment targets with the longer-term goals of achieving clinical remission and endoscopic healing.[85] As our understanding of IBD evolves, new molecular measures of serum and histological markers by transcriptome analysis are helping to predict which individuals are more likely to respond to treatment and identify those who are at higher risk of relapse.[86] Although not yet readily available, these non-invasive measures demonstrate how understanding the persistence of inflammation at a molecular level can help predict the natural progression of IBD and may help guide treatment and monitoring in the future.

1.1.3.3 Patient-reported outcome measures of disease activity in IBD

The primary goal of IBD management is to achieve a clinical response.[85] Improving clinical symptoms impacts patient engagement, quality of life, and physical health. Patient-reported outcome measures (PROMs) are completed by patients in relation to their own perception of their current symptoms. There are several validated questionnaires that incorporate these PROMs, and although similar in nature the heterogeneity can make direct comparisons challenging. In

CD the main clinical tools used in clinical trials are the Crohn's disease activity index (CDAI) and the Harvey Bradshaw Index (HBI). Other validated, but less frequently used, scores include the paediatric Crohn's disease activity index (PCDAI), the perianal Crohn's disease activity index, and the International Organisation for the Study of Inflammatory Bowel Disease Oxford Score. The CDAI was created in 1976, with eight variables covering the most significant gastrointestinal symptoms, extraintestinal features, or markers that may suggest complications of active disease.[87] It was further validated in 1979 and has been used extensively in over 250 clinical trials.[88, 89] The HBI was based on the CDAI, but aimed to simplify reporting to just three clinical symptoms and two examination findings. It has been validated and again used in several clinical trials.[85, 89, 90] With both the CDAI and HBI, patient interpretation of their general wellbeing and tolerance to pain remains subjective. Both measures exclude those with ileostomy or colostomy and do not account for complications, such as stenosis or perianal disease. In CD, PROMs alone fail to distinguish active from inactive disease,[84, 91] with biochemical markers proving to be significantly more sensitive (sensitivity 84%, specificity 74%) when compared with endoscopic activity. However, a combination of HBI and FC proved to have a stronger correlation with endoscopic activity (sensitivity 85%, specificity 82%) than biochemical markers alone.[92]

In UC the number of clinical indices is more extensive, with the most frequently used being the Clinical Activity Index (CAI) also known as the Rachmilewitz Index, the Disease Activity Index (DAI), the Mayo score, the Lichtiger index, the Truelove and Witts Index, the Powel-Tuck Index, and the Simple Clinical Colitis Activity Index (SCCAI). Many of these PROMs were originally designed to evaluate the efficacy and safety of mesalazine in UC, with clinical scores used in combination with endoscopic findings. Of these the CAI and SCCAI are validated.[93, 94] The simplicity of the SCCAI makes it attractive for large observational studies, its high correlation to the Seo Index, which involves more complex and objective biochemical markers further enhances its validity for use in practice.[95] A limitation of clinical indices is the focus on short-term symptom-reporting and failure to capture the longer-term impact on quality of life, work productivity, and impact on symptoms of depression, anxiety, and fatigue. For the physician's global assessment of disease activity, consideration of both subjective markers of clinical response, as well as objective markers of either endoscopic, radiological, or biochemical findings are needed, before escalating treatment.[85]

1.1.4 Management of IBD

The long-term aim in the management of IBD is to maintain both biochemical and clinical remission of disease. Pharmacological management is targeted towards the pro-inflammatory cascade released through dysregulation of the innate immune pathway in those genetically susceptible individuals, as discussed earlier. Induction of remission is typically achieved with glucocorticosteroids, 5-ASAs, immunomodulators, or biologic therapies. If pharmacological therapies are ineffective, or complications such as fistulae, abscess formation, stricture, or perforation have arisen, then surgical management may be necessary. Alternative therapies targeting modification of the microbiome through faecal microbial transplantation (FMT) and use of probiotics have been trialled in IBD. The effects of FMT appeared promising for induction of remission in UC. However, the burden of multiple antibiotics regimens and lack of sustained long-term benefit have left this a subject for further investigation.[96, 97] Similarly, the sustained effect of probiotics remains unproven, and would likely require frequent, large doses to maintain a competitive microbial advantage.[98]

As with most chronic diseases, an individual approach is often needed through a biopsychosocial care model, which may encompass a combination of medical and surgical management strategies, alongside psychological support. A summary of the evidence base for each of these modalities is discussed below.

1.1.4.1 Glucocorticosteroids

Glucocorticosteroids are effective in a range of autoimmune and inflammatory conditions due to their strong immunosuppressive effects. A number of mechanisms interplay, including interruption of gene transcription via the blockade of proinflammatory stimuli, such as IL-1β, and further inhibition of inflammatory cytokines by blocking transcription factors, such as nuclear factor-kappa-B (NF-κB) and activator protein-1.[99] Induction of proteins, such as I-kappa-B-alpha, inhibits NF-κB, suppresses prostaglandin release, and mediates progression of the inflammatory response.[99] Inhibition of messenger ribonucleic acid, in the presence of glucocorticosteroids, also inhibits production of inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, and TNF-α. Gene variability seen in IBD can lead to disruption of transportation proteins and excessive activation of these inflammatory cytokines, causing glucocorticosteroid resistance.[99, 100]

The use of glucocorticosteroids in practice is supported for the induction of remission in both CD and UC. In CD, glucocorticosteroids were found to be superior to both placebo and 5-ASAs at inducing remission (relative risk (RR) = 1.99; 95% CI 1.51-2.64 and RR = 1.65; 95% CI 1.33-2.03 respectively).[101] A meta-analysis, including five RCTs, also demonstrated superiority over placebo for the induction of remission in UC (RR of no remission = 0.65; 95% CI 0.45-0.93).[102] The risk of short-term glucocorticosteroid-related side effects such as acne, oedema, or sleep and mood disturbance is high.[102] Long-term use is associated with an increased risk of infection, diabetes, osteoporosis, cardiovascular disease, and suppression of the hypothalamic-pituitary-adrenal axis (HPAA). Thus, prolonged glucocorticosteroid use has a higher all-cause mortality rate and is not recommended.[103]

Budesonide is absorbed in the proximal small bowel and metabolised by the liver cytochrome p450 isoenzyme CYP3A.[104] Thus, with over 90% of oral Budesonide undergoing first-pass metabolism, the systemic bioavailability is reduced and generally creates a lower side effect profile for patients compared with other glucocorticosteroids (RR = 1.64; 95% CI 1.34-2.00).[102] Although inferior to standard glucocorticosteroids, budesonide was superior to placebo in active CD (RR of achieving remission = 1.93, 95% CI 1.37-2.73), and offers a short-term alternative for those intolerant of standard glucocorticosteroid therapy.[105] However, budesonide failed to maintain remission at 3 months (RR = 1.25; 95% CI 1.00-1.58), and is therefore unsuitable for long-term use.[106] Budesonide-MMX, a multimatrix oral preparation designed for controlled colonic release, was shown to be superior to placebo for active UC for both endoscopic and histological remission (RR = 1.56; 95%CI 1.13-2.16 and RR = 1.51; 95% CI 1.11-2.06 respectively), again offering an alternative to those intolerant of, or at higher risk of side effects with, standard glucocorticosteroid therapy.[107] As with 5-ASAs, oral preparations tend to be reserved for lower-risk patients and modified with pH-dependent release coating to target ileal or colonic disease. As with prednisolone, topical formulations can be administered per rectum, with foam preparations able to reach the mid-sigmoid.

1.1.4.2 5-Aminosalicylic acids

The mechanism of action of 5-ASAs involves both anti-inflammatory and immunosuppressive effects. Inhibition of cytokines including TNF-α and NF-κB, inhibition of prostaglandin and leukotriene synthesis, and scavenging of free radicals, to reduce inflammation of the intestinal mucosa.[108, 109]

Immunosuppressive properties of 5-ASAs also inhibit lymphocyte deoxyribonucleic acid, impair white cell function, and adhesion.[110]

Both oral and topical preparations of 5-ASAs are recommended as standard induction therapy for mild or moderately active UC. A meta-analysis, including 54 studies and over 9600 patients, showed 5-ASAs were significantly superior to placebo at achieving both clinical and endoscopic remission (RR = 0.86; 95% CI 0.82-0.89, and RR = 0.77; 95% CI 0.67-0.89 respectively), with a dose-responsive trend towards remission with higher dose preparations in those with moderately active disease (RR = 0.83; 95% CI 0.77-0.88).[111] There may be some chemoprotective effect with regular use of 5-ASAs in UC against colorectal carcinoma (RR = 0.50; 95% CI 0.38–0.64), with higher doses offering greater protection.[112] However, any chemoprotective role with high risk features, such as low grade dysplasia may be limited.[113] The use of 5-ASAs is not currently recommended for CD, with no convincing evidence to suggest it is effective in achieving remission, or maintenance of remission over placebo.[114]

Oral 5-ASAs are rapidly absorbed in the jejunum. Therefore, several delayed and modified release oral preparations have been formulated to resist gastric breakdown, adapted with pH-dependent coating to delay drug release until the pH reaches more than 7. Topical preparations deliver higher drug concentrations directly to the mucosa and are, therefore, preferred in proctitis,[115] with higher doses, or combined topical and oral preparations demonstrating superiority in achieving clinical and endoscopic remission.[116]

1.1.4.3 Immunomodulators

The use of immunomodulators encompasses ciclosporin, methotrexate, and the thiopurines, azathioprine and 6-mercaptopurine. The latter two are used in the medical management of both UC and CD.

The primary mechanism of action of ciclosporin is via inhibition of calcineurin, thus preventing activation of T-cell transcription of IL-2 and related cytokines.[117] Early studies demonstrated a significant and rapid clinical improvement for patients with corticosteroid-resistant UC,[118] and the drug is an option for medical rescue therapy, or as a bridge to alternative therapies, for those with acute severe colitis who are thiopurine-naïve.[119] The significant toxicity profile associated with ciclosporin, however, must be considered, with an increased risk of permanent nephrotoxicity (5.4%), seizures (3.6%), major infection (6.3%), anaphylaxis (0.9%), and death (1.8%).[120] Ciclosporin has not shown to be efficacious in CD.[121]

Methotrexate interferes with folate metabolism and, thus, decreases cell proliferation. Its immunosuppressive effects increase T cell apoptosis and reduce proinflammatory cytokine production. Methotrexate was not found to be superior to placebo in several studies in UC.[122, 123] In CD, methotrexate is effective in the maintenance of remission, with intramuscular administration demonstrating significant superiority over placebo (RR of maintained remission = 1.67; 95%CI 1.05-2.67).[124] Oral methotrexate has not been shown to be superior to thiopurines in CD (RR of maintaining remission = 1.36; 95% CI 0.92-2.00).[124] Given the variable oral bioavailability of methotrexate, subcutaneous administration is recommended to achieve therapeutic benefit.[125] The liver and gastrointestinal side effects, as well as the risk of teratogenic effects in pregnancy, mean that thiopurines are now favoured as first-line immunomodulators in practice.

Azathioprine is orally administered and rapidly converted from its pro-drug form to inactive 6-mercaptopurine. It is through the action of TPMT that 6-mercaptopurine is subsequently transformed into either inactive 6-methylthiopurine nucleotide, 6-thiourea acid, or active 6-thioguanine nucleotides. It is the apoptotic action of 6-thioguanine nucleotides that give the desired pharmacological action. However, it is also responsible for drug toxicity and therefore the concentration of 6-thioguanine nucleotides can be closely monitored in patients and doses adjusted to achieve a therapeutic response, without adverse effects.[126] The use of thiopurines to maintain glucocorticosteroid-free remission in IBD is supported, with a clear benefit in the use of azathioprine long-term compared with placebo (RR of failure to maintain remission = 0.68; 95% CI 0.54-0.86).[127] The use of thiopurines to induce remission is not proven in either CD or UC when compared with placebo (RR of induction of remission = 0.87; 95% CI 0.71-1.06 and RR = 0.85; 95% CI 0.71-1.01 respectively).[128] However, the same meta-analysis showed an overall long-term benefit of thiopurines in preventing relapse in those with quiescent UC (RR of failure to maintain remission = 0.60; 95% CI 0.37-0.95) and quiescent CD when data were pooled from three withdrawal trials (RR = 0.39; 95% CI 0.21-0.74).[128] TPMT testing prior to initiation of thiopurines is both cost-effective and safe,[129] helping to highlight those at increased risk of side effects, such as myelotoxicity and gastrointestinal upset, and who are, therefore, more likely to discontinue treatment early on.[130]

Immunomodulators also have a role in combination therapy with the aim of reducing the immunogenicity of biologic treatment. A 3-year observational study demonstrated significant reduction in the risk of developing anti-drug antibodies to anti-TNF-α therapy with concomitant immunomodulator use (hazard

ratio (HR) = 0.34; 95% CI 0.21-0.56).[131] Early studies looking at combination therapy of anti-TNF-α treatment alongside thiopurines was shown to be both safe and effective. The SONIC trial demonstrated higher rates of glucocorticosteroid-free clinical remission (56.8% vs. 44.4% compared with anti-TNF-α therapy alone vs. 30.0% compared with azathioprine alone; P=0.02 and P<0.001 respectively).[132] The role of biologic therapy is discussed in detail below.

1.1.4.4 Advanced therapies

The number of biologic therapies available to treat CD and UC has grown rapidly over the last 20 years. In the UK, the National Institute of Health and Care Excellence (NICE) has approved the use the anti-TNF-α drugs infliximab and adalimumab,[133, 134] the gut-selective α4β7 integrin antagonist vedolizumab,[135, 136] the IL-12 and IL-23 antagonist ustekinumab,[137, 138], the IL-23 antagonist risankizumab,[139, 140] and the janus kinase (JAK) inhibitor upadacitinib, for treating both UC and CD.[141, 142] The anti-TNF-α drug golimumab,[134] and more recently JAK inhibitors tofacitinib and filgotinib,[143, 144] the IL-23 antagonist mirikizumab[145] and the siphingospine-1-phosphate receptor inhibitor ozanimod have approval for use in moderately to severely active UC.[146] The market continues to grow with the approval of guselkumab, a dual acting human IgG1, IL-23p19 inhibitor, expected within the next few months.[147]

Infliximab targets TNF-α, as one of the main pathogenic factors produced by immune and non-immune cells in the gut of patients with IBD. In practice, anti-TNF-α therapy remains the most popular first-line biologic therapy for induction of remission and maintenance therapy in IBD. In CD, infliximab was shown to be superior to placebo in an RCT based on a single infusion (clinical response at 4 weeks 81% vs. 17%).[148] The efficacy of maintenance therapy of infliximab, at a dose of 5mg/kg, for those with a primary response was demonstrated in the ACCENT 1 RCT, with 39% of patients in clinical remission by week 30, compared with 21% with placebo (P=0.003).[149] Patients with enterocutaneous fistulas secondary to CD who were responsive to infliximab at induction, were shown to have an increased likelihood of sustained response, with a higher rate of fistula closure at 3 months (68% vs. 26% of placebo group, P=0.002).[150, 151] In active UC, unresponsive to glucocorticosteroids, infliximab reduced the rate of progression to colectomy at 3 months, when compared with placebo (29.2% vs. 66.7%; P=0.017).[152] The ACT 1 and ACT 2 RCTs further supported the use of infliximab (5mg/kg) for active UC, with significant improvement in both clinical activity scores and mucosal healing following induction with maintenance

therapy. At week 8, clinical remission with infliximab was 61.5% vs. 37.2% for placebo and mucosal healing greater for those receiving infliximab 62% vs. 33.9% (P<0.001 for all analyses). The ACT 1 RCT demonstrated a sustained clinical and endoscopic response for those assigned to infliximab. At week 54, 34.7% were in clinical remission vs. 16.5% for placebo (P=0.001) and mucosal healing was observed in 45.5% vs. 18.2% for placebo (P<0.001).[153]

An alternative anti-TNF-α therapy, adalimumab differs from infliximab in that it is loaded as a subcutaneous injection as opposed to an intravenous infusion. The CLASSIC-1 trial included those with active CD without prior exposure to anti-TNF-α therapy, and showed significantly higher remission rates by week 4 in those assigned to adalimumab, compared with placebo (36% vs. 12% respectively, P=0.001).[154] Maintenance therapy over 12 months in the EXTEND RCT demonstrated higher rates of both clinical remission and mucosal healing in those assigned to induction therapy (160mg at week 0, followed by 80mg at week 2) followed by maintenance adalimumab (40mg every other week) when compared with placebo by week 52.[155] In active UC, refractory to glucocorticosteroids or immunosuppressants, the ULTRA 1 RCT demonstrated the efficacy of adalimumab (loaded with 160mg at week 0, 80mg at week 2, 40mg every 2 weeks thereafter) compared with placebo, with 18.5% in remission by week 8 compared with 9.2% assigned to placebo (P=0.031).[156] In the ULTRA 2 RCT, adalimumab maintenance therapy was also shown to be beneficial in moderate to severe UC, in those receiving concurrent glucocorticosteroid or immunosuppressive therapy, with 17.3% reporting clinical remission by week 52 compared with 8.5% receiving placebo (P=0.004).[157] The benefit of adalimumab in UC appears more modest than that observed in CD, and was lower in those who had previously received anti-TNF-α therapy, with only 9.2% achieving remission at week 8 compared with 6.9% with placebo (P=0.559).[157]

Golimumab is an alternative subcutaneous anti-TNF-α therapy, licensed for use in moderate to severely active UC. The PURSUIT-SC trial included patients with disease refractory to glucocorticosteroids and demonstrated an improvement in both clinical (17.8% vs. 6.4% for placebo; P<0.0001) and endoscopic remission rates (42.3% vs 28.7% for placebo; P=0.0014) after 6 weeks, for those loaded with 200mg, followed by 100mg at week 2.[158] A sustained response was demonstrated by week 54, with both clinical remission rates (27.8% vs. 15.6%; P=0.004) and mucosal healing (42.4% vs. 26.6%; P=0.002) significantly higher in those receiving golimumab (100mg every 4 weeks) compared with placebo.[159]

Vedolizumab is a gut-selective α4β7 integrin antagonist, again licensed for both CD and UC. An RCT conducted by the GEMINI 2 study group demonstrated

a more modest effect on clinical activity scores in those with active CD. Vedolizumab was shown to be superior to placebo for both induction (14.5% vs. 6.8% achieved clinical remission respectively; P=0.02) and maintenance of remission for those that had initially responded, when compared with placebo (4-weekly vedolizumab 39% vs. 21.6% and 8-weekly vedolizumab 36.4% vs. 21.6%; P<0.001 and P=0.004 respectively).[160] In moderate to severe UC, patients received 300mg vedolizumab at week 0 and 2 in the GEMINI 1 RCT, with a significant clinical response shown at week 6 (47.1% vs. 25.5%; P<0.001). As maintenance therapy, with 8-weekly infusion, clinical remission was significant higher in the treatment group compared with placebo (41.8% vs. 15.9%; P<0.001).[161] Although vedolizumab was effective in those with previous anti-TNF-α exposure, the efficacy was more pronounced in those who were biologic-naïve both following induction and when established on maintenance therapy.[162]

The monoclonal antibody, ustekinumab, targets the p40 subunit of IL-12 and IL-23. In the UK, it is licenced as a second-line biologic therapy for those who have failed, or are unable to tolerate, anti-TNF-α therapy. Two RCTs, UNITI-1 and UNITI-2, were run alongside each other to assess the clinical response with induction therapy in CD (130mg or 6mg/kg of body weight, intravenous infusion) at week 6 when compared with placebo. UNITI-1 recruited those with active CD but who had previously failed anti-TNFα therapy, and UNITI-2 recruited those with intolerable side effects to, or failure of, conventional therapy. Both groups had a significant response to induction therapy compared with placebo (UNITI-1: 34.3% and 33.7% vs. 21.5% for placebo; P≤0.003 and UNITI-2: 51.7% and 55.5% vs. 28.7% for placebo; P<0.001), with subcutaneous ustekinumab (90mg 8-weekly, or 12-weekly) maintaining remission in those who achieved a clinical response at induction therapy (53.1% and 48.8% vs. 35.9% for placebo; P=0.005 and P=0.04 respectively).[163] In UC, the UNIFI study group demonstrated significant benefit of ustekinumab therapy in those with moderate to severe disease activity, with 15.6% in clinical remission by week 8, compared with 5.3% assigned placebo (P<0.001). For those who responded and were assigned maintenance therapy, either 90mg every 12 or 8 weeks, 38.4% and 43.8% responded compared with 24% of those assigned to placebo (P=0.002 and P<0.001 respectively).[164]

Risankizumab is a new intravenous or subcutaneous, selective IL-23p19 inhibitor, recently approved as second-line treatment for moderate to severe CD. Two RCTs, MOTIVATE and ADVANCE, assigned patients to 600mg, 1200mg, or placebo at weeks 0, 4, and 8, with previous biologic exposure differentiating the two studies. At week 12, all co-primary endpoints were achieved with both doses

across both trials (P<0.0001). Those with previous biologic exposure (42%) demonstrated clinical remission at the lower dose of 600mg compared with 20% assigned placebo, with 29% demonstrating endoscopic response compared with 11% of the placebo group.[73] FORTIFY assigned patient from the induction trials to 8-weekly subcutaneous risankizumab 180mg, 360mg, or placebo with co-primary endpoints of both clinical remission and endoscopic response at 52 weeks. The greatest response was observed with 360mg with 52% vs. 41% of placebo achieving clinical remission and 47% vs. 22% placebo demonstrating endoscopic response.[165] For risankizumab in UC, two double blinded, placebo controlled RCTs were conducted for induction (INSPIRE) and maintenance (COMMAND). Patients were randomly assigned to receive 1200mg or placebo, administered intravenously at 0, 4, and 8 weeks. Those with clinical response were then randomised to 180mg, 360mg, or placebo every 8 weeks via subcutaneous injection. Clinical and endoscopic end-points were assessed at week 12 and 52 for the induction and maintenance trials, respectively. Remission rates following induction were 20.3% vs. 6.2% with placebo (adjusted between-group difference, 14.0% [166], P<0.001). In the COMMAND trial, remission rates at 52 weeks were 40.2% vs. 37.6% vs. 25.1% for 180mg vs. 360mg vs. placebo respectively (adjusted between-group difference for 180mg vs. placebo, 16.3% (97.5.% CI, 4.0%-24.5%), P=0.002).[166]

Mirikizumab, a selective IL-23 p19 inhibitor, is licensed for UC. The LUCENT-1 RCT assessed response to induction therapy (300mg every 4 weeks intravenously for 12 weeks) versus placebo, with clinical remission significantly higher in the active treatment group (24.2% vs. 13.3; P<0.001). The LUCENT-2 maintenance trial assigned 544 patients with an initial response to 4-weekly infusions of 200mg, or placebo, again with a significant benefit seen in the active treatment group (clinical remission 49.9% vs. 25.1% with placebo; P<0.001). A small number of patients reported opportunistic infection (2.8%) and a new diagnosis of cancer was found in 1.5%.[167]

Of the JAK inhibitors, upadacitinib is licenced as second-line therapy for patients who have failed previous biologic therapy, or in whom anti-TNF-α therapy is contraindicated. In moderate to severe CD, two induction RCTs, U-EXCEL and U-EXCEED, demonstrated both clinical and endoscopic superiority of therapy (45mg daily) compared with placebo, with 49.5% and 38.9% reporting clinical remission compared with 29.1% and 21.1% of those assigned to placebo, and endoscopic response rates of 45.5% and 34.6% compared with 13.1% and 3.5%, respectively, among those assigned to placebo (P<0.001 for all comparisons). The U-ENDURE maintenance RCT demonstrated both superiority in achieving clinical remission and endoscopic response by week 52, with 15mg

upadacitinib (37.3% and 27.6%) and 30mg upadacitinib (47.6% and 40.1%) when compared with placebo (15.1% and 7.3%; P<0.001 across all comparisons).[74] For moderately to severely active UC, patients assigned 45mg daily of upadacitinib in the U-ACHIEVE and U-ACCOMPLISH induction RCTs, were significantly more likely to achieve clinical remission compared with placebo by week 8 (26% and 34% compared with 5% and 4% of placebo respectively; P<0.001 for all comparisons). For those with a clinical response and assigned to either 15mg, 30mg, or placebo in the follow-up maintenance trial U-ACHIEVE, active treatment was again superior, with significantly higher rate of clinical remission (42% and 52% vs. 12% of those on placebo; P<0.001) at 52 weeks.[168]

Tofacitanib is licenced for moderate to severe UC following failure of conventional or alternative biologic therapy. The OCTAVE 1 and 2 induction RCTs randomly assigned patients to 10mg twice daily of tofacitinib or placebo, with clinical remission significantly higher with active treatment in both trials by week 8 (18.5% vs. 8.2%; P=0.007 and 16.2% vs.3.6%; P<0.001 respectively). OCTAVE Sustain randomised patients who had a clinical response in the induction trials to either tofacitinib 5mg, 10mg, or placebo for 52 weeks, with remission rates of 34.3% and, 40.6% vs. 11.1% respectively (P<0.001 across all comparisons), demonstrating a clear benefit with active treatment in those with an initial response.[169]

Fligotanib, is again licensed for moderate to severe UC in those who are intolerant to, or have failed, conventional treatments or biologic therapy. The SELECTION RCT included patients with moderate or severely active UC and assigned them to either 200mg, 100mg, or placebo once daily. Following induction at week 10, the biggest difference was observed in those on 200mg (26.1% vs. 15.3% on placebo; P=0.157); by week 58 both the 100mg (23.8% vs. 13.5% on placebo; P=0.0420), and 200mg (37.2% vs 11.2% on placebo; P<0.0001) treatment groups showed significantly higher numbers of patients in clinical remission.[170]

Ozanimod is a selective sphingosine-1-phosphate receptor modulator. The True North Study group demonstrated a significant benefit of active therapy (1mg ozanimod hydrochloride, once daily) compared with placebo at 10 weeks (18.4% in clinical remission compared with 6.0% on placebo; P<0.001). Those who demonstrated a clinical response were reassigned to either maintenance therapy at the same dose, or placebo, with the results at 52 weeks again supporting the active treatment group (37.0% in clinical remission vs. 18.5% with placebo).[171]

The hierarchy of advanced therapies in practice is changing rapidly as new data comes to light and licencing agreements change. Few head-to-head trials exist. However, where such data are lacking, network meta-analyses can help to compare clinical outcomes and guide treatment selection, particularly in those with previous treatment failure or exposure with other advanced therapies.[172, 173, 174, 175]

1.1.4.5 Surgical management

Although the growing number of advanced therapies creates the opportunity to avoid surgery in IBD, around 20-40% of biologic-naïve patients do not respond to anti-TNF-α rescue therapy in the acute setting.[176] Surgical management in UC is often indicated after failure of medical therapy, or secondary to a complication of active disease such as haemorrhage, toxic megacolon, perforation, or dysplastic changes increasing the risk of colorectal carcinoma. Delays in surgery present the biggest risk of post-surgical complications, with major complications linked to prolonged pre-operative hospital admission and medical treatment (P=0.036 and P=0.044 respectively).[177] Counselling and planning for elective total proctocolectomy, with the potential for subsequent ileoanal pouch formation depending on patient suitability and preference, or permanent ileostomy, should occur with the support of a multidisciplinary team. With an increasing number of advanced therapies now available, those undergoing surgery are likely to have failed several treatments, and, therefore present with complications of persistently active disease, such as malnutrition or anaemia.[178] It should be highlighted that those on high dose glucocorticosteroids and biologic therapy are at increased risk of pelvic sepsis and, thus, a modified two-stage or three-stage approach to ileoanal pouch formation is often undertaken to give time to better manage the chronic and acute complications of active IBD.[178]

In CD, the need for, and timing of, surgery should consider the distribution and extent of disease involvement, inflammatory or fibrotic changes, as well as perianal involvement, fistulae, or abscess formation. Surgery is not necessarily restricted to those with poorly-controlled disease or those resistant to medical management. The LIR!C trial demonstrated that early surgery also has a role in uncomplicated terminal ileal CD, with evidence of better quality of life scores at 1 year, fewer complications, and it was more cost-effective when compared with biologics.[179] In more complex disease, preservation of bowel is prioritised with the type of surgery, anastomosis formation, and stricturoplasty techniques both patient- and surgeon-dependent. An multi-disciplinary team approach to surgery

is recommended and those at high risk of recurrence, or with aggressive or extensive disease, should have planned follow-up and early escalation of medical therapy.[70] The complications of short gut, bile acid diarrhoea, adhesions, anastomotic recurrence, and immediate risk of leak should all be considered and monitored in those undergoing intervention.

1.1.4.6 Psychological management

In IBD, the onset of gastrointestinal symptoms is common between the ages of 15-25 years. This can have a detrimental effect on education, employment, and relationships, as well as physical activity and health. Adherence to daily medications, infusion regimens, time out for investigations, and learning to manage flare symptoms can all have a negative impact on quality of life and psychological health.[64, 180, 181] There is an increasing focus on addressing PROMs and targeting treatment on those areas that each individual prioritises, to improve engagement and quality of life.

The high prevalence of anxiety and depression in IBD is well-documented, affecting up to one-third of patients, which increases further during periods of disease activity, where symptoms of anxiety are reported in over half of patients (57·6%; 95% CI 38·6-75·4), and depression in over one-third (38·9%; 95%CI 26·2-52·3).[4] Addressing gut-brain dysregulation through the use of psychological therapies and neuromodulators may have benefits. In a systematic review and meta-analysis of 25 RCTs, examining the efficacy of psychological therapies in IBD, an improvement in anxiety, depression, and stress scores, as well as quality of life, was observed. These effects were strongest in those studies that recruited a selected cohort of patients with existing common mental disorders, fatigue, or poor quality of life at baseline. Psychological therapy improved depression scores, which persisted over a period of follow-up, compared with a control group (standardised mean difference (SMD) -0·16, 95% CI -0·30 to -0·03).[182] Review of individual psychological therapies showed both cognitive behavioural therapy (CBT) (SMD = 0.37; 95% CI 0.02-0.72) and third-wave therapy (SMD = 0.37; 95% CI 0.16-0.57) had a significant benefit in improving quality of life scores.[182, 183] A substantial proportion of patients with common mental disorders also report gastrointestinal symptoms, which may not necessarily correlate with mucosal inflammation.[184] Neuromodulators, such as low dose tricyclic antidepressants, have the added advantage of targeting gastrointestinal symptoms, and have been shown to ameliorate chronic neuropathic pain.[185] A meta-analysis, including 48 RCTs, demonstrated a significant benefit with both tricyclic antidepressants and selective serotonin

reuptake inhibitors for improving gastrointestinal symptoms, with a RR of IBS not improving when compared with placebo of 0.67 (95% CI 0.58-0.77).[186] A large retrospective observational study found a significantly increased risk of developing IBD in those with pre-existing depression (adjusted HR = 2.11; 95% CI 1.65-2.70 and adjusted HR = 2.23; 95% CI 1.92-2.60 for CD and UC respectively), with selective serotonin reuptake inhibitors and tricyclic antidepressants being protective.[187]

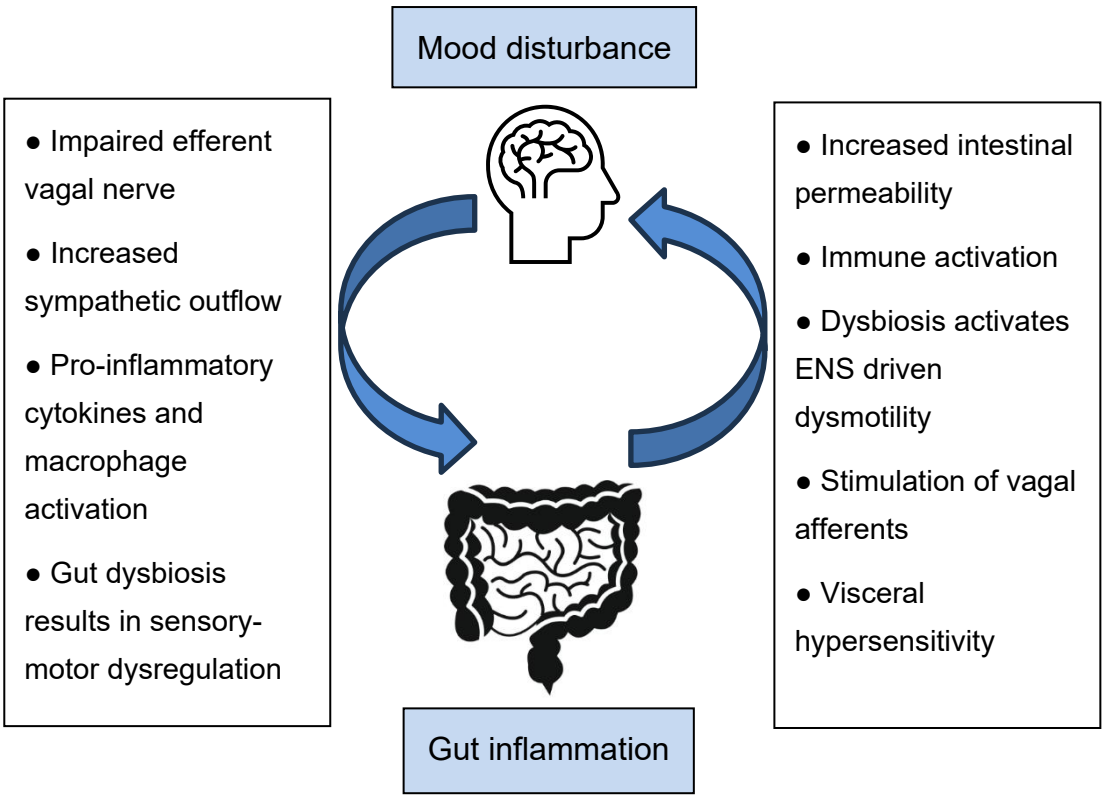
Targeting both mind and body may be a more holistic approach to care. The Gaining Resilience through Transitions (GRITT) programme used resilience training within an integrated care model and showed benefits in terms of health-care utilisation, with a 94% reduction in unplanned hospitalisations, 71% reduction in attendance to emergency departments, and a 73% reduction in glucocorticosteroid prescriptions from primary care.[188] Resilience is a modifiable trait, with high resilience linked to lower levels of IBD activity, fewer IBD-related surgeries, and better quality of life.[189] Modification of such characteristics, particularly in vulnerable cohorts, may provide a further therapeutic target in IBD. Targeted psychological support for selected IBD cohorts with underlying common mental disorders, may, therefore, be cost-effective in practice.[190]

1.2 The gut-brain axis

The gut-brain axis is a simplified term to describe the intricate and continuous interactions between several key mechanisms, including the autonomic (ANS), enteric (ENS), and central (CNS) nervous systems, endocrine (HPAA), gastrointestinal (corticotrophin-releasing factor system), and the intestinal barrier, including immune and microbial responses.

In both clinical and murine studies, psychological distress, anxiety, and depression have been shown to increase this risk of reactivation or development of colitis through activation of the gut-brain axis.[59, 65] The coexistence of gastrointestinal symptoms and depression are linked to the future development of IBD.[62] Understanding the complexities of the interaction between the gut and the brain, and the bidirectional nature of this communication, remain an area of ongoing research and is explored in further detail below.

Figure 2: Proposed pathways influencing the brain-gut axis.



