The role of Adverse Psychological Health on the Natural History of Inflammatory Bowel Disease, and Approaches to Identify and Manage These Symptoms.

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Intellectual Property and Publications Statement

The candidate confirms that the work submitted is his, 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. As a result of the work outlined in this thesis, the following joint publications have been written:

1. **Riggott C**, Ford AC, Gracie DJ. The role of the gut–brain axis in inflammatory bowel disease and its therapeutic implications. Aliment Pharmacol Ther. 2024 Nov;60(9):1200-14.

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Abstract

Introduction: Inflammatory burden shapes the natural history of inflammatory bowel disease (IBD), but psychological health may contribute substantially. However, before holistic care can be provided for patients, a better understanding of the prevalence, persistence, impact, identification, and treatment of poor psychological health in IBD is required.

Methods: Model-based clustering techniques to subclassify patients with IBD according to measures disease activity and psychological health have been performed. To ascertain the prevalence of symptoms of anxiety and depression throughout the disease course, these symptoms have been examined in patients with established disease and in an inception cohort. Using mood trajectories, the persistence of these symptoms been examined over a 2-year period. Across these observational studies, the impact on disease outcomes has been studied longitudinally. Finally, a systematic review and meta-analysis of randomised controlled trials examining the efficacy of psychological therapies in IBD was performed.

Results: Symptoms of anxiety and depression are highly prevalent at the point of an IBD diagnosis, affecting 39% of patients. The only factor significantly associated with symptoms of anxiety or depression during 24 months of longitudinal follow up is a fluctuating, or persistently abnormal or worsening baseline trajectory ($p<0.001$ for both trends). Rates of adverse disease outcomes are highest in patients with disease activity and poor psychological health. Patients with disease activity and psychological health have higher healthcare utilisation and experience more adverse disease events. Psychological therapies improve psychological health in the short-term, particularly in patients with evidence of poor psychological health, but have no impact on disease activity.

Conclusions: In addition to being highly prevalent amongst patients with established disease, poor psychological health is highly prevalent at the point of diagnosis suggesting genuine gut-brain effects. Symptoms of anxiety and depression persist for many patients and negatively impact the natural history of IBD, suggesting that addressing the inflammatory aspect of the disease in isolation fails to meet the needs of these patients. Gut-brain axis directed therapies may be of value in patients with evidence of poor psychological health.

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In Text Abbreviations

5-ASA	5-aminosalicylates
6-MMP	6-methylmercaptopurine
ANOVA	analysis of variance
BIC(LL)	Bayesian information criterion of the log-likelihood
CBT	cognitive behavioural therapy
CD	Crohn's disease
CI	confidence interval
CNS	central nervous system
EEN	exclusive enteral nutrition
FC	faecal calprotectin
FMT	faecal microbiota transplantation
GABA	gamma-aminobutyric acid
GBA	gut-brain axis
HADS	hospital anxiety and depression scale
HBI	Harvey-Bradshaw index
HR	hazard ratio
JAK	janus kinase
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
IBS	irritable bowel syndrome
IL	interleukin
LCA	latent class analysis
MeSH	medical subject heading
MRI	magnetic resonance imaging

NF-κB	nuclear factor kappa B
NOD	nucleotide-binding oligomerisation domain-containing protein
OR	odds ratio
PHQ	patient health questionnaire
RCT	randomised controlled trial
RR	relative risk
SCCAI	simple clinical colitis activity index
SD	standard deviation
SMD	standard mean difference
SNP	single nucleotide polymorphism
TNF-α	tumour necrosis factor alpha
UC	ulcerative colitis
VSI	visceral sensitivity index

Chapter 1: Introduction

The focus of this thesis pertains to the recognition, implications, and management of poor psychological health in inflammatory bowel disease (IBD). This chapter outlines the foundations for this work, providing a description of the aetiology, epidemiology, and natural history of IBD, and summarises current treatment strategies. The role of psychological health in IBD will be explored, drawing attention to the high prevalence of symptoms of anxiety and depression in this group of patients, describing the association of these symptoms with future disease outcomes, and highlighting plausible explanations for this relationship.

1.1 Evolution of IBD Through the Ages

Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing-remitting immune mediated disorders of the gastrointestinal tract, characterised by the presence of mucosal inflammation and debilitating gastrointestinal symptoms.[1] Although phenotypically distinct, CD and UC are indistinguishable in up to 15% of cases, and are collectively termed IBD to reflect the substantial overlap in their clinical presentation, endoscopic appearances, and management.[2] Historical documentation suggests that symptoms compatible with IBD date back as far as the 17th century, with depictions of colonic perforation associated with transmural inflammation cited in the literature.[3, 4] However, the first official description of IBD was made by Samuel Wilks during an autopsy in 1859, where transmural inflammation of the colon and terminal ileum was reported.[5] At the time this was labelled "simple ulcerative colitis", and it was not until almost a century later that this case was reclassified as CD.[5] In the early 20th century amongst the advent of the germ theory, an increasing number of cases of "non-infective ulcerative colitis" emerged across Europe and the United States, and UC became regarded as a distinct entity.[6] This was shortly followed, in 1932, by the release of a case series by Burril Crohn *et al.* of 14 patients with regional enteritis and

complications including strictures and fistulae formation, a landmark paper which would later see the condition become eponymous with his name.[7]

Several theories pertaining to aetiology of CD and UC were explored in the early 20th century. Food allergy was extensively studied but this theory was later discredited due to the inability to demonstrate reproducible allergens.[5] Between 1930 and 1950, clinicians classified IBD, particularly UC, as a psychosomatic disorder due to a persistent association between psychological distress and colonic inflammation.[6, 8] Although an association between poor psychological health and IBD was apparent, this explanation was largely dismissed due to the failure of psychotherapy to control inflammatory burden.[6] It was not until 1955, when Truelove and Witts published a randomised controlled trial (RCT) examining the effects of cortisone, a synthetic steroid, versus placebo, demonstrating an improvement in both symptom burden and endoscopic disease activity for patients with UC, that the focus shifted to the role of the immune system.[9] A later favourable response to corticosteroids was also identified in CD,[10] and collectively these studies shifted the understanding of the underlying pathogenesis of the disease, with IBD then recognised as it is today, as an immune mediated disorder.[11]

1.2 The Natural History of IBD

IBD typically fluctuates between periods of disease activity and quiescence. Mucosal inflammation is the hallmark of disease activity and is associated with debilitating gastrointestinal symptoms, which impact negatively on quality of life, relationships, and employment.[12, 13] Persistent mucosal inflammation is associated with complications, including intestinal obstruction and perforation, a significantly increased risk of developing colorectal cancer, and the need for intestinal resection.[13-15] In addition, the pro-inflammatory state is associated with systemic complications including venous thromboembolism.[15]

Current treatment paradigms therefore centre upon the prompt recognition and treatment of mucosal inflammation to mitigate future adverse disease outcomes.[16] Medical advances have improved the management of IBD substantially, but the condition remains uncurable and continues to carry an increased mortality compared with age-matched controls.[17]

1.2.1 Ulcerative Colitis

UC is characterised by inflammation confined to the large intestine, which begins distally in the rectum and spreads proximally in a continuous fashion. Inflammation is typically confined to the mucosal and submucosal layers.[18] Histological hallmarks of UC include neutrophilic infiltration of the mucosal crypts with an increase in lymphocytes and plasma cells in the crypt bases, depletion of mucin producing goblet cells, and surface erosions.[18] Symptoms include, but are not restricted to, abdominal pain, diarrhoea, rectal bleeding, urgency, and tenesmus. The disease can be subclassified according to extent or severity, with extent termed proctitis- disease confined to the rectum, left sided, or extensive- affecting the right colon.[19] Disease extent progresses in up to 30% of patients in the 10-year period following diagnosis.[19] Topical treatments are available to treat distal disease, but systemic therapy is required for extensive disease. In medically refractory disease, a total colectomy to remove the colon and rectum is considered curative.[20] A meta-analysis examining the prevalence of colectomy at 1-, 5-, and 10-years post-diagnosis estimated the risk to be 3%, 5%, and 10%, respectively.[21] However, improved medical therapies coincide with an overall decline in colectomy rates and the same meta-analysis suggested that since the introduction of advanced medical therapies the pooled relative risk (RR) of requiring a colectomy within 5 years of a diagnosis of UC is now 0.71.[21]

1.2.2 Crohn's disease

CD is a more complex disease, characterised by skip lesions, which represent inflamed areas of mucosa, interspersed with healthy tissue. It can affect the entirety of the gastrointestinal tract from mouth to anus.[6] Owing to extensive variation in the distribution of the disease, symptoms are less characteristic than UC, but include abdominal pain, diarrhoea, bloating, weight loss, anorexia, and perianal abscess or fistula.[22] Inflammation in CD can extend transmurally, giving rise to penetrating disease and additional complications, including stricture and enteric fistulae formation.[6] Histologically CD is differentiated from UC by the depth of inflammation, the presence of skip lesions, and the finding of non-caseating granulomas, which are the product of immune cell clusters without an area of central necrosis.[23] CD can be classified according to disease distribution, phenotype, age of onset, and the presence of perianal disease, with several classifications adopting these domains, including the widely used Vienna and Montreal classifications.[24, 25] Unlike UC, smoking has a strong association with negative outcomes in CD, including a more aggressive phenotype and an increased need for surgery.[26] Systemic immunosuppressive therapy is the only established treatment and, owing to the complications described above, intestinal resection is more commonplace than in UC, with up to one-third of patients requiring surgical intervention within the 5-year period post-diagnosis.[20] Due to the potential for pan gastrointestinal involvement, however, surgery is not considered curative in CD, and up to one-third of patients undergoing intestinal resection require further bowel resections.[27] Multiple bowel resections give rise to a distinct set of complications in CD, including short bowel, malabsorption, and the development of abdominal adhesions.[28] Similar to UC, intestinal resection rates continue to decline, suggesting positive developments in the treatment of CD. However, surgery remains a key treatment of this complex disease.[27]

1.3 Epidemiology of IBD

From the first recognition of CD and UC, the global prevalence of both conditions has been rising. It is estimated that 6.9 million individuals now have a diagnosis of IBD worldwide, of which 3.9 million are females and 3.0 million are males.[29, 30] The rising prevalence is attributable to a sharp increase in the number of incident cases across Europe and North America between the 1970s and 1990s, which is compounded by the increasing life expectancy in these populations, resulting in an increasing number of people living with the disease.[31, 32] Substantial variation in the prevalence of IBD exists between geographical areas, the highest prevalence being amongst white Caucasians in the Western world, where the prevalence of UC and CD is reported to be close to 400 per 100,000 population and 300 per 100,000 population respectively.[29, 30] A recent meta-analysis of epidemiological studies highlighted that the age standardised pooled prevalence of IBD is highest in the United States of America, affecting 464.5 per 100,000 of the population, followed closely by the United Kingdom, affecting 449.6 per 100,000, and declining further across West to Eastern Europe.[30]

Although the prevalence of IBD amongst Eastern populations is markedly lower than the West, a rapid acceleration in the incidence of the disease has occurred over the last two decades, particularly in newly industrialised nations.[30] Japan, which has the highest reported incidence of IBD in East Asia, reported roughly 0.4 cases of UC per 100,000 population in 1990,[33] compared with 2016 where the incidence had risen to almost 135 cases per 100,000.[34] Similar trends have been observed in CD and UC in South Korea, with a thirty-fold increase in the incidence of IBD during the same time period.[35, 36] These trends mirror the sharp rises in incidence amongst rapidly industrialised nations in the West following the second World War.[37] Based on these observations, four epidemiological stages of IBD have been proposed.[32] Emergence (stage 1) which is characterised by a combined low incidence and

prevalence; acceleration (stage 2), determined by a period with rapid rises in incidence; compounding prevalence (stage 3), marked by declining incidence but accumulating prevalence due to improved mortality trends; and, finally, prevalence equilibrium (stage 4), where the improved mortality can no longer overcome the plateau in incident cases, and the prevalence of the disease stabilises.[37]

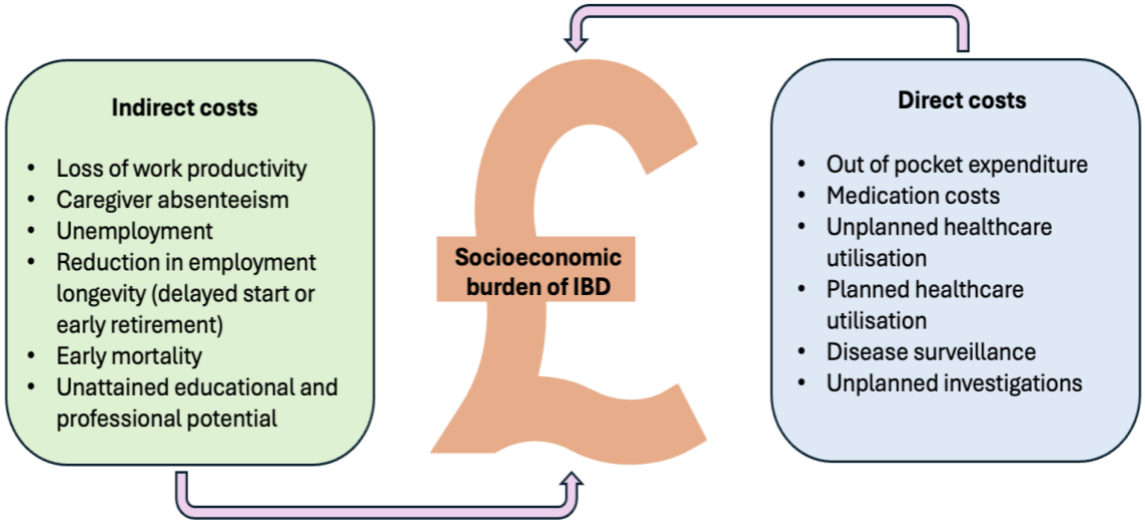
1.4 The Socioeconomic Impact of IBD

Substantial variability in the disease extent and severity, and the inconsistency in price of individual treatments, precludes an exact estimate of the direct costs of IBD in the United Kingdom, but the IBD national audit estimated an annual cost of around £1 billion.[38] Studies examining predictors of cost suggest that the annual per person costs exceed £10,000 for patients with active disease, which reduces by over 80% for patients in remission, highlighting the financial incentive in controlling inflammatory burden in publicly funded healthcare systems.[39] The socioeconomic burden of an illness encompasses not only the healthcare costs and out of pocket costs incurred by patients, which are directly attributable to the illness itself, but also the indirect impact the disease has on employment and education and the resulting negative influence on individual financial wealth.[40] The contributors to the overall cost of IBD are summarised in Figure 1.1.

The direct healthcare costs of IBD are high, exceeding those of diabetes mellitus on an annual per person basis,[41, 42] and a recent initiative of the Crohn's and Colitis Foundation in the United States emphasised a three-fold increase in direct healthcare expenditure associated with a diagnoses of IBD compared with matched controls.[42] In part, direct healthcare costs are driven by the price of medical therapies for IBD. However, drugs contribute only one-third of the overall healthcare expenditure, with the remainder consisting of unplanned healthcare utilisation, including emergency department visits and hospital admissions due to

uncontrolled disease activity, in addition to routine follow-up and disease surveillance requirements.[43] The peak incidence of IBD occurs between the second and fourth decades of life, with the majority of patients suffering with the disease being of a working age. This, in addition to the high direct healthcare costs, contributes a substantial indirect expenditure.[44] Annual out-of-pocket expenditure in patients with IBD, including healthcare-related travel expenses and lost work hours, is more than double that of age-matched controls.[42] **A**dditionally, the chronic nature of symptoms generates further indirect costs through restricted social interactions, impairment in work productivity, and development of functional disability, all of which further impact the economy negatively.[44, 45] Studies examining the effects of active IBD on employment demonstrate that these patients are twice as likely as matched controls to be unemployed (odds ratio (OR) = 2.14).[46] Furthermore, studies examining sick leave in IBD demonstrate a higher mean difference in the number of days absent from work in patients with UC than matched controls, in addition to an increase in the percentage of those claiming disability benefits (15% vs. 11% respectively).[47]

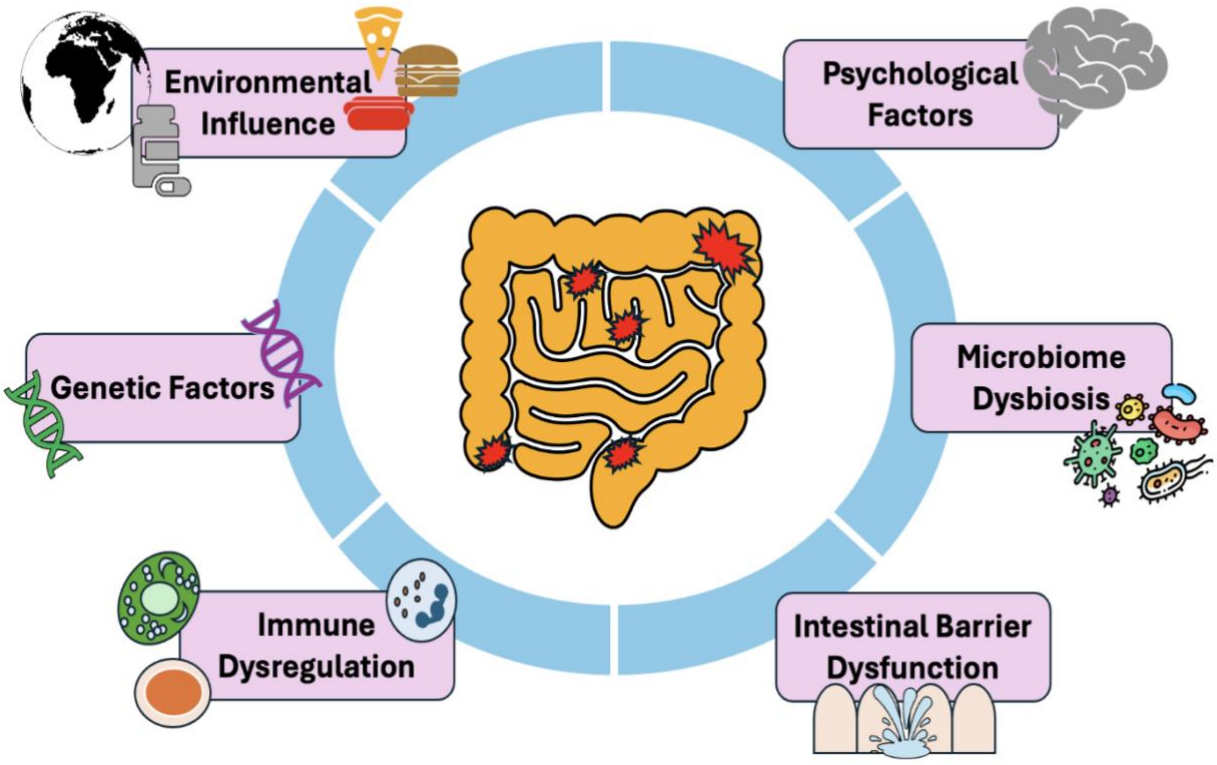
Figure 1.1. Contributors to the Socioeconomic Burden of IBD.



1.5 The Aetiology of IBD

Despite considerable advances in the understanding of IBD, the exact pathogenesis remains elusive. Current evidence suggests a multifactorial aetiology with inflammatory activity believed to arise from enteric immune system dysregulation in response to gut microbiome dysbiosis, influenced by certain genetic and environmental triggers.[48, 49] Furthermore, psychological stress may be a driver of persistent inflammatory burden through activation of the hypothalamic-pituitary-adrenal axis, in turn inducing systemic cortisol and catecholamine release, leading to an increased production of pro-inflammatory cytokines and subsequent inflammatory state.[1] Figure 1.2 provides an overview of the implicated mechanisms which will be detailed in this chapter.

Figure 1.2. The Proposed Aetiological Factors in IBD Development.



1.5.1 Genetic susceptibility

A family history of IBD imparts a greater risk of developing CD or UC than any recognised environmental influence.[50] Roughly 12% of patients with IBD report a first-degree relative with the disease,[50] and the lifetime risk of developing IBD in children born to two parents with the disease exceeds one-third.[51] These observations have seen heritability, the attribution of a phenotypic presentation to underlying genetic variance, garner much interest in IBD. Twin aggregation studies in IBD support a degree of heritability, with concordance between dizygotic pairs close to 10%, jumping substantially to over 50% in monozygotic pairs.[52-54] Genome-wide association studies have ensued, mapping over 10 million single-nucleotide polymorphisms (SNPs), which are variations in human DNA sequencing, to identify susceptibility genes in IBD. Located on chromosome 16q12 and

responsible for the recognition of bacterial peptidoglycans by toll-like receptors on the surface of innate immune cells, nucleotide-binding oligomerisation domain-containing protein 2 (NOD-2) was the first to be identified in CD. [55] NOD-2 drives innate immune reaction through activation of caspase-1 pathways to trigger an expression of proinflammatory factors.[55]

Since the discovery of NOD-2, almost 250 other SNPs, many of which are key regulators of epithelial barrier function and cellular innate immunity, have been identified.[55-58] Furthermore, monogenic IBD, arising from single genetic variants, has also been delineated.[56] This form of IBD exhibits typical Mendelian inheritance, with 100% penetrance, and 68 culprit genes identified, with interleukin (IL)-10RA being the most cited.[59] Typically, monogenic IBD has an aggressive disease course and presents in early childhood.[60] Genetic screening is now advocated in paediatric cohorts with IBD onset prior to 2 years of age.[61] However, monogenic IBD accounts for less than 1% of diagnoses in paediatric cohorts, and although SNPs provide mechanistic plausibility for the role of genetic susceptibility in IBD, marked variation across those identified through genome mapping does not fully explain the aetiology in the majority of IBD diagnoses. Genetics are, therefore, considered a contributory, but not a causative, factor in the majority of IBD diagnoses.