1.2.1 Gut-to-brain effects

The innervation of the ENS extends from the oesophagus to the anus, exerting control over motility, secretion, blood flow and intestinal absorption.[191]

Release of cytokines and pro-inflammatory molecules and metabolites from the microbiota activate this system, with persistent inflammation driving dysmotility of the gut. Over 30 years ago, the effect of the microbiota on brain function was recognised in those patients with hepatic encephalopathy, with a significant improvement in cognition after administration of oral antibiotic therapy and management of gut-derived toxins.[192] Certain taxonomic strains, such as *Oscillibacter* of which its metabolic by-product valeric acid is involved in gamma-aminobutyric acid neurotransmission, have been liked to increased rates of depressive disorder in human microbiota studies.[193] Certainly, there is increasing evidence that dysbiosis has a central role in functional gastrointestinal disorders, which are in themselves strongly associated with common mental disorders.[194] Dysbiosis in those with IBS is associated with changes in brain volume, suggesting microbial colonisation influences the development of brain structure.[195] This inflammatory-induced neuroplasticity may contribute to the persistent dysmotility and heightened visceral sensitivity observed in patients with IBD despite induction of remission, generating the IBS-type symptoms observed in so many.[196, 197] The translocation of inflammatory molecules across the blood-brain barrier leads to structural and functional changes in the CNS, with higher rates of demyelinating and neurodegenerative conditions observed in those with IBD.[198] Early treatment of disease activity can mitigate this risk. However, care should be taken in therapeutic selection, as anti-TNF-α agents may exacerbate demyelination in certain conditions, such as multiple sclerosis.[198, 199]

The study of germ-free murine models has demonstrated the influence of the microbiota over psychological function, with the development of both the ENS and CNS reliant upon colonisation of the gut.[200] Germ-free models lead to altered expression of neurotransmitters causing gastrointestinal upset through changes in sensory-motor functions. These germ-free murine studies have also demonstrated changes in behaviour, with lower levels of anxiety but increased stress response, likely through altered regulation of the HPAA.[201] Modulation of the microbiome, and thus HPAA through electroacupuncture has been shown to attenuate anxiety- and depression-like behaviours in murine models with medically-induced colitis, demonstrating a potential role for modification of the gut-brain axis in the treatment of common mental disorders.[202]

Prolonged or recurrent flares of IBD can result in periods of malabsorption and malnutrition. There are higher rates of both nutrient and vitamin deficiencies in IBD, which may be exacerbated further through surgical interventions. Specific vitamin deficiencies, such as prolonged low B12, can lead to physical (fatigue, sore mouth, loose stools, and anorexia), neurological (loss of myelin sheath

leading to peripheral neuropathy, poor memory, and visual disturbances), and psychological (depression and irritability) symptoms. As an important co-factor for enzyme reactions, deficiency of B12 leads to elevated levels of methylmalonic acid and homocysteine, which have been linked to an increased neurological decline in Alzheimer's disease, visual hallucinations, psychosis, insomnia, and agitation.[203] The use of certain medications, such as glucocorticosteroids, that are frequently used during disease activity can have direct effects on brain function and emotional regulation. Disruption to the HPAA, predominantly through the cortisol pathway, leads to preferential selection of synthetic glucocorticosteroids and inhibition of adrenal cortisol secretion, causing an imbalance of glucocorticoids to mineralocorticoids. These changes lead to impaired cognitive function and emotional disturbance and are thought to underpin the pathophysiology behind rare complications such as glucocorticosteroid induced psychosis, depression, and delirium.[204]

1.2.2 Brain-to-gut effects

Responses such as stress cause a cascade of endocrine, autonomic, visceral, and behavioural changes which can drive peripheral inflammation. The vagus nerve consists of 80% afferent and 20% efferent nerve fibres, which innervate the gastrointestinal tract providing motor and secretory functions. The vagus afferent fibres are triggered indirectly by compounds from microbial flora, enteroendocrine and enterochromaffin cells, and thus changes in the microbiota or cytokine release can lead to increased or decreased gut motility, resulting in diarrhoea or constipation.[205] Stimulation of these sympathetic nerve fibres, such as with a stress response or catecholamine release, can further stimulate the growth of bacteria.[206] The effects of stress are demonstrated in murine models though maternal separation, activating the HPAA response with increased corticosteroid levels, leading to heightened visceral sensitivity, and increased colonic motility.[207] Early life stress events were also associated with increased gut permeability and dysbiosis of the colonic epithelium.[208]

Beyond the pathophysiological changes described here, the brain-to-gut effects are multifactorial with common mental disorders demonstrating a significant effect over behaviours, such as adherence and symptom-reporting, particularly in chronic disease.[209, 210] A meta-analysis examining the effects of anxiety and depression on adherence to medication established those with underlying depression were three times more likely to be non-adherent to medical treatment, increasing the risk of exacerbating underlying inflammatory conditions.[209] Early stress and major life events are risk factors for common

mental disorders, such as depression, as well as somatoform symptoms such as chronic pain.[211] Chronic pain is a debilitating symptom that drives investigation but may not always correlate directly with mucosal inflammation.[184] Abdominal pain is independently associated with higher rates of antidepressant use in IBD, and coexisting common mental disorders in IBD increase the risk of abdominal pain reporting (OR = 5.76; 95%CI 1.39 – 23.89), while better coping strategies and supportive environments are protective factors.[212]

Observational studies have suggested that the presence of symptoms of a common mental disorder are strongly associated with the future development of IBD,[62, 187] and that symptoms of anxiety and depression are more likely to lead to worse outcomes in IBD.[56, 57, 58, 213] It can be difficult to determine the causality of this, given the changes to behaviour and environment that can arise with common mental disorders. To address this, a bidirectional randomisation study examined the genetic liability to both depression and IBD using GWAS. It was found that genetically-predicted depression was directly associated with a significantly increased risk of both CD (OR = 1.29; 95% CI 1.07-1.56) and UC (OR = 1.22; 95% CI 1.01-1.47).[214]

Sleep disturbance is almost twice as prevalent in those with IBD compared with the general population.[215] Disruptions to the quality, amount and timing of sleep are associated with anxiety and depression; a meta-analysis of 21 studies found insomnia increased the risk of future depression by two-fold in those with no prior history.[216] Sleep is essential for immune regulation, with disruption creating a physiological stress response. In a murine model both acute and chronic sleep deprivation were linked to exacerbation of inflammation in dextran sodium sulphate-induced colitis. Chronic and intermittent sleep deprivation had a greater effect over both histological and clinical manifestations of active disease.[217] With poor sleep so prevalent in IBD, this presents a further target for intervention and highlights the need to address both psychological and lifestyle issues in chronic disease.

1.2.3 Bidirectional interaction of the gut-brain axis in IBD

As demonstrated above, (Figure 2) the gut-brain axis is bidirectional in its communication along several complex neural, hormonal, and biochemical pathways, which in turn have a direct effect upon both physical and psychological manifestations of disease. Early longitudinal follow-up studies examining functional gastrointestinal diseases have demonstrated the bidirectional link in gut-to-brain and brain-to-gut interactions, with pre-existing psychological co-morbidity a risk factor for new onset functional gastrointestinal disorders (OR =

1.11; 95% CI 1.03-1.19, P=0.006).[218] Conversely, those without underlying psychological co-morbidity but symptoms of functional gastrointestinal disorders at baseline were significantly more likely to develop anxiety and depression at follow-up (P<0.001 for anxiety and P=0.001 for depression).[218] Murine models support that this interaction could also be applied to an acute inflammatory response in those susceptible to colitis. Mice with chemically-induced gastrointestinal inflammation were quick to display anxiety-like and depressive-like behaviours.[55] A further murine study demonstrated how suppression of vagal tone-induced depressive-like behaviours, resulting in exacerbation of intestinal inflammation; this study also demonstrated the protective effects of the tricyclic antidepressant, desmethylimipramine.[54] It therefore follows that this bidirectional relationship could extend to patients with IBD, with the effects observed in clinical practice. As discussed earlier, several large observational studies have shown an increased risk of developing IBD *de novo* in people with symptoms of anxiety or depression, compared with those with no psychological history.[62, 187] Conversely, a new diagnosis of IBD increased the risk of developing depression and anxiety almost two-fold.[219] The highest risk of psychological co-morbidity appears to be in the first year of diagnosis and those with more complex disease, including extraintestinal manifestations of IBD.[220] Gracie *et al.* highlighted this bidirectional relationship, with those with clinically active IBD at baseline but with no pre-existing psychological co-morbidity more likely to develop new abnormal anxiety scores at follow-up (P=0.03). Examining the same IBD population, those with underlying symptoms of anxiety at baseline but without clinical or biochemical markers of disease activity, were more likely to require treatment for flare (P=0.003), escalation of medical therapy (P=0.005), and hospitalisation for uncontrolled disease activity (P=0.02). Depressive-like symptoms at baseline were also associated with significantly higher rates of reported clinical disease activity at follow-up (P=0.01).[56]

Although most studies focus on common mental disorders, such as anxiety and depression, the gut-brain bidirectional relationship extends beyond this, with somatoform symptoms and co-morbid features of common mental disorders, such as insomnia, also displaying independent bidirectional interactions. The link between sleep and disease activity is bidirectional in IBD, with active disease inevitability leading to nighttime waking and poor sleep quality. A study of over 1200 patients with CD in remission demonstrated that those with impaired sleep were twice as likely to develop active disease within the next 6 months (OR = 2.0; 95% CI 1.45-2.76), with depression and narcotic use associated with poor sleep at enrolment.[221]

With many studies examining gut-to-brain and brain-to-gut effects only assessing these issues at a single time point, and limited duration of follow-up, the clinical significance of the trends observed is often lost. The fluctuating nature of both IBD and mental health is not accounted for, and thus, data may underrepresent the true impact of common mental disorders on IBD progression, and vice versa. Further studies are needed to understand the overall impact both poorly controlled mental health, and poorly controlled inflammatory conditions have over time; the existing literature is explored in more detail below.

1.3 Relationship between common mental disorders and IBD

Epidemiological studies have raised the importance of recognising the prevalence of common mental disorders in IBD. A meta-analysis including over 30,000 patients with IBD, demonstrated a pooled prevalence of symptoms of anxiety of 32.1% (95% CI 28.3-36.0) and depression of 25.2% (95% CI 22.0-28.5). Symptoms of common mental disorders were higher in women, those with CD, and in active disease.[4] The higher prevalence of symptoms during disease activity highlights the gut-brain interaction, and the potential impact this has in chronic disease. A meta-analysis by Neuendorf *et al.* suggested that symptoms of depression increase by nearly three-fold during periods of IBD activity, with 40.7% (31.1%-50.3%) of patients being affected, compared with 16.5% (7.4%-25.5%) in remission.[222]

This relationship between common mental disorders and IBD is slowly being recognised in practice, with the most recent UK guidelines acknowledging the high prevalence of common mental disorders in patients with IBD.[119] Despite this increasing recognition, poor accessibility to psychological services remains a barrier to a holistic IBD approach, enabling the gut-brain axis to drive this bidirectional inflammatory process. The underlying pathophysiology of common mental disorders and the link to IBD is explored below.

1.3.1 Pathophysiology of common mental disorders

Understanding the pathophysiology of common mental disorders and their associated symptomatology helps us recognise the strong links, and overlapping pathways, that control both mood and inflammation. This common ground enables us to highlight targets for intervention, to improve outcomes for both physical and mental health.

As with IBD, the underlying aetiology of common mental disorders is multifactorial, influenced by genetics, medications, psychosocial factors, and environment, as well as dysregulation of hormonal, immune, and neurological pathways.[223] Structural changes in grey matter distribution on MRI have also been observed in both CD and UC, which are likely to heighten visceral sensitivity and somatoform symptom-reporting in those with increased levels of anxiety and depression, compared with healthy controls.[224, 225] This section focuses on the overlapping pathophysiology and definition of common mental disorders with inflammatory conditions, such as IBD, and how these pathways may drive symptomatology though the gut-brain axis.

1.3.1.1 Depression

Depression is a complex and potentially life-threatening condition, with many subtypes and increasing burden worldwide. MDD, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) is the persistent feeling of depressed mood or anhedonia causing occupational or social impairment, along with four or more other symptoms, including feelings of guilt or worthlessness, tiredness or fatigue, poor concentration, changes to appetite or significant weight loss, psychomotor retardation or agitation, sleep disturbance or suicidal thoughts. Similarly, the International Classification of Diseases 11 (ICD-11) defines depression as low mood or interest in activity for most of the day most days, for 2 weeks or more, alongside symptoms as described above.[226]

MDD is of interest in chronic inflammatory conditions such as IBD, due to the significant overlap of cytokine release, with IL-6, TNF-α, and CRP significantly raised in those with MDD compared with healthy controls.[53] Cytokine production can vary between patients and may be dependent on previous exposure to medication. Monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine are both individually, and jointly, influential over symptoms such as feelings of sadness, altered appetite, reduced energy and fatigue, motivation, sleep disturbance, and psychomotor retardation.[223] Chronic or acute sickness can exacerbate feelings of pain, anorexia, sleep disturbance, and altered cognition, with TNF-α and IL-1β the predominant proinflammatory cytokines driving behavioural changes.[227] Although acute sickness, such as infection, may be temporary and reversible once the trigger is removed, vulnerable patients with maladaptive cytokine response are at risk of persistent symptoms. A murine model examining the effects of lipopolysaccharide-induced sickness demonstrated how depressive behaviour

persists beyond sickness symptoms. Pretreatment with minocycline, an anti-inflammatory drug, demonstrated amelioration of the prolonged depressive behaviour after sickness had subsided, highlighting the marked cytokine drive of common mental disorders observed in proinflammatory conditions.[228] Targeting the gastrointestinal tract through modification of the gut microbiome has also been shown to improve psychiatric co-morbidity, when assessed in a controlled environment, with alpha diversity and microbiota richness increasing the rate of remission among patients admitted with depression.[229]

Increased rates of depression are evident across many other chronic inflammatory conditions, such as chronic obstructive pulmonary disease and cardiovascular disease, with improvement in physical symptoms correlating with improved depression scores, and persistent depressive symptoms being associated with worse outcomes and increased mortality.[230, 231] Advanced age is associated with an increased number of co-morbidities and increased risk of clinical depression, with a worse course of MDD.[232] The risk of MDD among adolescents has also increased significantly in recent years, with a recent meta-analysis suggested that 37% (95% CI; 0.32-0.42) of adolescents report depressive symptoms, without the added risk factor of underlying chronic disease.[233] In a recent large, UK-based, cohort study, while the incidence of IBD in adult populations had decreased slightly in recent years, within the adolescent population (age 10-16 years) incidence of IBD has almost doubled from 13.1 (8.4-19.5) to 25.4 (19.5 to 32.4)/100,000 person years.[234] This further highlights the increasing need to manage symptoms of common mental disorders alongside physical symptoms early on in the course of treatment.

1.3.1.2 Anxiety

Anxiety differs from depression. However, risk factors such as female sex, childhood adversity, trauma, or sociodemographic factors overlap.[235] Again, there are many subtypes of anxiety from acute stress disorder to post-traumatic stress disorder, phobias, panic, and obsessive-compulsive tendencies. The DSM-V define generalised anxiety disorder (GAD) as excessive anxiety and worry, occurring for more days than not, for at least 6 months. This can be accompanied by physical symptoms that include sleep disturbance, motor tension, irritability, poor concentration, restlessness, and fatigue.[236] The ICD-11 requires symptoms of anxiety to be present on most days, for several months with feelings of apprehension, motor tension, and autonomic overactivity.[237]

The neurobiological mechanisms of GAD are linked to the stress response. An acute stress response is a normal adaptive response to manage

daily challenges but becomes pathological when the symptoms are permanent, or negatively affecting daily life. Repeated triggers to the stress response can result in a chronic stress situation, with cumulation of triggers leading to GAD.[236] The neuroendocrine system is a key feature in managing the stress response. Release of adrenocorticotrophic hormone and corticotropin-releasing factor from the hypothalamus, synthesises the release of pro-opiomelanocortin and cortisol into the blood. Dysregulation of the HPAA affects the release of cortisol and corticosterone, creating a sustained threat response, which leads to features of anxiety. The neural circuits associated with brief stress and sustained stress response differ. Studies examining this through MRI imaging of the brain show unpredictability and persistently anxious states effect emotional sensitivity.[238] The bed nucleus of the stria terminalis has been implicated as maintaining heightened anxiety, and thus disruption to hormones that potentiate its effect, in these human studies, as well as in murine models. Understanding the structures involved, and the dysregulation of the hormonal response, may help identify a potential target for intervention.[239]

Resilience training is an alternative therapy for which evidence is gradually building. An individual's resilience to repeated life stressors is influenced by both genetic and environmental factors. This modifiable trait has shown to be protective against both anxiety and depression during acute illness.[240] In a study looking at outcomes in IBD, high resilience was independently associated with better physical and psychological outcomes, lower rates of IBD activity, and IBD-related surgery, and better quality of life scores.[189] Programmes such as the GRITT method, mentioned earlier, identify those at risk of common mental disorders and target support via a multidisciplinary team, increasing resilience scores among those at risk, and decreasing reported flare symptoms, hospital utilisation, and the use of opiates.[188] In addition to this, resilience is independently associated with improved quality of life scores across all domains of both physical symptoms, as well as emotional, and social functioning.[241] This is of relevance in IBD, the STRIDE-II initiative highlighted the need for both short-term improvement in clinical remission, but also aiming for longer-term treatment targets of restoration of quality of life, and absence of disability.[85, 242]

1.3.1.3 Somatoform symptoms

Somatic symptom disorder is defined by DSM-V as a physical symptom lasting for over 6 months that may, or may not be, related to an underlying medical condition. This results in significant distress or dysfunction to daily living due to the feelings or behaviour, which occupy excessive time and energy, related to

that symptom.[243] In the ICD-11, this is named bodily distress syndrome, in which a symptom (or symptoms) is present most days for several months causing an individual significant distress, through which excessive energy and time are devoted to the symptom, and thus limiting daily functioning.[237]

Similar characteristics are seen between somatoform disorder and other common mental disorders, with a predominantly female representation of 10 to 1, and symptoms responsive to both psychological therapy, such as CBT, and pharmacological therapy, such as selective serotonin inhibitors or tricyclic antidepressants.[243] Somatoform disorders affect around 8% of the general population, and are associated with an increased risk of co-morbid common mental disorders (RR = 1.5, 95% CI 1.1-2.3). A 5-year longitudinal follow-up study showed symptoms are often persistent, leading to higher use of healthcare.[244] The underlying pathophysiology is incompletely understood, but likely related to increased autonomic drive, which can lead to symptoms such as muscle tension, pain, tachycardia, and gastric hypermotility. As such, the prevalence of somatoform disorders is higher in those with associated functional disorders, such as fibromyalgia and IBS.[245, 246]

Within IBD, the presence of IBS-type symptoms is reported in one-third of patients in remission, with symptoms of common mental disorders significantly higher in this patient group compared with those without IBS-type symptoms.[50] The presence of chronic pain and visceral hypersensitivity in IBD is common. A cross sectional survey of over 170 patients linked increased pain-reporting to additional somatoform symptoms, such as fatigue and sleep disturbance, as well as higher risk of co-morbid symptoms of depression and anxiety.[247] Somatoform symptom-reporting is independently associated with increased opiate use in IBD (OR = 2.54, 95% CI 1.34-4.84), which can have detrimental effects on outcomes in IBD.[248] Sleep disturbance also has a huge impact on both mental and physical health, and may affect over 75% of patients with IBD, with strong links between insomnia and chronic pain.[249, 250] A meta-analysis of 72 studies by Irwin *et. al* associated sleep disturbance with raised markers of inflammation seen with IBD activity, including CRP and IL-6, suggesting that somatoform symptoms can further drive the inflammatory cascade of the gut-brain axis in susceptible patients.[251] Interventions such as CBT-insomnia are useful tools that may be underutilised in practice. Although, the primary endpoint for CBT-insomnia therapy may be to reduce sleep disturbance, improvements in pain reporting and, symptoms of depression, and a reduction in inflammatory markers, are also evident.[249]

Somatoform symptoms are hugely varied in both organ involvement and severity of dysfunction. Using a validated scoring system to assess the impact

and account for underlying gastrointestinal symptoms is important in IBD.[252] Identifying those with overlapping functional gastrointestinal symptoms, higher sensitivity to visceral pain, or physical symptoms, that disrupt daily life identifies patients that are at increased risk of developing common mental disorders and increased healthcare utilisation.[197, 244] This may help to support patients and break the inflammatory drive of the gut-brain axis. The influence of psychological co-morbidity on the natural progression and prognosis of IBD is explored in more detail below.

1.3.2 Prevalence of common mental disorders in IBD

The prevalence of common mental disorders is increased across many immune medicated inflammatory conditions,[253, 254, 255] and chronic health conditions, compared with the general population.[210, 231, 256] The bidirectional communication of the gut-brain axis helps us to better understand the impact chronic inflammatory symptoms can have upon mental health, quality of life, and social functioning in IBD. A previous systematic review demonstrated significantly higher rates of anxiety and depression within the IBD adult population compared with healthy controls. However, reported rates of anxiety in IBD vary greatly from 15% to 40%, and depression from 7% to 59%.[257] A more recent comprehensive systematic review and meta-analysis of 58 studies, and almost 19,000 patients with IBD, reported a pooled prevalence of symptoms of anxiety at 32.1% (95% CI 28.3% - 36.0%; $p<0.001$), which was significantly higher when compared with healthy controls. In 75 studies recruiting over 29,000, the pooled prevalence of symptoms of depression was 25.2% (95% CI 22.0% - 28.5%; $p<0.001$) in patients with IBD.[4] Both of these studies demonstrated higher levels of symptoms of a common mental disorder in those with active disease, an underlying diagnosis of CD compared with UC, and female sex.[4, 257] Screening for symptoms of common mental disorders in patients with IBD is as equally important as recognising those with existing psychiatric co-morbidity, with undiagnosed depression affecting 40.1%, and undiagnosed anxiety affecting 30.6% in a survey of 242 patients with IBD.[258]

The incidence of common mental disorders and the trajectory of symptoms also vary in IBD, with significantly higher rates of anxiety (12.2% versus 8.7% of non-IBD controls; $p<0.001$) and depression (8.0% versus 3.7% of non-IBD controls; $p<0.001$) reported in the first year after diagnosis. Subgroup analysis showed a further increased risk of new symptoms of anxiety and depression if there was disease activity requiring escalation of therapy, including use of glucocorticosteroids, immunomodulators, or biologics, within the first year.[219]

Similarly, a retrospective cohort study found that aggressive (HR 1.4; 95% CI 1.02-1.90) or active disease (HR 1.5; 95% CI 1.1-2.0) were risk factors, along with female sex (HR 1.3; 95% CI 1.1-1.7), for the subsequent development of new depressive symptoms.[259] Conversely, the incidence of both anxiety (incident rate ratio 1.30; 95% CI 1.12-1.51) and depression (incident rate ratio 1.54; 95% CI 1.30-1.84) were found to be significantly higher up to 5 years prior to the diagnosis of an immune mediated inflammatory disorder, such as IBD, when compared with a matched cohort.[254] A nested case-control study by Blackwell *et al.*, found that it was those patients also reporting gastrointestinal upset alongside symptoms of common mental disorders that were at increased risk of a subsequent diagnosis of both CD (OR 1.41; 95% CI 1.04-1.92) and UC (OR 1.47; 95% CI 1.21-1.79).[62]

The prevalence of gastrointestinal symptoms and somatoform symptom reporting is high in IBD, even during periods of remission. In a systematic review and meta-analysis of over 3000 patients with IBD in remission, 32.5% (95% CI 27.4-37.9) reported IBS-type symptoms, which in turn correlated with higher anxiety and depression scores.[50] A recent longitudinal study suggested more than two-thirds of patients with IBD experienced IBS-type symptoms over 6 years of follow-up, which was unrelated to the need for medical intervention for disease activity.[260] Pain is common in IBD, in a cross-sectional survey of more than 400 patients with IBD, 76% reported the presence of pain. Pain was independently linked to female sex (CD OR = 2.09; 95% CI 1.23-3.53; UC OR = 2.84; 95% CI 1.57-5.16) and active disease (CD OR = 1.97; 95% CI 1.14-3.39; UC OR = 2.16; 95% CI 1.11-4.22), with increased symptoms of anxiety (OR = 2.80; 95% CI 1.52-5.16) and depression (OR = 3.45; 95% CI 1.51-7.85) associated with higher pain severity in patients with UC.[261] A meta-analysis of over 24,000 patients suggested sleep disturbance affects over half of patients with IBD (56%; 95% CI 51%-61%), which in turn has a substantial impact on quality of life scores.[262] Reported rates of fatigue are also high, with 54.1% of 1704 patients with IBD reported fatigue and 37.1% reporting severe fatigue in a cross-sectional survey. Fatigue is also independently linked to female sex (OR = 1.48; 95% CI 1.13-1.93), patient-reported active disease (clinical remission OR = 0.45; 95% CI 0.36-0.55), and somatoform symptoms, such as joint pain (OR = 1.60; 95% CI 1.17-1.93) and abdominal pain (OR = 1.78; 95% CI 1.29-2.45), all of which are in themselves risk factors for anxiety and depression.[263] The impact of common mental disorders on the progression of disease and the cumulative impact of symptoms of a common mental disorder in IBD is explored below.

1.3.3 Influence of symptoms of common mental disorders on the prognosis of IBD

Understanding the true longer-term impact and prognostic implications that common mental disorders have on patients with IBD remains an area that is poorly understood, and, therefore, poorly managed in practice. Over the last few years, it has been increasingly recognised that common mental disorders have an impact on symptom-reporting, and thus influence both patient and professional behaviours. A recent systematic review and meta-analysis, including 22 studies and over 630,000 patients with IBD, linked depression to adverse outcomes including increased risk of flare (RR = 1.37; 95% CI 1.16-1.63), hospitalisation (RR = 1.11; 95% CI 1.00-1.23), escalation of therapy (RR = 1.38; 95% CI 1.13-1.69), and need for surgery (RR = 1.38; 95% CI 1.08-1.76).[264] Similarly, in a longitudinal follow-up study of over 400 patients with IBD, despite quiescent disease at baseline, symptoms of anxiety predicted the future need for glucocorticosteroid use or flare of disease activity (HR = 2.08; 95% CI 1.31-3.30), and escalation of therapy (HR = 1.82; 95% CI 1.19-2.80).[56] Increasing healthcare utilisation has a significant implication for costs of care in IBD, which have risen substantially in the last 5 years. This is, in part, driven by the increasing cost of newer advanced therapies, but also additional services to manage psychological co-morbidity, or polypharmacy to manage associated symptoms, such as pain. A study of almost 53,000 patients with IBD suggested a three-fold direct cost of care increase compared with non-IBD controls, as well as the lost work hours due to additional healthcare encounters.[265]

Pain is common in IBD, which can be driven by active disease, but also non-gastrointestinal manifestations of disease or overlapping disorders of gut-brain interaction and visceral hypersensitivity, such as IBS. Opiate use in IBD is higher than in the general population, with an increase in primary care prescriptions for patients with IBD of 20% in recent years.[266, 267] Anxiety and depression are independent risk factors for opiate use, which can lead to adverse outcomes in IBD, increasing the risk of surgical intervention with a four times higher risk of intestinal resection (HR = 4.44; 95% CI 1.64-12.0).[248] A recent systematic review and meta-analysis of 31 studies supported these findings; opiate use in patients with IBD was almost double that of the general population, with opiate use linked to depression (RR = 1.99; 95% CI 1.80-2.19), gastrointestinal surgery (RR = 2.33; 95% CI 1.66-3.26), need for glucocorticosteroids (RR = 1.41; 95% CI 1.04-1.91), and use of biologic therapies (RR = 1.36; 95% CI 1.06-1.74).[268] A large retrospective cohort study of almost 8000 patients suggested that patient-reported outcomes of pain remained the highest risk factor for hospitalisation in the first year (OR = 1.09; 95% CI 1.05-

1.14), with anxiety and pain driving the risk of subsequent re-admission.[269] Common mental disorders, fatigue, and pain, are associated with higher body mass index in IBD. Obesity is independently associated with persistent disease activity in CD (OR = 1.86; 95% CI 1.30-2.68), with increased adipose tissue linked to a higher risk of penetrating or stricturing complications (OR = 1.7; 95% CI 1.1-2.9).[215] Physical activity has been shown to reduce TNF-α and may, therefore, augment biologic therapy, with improved fitness leading to better surgical outcomes, lower rates of surgical complications, and reduced morbidity.[215, 270]

The connection between common mental disorders, increased somatoform symptom-reporting, and IBS-type symptoms in IBD has been explored. A study of almost 700 patients with IBD examined the effect of increased psychological symptoms, alongside gastrointestinal symptoms, on outcomes in IBD. Riggott *et al.* showed the combination of common mental disorder symptoms and gastrointestinal symptoms increased the risk of flare or glucocorticosteroid prescription (HR = 2.13; 95% CI 1.46-3.10), escalation of medical therapy (HR = 1.92; 95% CI 1.34-2.76), and healthcare utilisation, including clinic appointments (P<0.001), contact with an IBD helpline (P=0.001), and radiological and endoscopic investigations (P<0.001 for both), when compared with those reporting below average gastrointestinal and psychological symptoms,[271] IBS-type symptoms in those with no biochemical evidence of disease activity, have increased healthcare utilisation with more investigations (P=0.008) which is comparable to those with evidence of occult inflammation or active disease.[197] The psychological impact of IBS-type symptoms in IBD, without evidence of active inflammation requiring intervention, is as detrimental to psychological health as severely active disease. Studies show, the perception of gastrointestinal symptoms resulted in comparable levels of anxiety, depression, somatisation, catastrophic thinking patterns, behaviour avoidance, and poor quality of life scores.[197, 272]

The gut-brain axis has a continuous, bidirectional, and influential role over both psychological and physical manifestations of disease. As the clinical consequences of common mental disorders remain uncertain, with varying results and lack of longitudinal data, anxiety and depression are rarely screened for, or addressed, in practice. Further research on their influence on prognosis, with longer duration of follow-up, will help us better understand which cohort of patients are more likely to benefit from targeted psychological intervention.

1.3.3.1 Natural history of common mental disorders in IBD

The fluctuating course of chronic disease can exacerbate common mental disorders through physiological changes in the gut-brain axis, as well as health behaviours in the way patients seek medical intervention and manage daily tasks, from self-care through to exercise and diet. Several studies show rates of anxiety and depression symptoms are higher during periods of flare, with evidence of disease activity increasing the reported symptoms of anxiety (57.6% vs. 38.1% with inactive disease) and depression (38.9% vs. 24.2% with inactive disease), but these are limited to data collected at a single time point.[4, 60, 184]

Few studies have examined the effect of fluctuating symptoms of common mental disorders over time. Marrie *et al.* observed the effect of anxiety and depression in 247 patients over a 3-year period with annual assessment of mood and disease activity. They found those patients with larger fluctuations in depressive symptoms were twice as likely to have active disease (OR = 2.45; 95% CI 1.17-5.16), suggesting emotional liability is a risk factor for poor outcomes.[213] A longitudinal study over 12 months, but with more frequent points of follow-up every 3 months, found that short-term stress was an individual risk factor for relapse of UC, irrespective of disease activity at baseline.[273] A smaller prospective study suggested that patient perception of long-term stress was also a predictor for risk of future exacerbation of UC (HR = 2.8; 95% CI 1.1-7.2).[274] A recent large cohort study, of over 22,000 patients, observed high levels of anxiety and depression 5 years before a diagnosis of IBD, with increased hospital contact for symptoms of common mental disorders and prescription of antidepressants persisting for at least 10 years after diagnosis, and with the highest risk in the first year after diagnosis (HR = 3.2; 95% CI 2.4-4.1).[275] A four year, longitudinal follow-up study of psychosomatic and psychiatric profiles in patients with IBD suggested that the presence of psychiatric co-morbidity is likely to persist or increase with time, with the development of anxiety and depression most common.[276]

Determining those individuals most at risk of persistent common mental disorders is important in order to understand who will benefit from targeted intervention. As an example of a major life event, the Covid-19 pandemic highlighted the impact of poor resilience in the general population. A study of over 35,000 college students showed increased risk of common mental disorder symptoms during periods of isolation, with five separate trajectories of anxiety and depression observed. Those with poor social or family support, negative mindset, and poor coping mechanisms, displayed characteristics of delayed or chronic mental health dysfunction.[277] The GRITT method, as described earlier, has been used to target those patients with IBD with low resilience, demonstrating

that resilience is a modifiable trait and it is possible to improve clinical outcomes through supportive measures.[188] Strategies such as resilience training, which target complex psychological behaviours, and encompass a more holistic approach, are favoured when combating physical symptoms. Yet, with resources stretched we need to better characterise patients with IBD to target direct intervention towards those who are likely to benefit. Further studies are required to assess how symptoms of common mental disorders fluctuate over time, and better determine which cohorts are at risk of persistent, psychological co-morbidity.

1.3.3.2 Cumulative impact of common mental disorders in IBD.

As discussed above, the characteristics and mechanisms behind common mental disorders overlap, and it is therefore not uncommon for patients to present with more than one psychological co-morbidity. A systematic review and meta-analysis of 171 studies showed significant co-morbidity between low mood and anxiety disorders, which is bidirectional in nature. Individuals reporting symptoms of one common mental disorder were six times more likely to acquire a second, when compared with those without any history of psychiatric co-morbidity.[278] The overlap of multiple common mental disorders triggers both an acute and chronic inflammatory response and, therefore, may exaggerate any underlying inflammatory condition.[223] Individuals with co-morbid anxiety and depression have been found to accumulate chronic health conditions at a more rapid rate across both sexes.[279] When we look at other long-term chronic health conditions, such as cardiovascular disease, those with symptoms of depression are observed to have an increasing number of additional co-morbid health conditions. A retrospective study, reviewed 1,274,118 admissions over a 10-year period, with an increased number of major adverse cardiac and cerebrovascular events seen in young hospitalised adults with co-morbid depression.[280] Reduced heart rate variability is a predictor of significant cardiac events and cardiac mortality. A case-control study found that those with MDD, despite no other physical health conditions, had reduced heart rate variability, and those with co-morbid MDD and GAD showed the greatest reductions when compared with those with no psychological co-morbidity.[281] In chronic obstructive pulmonary disease, patients with co-morbid anxiety and depression had an increased number of exacerbations and hospitalisations, higher rates of all-cause mortality, and reported poorer quality of life.[282]

The presence of functional somatic syndromes, such as IBS, is high in IBD, and the likelihood of bodily distress syndrome or somatic syndrome disorder

is also high, especially during periods of flare. These conditions are associated with poor quality of life, and increased rates of anxiety and depression, resulting in an accumulation of psychiatric co-morbidities.[283] In IBD the presence of IBS-type symptoms alone, without evidence of active inflammation, is strongly associated with higher anxiety (weighted mean difference WMD 2.5; 95%CI 0.8-4.3) and depression scores (standard mean difference SMD 0.64; 95%CI 0.44-0.84).[50, 284] Although IBS-type symptoms and somatoform symptom-reporting are associated with co-morbid anxiety and depression, symptom-reporting alone was not found to affect disease activity outcomes in IBD over a 2-year period.[197] It may be that these studies are limited by the duration of follow-up. Backwell *et al.* in a retrospective study of over 15,000 IBD cases, reviewed exposure to depression up to 5.5 years prior to a diagnosis of IBD and found that only depression, with gastrointestinal symptom-reporting was associated with future development of IBD (risk of developing CD: OR = 1.41; 95% CI 1.04-1.92, risk of UC: OR = 1.47; 95% CI 1.21-1.79), rather than depression alone.[62]

IBD has a similar natural history to many chronic inflammatory-driven conditions described above, with periods of remission and exacerbation during which the risk of co-morbid common mental disorders increases. The increasing inflammatory drive and complexity of multiple psychological and physical symptoms makes targeting therapy more challenging. The true effect of multiple psychological co-morbidities on prognosis remained understudied, and therefore this potentially high-risk group of patients remain unrecognised in practice as requiring additional biopsychosocial support.

1.4 Summary of introduction

In summary, the underlying aetiology of IBD is complex and multifactorial. One facet of this includes the influence of psychological co-morbidity, of which anxiety and depression are also complex in their underlying pathogenesis. These fluctuating conditions progress through periods of relapse and remission, often mimicking similar paths, further pushing the hypothesis of the influence of the gut-brain axis in IBD. During these periods of flare and resolution, there are shifts in inflammatory, microbial, neural, and hormonal pathways, as outlined earlier. These pathways are interlinked and appear to be bidirectional in nature, thus feeding the theory that symptoms of anxiety and depression may drive disease activity, and conversely that active disease can augment features of anxiety and depression.

The investigation of IBD incorporates both physical assessment through biochemical markers, and endoscopic and histological examination, alongside clinical markers and subjective interpretation of disease activity by the individual. There is an increasing drive for both objective and subjective markers of disease remission to be recognised, and met, in the outcomes of RCTs of new treatments. The pharmacological market in IBD has expanded extensively in the last decade with an increasing number of advanced therapies available, yet the psychological aspect of patient care is lagging behind this medical approach and leaves those cycling through failed treatment regimens increasingly vulnerable.

With no one pathway singularly involved, the complex relationship between the gut and the brain, through the gut-brain axis, warrants further investigation as a potential target for treatment. Current research has limitations due to unselected cohorts, and lack of longitudinal follow-up. Identifying those characteristics which increase the risk of common mental disorders in patients with IBD, and thus may increase risk of adverse IBD-related disease outcomes, would potentially improve future study design and yield more significant results. This thesis will aim to better understand the link between brain to gut, and gut to brain, interactions, and the impact of common mental disorders on adverse outcomes in IBD. These studies will support the increasing need for an individualised biopsychosocial approach to IBD management.

Chapter 2

Aims and Objectives

The aims of this thesis are to evaluate and better understand the link between common mental disorders and disease activity in those with IBD, to investigate bidirectional effects, and to better characterise those patients more likely to experience adverse disease outcomes or require increased healthcare, in order to improve patient selection in future studies.

These objectives are addressed through the following sections of work:

2.1 Summarising the bidirectional gut-brain axis effects and their influence on mood and prognosis in IBD.

The prevalence of common mental disorders in IBD is high, yet the impact of psychological co-morbidity over time is poorly recognised and therefore not effectively managed in practice. Studies examining brain-to-gut influences have suggested an association between common mental disorders and poor prognosis in IBD.[56, 58, 59, 60, 213] Separate studies investigating the link between active disease and future development of anxiety and depression have also suggested a gut-to-brain relationship.[56, 259] However, results from these studies often do not reach statistical significance due to limited periods of follow-up, and small numbers of participants, leading to small event numbers. The aims of the systematic review and meta-analysis described in Chapter 3 were to collate the evidence to date that there are both brain-gut and gut-brain effects in patients with confirmed IBD. This chapter selected those studies with validated measures of symptoms of anxiety and depression and assessed the longitudinal effect on prognosis of IBD according to several objective markers of disease activity. Conversely, those studies with confirmed disease activity in patients with no reported underlying symptoms of common mental disorders were evaluated for adverse psychological outcomes at follow-up.

2.2 Assessing the longitudinal effect of an increased burden of psychological co-morbidity on the prognosis of IBD.

The symptoms of anxiety, depression and somatoform behaviour often overlap, with the burden of one common mental disorder a risk factor for additional psychological co-morbidity. Recent studies have suggested that somatoform symptom-reporting, alongside pre-existing common mental disorders, is an additional risk factor of the future development of IBD.[62] Multiple psychological co-morbidities can make management more complex, and potentially drive the inflammatory burden in susceptible individuals. There is

increasing evidence that common mental disorders have negative long-term effects on the prognosis of IBD, yet any cumulative effect of these remains unstudied. Most research in this area is suboptimal, through the inclusion of unselected cohorts and limited duration of follow-up. Chapter 4 further aims to explore the effect of increasing burden of common mental disorders on outcomes in IBD. This longitudinal follow-up study selects individuals in biochemical remission and examines the effect of increasing psychological co-morbidity on both subjective and objective endpoints of IBD activity.

2.3 Assessing the relative contribution of disease activity and psychological health on the prognosis of IBD over 6.5 years of longitudinal follow-up.

The prevalence of common mental disorders is high in those with chronic disease, with evidence that depression and stress can lead to adverse events, and increased morbidity and mortality.[210, 256] In a study of over 900 patients with stable cardiovascular disease, provocation of mental stress-induced myocardial ischaemia, or conventional myocardial ischaemia through exercise or pharmacological means, demonstrated that those with mental stress-induced myocardial ischaemia where significantly more likely to have an adverse event, including death, non-fatal myocardial infarction, or hospitalisation for heart failure in the subsequent 5 years, compared with those without mental stress-induced ischaemia. The cumulative impact of conventional-induced and mental stress-induced ischaemia resulted in an almost four-fold increased risk of myocardial infarction or cardiovascular death.[285] Symptoms of anxiety and depression also peak during periods of disease activity in IBD. Although the presence of symptoms of common mental disorders appears to lead to a greater number of adverse outcomes in IBD, it is difficult to determine to what degree this is influenced by pre-existing inflammatory activity, or underlying psychological co-morbidity. The aim of Chapter 5 is to characterise individuals based on clinical activity, biochemical activity and the presence or absence of symptoms of a common mental disorder at baseline, in order to better understand the influences of each risk factor on the natural history of IBD over 6 years of longitudinal follow-up.

2.4 Assessing the characteristics and effects of anxiety and depression trajectories in IBD.

As with IBD, the underlying pathophysiology of common mental disorders is multifactorial, often involving genetic susceptibility combined with physical and environmental triggers which cause fluctuations in symptoms overtime. It is the persistence of these symptoms that helps define an underlying diagnosis of a common mental disorder.[237] As explored in Chapters 4 and 5, there may be a link between IBD activity and the reporting of symptoms of anxiety and depression, leading to poor quality of life, increased healthcare utilisation, and adverse disease outcomes. Targeting those individuals with poor mental health, to offer support and build resilience, could benefit both physical health, and reduce healthcare utilisation.[188, 189]

Many studies examining this issue rely on simple symptom-reporting, often at a single time point, as conducting structured interviews is not feasible in a large cohort of patients. Thus, a true diagnosis of common mental disorder becomes difficult to confirm without understanding the trajectory of each individual's symptom burden. There is a need to better understand and evaluate the trajectories of symptoms of common mental disorders in IBD. In Chapter 6 we aim to examine how symptoms of anxiety and depression fluctuate over time in individuals with IBD, identifying those patients with persistently poor or worsening scores, the impact of common mental disorder trajectories on clinical outcomes, and thus identify those individuals that could benefit from targeted intervention.

Chapter 3

A systematic review and meta-analysis of studies examining the brain-to-gut and gut-to-brain effects in IBD.

3.1 Introduction

The complex interactions of the neuroendocrine pathways, the HPAA, along with the CNS, ANS and ENS are described through the gut-brain axis. With common immune-inflammatory markers found in both depression and IBD,[286] symptoms of common mental disorders and gastrointestinal inflammation are interlinked, and have the potential to drive each other.

In a systematic review and meta-analysis, symptoms of common mental disorders were almost twice as prevalent in patients with IBD compared with the general population, and affected over half of patients during periods of disease activity,[4] suggesting gut-to-brain effects. Other studies have demonstrated that individuals with gastrointestinal symptoms and coexistent depression are more likely to develop IBD in the future.[62, 187] This suggests that common mental disorders may play an independent role in the aetiology of IBD, via brain-to-gut interactions. Despite this, studies examining these issues in patients with IBD are often relatively small or have reported conflicting results. A prior systematic review identified only four articles describing brain-to-gut effects that were suitable for meta-analysis.[287] They reported that although there was a trend towards depression influencing the course of CD, the results were not significant. In a systematic review examining gut-to-brain effects there was a statistically significant association between aggressive disease and subsequent development of depression in patients with IBD,[288] but only in a single study.[259] However, to date, there has been no definitive systematic assessment of gut-to-brain and brain-to-gut effects in patients with IBD.

To examine this issue, a contemporaneous systematic review and meta-analysis of observational studies was conducted. The hypothesis was that such effects, including deleterious effects of psychological co-morbidity at baseline on risk of future adverse outcomes related to IBD activity, and deleterious effects of IBD activity on future psychological health, would be apparent from the synthesis of all available data. This would support potential benefits from addressing both gastrointestinal inflammation and psychological health in patients with IBD.

3.2 Methods

3.2.1 Search strategy and selection criteria

A literature search of EMBASE Classic, EMBASE, MEDLINE and APA PsycInfo was conducted to search from inception up to July 2021 to identify longitudinal follow-up studies, examining the effect of anxiety or depression at baseline on adverse outcomes related to IBD activity (brain-to-gut) or, conversely, the influence of IBD activity at baseline upon subsequent symptoms of anxiety or depression (gut-to-brain).

Eligibility criteria was defined prospectively (Table 1). For studies examining brain-to-gut effects, a validated measure of anxiety or depression or registered ICD code was required at baseline, with subsequent assessment of adverse outcomes related to IBD activity during longitudinal follow-up. These included a flare of disease activity (via self-report, physician's global assessment, use of a validated disease activity index, or review of medical records) or glucorticosteroid prescription, escalation of therapy due to uncontrolled IBD activity, hospitalisation due to IBD activity, emergency department attendance due to IBD activity, IBD-related surgery, or a composite outcome of any of these combined. For studies examining gut-to-brain effects, an assessment of IBD activity was required at baseline, via a validated disease activity index, with subsequent assessment of symptoms of a common mental disorder, via a validated measure of anxiety or depression or registered ICD code during longitudinal follow-up. Only studies with ≥50 participants with radiologically, endoscopically, or histologically confirmed IBD, recruited from an unselected adult population of patients (i.e. studies recruiting only patients with a recent flare of disease activity or hospitalisation, or limiting recruitment by disease location, behaviour, or severity were excluded), with at least 90% aged ≥16 years, were included. Studies had to consist of a minimum of two points of follow-up, separated by ≥6 months.

Table 1: Eligibility Criteria

Eligibility Criteria
• Radiologically, endoscopically or histologically confirmed IBD. • At least 90% of participants aged ≥16 years. • Unselected adult population with ≥50 participants. • Longitudinal follow-up studies with at least 2 established time points separated by ≥6 months.

- Assessment for the presence or absence of symptoms of anxiety or depression* at baseline with the recording of the development of an adverse clinical outcome† during longitudinal follow-up in brain-to-gut studies.
- Assessment for the presence or absence of disease activity‡ at baseline with the recording of the development of symptoms of anxiety or depression* during longitudinal follow-up in gut-to-brain studies.

*Via a validated measure of anxiety or depression or registered ICD code.

†Flare of disease activity (via self-report, physicians global assessment, use of a validated disease activity index, or review of medical records) or glucocorticosteroid prescription, escalation of medical therapy for uncontrolled IBD activity, emergency department attendance for IBD activity, IBD-related surgery, or a composite outcome of any of these combined.

‡Via a validated disease activity index.

The following search terms were used to identify studies related to IBD, combined with the set operator OR: *inflammatory bowel disease, ulcerative colitis, Crohn$, regional enteritis, ileitis, IBD*. The following terms were used to identify studies related to common mental disorders, again combined with the set operator OR: *anxiety, depression, mood, mental health, soma$, psych$, gut AND brain*. These two searches were combined using the set operator AND. There were no language restrictions; we translated foreign language articles. Two investigators reviewed titles and abstracts independently and retrieved those felt to be relevant for further eligibility assessment. In addition, a recursive search for other potentially eligible studies among the bibliographies of selected articles was performed. Any disagreements between investigators were resolved by discussion.

3.2.2 Data extraction

Two investigators independently undertook data extraction onto a Microsoft Excel Spreadsheet (XP professional edition; Microsoft, Redmond, WA), with all disagreements resolved by discussion. For each eligible study the following data was collected: country, duration of longitudinal follow-up, number of participants with complete data, number of included participants with CD or UC, criteria used to define presence of a common mental disorder at baseline, criteria used to measure IBD activity at baseline, and whether the study examined

brain-to-gut effects, gut-to-brain effects, or both. For each of the events of interest, the adjusted HR or adjusted RR, with 95% CI, were extracted where possible. If unavailable, raw data was extracted according to presence or absence of symptoms of anxiety or depression at baseline and subsequent adverse outcomes related to IBD activity for brain-to-gut studies, or according to presence or absence of active IBD at baseline and subsequent symptoms of anxiety or depression for gut-to-brain studies. For studies where the adjusted HR, adjusted RR, or raw data were not reported, we used the unadjusted HR or unadjusted RR, depending on study reporting, with 95% CI. For studies that reported OR, authors were contacted for raw data to calculate unadjusted RRs and 95% CIs for pooled analyses, because if the prevalence of events of interest is greater than 10% the OR will no longer approximate the RR.[289] The quality of included studies was judged according to the Newcastle-Ottawa scale, with a total possible score of 9.[290] Higher scores indicated higher quality studies.

3.2.3 Data synthesis and statistical analysis

The degree of agreement between the two investigators for judging of study eligibility was measured using a kappa statistic. Heterogeneity between studies was assessed using the I^2 statistic with values of 0% to 24%, 25% to 49%, 50% to 74%, and ≥75% typically considered no, low, moderate, and high levels of heterogeneity, respectively, and the χ^2 test with a P value <0.10, as the threshold used to define statistically significant heterogeneity.[291] In line with published recommendations, Egger's test would be applied to funnel plots to assess for evidence of publication bias,[292] or other small study effects, where ≥10 studies were present, in line with published recommendations.[293] Data was pooled using the inverse variance method and a random effects model to provide a conservative estimate of the effect of symptoms of anxiety or depression at baseline on subsequent adverse outcomes related to IBD activity or the effect of IBD activity at baseline on subsequent symptoms of anxiety or depression.[294] The HR was assumed to be equivalent to the RR, so these were pooled together across studies to produce an overall RR with a 95% CI. This is an assumption that has been used by other groups previously in prior meta-analyses,[295, 296] this was tested by pooling HRs and RRs separately for the outcome with the largest number of contributing studies, and the pooled ratios were indeed similar. Stats Direct version 3.2.10 (StatsDirect Ltd, Sale, Cheshire, England) was used to generate Forest plots of pooled RRs with 95% CIs.

3.3 Results

3.3.1 Search Outcomes

The literature search identified 17,928 citations, of which 124 were obtained for further review. Following retrieval and review, seven articles fulfilled eligibility criteria and had data suitable for extraction (Figure 3).[57, 58, 259, 273, 274, 297, 298] The authors of a further eight articles were contacted for raw data.[56, 59, 60, 213, 299, 300, 301, 302] For two of these, the data were either unavailable or we received no response, so they were excluded.[300, 302] There was substantial agreement between reviewers for study eligibility (Kappa statistic = 0.86). The 13 eligible articles reported on 12 separate study populations,[56, 57, 58, 59, 60, 213, 259, 273, 274, 297, 298, 299, 301] containing 9192 patients. Ten articles examined brain-to-gut effects only,[57, 58, 59, 60, 213, 273, 274, 297, 298, 299] one gut-to-brain effects only,[259] and two articles both.[56, 301] Therefore, in total there were 12 articles examining brain-to-gut effects (Table 2), and three articles examining gut-to-brain effects (Table 3). One of the brain-to-gut articles was a duplicate publication of an earlier study.[57] However, the initial study only reported a composite endpoint of flare of disease activity, escalation of therapy due to uncontrolled IBD activity, or IBD-related surgery,[59] whereas the subsequent study reported these endpoints separately.[57] Study quality is provided in Table 4 and Table 5; five studies scored 7 or more on the Newcastle-Ottawa scale.[56, 259, 273, 274, 297]

Figure 3: Flow Diagram of Assessment of Studies Identified in the Systematic Review.

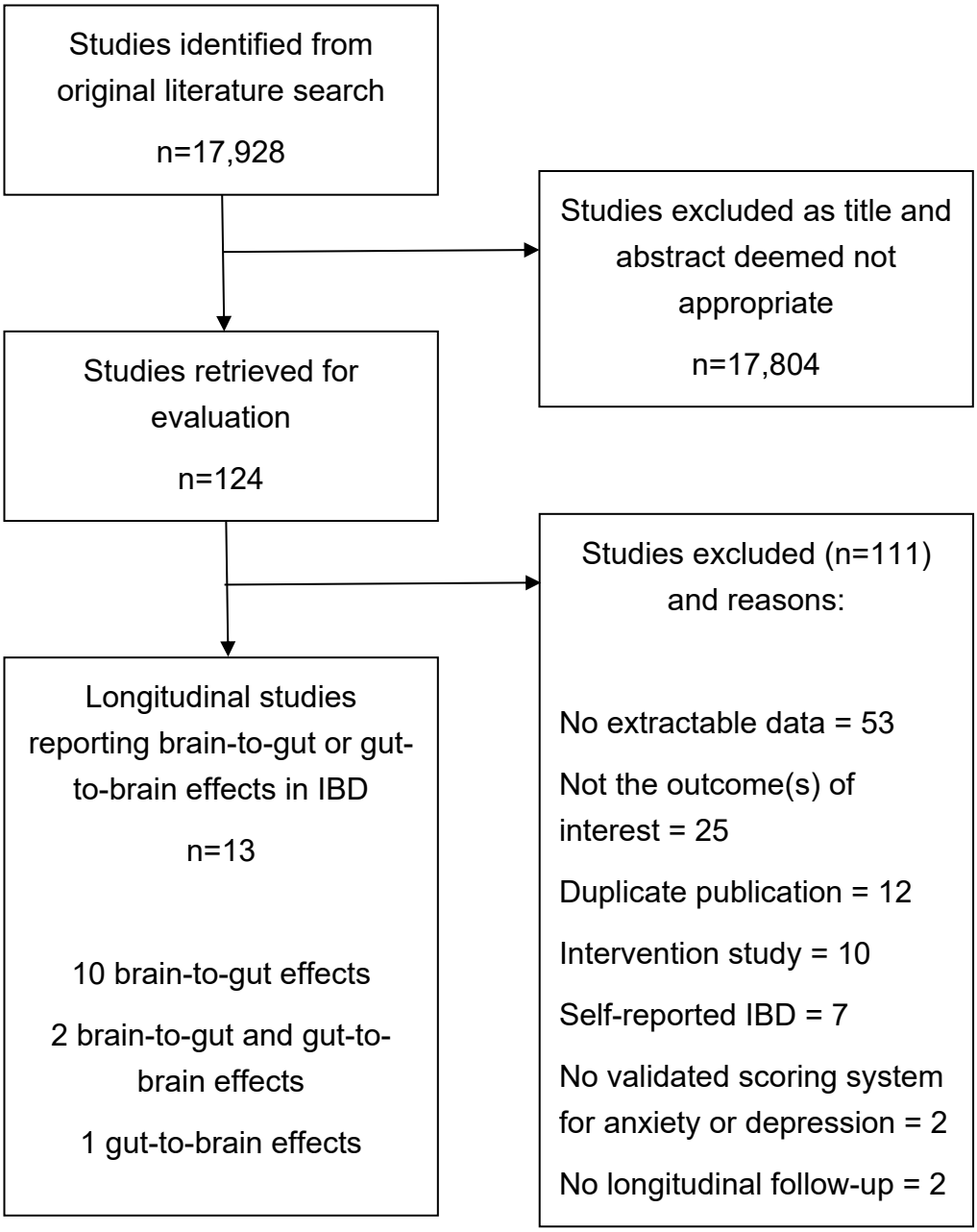


Table 2: Characteristics of Studies Examining Brain-to-Gut Effects in Inflammatory Bowel Disease

Study and year	Country and setting	Number of patients (CD, UC)	Number of subjects in remission at baseline (%)	Duration of follow-up (years)	Criteria used to define presence of symptoms of anxiety at baseline	Criteria used to define presence of symptoms of depression at baseline	Adverse outcomes related to IBD activity studied during longitudinal follow-up
Levenstein 2000[274]	Italy, tertiary care	62 (0, 62)	62 (100)	1.45	N/A	CES-D	Composite outcome of flare of disease activity defined by PGA, escalation of therapy due to uncontrolled IBD activity, or evidence of endoscopic disease activity.
Bitton 2008[297]	Canada, secondary and tertiary care	101 (101, 0)	101 (100)	1	SCL-90	SCL-90	Flare of disease activity defined by CDAI >150 and an increase of ≥70 points from baseline.
Mikocka-Walus 2008[301]	Australia, tertiary care	59 (32, 27)	40 (67.8)	1	HADS-A	HADS-D	Flare of disease activity defined by CDAI >150 for CD or SCCAI >2 for UC.

Langhorst 2013[273]	Germany, secondary care	75 (0, 75)	75 (100)	1	N/A	HADS-D	Flare of disease activity defined by CAI >4 and an increase of >3 from baseline, with endoscopic evidence of disease activity at the time of the flare.
Barreiro-De Acosta 2014[299]	Spain, tertiary care	716 (299, 417)	Not reported	1.5	HADS-A	HADS-D	Hospitalisation due to IBD. Emergency department attendance due to IBD.
Sirin 2014[298]	Turkey, tertiary care	381 (126, 255)	Not reported	2	BDAI	BDAI	Emergency department attendance due to IBD.

Mikocka-Walus 2016[59]	Switzerland, secondary and tertiary care	2007 (1122, 885)	Not reported	1	HADS-A	HADS-D	Composite outcome of PGA of flare of disease activity, escalation of therapy due to uncontrolled IBD activity, or IBD-related surgery.
Jordi 2021[57]†		1973 (1137, 836‡)	154 (9.2)	11.6	N/A	HADS-D	Flare of disease activity defined by CDAI ≥150 for CD or MTWAI ≥10 for UC/IC. Escalation of therapy due to uncontrolled IBD activity. IBD-related surgery.
Gracie 2018[56]	UK, tertiary care	423 (250, 173)	423 (100)	2.5	HADS-A	HADS-D	Flare of disease activity defined by glucocorticosteroid prescription or PGA. Escalation of therapy due to uncontrolled IBD activity. Hospitalisation due to IBD IBD-related surgery. Composite of any of the above.

Kochar 2018[58]	USA, tertiary care	4314 (2798, 1516)	2473 (57.3)	1.9	N/A	PHQ-8	Flare of disease activity defined by HBI ≥5 or SCCAI >2. Escalation of therapy due to uncontrolled IBD activity. Hospitalisation due to IBD. IBD-related surgery.
Narula 2019[60]	Canada, tertiary care	414 (227, 188)	65 (15.7)	3.9	HADS-A	HADS-D	Flare of disease activity defined by glucocorticosteroid prescription. Hospitalisation due to IBD. Emergency department attendance due to IBD. Composite of any of the above.
Marrie 2021[213]	Canada, secondary and tertiary care	247 (153, 94)	146 (59.1)	3	HADS-A	HADS-D	Flare of disease activity defined by defined by HBI ≥5 for CD or Powell-Tuck index ≥5 for UC. Escalation of therapy due to uncontrolled IBD activity.

†Dual of Mikocka-Walus 2016[59], but reported data for flare of disease activity, escalation of therapy due to uncontrolled IBD activity, and IBD-related surgery separately, so eligible for these analyses, as Mikocka-Walus 2016 only reported a composite endpoint.

‡Combined ulcerative colitis and inflammatory bowel disease unclassified

BDAI, Beck's depression and anxiety index; CAI, colitis activity index; CES-D, Center for Epidemiological Studies - depression; HADS-A, hospital anxiety and depression scale, anxiety subscale; HADS-D, hospital anxiety and depression scale, depression subscale; HBI, Harvey-Bradshaw index; N/A, not applicable as no data collected; PGA, physician's global assessment; PHQ, patient health questionnaire; SCCAI, simple clinical colitis activity index; SCL-90, symptom checklist-90.

Table 3: Characteristics of Studies Examining Gut-to-Brain Effects in Inflammatory Bowel Disease.

Study and year	Country and setting	Number of patients (CD, UC)	Number of subjects in remission at baseline (%)	Duration of follow-up (years)	Criteria used to define presence of clinically active disease at baseline	Criteria used to define presence of symptoms of anxiety at follow-up	Criteria used to presence of symptoms of depression at follow-up
Mikocka-Walus 2008[301]	Australia, tertiary care	57 (23, 29†)	35 (61.4)	1	CDAI >150 for CD or SCCAI >2 for UC.	HADS-A	HADS-D
Panara 2014[259]	USA, secondary and tertiary care	393 (272, 121)	Not reported	8	PGA assessment of medical records including endoscopy and radiology reports	N/A	ICD-9-CM
Gracie 2018[56]	UK, tertiary care	192 (112, 80)	124 (64.6)	2.6	HBI ≥5 for CD or SCCAI ≥5 for UC.	HADS-A	HADS-D

†Missing data n=5

CDAI, Crohn's disease activity index; HADS-A, hospital anxiety and depression scale, anxiety subscale; HADS-D, hospital anxiety and depression scale, depression subscale; HBI, Harvey-Bradshaw index; ICD-9-CM, International Classification of Diseases, clinical modification codes; PGA, physician's global assessment; SCCAI, simple clinical colitis activity index.

Table 4: Quality of Studies Examining Brain-to-Gut Effects in Inflammatory Bowel Disease.

Study and year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of the cohorts	Assessment of the outcome	Was follow-up long enough for the outcomes to occur	Adequacy of follow-up of the cohorts	Total score
Levenstein 2000[274]	1	1	1	1	1	1	1	1	8
Bitton 2008[297]	1	1	0	1	1	1	1	1	7
Mikocka-Walus 2008[301]	1	1	0	0	0	0	1	1	4
Langhorst 2013[273]	1	1	0	1	2	1	1	1	8
Barreiro-De Acosta 2014[299]	1	1	0	0	0	1	1	0	4
Sirin 2014[298]	1	1	0	0	0	1	1	0	4

Mikocka-Walus 2016[59]	1	1	0	0	1	1	1	1	6
Gracie 2018[56]	1	1	0	1	2	1	1	0	7
Kochar 2018[58]	1	1	0	0	2	1	1	0	6
Narula 2019[60]†	1	1	0	0	0	1	1	0	4
Marrie 2021[213]†	1	1	1	0	0	1	1	1	6
Jordi 2021[57]	1	1	0	0	2	1	1	0	6

†Studies reported multivariate/adjusted analysis in results; however raw data obtained for pooled meta-analysis.

Table 5: Quality of Studies Examining Gut-to-Brain Effects in Inflammatory Bowel Disease.

Study and year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of the cohorts	Assessment of the outcome	Was follow-up long enough for the outcomes to occur	Adequacy of follow-up of the cohorts	Total score
Mikocka-Walus 2008[301]	1	1	0	1	0	0	1	1	5
Panara 2014[259]	1	1	1	1	2	1	1	1	9
Gracie 2018[56]†	1	1	0	1	0	0	1	0	4

†Studies reported multivariate/adjusted analysis in results; however raw data obtained for pooled meta-analysis.

3.3.2 Adverse Outcomes Related to IBD Activity During Longitudinal Follow-up Among Patients with Symptoms of Anxiety at Baseline

Eight brain-to-gut studies reported adverse outcomes related to IBD activity in those with symptoms of anxiety at baseline[56, 59, 60, 213, 297, 298, 299, 301] (Table 6). The minimum duration of follow-up was 1 year, and the maximum 3.9 years. Only two studies restricted recruitment to patients in clinical remission, defined in one study by a CDAI <150 for at least 1 month prior to study inclusion,[297] or a SCCAI for UC and a HBI for CD of <5.[56] When data were pooled from five studies,[56, 60, 213, 297, 301] containing 1244 patients, the risk of developing a flare of disease activity was no higher among those with symptoms of anxiety at baseline (RR = 1.20; 95% CI 0.93-1.55), with moderate heterogeneity between studies (I^2=53.7%). When the analysis was restricted to include only the two studies that recruited patients in clinical remission,[56, 297] the risk of flare among those with symptoms of anxiety at baseline was significantly higher (RR = 1.80; 95% CI 1.24-2.61). Escalation of IBD therapy was more likely among those with symptoms of anxiety at baseline (RR = 1.68; 95% CI 1.18-2.40) in two studies,[56, 213] containing 670 patients. Three studies,[56, 60, 299] recruiting 1553 patients, reported risk of hospitalisation according to presence or absence of symptoms of anxiety at baseline, which again was significantly higher in those with symptoms of anxiety (RR = 1.72; 95% CI 1.01-2.95), but with high heterogeneity between studies (I^2=73.4%) (Figure 4). Emergency department attendance was also significantly more likely in those with symptoms of anxiety at baseline (RR = 1.30; 95% CI 1.21-1.39) in three studies,[60, 298, 299] recruiting 1511 patients, with no heterogeneity (I^2=1.0%) (Figure 5). Only one study reported that IBD-related surgery was no more likely in those with symptoms of anxiety at baseline (RR = 1.62; 95% CI 0.50-5.25).[56] Finally, among three studies that recruited 2844 patients,[56, 59, 60] and which reported a composite endpoint of one or more of these adverse outcomes, risk was significantly higher among those with symptoms of anxiety at baseline (RR = 1.21; 95% CI 1.08-1.36), with low heterogeneity (I^2=19.8%) (Figure 6).

Table 6: Adverse Outcomes Related to Inflammatory Bowel Disease Activity During Longitudinal Follow-up Among Patients with Symptoms of Anxiety or Depression at Baseline.

	Number of studies	Total number of patients	Pooled RR (95% CI)	I^2 (%)	P value for χ^2
Adverse outcomes related to IBD activity among patients with symptoms of anxiety at baseline					
Flare of IBD activity	5	1244	1.20 (0.93-1.55)	53.7	0.071
Escalation of therapy due to uncontrolled IBD activity	2	670	1.68 (1.18-2.40)	0.0	0.513
Hospitalisation due to IBD	3	1553	1.72 (1.01-2.95)	73.4	0.023
Emergency department attendance due to IBD	3	1511	1.30 (1.21-1.39)	1.0	0.364
IBD-related surgery	1	423	1.62 (0.50-5.25)	N/A	N/A
Composite endpoint combining any of the above	3	2844	1.21 (1.08-1.36)	19.8	0.291
Adverse outcomes related to IBD activity among patients with symptoms of depression at baseline					
Flare of IBD activity	8	7606	1.60 (1.21-2.12)	73.5	<0.001
Escalation of therapy due to uncontrolled IBD activity	4	6957	1.41 (1.08-1.84)	43.1	0.135
Hospitalisation due to IBD	3	5151	1.35 (1.17-1.57)	40.7	0.168

Emergency department attendance due to IBD	3	1511	1.38 (1.22-1.56)	0.0	0.985
IBD-related surgery	3	6710	1.63 (1.19-2.22)	57.4	0.070
Composite endpoint combining any of the above	4	2906	1.26 (1.07-1.48)	19.8	0.289

CI, confidence interval; RR, relative risk; N/A, not applicable – too few studies

Figure 4: Forest Plot for Risk of Hospitalisation Due to IBD Among Patients with Symptoms of Anxiety at Baseline.

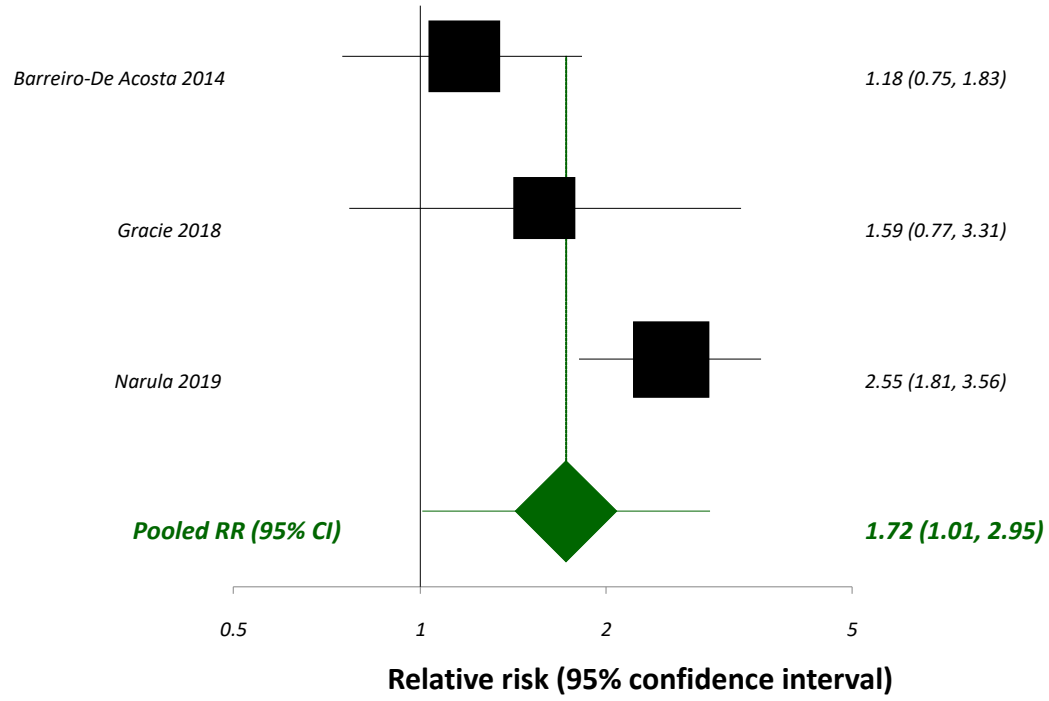


Figure 5: Forest Plot for Risk of Emergency Department Attendance Due to IBD Among Patients with Symptoms of Anxiety at Baseline.

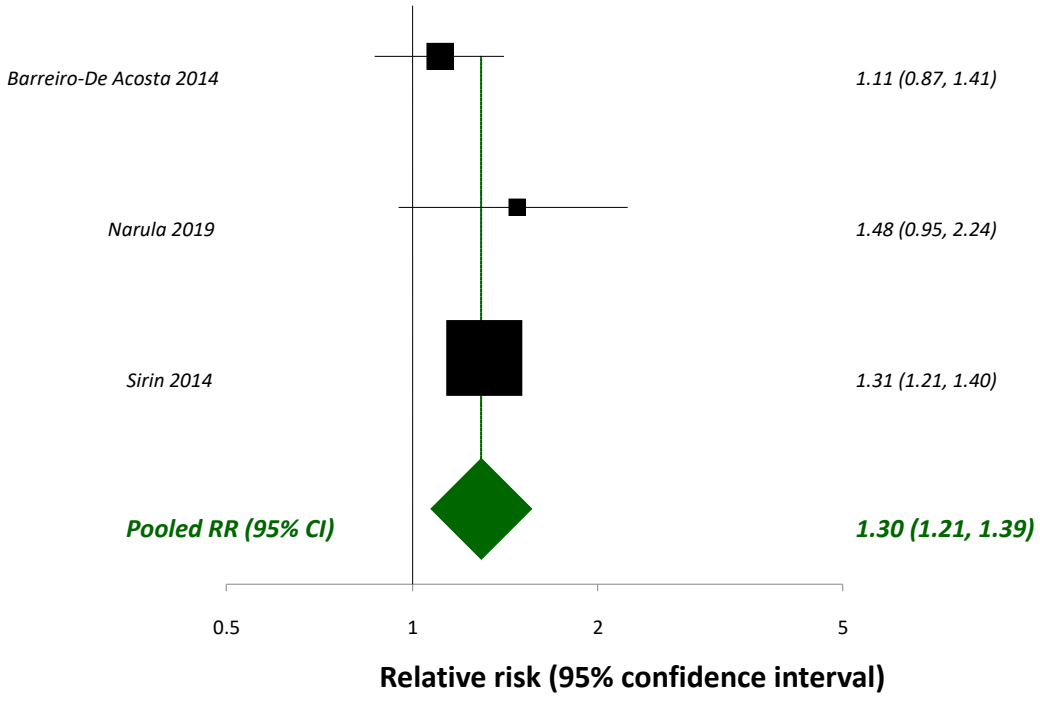
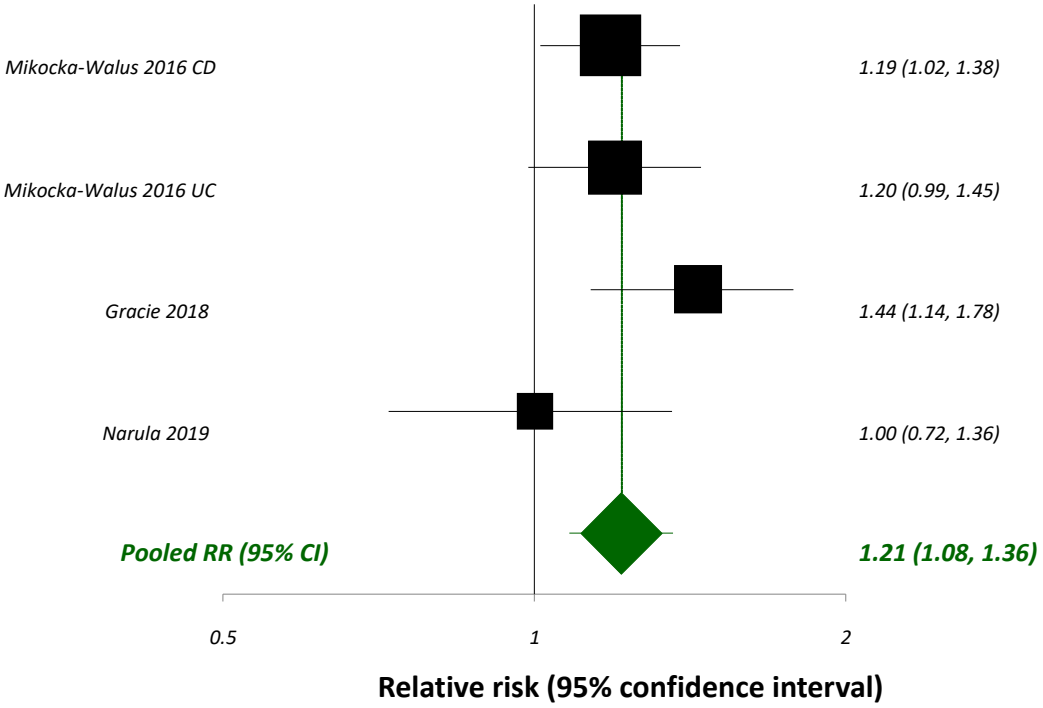


Figure 6: Forest Plot for Risk of Any of the Endpoints of Interest Among Patients with Symptoms of Anxiety at Baseline.



3.3.3 Adverse Outcomes Related to IBD Activity During Longitudinal Follow-up Among Patients with Symptoms of Depression at Baseline

All 12 brain-to-gut studies provided data for adverse outcomes related to IBD activity in patients with symptoms of depression at baseline[56, 57, 58, 59, 60, 213, 273, 274, 297, 298, 299, 301] (Table 6). Of these, four recruited only patients with evidence of remission at baseline, according to a CDAI <150,[297] a clinical colitis activity index ≤4,[273] stable disease with no use of glucocorticosteroids for 2 months prior to recruitment and in clinical remission according to a non-validated questionnaire,[274] or a SCCAI for UC and a HBI for CD of <5.[56] The minimum duration of follow-up was 1 year, and the maximum 11.6 years. When data were pooled from eight studies,[56, 57, 58, 60, 213, 273, 297, 301] which included 7606 patients, symptoms of depression at baseline were associated with a significantly increased risk of flare of disease activity during longitudinal follow-up (RR = 1.60; 95% CI 1.21-2.12), with high heterogeneity between studies (I^2=73.5%) (Figure 7). However, when the analysis was restricted to include only three studies that recruited only patients in clinical remission,[56, 273, 297] there was no longer a significant increase in risk (RR = 1.36; 95% CI 0.88-2.09). Pooling data from four studies,[56, 57, 58, 213] containing 6957 patients, there was an increased risk of escalation of therapy due to uncontrolled IBD activity in those reporting symptoms of depression at baseline (RR = 1.41; 95% CI 1.08-1.84) (Figure 8), with low heterogeneity (I^2=43.1%). Patients with symptoms of depression at baseline were also more likely to require hospitalisation due to IBD when data were pooled from three studies,[56, 58, 60] recruiting 5151 patients (RR = 1.35; 95% CI 1.17-1.57) (Figure 9), with moderate heterogeneity between studies (I^2=40.7%). Similarly, emergency department attendance was significantly more likely in those with symptoms of depression at baseline in three studies,[60, 298, 299] recruiting 1511 patients (RR = 1.38; 95% CI 1.22-1.56) (Figure 10), with no heterogeneity (I^2=0%). When data were pooled from three studies,[56, 57, 58] containing 6710 patients, IBD-related surgery was also significantly more likely among those with symptoms of depression at baseline (RR = 1.63; 95% CI 1.19-2.22) (Figure 11), with moderate heterogeneity between studies (I^2=57.4%). Finally, four studies reported a composite endpoint of one or more of the above,[56, 59, 60, 274] recruiting 2906 patients. In those with symptoms of depression at baseline there was a significantly increased risk of one or more adverse outcomes, compared with those without (RR = 1.26; 95% CI 1.07-1.48; I^2=19.8%) (Figure 12).

Figure 7: Forest Plot for Risk of Flare of IBD Activity Among Patients with Symptoms of Depression at Baseline.