1.5.2 Microbiome Dysbiosis

The gut microbiome is a complex network of more than 100 trillion prokaryotic cells that, under normal physiological conditions, maintain a symbiotic relationship with the host.[62] A full description of the widespread functions of the microbiome are beyond the scope of this thesis but, in brief, these include maintaining the integrity of the intestinal mucosal by acting as a first-line of defence against pathogenic microbes, supporting metabolism through insoluble fibre fermentation, providing enzymes which are essential in B vitamin synthesis,

and the production of short chain fatty acids, including acetate and butyrate, which have anti-inflammatory roles.[1, 61-64] Gut microbes also act as antigens that, through direct contact with the intestinal mucosa, instigate an innate immune system response, a process that is believed to contribute to the development of a functioning immune system early in life.[11] The absence of early exposure to harmless antigens has been linked with subsequent immune system dysregulation in murine models of colitis.[65] Furthermore, alterations in the human microbiome composition have been observed in several disease states, including mood disorders, Parkinson's disease, diabetes mellitus, liver disease, and IBD.[66-68] Reduced faecal bacterial diversity is consistently reported in CD and UC, particularly in samples obtained from individuals with evidence of current disease activity.[48, 69] Compared with healthy individuals, patients with IBD have reduced numbers of the anti-inflammatory Firmicutes phylum, including *Faecailbacterium prausnitzii*, and a higher abundance of pro-inflammatory Proteobacteria phylum, including *Escherichia coli* and Enterobacteriaceae.[70] In addition, mucosal samples obtained from patients with CD have demonstrated differences in microbiome diversity between areas of inflamed and non-inflamed mucosa.[71]

Whether microbiome dysbiosis is an instigator of the inflammatory process in IBD, or merely a consequence of intestinal inflammation is difficult to discern. However, dysbiosis is present in treatment-naïve individuals at the point of diagnosis, suggesting that these changes may predate clinical disease.[71] Furthermore, variation in microbiota composition between twins who are discordant for IBD has also been demonstrated, suggesting that the presence of dysbiosis in IBD extends beyond genetic and environmental influence, supporting the role of microbiome dysbiosis in the pathogenesis of the disease.[72]

1.5.3 Intestinal Barrier Dysfunction

The intestinal mucosa consists of epithelial cells bound together by tight junctions and desmosome proteins and, like all mucosal tissue, it secretes mucous.[73] At a cellular level this reduces intestinal permeability, via the creation of a physical barrier, forming a key component of the host's defence against potentially harmful luminal antigens.[73, 74] Furthermore, mucous secretions contain lysosomes, which break down bacterial cell walls, antimicrobial peptides, which kill microbes directly, and secretory immunoglobulins, which bind to pathogens and prevent adherence to the mucosal layer, collectively providing an additional chemical barrier to pathogens.[75, 76] Penetration of the intestinal barrier by luminal antigens, and subsequent exposure of the underlying lamina propria to microbes, instigates an inflammatory cascade resulting in enteric immune system upregulation and subsequent mucosal inflamamtion.[77] This process underpins the pathophysiology of infective colitis, triggering an appropriate inflammatory cascade to neutralise invasive pathogens.[78]

In UC and CD, alterations in the tight junction structure have been identified during histological analysis of segments of mild to moderately inflamed mucosa, with an associated net efflux of ions into the intestinal lumen, which is believed to be a key contributor to diarrhoea in these patients.[79, 80] Building on these findings, murine studies of colitis demonstrate that depletion of the colonic mucinous layer creates microbiome dysbiosis, which predates histological inflammation in genetically modified mice, suggesting that intestinal barrier dysfunction contributes directly to microbiome dysbiosis.[81, 82] Supporting animal studies, increased intestinal permeability has been observed in individuals who later go on to develop CD,[83] and in patients with quiescent CD who later experience a relapse of mucosal inflammation.[84] Finally, anti-tumour necrosis factor alpha (TNF-α) agents, which are commonly used drugs to induce mucosal healing in IBD, have been shown to ameliorate intestinal permeability through restoration of the gut epithelial barrier. This adds further

evidence for the underlying role of intestinal barrier dysfunction in the pathogenesis of the disease.[85, 86]

1.5.4 Immune System Dysregulation

The immune system encompasses innate and adaptive processes, which communicate through a series of signalling pathways to co-ordinate the necessary response to external pathogens.[11] In health, the immune system promotes tolerance of symbiotic organisms, whilst simultaneously providing defence against invasive pathogens.[87] Innate immunity provides the host with an immediate, but non-specific, immune response via toll-like receptors and caspase activating recruitment domain receptors on the surface of epithelial cells, macrophages, and mast cells, which detect pathogen associated molecular patterns on the surface of bacteria, and damage associated molecular patterns released by injured host cells.[88, 89] Mediated by nuclear factor kappa B (NF-κB), toll-like receptors elicit the maturation of dendritic cells to release pro-inflammatory signalling chemokines and cytokines, and produce major histocompatibility complexes, which circulate to lymphoid tissues and initiate the adaptive immune system.[87, 89] Adaptive immunity provides a highly sophisticated second-line immune response to pathogens.[87] Activated CD8+ cytotoxic T-lymphocytes deploy directly to the site of dendritic cell signals and kill infected or injured cells to prevent further invasion of pathogenic organisms.[87] Release of cytokines, including IL-23, from the surface of Th17 CD4+ T-helper cells stimulates neutrophil release towards inflamed tissue, perpetuating the innate immune response and maintaining mucosal defence. When necessary, T-helper regulatory cells also suppress the immune response, to maintain tolerance to symbiotic organisms. Finally, T-helper cells signal to B-lymphocytes, which in turn produce specific antibodies to neutralise pathogens and formulate immunological memory to provide a swifter response in the event of re-infection.[87]

Both innate and adaptive immune dysregulation are key elements of the pathogenesis of IBD. The initial inflammatory reaction is believed to stem from a loss of recognition of commensal organisms, with overexpression of NF-κB and subsequent increased production of inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-23.[90] High numbers of dendritic cells are seen in the epithelial layer of mice with dextran sulphate-induced colitis compared with healthy mice.[91] Similar observations have been noted in colonic mucosal tissue in humans with UC and CD compared with healthy controls, with higher numbers noted in participants with active intestinal inflammation.[92] An aberrant T-helper cell response ensues, with suppression of regulatory T-helper cells and increased release of interferon-γ, IL-17, and IL-22 in CD,[93] and IL-5 and IL-13 in UC, resulting in unchecked inflammation.[94] The resulting epithelial barrier dysfunction results in further bacterial translocation and perpetuation of the inflammatory process.[95]

1.5.5 Environmental Influence

The surge in number of incident cases of IBD amongst Western societies led to an interest in the role of environmental factors in the pathogenesis of IBD.[30] Epidemiological research highlights the plausibility of this school of thought, with compelling evidence first presented by Probert *et al.* in a prevalence study of UC conducted amongst immigrants to the UK during the 1970s.[96] The incidence of UC reported amongst first-generation South Asian immigrants was noted to be more than double that of first-generation European immigrants. This was in stark contrast to the incidence trends reported across Asia during the same time period, where IBD was considered to be relatively rare, suggesting factors other than genetics influence the development of the disease.[34, 96] Subsequent research underscored these findings, with the reported incidence of UC cases rising further in second-generation South Asian immigrants, raising the possibility of cumulative environmental influences.[97] Similarly

for CD, a birth cohort conducted in the UK highlighted a potential environmental influence, with British-Asian children having over six times the risk of incident IBD than White-British children.[98] These findings are not unique to immigrants to the UK, with similar trends in IBD incidence observed in South Asian immigrants in Canada.[99] Several environmental influences have been postulated, with the most widely studied including improved sanitation, expanding use of antimicrobials, and dietary factors, including exposure to processed foods.[100]

1.5.5.1 Antibiotic Exposure

The rising incidence of IBD in the post-war era correlates with the discovery and subsequent widespread use of antibiotics during this period.[101] In healthy individuals, antimicrobials modify gut microbiome composition, often resulting in a lower abundance of symbiotic organisms. This persists for up to 2 years following exposure.[102] Microbiome dysbiosis contributes to the pathogenesis of IBD and, therefore, antimicrobial exposure may also be implicated.[69] A small case-control study of paediatric patients identified an increased risk of future development of IBD in children prescribed antimicrobials within the first year of life.[103] Similar findings have been replicated in adult populations, with a case-control study conducted in Manitoba comparing 2,234 patients diagnosed with IBD with 22,346 age-, sex-, and geographically-matched controls, suggesting a dose dependent increase in risk of developing IBD up to 5 years following antibiotics, with the greatest risk observed amongst those having three or more courses of antibiotics in the 2 years prior to study inclusion (OR = 1.5; 95% confidence interval (CI) 1.3-1.8).[104] Furthermore, a recently published meta-analysis of over 150,000 patients with IBD supports these findings, demonstrating a positive non-linear dose response between prescription antibiotic use and future IBD.[105] It is noteworthy, however, that prescribing trends highlight an increasing exposure to antibiotics at a population level throughout the last decade, with significantly more exposed individuals

than incident cases of IBD, suggesting that the perceived effect of antimicrobials may not be truly causative.[106] A lack of large scale RCTs examining the specific microbiota changes in patients receiving antibiotics hinder formal conclusions regarding their contribution to the pathogenesis of IBD.[102]

1.5.5.2 The Hygiene Hypothesis

Early exposure to common pathogens during childhood may be a protective factor in the development of a healthy immune system, with a lack of exposure increasing an individual's susceptibility to the development of allergies and autoimmune diseases. This may explain the increasing prevalence of these conditions in the developed world.[107] For IBD, it is postulated that early childhood infection, and the ensuing inflammatory response, instigates a healthy balance between pro-inflammatory and regulatory T-cells in the developing immune system, mitigating future disproportionate pro-inflammatory responses to common antigens.[108] Certainly, cases of infectious gastroenteritis are highest in developing countries, where overcrowding and poor hygiene is considered more commonplace, and the prevalence of IBD is lowest.[29]

Lending support to these observations, the recorded number of helminth infections, a common parasitic worm in humans, is considered to be inversely proportional to the overall hygiene of a country.[109] Trends in the incidence of helminth infections are unchanged across sub-Saharan Africa, which also demonstrate stable low IBD incidence trends, but are decreasing in Southeast Asia where the incidence of IBD is increasing, suggesting that poor hygiene may be a protective factor.[110] Furthermore, a meta-analysis of 29 studies, including over 8000 patients with IBD, demonstrated that exposure to pets or farm animals, surrogate measures of overcrowding such as sharing a bedroom, and the presence of one or more siblings may be protective factors for developing IBD in Western populations.[111] However,

although these factors may relate to lower standards of hygiene, it is impossible to account for all the potential contributory factors in observational research and the role of improved sanitation in the pathogenesis of IBD may simply be a result of confounding.

1.5.5.3 Dietary Factors

Several dietary factors, including both macro and micronutrients, have been implicated in the development of IBD.[100] Of the studied dietary components, there appears to be an inverse association between dietary fibre intake and IBD risk, particularly in CD, suggesting a high fibre containing diet may protect against IBD.[112] Soluble fibres are digested to short chain fatty acids, which have proven anti-inflammatory properties, providing a scientific rationale for these observations.[112] Conversely, diets high in saturated fat appear to correlate with an increased IBD risk, which may be explained by the ensuing alterations in the gut microbiome seen in murine studies,[113] contributing to a pro-inflammatory state. Zinc is an essential micronutrient for autophagy and bacterial clearance, reduces intestinal permeability, and inhibits the transcription of inflammatory mediators in the NF-κB pathway, and could be protective in IBD.[114] Zinc deficiency has been associated with an increased risk of developing CD in prospective cohort studies,[115] and poor clinical outcomes in established disease.[116]

The surge in incident IBD across Western populations,[117] and later amongst newly industrialised Eastern nations,[118] closely mirrors ultra-processed food consumption trends.[117-119] Ultra-processed foods are energy-dense formulations, high in refined sugar and saturated fat, low in fibre and key micronutrients, and contain multiple additives, including emulsifiers, to prolong shelf-life.[117] In a large prospective cohort study of over 180,000 UK participants, consumption of ultra-processed foods was higher amongst patients with IBD than matched controls, and a diet higher in ultra-processed foods was associated with an increased risk of

incident CD.[119] Prospective studies, including small RCTs, have demonstrated reduced microbiome diversity and early loss of intestinal epithelial barrier function amongst individuals consuming ultra-processed foods compared with controls with a low intake of these foods, providing plausibility for the role of diet as a direct contributor to the pathogenesis of IBD.[120] Studies also suggest a dose dependent effect, with consumption of more than five ultra-processed foods per day more strongly associated with alterations in microbiome composition.[121] However, given the complex and varied composition of ultra-processed foods, individual causative ingredients have not been isolated and their role in the pathogenesis of IBD at this stage remains speculative.

1.6 Determining Disease Activity in IBD

Inflammatory activity is the main driver of adverse disease outcomes in both UC and CD, and the recognition of persistent inflammation is therefore of paramount importance to their management. Close monitoring of mucosal inflammation enables clinicians to alter medical therapies promptly and mitigate future adverse events. Currently, disease activity can be assessed by non-invasive clinical, biochemical, radiological, or endoscopic assessment. Reliability, cost, and patient preference are all important factors to consider when selecting an assessment modality. These are outlined below.

1.6.1 Clinical Disease Activity Indices

As discussed, inflammatory activity in UC and CD is associated with the development of debilitating gastrointestinal symptoms. For this reason, clinical remission was traditionally regarded as a primary therapeutic target in IBD, with the assumption that patient-reported symptoms represent persistent mucosal inflammation.[122] Clinical disease activity indices have been developed with this in mind and were, until recently, utilised in isolation to determine

underlying disease activity in IBD, both in clinical practice and as formal assessment tools in RCTs examining the efficacy of novel therapies against placebo. The Simple Clinical Colitis Activity Index (SCCAI) is commonly applied in UC, and assesses overall stool frequency, symptoms of faecal urgency, visible blood in the stool, overall wellbeing, and includes presence of extra-intestinal manifestations such as uveitis, pyoderma gangrenosum, erythema nodosum, and arthropathy.[123] The total possible SCCAI score ranges from 0 to 18, with disease activity defined by a score equal to or greater than 5. The Harvey Bradshaw Index (HBI) is commonly used in CD, measuring general wellbeing, number of liquid or soft stools per day, the presence of abdominal pain or an abdominal mass, and disease-related complications, including uveitis, pyoderma gangrenosum, erythema nodosum, arthralgia, aphthous ulcers, anal fissures, peri-anal abscess, or the development of a new fistula.[124] The total possible HBI score ranges from 0 to 16, with a score of equal to or greater than 5 again used to define disease activity.[124]

Although clinical disease activity indices are low cost and low intensity tools, high placebo response rates are noteworthy across RCTs in IBD that use these as their primary endpoint.[125] Placebo response rates are considerably lower when objective assessments of disease activity, such as endoscopic evaluation, are adopted.[125-127] Furthermore, observational studies report discordance between clinical disease activity indices and biochemical or endoscopic disease activity, suggesting that the former overestimate disease activity.[128, 129] For these reasons, it is now considered low-value care to determine disease activity based on assessments of clinical activity in isolation.[16] Nevertheless, these measures are still used frequently as endpoints in RCTs and add value in clinical practice by providing clinicians with a consistent measure of symptom burden over time.

1.6.2 Endoscopic Assessment

Endoscopic assessment, particularly ileocolonoscopy and histological sampling, are essential to make a formal diagnosis of IBD. Furthermore, these assessments enable determination of IBD subtype, and an assessment of disease extent and severity, which ultimately shape future treatment decisions. Mucosal healing is considered the most objective assessment of underlying disease activity in IBD,[122, 130] and is the current treatment target in IBD care, with many RCTs assessing the efficacy of medical therapies now adopting it as a primary endpoint.[131, 132] To maintain consistency in routine clinical care, and across RCTs, endoscopic disease severity scores have been developed to evaluate the severity of intestinal inflammation in both UC and CD. For CD, the simple endoscopic score, is perhaps most widely used in clinical practice due to its simplicity,[133] evaluating the size and percentage of area affected by ulceration or inflammation, and for the development of strictures.[133] The Rutgeerts score has also been developed in CD, specifically to assess for post-operative disease recurrence at the surgical anastomotic site, by recording the presence and extent of inflammation and luminal stenosis.[134] For UC, again several scores have been developed. Perhaps the most widely adopted are the ulcerative colitis endoscopic index of severity score, which assesses for the presence and extent of loss of vascular pattern, bleeding, and erosions or ulceration,[135] and the Mayo endoscopic score which combines these parameters to give a score of 0 (indicating remission), through to 3 (indicating severe inflammation), and can be further combined with clinical parameters including stool frequency, haematochaezia, impact on daily life, and a physicians assessment of severity, to form the global Mayo score.[136]

Endoscopies are invasive procedures with associated risks, including an approximately 0.01% risk of colonic perforation,[137] and up to a 5% risk of minor bleeding,[138] for diagnostic tests. It is perhaps, therefore, unsurprising that of the available tools to assess IBD activity, ileocolonoscopic disease assessment is consistently ranked as the least acceptable by

patients.[139-141] In addition, endoscopy is expensive, with the basic tariff of an elective colonoscopy being £488 in the UK.[142] Finally, owing to the need for single use kit, patient travel, and the required decontamination procedures, endoscopic procedures are the third biggest contributor to waste in the NHS,[143] in addition to each endoscopy unit contributing almost 21 tonnes of carbon emissions annually,[139] making unnecessary endoscopic procedures a substantial environmental concern. Cumulatively, these factors restrict the frequency of endoscopic assessments of disease activity in IBD to surveillance, and in cases of symptom persistence where there is a high suspicion of underlying disease activity.[60]

1.6.3 Radiological Assessment

Imaging is an essential assessment tool in CD, for both establishing initial disease extent and assessing response to treatment in patients with small bowel and perianal disease.[60] Magnetic resonance imaging (MRI) enterography and intestinal ultrasound provide comparable sensitivity in assessing small bowel disease and are advocated as first-line diagnostic tools to detect small bowel CD, and for the ongoing assessment of response to treatment.[60, 144] MRI is the gold standard non-invasive imaging technique for perianal CD.[60] Trans perineal ultrasound has also been studied, and although it demonstrates comparable sensitivity to MRI in the detection and classification of perianal fistulae, it has a relatively low sensitivity for the detection of complications such as abscess formation (47.8%).[145] The routine use of computerised tomography is dissuaded in national guidelines due to the cumulatively high levels of radiation that patients with IBD, particularly those with CD, would experience over their lifetime.[60, 146] However, it remains the first-line investigation to confirm a clinical suspicion of acute bowel perforation in both UC and CD in the emergency setting.[60]

1.6.4 Non-Invasive Biomarkers

Faecal calprotectin (FC), is a non-invasive biomarker that detects intestinal inflammation in IBD, and was first described by Roseth *et al.* in 1992.[147] This calcium-binding protein is released predominantly from the cytoplasm of neutrophils and is highly resistant to degradation in the gastrointestinal lumen. High levels of FC in the stool reflect increased neutrophil migration across the intestinal mucosa, providing an indirect measurement of intestinal inflammation.[148] A raised FC aids physicians to differentiate between gastrointestinal symptoms caused by underlying intestinal inflammation and those arising from irritable bowel syndrome (IBS), but also to provide evidence of ongoing inflammatory activity in those with established IBD experiencing persistent symptoms.[149] Studies demonstrate good correlation between FC measurements and endoscopic disease activity indices, with significant cost savings over endoscopic assessment.[150, 151] In comparison to colonoscopy, a FC measurement in the UK costs under £25,[152] and studies comparing endoscopic disease assessment of IBD activity in symptomatic patients versus endoscopic assessment determined by a raised FC, show that the latter approach more than halves costs.[153] Furthermore, studies examining the utility of routine FC monitoring in IBD show that asymptomatic patients with two or more raised levels have an 83% probability of a clinical relapse within 3 months.[154] The CALM trial, published in 2017, demonstrated unequivocally that the addition of proactive biomarker monitoring in CD is associated with improved mucosal healing, and fewer serious disease-related complications, in comparison to reliance on symptom-reporting in isolation, supporting the positive impact of pro-active non-invasive monitoring of inflammatory activity.[132] In addition, studies examining patient acceptance of FC monitoring demonstrate that it is well-received amongst IBD patients, in comparison to endoscopy.[141]

1.7 Current Therapeutic Landscape of IBD

Improvements in our understanding of the mechanisms of immune system dysregulation and subsequent drivers of persistent inflammatory activity in IBD has enabled the development a range of efficacious drugs to treat inflammatory aspect of the disease. Medical management is intended to induce and maintain mucosal healing, thereby reducing the development of disease-related complications and the need for surgery. A description of each of the established treatments in IBD is outlined below, along with a summary of the evidence pertaining to their use in UC and CD.

1.7.1 Glucocorticosteroids

Cortisol is a naturally occurring glucocorticoid hormone produced in the adrenal cortex of the brain in response to stress. It exerts potent anti-inflammatory effects through inhibition of the transcription factors NF-κB and activator protein-1, which in turn suppress T-lymphocyte proliferation and B-lymphocyte activity, by impeding production of pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6.[155] Glucocorticosteroids are synthetic analogues of cortisol, which first demonstrated efficacy in treating UC in the 1950s.[9] Several RCTs have been conducted in UC and CD following this, and a meta-analysis of the available RCTs comparing glucocorticosteroid against placebo suggest efficacy in inducing remission in UC (RR of failure to achieve remission = 0.65; 95% CI 0.45-0.93).[156] However, the benefits in CD are less clear (RR of failure to achieve remission = 0.46; 95% CI 0.17-1.28), which may be the result of significant heterogeneity between studies.[156] Owing to the ubiquitous glucocorticoid cytoplasmic receptor, cortisol has broad effects that stem beyond its intended therapeutic anti-inflammatory activity, including stored energy release, via stimulating gluconeogenesis and lipolysis, maintaining blood pressure,

through sensitisation of vessels to circulating catecholamines, and promoting bone remodelling, via simultaneous inhibition of osteoblasts and upregulation of osteoclast activity.[155] As such, adverse events are common during treatment,[156] with diabetes mellitus, hypertension, Cushing's syndrome, and osteoporosis all attributable to prolonged glucocorticosteroid exposure.[157] Despite proven efficacy in treating mucosal inflammation in IBD, this unfavourable adverse event profile prevents their use as a maintenance treatment. Indeed, corticosteroid-free remission is considered of equal importance to mucosal healing in RCTs examining newer medical therapies.[16]

Due to first-pass metabolism via CYP3A4 in the liver reaching almost 90%, the synthetic glucocorticosteroid budesonide has high topical availability and comparatively low systemic bioavailability and is the preferred choice of glucocorticosteroid when a favourable side effect profile is required. Optimising the high topical availability, pharmaceutical companies have developed terminal ileal and colonic release preparations accordingly. Meta-analyses have demonstrated superiority of budesonide versus placebo in CD (RR of failure to induce remission = 0.73; 95% CI 0.63-0.84),[156] but inferiority when compared with conventional glucocorticosteroids (RR of failure to induce remission = 0.82; 95% CI 0.68-0.98). Furthermore, despite a favourable safety profile, meta-analyses examining the effect of budesonide on maintaining remission in CD do not demonstrate superiority over placebo (RR = 1.13; 95% CI 0.94-1.35).[158]

1.7.2 5- Aminosalicylic Acids

The exact mechanism by which 5-aminsalicylic acid (5-ASA) preparations reduce intestinal inflammation is unclear, but several mechanisms have been postulated. Firstly, as with glucocorticosteroids, 5-ASA inhibits NF-κB and activator protein-1, thus downregulating cytokine production.[136] Additionally, through modulation of the arachidonic

acid pathway, 5-ASAs inhibit cyclooxygenase-2 and lipoxygenase-5 production, in turn reducing prostaglandin and leukotriene synthesis, which are potent mediators of the inflammatory cascade.[159] 5-ASA also acts as free radical scavenger, neutralising reactive oxygen species produced by immune cells, thus protecting the intestinal epithelium from oxidative-stress injury.[159] Finally, studies of patients with UC have demonstrated alterations in the composition of gut bacteria in patients taking 5-ASA, with decreased numbers of invasive species, suggesting a positive influence on the gut microbiome may also contribute to their anti-inflammatory effect.[160, 161] Mesalazine is the traditional 5-ASA used in the UK. It is available in oral and topical preparations, which can be used in isolation or combination, and has a favourable safety profile, making it a popular treatment choice in clinical practice.[60]

Data pertaining to the use of 5-ASA in UC are largely positive, with a recent network meta-analysis of RCTs demonstrating their efficacy in the induction of clinical and endoscopic remission, with both standalone topical and oral therapies, and combination therapies being superior to placebo.[162] Topical mesalazine alone ranked first (RR of failure to induce remission = 0.51; 95% CI 0.41-0.63, P-score 0.99), and combined oral and topical mesalazine ranked second (RR = 0.62; 95% CI 0.50-0.78, P-score 0.87).[162] In the same meta-analysis, these drugs were also determined to be effective in maintaining remission of UC, with combined oral and topical 5-ASA ranking first (RR of relapse of disease activity = 0.44; 95% CI 0.28-0.69, P-score 0.91), closely followed by oral 5- (RR = 0.54; 95% CI 0.42-0.71, P-score 0.75) and topical 5-ASA (RR = 0.56; 95% CI 0.45-0.68, P-score 0.72). Although, historically, the use of 5-ASA therapy has been widespread, data from a meta-analysis of RCTs examining the efficacy of mesalazine in CD demonstrated no definite benefit over placebo in induction of remission (RR of failure to achieve remission = 0.91; 95% CI 0.77-1.06), or preventing relapse in quiescent disease (RR of relapse = 0.97; 95% CI 0.90-1.05).[163] With the advent of the development of new therapies with proven efficacy, no compelling

evidence has since been produced to support the ongoing use of 5-ASAs in CD and, ultimately, their use has been withdrawn from best practice recommendations.[164] However, ongoing use, particularly in the case of mild colonic CD, remains a subject of ongoing debate amongst gastroenterologists and, according to real world data, despite declining usage in CD, many patients with mild colonic CD continue to receive 5-ASAs as a primary therapy, which may reflect a perceived lack of harm amongst clinicians.[165]

1.7.3 Immunomodulators

Unlike corticosteroids which simply suppress immune system function, immunomodulators work to alter the host's immune response, via inhibition of lymphocyte production or reducing their capacity to manufacture inflammatory cytokines.[166] Three main types are widely used in IBD: thiopurines; methotrexate; and calcineurin inhibitors.

1.7.3.1 Thiopurines

Azathioprine and mercaptopurine are the commonly used thiopurines in IBD, the former being a pro-drug that, following ingestion, is converted non-enzymatically to the active form, 6-mercaptopurine.[167] Following this, enzymatic pathways metabolise the drug into thioguanine nucleotides, a therapeutic metabolite that creates rogue nucleic acids. These interrupt DNA replication and RNA synthesis, a process most marked in rapidly dividing cells, such as T-lymphocytes, resulting in reduced proliferation.[167] Conclusive evidence supporting the superiority of thiopurines over placebo for the induction of remission in IBD is lacking. A meta-analysis of RCTs comparing their efficacy versus placebo demonstrated no superiority over placebo in both CD (RR of failure to achieve remission = 0.87; 95% CI 0.71-1.06) and UC (RR of failure to achieve remission = 0.85; 95% CI 0.71-1.01).[168] This may result from the pharmokinetics of the drug, with achievement of therapeutic levels of the drug

taking up to 6 weeks in clinical practice.[169] A meta-analysis of RCTs examining the role of thiopurines in maintaining remission in UC showed superiority over placebo (RR of failure to maintain remission = 0.68, 95% CI 0.54-0.86).[170] However, similar findings have not been demonstrated for maintenance of remission in quiescent CD, with a meta-analysis of the available RCTs identifying no superiority over placebo (RR of failure to maintain remission = 0.64; 95% CI 0.34-1.23).[168] Substantiating the findings of these meta-analyses, real world data collected from the UK BioResource of almost 12,000 patients initiated on thiopurine monotherapy suggests efficacy in over 50% of patients with UC compared with only one-in-three patients with CD (P<0.001).[171] Based on this evidence, IBD national guidelines now recommend use of thiopurines as a monotherapy in UC, but not CD.[60] Thiopurines have also been studied in specific subgroups of patients with CD, and a large RCT examining the role of secondary prophylaxis with thiopurines following surgical resection demonstrated no superiority of mercaptopurine over placebo, with the exception of a subgroup analysis of current smokers, where fewer recurrences were noted in the mercaptopurine group (hazard ratio (HR) for clinical recurrence = 0·13, 95% CI 0·04-0·46).[172]

Thiopurines are not solely metabolised to thioguanine nucleotides. Additional enzymatic pathways create 6-methylmercaptopurine (6-MMP), which is a hepatotoxic metabolite, and the inactive metabolite, thiouric acid.[167] Upon initiation, thiopurines require close blood monitoring to ensure that therapeutic levels of thioguanine and low levels of 6-MMP are achieved, ensuring the absence of complications including myelotoxicity and hepatotoxicity respectively. The occurrence of these complications necessitate alterations in dosing, and in some cases withdrawal of the drug.[173] Furthermore, a considerable number of patients experience side effects on thiopurine therapy, with vomiting being the most frequently cited adverse event.[173] Irrespective of their efficacy in IBD, studies report that adverse events lead to their discontinuation in roughly 25% of patients.[174]

1.7.3.2 Methotrexate

Through direct inhibition of dihydrofolate reductase, methotrexate acts as a folate antagonist, reducing purine synthesis and in turn inhibiting proliferation of lymphocytes.[175] Methotrexate is the most frequently used immunomodulator in inflammatory arthropathy, but is much less utilised in IBD, particularly in adult cohorts. To date only one RCT has examined its efficacy against placebo in inducing remission of CD in 142 patients, demonstrating superiority in with subcutaneous administration of methotrexate 25mg once weekly (RR=1.95; 95% CI 1.09-3.48) and with a significant steroid sparing effect noted in the methotrexate group (P=0.026).[176] A meta-analysis investigating the utility of methotrexate in maintaining clinical remission in CD demonstrated superiority over placebo (RR of inducing remission =1.50; 95% CI 1.08-2.07).[175] However in UC, a meta-analysis of RCTs examining the efficacy of methotrexate monotherapy against placebo, similar findings have not been replicated, with methotrexate monotherapy having no significant effect on induction of endoscopic remission (RR=1.37; 95% CI 0.77-2.46) or maintenance of steroid-free endoscopic remission (RR=0.79; 95% CI 0.43-1.46).[175]

1.7.3.3 Calcineurin Inhibitors

Ciclosporin is the most widely used calcineurin inhibitor in IBD and works by inhibiting the synthesis of IL-2, which is a key factor in both T-lymphocyte activation and differentiation.[177] One small RCT has demonstrated the efficacy of ciclosporin for induction of remission in CD.[178] Subsequent studies have failed to replicate these findings, and a Cochrane review highlighted no superiority over placebo but a significant increase in the reporting of adverse events when the results were pooled (RR= 16.63; 95% CI 10.65 - 25.95).[179] Ciclosporin does however have a strong evidence base as a rescue therapy in the context of acute severe steroid refractory UC, with data from a large meta-analysis

demonstrating improved colectomy free survival in the first month of therapy (RR of requiring colectomy= 0.40; 95% CI 0.21-0.77).[180] Furthermore, the 5-year colectomy free survival of ciclosporin is comparable to infliximab when used an initial rescue therapy.[177] However, despite the efficacy of ciclosporin in the treatment of acute severe colitis, serious adverse events including renal injury, electrolyte imbalances and hypertension are common, and limit its long term use of as a maintenance therapy.[180]

1.7.4 Advanced Therapies

Perhaps the greatest advance in IBD management came with the introduction of infliximab, the first biologically engineered antibody targeting a specific inflammatory cytokine known to contribute to the pathogenesis of the disease.[181] The introduction, and subsequent success of infliximab in achieving steroid-free clinical remission has led to a surge in the engineering of similar targeted therapies, with the most promising drugs granted approval by the National Institute of Health and Care Excellence for use in the UK. A complete overview of all existing data concerning individual biologics and small molecules is outside of the scope of this thesis, but pertinent data will be outlined for each of the individual therapies below.

1.7.4.1 Anti-Tumour Necrosis Factor α agents

Targan *et al.*[182] conducted the first trial of infliximab, a chimeric monoclonal anti-TNFα antibody, in patients with CD. A total of 108 participants with clinically active disease were randomised to receive a single intravenous dose of 5mg/kg, 10mg/kg, or 20mg/kg of infliximab, or placebo.[182] Infliximab demonstrated significant benefit, with 33% of all patients assigned to the treatment arms entering clinical remission after a single dose, versus 17% in the placebo arm.[182] The ACCENT-1 RCT shortly followed, assigning patients with

active CD to receive an infliximab 5mg/kg induction followed by either placebo at weeks 2 and 6, and 8 weekly intervals thereafter, or continued 5mg/kg infliximab in the same dosing schedule, or to complete the induction of 5mg/kg infliximab and then revert to 10mg/kg for 8 weekly infusions thereafter. The percentage of patients achieving clinical remission at 30 weeks were 21%, 39%, and 45% respectively suggesting clear superiority of infliximab over placebo (p=0.002).[181] These findings were echoed in a RCT examining the efficacy of infliximab in complex fistulating and perianal disease, with resolution of discharging fistulae at week 54 seen in 36% of participants in the infliximab arm versus 19% receiving placebo (p=0.009). The efficacy of infliximab was later proven in the ACT-1 RCT to have efficacy in steroid refractory UC, with 69% of participants randomised to infliximab achieving a clinical response at 8 weeks versus 37% of those randomised to receive placebo (p<0.001), ACT-2 demonstrated similar findings during 30-weeks of follow-up.[183]

Adalimumab, a human monoclonal antibody, is licensed for the treatment of CD and UC. The drug was first trialled in anti-TNFα naïve patients with active CD in the CLASSIC-1 RCT, with subcutaneous adalimumab induction with 160mg followed by 80mg at week 2 demonstrating superiority for clinical remission at week 4 versus placebo (36% vs. 12%, p=0.001).[184] The EXTEND study evaluated the use of adalimumab maintenance treatment in CD, all patients received induction with 160mg/80mg of adalimumab, followed by randomisation to either fortnightly 40mg of adalimumab or placebo. Using the strict primary endpoint of mucosal healing, this study demonstrated superiority of adalimumab over placebo at week 52 (28% vs. 3%, p<0.001).[185] The efficacy of adalimumab has also been studied in UC, with ULTRA-1 and ULTRA-2 again demonstrating superiority of adalimumab over placebo, however, the results are underwhelming in comparison to CD, with mucosal healing in ULTRA-2 at 52 weeks being 25% and 15.4% respectively (p=0.009).[186]

Golimumab, another monoclonal antibody to anti-TNFα, is licensed for the treatment of UC, with data from the PURSUIT-SC trial of biologic naïve patients with moderate-severe UC who were non responders to conventional therapies demonstrating superiority of golimumab 200mg/100mg induction at weeks 0 and 2 in achieving mucosal healing versus placebo at week 6 (42.3% vs. 28.7%, p=0.001),[187] and maintenance of mucosal healing at week 54 (42.4% vs. 26.6%; p=0.002).[188]

1.7.4.2 Anti-TNF and Thiopurine Combination Therapy

One issue with anti-TNF use, particularly infliximab, is immunogenicity- the development of drug specific antibodies which result in a loss of immune response. Thiopurines activate RAC1 in activated lymphocytes which induces apoptosis, diminishing pathogenic T-cells, and inhibiting the production of antibodies by B-lymphocytes, which reduced the prevalence of immunogenicity when used in conjunction with TNF-α therapies.[166, 167] The SONIC RCT compared the efficacy of azathioprine monotherapy, infliximab monotherapy, and combination therapy in CD, with 30%, 44%, and 57% of participants achieving corticosteroid-free clinical remission at week 26 respectively.[189] A post-hoc analysis of the SONIC trial suggested this is most likely due to a synergistic effect of immunomodulators, than merely prevention of immunogenicity alone.[190] Furthermore, real world observational data highlights that low drug concentrations of anti-TNF at week 14 predict both primary drug failure and immunogenicity, with combination therapy reducing the risk of developing anti-drug antibodies significantly for infliximab (HR=0.39; 95% CI 0.32-0.46) and adalimumab (HR=0·44; 95% CI 0·31–0·64).[191] The recently published PROFILE RCT has illustrated that employing a top-down approach of infliximab in combination with an immunomodulator early in patients with newly diagnosed CD is superior to an accelerated step-up approach in achieving steroid and surgery free remission at

1 year (79% vs. 15%; 95% CI 57-72, p<0·0001), and has cemented the role of combination therapy in this context.[192]

1.7.4.3 Anti-Integrin Therapy

Vedolizumab, the only anti-integrin licensed for the treatment of CD or UC, is considered a gut-selective therapy, as it binds selectively to α4β7 integrin and inhibits subsequent interaction with MAdCAM-1, which is mostly expressed on gut endothelial cells, thereby preventing lymphocytes entering the gastrointestinal tract and reducing inflammation.[193] The GEMINI-1 RCT compared the efficacy of vedolizumab versus placebo for induction of remission in moderate-severe UC, with patients randomised to vedolizumab 300mg or placebo at weeks 0 and 2.[194] This study demonstrated superiority of vedolizumab over placebo in achieving mucosal healing at week 6 (40.9% vs. 24.8%, p=0.001). Patients who had a clinical response to vedolizumab were enrolled into a maintenance study, and sustained mucosal healing at week 52 was higher in those allocated to vedolizumab 8 weekly infusions, versus placebo (51.6% vs. 19.8%, p<0.001). Adopting the same trial design, GEMINI-2 demonstrated efficacy of vedolizumab in CD for achieving clinical remission at 6 weeks (14.5% vs. 6.8%, p=0.002), and of the patients in the induction phase reporting a response at week 6, clinical remission was sustained at week 52 in the maintenance phase for the vedolizumab group (39% vs. 21.6%, p<0.001).[195] Although it is worth noting that unlike GEMINI-1, GEMINI-2 did not report endoscopic outcomes. Building on these findings, GEMINI-3 explored the efficacy of vedolizumab in CD amongst patients with prior exposure to anti-TNFα agents, demonstrating no superiority over placebo, inferring an attenuated response in biologic experienced patients, and raising the question regarding the correct sequencing of drugs in IBD.[196]

1.7.4.4 Interleukin-23 Inhibitors

Composed of a p19 subunit and a p40 subunit, IL-23 is produced by antigen presenting cells, including macrophages and dendritic cells, and promotes the differentiation and expansion of Th17 lymphocytes.[197] Activation of this pathway results in intestinal inflammation.[197] Ustekinumab works by targeting the p40 subunit on IL-23 and was the first drug within its class to be approved for use in CD and UC.[131] The UNITI-1 and UNITI-2 RCTs assessed the response to ustekinumab as an induction therapy in patients with moderate to severely active CD, in anti-TNFα exposed and anti-TNFα naïve patient groups respectively. [198] UNITI-IM subsequently re-randomised responders of ustekinumab to receive 8 or 12 weekly subcutaneous ustekinumab or placebo to assess the efficacy of the drug in maintain remission at 44 weeks.[198] UNITI-1 demonstrated a higher rate of achieving clinical response amongst patients receiving 6m/kg of Ustekinumab vs. placebo at 6 weeks (33.7% vs. 21.5% p=0.003), and in UNITI-2 the anti-TNFα naïve patients randomised to Ustekinumab had even higher rates of clinical remission than placebo (55.5% vs. 28.7% p<0.001). UNITI-IM established ustekinumab as a maintenance treatment for CD with superiority of 8 weekly, and 12 weekly subcutaneous ustekinumab achieving higher rates of clinical remission (51.3% vs. 48.8% vs. 35.9% placebo, p=0.005 and p=0.004). A later post-hoc analysis of UNITI-1 and UNITI-2 demonstrated an improvement in endoscopic disease severity scores at 8 weeks in those assigned to ustekinumab versus placebo (reduction of endoscopic severity score of 2.8 vs. 0.7, p=0.012), but this was not statistically significant at 44 weeks in UNITI-IM for 12 weekly or 8 weekly injections versus placebo (reduction of endoscopic severity score of 2.5 vs. 3.1 vs. 1.9, p=0.176 and p=0.107).[131] The UNIFI-UC RCT adopted the same trial design as UNITI in patients with UC and demonstrated higher rates of clinical remission at week 8 for those taking ustekinumab (15.5% vs. 5.3%, p<0.001),

and higher rates of maintained remission at 44 weeks for those taking 12 weekly or 8 weekly ustekinumab versus placebo (38.4% vs. 43.3% vs. 24.0%, p=0.002 and p<0.001).

Risankizumab targets the p19 subunit of IL-23 and is currently licensed for use in CD as a second-line advanced therapy.[199] Findings from the ADVANCE induction RCT for biologic naïve, and MOTIVATE induction RCTs for biologic exposed patients met the primary co-endpoints of achieving clinical remission and endoscopic response across both studies.[200] The outcomes were more marked anti-TNFα naïve participants with a greater proportion of patients in ADVANCE treated with risankizumab 600mg, or 1200mg achieving endoscopic response than placebo (40% vs. 28% vs. 12% respectively, p<0.0001). In the follow-up FORTIFY RCT, subjects from the initial induction trials were re-randomised to risankizumab 180mg, 360mg or placebo every 8 weeks, and the primary co-endpoints of clinical remission and endoscopic response were again achieved (38% vs. 36% vs. 16% respectively, p<0.0001).

Mirikizumab, also targeting the p19 subunit of IL-23, was initially approved for use in UC as a second-line advanced therapy, and as of July 2025 has attained approval for use in CD across the UK.[201] LUCENT-1, an RCT examining the efficacy of 300mg of mirikizumab administered every 4 weeks over a period of 12 weeks, against placebo for the induction of remission in moderate-severe UC, demonstrated superiority of mirikizumab in achieving combined clinical and endoscopic remission at 12 weeks (36.3% vs. 21.1%, p<0.001).[201] LUCENT-2, A 40-week maintenance RCT, followed on from LUCENT-1 with patients responding to mirikizumab induction re-randomised to receive, mirikizumab 200mg or placebo at 4-weekly intervals, and demonstrated the efficacy in maintaining clinical and endoscopic remission (58.6% vs. 29.1%, p<0.001).[201] Data from the VIVID-1 RCT examining the efficacy of mirikizumab for the induction of remission in CD has also recently been published, with promising

results for achieving endoscopic response at week 52 versus placebo (38.0% vs. 9.0%, p <0.001).[202]

1.7.4.5 Janus Kinase inhibitors

Inflammatory cytokines receive signals via receptors that rely on the Janus kinase (JAK) and signal transducer and activator of transcription pathway. Orally administered JAK inhibitors block these receptors and lessen the inflammatory response.[203] There are 4 JAK receptors, with JAK-1 serving the most crucial role in IBD.[203] The first JAK inhibitor approved for use in IBD was tofacitinib, which targets JAK 1-3, and was granted approval to treat moderate to severe UC as a second-line advanced therapy.[204] OCTAVE-1 and OCTAVE 2 were induction RCTs which demonstrated superiority of tofacitinib 10mg twice daily over placebo in achieving endoscopic remission at week 8 (31.3% vs. 15.6%, p<0.001 and 28.4% vs. 11.6%, p<0.001).[204] OCTAVE sustain re-randomised patients with an initial response to tofacitinib during the induction study, to receive maintenance tofacitinib 5mg, 10mg or placebo daily for 52 weeks, and also demonstrated mucosal healing in both the 5mg and 10mg groups versus placebo (37.4% vs. 45.7% vs. 13.1, p<0.001 for both comparisons), establishing its efficacy as a maintenance therapy for UC.[204]

Filgotinib is a selective JAK-1 inhibitor with the same licensing indications as for tofacitinib. In the SELECTION induction RCT, participants were assigned to receive 200mg, 100mg of filgotinib, or placebo once daily.[205] Only modest effects, which did not reach statistical significance, were noted in achieving clinical remission at week 10 (26.1% vs. 19.1% vs. 15.3%, p=0.157) and there was no difference between groups for endoscopic remission.[205] In the 58-week maintenance study, clinical remission was higher in both 200mg of filgotinib daily vs. placebo (37.2% vs. 11.2%, p<0.001) and 100mg filgotinib vs. placebo (23.8% vs. 13.5%, p=0.042).[205]

Perhaps the most promising JAK inhibitor to emerge in IBD is upadacitinib, which like filgotinib, selectively blocks JAK-1 enzyme activity.[206] Upadacitinib is licensed for use in both CD and UC. The induction RCTs U-EXCEL and U-EXCEED, in addition to achieving clinical remission, clearly demonstrate the superiority of 45mg daily of upadacitinib over placebo in achieving an endoscopic response at 12 weeks in moderate-severe CD (45.5% vs. 13.1%, $p<0.001$ and 34.6% vs. 3.5%, $p<0.001$).[206] U-ENDURE, the 52-week maintenance study, re-randomised those with a clinical response at week 12 to receive 30mg, 15mg upadacitinib, or placebo, and demonstrated superiority of upadacitinib over placebo in maintaining clinical remission, and endoscopic response (40.1% vs. 27.6% vs. 7.3%, $p<0.001$ for both comparisons).[206] Following on from this, the U-ACHIEVE and U-ACCOMPLISH induction RCTs for moderate to severely active UC again demonstrated the superiority of upadacitinib 45mg once daily dose over placebo in achieving clinical remission, and endoscopic improvement (36% vs. 7% and 44% vs. 8%, $p<0.001$ for both comparisons).[207] In the 52-week maintenance RCT U-ACCOMPLISH, participants responding during the induction phase were re-randomised to receive upadacitinib 30mg/15mg or placebo, and similar endoscopic improvements were noted (62% vs. 49% vs. 14%, $p<0.001$ for both comparisons).[207]