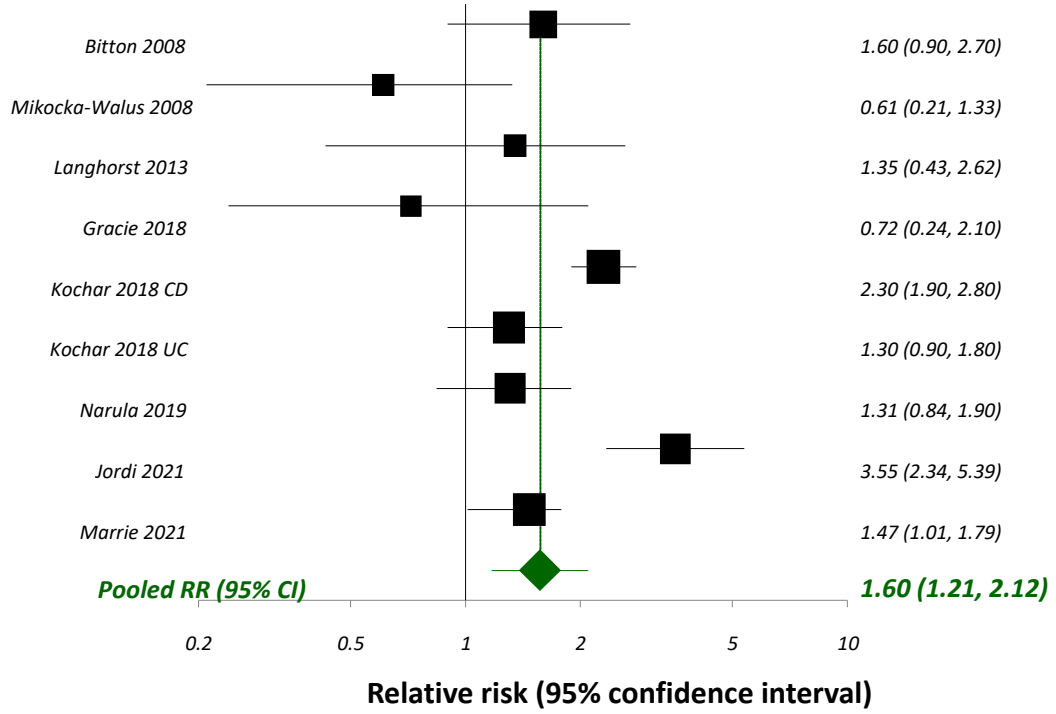


Figure 8: Forest Plot for Risk of Escalation of Therapy Due to Uncontrolled IBD Activity Among Patients with Symptoms of Depression at Baseline.

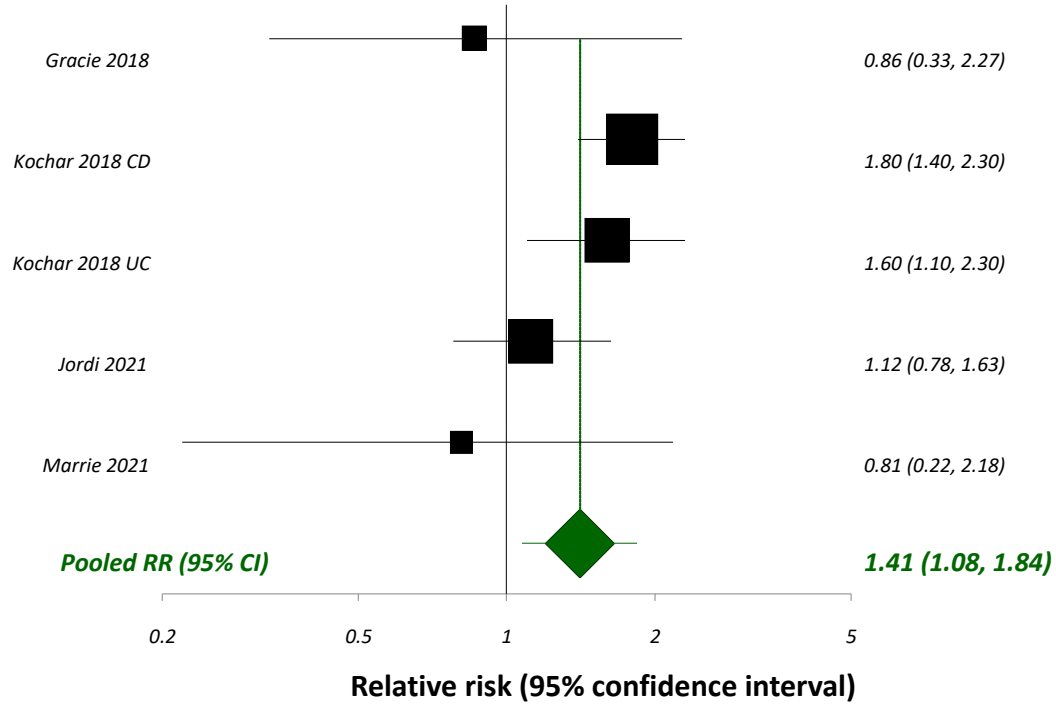


Figure 9: Forest Plot for Risk of Hospitalisation Due to IBD Among Patients with Symptoms of Depression at Baseline.

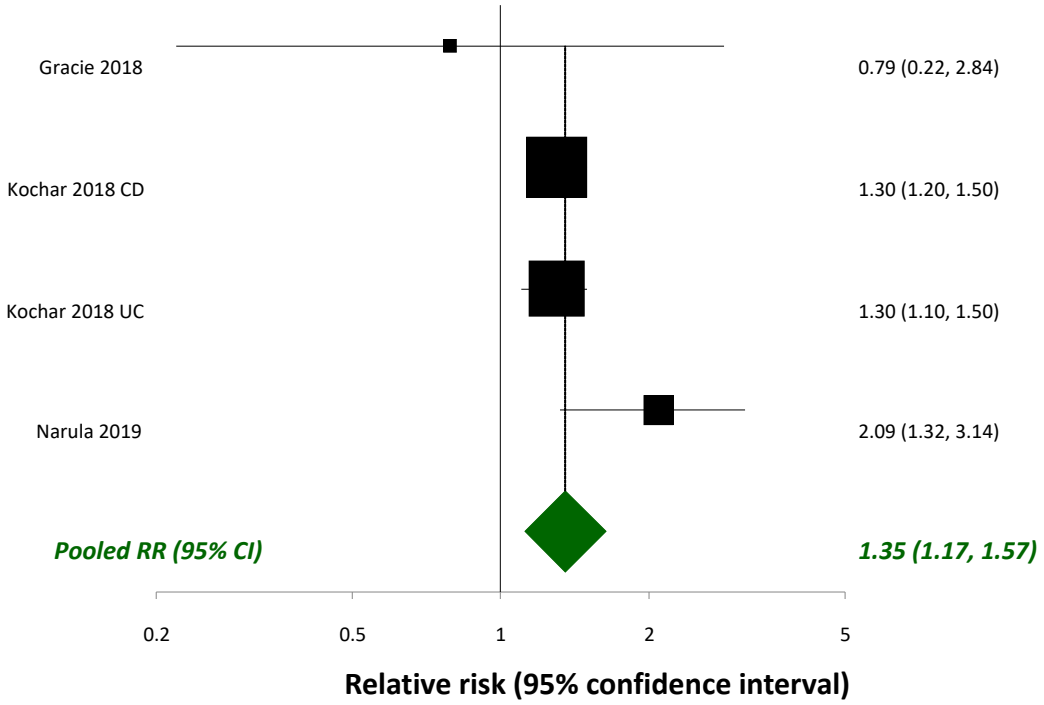


Figure 10: Forest Plot for Risk of Emergency Department Attendance Due to IBD Among Patients with Symptoms of Depression at Baseline.

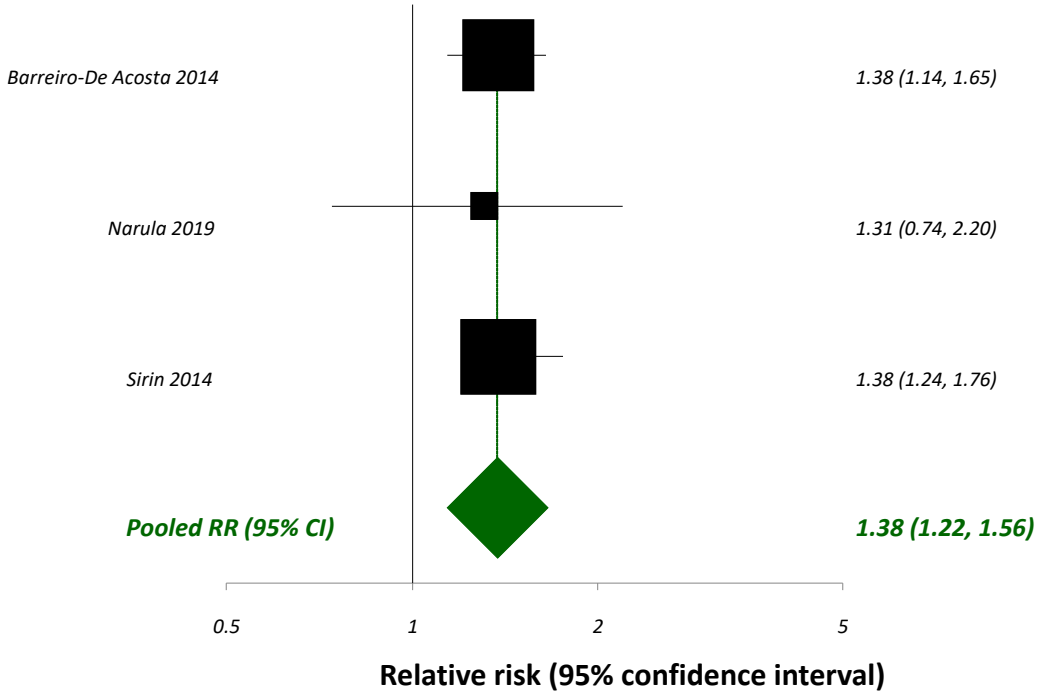


Figure 11: Forest Plot for Risk of IBD-related Surgery Among Patients with Symptoms of Depression at Baseline.

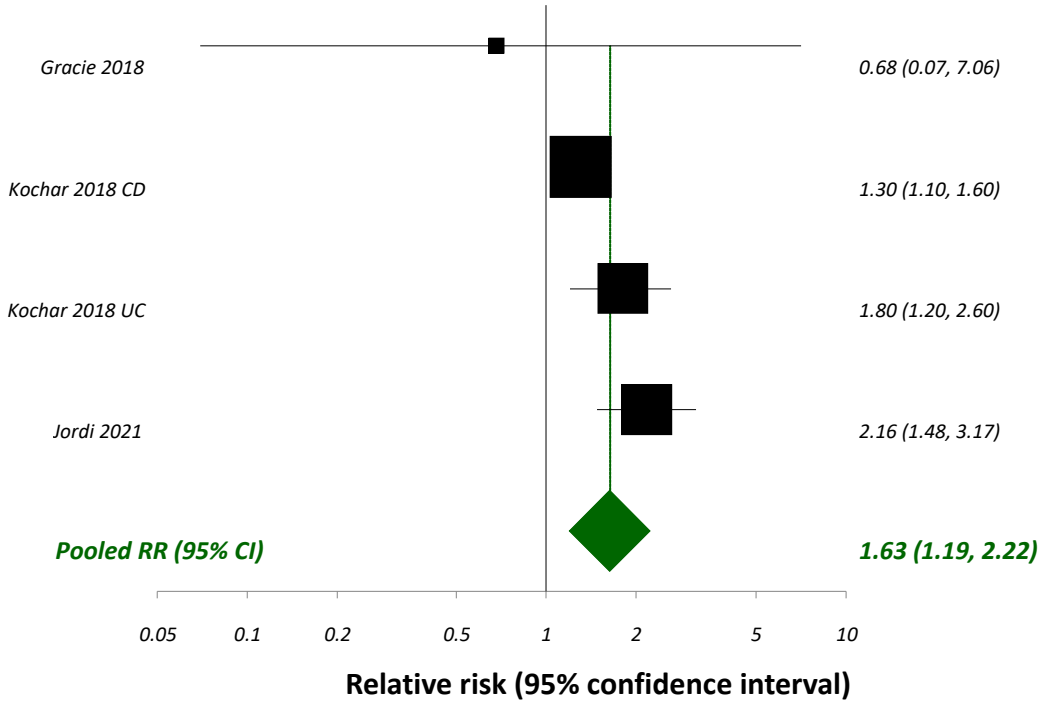
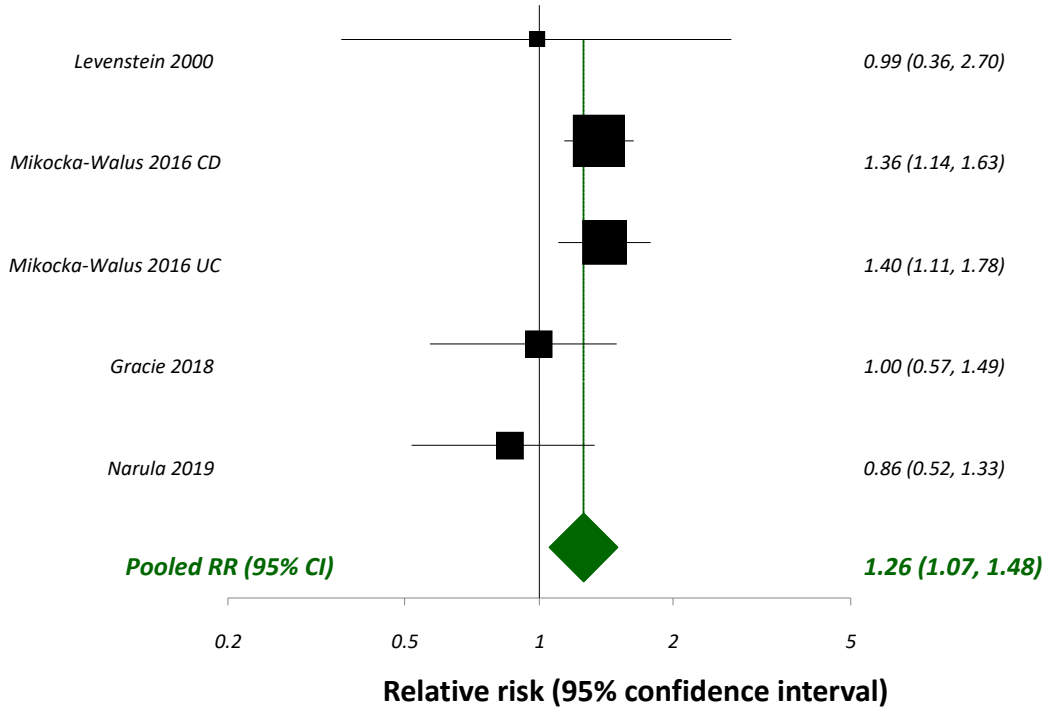


Figure 12: Forest Plot for Risk of Any of the Endpoints of Interest Among Patients with Symptoms of Depression at Baseline.



3.3.4 Development of Symptoms of Anxiety or Depression During Longitudinal Follow-up Among Patients with IBD with Clinically Active Disease at Baseline

Only two gut-to-brain studies, with a minimum duration of follow-up of 1 year and a maximum of 2.6 years, examined effect of active IBD at study entry on subsequent symptoms of anxiety in a total of 249 patients[56, 301] (Table 7). Three gut-to-brain studies, with a minimum duration of follow-up of 1 year and a maximum of 8 years, examined effect of active IBD at baseline on subsequent development of depression in 642 patients.[56, 259, 301] All studies in these analyses only included patients with normal anxiety or normal depression scores at baseline, or no history of psychiatric symptoms or common mental disorder, for each analysis. There was a significant impact of clinically active disease at baseline on the future development of symptoms of anxiety (RR = 2.24; 95% CI 1.25-4.01), with no heterogeneity between studies (I^2=0%).[56, 301] Similarly, the effect of clinically active disease at baseline on future symptoms of depression was also significant (RR = 1.49; 95% CI 1.11-1.98), with no heterogeneity (I^2=0%).[56, 259, 287, 301]

Table 7: Development of Symptoms of Anxiety or Depression During Longitudinal Follow-up Among Patients with Inflammatory Bowel Disease with Clinically Active Disease at Baseline.

	Number of studies	Total number of patients	Pooled RR (95% CI)	I^2 (%)	P value for χ^2
Development of symptoms of anxiety among patients with IBD with clinically active disease at baseline	2	249	2.24 (1.25-4.01)	0.0	0.828
Development of symptoms of depression among patients with IBD with clinically active disease at baseline	3	642	1.49 (1.11-1.98)	0.0	0.964

CI, confidence interval; RR, relative risk.

3.4 Discussion

This systematic review and meta-analysis has demonstrated that patients with symptoms of anxiety at baseline were at significantly increased risk of escalation of therapy due to uncontrolled IBD activity, hospitalisation due to IBD activity, emergency department attendance due to IBD activity, or a composite outcome of any of the adverse outcomes of interest we examined. When we restricted the analysis to studies recruiting patients in clinical remission at baseline, there was also a significant increase in risk of flare of disease activity in patients with symptoms of anxiety at baseline. Patients with symptoms of depression at baseline were at increased risk of all the adverse outcomes of interest, including flare of disease activity and IBD-related surgery. Finally, patients with clinically active disease at baseline, but no evidence of symptoms of anxiety or depression at study entry, were at increased risk of developing new symptoms of anxiety or symptoms of depression during longitudinal follow-up. These findings support the existence of bidirectional brain-gut axis effects in IBD.

An exhaustive search strategy and rigorous inclusion criteria were used to ensure assessment of the temporal association between symptoms of anxiety or depression at baseline and future disease activity, and active disease at baseline and future symptoms of anxiety or depression. Several longitudinal follow-up studies recruiting large numbers of patients with follow-up beyond 3 years in some instances, were included. This enabled pooling data for rarer events such as hospitalisation for active IBD and IBD-related surgery, which have been examined in previous studies, but were likely underpowered for these endpoints. A random effects model was used to pool data in all our analyses so as not to overestimate the impact of either brain-to-gut or gut-to-brain effects. We also contacted original investigators and obtained additional data from six studies,[56, 59, 60, 213, 299, 301] to maximise the number of eligible studies for analysis. We performed subgroup analyses for brain-to-gut studies, where we included only studies recruiting patients in remission at baseline, given that a potential confounding factor on adverse disease outcomes in those with symptoms of anxiety or depression at baseline could be ongoing disease activity. Notably, all three studies that examined gut-to-brain effects only recruited individuals with no symptoms of anxiety or depression at baseline, or no history of psychiatric illness, increasing the likelihood that IBD activity is an independent risk factor for the new development of symptoms of anxiety or depression.

Despite an extensive search, and contact with original investigators, this meta-analysis is limited by a relatively small number of eligible studies, of variable quality, for some of the outcomes of interest. This was particularly the case for

studies examining gut-to-brain effects, and for studies reporting on escalation of therapy and IBD-related surgery in patients with symptoms of anxiety at baseline. Although longitudinal follow-up was up to 11 years in one study, four studies had a follow-up duration of 12 months or less, which is likely too short for some of the endpoints of interest to have occurred. We extracted adjusted HRs or RRs, wherever possible, but also relied on raw data from the studies or unadjusted HRs or RRs in some instances, which do not consider potential confounding. There was significant heterogeneity in some of our analyses, and too few studies to examine reasons for this. This heterogeneity is likely to have affected the accuracy of some of the estimates. We were also unable to examine for publication bias in any of our analyses, again due to the number of studies eligible for each analysis, although this is probable given the small number of studies for some of our outcomes of interest. The eligible studies we identified came from several different countries, in almost all instances these were conducted in North America, Europe, or Australia, and all were conducted in hospital settings. However, our findings cannot be generalised to patients with IBD in other geographical regions or in community settings. In addition, data were not reported for patients with CD or UC separately in sufficient studies for us to examine whether these bidirectional effects are more pronounced according to IBD subtype. Finally, although we excluded cross-sectional studies from this meta-analysis, to be able to examine temporal associations, there were only four brain-to-gut studies that restricted their recruitment to patients who were in clinical remission at baseline. It is, therefore, possible that those with symptoms of anxiety or depression at baseline were also more likely to be suffering from active, or more aggressive, disease at study entry and, as a result, were at higher risk of experiencing one or more of the adverse disease outcomes we examined.

This review identified more studies, with follow-up over an extended period, and were able to pool data from more patients than the prior meta-analysis studying brain-to-gut effects in IBD.[287] As a result, we have been able to demonstrate, for the first time, a significant association between symptoms of anxiety or depression and subsequent adverse outcomes related to disease activity in IBD, including hospitalisation or IBD-related surgery, rather than trends as described previously. Some of this may relate to patients with IBD with symptoms of a common mental disorder being more likely to report gastrointestinal symptoms, and therefore meet criteria for a flare of IBD.[184] Gastrointestinal symptoms, despite evidence of endoscopic or histological remission, affect more than one-in-four patients with IBD and are also associated with a higher risk of symptoms of anxiety or depression.[50] However, most of our endpoints were objective markers of IBD activity, such as escalation of

therapy, hospitalisation, or IBD-related surgery. Studies examining gut-to-brain effects remain limited and our results are similar to those already observed.[288] However, all of the brain-to-gut studies we identified only included individuals without pre-existing common mental disorders at baseline, which strengthens our findings as it means there is unlikely to be confounding.

This meta-analysis has demonstrated significant bidirectional effects of brain-gut interactions in patients with IBD. The time scales involved in these events is difficult to ascertain, due to the variable duration of follow-up. It is, therefore, hard to determine the point at which a deterioration in disease activity or the new onset of symptoms of common mental disorders occurs in brain-to-gut and gut-to-brain studies, respectively. Given the association between symptoms of a common mental disorder at baseline and subsequent adverse disease outcomes there is the potential to improve the natural history of IBD by screening for these symptoms and instituting appropriate therapy. However, symptoms of common mental disorders are likely to fluctuate over time and the brain-to-gut studies included in this meta-analysis only report the presence of symptoms compatible with a common mental disorder at a single point in time, rather than the trajectory of symptoms observed over time among those individuals, this is addressed later in Chapter 6. Studies of these trajectories conducted in other chronic conditions, including ischaemic heart disease, diabetes, and chronic obstructive pulmonary disease, have demonstrated that persistent symptoms of a common mental disorder during follow-up are more likely to lead to adverse outcomes of these diseases, increased healthcare consumption, and higher costs.[210, 256, 303] In patients with IBD, depression has been linked to poor adherence to therapy,[304] higher healthcare utilisation and costs,[305] as well as a higher risk of failure to achieve remission despite escalation of therapy.[61] Unfortunately, the evidence to date for any benefit of gut-brain neuromodulators[306] or psychological therapies,[183] including CBT, gut-directed hypnotherapy, and mindfulness as an adjunct to conventional treatment in IBD is inconclusive, largely due to the fact that these have been tested in unselected patients. High levels of resilience appear to be associated with fewer adverse disease outcomes, and resilience may be modifiable.[189] There is preliminary evidence to suggest that resilience training may be a useful alternative biopsychosocial approach.[188] In addition, there have been no studies of symptom trajectories of common mental disorders in patients with IBD. Such studies might better characterise groups of patients with persistent symptoms of a common mental disorder who are more likely to respond to such interventions, and this may improve the natural history of the disease and reduce healthcare costs.

Although the effect sizes seen in this meta-analysis are relatively modest, they are likely to be driven by patients who are high utilisers of medical care, much of which is unplanned,[307] and in whom intervention is likely to lead to substantial reductions in the costs of managing IBD.[308] Despite this, access to mental health services is limited for many patients. A recent survey suggested that only 15% of patients were currently seeing a mental health practitioner, only 16% reported having been asked about their mental health by their gastroenterologist, and only 12% stated that they had access to a mental health practitioner as part of their outpatient service.[309] In a Crohn's and Colitis Australia survey less than 5% of hospitals surveyed reported that their IBD service included a mental health clinician.[310] Finally, in the Royal College of Physician's national audit of IBD service provision in the UK, only 12% of centres surveyed stated that they had access to clinical psychology via a defined referral pathway.[311]

In conclusion, this systematic review and meta-analysis has shown a significant association between symptoms of a common mental disorder and future adverse disease outcomes, as well as clinical activity and future development of symptoms of a common mental disorder, in patients with IBD. These findings support bidirectional effects of the brain-gut axis in IBD. Future studies should focus on identifying patients at highest risk of these deleterious effects, such as those with increased psychological burden, or by examining symptom trajectories during longitudinal follow-up, to institute appropriate treatments to minimise the impact of poor psychological health on IBD activity, as well as active disease on psychological health. These ideas are explored further in Chapters 4 and 6 of this thesis. This has the potential to inform the design of future clinical trials to improve long-term outcomes in patients with IBD.

Chapter 4

Longitudinal Follow-up Study: Effect of Greater Psychological Co-morbidity on the Prognosis of Inflammatory Bowel Disease.

4.1 Introduction

Although CD and UC are primarily chronic inflammatory conditions of the gastrointestinal tract, there is increasing evidence that activation of the gut-brain axis through stimulation of the ANS and CNS, combined with influences from the HPAA, signalling a hormonal, neural and immune response, play a role in IBD.[286, 312, 313] Although the impact of psychological factors in IBD is not fully understood, psychological co-morbidity is more common in patients with IBD, compared with the general population. A meta-analysis reported the pooled prevalence of anxiety or depression in IBD was 32% and 25% respectively, but this was as high as 58% and 39% during periods of disease activity.[4] Common mental disorders can lead to suppression of parasympathetic activity. For those with IBD with MDD this can lead to difficulty in achieving remission, and the need for early escalation of therapy.[61] As described in Chapter 3, an increasing number of large observational studies have reported independent associations between self-reported features of anxiety or depression and adverse outcomes in IBD, including higher rates of relapse of disease activity, hospitalisation, and escalation of therapy, as well as an increased risk of intestinal surgery.[56, 59, 314, 315]

Most studies examining the impact of psychological disturbance in IBD have used self-reported measures, whereas a diagnosis of anxiety or depression requires persistent symptoms for a prolonged period in several domains. The ICD-11 includes low energy, diminished appetite, and disturbed sleep as associated symptoms in the diagnostic criteria for depression, suggesting an overlap with features of somatisation. Recent studies have suggested that common mental disorders can predate a diagnosis of IBD by several years, but those with coexistent somatic symptoms, rather than cognitive elements alone, appear to be at higher risk.[62, 254] This would suggest that somatisation, alongside mood disturbance, is more likely to result in an adverse disease course. A number of RCTs focusing on efficacy of psychological interventions in IBD have failed to show any effect on disease activity outcomes, despite improved mood scores.[183] Targeting patients with features of psychological co-morbidity, alongside persistent gastrointestinal symptoms, may be more likely to demonstrate that such an approach is beneficial.

Although the evidence to support an impact of psychological co-morbidity on IBD activity is increasing, there is little published on the cumulative impact of multiple psychological co-morbidities on disease outcomes in IBD, unlike in functional

gastrointestinal disorders, such as IBS.[194] This study aims to examine the effect of increasing levels of psychological co-morbidity on subsequent IBD activity during longitudinal follow-up in patients in remission at study entry. Due to the potential confounding effects of psychological co-morbidity on gastrointestinal symptom-reporting, and therefore clinical disease activity indices,[184] this cohort of patients was restricted to those with confirmed biochemical remission at baseline.

4.2 Methods

4.2.1 Participants and Setting

Between November 2012 to June 2015 patients aged 16 years and over, with an established radiological, endoscopic or histological diagnosis of CD or UC attending IBD clinics at St. James University Hospital, Leeds, UK, were recruited into a cross-sectional study. St James University Hospital is a tertiary referral hospital covering a population of around 800,000 people, those participants invited through the IBD clinics were consecutive and unselected. Patients with IBD-unclassified (IBD-U), end ileostomy, or colostomy were excluded due to potential inaccuracies in assessing clinical disease activity. Inability to understand written English was also an exclusion criterion. Patients were offered a patient information sheet of the study, and those agreeable were provided with a written consent form. Longitudinal follow up was conducted between September 2014 to June 2017. At 2 years, a follow-up questionnaire with consent form and patient information sheet was sent out to all those who responded to the baseline survey, with non-responders to postal questionnaires asked to participate during their scheduled outpatient appointments (Research Ethics Committee reference: 12/YH/0443). Study findings were reported in accordance with the STROBE guidelines for reporting observational studies.[316]

4.2.2 Data Collection and Synthesis

4.2.2.1 Demographics and disease characteristics

Demographic data including the date of original recruitment, age, sex, body mass index, marital status, educational level, tobacco and alcohol use, medications history (including use of glucocorticosteroids, 5-ASAs, immunosuppressants,

biologic therapy), IBD type (including disease location and distribution), and previous intestinal surgeries were recorded.

4.2.2.2 Definition of common mental disorders and quality of life

At baseline and follow-up, symptoms of anxiety and depression were assessed with the hospital anxiety and depression scale (HADS),[317] and somatisation via the patient health questionnaire-12 (PHQ-12).[252] Quality of life was measured using the medical outcomes study 36-item short form (SF-36).[318] As recommended in the original validation study, a HADS anxiety or depression score of ≥11 was classified as abnormal. This is a 14-item questionnaire with seven screening questions for anxiety symptoms, and seven questions for depression symptoms.[317] The PHQ-12 is derived from the validated PHQ-15.[319] This questionnaire enquires about 12 somatic symptoms over the past 4 weeks, specifically excluding those questions related directly to gastrointestinal symptoms to limit bias towards active disease. Individuals rate each symptom as ‘not bothered at all’ (score 0), ‘bothered a little’ (score 1), or ‘bothered a lot’ (score 2). Somatisation severity was classified as high if the total PHQ-12 was ≥13.[252]

These data were used to categorise patients according to the total number of psychological co-morbidities they exhibited, from a possible total of three, including one or more of abnormal anxiety scores, abnormal depression scores, and high somatisation scores.

4.2.2.3 Definition of disease activity

Clinical disease activity was measured using the HBI for CD,[90] and the SCCAI for UC,[94] with a score of <5 used to define clinical remission in both, as recommended previously.[95, 320] Alongside this, patients provided an FC sample within 1 week of inclusion for analysis with biochemical remission defined as FC <250μg/g of stool, as supported by international consensus.[321] The FC level was measured using and enzyme-linked immunosorbent assay (ELISA) (Immundiagnostik AG, Bensheim, Germany) as per manufacturer’s instructions.

4.2.2.4 Physicians global assessment

A sole investigator (KMF), who was blinded to the baseline questionnaire data, reviewed each participant's medical records to make an objective assessment of disease activity during longitudinal follow-up. The following end points were extracted, along with the date of their occurrence: glucocorticosteroid prescription or flare of disease activity based on a physician's global assessment; escalation of medical therapy due to disease activity; hospitalisation due to disease activity; and intestinal resection due to disease activity. Changes to medication without evidence of uncontrolled inflammatory activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, were not included as endpoints. All participants were followed up for a minimum of 2 years to maximise frequency of occurrence of the selected endpoints.

4.2.3 Statistical Analysis

The characteristics of those with no psychological co-morbidity at baseline to those with one, two, or three psychological co-morbidities were compared. A χ^2 test was used for categorical variables, an independent samples *t*-test for normally distributed continuous data, and the Mann-Whitney U test for non-parametric continuous data. For comparison across all four groups, a χ^2, one-way analysis of variance (ANOVA), or a Kruskal-Wallis ANOVA test were applied, as appropriate.

The impact of increasing psychological co-morbidity was assessed at baseline on each of the subsequent disease activity outcomes (glucocorticosteroid prescription or flare of disease activity, escalation of therapy, hospitalisation, or intestinal resection) using a χ^2 test for all categorical data across the four groups. The impact of increasing psychological co-morbidity at baseline on composites of the various outcomes including the occurrence of any of the four outcomes of interest, or the occurrence of escalation, hospitalisation, or resection, was also examined, again by applying a χ^2 test. During longitudinal follow-up the effect of degree of psychological co-morbidity at baseline on both individual and combined outcomes was examined, as described above, using multivariate Cox regression analysis, controlling for age, sex, marital status, tobacco and alcohol intake, ethnicity, educational level, type of IBD, and IBD-related medications. Results were expressed as HR with 95% CI. All analyses were performed using SPSS for Windows Version 26.0 (SPSS Inc., Chicago, IL, USA).

4.3 Results

4.3.1 Baseline demographics

In total, 228 individuals provided complete HADS and PHQ-12 data at baseline and were in biochemical remission at study entry, with a FC ≤250µg/g. Of these, 218 (95.6%) participants provided complete data during longitudinal follow-up, with 48 (22.0%) participants reporting symptoms compatible with one, 13 (6.0%) two, and nine (4.1%) three psychological co-morbidities. Those with no psychological co-morbidity at baseline were significantly older (p = 0.001), and more likely to be in clinical remission at baseline (HBI or SCCAI score <5; p <0.001) (Table 8). There were no other significant differences according to other baseline characteristics including current medical therapy, IBD sub-type, disease extent, or disease distribution. Quality of life scores, according to the SF-36, were significantly lower across all domains with increasing number of psychological co-morbidities.

4.3.2 Effect of Psychological Co-morbidity at Baseline on Individual Disease Activity Outcomes During Longitudinal Follow-up

4.3.2.1 Glucocorticosteroid Prescription or Flare of Disease Activity

Of the 218 patients in biochemical remission at baseline, 81 (37.2%) required a prescription of glucocorticosteroids or reported a flare of disease activity during a mean of 858.5 days of longitudinal follow-up. Of these, 37 (45.7%) had at least one psychological co-morbidity at baseline, with an increased risk of glucocorticosteroid prescription or flare compared with those with no psychological co-morbidity at baseline (p = 0.004; Table 9). Following multivariate Cox regression analysis controlling for baseline data, rates of glucocorticosteroid prescription or flare were significantly higher among those with either two (HR = 3.18; 95% CI, 1.44 to 7.02) or three (HR = 3.53; 95% CI 1.26 to 9.92) psychological co-morbidities (Figure 13). There was no impact of sex, type of IBD, or IBD-related medications in Cox regression analysis.

Table 8: Baseline Characteristics of Patients According to Number of Psychological Co-morbidities at Baseline.

	No psychological co-morbidity (n = 148)	One psychological co-morbidity (n = 48)	*p* value*	Two psychological co-morbidities (n = 13)	*p* value*	Three psychological co-morbidities (n = 9)	*p* value*	*p* value**
Mean age in years (SD)	51.5 (17.0)	41.7 (11.8)	<0.001	42.4 (15.1)	0.06	45.8 (13.6)	0.33	0.001
Female sex (%)	82 (55.4)	30 (62.5)	0.39	10 (76.9)	0.13	7 (77.8)	0.19	0.25
BMI (SD)	26.2 (5.1)	26.1 (5.6)	0.88	25.8 (4.8)	0.78	26.89 (8.4)	0.83	0.98
Married or co-habiting (%)	103 (69.6)	32 (66.7)	0.70	9 (69.2)	0.98	2 (22.2)	0.003	0.03
Caucasian ethnicity (%)	143 (96.6)	48 (100)	0.20	13 (100)	0.50	8 (88.9)	0.24	0.23
University graduate/professional (%)	47 (31.8)	13 (27.1)	0.54	3 (6.3)	0.52	1 (11.1)	0.19	0.53
Tobacco user (%)	16 (10.8)	7 (14.6)	0.48	4 (30.8)	0.04	2 (22.2)	0.297	0.18
Alcohol user (%)	99 (66.9)	33 (68.8)	0.86	8 (61.5)	0.67	4 (44.4)	0.159	0.52
CD (%)	82 (55.4)	30 (62.5)	0.39	8 (61.5)	0.67	3 (33.3)	0.197	0.41

CD distribution (%)								
Ileal	11/82 (13.4)	10/30 (33.3)		1/8 (12.5)		1/3 (33.3)		
Colonic	34/82 (41.5)	8/30 (26.7)		4/8 (50.0)		1/3 (33.3)		
Ileocolonic	37/82 (45.1)	12/30 (40.0)	0.05	3/8 (37.5)	0.89	1/3 (33.3)	0.62	0.32
CD behaviour (%)								
Non-stricturing, non-penetrating	75/82 (91.5)	24/30 (80.0)		7/8 (87.5)		2/3 (66.7)		
Stricturing	4/82 (4.9)	4/30 (13.3)		0/8		0/3		
Penetrating	3/82 (3.7)	2/30 (6.7)	0.23	1/8 (12.5)	0.43	1/3 (33.3)	0.06	0.17
Perianal CD (%)	7/82 (8.5)	2/30 (6.7)	0.75	0/8	0.39	0/3	0.60	0.79
Previous intestinal resection in CD (%)	26/82 (31.7)	10/30 (33.3)	0.870	3/8 (37.5)	0.738	2/3 (66.7)	0.206	0.65

UC extent (%)								
Proctitis	16/65 (24.6)	6/18 (33.3)		2/5 (40.0)		3/6 (50.0)		
Left-sided	34/65 (52.3)	9/18 (50.0)		1/5 (20.0)		2/6 (33.3)		
Extensive	15/65 (23.1)	3/18 (16.7)	0.71	2/5 (40.0)	0.38	1/6 (16.7)	0.40	0.67
5-ASA use (%)	84 (56.8)	22 (45.8)	0.19	5 (38.5)	0.20	7 (77.8)	0.22	0.17
Immunomodulator use (%)	53 (35.8)	20 (41.7)	0.47	4 (30.8)	0.72	2 (22.2)	0.41	0.67
Anti-TNF-α use (%)	28 (18.9)	14 (29.2)	0.13	2 (15.4)	0.75	0	0.15	0.17
Glucocorticosteroid use (%)	9 (6.1)	6 (12.5)	0.146	2 (15.4)	0.202	2 (22.2)	0.065	0.18
HBI/SCCAI <5 (%)	107 (74.8)	27 (57.4)	0.02	6 (46.2)	0.03	0	<0.001	<0.001
Median FC (IQR)	57.6 (40.5-97.2)	83 (40.4-126.6)	0.19	178 (47.4-207.1)	0.03	69.3 (31.5-100.2)	0.96	0.112
Median HADS anxiety score (IQR)	5 (2-7)	12 (11-14)	<0.001	15 (12-17)	<0.001	18 (12-20)	<0.001	<0.001

Anxiety categories (%)								
Normal	117 (79.1)	3 (6.3)		0		0		
Borderline abnormal	31 (20.9)	8 (16.7)		0		0		
Abnormal	0	37 (77.1)	<0.001	13 (100)	<0.001	9 (100)	<0.001	<0.001
Median HADS depression score (IQR)	2(1-4)	7 (5-9)	<0.001	11 (9-16)	0.001	14 (12.5-17.5)	<0.001	<0.001
Depression categories (%)								
Normal	142 (95.9)	25 (52.1)		2 (15.4)		0		
Borderline abnormal	6 (4.1)	19 (39.6)		2 (15.4)		0		
Abnormal	0	4 (8.3)	<0.001	9 (69.2)	<0.001	9 (100)	<0.001	<0.001
Median PHQ-12 score (IQR)	5 (3-8)	9 (6-12)	<0.001	11 (11-13.5)	<0.001	14 (13.3-16.5)	<0.001	<0.001

PHQ-12 somatisation categories (%)								
Mild	46 (31.1)	3 (6.3)		0		0		
Low	64 (43.2)	15 (31.3)		2 (15.4)		0		
Medium	38 (25.7)	23 (47.9)		7 (53.8)		0		
High	0	7 (14.6)	<0.001	4 (30.8)	<0.001	9 (100)	<0.001	<0.001

Median SF-36 score (IQR)								
Physical functioning	92.5 (75-100)	80 (57.5-90)	0.001	65 (47.5-87.5)	0.003	30 (15-75)	0.001	<0.001
Role limitations physical	100 (50-100)	25 (0-75)	<0.001	0 (0-50)	<0.001	0 (0-12.5)	<0.001	<0.001
health	100 (100-100)	33.3 (0-100)	<0.001	0 (0-33.3)	<0.001	0 (0-25)	<0.001	<0.001
Role limitations emotional problems	57.5 (40-70)	32.5 (15-45)	<0.001	30 (13.8-50)	0.001	10 (1.3-15)	<0.001	<0.001
Energy/fatigue	80 (68-88)	52 (44-64)	<0.001	40 (34-58)	<0.001	22 (20-33)	<0.001	<0.001
Emotional well-being	87.5(62.5-100)	50 (37.5-75)	<0.001	25 (18.8-50)	<0.001	31.3 (6.3-50)	<0.001	<0.001
Social functioning	77.5 (57.5-90)	55 (35.6-80)	0.002	32.5 (32.5-56.3)	<0.001	22.5 (15-39.4)	<0.001	<0.001
Pain	60 (42.5-75)	40 (25-50)	<0.001		<0.001	15 (10-18.8)	<0.001	<0.001
General health				25 (20-33.8)				

*****Independent samples t-test for comparison of normally distributed continuous data, Mann-Whitney U test for comparison of non-parametric data, or $\chi 2$ for comparison of categorical data with those with no psychological co-morbidity at baseline.