1.7.4.6 Sphingosine-1-phosphate inhibitors

Sphingosine-1-phosphate receptors are present on the surface of various cells throughout the body but are abundant in T and B-lymphocytes where their activation promotes migration of lymphocytes from lymph tissue into the circulation. Ozanimod is a selective Sphingosine-1-phosphate inhibitor which is licensed for the treatment of moderate to severe UC. In the True North 10-week induction trial, participants with moderate to severe UC were randomised to 1mg daily of ozanimod or placebo, and ozanimod demonstrated

superiority in achieving endoscopic improvement (27.3% vs. 11.6%, $p<0.001$).[208] In the 52-week maintenance trial, patients achieving a clinical response were re-randomised to ozanimod 1mg daily or placebo, with ozanimod again demonstrating superiority over placebo in achieving endoscopic improvement (45.7% vs. 26.4%, $p<0.001$).[208] Etrasimod is also licensed for the treatment of moderate to severe UC, and the ELEVATE-UC induction RCT has demonstrated superiority of etrasimod 2mg over placebo in achieving endoscopic improvement at 12 weeks (35% vs. 19%, $p=0.009$) in those with moderate disease. Similarly in the 52-week maintenance study, where participants achieving clinical remission during induction were re-randomised to etrasimod 2mg daily or placebo, etrasimod again demonstrated superiority over placebo in achieving endoscopic response (39% vs. 13%, $p<0.001$).[209]

1.7.4.7 Advanced Therapy Drugs Sequencing

The reduction in efficacy of novel medical therapies seen amongst RCTs in patients with prior exposure to advanced therapies highlights the importance of correct drug sequencing in IBD.[196, 198, 210] Limited head-to-head trials have been conducted between advanced therapies, VARSITY, comparing the efficacy of standard treatment regimens of vedolizumab versus adalimumab in UC demonstrated superiority of the former with regards to endoscopic improvement after 52-weeks of therapy (39.7% vs. 27.7%, $p<0.001$) which was more marked in anti-TNFα naïve patients (43.1% vs. 29.5%, $p<0.001$).[210] The SEAVUE head to head trial comparing conventional doses of ustekinumab and adalimumab in anti-TNFα naïve patients with CD, demonstrated no superiority in achieving an endoscopic response at 52-weeks (42% vs. 37%, $p=0.35$).[211] Finally, the recently published SEQUENCE trial comparing the two IL-23 inhibitors risankizumab and ustekinumab in CD demonstrated superiority of the former in achieving endoscopic remission at week 48 (31.8% vs. 16.2%,

$p<0.001$).[199] The limited number of head-to-head trials summarised above mean that currently network meta-analyses provide the most comprehensive evidence on drug sequencing for advanced therapies. Infliximab 5mg/kg ranking first for induction of clinical remission across all groups of patients with luminal CD, and upadacitinib 30mg once daily for maintenance of remission.[212] Similarly for UC, upadacitinib 45mg once daily ranked first for all drugs in inducing clinically remission, with infliximab 10mg/kg ranking first for endoscopic improvement.[213] However, drug efficacy is not the only consideration when sequencing drugs in IBD. Patient preferences, including method of delivery, frequency of administration, risk-safety profile, and drug monitoring requirements must also be considered.[214] Furthermore, drug cost and availability are important determinants for healthcare providors.[214]

1.7.5 Microbiome Directed Therapies

A range of microbiome-directed therapies have been trialled in IBD including pre-biotics, fibre-containing supplements to boost gut microflorae nourishment, probiotics, living microorganisms that positively influence the biodiversity of the microflora, and synbiotics, the two in combination. The effects of probiotics have been most widely studied and VSL#3 has shown similar efficacy to oral mesalazine in maintaining remission of UC, but the efficacy of other individual compositions is less clear.[215] Another meta-analysis has demonstrated good safety and tolerability of all three treatment types, with synbiotics appearing to have the greatest effect, potentially even inducing remission in UC.[62] However, with significant heterogeneity between the existing RCTs, and the majority of studies having a short duration of follow-up, little known regarding the long-term efficacy of these therapies in maintaining remission.[62, 215] Moreover, most studies examining the role of microbiome directed therapies in IBD utilise clinical disease activity indices to determine underlying

disease activity, and fail to correlate perceived improvements in symptoms with comparative assessments of endoscopic disease activity, which may overestimate the efficacy of individual therapies.[215] Furthermore, on the whole, the available RCTs fail to consider alterations in the microbiome composition with therapy, therefore the mechanistic benefit of these treatments in IBD remains unclear.[215]

An assortment of herbal remedies may also influence the gut microbiome composition. Curcumin as a complimentary treatment alongside mesalazine has been shown to improve mucosal healing for those with active UC.[216] Similarly, the use of curcumin with qing-dai, versus placebo was associated with endoscopic improvement in 75% of patients at week 8 of therapy versus 20% of those receiving placebo in one small RCT in patients with active UC.[217] However, the available RCTs are small and would need replicating in larger cohorts before formal recommendations regarding their routine use in IBD can be made.

Faecal microbiota transplantation (FMT) has an evidence base in the treatment of recurrent *Clostridium difficile* infection and its use has been studied in IBD.[218] A meta-analysis of RCTs in 324 patients with active UC reports short-term improvements in clinical and endoscopic scores, and a good safety profile.[219] One RCT of only 17 patients has examined the efficacy of FMT for induction of remission in CD, with endoscopic improvements demonstrated in those receiving FMT, [220] however, escalation of medical therapy was permitted during flares, and no significant alteration in gut microbiome composition was apparent in the treatment group, making it difficult to determine that these patients truly responded to the FMT. Insufficient evidence therefore restricts the use of FMT in IBD outside of proven *Clostridium difficile* infection.[221]

1.7.6 Exclusive Enteral Nutrition

Exclusive enteral nutrition (EEN) is the removal of conventional foods from the diet and replacement with a nutritionally complete liquid formulation. Elemental formulas contain pre-digested nutrients in their simplest form to enable immediate absorption, whereas polymeric formulas contain intact peptides, carbohydrates, and fats, requiring digestive processing prior to their absorption.[222] EEN demonstrates comparative efficacy to glucocorticosteroids in paediatric cohorts for the induction of remission in CD, in addition to positive effects on growth, and is recommended as a primary therapy in this setting.[223] Multiple suggestions for the efficacy of EEN have been proposed, including microbiome alterations, changes in intestinal barrier permeability, and attenuation of the immune system dysregulation, but the exact mechanism is unclear.[222]

The role of EEN is less clear in adult patients, and in contrast to the evidence presented in paediatric patients, a meta-analysis of 8 RCTs examining the efficacy of both elemental and polymeric feeds for the induction of remission in adults with CD demonstrates their inferiority to corticosteroids.[224] A small study examining the effect of administering EEN to patients with CD in the perioperative setting, demonstrated that administration of EEN over a mean of 6 weeks was associated with lower rates of post-surgical complications including anastomotic leak, and abscess formation.[225] Similarly in a small prospective study, 35 patients with CD at high risk of surgical complications (steroid dependent, obstructive disease, more than 10% loss of total body weight, and penetrating disease) were treated with EEN for a mean of 3 weeks and had similar postoperative complication rates when compared to patients who were deemed low risk of surgical complications in the pre-operative period.[226] EEN has also been examined in adult cohorts of patients with UC, but evidence from a meta-analysis of 10 RCTs found that the addition of EEN was not superior to standard treatment with corticosteroids alone for the induction of remission, corticosteroid response, or

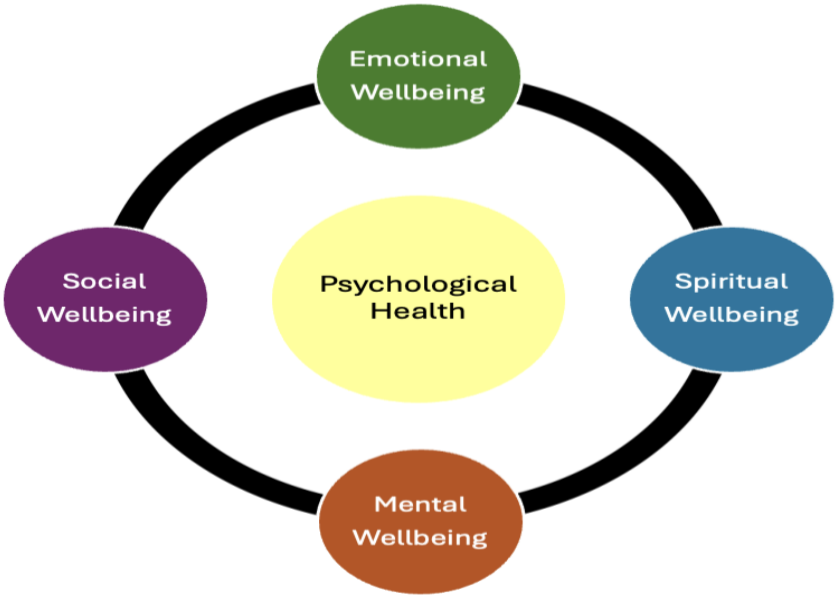
risk of colectomy, in acute severe colitis.[227] Furthermore substantial barriers to patient adherence of EEN in adult cohorts have been highlighted, including poor tolerability, social isolation due to loss of meal based social interaction, and insufficient support from allied healthcare professionals.[228] Currently there is insufficient evidence to recommend the routine use of EEN in adult patients with IBD, but their use can be considered for patients with CD in the perioperative period for patients who are malnourished with fibrotic or penetrating disease.[60]

1.8 Psychological Health: The Role in Chronic Disease States

Though often used interchangeably with mental health, psychological health is an encompassing term for emotional, spiritual, mental, and social wellbeing (Figure 1.3).[229] Psychological health influences an individual's response to daily life stressors, their work productivity, personal relationships, and decision making, in addition to directly impacting upon physical health.[230] It is not considered a binary state, rather a continuum, fluctuating between optimal and poor psychological wellbeing, the latter of which is characterised by emotional lability, increased stress levels, and the development of symptoms of common mental disorders, including anxiety and depression.[231] Environmental factors exert a considerable influence over psychological wellbeing, with poverty, unemployment, and poor housing, consistently associated with poor psychological health in population based studies.[232] Furthermore, past life events, including mental and physical trauma can be contributary.[232] Physical illness is an independent risk factor for the development of poor psychological health, associated with a twofold risk of developing symptoms of depression.[231] In some chronic health conditions, this may be a direct effect of the primary pathology, for example chronic microvascular inflammation in diabetes leading to cerebral degeneration.[233] However, in the majority of cases poor psychological health arises from a

difficulty in adapting to life with a chronic illness, the threat of shortened life expectancy, and a loss of social support.[234] When present alongside chronic illness, poor psychological health contributes to poor adherence to medical treatment, social isolation, and the development of physical disability, making it an important factor to consider.[231, 235]

Figure 1.3. The Key Components of Psychological Health



1.8.1 Anxiety

Anxiety, the characteristic stress response to a perceived danger, is the cumulation of enhanced vigilance, anticipation, and physiological arousal.[236] In nature, this is a protective mechanism to sense and avert a threat.[236] The exact physiologic mechanisms involved in triggering the anxiety response are unclear, but are believed to include sensory afferents which activate the amygdala and inhibit the prefrontal cortex to inhibit the release of gamma-aminobutyric acid (GABA) and serotonin.[237] These are potent mood regulators, which trigger a surge of corticotrophin releasing hormone from the hypothalamus in turn activating the hypothalamic-pituitary-adrenal axis, resulting in sustained cortisol release and subsequent clinical stress response.[237] A disproportionate and persistent level of anxiety in response to

everyday stressors is abnormal, the sequalae of which are excessive worry, irritability, poor concentration, sleep disturbance, and restlessness.[237] These symptoms can have a devastating impact on functional ability and quality of life.[238] Symptoms of anxiety are associated with significant increases in healthcare utilisation, particularly when co-existing alongside chronic physical illness.[239] Generalised anxiety disorder is defined as the presence of symptoms of anxiety on most days over the course of a minimum 6-month period,[240] and is estimated to affect close to 4% of the global population.[241, 242]

1.8.2 Depression

Symptoms of depression include low mood, anhedonia, alterations in appetite, cognitive disturbance, and somatoform symptoms which are negative physical perceptions, such as pain, dizziness, and fatigue, occurring in the absence of a medically identifiable cause.[235] The pathophysiology of depression is multifactorial, with genetic predisposition, low levels of the neurotransmitters serotonin, noradrenaline, and dopamine, and upregulation of the hypothalamic pituitary axis and subsequent stress response all providing plausible explanations for the clinical presentation.[243] More recently, neuroinflammation has been proposed.[243] High levels of circulating pro-inflammatory cytokines TNF-α, IL-6, and IL-10 have been demonstrated in patients with depression,[244] in addition to raised levels of the acute phase reactant, C-reactive protein and reduced levels of the negative acute phase reactant albumin.[245, 246] Supporting this theory, the development of depressive type behaviours have been observed in mice following the administration of synthetic TNF-α, and may explain the high prevalence of concurrent symptoms of depression seen in chronic inflammatory disorders.[247] The current diagnostic criteria for depression require the symptoms to be present for a minimum of 2 weeks prior to making a formal diagnosis,[240] and the global prevalence is estimated to be close to 5%, with the highest prevalence in Western societies.[242] A meta-

analysis of population based studies demonstrates that depressive symptoms, irrespective of their association with chronic illness, are associated with a significant increase in mortality (OR=1.7; 95% CI 1.5-2.0),[248] and individuals with a chronic illness have greater risk of depression than healthy individuals (OR=1.45; 95% CI 1.28–1.64).[249]

1.8.3 The Epidemiology and Natural History of Poor Psychological Health in IBD

Though no longer regarded as a psychological disorder, the high prevalence of poor psychological health amongst patients with IBD is striking. Data from a large systematic review and meta-analysis of over 30,000 individuals with IBD highlights a significantly higher prevalence of symptoms of anxiety and depression than the general population, affecting close to a third and one quarter respectively.[250] Several factors have been linked with poor psychological health in IBD, including an aggressive disease phenotype, CD, female sex, the presence of IBS-type symptoms and somatoform symptom-reporting.[128, 235, 251] The prevalence of IBS-type symptoms in individuals with objectively confirmed quiescent IBD is itself close to one quarter, which is also significantly higher than the general population prevalence of between 5-10%,[252] and may provide a plausible explanation for the relationship between poor psychological health in quiescent IBD.[128] However, symptoms of poor psychological health appear to peak during periods of disease activity, affecting almost half of patients during a flare, therefore the inflammatory burden itself may directly influence psychological health.[250] Finally, negative life experiences are proven to influence the future development of poor psychological health, and a preceding adverse disease course may also provide an explanation for the high prevalence of symptoms of anxiety and depression seen in patients with established IBD.[230]

The existing pool of data examining the relationship between poor psychological health and IBD has in large has been conducted amongst patients with established disease,

whom have the potential to be influenced by a prior adverse disease course, making it difficult to discern the underlying cause of these symptoms.[253] To date, only one study has been conducted amongst newly diagnosed patients. This multicentre observational study included only 155 patients recruited within 6 months of a diagnosis of IBD, and reported similarly high prevalences of symptoms of anxiety and depression at 30% and 15% respectively, suggesting that the presence of these symptoms is more likely to be linked to inflammatory activity, but further studies are needed to validate these findings, particularly at the time of diagnosis prior to the onset of any adverse disease outcomes including treatment failure and hospitalisation.[254] Furthermore, psychological health is a continuum, with substantial fluctuation in mood observed in population based studies.[255] Most studies examining the temporal effects of poor psychological health in IBD examine psychological health at a single time-point, and as such, very little is known regarding the stability of symptoms of anxiety and depression over the disease course.[253] This is an important consideration because if the symptoms of anxiety and depression are a result of the inflammatory activity itself, treating the disease may be sufficient to tackle poor psychological health in this patient group. A recent longitudinal follow-up study examining mood trajectories at 3-monthly intervals over the course of a year highlights that abnormal anxiety or depression scores improve in only 1 in 10 patients, suggesting that poor psychological health is a persistent issue, at least in the short term, for the patients reporting these symptoms.[251] However, currently there is no clear understanding of the longevity of symptoms of anxiety and depression in IBD.

1.8.4 The Gut-Brain Axis in Health and Disease

The gut-brain axis (GBA) is complex communication network in which neural, endocrine, immune, and humoral signals serve to modulate peripheral gut functions by

linking the central (CNS), autonomic, and enteric nervous systems with the hypothalamic-pituitary-adrenal axis.[256] In health the functions of the GBA include regulation of intestinal motility, secretions, and absorption, in addition to the synthesis of key neurotransmitters including serotonin, dopamine, GABA, and acetylcholine.[257] Finally, the GBA regulates the production of cortisol in the hypothalamus, contributing to the natural stress response.[257] Traditionally GBA communications were considered unidirectional, with the CNS centrally controlling peripheral gut functions via brain-gut signalling pathways to directly influence the enteral nervous system, but an increasing body of evidence suggests that communications are in fact bi-directional.[68] Microbiome dysbiosis and translocation of pro-inflammatory cytokines across the gut-epithelial and blood-brain barrier have been linked with subsequent alterations in the CNS, and the development of psychiatric disorders including anxiety and depression, and neurological conditions including Alzheimer's dementia, multiple sclerosis, and Parkinson's disease, suggesting that gut-brain communications are also present.[68, 258] Bi-directional GBA interactions have been demonstrated in common gastrointestinal disorders, including IBS, whereby psychological stress is proven to negatively impact gastrointestinal symptoms and a higher than expected prevalence of symptoms of anxiety and depression is apparent.[259, 260] Manipulation of the GBA, using psychological therapies and gut-brain neuromodulators have demonstrated good efficacy in treating the symptoms of IBS and are advocated in treatment guidelines for these patients.[261]

1.8.5 The Gut-Brain Axis in IBD: Pathophysiological Mechanisms for the High Prevalence of Poor psychological health.

Stressful life events are highly reported amongst patients with IBD, including those newly diagnosed, indicating that in addition to the aspects of physical health outlined previously in this thesis, psychological health may also be implicated in the development of the disease.[254,

[255] A population based cohort study including more than 22,000 patients with IBD and 100,000 matched controls, highlighted that, in addition to a comparably high prevalence of symptoms of both anxiety and depression in those with IBD, the development of these symptoms precedes the diagnosis of IBD by up to 5 years.[255] Supporting these findings, a meta-analysis, including over 9 million individuals, has examined the temporal effects of depression on incident IBD, indicating a 17% risk of CD and a 23% risk of UC, which are significantly higher than the background population risks of both conditions.[262]

Observational research formulates much of the evidence base pertaining to the role of psychological health in the pathogenesis of IBD, however, in murine models of colitis direct hypothalamic stimulation increases the release of corticotropin-releasing factor and adrenocorticotropic hormone, inducing mast cell degranulation and cytokine secretion, and has been demonstrated to increase intestinal permeability and impair intestinal barrier function.[263]

The proposed mechanism by which the GBA adversely impacts psychological health in IBD is through release of pro-inflammatory cytokines including IL-1β, IL-6, and TNFα, which enter the systemic circulation and cross the blood brain barrier, whilst simultaneously activating the enteric nervous system, and vagus nerve afferents.[257] Together these humoral and neural pathways activate the hypothalamic-pituitary-adrenal axis to upregulate the production of glucocorticoids which serves anti-inflammatory roles, but are also implicated in the pathogenesis of depression.[264] Conversely, stress induced activation of the sympathetic nervous system stimulates catecholamine release in the adrenal medulla, which in turn leads to macrophage activation through nuclear factor kB signalling pathways.[265] The vagus nerve, which inhibits pro-inflammatory cytokines, is downregulated during the acute stress response.[266] Together these mechanisms contribute to a pro-inflammatory state, and may explain why perceived stress has been shown to increase the number of circulating pro-

inflammatory cytokines in quiescent IBD.[267, 268] A summary of the proposed bi-directional effects of the GBA in IBD is provided in Figure 1.4.

Figure 1.4. The proposed Bidirectional Effects of the GBA in IBD

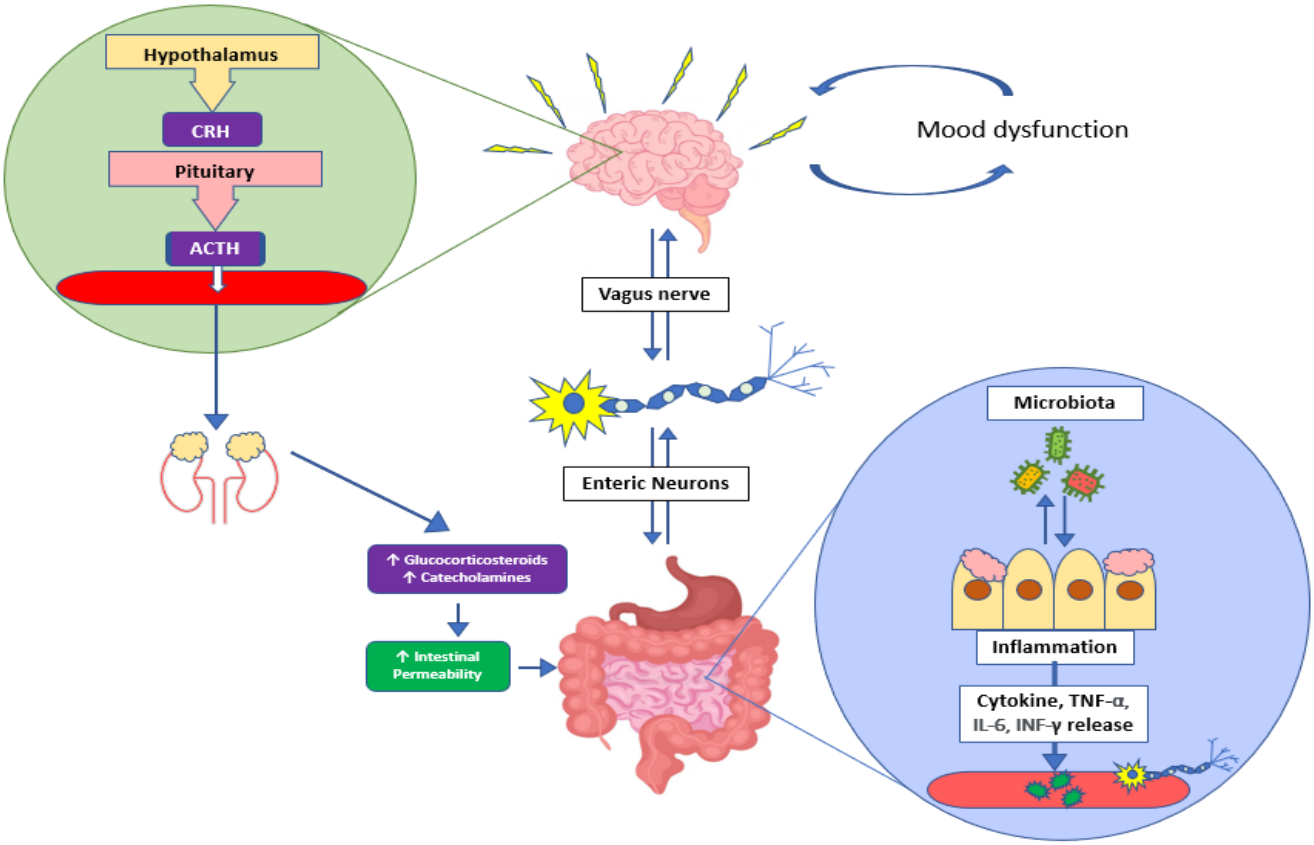


Figure reproduced from Riggott C, Ford AC, Gracie DJ. The role of the gut–brain axis in inflammatory bowel disease and its therapeutic implications. Aliment Pharmacol Ther. 2024 Nov;60(9):1200-14.

1.8.6 Brain-gut interactions: Exploring the impact of Poor Psychological Health on Disease Outcomes in IBD

The association between symptoms of anxiety and depression and adverse disease outcomes in patients with IBD is well-documented.[253] Studies in quiescent IBD highlight that patients exhibiting these symptoms are more likely to experience future adverse disease

outcomes, including experiencing a flare of disease activity, requiring escalation of medical therapy, or being hospitalised secondary to uncontrolled IBD activity,[269-272] with symptoms of anxiety exerting the greatest effect.[250, 253] Many of these studies however, do not recruit patients solely in remission, which confounds the findings, as persistent inflammation is an independent driver of adverse disease outcomes in IBD.[273] A systematic review and meta-analysis of over 9000 patients with IBD has addressed this issue by conducting a subgroup analysis of studies including only patients in clinical remission and has demonstrated that patients with symptoms of anxiety are more likely to experience a future flare of disease activity (RR = 1.80; 95% CI 1.24-2.61), require escalation of medical therapy (RR = 1.68; 95% CI 1.18-2.40), or be hospitalised due to poorly controlled IBD (RR = 1.72; 95% CI 1.01-2.95).[253] Attenuated response to medical therapies has also been suggested in patients with IBD and symptoms of a common mental disorder, both due to non-adherence,[274] and primary non-response.[275] Finally, poor psychological health may also negatively influence healthcare utilisation in IBD.[128, 251, 269, 276] Symptoms of anxiety or depression are associated with double the annual healthcare costs compared with those without,[42] and studies demonstrate that these patients attend a greater number of primary and secondary care appointments,[277] have more unplanned emergency department visits,[276] and are more likely require a prolonged hospitalisation due to IBD activity.[278]

The discrepancy between objective assessments of disease activity and patient-reported symptoms in observational IBD research has been alluded to previously,[128, 129] In a *post hoc* analysis of the multicentre SONIC RCT examining the efficacy of infliximab, azathioprine, and combination therapy in patients with active CD, this disconnect was again demonstrated, with a fifth of patients continuing to experience gastrointestinal symptoms despite endoscopically quiescent disease.[125] Poor psychological health is associated with the persistence of symptoms in quiescent disease, and it is therefore possible that these are

somatic symptoms, in part driven by poor psychological health.[128] Few studies have examined the influence of poor psychological health in patients with objectively confirmed disease activity, with conflicting results. Using FC levels to determine biochemical remission, Mules *et al.* found no association between symptoms of a common mental disorder and subsequent disease activity in 52 patients with IBD, but did demonstrate that symptom-reporting was linked with poor psychological health.[279] Conversely, in a larger group of 218 patients in disease remission defined by an FC <250µg/g of stool, *Fairbrass et al.* demonstrated that poor psychological health was associated with future flares of disease activity and escalation of medical therapy, suggesting genuine brain-gut effects in IBD.[269]

1.8.7 Gut-brain interactions: Exploring the Impact of Disease Activity on Psychological Health in IBD

The high prevalence of symptoms of both anxiety and depression during flares of IBD indicates that their development may be directly influenced by inflammatory activity,[250 253] and observational studies highlight an association between baseline disease activity and subsequent development of symptoms of a common mental disorder in IBD.[273, 280] Gracie *et al.* reported that baseline clinical disease activity was associated with an almost 6-fold increase in the subsequent risk of developing symptoms of anxiety in 192 patients with IBD (HR= 5.77; 95% CI, 1.89–17.7).[280] Panara *et al.* reported more modest effects of baseline disease activity on the subsequent development of depressive symptoms in 393 patients with IBD (HR=1.5; 95% CI 1.1-2.0).[281] A meta-analysis of studies reporting the prevalence of common mental disorders in IBD suggests that over half of patients with active disease have symptoms of a common mental disorder, and longitudinal follow-up studies have demonstrated an association between disease activity at baseline and the subsequent

development of symptoms of a common mental disorder.[128, 273, 280, 282, 283] These findings are supported in a recent meta-analysis examining gut-brain interactions in IBD, with baseline clinical disease activity associated with future development of anxiety (RR=2.24; 95% CI 1.25-4.01) and depression (RR=1.49; 95% CI 1.11-1.98).[253] Outside of observational study, there is little human research pertaining to gut-brain interactions in IBD, however chemically-induced colitis appears to induce depressive and anxiety-like behaviours in mice,[284] with an associated increased expression of inflammatory cytokines, and alteration of mitochondrial function in the hippocampus demonstrated at autopsy, providing a biological explanation of the observed gut-to-brain effects demonstrated in observational IBD research studies.[285]

1.8.8 The Effect of Conventional IBD Therapies on Psychological Health

Given the inflammatory theory of depression, it is possible that conventional immunosuppressive therapies used to treat mucosal inflammation in IBD may also impart direct effects on mood. This area is relatively understudied, but an RCT comparing infliximab with placebo in 60 patients with depression without a diagnosis of IBD found no significant improvement in depressive symptoms between those treated with anti-TNFα compared with placebo.[286] However, prospective studies in IBD are in contrast to these findings; in one study conducted amongst patients newly diagnosed with CD, improved anxiety and depression scores occurred in patients receiving infliximab 30 weeks after commencing therapy.[287] Similar findings have been reported amongst patients with UC receiving adalimumab.[288] Furthermore, a small observational study examining the effect of vedolizumab and anti-TNFα therapies on disease activity and mood scores in 183 patients with IBD identified improvements in mood with both drugs, with comparable efficacy.[193] Given the gut-selectivity of vedolizumab, and the lack of improvements seen in non-IBD

patient cohorts, it is more likely that the improvement in anxiety and depression symptoms reported in these studies is because of GBA-mediated effects, rather than direct effects on the CNS, but this area requires more research before conclusions can be formalised.

1.8.9 Effects of Gut-Brain Neuromodulators on Disease Activity and Psychological Health in IBD

Antidepressants, better termed gut-brain neuromodulators, to recognise that their pharmacological properties extend beyond their effects on the brain, include selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and atypical antidepressants. Their role has been studied in IBD. In mice with quiescent colitis, induced depression results in reactivation of mucosal inflammation, with pre-administration of gut-brain neuromodulators appearing to alleviate this process.[289] Similarly, in murine study, the administration of tricyclic antidepressants has been shown to reduce colonic inflammation, irrespective of pre-existing depressive symptoms.[290] Observational research in IBD supports these pre-clinical trials, with results from an epidemiological study of over 400,000 participants suggesting that although depression is associated with an increased risk of later developing IBD, gut-brain neuromodulators may be protective.[291] Similarly, lower rates of disease activity have been reported in over 43,000 patients with CD and UC taking gut-brain neuromodulators in comparison to those who are not (Incidence rate ratios 0.75; 95% CI 0.68-0.82, and 0.90; 95% CI 0.84-0.95 respectively).[292] However, these studies adopted clinical codes as proxy measures to determine IBD activity, which limits the reliability of the results.

Gut-brain neuromodulators reduce abdominal pain in IBS,[293, 294] and are advocated as second-line therapy in current IBS treatment guidelines.[261] Alleviation of gastrointestinal symptoms is believed to occur through the upregulation of neurotransmitters, including

serotonin, corticotropin releasing factor, and norepinephrine, which are key determinants of intestinal motility and visceral sensitivity.[295] In the case of IBD, neuromodulators may also exert anti-inflammatory effects, via modulation of pro-inflammatory cytokines, and their direct effects on neurogenesis, serotonin metabolism, intracellular cyclic adenosyl monophosphate production, and the hypothalamic pituitary adrenal axis.[296] A meta-analysis of 603 individuals with depression supports this theory, demonstrating that serotonin reuptake inhibitors downregulate IL-6 and TNF-α, both of which are implicated in the immunopathogenesis of IBD.[297]

To date only two RCTs have explored the effect of gut-brain neuromodulators on disease activity in IBD,[298, 299] and neither study restricted recruitment to only include participants with pre-existing evidence of poor psychological health. In 44 patients with IBD, duloxetine, a serotonin-noradrenaline reuptake inhibitor, reduced clinical disease activity scores, and anxiety and depression scores, in addition to improving quality of life scores.[298] Fluoxetine, a selective serotonin reuptake inhibitor, however, did not demonstrate superiority over placebo with regard to each of these outcomes in CD.[299] Wang *et al.* conducted a systematic review and meta-analysis of 13 RCTs examining the efficacy of gut-brain neuromodulators in 884 patients with IBD, highlighting superiority in reducing symptoms of anxiety and depression, disease activity scores, and improving quality of life in comparison to placebo.[300] However, only the two aforementioned trials, were conducted outside of China, which may limit the generalisability of the evidence presented. In addition, despite most studies recruiting selected patients, with pre-existing anxiety or depression, subgroup analyses were not performed to determine if gut-brain neuromodulators performed better in individuals with evidence of poor psychological health.[300]

1.8.10 Effects of Brain-Gut Behavioural Treatments on Disease Activity and Psychological Health in IBD

Brain-gut behavioural therapies focus on enabling individuals to recognise distressing thoughts, emotions, or behaviours, and modify them.[301] A detailed explanation of individual therapies is beyond the scope of this thesis; however, they include talking therapies such as cognitive behavioural therapy (CBT), which focuses on the recognition of harmful thoughts and beliefs and modifying the ensuing emotional and behavioural responses,[301] third wave therapies such as mindfulness and acceptance and commitment therapy, which have evolved from CBT, and focus on identification of how the individual relates to internal experiences, to identify how changes in this process can be implemented,[301] and solution focussed therapy, which emphasises the importance of setting realistic goals and taking small consistent steps to achieve them.[302] Furthermore, non-talking therapies, such as hypnotherapy, the induction of a deeply relaxed state, where psychological change can be implemented through heightened suggestibility,[303] and psychodynamic psychotherapy, which promotes self-awareness through identification of unconscious processes that manifest in the individuals behaviour, are also widely used.[304] Individual therapies are summarised in Table 1.

The efficacy of brain-gut behavioural therapies is proven in IBS, and features in the associated national guideline as a recommended adjunct to routine clinical care.[261] In the context of IBD their efficacy is less clear. Studies examining the effects of psychological therapies on psychological health report improvements in anxiety, depression, and perceived stress scores, in addition to improvements in quality of life.[305] A meta-analysis including 14 RCTs examining the efficacy of gut-brain behavioural therapies in IBD by Gracie *et al.* demonstrated improvements in depression scores versus control (Standard Mean Difference (SMD) -0.17; 95% CI -0.33 to -0.01) and quality of life (SMD 0.30; 95% CI 0.07-0.52) for patients receiving active treatment at the conclusion of therapy, but no sustained

improvement at the final point of follow-up, suggesting these benefits may be short-lived.[215] Furthermore, the evidence base for brain-gut behavioural therapies as a treatment for disease activity is less clear. One RCT examining the efficacy of psychotherapy versus treatment as usual in 114 patients with IBD reported that 12 (21.1%) of 57 patients undergoing psychological therapy entered clinical remission, versus 2 (3.5%) of 57 patients receiving standard treatment over 18 months of follow-up.[306] However, these findings have not been replicated, precluding a formal meta-analysis of their efficacy as a primary treatment in IBD.[215] As such, national guidelines do not advocate their routine use in IBD care, instead suggesting they be offered as an adjunctive treatment for interested patients.[60]

Table 1.1: Brain-gut Behavioural Treatments used to Treat Gastrointestinal Symptoms.

Intervention	Underlying model of therapy	Third wave	Talking therapy
Cognitive behavioural therapy	Identifies problematic thinking styles and their occurrence in daily life. Aims to modify these thought processes to alleviate anxiety and boost mood.	No	Yes
Mindfulness	Identifies how patients perceive particular triggering moments and equips them with skills to redirect their attention to other aspects of the experience.	Yes	Yes
Acceptance and commitment therapy	Utilises aspects of mindfulness and CBT to allow flexibility when dealing with different stressful events.	Yes	Yes
Hypnotherapy	Induces a deeply relaxed where they are more receptive to changing habits.	No	No
Psychodynamic psychotherapy	Unmasks unconscious processes which influence an individual's behaviour. Instructs self-awareness and understanding of how past experiences influence current behaviours.	No	Yes
Solution-focused therapy	Sets goals and implements steps to achieve them, re-focusing on what is possible rather than what is not.	No	Yes

1.9 Disentangling the Role of the Gut Brain Axis in IBD: Future Directions and the Foundations for this Thesis

Despite compelling evidence supporting the bi-directional effects of the GBA on both disease outcomes and psychological health in IBD, important gaps in knowledge exist in the current research pool. Firstly, little is known regarding the persistence of symptoms of anxiety and depression over time, which, given the fluctuant nature of IBD activity is key to validating the findings of the existing studies in which poor psychological health is suggested to negatively impact the natural history of the disease, based on a single assessment of mood. Secondly, given the apparent relationship between disease activity and poor psychological health, the impact of mood on future adverse disease outcomes could be the result of confounding, and studies examining the relative contribution of disease activity and psychological health are therefore required to further disentangle this relationship. Similarly, it is unclear if an adverse disease course drives poor psychological health in this scenario, or whether genuine gut-brain effects contribute, and studies examining the prevalence of poor psychological health in patients newly diagnosed with IBD, prior to the onset of an adverse disease course, are required to fully appreciate a causal relationship between inflammatory activity and poor psychological health. Finally, if genuine brain-gut effects are apparent in IBD, targeting these pathways should improve the psychological health of those affected by symptoms of anxiety or depression, and examining the role of such therapies in this context may aid policy makers to implement these therapies into best practice recommendations. The individual chapters of this thesis aim to address these pertinent issues in detail.

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Chapter 2: Prevalence and Predictors of Symptoms of Anxiety or Depression at Diagnosis in Patients with Inflammatory Bowel Disease: An Inception Cohort.

2.1 Summary

Background: The prevalence of symptoms of a common mental disorder, including anxiety or depression, is high amongst patients with established inflammatory bowel disease (IBD). This may represent a therapeutic target for affected patients. However, whether these symptoms arise from genuine gut-brain effects, or are merely a consequence of a preceding adverse disease course is unclear.

Aims: To assess prevalence and predictors of anxiety and depression in an inception cohort of patients with IBD.

Methods: We collected demographic data, disease-related information, diagnosis of a pre-existing common mental disorder, symptoms of a common mental disorder, using the hospital anxiety and depression score, and gastrointestinal symptom-specific anxiety, using the visceral sensitivity index (VSI), from individuals newly diagnosed with IBD during their index outpatient appointment or inpatient admission. The prevalence of symptoms of a common mental disorder at diagnosis, and predictors of the presence of these symptoms, were examined.

Results: Of 300 participants, 117 (39.0%) reported symptoms of a common mental disorder (107 (35.7%) anxiety, 47 (15.7%) depression). Younger age, female sex, tobacco use, a longer duration of symptoms prior to diagnosis, higher gastrointestinal symptom-specific anxiety, and stressful life events in the preceding 12-month period were associated with a significantly increased likelihood of reporting these symptoms. Higher gastrointestinal symptom-specific anxiety remained significant following logistic regression (OR 2.19; 95% CI 1.00-4.79 for VSI moderate and OR 13.5; 95% CI 5.86-31.2 for VSI high, P <0.001 for trend).

Conclusion: Poor psychological health is highly prevalent at the time of an IBD diagnosis, suggesting genuine gut-brain effects.

2.2 Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing-remitting immune-mediated inflammatory bowel diseases (IBD) affecting over 8 million individuals worldwide.[1] Mucosal inflammation is the hallmark of disease activity and a presumed consequence of immune dysregulation in response to environmental and microbiome triggers in genetically susceptible individuals.[2] Gastrointestinal inflammatory activity produces troublesome symptoms, including abdominal pain, diarrhoea, and faecal urgency, which are associated with a reduced quality of life, the development of functional disability and, ultimately, progressive digestive damage with resulting disease complications. Therefore, current treatment paradigms focus on proactive treatment of mucosal inflammation.[3-7]

The gut-brain axis may also exert an influence on the natural history of IBD.[8, 9] The prevalence of symptoms of a common mental disorder, such as anxiety or depression, is more than double that of the general population, and peaks during periods of disease activity, suggesting a possible link with inflammation.[8-11] Furthermore, symptoms of a common mental disorder in individuals with IBD are associated with future adverse disease outcomes, including flare of disease activity, treatment escalation, hospitalisation, and intestinal resection, in addition to increased healthcare utilisation and increased healthcare costs, compared with individuals without such symptoms.[8, 11-15] Such findings suggest that, alongside managing co-existing inflammatory burden, the gut-brain axis may be a therapeutic target in IBD.[9, 16, 17]

To examine whether the high prevalence of symptoms of anxiety and depression among patients with IBD are mainly a consequence of a pre-existing adverse disease course, such as repeated hospitalisation or intestinal resection, studies assessing the reporting of these symptoms in patients with newly diagnosed IBD, and before the onset of disease related complications, are essential. If such studies determine poor psychological health to be highly

prevalent in this group of patients, it would support a move towards a biopsychosocial model of care,[19] where integrated psychological input may serve to mitigate future disease complications. This is of particular relevance as gut-brain axis directed therapies, including psychological therapies and gut-brain neuromodulators, have demonstrated a benefit in patients with IBD with evidence of poor psychological health.[20, 21]

To date, however, there have been few studies reporting the prevalence of symptoms of a common mental disorder in patients with newly diagnosed IBD. In a Spanish study of 156 patients, the authors reported a 37% prevalence of symptoms of anxiety and a 17% prevalence of symptoms of depression in 155 patients with a recent diagnosis of IBD.[22] These rates are comparable to those in patients with established disease.[10] However, this study recruited participants whom had received the diagnosis of IBD within the preceding 6 months, and failed to control for any adverse disease outcomes occurring during the time since diagnosis, but prior to study recruitment.[22] This could be a confounding factor, particularly as hospitalisation and surgery have the potential to negatively impact subsequent psychological health.[23] In another study from New Zealand, which included data from 53 newly diagnosed patients with IBD, abnormal anxiety scores were reported by 23%, and abnormal depression scores by 9%.[24]

We, therefore, examined the prevalence of symptoms of anxiety and depression, and associated factors, in a large inception cohort of patients with IBD, with the hypothesis that these symptoms are already highly prevalent at the time of diagnosis.

2.3 Methods

2.3.1 Participants and Setting

Consecutive adult patients ≥18 years old with a new diagnosis of CD, UC, or IBD unclassified (IBD-U) based on endoscopic, histological, or radiological findings were invited to participate in this prospective cross-sectional survey conducted in Leeds Teaching Hospitals NHS Trust between March 2023 and January 2025. Participation in the study required the completion of a baseline questionnaire and, therefore, patients who were unable to understand written English were excluded. Furthermore, as surgery may independently influence psychological health,[23] patients who underwent emergency surgery for IBD during their index presentation, prior to enrolment in the study, were excluded.

Individuals were identified by an individual assessor (CR) by performing a weekly review of IBD clinic patient lists and inpatient admission sheets against the study eligibility criteria. Following this, participants deemed by the assessing clinician to have an alternate pathology, including infective, ischaemic, drug-induced, or diverticular-associated colitis were excluded. Participants with non-specific terminal ileitis, in whom there was insufficient histological or radiological evidence to confirm a formal diagnosis of IBD, were excluded from participation until a definitive diagnosis was reached.

Eligible individuals were recruited in-person, at their index clinic consultation or during their index hospital admission. This study was approved by the Wales Research and Ethics Committee (REC ref: 22/WA/0368).

2.3.2 Data Collection and Synthesis

The date of study recruitment, type of IBD, including disease extent, location, and phenotype, and IBD-related medications commenced at diagnosis (5-aminosalicylates, immunomodulators, such as azathioprine or mercaptopurine, corticosteroids, or advanced

therapies, including biologics and small molecules) were recorded at baseline, in addition to demographic data, including age, sex, and lifestyle factors, and the presence of an existing formal diagnosis of either anxiety or depression at baseline. Furthermore, we collected data regarding total duration of gastrointestinal symptoms prior to the diagnosis of IBD being made, and the occurrence of any potentially stressful life events in the 12 months prior to diagnosis, both by self-report. These included the death of a loved one, birth of a child, separation or divorce, getting married, loss of a job, commencing a new job, stress at work, financial problems, or moving to a new home.

We collected data on gastrointestinal symptom-specific anxiety, which is a cumulative cognitive and behavioural response arising from fear of gastrointestinal symptoms. For this purpose, we used the visceral sensitivity index (VSI), which is a 15-item scale with scores for each item ranging from 0 to 6, and a total possible score of 90.[25] As there are currently no validated cut-offs to define low, medium, or high levels of gastrointestinal symptom-specific anxiety we divided total VSI scores into three evenly distributed tertiles, representing low, medium, or high levels of gastrointestinal symptom-specific anxiety respectively.

The presence of symptoms suggestive of anxiety or depression was assessed using the 14-item hospital anxiety and depression scale (HADS), with scores for each item ranging from 0 to 3, and a total score of 21 for either anxiety or depression.[26] A score of 0 to 7 is considered normal, 8 to 10 borderline abnormal, and ≥11 abnormal, according to the original validation study. We, therefore, used a cut-off of ≥11 to define the presence of symptoms of either anxiety or depression in this study.

All participants had undergone investigation for gastrointestinal symptoms, with endoscopic, histologic, or radiologic assessment demonstrating active mucosal inflammation to confirm the diagnosis of IBD. Hence, disease activity questionnaires were not administered

at baseline as, essentially, all enrolled patients had mucosal disease activity around the time of recruitment. Participants with IBD-U and UC were considered collectively for all analyses.

2.3.3 Statistical Analysis

We compared baseline characteristics of participants, including demographics, disease extent, location, and phenotype, IBD-related medications, and levels of gastrointestinal symptom-specific anxiety, according to presence or absence of symptoms compatible with anxiety or depression at baseline using a χ^2 test for categorical variables and an independent samples *t*-test for continuous data. Due to multiple comparisons, a 2-tailed *p* value of <0.01 was considered statistically significant for all analyses. To determine factors independently associated with the reporting of symptoms of a common mental disorder, we performed logistic regression, controlling for all baseline demographic data, in addition to gastrointestinal symptom-specific anxiety, presence of stressful life events in the year prior to diagnosis, and duration of symptoms prior to diagnosis. These were reported using odds ratios (OR) with 95% confidence intervals (CI). We used SPSS for Windows version 29.0 (SPSS Inc., Chicago, IL, USA) to perform all statistical analyses.