**One-way ANOVA for comparison of normally distributed continuous data, Kruskal-Wallis ANOVA for comparison of non-parametric data, $\chi 2$ for comparison of categorical data across all four groups.

Table 9: Clinical Outcomes of Patients According to Number of Psychological Co-morbidities at Baseline.

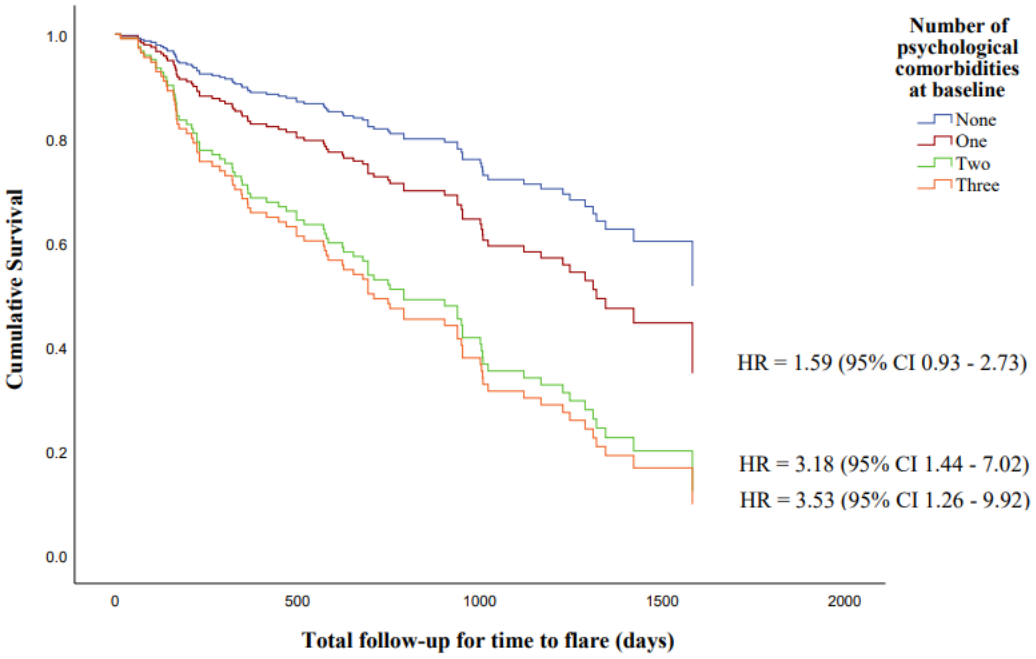
	No psychological co-morbidity (n = 148)	**One psychological co-morbidity (n = 47)**	***p* value***	**Two psychological co-morbidities (n = 13)**	***p* value***	**Three psychological co-morbidities (n = 9)**	***p* value***	***p* value****
Individual disease activity outcomes (%)								
Flare (n = 81)	44 (29.7)	23 (48.9)	0.02	9 (69.2)	0.004	5 (55.6)	0.10	0.004
Escalation (n = 73)	40 (27)	20 (42.6)	0.05	7 (53.8)	0.04	6 (66.7)	0.01	0.01
Hospitalisation (n = 19)	9 (6.1)	8 (17.0)	0.02	0 (0.0)	0.36	2 (22.2)	0.07	0.04
Resection (n = 7)	3 (2.0)	4 (8.5)	0.04	0 (0.0)	0.60	0 (0.0)	0.67	0.13

Composite disease activity outcomes (%)								
Flare, escalation, hospitalisation, or resection (n = 95)	52 (35.1)	28 (59.6)	0.003	9 (69.2)	0.02	6 (66.7)	0.06	0.002
Escalation, hospitalisation, or resection (n = 78)	43 (29.1)	22 (46.8)	0.02	7 (53.8)	0.06	6 (66.7)	0.02	0.01

*χ^2 for comparison with those with no psychological co-morbidity at baseline.

**χ^2 for comparison across all four groups.

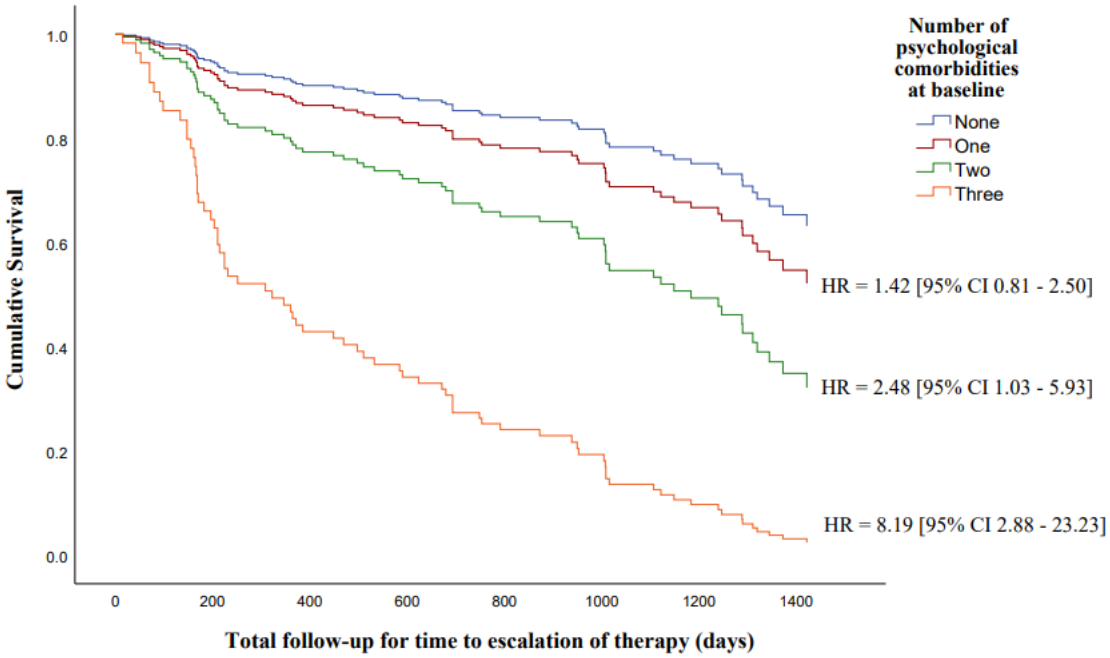
Figure 13: Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity According to Number of Psychological Co-morbidities at Baseline.



4.3.2.2 Escalation of Medical Therapy due to Disease Activity

In total 73 (33.5%) of the 218 patients required escalation of therapy for IBD activity during a mean follow-up of 882.6 days. Of these, 33 (45.2%) had at least one psychological co-morbidity. The proportion of patients requiring escalation increased according to number of psychological co-morbidities (p = 0.01; Table 9). Following multivariate Cox regression analysis, again presence of two (HR = 2.48; 95% CI 1.03 to 5.93) or three (HR = 8.19; 95% CI 2.88 to 23.23) psychological co-morbidities was significantly associated with escalation of medical therapy (Figure 14), but there was no impact of sex, type of IBD, or IBD-related medications.

Figure 14: Survival Analysis for Occurrence of Escalation of Medical Therapy due to Disease Activity According to Number of Psychological Co-morbidities at Baseline.



4.3.2.3 Hospitalisation or Intestinal Resection due to Active IBD

The numbers of patients requiring hospitalisation or intestinal resection during the study period were smaller. Overall, 19 (8.7%) patients required hospitalisation, and seven (3.2%) intestinal resection during a mean of 1064.7 and 1100.9 days of follow-up respectively. Among those hospitalised, 10 (52.6%) had at least one psychological co-morbidity at baseline (p = 0.04; Table 9). Among those requiring intestinal resection four (57.1%) had at least one psychological co-morbidity at baseline. However, there was no association between number of psychological co-morbidities at baseline and need for hospitalisation or intestinal resection after multivariate Cox regression, and no impact of sex, type of IBD, or IBD-related medications.

4.3.3 Effect of Psychological Co-morbidity at Baseline on Composite Disease Activity Outcomes During Longitudinal Follow-up

4.3.3.1 Glucocorticosteroid Prescription or Flare of Disease Activity, Escalation of Medical Therapy due to Disease Activity, Hospitalisation, or Intestinal Resection due to Active IBD

In total, 95 (43.6%) patients experienced one or more of the four endpoints of interest. Using a composite endpoint of the occurrence of any of these four outcomes there were significantly higher rates of one or more of these endpoints occurring among those with one (p = 0.003) or two (p = 0.02) psychological co-morbidities at baseline, compared with those with none (Table 9). After multivariate Cox regression analysis, increasing psychological co-morbidity at baseline was significantly associated with the occurrence of one or more of the four outcomes of interest (HR = 1.74; 95% CI 1.07 to 2.82 for one psychological co-morbidity, HR = 2.47; 95% CI 1.12 to 5.46 for two, and HR = 4.93; 95% CI 1.84 to 13.17 for three psychological co-morbidities) (Figure 15). There was no impact of sex, type of IBD, or IBD-related medications in Cox regression analysis.

4.3.3.2 Escalation of Medical Therapy due to Disease Activity, Hospitalisation, or Intestinal Resection due to Active IBD

Of the 218 patients included at baseline, 78 (35.8%) required escalation, hospitalisation, or intestinal resection due to active IBD, and 35 (44.9%) of these had at least one psychological co-morbidity at baseline. There was an

increasing likelihood of one or more of these endpoints occurring with increasing numbers of psychological co-morbidities at baseline (p = 0.01; Table 9). After multivariate Cox regression analysis, there was no significant increase in likelihood of any of these events of interest among patients with one or two psychological co-morbidities at baseline, but those with three psychological co-morbidities were more likely to need to escalate therapy, require hospitalisation, or undergo intestinal resection during the study period (HR = 5.92; 95% CI 2.12 to 16.52) (Figure 16). There was no impact of sex, type of IBD, or IBD-related medications in Cox regression analysis.

Figure 15: Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity, Escalation of Medical Therapy due to Disease Activity, Hospitalisation, or Intestinal Resection due to Active IBD According to Number of Psychological Co-morbidities at Baseline.

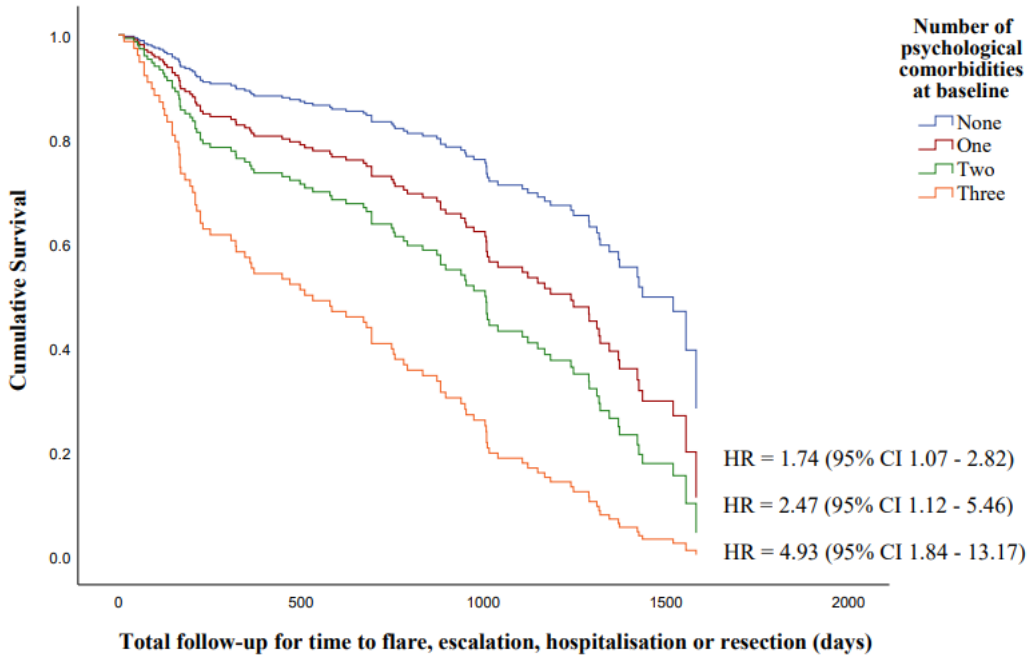
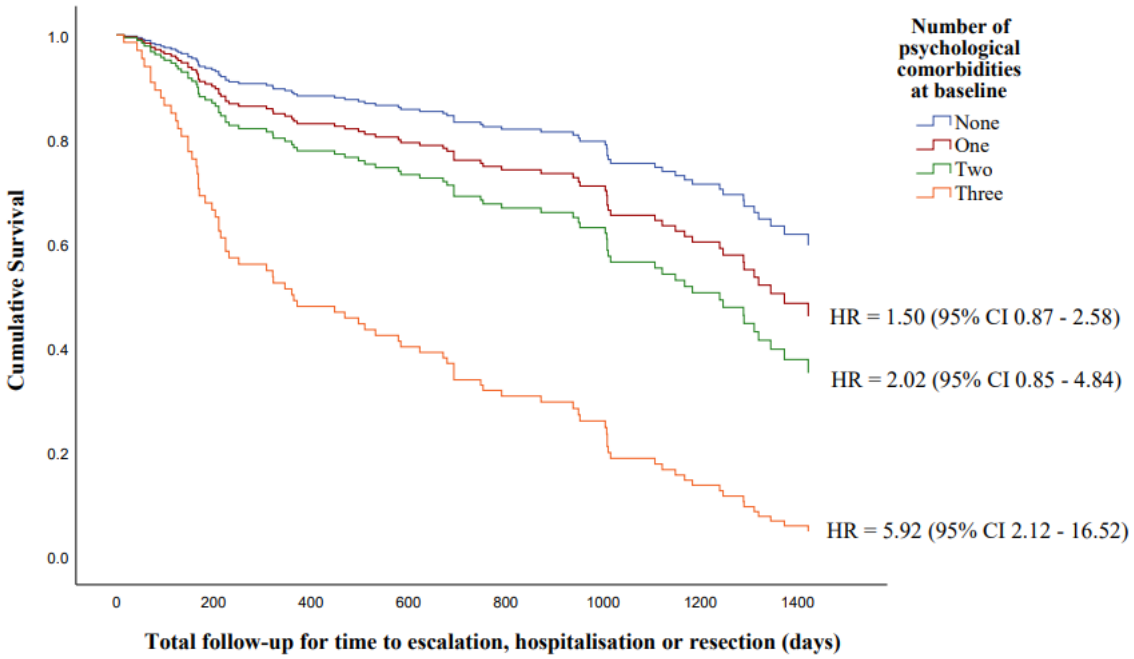


Figure 16: Survival Analysis for Occurrence Escalation of Medical Therapy due to Disease Activity, Hospitalisation, or Intestinal Resection due to Active IBD According to Number of Psychological Co-morbidities at Baseline.



4.4 Discussion

This longitudinal study supports other existing literature suggesting that psychological co-morbidity is independently linked to future adverse outcomes in patients with IBD in remission. As previously described,[4, 222] one-in-three of the patients with IBD in biochemical remission in this study self-reported symptoms consistent with at least one psychological co-morbidity at baseline. Importantly, this study was able to demonstrate a cumulative impact of the number of psychological co-morbidities on subsequent disease behaviour. Those with more than one psychological co-morbidity had a significantly higher risk of glucocorticosteroid prescription or flare of disease activity, as well as a need to escalate therapy due to poorly controlled IBD activity. Using a composite of any of the four outcomes of interest the same pattern was observed, and even when the more subjective glucocorticosteroid prescription or flare of disease activity was omitted, the results of these analyses remained the same. The results of this study underline the need to integrate a holistic biopsychosocial care model into the management of patients with IBD.

By recruiting an unselected cohort of patients via their routine outpatient appointments, these findings are likely to be generalisable to the many patients with IBD in remission. A stringent definition of remission was used, according to FC results at study entry, to remove any influence of ongoing occult inflammation, and control for the potential relationship between clinical disease activity indices, which rely on patient report, and psychological co-morbidity on our results. An FC of ≥250μg/g is accepted by expert opinion as an appropriate level to detect a flare of IBD activity and supported by international consensus.[321] Cox regression analyses were adjusted for all baseline characteristics, including age, sex, marital status, educational level, type of IBD, and use of glucocorticosteroids, immunomodulators and anti-TNF-α therapy. The criteria for defining presence of psychological co-morbidity was also conservative, only classifying those with definitely abnormal HADS scores as having evidence of psychological co-morbidity.

Nevertheless, there are some limitations. Although patients were in biochemical remission at study entry, this does not exclude the fact that they may have had severe disease at some point prior to recruitment, and that this has led to psychological co-morbidity. In this case, it may be that it is the continuing impact of the severity of disease prior to study entry, rather than psychological co-morbidity, that is affecting the natural history of the disease adversely. The study also relied on evidence of psychological co-morbidity measured at a single time point, and via self-report, which is not a definitive diagnosis of a common

mental disorder. Psychological disorders have the potential to fluctuate in severity over time, but persistently abnormal mood scores, such as those seen in major depressive disorder, may be associated with higher disease activity scores, poorer quality of life, and lower rates of remission.[322] The limited time points examined in this longitudinal study may not take into account potential variations in symptoms of psychological co-morbidity over time, which might help better characterise a particularly high risk group of patients.

Due to the stringent criteria for inclusion, the number of patients eligible for inclusion was relatively small, and the study is likely underpowered for some of the less frequently occurring endpoints. Despite this, when all four endpoints of interest were combined, or when escalation due to disease activity, hospitalisation, and intestinal resection were considered, there remained a cumulative effect of increasing psychological co-morbidity on adverse disease outcomes. Flare and glucocorticosteroid prescription events were the most common occurrences. A flare of disease activity based on a physician's global assessment could be influenced by the subjective nature of self-reported gastrointestinal symptoms without evidence of ongoing inflammation, and an association between psychological co-morbidity and gastrointestinal symptom-reporting *per se* has been recognised in several studies.[59, 323, 324] Escalation of therapy based on clinical indices alone, particularly in those with common mental disorders, has not been shown to alter long-term outcomes in IBD.[61, 325] Previous research from our group supports this, with no evidence of an association between the reporting of symptoms compatible with IBS in patients with IBD in remission, and future adverse clinical outcomes during longitudinal follow-up.[197]

Functional gastrointestinal disorders are common in patients with IBD, with a prevalence of symptoms compatible with IBS in up to 25% despite histological or endoscopic evidence of remission,[50] which is much higher than in the general population.[326] Anxiety and depression are also more prevalent in patients with IBD with IBS-type symptoms,[284, 327] and may pre-date symptom onset.[328] The gut-brain axis incorporates a bidirectional effect; as psychological co-morbidity increases, so does the likelihood of developing gastrointestinal symptoms in the future.[218] Conversely, persistent IBD activity is associated with future development of psychological co-morbidity.[56] Although both psychological therapies and gut-brain neuromodulators are beneficial in patients with IBS,[186] the evidence for their use in IBD is not as conclusive. In a meta-analysis of 14 RCTs there appeared to be some short-term benefit on depression scores from psychological therapies, however this effect waned over time.[183] Despite this, there are few RCTs examining the efficacy of gut-brain

neuromodulators in IBD on common mental disorders, although there have been some encouraging results from observational and retrospective studies.[306] One of the reasons for lack of convincing efficacy observed in trials to date may be the recruitment of unselected patients with IBD, rather than focusing on only those with evidence of psychological co-morbidity. A recent retrospective analysis of those undergoing major abdominal surgery in relation to IBD, highlighted a significant association to those patients with a pre-existing established diagnosis of anxiety or depression,[329] supporting the bidirectional influence of the gut-brain axis. The objective endpoints highlighted in our study, further support this theory that increased psychological burden independently increase the risk of occult inflammation over time.

By limiting included patients to those with objective evidence of biochemical remission and having controlled for multiple demographic and disease characteristics in these analyses, it is likely that the occurrence of the endpoints of interest in this study were primarily influenced by psychological co-morbidity. This study has, therefore, highlighted the importance of not only recognising the impact of psychological co-morbidity on the course of IBD, but also the increased risk of multiple psychological co-morbidities on adverse clinical outcomes. Longer follow-up in this cohort, or similar studies recruiting a larger number of participants, may increase the number of events of interest for some of the rarer endpoints studied. If hospitalisation or surgery were independently associated with degree of psychological co-morbidity this might provide further support for management strategies centred around early intervention and support in those patients with IBD most at risk of psychological illness. It is clear that further studies are needed, with more frequent assessment of degree of psychological health, to better characterise the fluctuating nature of psychological co-morbidity in IBD and the overall impact on patient outcomes.

Chapter 5

Relative Contribution of Disease Activity and Psychological Health to Prognosis of Inflammatory Bowel Disease During 6.5 Years of Longitudinal Follow-Up

5.1 Introduction

The chronic and unpredictable nature of IBD has been linked to an increased prevalence of symptoms of common mental disorders, such as anxiety or depression, which affect more than 30% and 25% of patients with IBD, respectively.[4] Studies have shown that patients with active disease at baseline, without prior history of a common mental disorder, are also more likely to develop symptoms of anxiety or depression in the future,[56, 259] suggesting gut-brain axis effects.[312]

Conventionally, uncontrolled symptoms or biochemical activity of disease, as evidenced by raised CRP or FC, may be adverse prognostic factors in IBD.[330, 331, 332, 333, 334, 335, 336] As such, these are recommended therapeutic targets according to the International Organization for the Study of Inflammatory Bowel Diseases.[85] As outlined in Chapter 3, this meta-analysis involving over 9000 patients, provides further evidence that gut-brain axis effects are bidirectional in IBD, with the presence of common mental disorders appearing to influence future clinical course, and vice versa. Previous studies have demonstrated how symptoms of anxiety or depression are linked with increased rates of flare of disease activity or escalation of medical therapy,[56, 213] and depression with higher rates of hospitalisation or intestinal surgery.[58, 60] There also appears to be a cumulative impact of these symptoms as demonstrated in our own cohort of patients, described in Chapter 4.

A negative impact of common mental disorders on prognosis in other chronic medical conditions, including diabetes mellitus, coronary heart disease, and chronic obstructive pulmonary disorder, has been reported previously.[210, 256, 303] In one study, rates of cardiovascular death or myocardial infarction were recorded in patients with coronary heart disease according to the presence or absence of myocardial ischaemia induced by psychological stress or conventional exercise-induced myocardial ischaemia at baseline during longitudinal follow-up.[285] Compared with patients with neither psychological stress-induced nor conventional exercise-induced ischaemia, rates of death or myocardial infarction were significantly higher among those with psychological stress-induced, but not exercise-induced, ischaemia. In addition, there was a cumulative impact, with patients with both psychological stress-induced and exercise-induced myocardial ischaemia having almost four-fold higher rates of myocardial infarction or cardiovascular death than patients with neither, and three-fold higher rates compared with those with exercise-induced myocardial

ischemia alone. This suggests that psychological factors may be more important than physiological factors in determining outcomes in chronic disease.

The influence of psychological factors in addition to proposed therapeutic targets, such as the gastrointestinal symptoms incorporated into clinical disease activity indices or biochemical markers of disease activity, on the prognosis of IBD has not been studied. This longitudinal follow-up study of over 700 patients with well characterised IBD, aimed to examine this issue further, during an average follow-up of 6.5 years.

5.2 Methods

5.2.1 Participants and Setting

Between November 2012 and June 2015, patients aged ≥16 years with an established radiological, endoscopic, or histological diagnosis of CD or UC were recruited into a cross-sectional study, as described in Chapter 4.[184] All participants were recruited from the IBD clinic at St. James's University Hospital, Leeds, United Kingdom, which is the sole provider of IBD care to these patients. Patients with IBD-U, end ileostomy, or colostomy were excluded due to potential inaccuracies in assessing clinical disease activity. Inability to understand written English was also an exclusion criterion. Prospective longitudinal follow-up was conducted between September 2014 and November 2021 (Research Ethics Committee reference: 12/YH/0443/AM03). Study findings were reported in accordance with the STROBE guidelines.[316]

5.2.2 Data Collection and Synthesis

The date of original recruitment, type of IBD, IBD-related medications, and demographic data, including age, sex, and lifestyle factors, were recorded at baseline. Data concerning symptoms of a common mental disorder (anxiety or depression) using the HADS,[317] and somatisation via the PHQ-15[319] was collected. As recommended in the original validation study, a HADS anxiety or depression score of ≥11 was classified as abnormal.[317]

Clinical disease activity was measured using the HBI[90] for CD, and the SCCAI for UC.[94] A score of <5 was used to define clinical remission in both, as recommended previously.[95, 320] Patients were asked to provide a FC sample for analysis (Immundiagnostik, Blensheim, Germany). Biochemical remission

was defined using a FC threshold of <250mcg/g of stool, as supported by international consensus.[321]

A sole investigator, blinded to the baseline questionnaire data, reviewed each participant's medical records during longitudinal follow-up to make an objective assessment of disease activity. The following endpoints were extracted, along with the date of their occurrence: glucocorticosteroid prescription or flare of disease activity based on a physician's global assessment; escalation of medical therapy due to uncontrolled IBD activity, hospitalisation due to uncontrolled IBD activity; intestinal resection due to uncontrolled IBD activity; and death. Changes to medication without evidence of uncontrolled IBD activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, were not included as endpoints. The number of each of these events of interest, the number of IBD-related clinic appointments, and the number of radiological and endoscopic investigations performed for assessment of disease activity to examine healthcare utilisation were also recorded.

5.2.3 Statistical Analysis

All individuals were classified at baseline according to presence or absence of either clinical disease activity (clinical remission or clinical activity) as well as presence or absence of symptoms of a common mental disorder at baseline. This led to all individuals being categorised into four groups: clinical remission (HBI or SCCAI <5) with no evidence of symptoms of a common mental disorder at baseline, clinical remission with evidence of symptoms of a common mental disorder at baseline, clinical activity (HBI or SCCAI ≥5) with no evidence of symptoms of a common mental disorder at baseline, and clinical activity with evidence of symptoms of a common mental disorder at baseline. This exercise was repeated for the subgroup of individuals who provided a FC sample, creating a further four groups: biochemical remission (FC <250mcg/g) with no evidence of symptoms of a common mental disorder at baseline, biochemical remission with evidence of symptoms of a common mental disorder at baseline, biochemical activity (FC ≥250mcg/g) with no evidence of symptoms of a common mental disorder at baseline, and biochemical activity with evidence of symptoms of a common mental disorder at baseline. Sensitivity analyses were performed using a FC of <100mcg/g to define biochemical remission and a combined definition of activity or remission that incorporated both clinical and biochemical indices (clinical and biochemical remission or clinical and biochemical activity).

To assess the impact of both clinical and biochemical activity and symptoms of a common mental disorder at baseline on each of the disease activity outcomes of interest (glucocorticosteroid prescription or flare of disease activity, escalation of therapy, hospitalisation, intestinal resection, or death) during longitudinal follow-up we compared their rates in each of the four groups using a χ^2 test. Independent predictors of the development of each of these outcomes were determined by performing multivariate Cox regression analysis to control for baseline characteristics including age, sex, marital status, tobacco and alcohol intake, educational level, type of IBD, IBD-related medications at baseline, and level of somatisation according to the PHQ-15. Due to multiple comparisons, a 2-tailed P value of <0.01 was considered statistically significant, and the results were expressed as HR with 95% CI. We compared healthcare utilisation between the four groups using one way ANOVA. All statistical analyses were performed using SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA).

5.3 Results

5.3.1 Baseline demographics

In total, 760 individuals were recruited, with 718 (94.5%) providing complete clinical activity data at baseline (396 (55.2%) female, mean age at baseline 44.0 years, 412 (57.4%) CD), and 379 (49.9%) providing a FC sample at baseline. Among the 718 providing clinical activity data at baseline, the number of individuals for whom longitudinal follow-up data was collected, varied between 572 (79.7%) (flare of disease activity or need for glucocorticosteroids) and 703 (97.9%) (death) with a mean duration of follow-up of 6.5 years. Among the 379 who provided a FC sample at baseline, the number of individuals who provided longitudinal follow-up data varied between 323 (85.2%) (flare of disease activity or need for glucocorticosteroids) and 373 (98.4%) (death) with mean follow-up 6.7 years. When comparing patient characteristics according to clinical disease activity and presence or absence of symptoms of a common mental disorder at baseline, those with clinical activity and symptoms of a common mental disorder were significantly more likely to smoke, to have high levels of somatisation, and significantly less likely to drink alcohol (Table 10). There were no other significant differences according to other baseline characteristics including sex, IBD-related medications at baseline, type of IBD, or disease location, behaviour, or extent.

Table 10: Baseline Characteristics of Patients According to Clinical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Clinical remission, no symptoms of a common mental disorder (n = 338)	Clinical remission, symptoms of a common mental disorder (n = 85)	Clinical activity, no symptoms of a common mental disorder (n = 172)	Clinical activity, symptoms of a common mental disorder (n=123)	*p* value*
Mean age in years at baseline (SD)	45.6 (18.3)	43.5 (15.1)	43.4 (15.7)	40.7 (14.3)	0.13
Female sex (%)	166 (49.1)	48 (56.5)	102 (59.3)	80 (65.0)	0.011
Married or co-habiting (%)	206 (61.3)	50 (60.2)	109 (64.1)	72 (58.5)	0.80
University graduate/professional (%)	107 (32.0)	20 (24.1)	50 (29.2)	24 (19.5)	0.051
Tobacco user (%)	49 (14.5)	10 (12.0)	29 (16.9)	33 (27.0)	0.008
Alcohol user (%)	234 (69.2)	53 (63.1)	118 (69.0)	60 (49.2)	<0.001
CD (%)	183 (54.1)	50 (58.8)	104 (60.5)	75 (61.0)	0.42

CD location (%)					
Ileal	37/183 (20.2)	11/50 (22.0)	20/104 (19.2)	24/75 (32.0)	
Colonic	61/183 (33.3)	16/50 (32.0)	24/104 (23.1)	17/75 (22.7)	
Ileocolonic	85/183 (46.4)	23/50 (46.0)	60/104 (57.7)	34/75 (45.3)	0.14
Non-stricturing, non-penetrating CD (%)	157/183 (85.8)	39/50 (78.0)	86/104 (82.7)	58/75 (77.3)	0.67
Perianal CD (%)	15/183 (8.2)	5/50 (10.0)	14/104 (13.5)	6/75 (8.0)	0.49
UC extent (%)					
Proctitis	36/155 (23.2)	12/35 (34.3)	14/68 (20.6)	11/49 (22.4)	
Left-sided	74/155 (47.7)	13/35 (37.1)	30/68 (44.1)	24/49 (49.0)	
Extensive	45/155 (29.0)	10/35 (28.6)	24/68 (35.3)	14/49 (28.6)	0.74
5-ASA use (%)	169 (50.0)	39 (45.9)	81 (47.1)	53 (43.1)	0.59
Immunomodulator use (%)	121 (35.8)	27 (31.8)	64 (37.2)	42 (34.1)	0.84
Anti-TNF-α use (%)	68 (20.1)	18 (21.2)	30 (17.4)	18 (14.6)	0.51

Glucocorticosteroid use (%)	27 (8.0)	9 (10.6)	25 (14.5)	17 (13.8)	0.094
High levels of somatisation on PHQ-15 (%)	6 (1.8)	9 (11.5)	15 (9.0)	30 (25.9)	<0.001
FC <250mcg/g	114/182 (62.6)	29/44 (65.9)	40/77 (51.9)	37/62 (59.7)	0.353

*One-way ANOVA for comparison of normally distributed continuous data, χ^2 for comparison of categorical data across all four groups.

5.3.2 Need for glucocorticosteroid prescription or flare of disease activity

In total, 308 (53.8%) of 573 patients needed a prescription for glucocorticosteroids or had a flare of disease activity during a mean duration of follow-up of 4.0 years (range 7 days to 8.7 years). Rates were highest in those with symptoms of a common mental disorder at baseline, irrespective of clinical disease activity, with 60.5% of those in clinical remission with symptoms of a common mental disorder and 70.2% of those with clinical activity and symptoms of a common mental disorder reaching this endpoint, compared with 48.0% of those in clinical remission without symptoms of a common mental disorder (p=0.002) (Table 11). After multivariate Cox regression analysis, rates remained highest in those with clinical remission with symptoms of a common mental disorder at baseline (HR = 1.57; 95% CI 1.08 to 2.27) and those with clinical activity and symptoms of a common mental disorder at baseline (HR = 2.36; 95% CI 1.58 to 3.54) (p<0.001 for trend) (Table 11 and Figure 17), although only rates among those with clinical activity and symptoms of a common mental disorder were statistically higher (p<0.001). Younger age (HR per year = 0.98; 95% CI 0.97 to 0.99, p<0.001) was associated with a reduced likelihood of need for glucocorticosteroid prescription or flare and UC (HR = 1.69; 95% CI 1.22 to 2.32, p=0.001) an increased likelihood.

When we performed multivariate Cox regression analysis according to biochemical activity at baseline in those providing a sample for FC, rates of glucorticosteroid prescription or flare were higher among those with biochemical remission and symptoms of a common mental disorder at baseline (HR = 1.67; 95% CI 1.07 to 2.62) and significantly raised in those with biochemical activity and symptoms of a common mental disorder at baseline (HR = 2.48; 95% CI 1.38 to 4.46, p=0.002) (Table 12 and Figure 18). Again, younger age was associated with a reduced likelihood of need for glucocorticosteroid prescription or flare (HR per year = 0.98; 95% CI 0.97 to 1.00, p=0.004). Sensitivity analyses using a FC of <100mcg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices yielded similar results (Table 13 and Table 14).

Table 11: Clinical Outcomes of Patients According to Clinical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Clinical remission, no symptoms of a common mental disorder	Clinical remission, symptoms of a common mental disorder	Clinical activity, no symptoms of a common mental disorder	Clinical activity, symptoms of a common mental disorder	*p* value
Glucorticosteroid prescription or flare of disease activity (%)	144/300 (48.0)	46/76 (60.5)	59/112 (52.7)	59/84 (70.2)	0.002*
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.57 (1.08 – 2.27)	1.50 (1.09 – 2.07)	2.36 (1.58 – 3.54)†	<0.001
Escalation of medical therapy due to uncontrolled IBD activity (%)	155/311 (49.8)	49/80 (61.3)	79/141 (56.0)	62/99 (62.6)	0.073*
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.47 (1.03 – 2.09)	1.43 (1.07 – 1.92)	1.65 (1.14 – 2.40)†	0.014

Hospitalisation due to uncontrolled IBD activity (%)	62/326 (19.0)	25/82 (30.5)	41/169 (24.3)	43/115 (37.4)	0.001*
Multivariate HR for hospitalisation due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.51 (0.89 – 2.56)	1.37 (0.90 – 2.08)	1.71 (1.06 – 2.75)	0.13
Intestinal resection due to uncontrolled IBD activity (%)	26/326 (8.0)	12/82 (14.6)	21/170 (12.4)	26/118 (22.0)	0.001*
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.22 (0.52 – 2.87)	1.57 (0.84 – 2.92)	2.09 (1.06 – 4.13)	0.18
Death (%)	25/331 (7.6)	5/82 (6.1)	5/170 (2.9)	7/120 (5.8)	0.24*
Multivariate HR for death (95% CI)	1.00 (reference)	1.68 (0.55 – 5.13)	0.65 (0.22 – 1.98)	4.99 (1.80 – 13.88)†	0.007

*For comparison across all four groups.

†$p<0.01$ versus reference category.