2.4 Results

A total of 309 patients were approached to participate in the study, of whom 300 consented (97.1%). Of these, 282 (94.0%) were recruited in outpatient clinics, and the remaining 18 were recruited during an index inpatient admission. The mean duration from diagnosis to recruitment was 7 days. Data capture at baseline was complete for all 300 participants (mean age at baseline 41.6 years (range 18 to 87 years), 142 (47.3%) female, 99 (33.0%) CD, 162 (54.0%) UC and 39 (13.0%) IBD-U, 249 (83.0%) White) (Table 2.1). In total, 264 (88.0%) patients were commenced on an IBD-related medication at the time they were recruited to the study. The number of patients reporting each of the stressful life events of interest in the 12 months prior to diagnosis is reported in Figure 2.1.

Figure 2.1. Number of each of the stressful life events of interest in the 12 months prior to diagnosis among 300 patients with newly diagnosed IBD at baseline.

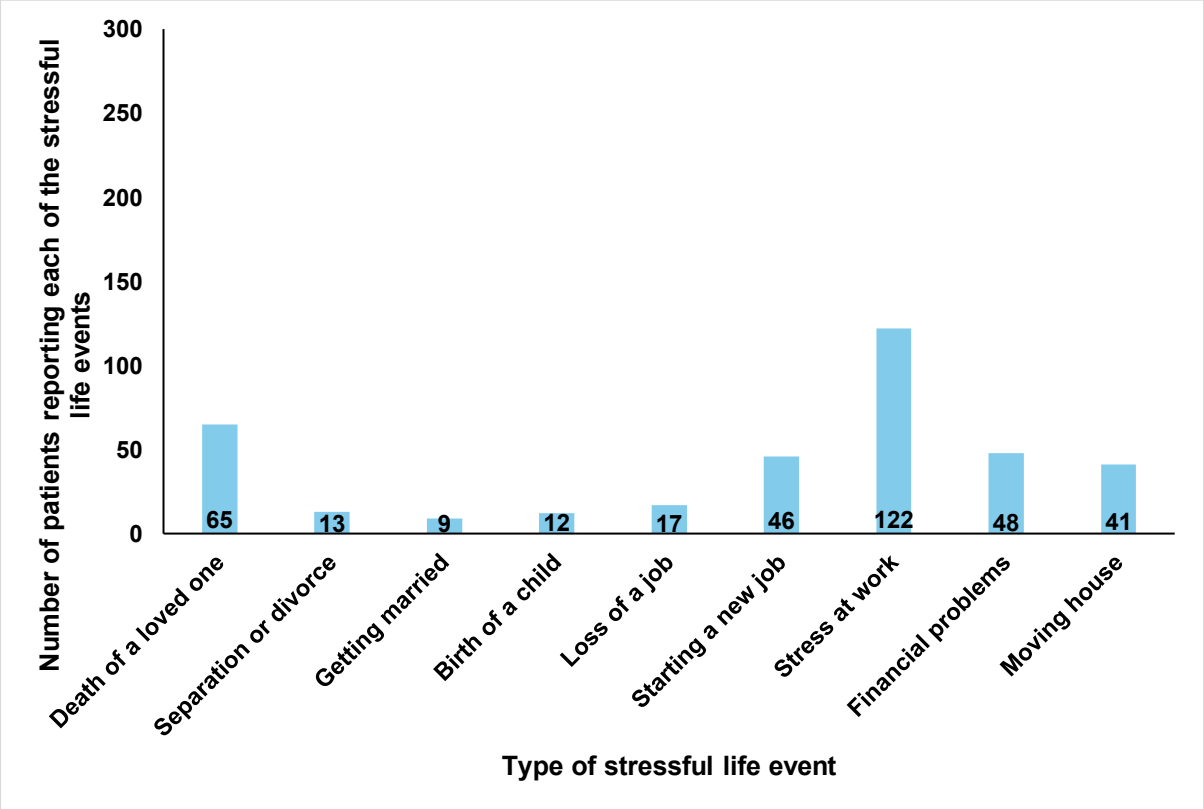

Table 2.1. Characteristics of 300 patients with newly diagnosed IBD according to the presence or absence of symptoms of anxiety or depression at baseline.

	All patients (n=300)	Patients with symptoms of anxiety at baseline (n=107)	Patients without symptoms of anxiety at baseline (n=193)	*p* value*	Patients with symptoms of depression at baseline (n=47)	Patients without symptoms of depression at baseline (n=253)	*p* value*	Patients with symptoms of anxiety or depression at baseline (n=117)	Patients without symptoms of anxiety or depression at baseline (n=183)	*p* value*
Mean age in years (SD)	41.6 (16.2)	37.3 (13.5)	43.9 (17.1)	<0.001	37.7 (13.7)	42.3 (16.5)	0.078	37.6 (13.9)	44.1 (17.0)	<0.001
Female sex (%)	142 (47.3)	64 (59.8)	78 (40.4)	<0.001	24 (51.1)	118 (46.6)	0.58	68 (58.1)	74 (40.4)	0.003
Married or co-habiting (%)	170 (56.7)	53 (49.5)	117 (60.6)	0.063	21 (44.7)	149 (58.9)	0.071	58 (49.6)	112 (61.2)	0.05
White Caucasian (%)	249 (83.0)	93 (86.9)	156 (80.8)	0.18	37 (78.7)	212 (83.8)	0.40	101 (86.3)	148 (80.9)	0.22
University graduate/professional (%)	103 (34.3)	19 (17.8)	31 (16.1)	0.71	5 (10.6)	45 (17.8)	0.23	37 (31.6)	66 (36.1)	0.43

Tobacco user (%)	45 (15.0)	24 (22.4)	21 (10.9)	0.007	13 (27.7)	32 (12.6)	0.008	26 (22.2)	19 (10.4)	0.005
Alcohol user (%)	186 (62.0)	63 (58.9)	123 (63.7)	0.41	21 (44.7)	165 (74.0)	0.008	67 (57.3)	119 (65.0)	0.18
Outpatient diagnosis (%)	282 (94.0)	101 (94.4)	181 (93.8)	0.83	43 (91.5)	239 (94.5)	0.43	108 (92.3)	174 (95.1)	0.32
IBD type (%)										
CD	99 (33.0)	41 (38.3)	58 (30.1)		16 (34.0)	83 (32.8)		43 (36.8)	56 (30.6)	
UC	162 (54.0)	53 (49.5)	109 (56.5)		26 (55.3)	136 (53.8)		59 (50.4)	103 (56.2)	
IBD-U	39 (13.0)	13 (12.1)	26 (13.5)	0.34	5 (10.6)	34 (13.4)	0.87	15 (12.8)	24 (13.1)	0.53
Commenced 5-aminosalicylate (%)	179 (59.7)	55 (51.4)	124 (64.2)	0.030	24 (51.1)	155 (61.3)	0.19	61 (51.2)	118 (64.5)	0.034
Commenced immunomodulator (%)	13 (4.3)	5 (4.7)	5 (2.6)	0.83	4 (8.5)	9 (3.6)	0.13	7 (6.0)	6 (3.3)	0.26
Commenced advanced therapy (%)	39 (13.0)	18 (16.8)	21 (10.9)	0.14	10 (21.3)	29 (11.5)	0.066	20 (17.1)	19 (10.4)	0.092
Commenced glucocorticosteroids (%)	95 (31.7)	40 (37.4)	55 (28.5)	0.11	18 (38.3)	77 (30.4)	0.29	43 (36.8)	52 (28.4)	0.13
Commenced any IBD-related medication(%)	264 (88.0)	93 (86.9)	171 (88.6)	0.68	42 (89.4)	222 (87.7)	0.75	102 (87.2)	162 (88.5)	0.73

Level of gastrointestinal symptom-specific anxiety on VSI										
Low	100 (33.3)	12 (11.2)	88 (45.6)		6 (12.8)	94 (37.2)		15 (12.8)	85 (46.4)	
Moderate	100 (33.3)	30 (28.0)	70 (36.3)		6 (12.8)	94 (37.2)		31 (26.4)	69 (37.7)	
High	100 (33.3)	65 (60.7)	35 (18.1)	<0.001	35 (74.5)	65 (25.7)	<0.001	71 (60.7)	29 (15.8)	<0.001
One or more stressful life events in the preceding 12 months (%)	197 (65.7)	81 (75.7)	116 (60.1)	0.006	39 (83.0)	158 (62.5)	0.006	89 (76.0)	108 (59.0)	0.002

Number of stressful life events in the preceding 12 months (%)										
None	103 (34.3)	26 (24.3)	77 (39.9)		8 (17.0)	95 (37.5)		28 (23.9)	75 (41.0)	
One	102 (34.0)	38 (35.5)	64 (33.2)		17(36.2)	85 (33.6)		43 (36.8)	59 (32.2)	
Two	48 (16.0)	17 (15.9)	31 (16.1)		8 (17.0)	40 (15.8)		18 (15.3)	30 (16.4)	
Three	29 (9.7)	14 (13.1)	15 (7.8)		7 (14.9)	22 (8.7)		14 (12.0)	15 (8.2)	
Four	9 (3.0)	7 (6.5)	2 (1.0)		3 (6.4)	6 (2.4)		8 (6.8)	1 (0.5)	
Five	5 (1.7)	2 (1.9)	3 (1.6)		2 (4.3)	3 (1.2)		3 (2.6)	2 (1.1)	
Six	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Seven	1 (0.3)	1 (0.9)	0 (0)		1 (2.1)	0 (0)		1 (0.9)	0 (0)	
Eight	3 (1.0)	2 (1.9)	1 (0.5)	0.017	1 (2.1)	2 (0.8)	0.017	2 (1.7)	1 (0.5)	0.005

Duration of symptoms prior to diagnosis (%)										
<1 month	17 (5.7)	4 (3.7)	13 (6.7)		2 (4.3)	15 (5.9)		5 (4.3)	12 (6.6)	
1-3 months	95 (31.7)	25 (23.4)	70 (36.2)		12 (25.5)	83 (32.8_		29 (24.8)	66 (36.1)	
4-6 months	60 (20.0)	16 (15.0)	44 (22.8)		8 (17.0)	52 (20.6)		18 (15.4)	42 (23.0)	
7-12 months	40 (13.5)	23 (21.5)	17 (8.8)		10 (21.3)	30 (11.9)		25 (21.4)	15 (8.2)	
>12 months	31 (10.3)	12 (11.2)	19 (9.8)		4 (8.5)	27 (10.7)		12 (10.3)	19 (10.4)	
>24 months	57 (19.0)	27 (25.2)	30 (15.5)	0.002	11 (23.4)	46 (18.2)	0.48	28 (23.9)	29 (15.8)	0.004
Symptoms >6 months prior to diagnosis	128 (42.7)	62 (57.9)	66 (34.2)	<0.001	25 (53.2)	103 (40.7)	0.11	65 (55.6)	63 (34.4)	<0.001
Prior diagnosis of anxiety or depression	48 (16.0)	33 (30.8)	15 (7.8)	<0.001	15 (31.9)	33 (13.0)	0.001	36 (30.8)	12 (6.6)	<0.001

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

2.4.1 Presence of symptoms or a formal diagnosis of a common mental disorder

Symptoms of anxiety were reported by 107 (35.7%) participants, and symptoms of depression by 47 (15.7%). Overall, 117 (39.0%) participants reported symptoms of either anxiety or depression. There was no significant difference according to type of IBD. Of the 99 patients with CD, the prevalence of symptoms of anxiety and depression were similar, with symptoms of anxiety reported by 41 (41.1%), symptoms of depression by 16 (16.2%), and symptoms of either anxiety or depression in 43 (43.4%). Similarly for the 201 participants with UC or IBD-U, 66 (32.8%) reported symptoms of anxiety, and 31 (15.4%) symptoms of depression, with 74 (36.8%) participants reporting symptoms of either anxiety or depression. There were 22 patients (7.3%) with an existing formal diagnosis of anxiety and 39 (13.0%) with an existing formal diagnosis of depression. Of the 107 participants with symptoms of anxiety, 18 (16.8%) had an existing formal diagnosis of anxiety, and among 47 patients with symptoms of depression, 11 (23.4%) had an existing formal diagnosis of depression.

2.4.2 Factors associated with symptoms of a common mental disorder

Patients with symptoms of a common mental disorder were significantly more likely to be younger, female, and consume tobacco. No disease factors were associated with an increased likelihood of reporting symptoms of either anxiety or depression. However, a longer duration of symptoms prior to a diagnosis of IBD, higher levels of gastrointestinal symptom-specific anxiety, and the presence of one or more stressful life events in the preceding 12-month period, were also associated with a significantly increased likelihood of reporting these symptoms (Table 2.1). Furthermore, an increasing number of stressful life events in the 12 months prior to diagnosis was significantly associated with reporting of symptoms of either anxiety or depression (Table 2.1). Participants with CD and symptoms of

a common mental disorder were again significantly more likely to be younger and have higher levels of gastrointestinal symptom-specific anxiety (Supplementary Table 2.1). Participants with UC or IBD-U and symptoms of a common mental disorder were significantly more likely to have higher levels of gastrointestinal symptom-specific anxiety and to have had a duration of symptoms prior to diagnosis of >6 months (Supplementary Table 2.2). Removing the 48 patients with a prior diagnosis of anxiety or depression did not significantly alter the results (Table 2.2).

Following logistic regression, the only predictors of symptoms of a common mental disorder at the time of diagnosis were increased gastrointestinal symptom-specific anxiety (OR 2.19; 95% CI 1.00-4.79 for moderate levels of gastrointestinal symptom specific anxiety and OR 13.5; 95% CI 5.86-31.2 for high levels of gastrointestinal symptom specific anxiety, P <0.001 for trend), the presence of one or more stressful life events in the 12 months prior to diagnosis (OR 2.45; 95% CI 1.23-4.90, P =0.01), and a prior diagnosis of anxiety or depression (OR 7.60; 95% CI 3.23-17.9, P <0.001). Excluding the 48 patients with a prior diagnosis of anxiety or depression from the logistic regression model strengthened the findings. Increased gastrointestinal symptom-specific anxiety (OR 2.52; 95% CI 1.05-6.10 for moderate levels of gastrointestinal symptom specific anxiety and OR 15.6; 95% CI 6.05-40.0 for high levels of gastrointestinal symptom specific anxiety, P <0.001 for trend) and the presence of one or more stressful life events in the 12 months prior to diagnosis (OR 2.87; 95% CI 1.30-6.34, P =0.009) remained significantly associated with the reporting of symptoms of a common mental disorder at the time of diagnosis of IBD.

Table 2.2. Characteristics of 252 patients with newly diagnosed IBD without a prior diagnosis of anxiety or depression according to the presence or absence of symptoms of anxiety or depression at baseline.

	All patients (n=252)	Patients with symptoms of anxiety at baseline (n=74)	Patients without symptoms of anxiety at baseline (n=178)	*p* value*	Patients with symptoms of depression at baseline (n=32)	Patients without symptoms of depression at baseline (n=220)	*p* value*	Patients with symptoms of anxiety or depression at baseline (n=81)	Patients without symptoms of anxiety or depression at baseline (n=171)	*p* value*
Mean age in years (SD)	41.7 (16.4)	36.0 (13.1)	44.1 (17.1)	<0.001	37.2 (14.9)	42.4 (16.5)	0.098	36.5 (13.9)	44.3 (16.9)	<0.001
Female sex (%)	112 (44.4)	41 (55.4)	71 (39.9)	0.024	16 (50.0)	96 (43.6)	0.50	44 (54.3)	68 (39.8)	0.030
Married or co-habiting (%)	145 (57.5)	36 (48.6)	109 (61.2)	0.066	15 (46.9)	130 (59.1)	0.19	39 (48.1)	106 (70.0)	0.038
White Caucasian (%)	202 (80.2)	61 (82.4)	141 (79.2)	0.56	23 (71.9)	179 (81.4)	0.21	66 (81.5)	136 (79.5)	0.72
University graduate/professional (%)	46 (18.3)	17 (23.0)	29 (16.3)	0.211	4 (12.5)	42 (19.1)	0.37	17 (21.0)	29 (17.0)	0.44

Tobacco user (%)	34 (13.5)	15 (20.3)	19 (10.7)	0.042	9 (28.1)	25 (11.4)	0.10	17 (21.0)	17 (9.9)	0.017
Alcohol user (%)	157 (62.3)	43 (58.1)	114 (64.0)	0.38	13 (40.6)	144 (65.5)	0.007	46 (56.8)	111 (64.9)	0.21
Outpatient diagnosis (%)	236 (93.7)	70 (94.6)	166 (93.3)	0.69	28 (87.5)	208 (94.5)	0.13	74 (91.4)	162 (94.7)	0.30
IBD type (%)										
CD	86 (34.1)	30 (40.5)	56 (31.5)		12 (37.5)	74 (33.6)		32 (39.5)	54 (31.6)	
UC	133 (52,8)	34 (45.9)	99 (55.6)		16 (50.0)	117 (53.2)		38 (46.9)	95 (55.6)	
IBD-U	33 (13.1)	10 (13.5)	23 (12.9)	0.33	4 (12.5)	29 (13.2)	0.91	11 (13.6)	22 (12.9)	0.40
Commenced 5-aminosalicylate (%)	147 (58.3)	35 (47.3)	112 (62.9)	0.022	14 (43.8)	133 (60.5)	0.073	38 (46.9)	109 (63.7)	0.011
Commenced immunomodulator (%)	13 (5.2)	5 (6.5)	8 (4.5)	0.46	4 (12.5)	9 (4.1)	0.044	7 (8.6)	6 (3.5)	0.085
Commenced advanced therapy (%)	34 (13.5)	14 (18.9)	20 (11.2)	0.10	9 (28.1)	25 (11.4)	0.010	16 (19.8)	18 (10.5)	0.045
Commenced glucocorticosteroids (%)	84 (33.3)	32 (43.2)	52 (29.2)	0.031	15 (46.9)	69 (31.4)	0.082	35 (43.2)	49 (28.7)	0.022
Commenced any IBD-related medication(%)	222 (88.1)	64 (86.5)	158 (88.8)	0.61	29 (90.6)	193 (87.7)	0.64	70 (86.4)	152 (88.9)	0.57

Level of gastrointestinal symptom-specific anxiety on VSI										
Low	90 (35.7)	9 (12.2)	81 (45.5)		3 (9.4)	87 (39.5)		10 (12.3)	80 (46.8)	
Moderate	86 (69.8)	21 (28.4)	65 (36.5)		6 (18.8)	80 (36.4)		22 (27.2)	64 (37.4)	
High	76 (30.2)	44 (59.5)	32 (18.0)	<0.001	23 (71.9)	53 (24.1)	<0.001	49 (60.5)	27 (15.8)	<0.001
One or more stressful life events in the preceding 12 months (%)	170 (67.5)	63 (85.1)	107 (60.1)	<0.001	28 (87.5)	142 (64.5)	0.010	69 (85.2)	101 (59.1)	<0.001
Symptoms >6 months prior to diagnosis	105 (41.7)	44 (59.5)	61 (34.3)	<0.001	17 (53.1)	88 (40.0)	0.16	46 (56.8)	59 (34.5)	<0.001

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

2.5 Discussion

In this cross-sectional survey we examined the prevalence and predictors of symptoms of a common mental disorder amongst patients newly diagnosed with IBD with objectively confirmed disease activity. Our findings demonstrate that symptoms of anxiety or depression are highly prevalent in this patient group, affecting almost 40% of patients at the time of diagnosis. The majority of patients exhibiting these symptoms at the time of their IBD diagnosis did not have a formal existing diagnosis of a common mental disorder. Disease-related factors, such as IBD type, location, extent, or phenotype did not appear to be associated with the presence of symptoms of either anxiety or depression. Although demographic factors including female sex, younger age, and tobacco consumption appear to be associated with symptoms of a common mental disorder at diagnosis, following logistic regression analysis, no baseline demographic characteristics were significantly associated with the reporting of these symptoms. The reporting of stressful life events in the 12 months prior to diagnosis and an increasing level of gastrointestinal symptom-specific anxiety, as measured by the VSI, and a longer duration of symptoms prior to diagnosis were significantly associated with symptoms of a common mental disorder. Both the reporting of stressful life events in the 12 months prior to diagnosis and increasing levels of gastrointestinal symptom-specific anxiety remained significant associations after logistic regression.

Eligible individuals were all identified by a single assessor, ensuring a standardised process for determining study eligibility was adhered to throughout recruitment. Being the sole provider of IBD-related care for participants, coupled with the use of fully digitalised medical records and clinic schedules, ensures that we have included almost all eligible individuals for participation and that participants' disease characteristics are accurately recorded. Using in-person recruitment promotes inclusivity and has resulted in over 95% of eligible individuals consenting to take part, this may, in part, have facilitated 17% of those

participating being non-White. Ethnic minorities are generally underrepresented in IBD research, despite making up almost 20% of the UK population, meaning that our findings are likely to be more representative of the UK population with IBD.[27] The inclusion of inpatients is also a strength, as these participants often have the highest gastrointestinal symptom burden and, if genuine gut-brain effects are present in IBD, may be more likely to suffer from poor psychological health.[23] Furthermore, we recruited participants during their index presentation, when most patients were not yet well-established on medical therapies to reduce inflammatory burden. Therefore, all were considered to have current inflammatory activity, which increases the likelihood that the effects we demonstrate represent genuine gut-brain effects.

There are limitations of the study. We report a higher prevalence of IBD-U than is seen amongst established cohorts of patients with IBD, which may affect the validity of the associations between disease-specific factors and the presence of symptoms of a common mental disorder. However, IBD extent and phenotype often evolves with time, and our findings are in keeping with the prevalence of IBD-U reported by others in newly diagnosed patients.[28] Endoscopies in our institution are conducted by a range of healthcare professionals across several hospital sites and, therefore, application of validated endoscopic severity scoring systems could not be mandated. Assigning endoscopic severity retrospectively based on image documentation, the quality of which may vary, could introduce bias. The inability to examine symptoms of anxiety or depression according to degree of mucosal activity is, therefore, a potential limitation, although given all patients had endoscopic and/or radiological evidence of disease activity at the point of diagnosis, we feel this is unlikely to have impacted our findings. The multi-site recruitment also meant it was impractical to recruit patients at the time of their diagnostic test. As such, the information and subsequent education given to patients regarding the diagnosis prior to their recruitment may vary

substantially. This is of relevance, as numerous information resources are now readily accessible to patients, and although official educational resources have been demonstrated to improve anxiety levels,[29] accessing alternative healthcare resources may be associated with higher anxiety.[30] Therefore, we cannot rule out that access to, or type of, information could have influenced psychological health independently prior to recruitment. Furthermore, some participants were commenced on a medical treatment at the time of their diagnosis at endoscopy, which could have improved symptom burden, and in turn psychological health. With a mean time to recruitment of 7 days, we feel that both these factors are unlikely to have influenced our results substantially.

Inferring a diagnosis of anxiety or depression using HADS questionnaire scores may be criticised as inferior to more formal assessments of mental health, such as structured interviews. However, these questionnaires have demonstrated good specificity in patients with IBD, with the conservative cut-offs used in our study meaning we are unlikely to have overestimated the prevalence of such symptoms.[31] In any case, the use of a structured interview would be impractical, given the large sample size. Nevertheless, we recorded whether patients had a prior existing diagnosis of anxiety or depression at the time of the initial consultation. The rates of symptom reporting we observed were in excess of the proportion of patients with a formal existing diagnosis of anxiety or depression, and most of the symptom-reporting occurred in those without a diagnosis of either. In addition, the prevalence of symptoms of a common mental disorder we report in this study is similar to those using structured interviews and is, therefore, likely to be accurate.[22] Inferring a diagnosis of a common mental disorder on the basis of symptom reporting at the time of a single assessment may also be criticised. However, the stability of poor psychological health has been demonstrated previously in a large cohort of patients with IBD, with almost 90% of those with abnormal anxiety or depression scores at baseline continuing to have abnormal

scores during longitudinal follow-up.[11] Finally, despite our rigorous methodology, it is possible that some individuals meeting eligibility criteria were not recruited, for example patients mis-triaged to general gastroenterology clinics. We feel this is unlikely as, in our hospital, endoscopic findings suggestive of a diagnosis of IBD are triaged to dedicated specialist clinics.

The estimated prevalence of symptoms of anxiety and depression in the UK general population using HAD scores of 11 and above for each is 16.2% and 6.9% respectively.[32] Our study has identified that, for individuals newly diagnosed with IBD, the prevalence is more than double this estimate, at 35.7% and 15.7% respectively. This is comparable with the estimated prevalence of symptoms of common mental disorders in patients with an established diagnosis of IBD,[33-37] and in line with the pooled results of a recent meta-analysis of over 30,000 patients, where symptoms of anxiety were reported to affect more than one-third of patients with established disease and depression more than 20%.[10] In this inception cohort we identified a higher prevalence of symptoms of both anxiety and depression than demonstrated previously in an established cohort of 1119 patients within our centre, where the prevalence of anxiety and depression was reported as 21.4% and 10.3% respectively.[11] This refutes the suggestion that the high rates of symptoms of a common mental disorder observed in IBD are merely a consequence of experiencing an adverse disease course and, in turn, supports genuine gut-brain effects, which are more likely linked to co-existing inflammatory burden. This is of particular relevance when considering that poor psychological health has been shown to not only influence the natural history of IBD negatively, but appears to exert a cumulative adverse effect alongside inflammatory activity.[12] Furthermore, the prevalence of a formal existing diagnosis of a common mental disorder amongst patients in this study is similar to that reported amongst the general population.[32] Stress has been implicated as a risk factor for future disease flares in IBD,

predating subsequent inflammatory activity by up to 18 months.[38] Our study, similar to another inception cohort,[22] has identified that prior stressful life events are highly prevalent in patients with newly diagnosed IBD, and are associated with symptoms of anxiety and depression. It is possible, therefore, that as is seen in cardiovascular disease, stress may factor in the development and progression of IBD.[39] Finally, socioeconomic status has been reported to influence psychological health, with epidemiological studies suggesting that, particularly for depression, lower socioeconomic status correlates inversely with the development of common mental disorders, and our study could therefore be criticised for its single centre design.[40] However, our findings are very similar to a multi-centre study conducted recently in Spain,[22] suggesting our results are likely to be applicable to other cohorts.

Bi-directionality of gut-brain interactions in IBD has been demonstrated previously,[8, 9] and may confound the results of studies examining the impact of poor psychological health on future disease outcomes. Specifically, an already adverse disease course, which may then be associated with the development of symptoms of anxiety or depression, could be the main driver of a future poor prognosis, rather than symptoms of anxiety or depression driving disease activity independently. It is impossible to fully unpick the implications of poor psychological health in IBD from an assessment at one point in time. However, the current study does demonstrate that symptoms of a common mental disorder are already highly prevalent among patients with IBD at the time of their diagnosis, and prior to the development of disease-related complications. Furthermore, most patients exhibiting these symptoms did not have a prior diagnosis of anxiety or depression, which may suggest that inflammatory activity is a true driver of poor psychological health, via gut-brain interactions, and so may provide a plausible therapeutic target.

To our knowledge this is the first inception cohort study to examine the relationship between symptoms of anxiety or depression and gastrointestinal symptom-specific anxiety in IBD. Again, the association between the two supports gut-brain effects at the time of diagnosis. Higher levels of gastrointestinal symptom-specific anxiety have been demonstrated consistently in patients with irritable bowel syndrome and some researchers have highlighted improvements with the use of gut-brain neuromodulators and psychological therapies in this patient group.[41-43] A recent study demonstrated comparable reliability of the VSI in patients with IBD, which is not affected by the presence of trait anxiety, suggesting it may also represent a therapeutic target in IBD.[44] However, as most studies using the VSI are in irritable bowel syndrome, future studies examining levels of gastrointestinal symptom-specific anxiety in patients in IBD in the context of mucosal disease activity are required to facilitate interpretation of whether these symptoms are independent of the severity of underlying inflammation.

In summary, symptoms of a common mental disorder are highly prevalent at the point of diagnosis for patients with IBD, and most occurred in patients without a formal diagnosis of anxiety or depression. They were significantly associated with gastrointestinal symptom-specific anxiety and stressful life events occurring within the previous 12 months. To further disentangle the relationship between psychological health and disease activity and determine whether there are subsequent brain-gut effects, longitudinal follow-up studies of IBD inception cohorts are required to study the effects of the presence of these symptoms at diagnosis on the future course of the disease.

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Supplementary Table 2.1. Characteristics of patients with CD according to the presence or absence of symptoms of anxiety or depression.

	All patients (n=99)	Patients with symptoms of anxiety at baseline (n=41)	Patients without symptoms of anxiety at baseline (n=58)	*p* value*	Patients with symptoms of depression at baseline (n=16)	Patients without symptoms of depression at baseline (n=83)	*p* value*	Patients with symptoms of anxiety or depression at baseline (n=43)	Patients without symptoms of anxiety or depression at baseline (n=56)	*p* value*
Mean age in years (SD)	43.1 (17.4)	36.8 (13.3)	47.5 (18.6)	0.001	36.3 (15.4)	44.4 (17.5)	0.07	37.4 (14.8)	47.4 (18.1)	0.002
Female sex (%)	43 (43.4)	23 (56.1)	20 (34.5)	0.033	7 (43.8)	36 (43.4)	0..98	24 (55.8)	19 (33.9)	0.029
Married or co-habiting (%)	61 (61.6)	21 (51.2)	40 (70.0)	0.074	6 (37.5)	55 (66.3)	0.030	22 (51.2)	39 (69.6)	0.06
White Caucasian (%)	81 (81.8)	37 (92.0)	44 (75.9)	0.068	13 (81.3)	68 (81.9)	0.95	38 (88.4)	43 (76.8)	0.14
University graduate/professional (%)	15 (15.2)	8 (19.5)	7 (12.1)	0.31	0 (0)	15 (18.1)	0.065	8 (18.6)	7 (12.5)	0.40
Tobacco user (%)	20 (20.2)	10 (24.4)	10 (17.2)	0.38	7 (43.8)	13 (15.7)	0.010	11 (25.6)	9 (16.1)	0.24

Alcohol user (%)	58 (58.6)	23 (56.1)	35 (60.3)	0.67	7 (43.8)	51 (61.4)	0.19	24 (55.8)	34 (60.7)	0.62
CD location (%)										
Ileal	41 (41.1)	17 (41.5)	24 (41.4)		7 (43.8)	34 (41.0)		19 (44.2)	22 (39.3)	
Colonic	40 (40.4)	16 (39.0)	24 (41.4)		4 (25.0)	36 (43.4)		16 (37.2)	24 (42.9)	
Ileocolonic	17 (17.2)	8 (19.5)	9 (15.5)		5 (31.3)	12 (14.5)		8 (18.6)	9 (16.1)	
Ileal and upper gastrointestinal	1 (1.0)	0 (0)	1 (1.7)	0.81	0 (0)	1 (1.2)	0.32	0 (0)	1 (1.8)	0.76
Non-stricturing non-penetrating CD (%)	92 (92.9)	40 (99.5)	52 (89.7)	0.28	16 (100)	76 (91.5)	0.48	42 (97.7)	50 (89.2)	0.24
Perianal CD (%)	4 (4.0)	1 (2.4)	3 (5.2)	0.50	0 (0)	4 (4.8)	0.37	1 (2.3)	3 (5.4)	0.45
Commenced 5-aminosalicylate (%)	2 (2.0)	0 (0)	2 (2.4)	0.23	0 (0)	2 (2.3)	0.53	0 (0)	2 (3.6)	0.21
Commenced immunomodulator (%)	11 (11.1)	4 (9.8)	7 (12.1)	0.72	2 (12.5)	9 (10.8)	0.85	5 (11.6)	6 (10.7)	0.89
Commenced advanced therapy (%)	29 (29.3)	12 (29.3)	17 (29.3)	1.00	6 (37.5)	23 (27.7)	0.43	13 (30.2)	16 (28.5)	0.86
Commenced glucocorticosteroids (%)	51 (51.5)	23 (56.1)	28 (48.3)	0.44	8 (50.0)	43 (51.8)	0.90	23 (50.5)	28 (50.0)	0.73

Commenced any IBD-related medication(%)	70 (70.7)	30 (73.2)	40 (70.0)	0.65	12 (75.0)	58 (69.9)	0.68	31 (72.1)	39 (69.6)	0.79
Level of gastrointestinal symptom-specific anxiety on VSI										
Low	35 (35.4)	4 (9.8)	31 (53.4)		2 (12.5)	33 (39.8)		5 (11.6)	30 (53.6)	
Moderate	34 (34.3)	14 (34.1)	20 (34.5)		3 (18.8)	31 (37.3)		14 (32.6)	20 (35.7)	
High	30 (30.3)	23 (56.1)	7 (12.1)	<0.001	11 (68.8)	19 (22.9)	0.001	24 (55.8)	6 (10.7)	<0.001
One or more stressful life events in the preceding 12 months (%)	68 (68.7)	33 (80.5)	35 (60.3)	0.033	13 (81.3)	55 (66.3)	0.24	34 (79.1)	34 (60.7)	0.051

Number of stressful life events in the preceding 12 months (%)										
None	31 (31.3)	8 (19.5)	23 (39.7)		3 (18.8)	28 (33.7)		9 (20.9)	22 (39.3)	
One	33 (33.3)	14 (34.1)	19 (32.8)		4 (25.0)	29 (34.9)		15 (34.9)	18 (32.1)	
Two	12 (12.1)	5 (12.2)	7 (12.1)		3 (18.8)	9 (10.8)		5 (11.6)	7 (12.5)	
Three	15 (15.2)	8 (19.5)	7 (12.1)		4 (25.0)	11 (13.3)		8 (18.6)	7 (12.5)	
Four	4 (4.0)	4 (9.8)	0 (0)		1 (6.3)	3 (3.6)		4 (9.3)	0 (0)	
Five	2 (2.0)	0 (0)	2 (3.4)		0 (0)	2 (2.4)		0 (0)	2 (3.6)	
Six	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Seven	1 (1.0)	1 (2.4)	0 (0)		1 (6.3)	0 (0)		1 (2.3)	0 (0)	
Eight	1 (1.0)	1 (2.4)	0 (0)	0.053	0 (0)	1 (1.2)	0.23	1 (2.3)	0 (0)	0.08

Duration of symptoms prior to diagnosis (%)										
<1 month	6 (6.1)	2 (4.9)	4 (6.9)		2 (12.5)	4 (4.8)		3 (7.0)	3 (5.4)	
1-3 months	16 (16.2)	8 (19.5)	8 (13.8)		1 (6.3)	15 (18.1)		8 (18.6)	8 (14.3)	
4-6 months	18 (18.2)	4 (9.8)	14 (24.1)		3 (18.8)	15 (18.1)		4 (9.3)	14 (25.0)	
7-12 months	19 (19.2)	12 (29.3)	7 (12.1)		4 (25.0)	15 (18.1)		13 (30.2)	6 (10.7)	
>12 months	13 (13.1)	3 (7.3)	10 (17.2)		2 (12.5)	11 (13.3)		3 (7.0)	10 (17.9)	
>24 months	27 (27.3)	12 (29.3)	15 (25.9)	0.11	4 (25.0)	23 (27.7)	0.72	12 (27.9)	15 (26.8)	0.06
Symptoms >6 months prior to diagnosis	59 (59.6)	27 (65.9)	32 (55.2)	0.29	10 (62.5)	49 (59.0)	0.80	28 (65.1)	31 (55.4)	0.33

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

Supplementary Table 2.2. Characteristics of patients with UC/IBDU according to the presence or absence of symptoms of anxiety or depression.

	All patients (n=201)	Patients with symptoms of anxiety at baseline (n=66)	Patients without symptoms of anxiety at baseline (n=135)	*p* value*	Patients with symptoms of depression at baseline (n=31)	Patients without symptoms of depression at baseline (n=170)	*p* value*	Patients with symptoms of anxiety or depression at baseline (n=74)	Patients without symptoms of anxiety or depression at baseline (n=127)	*p* value*
Mean age in years (SD)	40.8 (15.6)	37.6 (13.7)	42.4 (16.2)	0.031	38.5 (12.9)	41.2 (16.0)	0.30	37.7 (13.5)	42.6 (16.4)	0.022
Female sex (%)	99 (49.3)	41 (62.1)	58 (43.0)	0.011	17 (54.8)	82 (48.2)	0.50	44 (59.5)	55 (43.3)	0.027
Married or co-habiting (%)	109 (54.2)	32 (48.5)	77 (57.0)	0.25	15 (48.4)	94 (55.3)	0.48	36 (48.6)	73 (57.5)	0.23
White Caucasian (%)	168 (83.6)	56 (84.8)	112 (83.0)	0.74	24 (77.4)	144 984.7)	0.31	63 (85.1)	105 (82.7)	0.65
University graduate/professional (%)	35 (17.4)	11 (16.7)	24 (17.8)	0.85	5 (16.1)	30 (17.6)	0.84	11 (14.9)	24 (18.9)	0.47
Tobacco user (%)	25 (12.4)	14 (21.2)	11 (8.1)	0.008	6 (19.4)	19 (11.2)	0.20	15 (20.3)	10 (7.9)	0.010

Alcohol user (%)	128 (63.7)	40 (60.6)	88 (65.2)	0.53	14 (45.2)	114 (67.1)	0.020	43 (58.1)	85 (66.9)	0.21
UC/IBD-U extent (%)										
Proctitis	80 (39.8)	25 (37.9)	55 (40.7)		11 (35.5)	69 (40.6)		28 (37.8)	52 (40.9)	
Left-sided	59 (29.4)	18 (27.3)	41 (30.4)		10 (32.3)	49 (28.8)		20 (27.0)	39 (30.7)	
Extensive	62 (30.8)	23 (24.8)	39 (28.9)	0.69	10 (32.3)	52 (30.6)	0.86	26 (35.1)	36 (28.3)	0.60
Commenced 5-aminosalicylate (%)	177 (88.1)	55 (83.3)	122 (90.4)	0.15	24 (77.4)	153 (90.0)	0.047	61 (82.4)	116 (91.3)	0.060
Commenced immunomodulator (%)	2 (1.0)	1 (1.5)	1 (0.7)	0.60	2 (6.5)	0 (0)	<0.001	2 (2.7)	0 (0)	0.063
Commenced advanced therapy (%)	10 (5.0)	6 (9.1)	4 (3.0)	0.061	4 (12.9)	6 (3.5)	0.027	7 (9.5)	3 (2.4)	0.026
Commenced glucocorticosteroids (%)	44 (21.9)	17 (25.8)	27 (20.0)	0.35	10 (32.3)	34 (20.0)	0.13	20 (27.0)	24 (18.8)	0.18
Commenced any IBD-related medication(%)	194 (96.5)	63 (95.5)	131 (97.0)	0.57	30 (96.8)	164 (96.5)	0.93	71 (95.9)	123 (96.9)	0.74

Level of gastrointestinal symptom-specific anxiety on VSI										
Low	65 (32.3)	8 (12.1)	57 (42.2)		4 (12.9)	61 (35.9)		10 (13.5)	55 (43.3)	
Moderate	66 (32.8)	16 (24.2)	50 (37.0)		3 (9.7)	63 (37.1)		17 (23.0)	49 (38.6)	
High	70 (34.8)	42 (63.6)	28 (20.7)	<0.001	24 (77.4)	46 (27.1)	<0.001	47 (63.5)	23 (18.1)	<0.001
One or more stressful life events in the preceding 12 months (%)	129 (64.2)	48 (72.7)	81 (60.0)	0.077	26 (83.9)	103 (60.6)	0.013	55 (74.3)	74 (58.3)	0.022

Number of stressful life events in the preceding 12 months (%)										
None	72 (35.8)	18 (27.3)	54 (40.0)		5 (16.1)	67 (39.4)		19 (25.7)	53 (41.7)	
One	69 (34.3)	24 (36.4)	45 (33.3)		13 (41.9)	56 (32.9)		28 (37.8)	41 (32.3)	
Two	36 (17.9)	12 (18.2)	24 (17.8)		5 (16.1)	31 (18.2)		13 (17.6)	23 (18.1)	
Three	14 (7.0)	6 (9.1)	8 (5.9)		3 (9.7)	11 (6.5)		6 (8.1)	8 (6.3)	
Four	5 (2.5)	3 (4.5)	2 (1.5)		2 (6.5)	3 (1.8)		4 (5.4)	1 (0.8)	
Five	3 (1.5)	2 (3.0)	1 (0.7)		2 (6.5)	1 (0.6)		3 (4.1)	0 (0)	
Six	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Seven	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Eight	2 (1.0)	1 (1.5)	1 (0.7)	0.40	1 (3.2)	1 (0.6)	0.019	1 (1.4)	1 (0.8)	0.038

Duration of symptoms prior to diagnosis (%)										
<1 month	11 (5.5)	2 (3.0)	9 (6.7))		0 (0)	11 (6.5)		2 (2.7)	9 (7.1)	
1-3 months	79 (39.3)	17 (25.8)	62 (45.9)		11 (35.5)	66 (38.8)		21 (28.4)	58 (45.7)	
4-6 months	42 (20.9)	12 (18.2)	30 (22.2)		5 (16.1)	37 (21.8)		14 (18.9)	28 (22.0)	
7-12 months	41 (20.4)	11 (16.7)	10 (7.4)		6 (19.4)	15 (8.8)		12 (16.2)	9 (7.1)	
>12 months	18 (9.0)	9 (13.6)	9 (6.7)		2 (6.5)	16 (9.4)		9 (12.2)	9 (7.1)	
>24 months	30 (14.9)	15 (22.7)	15 (11.1)	0.007	7 (22.6)	23 (13.5)	0.22	16 (21.6)	14 (11.0)	0.016
Symptoms >6 months prior to diagnosis	69 (34.3)	35 (53.0)	34 (25.2)	<0.001	15 (48.3)	54 (31.8)	0.073	37 (50.0)	32 (25.2)	<0.001

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

Chapter 3: Persistence of Symptoms of Anxiety and Depression in Inflammatory Bowel Disease: A Longitudinal Follow-Up Study.

3.1 Summary

Introduction: Poor psychological health affects many patients with inflammatory bowel disease (IBD), but persistence of these symptoms is unclear.

Methods: We performed a longitudinal follow-up study of patients whose anxiety and depression trajectories were established by symptom data collected at 3-monthly intervals over the course of 1 year. We collected further anxiety and depression symptom data at yearly intervals over 2-years to determine persistence of these symptoms in patients with IBD. Disease outcomes (flare/need for glucocorticosteroids, escalation of medical therapy, hospitalisation, or intestinal resection) were recorded to determine effect of mood trajectories on the natural history of IBD.

Results: Of 770 patients with established anxiety trajectories, 486 (63.1%) provided further anxiety symptom data at 12 months, and 358 (45.5%) at 24 months. Of the 777 patients with established depression trajectories, 491 (63.2%) provided further depression symptom data at 12 months, and 362 (45.6%) at 24 months. Participants with symptoms of anxiety at 24 months were more likely to have a fluctuating, or persistently abnormal or worsening, anxiety trajectory during the first year (p<0.001 for trend). Participants with symptoms of depression at 24 months were more likely to have a fluctuating, or persistently abnormal or worsening, depression trajectory during the first year (p<0.001 for trend). Adverse disease outcomes were no more likely according to anxiety or depression trajectories.

Discussion: Poor psychological health persists for a substantial number of patients with IBD. Further work is needed to establish the long-term effect of mood-trajectories on disease outcomes.

3.2 Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) with debilitating gastrointestinal symptoms. These diseases impact work productivity, personal relationships, and quality of life negatively,[1-4] and can result in complications, including stricture and fistula formation, intestinal obstruction, and perforation.[1] Equipped with an expanding arsenal of efficacious medical therapies,[5, 6] and a drive to reduce these adverse outcomes, the standard of IBD care now demands the prompt recognition and treatment of persistent mucosal inflammation.[7, 8] This approach has been associated with a reduction in both the number of IBD-related surgeries and mortality over the last two decades.[9] Healthcare utilisation trends, however, remained unchanged, suggesting that factors other than inflammatory activity contribute to the natural history of IBD.[10, 11]

Poor psychological health is a substantial issue for patients with IBD. Common mental disorders, including anxiety and depression, are twice as prevalent as in the general population.[12-15] Moreover, these symptoms may be associated with future adverse disease outcomes and increased healthcare utilisation.[16-18] Symptoms of anxiety or depression peak during a flare, affecting almost half of patients,[15] which may be attributable to the release of pro-inflammatory cytokines crossing the blood-brain barrier and upregulating the hypothalamic-pituitary-adrenal axis, inducing a stress response.[19] However, this fails to explain why almost one-third of patients experience poor psychological health during periods of disease quiescence,[15] which may imply gut-brain axis communication is involved.[12, 14, 20] In health, these complex bi-directional signals serve to enable central regulation of peripheral gut functions.[19] Dysregulation in these communications could explain both the high prevalence of symptoms of anxiety and depression in IBD and their apparent negative impact on the subsequent disease course.[21]

In the general population symptoms of anxiety and depression fluctuate over time,[22] but most existing studies in IBD usually assess mood at a single time point,[14, 15] which falls short of the official recommendation of the diagnostic and statistical manual of mental disorders, that symptoms of depression must be present consistently over a minimum period of two weeks, and anxiety over 6 months.[23] Unless these symptoms remain stable over time in IBD, the results of studies examining their impact on prognosis of IBD may be inaccurate.[22] To address this issue, our group has previously examined mood trajectories at 3-month intervals over the course of 1 year in a large cohort of patients with IBD. We demonstrated that improvement in anxiety and depression scores occurred in only 10% of patients reporting these symptoms at baseline,[24] suggesting symptoms persist for most patients with IBD. However, poor psychological health is not unique to IBD, and mood trajectories in multiple sclerosis, another chronic immune mediated relapsing-remitting inflammatory disease, do not remain stable beyond 1 year.[25] Similarly, researchers examining mood trajectories in chronic obstructive pulmonary disease demonstrated that mood remained stable in only 25% of patients over 3 years.[26] Mood may, therefore, also be more fluctuant over a prolonged period in IBD. This is of particular relevance, given the positive impact of initiating biological therapy on mood in IBD,[27-29] and the negative impact of anxiety or depression symptoms on longitudinal disease activity outcomes.[12, 14]

Whether symptoms of anxiety and depression demonstrate long-term stability in IBD remains unclear. Furthermore, although we have established that persistently abnormal or worsening mood trajectories in IBD are associated with increased healthcare utilisation, less is known regarding the effects of these trajectories on adverse disease outcomes.[24] We, therefore, performed a longitudinal follow-up study, examining these issues.