Table 12: Clinical Outcomes of Patients According to Biochemical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Biochemical remission, no symptoms of a common mental disorder	**Biochemical remission, symptoms of a common mental disorder**	**Biochemical activity, no symptoms of a common mental disorder**	**Biochemical activity, symptoms of a common mental disorder**	***p* value**
Glucorticosteroid prescription or flare of disease activity (%)	71/153 (46.4)	43/64 (67.2)	37/76 (48.7)	19/30 (63.3)	0.022*
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.67 (1.07 – 2.62)	1.09 (0.71 – 1.66)	2.48 (1.38 – 4.46)†	0.009
Escalation of medical therapy due to uncontrolled IBD activity (%)	67/154 (43.5)	40/65 (61.5)	48/91 (52.7)	24/35 (68.6)	0.014*

Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.58 (1.02 – 2.44)	1.40 (0.94 – 2.08)	2.97 (1.74 – 5.06)†	0.001
Hospitalisation due to uncontrolled IBD activity (%)	21/154 (13.6)	15/65 (23.1)	20/107 (18.7)	14/41 (34.1)	0.022*
Multivariate HR for hospitalisation due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.76 (0.84 – 3.71)	1.22 (0.63 – 2.37)	3.10 (1.43 – 6.68)†	0.030
Intestinal resection due to uncontrolled IBD activity (%)	8/154 (5.2)	6/65 (9.2)	8/107 (7.5)	9/42 (21.4)	0.009*
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.25 (0.38 – 4.13)	1.12 (0.38 – 3.30)	4.11 (1.37 – 12.33)	0.049
Death (%)	13/156 (8.3)	1/66 (1.5)	9/109 (8.3)	10/42 (23.8)	0.001*
Multivariate HR for death (95% CI)	1.00 (reference)	0.64 (0.08 – 5.45)	0.98 (0.40 – 2.39)	6.26 (2.23 – 17.56)†	0.003

*χ^2 for comparison across all four groups.

†p<0.01 versus reference category.

Figure 17: Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity According to Clinical Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

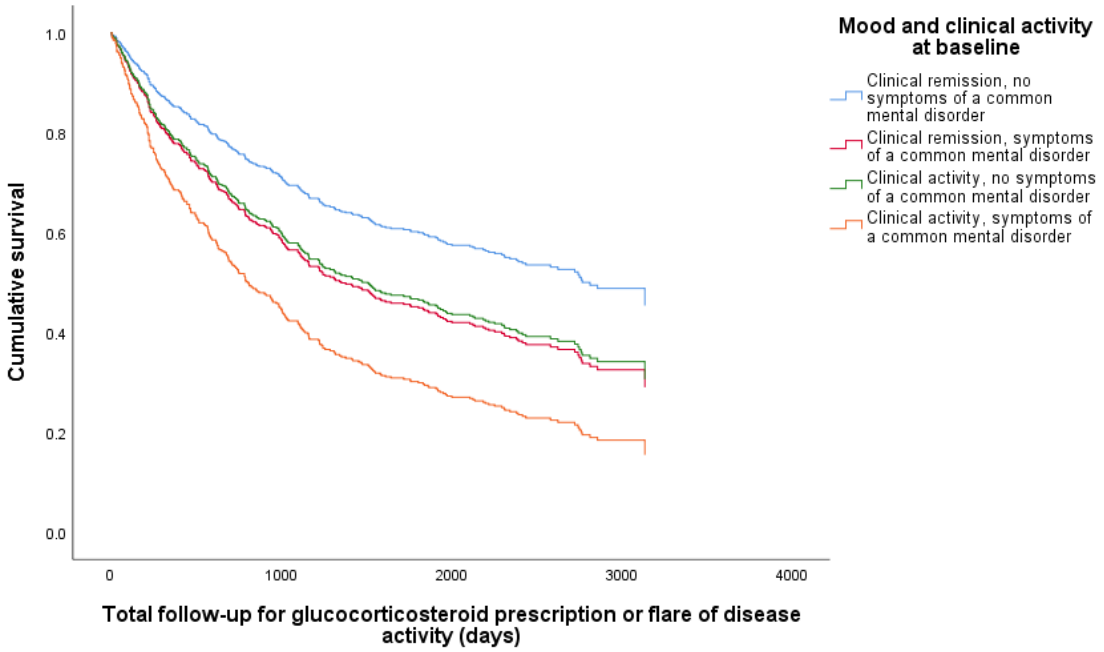


Figure 18: Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity According to Biochemical Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

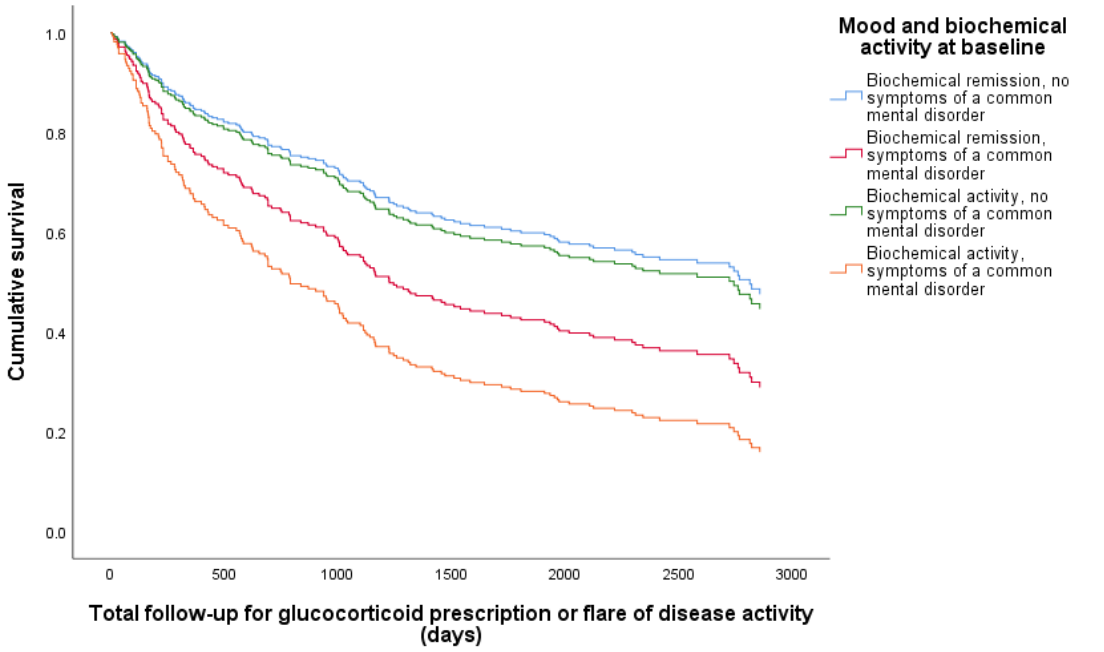


Table 13: Clinical Outcomes of Patients According to Biochemical Disease Activity (FC <100mcg/g) and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Biochemical remission, no symptoms of a common mental disorder	Biochemical remission, symptoms of a common mental disorder	Biochemical activity, no symptoms of a common mental disorder	Biochemical activity, symptoms of a common mental disorder	*p* value
Glucorticosteroid prescription or flare of disease activity (%)	52/114 (45.6)	26/35 (74.3)	56/115 (48.7)	36/59 (61.0)	0.011*
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.99 (1.16 – 3.39)	1.14 (0.77 – 1.70)	1.92 (1.18 – 3.12)†	0.020
Escalation of medical therapy due to uncontrolled IBD activity (%)	48/115 (41.7)	24/36 (66.7)	67/130 (51.5)	40/64 (62.5)	0.013*

Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.72 (0.99 – 2.97)	1.39 (0.94 – 2.05)	2.22 (1.39 – 3.53)†	0.009
Hospitalisation due to uncontrolled IBD activity (%)	14/115 (12.2)	6/36 (16.7)	27/146 (18.5)	23/70 (32.9)	0.006*
Multivariate HR for hospitalisation due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.22 (0.41 – 3.57)	1.40 (0.71 – 2.76)	3.24 (1.57 – 6.67)†	0.007
Intestinal resection due to uncontrolled IBD activity (%)	4/115 (3.5)	3/36 (8.3)	12/146 (8.2)	12/71 (16.9)	0.016*
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.48 (0.25 – 8.88)	2.04 (0.63 – 6.63)	4.35 (1.28 – 14.86)	0.088
Death (%)	8/116 (6.9)	0/37 (0.0)	14/149 (9.4)	11/71 (15.5)	0.044*
Multivariate HR for death (95% CI)	1.00 (reference)	n/a	1.58 (0.64 – 3.88)	5.81 (2.04 – 16.52)†	0.009

*χ^2 for comparison across all four groups.

†p<0.01 versus reference category.

Table 14: Clinical Outcomes of Patients According to Combined Clinical and Biochemical Disease Activity (FC <250mcg/g) and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Combined clinical and biochemical remission, no symptoms of a common mental disorder	Combined clinical and biochemical remission, symptoms of a common mental disorder	Combined clinical and biochemical activity, no symptoms of a common mental disorder	Combined clinical and biochemical activity, symptoms of a common mental disorder	*p* value
Glucorticosteroid prescription or flare of disease activity (%)	48/109 (44.0)	18/29 (62.1)	12/16 (75.0)	12/14 (85.7)	0.004*
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.73 (0.93 – 3.21)	4.12 (1.95 – 8.68)†	5.58 (2.30 – 13.6)†	<0.001
Escalation of medical therapy due to uncontrolled IBD activity (%)	48/109 (44.0)	18/29 (62.1)	19/24 (79.2)	15/18 (83.3)	0.001*

Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.86 (1.02 – 3.38)	3.79 (2.06 – 6.97)†	4.37 (2.02 – 9.46)†	<0.001
Hospitalisation due to uncontrolled IBD activity (%)	15/109 (13.8)	6/29 (20.7)	9/37 (24.3)	9/24 (37.5)	0.051*
Multivariate HR for hospitalisation due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.60 (0.58 – 4.45)	1.55 (0.62 – 3.85)	5.94 (2.20 – 16.1)†	0.006
Intestinal resection due to uncontrolled IBD activity (%)	4/109 (3.7)	2/29 (6.9)	4/37 (10.8)	7/25 (28.0)	0.001*
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.55 (0.25 – 9.45)	2.42 (0.51 – 11.4)	13.8 (3.17 – 60.2)†	0.004
Death (%)	10/111 (9.0)	1/29 (3.4)	0/37 (0.0)	6/25 (24.0)	0.007*
Multivariate HR for death (95% CI)	1.00 (reference)	1.20 (0.13 – 10.9)	n/a	17.8 (4.00 – 78.8)†	0.002

*χ^2 for comparison across all four groups.

†p<0.01 versus reference category.

5.3.3 Escalation of medical therapy due to uncontrolled IBD activity

Of 631 patients with complete data, 345 (54.7%) required escalation of medical therapy due to uncontrolled IBD activity over a mean follow-up period of 3.8 years (range 4 days to 8.7 years). Rates of escalation of therapy were highest in patients with symptoms of a common mental disorder at baseline for both those in clinical remission (61.3%) and those with clinically active disease (62.6%), although this failed to reach statistical significance (p=0.073 for trend) (Table 11). After multivariate Cox regression, escalation rates were significantly higher in those with clinically active disease and symptoms of a common mental disorder at baseline (HR = 1.65; 95% CI 1.14 to 2.40, p=0.008) (Table 11 and Figure 19). Younger age (HR per year = 0.98; 95% CI 0.97 to 0.99, p<0.001) was associated with a reduced likelihood of escalation of medical therapy and need for glucocorticosteroids at baseline (HR = 1.73; 95% CI 1.22 to 2.45, p=0.002) an increased likelihood.

Results were similar, though more pronounced, according to biochemical activity at baseline (Table 12). On multivariate analysis, rates of escalation were significantly higher for patients with biochemical activity and symptoms of a common mental disorder at baseline (HR = 2.97; 95% CI 1.74 to 5.06, p<0.001) (Table 12 and Figure 20). There were no other significant predictors of escalation identified. Again, sensitivity analysis using a FC of <100mcg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices yielded similar results (Table 13 and Table 14).

Figure 19: Survival Analysis for Occurrence of Escalation of Medical Therapy due to Uncontrolled IBD Activity According to Clinical Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

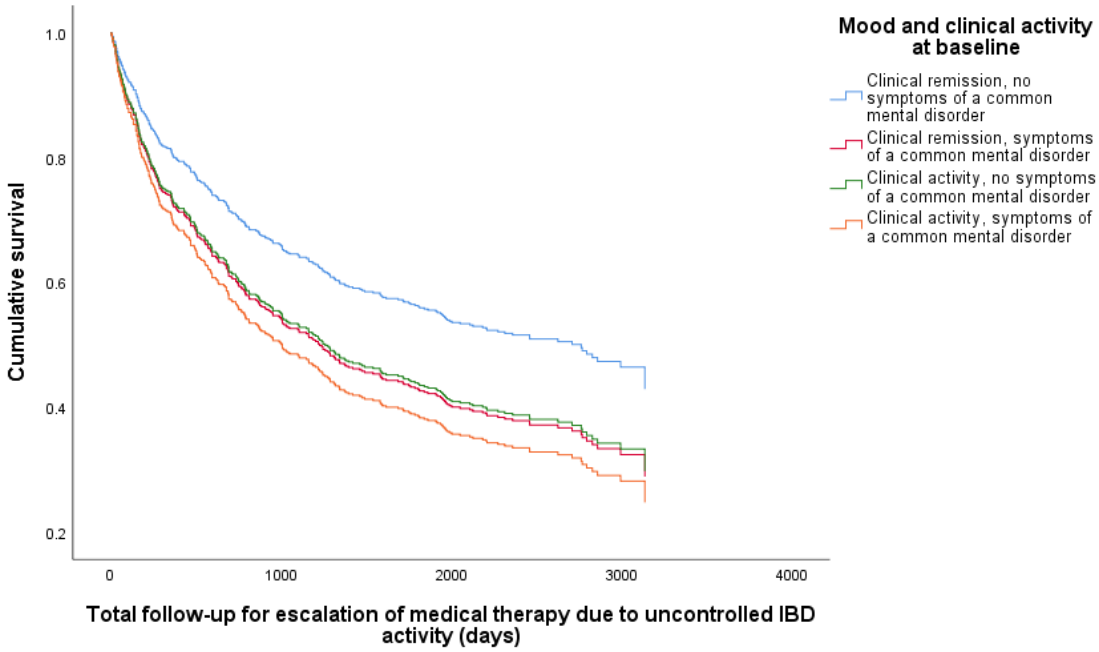
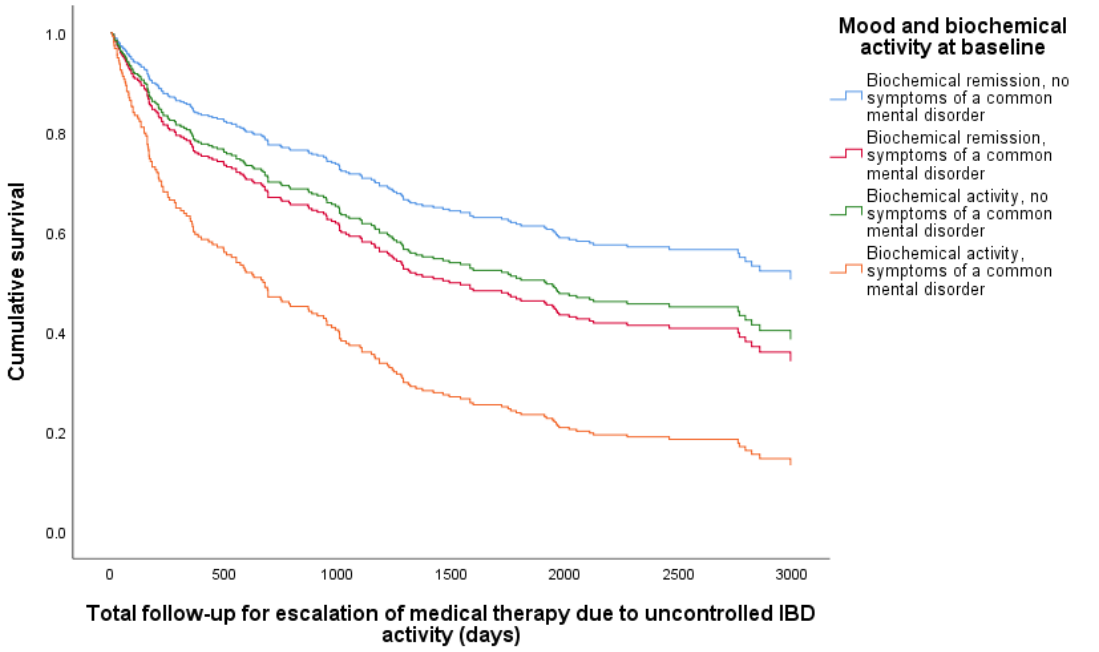


Figure 20: Survival Analysis for Occurrence of Escalation of Medical Therapy due to Uncontrolled IBD Activity According to Biochemical Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

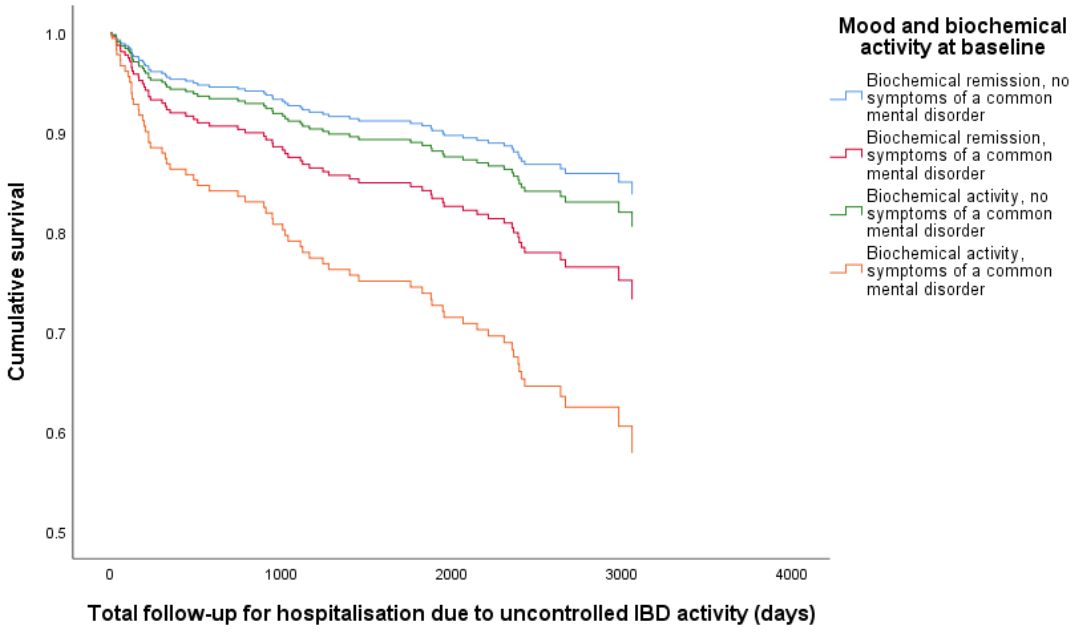


5.3.4 Hospitalisation due to uncontrolled IBD activity

In total, 171 (24.7%) of 692 patients required hospitalisation over a mean follow-up period of 5.4 years (range 2 days to 8.7 years). Again, hospitalisation rates were significantly higher among those with symptoms of a common mental disorder at baseline, irrespective of clinical activity (p=0.001 for trend) (Table 11). However, after multivariate Cox regression, rates were not significantly higher in any of the three groups (Table 11). Younger age (HR per year = 0.98; 95% CI 0.96 to 0.99, p<0.001), alcohol use (HR = 0.57; 95% CI 0.41 to 0.79, p<0.001), and 5-ASA use at baseline (HR = 0.53; 95% CI 0.35 to 0.81, p=0.003) were all associated with a reduced likelihood of hospitalisation, and need for glucocorticosteroids at baseline (HR = 2.01; 95% CI 1.32 to 3.05, p<0.001) and smoking (HR = 1.70; 95% CI 1.16 to 2.49, p=0.006) an increased likelihood.

When considering biochemical activity, rates of hospitalisation were generally higher in all three groups, compared with those in biochemical remission without symptoms of a common mental disorder at baseline (p=0.022 for trend) (Table 12). On multivariate analysis, hospitalisation due to uncontrolled IBD activity was significantly more likely among those with biochemical activity and symptoms of a common mental disorder at baseline (HR = 3.10; 95% CI 1.43 to 6.68, p=0.004) (Table 12 and Figure 21), with no other predictors identified. Again, when we performed a sensitivity analysis using a FC of <100mcg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices results were similar (Table 13 and Table 14).

Figure 21: Survival Analysis for Occurrence of Hospitalisation due to Uncontrolled IBD Activity According to Biochemical Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

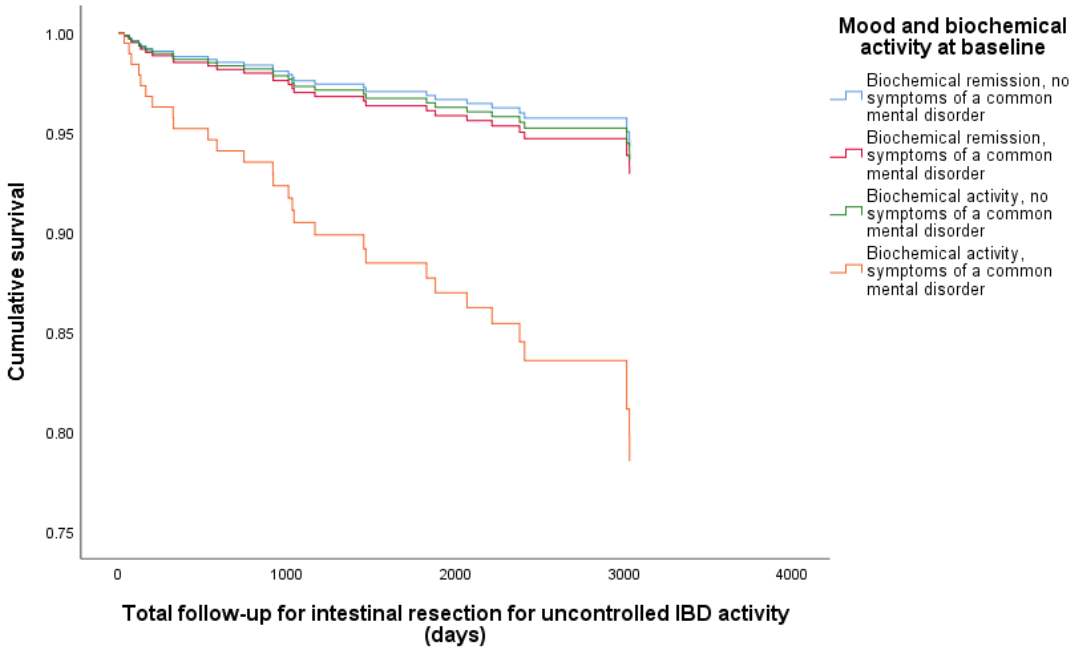


5.3.5 Intestinal resection due to uncontrolled IBD activity

Of 696 patients, 85 (12.2%) underwent intestinal resection for uncontrolled IBD activity, during a mean follow-up of 6.0 years (range 4 days to 8.7 years). Progression to intestinal resection was greatest in those reporting symptoms of a common mental disorder at baseline in those with clinical activity (22.0%) and in those in clinical remission (14.6%), compared with those without symptoms of a common mental disorder (p=0.001 for trend) (Table 11). However, after multivariate Cox regression these differences were not statistically significant (Table 11). Again, younger age (HR per year = 0.98; 95% CI 0.96 to 0.99, p=0.007) was associated with a reduced likelihood of intestinal resection.

When we limited the analysis to those patients providing an FC sample, rates of intestinal resection were significantly higher among all three groups, compared with those in biochemical remission without symptoms of a common mental disorder at baseline (p=0.009 for trend) (Table 12). However, on multivariate Cox regression analysis, this trend failed to reach significance, although for those with biochemical activity with symptoms of a common mental disorder at baseline this approached statistical significance (HR = 4.11; 95% CI 1.37 to 12.33, p=0.012) (Table 12, Figure 22). There were no other significant predictors of intestinal resection identified. Sensitivity analysis using a FC of <100mcg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices yielded similar results (Table 13 and Table 14).

Figure 22: Survival Analysis for Occurrence of Intestinal Resection due to Uncontrolled IBD Activity According to Biochemical Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline



5.3.6 Mortality

In total, 42 (6.0%) of 703 patients died over a mean follow-up period of 6.6 years (range 4 days to 8.8 years). There was no significant difference in mortality rates between those with symptoms of a common mental disorder and clinical activity (5.8%) or clinical remission (6.1%), compared with those in clinical remission without symptoms of a common mental disorder at baseline (7.6%) (p=0.24 for trend) (Table 11). However, after multivariate Cox regression analysis, mortality rates were significantly higher in those with clinical activity and symptoms of a common mental disorder at baseline (HR = 4.99; 95% CI 1.80 to 13.88, p=0.002) (Table 11 and Figure 23). Higher age was also associated with an increased risk of death (HR per year = 1.12; 95% CI 1.09 to 1.15, p<0.001).

According to biochemical activity at baseline, mortality was significantly higher in those with biochemical activity and symptoms of a common mental disorder at baseline (23.8%), compared with those in remission without symptoms of a common mental disorder (8.3%) (p=0.001 for trend) (Table 12). Again, after multivariate Cox regression analysis, mortality rates were significantly higher in those with biochemical activity and symptoms of a common mental disorder (HR = 6.26; 95% CI 2.23 to 17.56, p<0.001) (Table 13 and Figure 24). Higher age was again associated with an increased risk of death (HR per year = 1.11; 95% CI 1.07 to 1.15, p<0.001). Again, results were similar when we performed a sensitivity analysis using a FC of <100mcg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices (Table 13 and Table 14).

Figure 23: Survival Analysis for Occurrence of Death According to Clinical Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

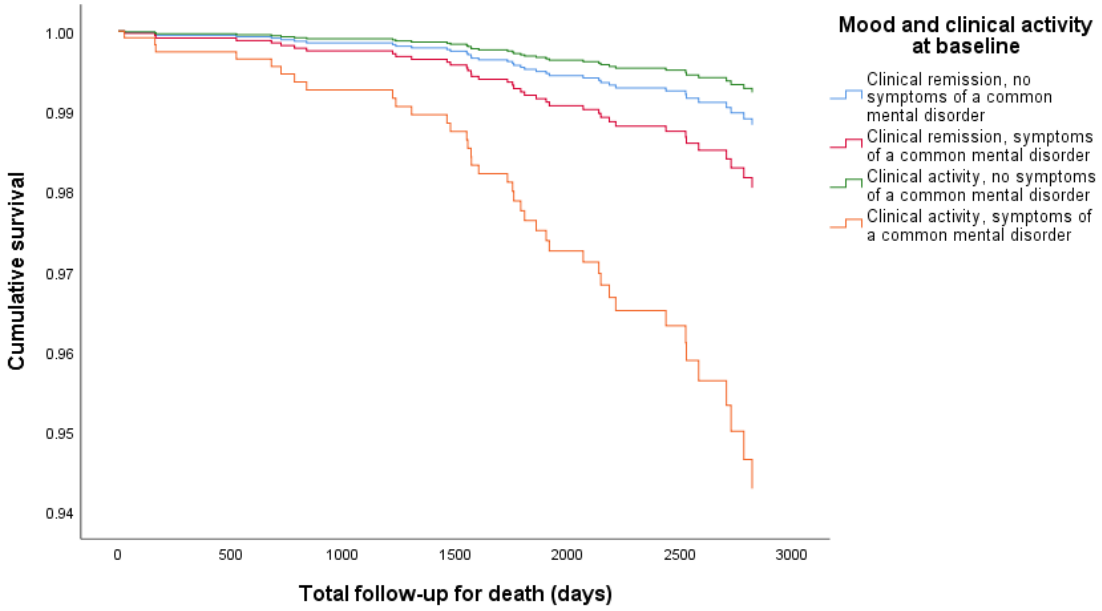
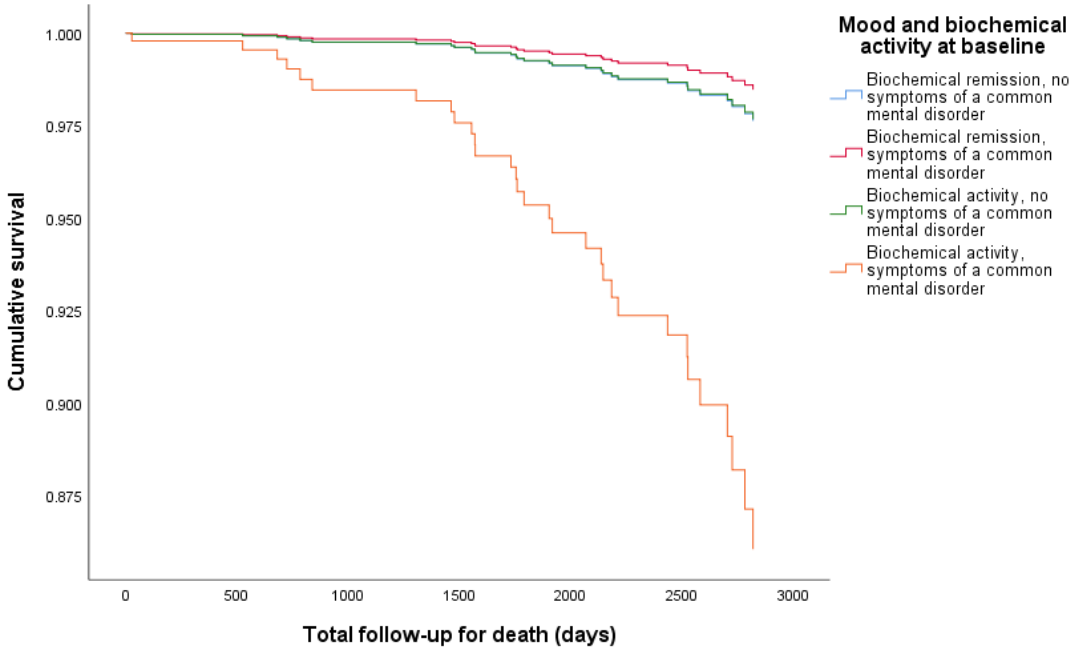


Figure 24: Survival Analysis for Occurrence of Death According to Biochemical Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline



5.3.7 Healthcare utilisation during longitudinal follow-up

The mean number of flares of disease activity, glucocorticosteroid prescriptions, hospitalisations, intestinal resections, outpatient appointments, and investigations were all significantly higher among those with clinical activity and symptoms of a common mental disorder at baseline (Table 15). The mean number of these events was also generally higher among those with biochemical activity and symptoms of a common mental disorder at baseline, although these differences did not reach statistical significance (Table 16).

Table 15: Healthcare Utilisation According to Clinical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Clinical remission, no symptoms of a common mental disorder	Clinical remission, symptoms of a common mental disorder	Clinical activity, no symptoms of a common mental disorder	Clinical activity, symptoms of a common mental disorder	*p* value*
Mean number of flares of disease activity (SD)	1.2 (1.6)	1.4 (1.6)	1.8 (1.8)	2.0 (1.9)	<0.001
Mean number of glucocorticosteroid prescriptions (SD)	0.6 (1.2)	0.7 (1.1)	1.0 (1.3)	1.1 (1.3)	0.001
Mean number of escalations (SD)	0.9 (1.2)	1.1 (1.2)	1.3 (1.3)	1.3 (1.3)	0.015
Mean number of hospitalisations (SD)	0.3 (0.7)	0.4 (0.7)	0.4 (0.8)	0.6 (1.0)	0.001
Mean number of intestinal resections (SD)	0.1 (0.3)	0.2 (0.4)	0.1 (0.4)	0.2 (0.4)	0.005

Mean number of outpatient appointments (SD)	8.1 (6.2)	9.1 (6.5)	10.5 (6.1)	11.7 (6.3)	<0.001
Mean number of radiological investigations (SD)	0.7 (1.3)	0.8 (1.5)	1.0 (1.4)	1.5 (1.9)	<0.001
Mean number of endoscopic investigations (SD)	0.7 (1.0)	0.9 (1.0)	1.1 (1.1)	1.2 (1.3)	<0.001

*p value for one-way ANOVA

Table 16: Healthcare Utilisation According to Biochemical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Biochemical remission, no symptoms of a common mental disorder	Biochemical remission, symptoms of a common mental disorder	Biochemical activity, no symptoms of a common mental disorder	Biochemical activity, symptoms of a common mental disorder	*p* value*
Mean number of flares of disease activity (SD)	1.1 (1.9)	1.4 (1.5)	1.6 (1.8)	1.9 (2.0)	0.057
Mean number of glucocorticosteroid prescriptions (SD)	0.6 (1.4)	0.7 (1.1)	0.9 (1.3)	1.1 (1.5)	0.15
Mean number of escalations (SD)	0.8 (1.3)	1.0 (1.1)	1.1 (1.2)	1.5 (1.5)	0.012
Mean number of hospitalisations (SD)	0.2 (0.7)	0.3 (0.5)	0.2 (0.6)	0.5 (0.8)	0.082
Mean number of intestinal resections (SD)	0.1 (0.2)	0.1 (0.4)	0.1 (0.3)	0.2 (0.4)	0.013

Mean number of outpatient appointments (SD)	8.4 (6.6)	10.1 (5.4)	9.2 (6.7)	10.9 (7.1)	0.087
Mean number of radiological investigations (SD)	0.6 (1.1)	0.8 (1.2)	0.9 (1.4)	1.4 (2.0)	0.006
Mean number of endoscopic investigations (SD)	0.9 (1.3)	1.2 (1.1)	0.8 (0.9)	0.9 (1.3)	0.15

*p value for one-way ANOVA

5.4 Discussion

This well-characterised cohort of IBD participants, builds from the data presented in Chapter 4, with longitudinal follow-up over a mean of 6.5 years. This chapter further examines the relative contribution of psychological health and clinical or biochemical activity on adverse disease outcomes in IBD, as well as to assess whether there is a cumulative impact of poor psychological health and disease activity. This study demonstrates that symptoms of common mental disorders influence IBD prognosis independently. Patients with disease activity reporting symptoms of a common mental disorder at baseline were at significantly higher risk of need for glucocorticosteroid therapy or flare of disease activity, escalation of therapy, hospitalisation for uncontrolled IBD activity, or death. Rates of intestinal resection were also higher in this patient group, although this difference did not reach statistical significance. In contrast, these endpoints were not significantly more common in those with clinical or biochemical activity without symptoms of a common mental disorder, or in patients with clinical or biochemical remission with symptoms of a common mental disorder. Mean numbers of each of these events of interest were also higher in those with clinical activity and symptoms of a common mental disorder at baseline, as were other markers of healthcare utilisation. These results suggest that aiming for clinical or biochemical remission alone is an inadequate therapeutic target in IBD. Psychological health is also an important driver of disease activity and may even be more important than clinical or biochemical disease activity in determining outcomes. Unless this is assessed and addressed, prognosis is likely to be worse. The evidence presented here underline the need to provide a service for patients with IBD that incorporates psychological support alongside medical management, particularly during periods of disease activity.

The long duration of follow-up allowed more time to for rarer events such as hospitalisation, intestinal resection, or death to occur, which previous studies examining the impact of psychological health on prognosis of IBD may have been underpowered to assess.[56] Data collection via the patients' electronic medical records is likely to have increased reliability and accuracy of the endpoints recorded, and collection of these events was carried out by an assessor blinded to all baseline data to reduce the risk of potential bias. As the hospital is the sole provider of IBD care to all participants, it is unlikely that occurrence of any of the endpoints of interest has been missed. We used multivariate Cox regression controlling for demographic and disease characteristics including somatoform-type behaviour, which may be an important confounder, to assess whether our observations on univariate analysis were likely to be independent predictors of

adverse outcomes. Very few other patient characteristics, including sex, marital status, tobacco and alcohol intake, educational level, type of IBD, IBD-related medications at baseline, or somatoform-type behaviour were associated with our endpoints of interest. Several of the endpoints we examined were objective, such as hospitalisation, intestinal resection, or death, which means our findings are unlikely to be driven by patients with poor psychological health being more likely to report gastrointestinal symptoms.[184] The fact that rates of outpatient consultation were, if anything, higher among those with the worst outcomes, and that glucocorticosteroid prescriptions, although higher, were not unreasonably so given the duration of the study, suggests that our observations are not an epiphenomenon related to poor quality care in this patient group. Finally, we used both clinical and biochemical measures of disease activity and conducted sensitivity analyses based on an FC of <100mcg/g, and a combined definition of disease activity or remission that incorporated both clinical and biochemical indices. Our results in these analyses were virtually unchanged, and in some cases the magnitude and significance of the difference in these endpoints seen in the group with disease activity and symptoms of a common mental disorder at baseline increased further.

With approximately half of patients providing FC samples for analysis at baseline, analyses in this group may be less robust, particularly for some of the rarer outcomes, although direction and magnitude of effects were similar for all analyses. Review of electronic medical records rather than real-time assessment of endpoints of interest, is also a limitation, as interpretation of some, such as glucocorticosteroid prescription or flare of disease activity, may still be subjective as they depend on the physician's interpretation of patient-reported symptoms. Escalation of therapy may also be at risk of subjective influence, although this tertiary centre adheres to the NICE guidelines,[133, 134] which state that there must be definitive evidence of disease activity before escalating medical therapy. Although the patients' electronic medical records were reviewed by one individual, blinded to the baseline questionnaire data, there is the possibility that a diagnosis of a common mental disorder was recorded within them, which may have introduced bias in assessing endpoints. The assessment of presence or absence of common mental disorders was based on the HADS, which measures symptoms of depression and anxiety at one point in time, rather than being based on a physician's diagnosis of anxiety or depression. The choice of the HADS was made prior to a study assessing the performance of various screening measures, versus a structured clinical interview, for common mental disorders in patients with IBD.[337] This study reported that the PHQ-9 had the highest sensitivity for detecting depression and the anxiety short form 8a (PROMs) for anxiety, although

all symptom scales performed similarly. In addition, the HADS does not collect data concerning somatic depressive symptoms, such as anhedonia, change in appetite, or irritability so may underestimate the prevalence of depression. It is acknowledged that a structured clinical interview to assess for presence of a common mental disorder would be preferable but, with almost 800 participants, this was not feasible.

Whether common mental disorders have a negative impact on the prognosis of IBD has been examined previously. However, many of these studies have not characterised patients based on presence or absence of disease activity at baseline.[57, 58, 60, 213] In one study that restricted recruitment to patients with IBD in remission, a significant increase in risk of flare of disease activity and escalation was seen in those with symptoms of common mental disorders at baseline.[56] In other studies of similar design stress also appears to be a predictor of relapse.[273, 274, 297] Patients with active disease with a history of major depressive disorder or symptoms of anxiety at baseline appear less likely to achieve remission, despite an escalation in therapy.[61] In addition, those with symptoms of depression and a recent flare of disease activity requiring hospitalisation, were more likely to require re-admission, compared with those without an underlying common mental disorder.[338] These results, demonstrate a cumulative impact of common mental disorders and disease activity on IBD-related outcomes and mortality, mirror recent findings from a study conducted in patients with coronary heart disease, in which psychological stress-induced myocardial ischaemia increased risk of future myocardial infarction or cardiovascular death significantly, compared with conventional exercise-induced ischaemia alone.[285] This effect was cumulative; those with both psychological stress-induced and conventional ischaemia were at greatest risk of myocardial infarction or cardiovascular death. We are not aware of any similar studies in the IBD literature, to date.

The possibility that psychological health may have a greater impact on IBD prognosis than disease activity raises important questions as to how patients are managed. This study has identified a cohort of patients with a high psychological and disease burden, who are more likely to require investigation, escalation, and intervention over time, and who are likely to be long-term high utilisers of health care. Where psychological support has been enlisted alongside physician input for patients, there is evidence of improved outcomes and reduced service need, with fewer unplanned admissions.[339] Higher levels of psychological resilience, the innate ability of the individual to overcome psychological and physical adversity, are also associated with fewer flares, lower rates of IBD-related surgery, and better quality of life.[189] Preliminary results in the field of resilience

training appear promising. A recent study recruiting patients with IBD with low resilience demonstrated that an integrated programme of resilience-based management reduced emergency department attendances, unplanned hospitalisations, and glucorticosteroid use.[188] Our study results also suggest that clinicians need to target more than just clinical or mucosal remission when treating patients with IBD. There is a need to incorporate psychological health as an independent therapeutic target in updates to current guidelines,[85] for both long-term prognostic benefits, as well as a likely reduction in the economic burden of IBD.

With limited RCTs of antidepressants or anxiolytics in patients with IBD their role remains unclear.[306] There have been more RCTs of psychological therapies, summarised in a prior meta-analysis;[183] in one trial hypnotherapy led to a significant reduction in likelihood of relapse in UC.[340] A subsequent RCT of CBT demonstrated beneficial effects on health-related quality of life, anxiety, and depression.[341] However, most trials have recruited unselected groups of patients. Another consideration is that psychological health may fluctuate, and there may be a subset of patients who are at even higher risk of poor prognostic outcomes. There is supportive evidence of this from other chronic diseases. For example, in a 3-year longitudinal follow-up study in chronic obstructive pulmonary disease persistent depression was associated with increased morbidity and mortality, whereas those whose depression remitted were comparable with those who were never depressed, showing improved walking distance and reduced frequency of exacerbations.[256] There remains a need for further RCTs of psychological therapies and antidepressants in more selected groups of patients with IBD, after appropriate screening for common mental disorders and objective quantification of inflammatory burden, as well as studies examining the trajectories of common mental disorders in IBD, and whether this influences prognosis. Replication of our results by studies recruiting patients subjected to a structured interview to assess formally for presence of common mental disorders would also be important.

In summary, patients with IBD with symptoms of a common mental disorder at baseline as well as clinical or biochemical evidence of disease activity were more likely to experience adverse disease outcomes. Rates of glucocorticosteroid prescription or flare, escalation, and hospitalisation were two to three times higher. Likelihood of intestinal resection was up to four times higher, although this did not reach statistical significance in our primary analysis. Finally, mortality rates were significantly higher in this patient group. Rates of these endpoints were not significantly higher in patients with active disease without symptoms of a common mental disorder. These data suggest that

common mental disorders are a risk factor for a poor prognosis in IBD. Their presence should be screened for routinely and, if present, considered as a therapeutic target.

Chapter 6

Characteristics and Effects of Anxiety and Depression Trajectories in Inflammatory Bowel Disease.

6.1 Introduction

Gut-brain axis communication occurs via complex interactions between the HPAA and neural and inflammatory pathways. Environmental and emotional stimuli may activate the HPAA, leading to release of cortisol and pro-inflammatory cytokines.[342] In addition, afferent signals from the gut can be transmitted to the brain, which can send signals via efferent pathways back to the intestine. Thus, there is bidirectional gut-brain communication.[195, 312]

Patients with IBD may report symptoms compatible with common mental disorders, with up to 50% reporting anxiety or depression during a flare.[4] A case-control study of almost 12,500 patients demonstrated significantly higher levels of both anxiety and depression, compared with the general population, particularly in the 12 months after diagnosis.[343] Depression is a pro-inflammatory condition associated with elevations in plasma cytokine levels, including TNF-α and IL-6,[344, 345] supporting a role for mood in immune dysregulation and inflammation. This highlights the influence common mental disorders may have on the natural history of IBD, not only via inflammatory pathways, but also due to altered neural input. In turn, common mental disorders are influenced by physical aspects of disease severity, activity, and chronicity,[346, 347] as well as sex,[259] age,[347] socioeconomic status,[347] adherence to treatment,[348] and past history of mental stress or mental ill health.[349]

As demonstrated in Chapter 3, there is increasing interest in brain-gut axis effects in IBD. Symptoms of common mental disorders increase subsequent risk of adverse outcomes, including flare or need for glucorticosteroids,[56, 57, 58] escalation of therapy,[56, 58] hospitalisation,[58, 60] and intestinal resection.[57, 58] Among individuals with no history of a common mental disorder, active disease is significantly associated with the *de novo* development of symptoms of anxiety or depression.[56, 259] There may also be a cumulative negative impact of psychological co-morbidity on IBD. As demonstrated in Chapter 4, individuals in biochemical remission, but with symptoms of more than one common mental disorder, were at significantly increased risk of glucocorticosteroid prescription, flare of disease activity, escalation of therapy, or a composite of these that also included hospitalisation and intestinal resection, during longitudinal follow-up. Finally, the results reported in Chapter 5 further suggest that symptoms of common mental disorders may influence IBD prognosis, independent of disease activity.

Most studies only examine prevalence or impact of symptoms of a common mental disorder at a single time point, which may be overly simplistic. Persistent or worsening anxiety and depression are associated with poor outcomes in other chronic diseases, such as ischaemic heart disease, chronic obstructive pulmonary disease, and type 1 diabetes mellitus,[210, 256, 303] but this has not been well-studied in IBD. All-cause and cardiovascular mortality was two-fold higher among depressed individuals post-myocardial infarction,[230] with persistent or worsening depression associated with significantly greater healthcare costs.[303] In patients with chronic obstructive pulmonary disease, persistent depression was associated with increased mortality, more frequent and severe disease exacerbations, more frequent hospitalisations, shorter walking distance, and reduced quality of life.[256]

This 12-month longitudinal follow-up study examines the natural history of symptoms of common mental disorders in patients with IBD, to better understand the characteristics of patients with different symptom courses, and how such symptom trajectories influence disease outcomes and healthcare utilisation.

6.2 Methods

6.2.1 Participants and Setting

Postal invitations were sent to all patients aged ≥18 years with an established histological, endoscopic, or radiological diagnosis of CD, UC, or IBD-U who had attended outpatient clinics between 2017 and 2020 at Leeds Teaching Hospitals NHS Trust. Each invitation included a web-link with a personalised uniform resource locator to an online patient information sheet, consent form, and online questionnaire. If preferred, a paper version of these documents was offered. Four follow-up questionnaires were sent at 3-month intervals, over a 12-month period. To limit losses to follow-up, a second reminder was sent to all those who initially consented to participate but did not respond to each of the 3-monthly questionnaires. Individuals with end ileostomy, colostomy, or ileo-anal pouch were excluded from follow-up due to potential inaccuracies in assessing clinical disease activity. The Wales research ethics committee approved this longitudinal study in February 2020 (Research Ethics Committee reference: 20/WA/0044).

6.2.2 Data Collection and Synthesis

Demographic data, including sex, age, marital status, ethnicity, educational level, and lifestyle factors, including tobacco and alcohol use was recorded. Clinical disease activity was assessed using a modified HBI for CD, excluding examination for abdominal mass,[90, 350] and the SCCAI for UC,[94] with a score of <5 used to define remission for both, as recommended.[95, 320] The HADS was used to assess for symptoms of anxiety or depression.[317] The total HADS scores range from 0 to 21. HADS-anxiety or depression scores were defined as normal (score 0-7), borderline (8-10), or abnormal (≥11), as previously recommended.[317] These data were used to create anxiety or depression trajectories, based on data provided at baseline and at least two points of follow-up. Patients were classified with normal HADS-anxiety or HADS-depression scores throughout, or those with a score of ≥11 at baseline that improved to <8 at the last point of follow-up, as having normal or improving HADS-anxiety or HADS-depression scores. Those with scores of ≥11 throughout, or those with a score of <8 at baseline that worsened to ≥11 at the last point of follow-up, were classified as having persistently abnormal or worsening HADS-anxiety or HADS-depression scores. All other individuals were classified as having fluctuating HADS-anxiety or HADS-depression scores. Identical trajectories were created for those providing data at baseline and all four points of follow-up. Somatoform symptom data using the PHQ-12 was collected,[252] which is derived from the PHQ-15,[319] with scores ranging from 0 to 24. Severity was characterised as high (total score ≥13), medium (8-12), low (4-7), or minimal (≤3). We assessed quality of life using the short IBD questionnaire (SIBDQ) health survey.[351]

One investigator, blinded to questionnaire responses, reviewed electronic medical records for all participants. IBD type (CD, UC, or IBD-U), extent and location of disease, and prior IBD-related intestinal resection were all verified. All current IBD-related medication use, including 5-ASAs, immunosuppressants, biologic therapies, or glucocorticosteroids, as well as current use of antidepressant drugs or opioids was documented. Healthcare utilisation data was also collected during the 12 months of follow-up, including number of physician-led or nurse-led IBD outpatient clinic visits, contact with the IBD helpline through either telephone calls or e-mails, and clinic visits related to extra-intestinal manifestations of IBD, as well as the number of endoscopic and radiological investigations requested to assess IBD activity. Investigations arranged for surveillance, therapeutic indications, or routine follow-up were excluded. Finally, the following clinical outcomes, along with the date of their occurrence were extracted: flare of disease activity based on a physician's global assessment; glucocorticosteroid prescription; escalation of medical therapy due to

uncontrolled IBD activity; hospitalisation due to uncontrolled IBD activity; intestinal resection due to uncontrolled IBD activity; or death. The number of each of these events of interest, other than death, were recorded. Changes to medication without evidence of uncontrolled IBD activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, as endpoints were not included.

6.2.3 Statistical Analysis

Data from SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA) was converted into tables in R for Windows version 4.0.2 and RStudio for Windows version 2022.02.0.443 (2009-2022 RStudio Inc., Boston, MA). Alluvial diagrams were created to display anxiety or depression trajectories visually for those providing data at baseline and all four points of follow-up using packages 'gg_plot' and 'gg_alluvial'. Characteristics were compared among those providing data at baseline and at least two points of follow-up, for those with persistently normal or improving, fluctuating, or persistently abnormal or worsening HADS-anxiety or HADS-depression scores. Healthcare utilisation across these three trajectories were also compared. To assess the impact of the three anxiety or depression trajectories on each of the disease activity outcomes of interest (flare of disease activity, glucocorticosteroid prescription, escalation of therapy, hospitalisation, intestinal resection, or death) their rates in each trajectory were compared during longitudinal follow-up. A Pearson's χ^2 test was used for categorical data where at least 75% of groups had counts ≥5. In cases where counts <5 were expected in ≤75% of groups, the Fisher's exact Test was applied. For continuous data, the Kruskal-Wallis one-way ANOVA was used for comparisons between >2 groups, while the Mann-Whitney U was used for comparison of continuous data between 2 groups. Due to multiple comparisons, a 2-tailed P value of <0.01 was considered statistically significant. These analyses were performed using SPSS for Windows version 26.0.

6.3 Results

6.3.1 Baseline demographics

Between January 2017 and June 2020, 4823 patients with IBD were seen in the outpatient clinic and contacted via letter invitation. A total of 1119 (23.2%) responded to the baseline questionnaire. Of these, 88 (7.9%) were ineligible due to either a stoma or ileo-anal pouch, meaning 1031 (92.1%) responders (mean age 52.6 years (SD 16.9 years), 565 (54.8%) female, 460 (44.6%) CD) were eligible for the study. In total, 771 (74.8%) of these 1031 patients provided HADS-anxiety data at baseline and two or more follow-up points and 777 (75.4%) provided HADS-depression scores at baseline and at least two points of follow-up. There were no significant differences in characteristics between responders and non-responders, including baseline HADS-anxiety or depression scores, other than those who provided data at baseline and two or more follow-up points were older (Table 17).

Table 17: Baseline Characteristics of Patients Providing HADS-anxiety or HADS-depression Data at Two Or More Points of Follow-up and Those Who Did Not.

	Responded to two or more follow-up questionnaires (n = 771)	**Did not respond to two or more follow-up questionnaires (n = 260)**	***p* value***
Mean age in years at baseline (SD)	53.7 (16.5)	49.1 (17.7)	<0.001
Female sex (%)	416 (54.2)	147 (56.8)	0.48
Married or co-habiting (%)	538 (70.3)	171 (66.3)	0.22
University graduate/professional (%)	296 (38.8)	92 (35.8)	0.39
Tobacco user (%)	52 (6.8)	16 (6.3)	0.75
Alcohol user (%)	546 (71.4)	200 (78.4)	0.028
IBD type (%)			
CD	338 (44.3)	125 (48.6)	
UC	375 (49.1)	117 (45.5)	
IBD-U	50 (6.6)	15 (5.8)	0.48
CD location (%)			
Ileal	121/337 (35.9)	36/125 (28.8)	
Colonic	95/337 (28.2)	44/125 (35.2)	
Ileocolonic	121/337 (35.9)	45/125 (36.0)	0.24
Stricturing CD (%)	96/337 (28.4)	34/125 (27.2)	0.80
Penetrating CD (%)	50/337 (14.8)	18/125 (14.4)	0.92
Perianal CD (%)	45/337 (13.3)	23/125 (18.4)	0.17
Previous intestinal resection (%)	149 (19.5)	39 (15.2)	0.12

UC extent (%) Proctitis Left-sided Extensive	 107/364 (29.4) 143/364 (39.3) 114/364 (31.3)	 39/114 (34.2) 37/114 (32.5) 38/114 (33.3)	 0.40
Current 5-ASA use (%)	408 (53.5)	125 (48.6)	0.18
Current immunomodulator use (%)	215 (28.2)	70 (27.2)	0.77
Current biologic use (%)	126 (16.5)	42 (16.3)	0.95
Current glucocorticosteroid use (%)	19 (2.5)	11 (4.3)	0.14
Current antidepressant use (%)	131 (17.0)	41 (15.8)	0.65
Current opiate use (%)	89 (11.6)	30 (11.6)	1.00
Diagnosed with IBD in the last 12 months (%)	58 (7.6)	16 (6.3)	0.47
Self-reported a flare at baseline (%)	135 (17.6)	54 (20.9)	0.24
Active disease on HBI or SCCAI at baseline (%)	289 (37.9)	90 (36.4)	0.69
HADS-anxiety categories at baseline (%) Normal Borderline abnormal Abnormal	 452 (58.6) 159 (20.6) 160 (20.8)	 118 (50.2) 56 (23.8) 61 (26.0)	 0.069

HADS-depression categories at baseline (%)			
Normal	578 (75.5)	183 (73.8)	
Borderline abnormal	108 (14.1)	37 (14.9)	
Abnormal	80 (10.4)	28 (11.3)	0.87
PHQ-12 somatoform symptom categories at baseline (%)			
Minimal	210 (29.2)	59 (26.0)	
Low	265 (36.9)	82 (36.1)	
Medium	182 (25.3)	54 (23.8)	
High	61 (8.5)	32 (14.1)	0.096
Mean SIBDQ score at baseline (SD)	51.2 (12.9)	49.2 (13.3)	0.044

*Independent samples *t*-test for comparison of normally distributed continuous data and χ^2 for comparison of categorical data.

6.3.2 Characteristics of Patients According to HADS-anxiety Trajectories.

Among the 771 patients providing HADS-anxiety data at baseline and two or more follow-up points, those with either fluctuating (266 (34.5%) patients) or persistently abnormal or worsening (105 (13.6%) patients) HADS-anxiety scores were significantly younger (p <0.001) and more likely to be female (p <0.001) compared with those with persistently normal or improving (400 (51.9%) patients) scores (Table 18). Although there were no significant differences between groups with respect to IBD-related therapy, those with either fluctuating or persistently abnormal or worsening HADS-anxiety scores were significantly more likely to be prescribed opiates (p = 0.001) and antidepressants (p <0.001). In addition, those with either fluctuating or persistently abnormal or worsening HADS-anxiety scores were more likely to have been diagnosed with IBD in the last 12 months (p = 0.001), to self-report a flare of disease activity at baseline, and to have active disease according to either the HBI or SCCAI at baseline (p <0.001 for both). These individuals were also more likely to have higher somatoform symptom scores on the PHQ-12 and reported lower quality of life according to the SIBDQ (p <0.001 for both), compared with those with persistently normal or improving HADS-anxiety scores.

There were 449 (45.8%) individuals (mean age 56.6 years (SD 15.7 years), 235 (52.3%) female, 197 (43.9%) CD) who provided HADS-anxiety data at baseline and all four follow-up points, with 204 (45.4%) having persistently normal or improving scores, 192 (42.8%) fluctuating, and 53 (11.8%) persistently abnormal or worsening scores. Of 282 patients with normal HADS-anxiety scores at baseline, 195 (69.1%) had persistently normal scores throughout 12 months of follow-up, 77 (27.3%) fluctuating, and 10 (3.5%) worsening (Figure 25). Of 81 patients with abnormal HADS-anxiety scores at baseline, 43 (53.1%) had persistently abnormal scores throughout, 29 (35.8%) fluctuating, and nine (11.1%) improving (p <0.001 for comparison).

Table 18: Baseline Characteristics of Patients According to HADS-anxiety Trajectories.

	Persistently normal or improving (n = 400)	**Fluctuating (n = 266)**	**Persistently abnormal or worsening (n = 105)**	***p* value***
Mean age in years at baseline (SD)	56.2 (16.6)	52.0 (15.9)	48.6 (15.9)	<0.001
Female sex (%)	181 (45.4)	170 (64.4)	65 (62.5)	<0.001
Married or co-habiting (%)	292 (73.6)	183 (69.3)	66 (63.5)	0.11
University graduate/professional (%)	150 (38.1)	103 (39.0)	43 (41.3)	0.83
Tobacco user (%)	24 (6.1)	18 (6.8)	10 (9.5)	0.46
Alcohol user (%)	285 (72.0)	190 (72.0)	71 (67.6)	0.66
IBD type (%)				
CD	174 (43.9)	118 (44.7)	46 (44.7)	
UC	196 (49.5)	130 (49.2)	49 (47.6)	
IBD-U	26 (6.6)	16 (6.1)	8 (7.8)	0.98

CD location (%)[†]				
Ileal	60/174 (34.5)	43/118 (36.4)	18/45 (40.0)	
Colonic	67/174 (33.3)	26/118 (22.0)	12/45 (24.4)	
Ileocolonic	56/174 (32.2)	49/118 (41.5)	16/45 (35.6)	0.24
Stricturing CD (%)	53/174 (30.5)	30/118 (25.4)	13/46 (28.3)	0.65
Penetrating CD (%)	18/174 (10.3)	27/118 (22.9)	5/46 (10.9)	0.01
Perianal CD (%)	19/174 (10.9)	16/118 (13.6)	10/46 (21.7)	0.16
Previous intestinal resection (%)	77 (19.4)	52 (19.7)	20 (19.2)	0.99
UC extent (%)[‡]				
Proctitis	56/190 (29.5)	37/128 (28.9)	14/46 (30.4)	
Left-sided	70/190 (36.8)	53/128 (41.4)	20/46 (43.5)	
Extensive	64/190 (33.7)	38/128 (29.7)	12/46 (26.1)	0.82
Current 5-ASA use (%)	214 (54.0)	143 (54.2)	51 (49.5)	0.69
Current immunomodulator use (%)	106 (26.8)	77 (29.2)	32 (31.1)	0.62
Current biologic use (%)	81 (20.5)	55 (20.8)	27 (26.2)	0.43
Current glucocorticosteroid use (%)	9 (2.3)	6 (2.3)	4 (3.9)	0.62
Current antidepressant use (%)	49 (12.3)	52 (19.7)	30 (28.6)	<0.001
Current opiate use (%)	31 (7.8)	38 (14.3)	20 (19.0)	0.001

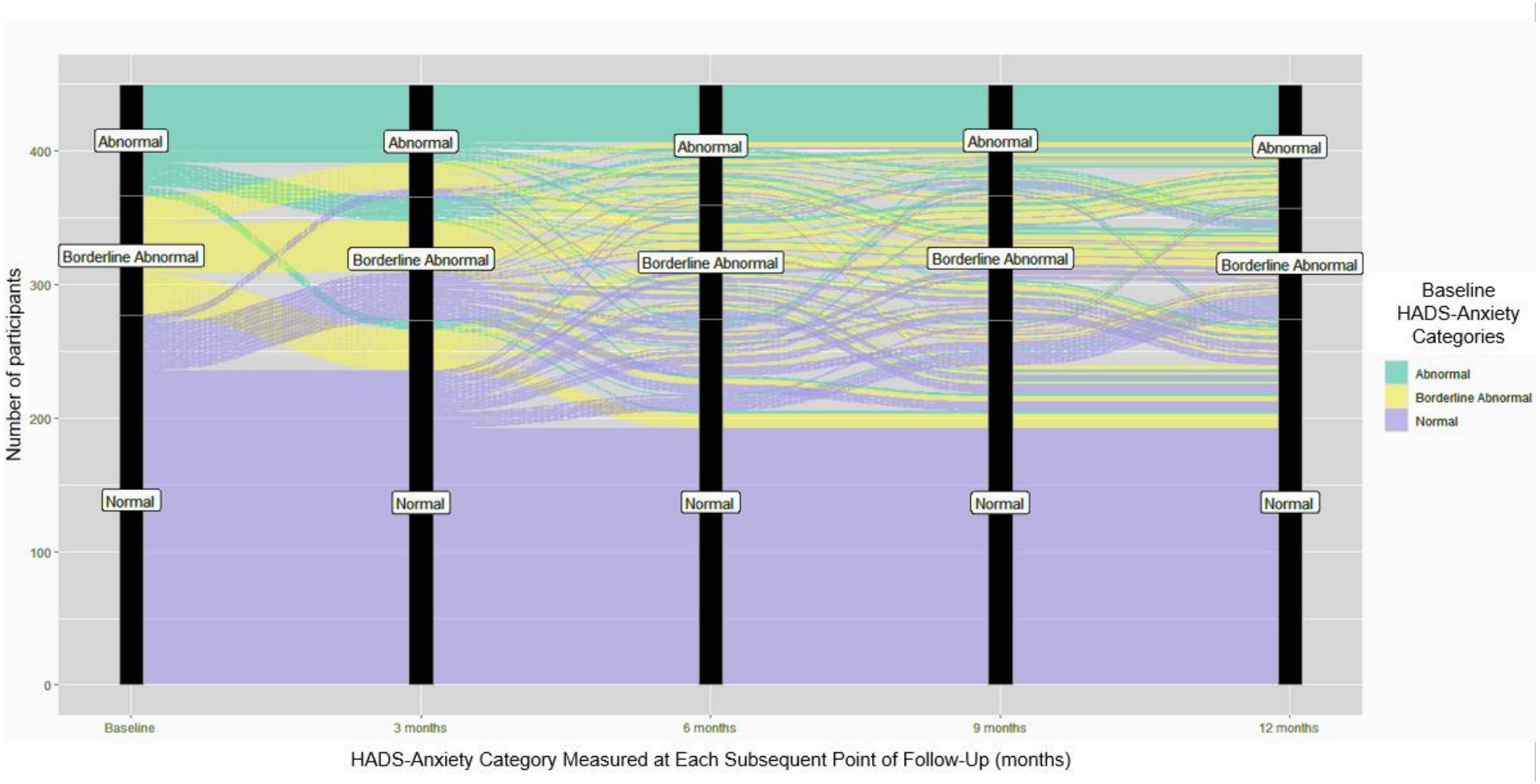
Diagnosed with IBD in the last 12 months (%)	20 (5.0)	21 (8.0)	17 (16.3)	0.001
Self-reported a flare at baseline (%)	43 (10.8)	62 (23.5)	30 (28.8)	<0.001
Active disease on HBI or SCCAI at baseline (%)	105 (26.6)	124 (47.0)	60 (57.1)	<0.001
PHQ-12 somatoform symptom categories at baseline (%)				
Minimal	159 (42.7)	42 (16.7)	9 (9.6)	
Low	136 (36.6)	108 (42.9)	21 (22.3)	
Medium	65 (17.5)	79 (31.3)	38 (40.4)	
High	12 (3.2)	23 (9.1)	26 (27.7)	<0.001
Mean SIBDQ score at baseline (SD)	57.2 (9.3)	47.1 (12.1)	37.3 (12.9)	<0.001

*One-way ANOVA for comparison of normally distributed continuous data, χ^2 for comparison of categorical data across all three groups.

†Data on CD location missing for one patient with persistently abnormal or worsening HADS-anxiety scores.

‡Data on UC extent missing for 11 patients; six with persistently normal or improving HADS-anxiety scores, two with fluctuating HADS-anxiety scores, and three with persistently abnormal or worsening HADS-anxiety scores.

Figure 25: Trajectory of HADS-Anxiety scores over 12-month longitudinal follow-up



6.3.3 Healthcare Utilisation and Clinical Outcomes of Patients According to HADS-anxiety Trajectories.

Individuals with persistently abnormal or worsening HADS-anxiety scores were significantly more likely to see a gastroenterologist in the outpatient clinic (p <0.001) and more likely to access the IBD helpline (p <0.001) (Table 19 and Figure 26). Those with persistently abnormal or worsening HADS-anxiety trajectories were also more likely to undergo more radiological investigations (p = 0.002) and endoscopic procedures (p = 0.002) for suspected IBD activity, compared with those with persistently normal or improving HADS-anxiety scores, and this trend persisted across all three groups (p = 0.007 and p = 0.008 respectively). Finally, individuals with persistently abnormal or worsening HADS-anxiety trajectories were significantly more likely to be seen in other clinics for extra-intestinal manifestations of IBD (p <0.001, overall trend p = 0.002). In terms of disease activity outcomes over the 12-month period, those with persistently abnormal or worsening trajectories were more likely to experience a flare of disease activity compared with those with persistently normal or improved HADS-anxiety trajectories (p = 0.004), and the number of flares was also significantly higher (p = 0.009), but no other significant differences were detected. Results for all these analyses were similar when patients diagnosed with IBD within the last 12 months were excluded from the analysis (Table 20).

Table 19: Healthcare Utilisation and Clinical Outcomes of Patients According to HADS-anxiety Trajectories Over 12-month Longitudinal Follow-up.

	Persistently normal or improving (n = 400)	Fluctuating (n = 266)	*p* value*	Persistently abnormal or worsening (n = 105)	*p* value*	*p* value**
Healthcare utilisation						
Median number of clinic appointments with a gastroenterologist (IQR)	1 (0-2)	1 (0-2)	0.024	1 (0-2)	<0.001	<0.001
Median number of clinic appointments with an IBD specialist nurse (IQR)	1 (0-1)	0 (0-1)	0.34	0 (0-1)	0.22	0.40
Median number of IBD helpline calls (IQR)	0 (0-2)	0 (0-2)	0.31	1 (0-4)	<0.001	<0.001
Median number of radiological investigations related to IBD activity (IQR)	0 (0-0)	0 (0-0)	0.07	0 (0-0)	0.002	0.007

Median number of endoscopic investigations related to IBD activity (IQR)	0 (0-0)	0 (0-0)	0.38	0 (0-0)	0.002	0.008
Median number of other specialty clinics related to extra-intestinal manifestations of IBD (IQR)‡	0 (0-0)	0 (0-0)	0.10	0 (0-1)	<0.001	0.002
Clinical outcomes						
Flare of disease activity (%)	47 (11.8)	38 (14.3)	0.34	24 (22.9)	0.004	0.015
Median number of flares of disease activity (IQR)	0 (0-0)	0 (0-0)	0.33	0 (0-0)	0.009	0.032
Glucocorticosteroid prescription due to uncontrolled disease activity (%)	29 (7.2)	17 (6.4)	0.67	11 (10.5)	0.28	0.40
Median number of glucocorticosteroid prescriptions due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.68	0 (0-0)	0.27	0.40

Escalation of IBD therapy due to uncontrolled disease activity (%)	40 (10.0)	36 (13.5)	0.16	18 (17.1)	0.04	0.10
Median number of escalations of IBD therapy due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.17	0 (0-0)	0.04	0.10
Hospitalisation due to uncontrolled disease activity (%)	11 (2.8)	15 (5.6)	0.06	2 (1.9)	0.63	0.089
Median number of hospitalisations due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.06	0 (0-0)	0.62	0.09
Intestinal resection due to uncontrolled disease activity (%)	3 (0.8)	6 (2.3)	0.10	0 (0)	0.50	0.10
Median number of intestinal resections due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.10	n/a	0.37	0.10
Death (%)[†]	4 (1.0)	1 (0.4)	0.34	3 (2.9)	0.16	0.10
Median number of deaths (IQR)	0 (0-0)	0 (0-0)	0.36	0 (0-0)	0.15	0.10

*Mann-Whitney U for continuous data, χ^2 for categorical data with counts ≥5 and Fisher's Exact Test for categorical data with <5 counts, for comparison to those with persistently normal or improving HADS-anxiety trajectories.

**Kruskal-Wallis One-way ANOVA for comparison of continuous data, and χ^2 for comparison of categorical data across all three groups.

‡Clinics included rheumatology, dermatology, hepatology, oral medicine, or colorectal surgery.

†No deaths were related directly to complications of IBD.

Figure 26: Future adverse disease outcomes according to HADS-anxiety trajectories over 12-month longitudinal follow-up. HADS, hospital anxiety and depression scale; IBD, inflammatory bowel disease.

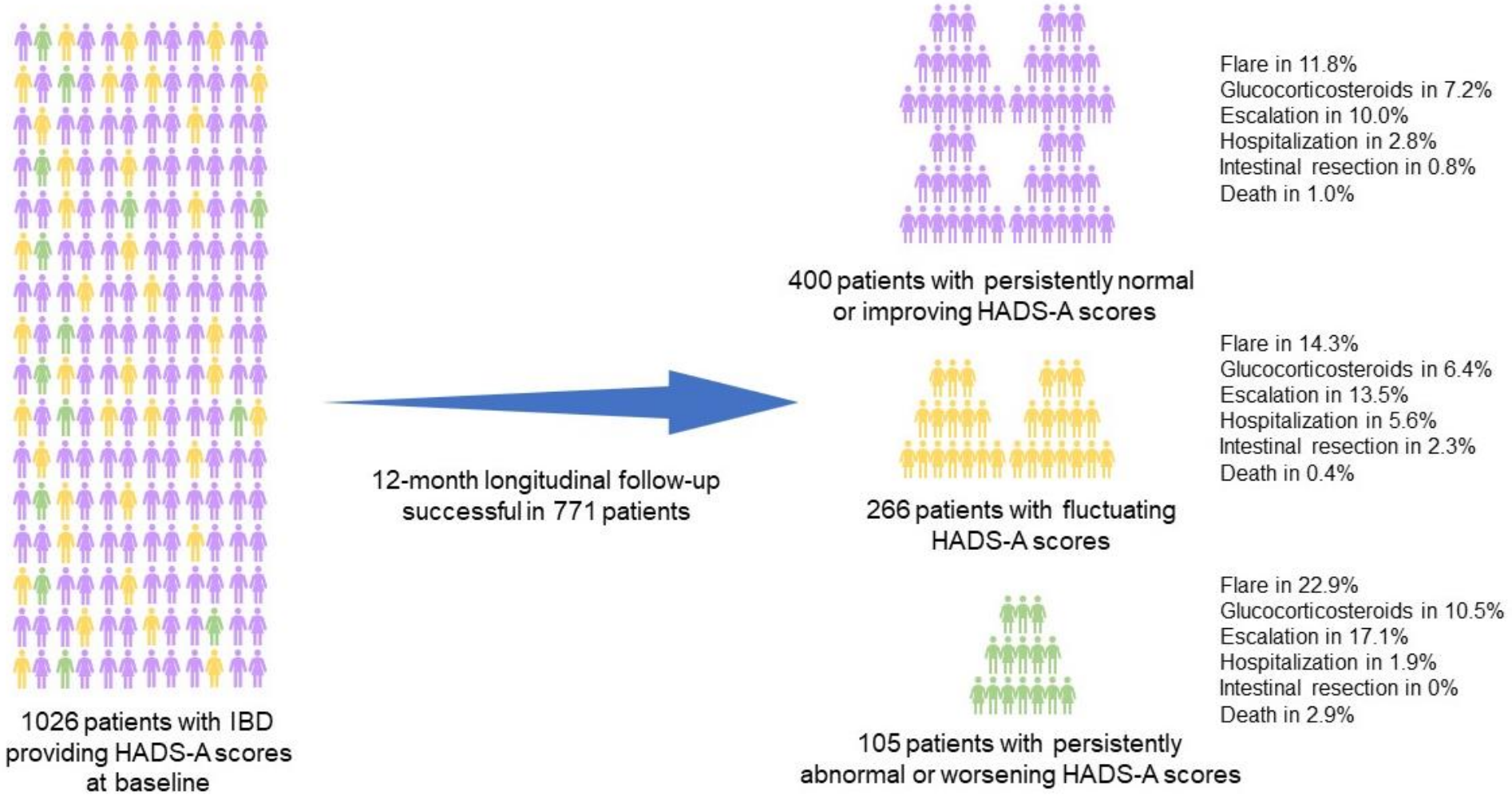


Table 20: Healthcare Utilisation and Clinical Outcomes of Patients According to HADS-anxiety Trajectories Over 12-month Longitudinal Follow-up with Patients with IBD Diagnosed in the Last 12 Months Excluded.

	Persistently normal or improving (n = 377)	Fluctuating (n = 241)	Persistently abnormal or worsening (n = 87)	*p* value*
Healthcare utilisation				
Median number of clinic appointments with a gastroenterologist	1	1	1	<0.001
Median number of clinic appointments with an IBD specialist nurse	1	0	0	0.50
Median number of IBD helpline calls	0	0	1	<0.001
Median number of radiological investigations related to IBD activity	0	0	0	0.090
Median number of endoscopic investigations related to IBD activity	0	0	0	0.004

Median number of other specialty clinics related to extra-intestinal manifestations of IBD‡	0	0	0	0.010
Clinical outcomes				
Flare of disease activity (%)	42 (11.1)	31 (12.9)	20 (23.0)	0.013
Median number of flares of disease activity	0	0	0	0.026
Glucocorticosteroid prescription due to uncontrolled disease activity (%)	25 (6.6)	16 (6.6)	9 (10.3)	0.45
Median number of glucocorticosteroid prescriptions due to uncontrolled disease activity	0	0	0	0.45
Escalation of IBD therapy due to uncontrolled disease activity (%)	35 (9.3)	30 (12.4)	15 (17.2)	0.087
Median number of escalations of IBD therapy due to uncontrolled disease activity	0	0	0	0.090
Hospitalisation due to uncontrolled disease activity (%)	10 (2.7)	13 (5.4)	1 (1.1)	0.087

Median number of hospitalisations due to uncontrolled disease activity	0	0	0	0.089
Intestinal resection due to uncontrolled disease activity (%)	3 (0.8)	5 (2.1)	0 (0)	0.19
Median number of intestinal resections due to uncontrolled disease activity	0	0	n/a	0.19
Death (%)[†]	3 (0.8)	1 (0.4)	3 (3.4)	0.043
Median number of deaths	0	0	0	0.10

*Kruskal-Wallis One-way ANOVA for comparison of continuous data and χ^2 for comparison of categorical data.

[‡]Clinics included rheumatology, dermatology, hepatology, oral medicine, or colorectal surgery.

[†]No deaths were related directly to complications of IBD.

6.3.4 Characteristics of Patients According to HADS-depression Trajectories.

Among the 777 patients providing HADS-depression scores at baseline and at least two points of follow-up, those with either fluctuating (209 (26.9%) patients) or persistently abnormal or worsening (53 (6.8%) patients) scores were less likely to have reached a university or postgraduate level of education (p = 0.004) but there were no other significant differences in demographic or disease characteristics (Table 21). Again, those with persistently abnormal or worsening scores were more likely to be prescribed opiates (p <0.001) and antidepressants (p <0.001), but there were no significant differences according to IBD-related therapy. Significantly more individuals with either fluctuating or persistently abnormal or worsening HADS-depression scores had been diagnosed with IBD in the last 12 months (p = 0.006), and significantly more reported a flare at baseline and had active disease according to either the HBI or SCCAI (p <0.001 for both). Those with either fluctuating or worsening or persistently abnormal HADS-depression scores had higher somatoform symptom scores and reported lower quality of life according to the SIBDQ (p <0.001 for both).

There were 458 (44.6%) individuals (mean age 56.6 years (SD 15.7 years), 241 (52.6%) female, 200 (43.7%) CD) providing HADS-depression scores at all five time points. Of these, 284 (62.0%) had persistently normal or improving scores, 147 (32.2%) fluctuating, and 27 (5.9%) persistently abnormal or worsening scores. Of 355 patients with normal HADS-depression scores at baseline, 279 (78.6%) had persistently normal scores throughout 12 months of follow-up, 69 (19.4%) fluctuating, and seven (2.0%) worsening (Figure 27). Of 47 patients with abnormal HADS-depression scores at baseline, 20 (42.6%) had persistently abnormal scores throughout, 22 (46.8%) fluctuating, and five (10.6%) improving (p <0.001 for comparison).

Table 21: Baseline Characteristics of Patients According to HADS-depression Trajectories.

	Persistently normal or improving (n = 515)	**Fluctuating (n = 209)**	**Persistently abnormal or worsening (n = 53)**	***p* value***
Mean age in years at baseline (SD)	54.3 (16.7)	53.0 (16.1)	50.5 (15.4)	0.15
Female sex (%)	267 (52.0)	121 (58.5)	33 (62.3)	0.15
Married or co-habiting (%)	376 (73.7)	138 (66.0)	29 (55.8)	0.01
University graduate/professional (%)	213 (42.0)	72 (34.6)	11 (20.8)	0.004
Tobacco user (%)	27 (5.3)	19 (9.1)	6 (11.3)	0.07
Alcohol user (%)	376 (73.9)	143 (68.8)	30 (56.6)	0.019
IBD type (%)				
CD	219 (42.8)	94 (45.9)	27 (51.9)	
UC	261 (51.0)	97 (47.3)	21 (40.4)	
IBD-U	32 (6.3)	14 (6.8)	4 (7.7)	0.64
CD location (%)[†]				
Ileal	74/219 (33.8)	39/93 (41.9)	7/27 (25.9)	
Colonic	68/219 (31.1)	19/93 (20.4)	8/27 (29.6)	
Ileocolonic	77/219 (35.2)	35/93 (37.6)	12/27 (44.4)	0.27

Stricturing CD (%)	64/219 (29.2)	29/94 (30.9)	3/27 (11.1)	0.12
Penetrating CD (%)	27/219 (12.3)	21/94 (22.3)	3/27 (11.1)	0.06
Perianal CD (%)	25/219 (11.4)	15/94 (16.0)	6/27 (22.2)	0.22
Previous intestinal resection (%)	95 (18.6)	46 (22.3)	11 (21.2)	0.50
UC extent (%)‡				
Proctitis	73/254 (28.7)	29/95 (30.5)	7/19 (36.8)	
Left-sided	101/254 (39.8)	36/95 (37.9)	7/19 (36.8)	
Extensive	80/254 (31.5)	30/95 (31.6)	5/19 (26.3)	0.96
Current 5-ASA use (%)	282 (55.1)	106 (51.7)	22 (42.3)	0.18
Current immunomodulator use (%)	139 (27.1)	59 (28.8)	21 (40.4)	0.13
Current biologic use (%)	104 (20.3)	45 (22.0)	14 (26.9)	0.51
Current glucocorticosteroid use (%)	13 (2.5)	4 (2.0)	2 (3.8)	0.72
Current antidepressant use (%)	52 (10.1)	62 (29.7)	19 (35.8)	<0.001
Current opiate use (%)	38 (7.4)	34 (16.3)	18 (34.0)	<0.001
Diagnosed with IBD in the last 12 months (%)	28 (5.5)	22 (10.6)	8 (15.1)	0.006
Self-reported a flare at baseline (%)	61 (12.0)	56 (26.8)	17 (32.7)	<0.001
Active disease on HBI or SCCAI at baseline (%)	148 (29.1)	106 (51.0)	38 (71.7)	<0.001

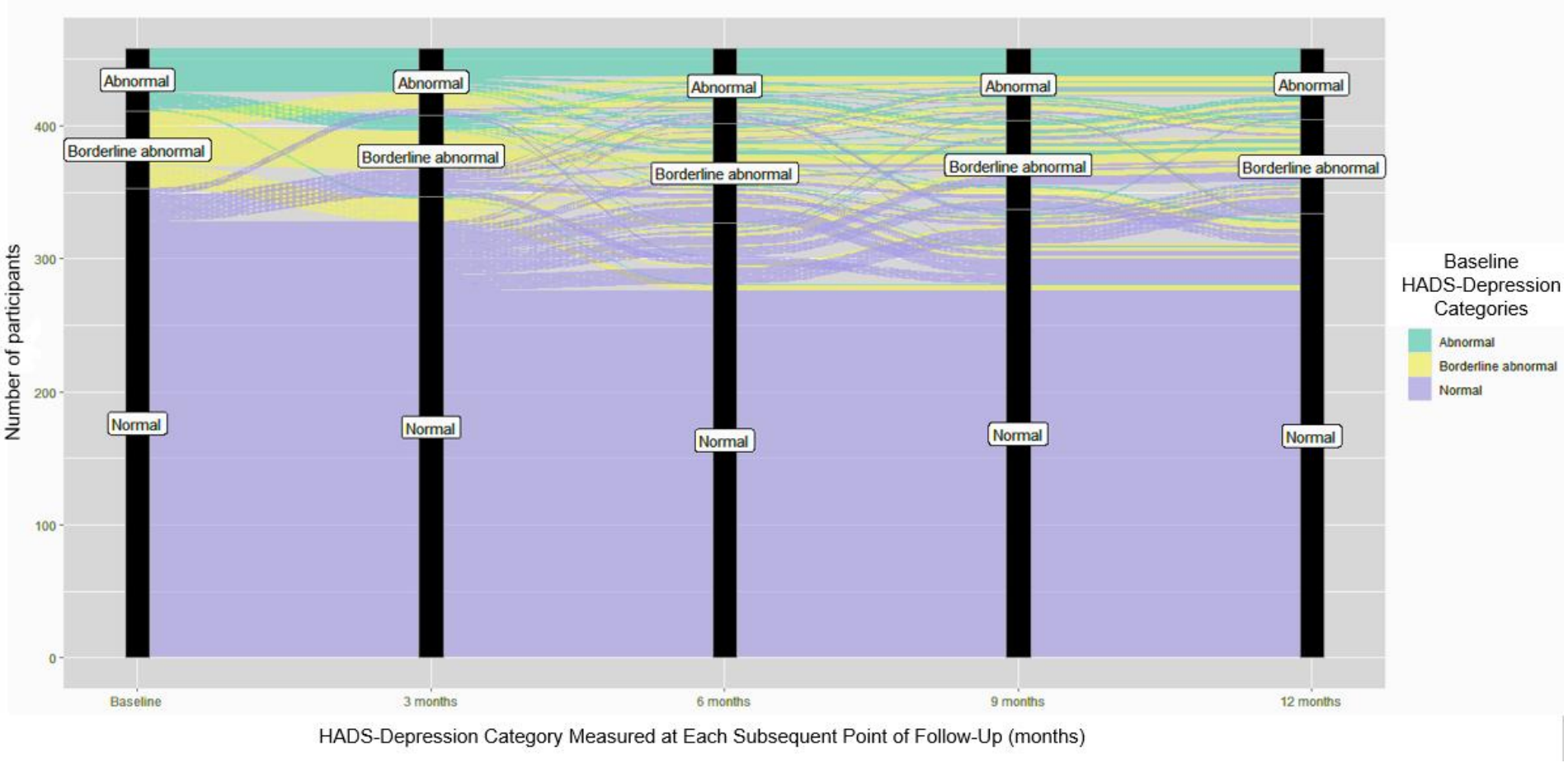
PHQ-12 somatoform symptom categories (%)				
Minimal	188 (38.9)	20 (10.4)	3 (6.5)	
Low	197 (40.8)	65 (33.9)	6 (13.0)	
Medium	84 (17.4)	79 (41.1)	18 (39.1)	
High	14 (2.9)	28 (14.6)	19 (41.3)	<0.001
Mean SIBDQ score (SD)	56.1 (9.9)	43.0 (11.6)	33.0 (12.8)	<0.001

*One-way ANOVA for comparison of normally distributed continuous data, χ^2 for comparison of categorical data across all three groups.

†Data on CD location missing for one patient with fluctuating HADS-depression scores.

‡Data on UC extent missing for 11 patients; seven with persistently normal or improving HADS-depression scores, two with fluctuating HADS-depression scores, and two with persistently abnormal or worsening HADS-depression scores.

Figure 27: Trajectory of HADS-Depression scores over 12-month longitudinal follow-up



6.3.5 Healthcare Utilisation and Clinical Outcomes of Patients According to HADS-depression Trajectories.

Individuals with persistently abnormal or worsening HADS-depression scores were more likely to see a gastroenterologist or an IBD nurse specialist in the outpatient clinic (p <0.001 for both) (Table 22 and Figure 28). The number of endoscopic investigations performed for suspected IBD activity was higher in those with fluctuating HADS-depression scores (p = 0.002) compared with those with persistently normal or improving scores. Similarly, fluctuating scores were associated with a greater number of appointments in other clinics for extra-intestinal manifestations of IBD (p = 0.003). There were no significant differences between groups with regards to any disease activity outcomes. Again, results were similar when patients diagnosed with IBD within the last 12 months were excluded from the analysis (Table 23).

Table 22: Healthcare Utilisation and Clinical Outcomes of Patients According to HADS-depression Trajectories Over 12-month Longitudinal Follow-up.

	Persistently normal or improving (n = 515)	Fluctuating (n = 209)	*p* value*	Persistently abnormal or worsening (n = 53)	*p* value*	*p* value**
Healthcare utilisation						
Median number of clinic appointments with a gastroenterologist (IQR)	1 (0-2)	1 (0-2)	0.01	1 (1-2)	<0.001	<0.001
Median number of clinic appointments with an IBD specialist nurse (IQR)	1 (0-1)	1 (0-1)	0.22	0 (0-1)	<0.001	<0.001
Median number of IBD helpline calls (IQR)	0 (0-2)	1 (0-3)	0.051	1 (0-3.5)	0.84	0.065
Median number of radiological investigations related to IBD activity (IQR)	0 (0-0)	0 (0-0)	0.013	0 (0-0)	0.10	0.03
Median number of endoscopic investigations related to IBD activity (IQR)	0 (0-0)	0 (0-0)	0.002	0 (0-0)	0.10	0.005

Median number of other specialty clinics related to extra-intestinal manifestations of IBD (IQR)‡	0 (0-0)	0 (0-1)	0.003	0 (0-1)	0.02	0.003
Clinical outcomes						
Flare of disease activity (%)	68 (13.2)	33 (15.8)	0.36	10 (18.9)	0.25	0.41
Median number of flares of disease activity (IQR)	0 (0-0)	0 (0-0)	0.55	0 (0-0)	0.13	0.04
Glucocorticosteroid prescription due to uncontrolled disease activity (%)	39 (7.6)	15 (7.2)	0.85	5 (9.4)	0.63	0.86
Median number of glucocorticosteroid prescriptions due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.90	0 (0-0)	0.62	0.40
Escalation of IBD therapy due to uncontrolled disease activity (%)	58 (11.3)	27 (12.9)	0.43	9 (17.0)	0.22	0.44
Median number of escalations of IBD therapy due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.50	0 (0-0)	0.21	0.11

Hospitalisation due to uncontrolled disease activity (%)	19 (3.7)	9 (4.3)	0.70	0 (0)	0.16	0.32
Median number of hospitalisations due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.70	n/a	0.16	0.09
Intestinal resection due to uncontrolled disease activity (%)	5 (1.0)	4 (1.9)	0.24	0 (0)	0.61	0.40
Median number of intestinal resections due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.30	n/a	0.47	0.10
Death (%)†	3 (0.6)	3 (1.4)	0.23	2 (3.8)	0.071	0.072
Median number of deaths (IQR)	0 (0-0)	0 (0-0)	0.25	0 (0-0)	0.02	0.11

*Mann-Whitney U for continuous data, χ^2 for categorical data with counts ≥5 and Fisher's Exact Test for categorical data with <5 counts, for comparison to those with persistently normal or improving HADS-depression trajectories.

**Kruskal-Wallis One-way ANOVA for comparison of continuous data, and χ^2 for comparison of categorical data across all three groups. ‡Clinics included rheumatology, dermatology, hepatology, oral medicine, or colorectal surgery.

†No deaths were related directly to complications of IBD.

Figure 28: Future Adverse Disease Outcomes According to HADS-Depression Trajectories Over 12-month Longitudinal Follow-up.

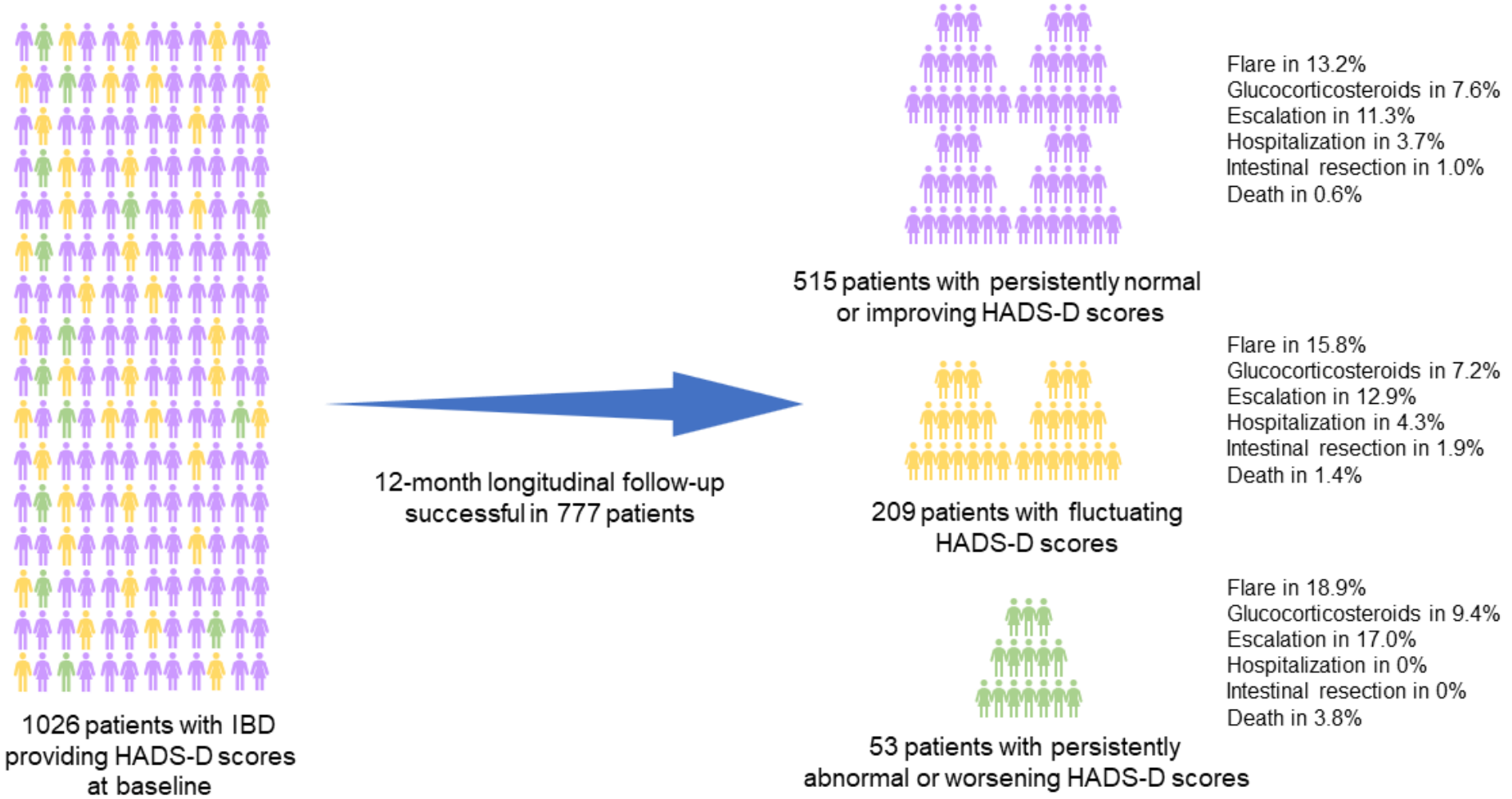


Table 23: Healthcare Utilisation and Clinical Outcomes of Patients According to HADS-depression Trajectories Over 12-month Longitudinal Follow-up with Patients with IBD Diagnosed in the Last 12 Months Excluded.

	Persistently normal or improving (n = 481)	Fluctuating (n = 185)	Persistently abnormal or worsening (n = 45)	*p* value*
Healthcare utilisation				
Median number of clinic appointments with a gastroenterologist	1	1	1	0.001
Median number of clinic appointments with an IBD specialist nurse	1	1	0	0.001
Median number of IBD helpline calls	0	1	1	0.097
Median number of radiological investigations related to IBD activity	0	0	0	0.30
Median number of endoscopic investigations related to IBD activity	0	0	0	0.005
Median number of other specialty clinics related to extra-intestinal manifestations of IBD‡	0	0	0	0.017
Clinical outcomes				

Flare of disease activity (%)	57 (11.9)	29 (15.7)	9 (20.0)	0.17
Median number of flares of disease activity	0	0	0	0.22
Glucocorticosteroid prescription due to uncontrolled disease activity (%)	34 (7.1)	13 (7.0)	5 (11.1)	0.60
Median number of glucocorticosteroid prescriptions due to uncontrolled disease activity	0	0	0	0.60
Escalation of IBD therapy due to uncontrolled disease activity (%)	50 (10.4)	23 (12.4)	7 (15.6)	0.49
Median number of escalations of IBD therapy due to uncontrolled disease activity	0	0	0	0.46
Hospitalisation due to uncontrolled disease activity (%)	17 (3.5)	7 (3.8)	0 (0)	0.43
Median number of hospitalisations due to uncontrolled disease activity	0	0	n/a	0.43
Intestinal resection due to uncontrolled disease activity (%)	5 (1.0)	3 (1.6)	0 (0)	0.62
Median number of intestinal resections due to uncontrolled disease activity	0	0	n/a	0.62
Death (%)[†]	3 (0.6)	2 (1.1)	2 (4.4)	0.045

Median number of deaths	0	0	0	0.11

*Kruskal-Wallis One-way ANOVA for comparison of continuous data and χ^2 for comparison of categorical data.

‡Clinics included rheumatology, dermatology, hepatology, oral medicine, or colorectal surgery.

†No deaths were related directly to complications of IBD.

6.4 Discussion

This study has examined the natural history of symptoms of common mental disorders in patients with IBD and to assess the impact of trajectories of these symptoms on healthcare utilisation and prognosis. Of note, high HADS-anxiety or depression scores at study entry were a strong predictor of future anxiety or depression trajectory, with most individuals reporting abnormal HADS scores at baseline continuing a trajectory of persistently abnormal or fluctuating scores, and only one in 10 individuals with abnormal scores at baseline improving subsequently. Characteristics associated with persistently abnormal or worsening scores, included female sex and younger age for anxiety, lower educational level for depression, and higher levels of somatoform symptom-reporting, and opiate and antidepressant use for both anxiety and depression. Those with persistently abnormal or worsening anxiety or depression scores were more likely to have received a diagnosis of IBD within the preceding 12 months, more likely to self-report a flare of disease activity at study entry, and significantly more likely to have elevated clinical disease activity scores and lower IBD-related quality of life scores at baseline. Finally, although rates of escalation of therapy, hospitalisation, or intestinal resection were not significantly higher in these individuals, those with persistently abnormal or worsening HADS scores were significantly more likely to require clinical contact, via appointments and helpline support, and underwent a greater number of investigations.

A large, unselected cohort of patients with IBD was recruited, which means these results are likely to be generalisable to many secondary and tertiary centres managing such patients. Initial enrolment, and subsequent follow-up, was predominantly via personalised links to online questionnaires, minimising missing data from participants. Although a structured interview may have provided greater sensitivity or specificity than the HADS for the detection of common mental disorders,[337] the additional use of the PHQ-12 questionnaire, collected other somatic symptoms of depression, such as sleep and fatigue, which are not captured by the HADS. In addition, the use of validated online questionnaires enabled distribution at regular intervals to a large cohort of over 1000 patients enrolled at baseline. This regular contact with participants, at 3-monthly intervals, allows better understanding of the fluctuation of symptoms of a common mental disorder, and assessment of the impact of these trajectories on disease outcomes was enabled by a thorough blinded review of medical records, including clinic appointments and investigations, undertaken by a single investigator, thereby limiting variation in their assessment between different observers.

Although the sample size was large and rates of most adverse disease outcomes of interest were numerically higher among those with persistently abnormal or worsening anxiety or depression scores, the 12-month study duration resulted in relatively low event rates for some endpoints. This is a limitation, and studies with longer follow-up will be important, as demonstrated in Chapter 5. It was not possible to assess the characteristics of non-responders to the baseline questionnaire and, therefore, cannot exclude a volunteer bias, with those with abnormal anxiety or depression scores being more likely to participate. This may have led to an overestimation of the impact of anxiety or depression trajectories on disease course and healthcare utilisation. However, the converse could also be true, which may have reduced the likelihood of detecting a significant impact of the trajectories on either of these endpoints. In addition, approximately 25% of participants did not provide follow-up anxiety or depression scores at a sufficient number of time points to assess their trajectories. However, there were few differences between those who did and those who did not respond meaning those successfully followed-up were broadly representative of the original participants. Finally, patient-reported clinical disease activity scores were relied on, rather than an objective measure of inflammation, such as FC, to assess IBD activity at baseline. Given the COVID-19 pandemic, persuading patients with IBD to attend an appointment in-person to provide a stool sample would have been impractical. Previous studies have shown that the SCCAI is correlated with both FC and the endoscopic Mayo sub-score in UC. However, in small bowel CD even objective markers such as FC may overlook active disease and invasive measures such as regular endoscopy would not have been feasible for such a large cohort.[352, 353]

Recruitment began in 2020, at the height of the COVID-19 pandemic, and at the end of the first lockdown period in the UK. Thus, IBD management over the subsequent 12 months is likely to have differed substantially from usual practice pre-COVID-19, with fewer routine clinic appointments available, and surgery restricted only to emergency or urgent cases. In addition, escalation of therapy for persistently active disease may have been more commonplace, to avoid requirement for hospitalisation. Furthermore, concerns from patients regarding continuation of immunosuppressant drugs or presentation to an inpatient or outpatient setting during this period could have influenced these findings. It is difficult to evaluate the impact of repeated lockdowns and concerns over shielding, among a group of patients who are clinically vulnerable to COVID-19, which may have affected mental health among those who took part in our study. Somatoform symptom-reporting and “functional” gastrointestinal symptoms are

also associated with increased healthcare use and symptoms of common mental disorders in IBD.[197]

Changes in physical illness and symptoms of common mental disorders track closely together in chronic disease, including IBD,[231, 354] with both mental and physical aspects influencing the course of disease.[285] These results support existing literature describing the prevalence and negative impact of persistent symptoms of anxiety or depression in other chronic diseases. In a 3-year study involving over 1500 patients with chronic obstructive pulmonary disease, 24% had persistent depression.[256] These individuals were more likely to undergo treatment for disease exacerbations and experience a loss in exercise tolerance during the study. A 5-year longitudinal study of patients with newly diagnosed type 1 diabetes demonstrated almost one-in seven individuals followed a trajectory of worsening depressive symptoms, and these patients were significantly more likely to have higher HbA_{1c} values and worse disease control.[210] In these studies, those with persistently abnormal mood scores shared similar baseline characteristics to our participants, being younger, more likely to be female,[256, 303] and having attained a lower level of education.[231] In addition, in this study persistently abnormal or worsening anxiety or depression scores were more prevalent in those with IBD diagnosed within the prior 12 months. These latter findings are supported by observations from two large case-control studies, which demonstrated a significant association between new initiation of antidepressant therapy or new presentation of a psychiatric disorder in the first year after a diagnosis of IBD.[220, 355] There have been few other studies examining the impact of fluctuations in mood on natural history of IBD. One small study, recruiting 32 patients with IBD who answered monthly depression questionnaires, reported that there was no evidence that depressed mood led to worse disease outcomes.[356]

Common mental disorders may be underdiagnosed in chronic diseases, as symptoms of physical illness such as changes in appetite, sleeping patterns, pain, fatigue, and side effects from medications, can overlap those of anxiety and depression. Recognition of, and screening for, common mental disorders in clinical practice in patients with IBD remains poor,[309] and although there is increasing acceptance that anxiety and depression have a detrimental impact on disease outcomes, there is a lack of consensus on management.[70] Based on these findings, higher risk patients with IBD, such as younger or newly diagnosed individuals, may benefit from regular routine screening for common mental disorders,[357] with appropriate intervention. However, despite UK national recommendations for IBD services to have a defined referral pathway to a clinical psychologist or counsellor with an interest in IBD, in a 2014 survey by the Royal

College of Physicians only 12% of centres provided this service.[311] Whether treatment of anxiety or depression in IBD has a beneficial effect on disease activity and outcomes is unclear, with most RCTs assessing antidepressant drugs or psychological therapies in unselected groups of patients.[183, 358] There is some support for an effect of antidepressants on mood, but relatively few studies.[306] In unselected patient groups, evidence suggests that psychological therapies with the potential for benefit in IBD, such as CBT, tend to lose efficacy over time.[183] A systematic review of 31 studies, containing almost 2400 patients, demonstrated those with active IBD had a significant improvement in quality of life scores following psychological therapy, including CBT, stress management, mindfulness, or hypnotherapy, with CBT demonstrating the most consistent positive impact.[359] Recently, there has been increasing focus on resilience training, incorporating a personalised approach to psychotherapy including CBT and mindfulness-based training. In patients with IBD with low resilience this approach has been shown to have a beneficial effect, reducing hospitalisations by over 90% in 12 months, opiate use by almost 50%, and primary care prescriptions for glucocorticosteroids by more than 70%.[188] High resilience among individuals with IBD is associated with lower anxiety scores, improved quality of life, lower disease activity scores, and reduced need for IBD-related surgery.[189, 360] These findings require replication using rigorous methodology but underline the need to identify patients at high risk of adverse outcomes, to select those most likely to respond to psychological interventions.

This study reports the trajectories of symptoms of common mental disorders in patients with IBD over a 12-month period and their associated characteristics. Identifying those with worsening or persistently high anxiety or depression scores, highlights a cohort that are significantly higher utilisers of healthcare, requiring more appointments and undergoing more investigations. This exposes a potentially vulnerable group of patients, particularly those early on in their diagnosis or with active IBD, who may be at higher risk of future adverse disease outcomes, although further longitudinal follow-up studies are needed to confirm or refute this. In addition, 90% of patients with abnormal anxiety or depression scores at baseline continued a trajectory of persistently abnormal or fluctuating scores, and only 10% improved, suggesting that if any clinical assessment of mood detects an abnormality, then this is likely to persist, and may affect future healthcare utilisation. Based on these findings, there is a clear need to offer formal psychological support to a subgroup of patients with IBD, via a defined referral pathway, to reduce healthcare utilisation and, potentially, improve disease prognosis. There is a need to advocate for screening for common mental disorders in all patients with IBD, with appropriate

intervention, particularly within the first year of diagnosis, and again routinely during periods of flare of disease activity, so that the treatment of both physical and mental health problems can be addressed simultaneously.

Chapter 7

Conclusions

The prevalence of IBD is rising worldwide, with more than 0.8% of the UK population affected,[36] due to better understanding and awareness, alongside more advanced biochemical, radiological and endoscopic modalities to aid early diagnosis. The medical management of IBD has also evolved dramatically over the last 10 years, with the development of new advanced therapies and minimally invasive surgical techniques. Treatment of IBD remains heavily focused on the management of disease activity with attention to the adaptive immunological response, alongside management of its associated physical complications. There is an increasing push for a ‘top down’ approach with early escalation to immunosuppressive therapies to achieve rapid biochemical and histological remission.[361] The PROFILE (PRedicting Outcomes For Crohn’s disease using a molecular biomarker) multicentre RCT demonstrated an advantage in a ‘top-down’ treatment strategy with combined anti-TNF-α and immunomodulator therapy, compared with an accelerated conventional ‘step-up’ treatment plan, with fewer adverse events at 12 months.[361] These advances allow us to persevere for longer with medical interventions, and those with poorly controlled disease are now able to cycle through multiple biologic therapies.

When determining therapeutic targets, the STRIDE initiative highlighted the need for both clinical remission, as well as biochemical and endoscopic normalisation, stressing the importance of patient perception of disease control, and better quality of life.[85] The reporting of IBS-type symptoms is high in IBD, despite evidence of endoscopic or histological remission, and is linked with higher rates of anxiety and depression.[50] It has become more apparent in recent years that the presence of gastrointestinal symptoms is associated with higher rates of service use, increased numbers of investigations, but that these physical symptoms alone do not necessarily result in an increased risk of disease activity.[260] Using targeted interventions, brain-gut behavioural treatments have demonstrated positive outcomes in managing gastrointestinal symptoms, such as improved pain control, through techniques such as face-to-face gut-directed hypnotherapy, and self-directed CBT.[362] In IBD cohorts, the use of psychological therapies is also associated with improvements in quality of life, stress, anxiety and depression scores, with the greatest effects in those with worse psychological health at baseline.[182]. However, in practice, the psychological impact that persistent disease activity has upon an individual, as well as the potential impact of common mental disorders on adverse IBD outcomes, is often overlooked and underestimated. Despite the perception from patients that there is an increased need for psychological support, very few centres offer this early in the patient journey, with dedicated services sparse and

reserved for those with substantial need, rather than a pre-emptive approach.[311, 363]

The subsequent impact of symptoms of anxiety and depression on the outcomes of chronic disease is multifaceted, from a theoretical increase in inflammatory cytokine exposure, to lack of engagement and functional overlay, exacerbated by the perception of treatment 'failure'. Previous studies have suggested there is a bidirectional link between common mental disorders and disease activity; however the lack of statistical significance, with rare endpoints, left this theoretical.[56] The increasing evidence that biopsychosocial support models improve outcomes in other chronic diseases, has led to recognition of this issue in gastrointestinal disease, particularly highlighting the role of the gut-brain axis in IBD. These foundations inspired the work described in this thesis, to further explore the gut-brain axis and its role in IBD and, thus, better understand the impact common mental disorders have on natural disease progression. Through a rigid selection process, the systematic review and meta-analysis described in Chapter 3, showed significant bidirectional associations between disease activity and common mental disorders. This study identified an increased risk in those with either anxiety or depression at baseline, of future adverse IBD-related outcomes including escalation of therapy and hospitalisation. Conversely, the presence of active IBD at baseline was associated with new symptoms of common mood disorders, in those with no prior reported psychological co-morbidity. This study demonstrated the bidirectional nature of the gut-brain axis in IBD, and emphasised the need to further explore the natural progression of IBD in those with common mental disorders.

Chapter 4 explored the effect of the increasing burden of common mental disorders, and impact on IBD-related outcomes. This chapter demonstrated that in those patients with IBD in biochemical remission, reporting symptoms of more than one of anxiety, depression, or somatoform behaviours, led to a higher risk of at least one outcome of interest, including glucocorticosteroid prescription or flare of disease activity, escalation of medical therapy, hospitalisation, or intestinal resection due to active IBD. This study identified the need to better understand the natural history of common mental disorders in patients with IBD, and their relationship with disease activity outcomes over time. This issue was explored further in Chapter 5, in a longitudinal study of over 700 patients, examining the effects of clinical disease activity, and presence of reported symptoms of a common mental disorder on disease outcomes. As expected, the presence of both clinical disease activity and symptoms of a common mental disorder, projected poor outcomes, including increased risk of flare, hospitalisation, intestinal resection, and death. Of interest, across all end points,

those reporting symptoms of common mental disorders despite no clinical disease activity had similar, or worse, projected risk compared to those with clinical disease activity, but without symptoms of a common mental disorder. This demonstrates that symptoms of a common mental disorder have the potential to affect the natural history of IBD, and that proactive management of psychological wellbeing is a valid treatment goal, addressed in conjunction with equivalent PROMs, and more objective disease activity treatment targets identified by STRIDE II.[85]

To understand the way in which co-morbid anxiety and depression fluctuate in IBD is equally important, if we are to know not just who to target, but when. The findings demonstrated in Chapter 6 show that like many chronic diseases, symptoms of common mental disorders may fluctuate during extended follow-up. This study identified a small cohort of patients that have persistent poor mood. This lack of recovery from reported poor mood, is a risk factor for increased healthcare utilisation, with higher numbers of investigations and clinical contacts, but no association with adverse disease activity outcomes during 12 month follow-up. Understanding the wider impact that common mental disorders have in IBD, as demonstrated throughout this thesis, it would be expected that with further longitudinal follow up, and thus a greater number of disease endpoints met, that this cohort could also be at risk of worse IBD-related disease outcomes. Together, the studies described in this thesis support the increasing need to identify those at risk of expressing and developing symptoms of common mental disorders, alongside the physical symptoms of disease activity. Those with underlying common mental disorders, particularly those with very poor mood scores, or more than one common mental disorder, are at increasing risk of poor physical outcomes and persistent poor mood.

The impact of both physical and mental health is multifaceted from education and employability, to social functioning. As is the nature of IBD, the financial implications fluctuate in a similar fashion, and the greatest costs expected in the first year of diagnosis, often driven by hospital admissions and productivity losses.[364] The rising costs of advanced therapies are also associated with increased expenditure, particularly in those with poorly controlled, or extensive disease.[365] The financial impact extends beyond the individual treatment, with additional impact on secondary care services, contact and investigations.[265] The co-morbid impact of both common mental disorders and IBD may increase healthcare costs by over 50%, due to higher number of emergency presentations, hospitalisations, and IBD-related surgical costs.[366] There is increasing evidence that psychological services in IBD are cost-effective through reducing secondary care service utilisation, with those who engage in

psychological support requiring fewer investigations, outpatient appointments, and emergency department attendances.[190, 367]

The findings presented in this thesis highlight opportunities for further research. A large meta-analysis, incorporating 25 RCTs, supported our findings of a fluctuating and relapsing pattern to common mental disorders, with prolonged therapy strategies found to be more beneficial in terms of quality of life outcomes, and improved common mental disorder scores.[182] The greatest improvements were observed in selected cohorts with underlying common mental disorders, or active IBD at baseline.[182, 368] A small RCT did demonstrate improvements in both subjective and objective markers of disease activity following a prolonged course of psychological intervention in those with active CD, however it was those with the most severe mood disorder scores at baseline that demonstrated the greatest effect.[369] A further meta-analysis supported the use of psychological therapies, which were shown to be superior to exercise and antidepressant use, on the effect of CRP and calprotectin in the IBD population. An increasing difference in mood scores, was associated with a more substantial improvement in biochemical markers.[370] These studies show that psychological therapies are evidenced to effect mood, and there is a suggestion with better patient selection this may also impact disease activity.

Investigating the efficacy of psychological therapies in IBD, may be underestimated due to the inclusion of unselected patients, with and without symptoms of common mental disorders, in clinical trials of these interventions. There is an increasing need to better identify those characteristics that will help inform future study designs, with ongoing longitudinal studies enabling us to better understand the risk factors for rarer endpoints. The data presented throughout this thesis, has identified characteristics associated with the presence of common mental disorders, including younger age, female sex, concurrent opiate or antidepressant use, those in their first year of diagnosis, or reporting symptoms of flare. Interestingly, this replicates the characteristics known to be associated with the reporting of IBS-type symptoms in patients with quiescent IBD, which is independently associated with co-morbid common mental disorders.[371] As described in Chapter 5, the combination of both symptoms of disease activity symptoms, alongside common mental disorders, increases the risk of disease progression. This presents the hypothesis that those clusters of greatest gastrointestinal symptom burden, alongside greatest psychological symptom burden are most likely to have adverse disease-related outcomes, and should be a target for intervention early on. Future RCTs should recruit with a selective approach to interventions, focusing those psychological therapies in those with poor mood scores at baseline, higher burden of gastrointestinal

symptoms, or a combination of the two, in order to better understand the effects of intervention and who to target in practice.

The common theme described throughout this thesis is of an association between mood and adverse clinical outcomes in patients with IBD, suggesting a need for proactive management of psychological co-morbidity in this patient group. The UK national IBD survey in 2023 demonstrated that while there was some improvement in discussing mental health issues in clinical practice, only 20% of patients felt this was addressed by clinicians, and only 3% of patients had the opportunity to speak to a counsellor or psychologist prior to an operation.[372] There remains a significant gap between current service provision and the needs of these patients. One way of addressing this may be through online psychological services and self-referral, or more tailored programmes such as COMPASS-IBD, which combine an online CBT-based programme alongside psychological support, easing pressure on services and reaching a wider patient cohort.[373] Being able to identify those individuals who would benefit from such intervention, and signposting appropriately, is key to allow us to continue funding a patient-centric model of care.

In summary, this thesis describes the influence, and bidirectionality, of gut-brain axis interactions, and their impact, on the long-term prognosis in IBD. These studies have highlighted that symptoms of common mental disorders are an independent risk factor for adverse outcomes in patients with IBD. Even after achieving clinical, or biochemical remission, the presence of symptoms of a common mental disorder perpetuate the bidirectional cycle of the gut-brain axis. Better characterisation of a subgroup of patients, with a persistent, high psychological burden, who are more likely to have adverse IBD-related outcomes, may offer a chance for proactive psychological support. This presents a hypothesis, that better identification and characterisation of these patients, and thus improved patient selection, could improve outcomes of future RCTs examining the effects of both psychological and neuromodulator interventions. There remains a significant need to push for psychological support, and better education in the recognition of common mental disorders in chronic disease. This thesis supports the need to grow the limited psychological service in the UK, and better identify those at risk, in order to use this limited service in the most cost-effective way.

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