3.3 Methods

3.3.1 Participants and Setting

All adult patients aged ≥18 years with an established diagnosis of CD, UC, or IBD-unclassified (IBD-U) based on histological, endoscopic, or radiological findings, under active follow-up within the Leeds Teaching Hospitals NHS Trust IBD service were sent a postal invitation to participate in this study between June and September of 2020. The invitation contained both a web-link and a personalised uniform resource locator to access a participant information sheet, consent form, and an online questionnaire. Patients preferring written documentation were provided with paper versions. Follow-up questionnaires were distributed, in the preferred format for each participant, at 3-month intervals throughout an initial 12-month period. All participants were invited to participate in the longitudinal follow-up extension study in September 2022. Mood symptom data was then collected annually over the subsequent 2 years. To mitigate losses to follow-up, a single reminder letter was issued to each consenting participant who did not respond to one or more of the follow-up questionnaires. Due to a lack of validated disease activity indices to determine clinical disease activity, participants with an ileo-anal pouch or end stoma were excluded. There were no other exclusion criteria. The study and longitudinal follow-up extension were both approved by the Wales research ethics committee (REC ref: 20/WA/0044 and 20/WA/0044/01).

3.3.2 Data Collection and Synthesis

Demographic data, including age, sex, ethnicity, marital status, educational level, and lifestyle factors, including tobacco and alcohol consumption were recorded at baseline. We used the Harvey-Bradshaw index (HBI) to determine clinical disease activity for patients with

CD, excluding the detection of an abdominal mass,[30, 31] and the simple clinical colitis activity index (SCCAI) for patients with UC.[32] A score of <5 was considered as clinical remission for both, as previously recommended.[33, 34] We collected somatoform symptom data using the patient health questionnaire-12 (PHQ-12).[35] The score ranges from 0 to 24 and is derived from the PHQ-15 by omission of gastrointestinal symptom-related questions and symptom severity classified as high (total score ≥13), medium (8-12), low (4-7), or minimal (≤3). Quality of life was assessed using the short IBD questionnaire (SIBDQ) health survey.[36] Finally, to determine the presence of symptoms of anxiety or depression, we used the hospital anxiety and depression scale (HADS).[37] This 14-item validated questionnaire gives a total score for anxiety or depression of 0 to 21, with scores considered normal (score 0-7), borderline (8-10), or abnormal (≥11) in either domain.[37] We utilised these to create initial anxiety and depression trajectories for participants who provided data at baseline and a minimum of two further points of follow up in the first 12 months of the study. Normal or improving trajectories were classified as a normal HADS-anxiety or HADS-depression scores throughout, or a baseline score of ≥11 improving to <8 at the last point of follow-up. Similarly, abnormal or worsening trajectories were classified as HADS-anxiety or HADS-depression scores of ≥11 throughout or having a score of <8 at baseline which worsened to ≥11 at the last point of follow-up. The remaining individuals were classified as fluctuating trajectories. To determine the stability of anxiety or depression symptoms over time, we then compared the initial symptom trajectories with the presence or absence of anxiety or depression symptoms at subsequent annual intervals, again using HADS-anxiety and HADS-depression scores, with identical cut-off values applied to determine normal, borderline abnormal, or abnormal scores.

A single investigator (KMF), blinded to questionnaire responses, reviewed the electronic medical records for each participant to verify the type (CD, UC, or IBD-U), extent

and location of IBD, and determine any prior IBD-related intestinal resections. Baseline IBD-related medication use, including 5-aminosalicylates (5-ASAs), immunosuppressants, biologic therapies, or glucocorticosteroids, as well as current use of antidepressant drugs or opioids was recorded. Two assessors (KMF or CR) extracted clinical outcome data during longitudinal follow-up, including 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. In addition, we recorded the date of occurrence of each outcome. Escalation of medical therapy without evidence of uncontrolled IBD activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, were excluded as endpoints.

3.3.3 Statistical Analysis

As described, the initial anxiety or depression trajectories were established among patients providing baseline data and a minimum of two further points of follow-up during the first year of the study.[24] To understand the influence of these initial symptom trajectories on the persistence of symptoms of anxiety or depression subsequently, we then calculated the prevalence of symptoms of subsequent anxiety or depression, defined by the presence of abnormal HADS-anxiety or HADS-depression scores, at both 12 and 24 months in patients providing further longitudinal follow-up data at these time points, in each of the three initial anxiety or depression symptom trajectories. To determine if the three initial anxiety and depression symptom trajectories influenced the natural history of IBD, we compared rates of adverse disease outcomes, including flare of disease activity, glucocorticosteroid prescription, escalation of therapy, hospitalisation, intestinal resection, or death during longitudinal follow-up between them. When examining categorial data we applied a Pearson's χ^2 test for all

analyses. For continuous data we applied a one-way analysis of variance (ANOVA) for comparisons between more than two groups, or a two-sided t-test to compare continuous data between two groups. Due to multiple comparisons, a 2-tailed P value of <0.01 was considered statistically significant. If the univariate analyses were significant for persistence of symptoms of anxiety or depression, we performed logistic regression controlling for all baseline characteristics, including sex, age, marital status, tobacco and alcohol consumption, educational level, type of IBD, baseline clinical disease activity, IBD-related medications, level of somatoform symptom-reporting according to the PHQ-12, and initial anxiety and depression trajectories, to identify independent predictors of persistence of these symptoms, with the outcomes expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Similarly, if the results on univariate analysis were statistically significant for adverse disease outcomes, we performed multivariate Cox regression analyses controlling for all baseline characteristics, with the outcomes expressed as hazard ratios (HRs) with 95% CIs. All analyses were performed using SPSS for Windows version 29.0.

3.4 Results

Of the 4823 patients with IBD under the care of the IBD service in Leeds Teaching Hospitals NHS trust who were contacted between June and September of 2020, 1027 (21.3%) responded to the baseline questionnaire and did not have either an ileo-anal pouch or end stoma. The mean age of these 1027 participants was 52.6 years (SD 16.9 year), 564 (54.9%) were female, and 457 (44.5%) had CD. Of these, 770 (75.0%) provided at least two further follow-up questionnaires to enable establishment of anxiety trajectories and 777 (75.7%) depression trajectories. The baseline characteristics of the 770 participants providing data for anxiety trajectories and for the 777 providing data for depression trajectories have been described previously,[24] and are provided in Supplementary Table 3.1.

3.4.1 Presence of Subsequent Symptoms of Anxiety According to Baseline Disease Characteristics and Initial Anxiety or Depression Trajectories

Of the patients providing sufficient anxiety symptom data to establish their initial anxiety trajectory, 486 (63.1%) patients provided subsequent anxiety symptom data at 12 months, and 358 (45.5%) at 24 months. For patients who provided sufficient depression symptom data to establish initial depression trajectories, 491 (63.2%) patients provided subsequent anxiety symptom data at 12 months, and 362 (46.6%) at 24 months. Of the patients reporting symptoms of anxiety at 12 months, 8 (3.0%) belonged to a persistently normal or improving, 50 (30.5%) to a fluctuating, and 41 (71.9%) to a persistently abnormal or worsening anxiety trajectory (Table 3.1). Of the patients reporting symptoms of anxiety at 24 months, 4 (2.1%) belonged to a persistently normal or improving, 37 (29.8%) to a fluctuating, and 32 (76.2%) to a persistently abnormal or worsening anxiety trajectory (Table 3.1). Baseline factors associated with the reporting of symptoms of anxiety at 12 months

included having received a diagnosis of IBD within the 12 months prior to recruitment (p=0.001), active disease according to HBI or SCCAI scores (p <0.001), higher levels of somatoform symptom-reporting on the PHQ-12 (p <0.001) and use of antidepressants (p <0.001). In addition, both persistently abnormal or worsening anxiety trajectories (p <0.001) and persistently abnormal or worsening depression trajectories (p <0.001) were significantly associated with the reporting of symptoms of anxiety at 12 months. Of these factors, only the use of antidepressants (p <0.001), higher levels of somatoform symptom-reporting (p <0.001), and persistently abnormal or worsening anxiety or depression trajectories (p <0.001 for both) remained significantly associated with the reporting of symptoms of anxiety at 24 months. The reporting of symptoms of anxiety at 24 months was also significantly associated with female sex (p<0.001) and a self-reported disease flare at baseline (p=0.002).

Following multivariate logistic regression, controlling for all baseline data, factors significantly associated with the reporting of anxiety at 12 months were antidepressant use (OR 2.86; 95% CI 1.23-6.66, p=0.015), being married (OR 2.93; 95% CI 1.31-6.54, p=0.009), and a fluctuating anxiety trajectory (OR 18.1; 95% CI 6.54-50.3, p<0.001) as well as a persistently abnormal or worsening anxiety trajectory (OR 58.8 95% CI 17.2-202 p<0.001) (p<0.001 for trend) (Table 3.1). The use of antidepressants (OR 4.42; 95% CI 1.60-12.2, p=0.004) and a fluctuating anxiety trajectory (OR 23.8; 95% CI 5.94-95.0, p<0.001), as well as a persistently abnormal or worsening anxiety trajectory (OR 199 95% CI 34.1-1160 p<0.001) (p<0.001 for trend) (Table 3.1) remained significantly associated with the reporting of symptoms of anxiety at 24 months. No other baseline characteristics were significantly associated with the subsequent reporting of symptoms of anxiety at either time point.

Table 3.1. Presence of Subsequent Symptoms of Anxiety or Depression at 12 and 24 Months According to Anxiety or Depression Trajectories

	Anxiety Trajectories				Depression Trajectories			
	Normal or improving	**Fluctuating**	**Abnormal or worsening**	***p* value***	**Normal or improving**	**Fluctuating**	**Abnormal or worsening**	***p* value***
Symptoms of anxiety at 12 months (%)	8/265 (3.0)	50/164 (30.5)	41/57 (71.9)	<0.001	30/330 (9.1)	50/136 (36.8)	19/25 (76.0)	<0.001
OR for symptoms of anxiety at 12 months	1.00 (reference)	18.1 (6.54-50.3)	58.8 (17.2-202)	<0.001	1.00 (reference)	1.80 (0.84-3.86)	5.71 (1.30-25.1)	0.056
Symptoms of anxiety at 24 months (%)	4/192 (2.1)	37/124 (29.8)	32/42 (76.2)	<0.001	27/250 (10.8)	35/96 (36.5)	12/16 (75.0)	<0.001
OR for symptoms of anxiety at 24 months	1.00 (reference)	23.8 (5.94-95.0)	199 (34.1-1160)	<0.001	1.00 (reference)	0.70 (0.27-1.83)	1.47 (0.24-8.96)	0.55
Symptoms of depression at 12 months (%)	5/265 (1.9)	19/164 (11.6)	17/57 (29.8)	<0.001	3/330 (0.9)	24/136 (17.6)	14/25 (56.0)	<0.001
OR for symptoms of depression at 12 months	1.00 (reference)	1.21 (0.32-4.68)	1.89 (0.39-9.27)	0.69	1.00 (reference)	11.9 (2.80-50.8)	51.2 (7.77-337)	<0.001
Symptoms of depression at 24 months (%)	4/192 (2.1)	16/124 (12.9)	16/42 (38.1)	<0.001	2/250 (0.8)	23/96 (24.0)	11/16 (68.8)	<0.001
OR for symptoms of depression at 24 months	1.00 (reference)	1.57 (0.35-7.11)	2.84 (0.49-16.6)	0.49	1.00 (reference)	26.1 (4.34-157)	202 (16.2-2521)	<0.001

*****_P_ value for trend.

3.4.2 Clinical Outcomes According to Initial Anxiety Trajectories

During a mean duration of follow-up of 3.9 years, patients with a persistently abnormal or worsening anxiety trajectory were significantly more likely than those with a persistently normal or improving trajectory to experience a flare of disease activity or require glucocorticosteroids (p=0.003), but there was no significant difference between any of the trajectories for escalation of medical therapy, hospitalisation, or intestinal resection due to uncontrolled disease activity (Table 3.2). Furthermore, mortality was not significantly different between trajectory groups. Following multivariate Cox regression, experiencing a flare or requiring glucocorticosteroids was no longer significantly associated with a persistently abnormal or worsening anxiety trajectory.

3.4.3 Presence of Subsequent Symptoms of Depression According to Baseline Disease Characteristics and Initial Anxiety or Depression Trajectories

Of the patients providing sufficient depression symptom data to establish their initial depression trajectory, 491 (63.2%) patients provided subsequent depression symptom data at 12 months, and 362 (45.6%) at 24 months. For patients who provided sufficient anxiety symptom data to establish initial anxiety trajectories, 486 (63.1%) patients provided subsequent depression symptom data at 12 months, and 358 (46.5%) at 24 months. Of the patients reporting symptoms of depression at 12 months, 3 (0.9%) belonged to a persistently normal or improving, 24 (17.6%) to a fluctuating, and 14 (56.0%) to a persistently abnormal or worsening depression trajectory (Table 3.1). Of the patients reporting symptoms of depression at 24 months, 2 (0.8%) belonged to a persistently normal or improving, 23 (24.0%) to a fluctuating, and 11 (68.8%) to a persistently abnormal or worsening depression trajectory (Table 3.1). Baseline factors associated with the reporting of symptoms of

depression at 12 months included having received a diagnosis of IBD within the previous 12 months (p=0.008), self-reporting of a flare (p=0.004), active disease according to HBI or SCCAI scores (p <0.001), higher levels of somatoform symptom-reporting on the PHQ-12 (p <0.001), and use of either antidepressants (p <0.001) or opioids (p <0.001). In addition, both persistently abnormal or worsening anxiety trajectories (p <0.001) and persistently abnormal or worsening depression trajectories (p <0.001) were significantly associated with the reporting of symptoms of depression at 12 months. Of these factors, self-reporting of a flare (p <0.001), having active disease according to HBI or SCCAI scores (p=0.002), higher levels of somatoform symptom-reporting (p <0.001), the use of antidepressants (p <0.001) or opioids (p <0.001), and both persistently abnormal or worsening anxiety or depression trajectories (p <0.001 for both) continued to be significantly associated with the reporting of symptoms of depression at 24 months. In addition, consumption of any alcohol (p=0.008) was significantly associated with the reporting of symptoms of depression at 24 months.

Following multivariate logistic regression, factors significantly associated with the reporting of depression at 12 months included clinical disease activity according to the HBI or SCCAI (OR 4.29; 95% CI 1.44-12.8, p=0.009), a fluctuating depression trajectory (OR 11.9; 95% CI 2.80-50.8, p<0.001), and a persistently abnormal or worsening depression trajectory (OR 51.2; 95% CI 7.77-337, p<0.001) (p<0.001 for trend) (Table 3.1). This association persisted at 24 months, for both a fluctuating depression trajectory (OR 26.1; 95% CI 4.34-157, p<0.001) and a persistently abnormal or worsening depression trajectory (HR 202; 95% CI 16.2-2520, p<0.001). Antidepressant use (OR 3.17; 95% CI 1.05-9.64, p=0.042) was the only other factor associated with the reporting of symptoms of depression at 24 months.

Table 3.2. Occurrence of Subsequent Adverse Disease Outcomes According to Initial Anxiety or Depression Trajectories.

	Anxiety Trajectories						Depression Trajectories					
	Normal or improving (n=399)	**Fluctuating (n=268)**	***p value****	**Abnormal or worsening (n=103)**	***p* value†**	***p* value‡**	**Normal or improving (n=515)**	**Fluctuating (n=212)**	***p value****	**Abnormal or worsening (n=50)**	***p* value†**	***p* value‡**
Flare or glucocorticosteroid prescription (%)	96 (24.1)	74 (27.6)	0.30	40 (38.8)	0.003	0.011	123 (23.9)	71 (33.5)	0.008	17 (34.0)	0.11	0.016
Escalation (%)	90 (22.6)	68 (25.4)	0.40	29 (28.2)	0.23	0.44	120 (23.3)	56 (26.4)	0.37	11 (22.0)	0.84	0.63
Hospitalisation (%)	24 (6.0)	28 (10.4)	0.036	9 (8.7)	0.32	0.11	35 (6.8)	19 (9.0)	0.31	7 (14.0)	0.064	0.15
Intestinal resection (%)	14 (3.5)	14 (5.2)	0.28	4 (3.9)	0.86	0.55	18 (3.5)	10 (4.7)	0.44	4 (8.0)	0.12	0.27
Death (%)	15 (3.8)	9 (3.4)	0.80	7 (6.9)	0.18	0.30	15 (3.0)	11 (5.2)	0.14	5 (10.4)	0.008	0.026

**P* value for comparison between normal or improving and fluctuating trajectories.

†*P* value for comparison between normal or improving and abnormal or worsening trajectories.

‡*P* value for trend.

3.4.4 Clinical Outcomes According to Initial Depression Trajectories

During a mean duration of follow-up of 3.9 years, patients with a persistently abnormal or worsening depression trajectory were not significantly more likely to experience a flare of disease activity or require glucocorticosteroids, an escalation of medical therapy, hospitalisation, or intestinal resection due to uncontrolled disease activity (Table 3.2). Mortality was significantly higher in those with a persistently abnormal or worsening depression trajectory than those with a persistently normal or improving trajectory. Following multivariate Cox regression, mortality was no longer significantly associated with a persistently abnormal or worsening depression trajectory.

3.5 Discussion

We have previously established mood trajectories using anxiety and depression symptom data taken at 3-monthly intervals over the course of 1 year in this cohort of patients with IBD. In that study, we demonstrated that almost 90% of patients with abnormal anxiety or depression scores at baseline continued to have abnormal scores, and that persistently abnormal or worsening mood trajectories were associated with increased healthcare utilisation.[24] In the current study we examined the persistence of symptoms of a common mental disorder in IBD, by examining the effect of these baseline anxiety and depression trajectories on subsequent symptoms of anxiety or depression at yearly intervals. Both anxiety and depression trajectories established during the initial 1 year of the study were significantly associated with the reporting of symptoms of anxiety and depression in the subsequent 12 and 24 months of longitudinal follow-up. This suggests that these symptoms persist for the majority of patients with IBD during extended follow-up. When considering all baseline characteristics, the only factors that remained significantly associated with symptoms of anxiety at both 12 and 24 months were fluctuating anxiety trajectories, persistently abnormal or worsening anxiety trajectories, and the use of antidepressants. Similarly for symptoms of depression, fluctuating depression trajectories or persistently abnormal or worsening depression trajectories remained the only factor significantly associated with symptoms of depression at both subsequent time points. We also examined the impact of anxiety and depression trajectories on adverse disease outcomes during almost 4 years of follow-up but found no significant association between these and any of the adverse disease outcomes of interest.

Our study has several strengths. Firstly, by using validated questionnaires in an online format, we were able to distribute initial invitations to the entirety of the IBD population that we serve. Furthermore, the option for participants to receive a postal questionnaire, if

preferred, reduced the risk of age- and wealth-related bias in our recruitment selection, allowing those without access to modern technology an equal chance to participate. Attrition is a significant issue in observational research. Therefore, offering a single reminder at each longitudinal follow-up point contributed to our large cohort size, and the successful establishment of anxiety and depression trajectories during the first year in three-quarters of participants, and with data for subsequent mood in just over 50% of the original cohort at 24 months. We, therefore, present data from a large, unselected IBD cohort with a range of disease characteristics, who are likely to be generalisable to many patients in secondary care. Finally, the combination of electronic health records and two assessors, blinded to symptom response data, assessing adverse disease outcomes against pre-defined criteria ensured that these endpoints were captured accurately during longitudinal follow-up.

There are, of course limitations which must be acknowledged. Validated questionnaires have a lower sensitivity and specificity in detecting common mental disorders than structured interviews,[38] and our study could be criticised for using HADS scores as a surrogate for the presence of a common mental disorder. However, in this large observational study, which was conducted in parallel with routine clinical care, it was not feasible to conduct structured interviews, without impacting participant retention negatively, and the cut-offs we have used demonstrate good specificity in IBD, suggesting this is an accurate assessment of the prevalence of such symptoms.[38] By inviting all patients with IBD in our centre to participate, we avoided selection bias, but volunteer bias is an inherent flaw of observational research,[39] and we cannot rule out that patients with symptoms of anxiety or depression were more likely to participate in the study, creating the potential to overestimate the prevalence of these symptoms in our cohort. That said, the prevalence of symptoms of a common mental disorder we report is similar to that in other studies.[15] Patient-reported disease activity measures demonstrate inferiority to non-invasive biomarkers and endoscopic

assessments in determining the degree of inflammatory activity in IBD, with the former likely to overestimate disease activity.[40, 41] As the study commenced during the COVID-19 pandemic, collection of faecal calprotectin samples would have required patients to return a specimen in-person to an NHS location for research purposes, which was not feasible at the time. In addition, a recent study examining symptoms of anxiety and depression in IBD determined that both endoscopic and biochemical activity did not predict symptoms of a common mental disorder, with only perceived disease activity, as determined by disease activity scores, being independently associated with such symptoms. This suggests that perceived symptoms of a flare correlate with mood rather than genuine underlying disease activity.[42] Persistent depression is associated with several key risk factors, including a history of childhood adversity and maltreatment, a family history of depression, earlier onset of depressive symptoms, comorbidity with anxiety and other psychiatric disorders, poor social support and a higher frequency of depressotypic cognitions.[43] It was not possible to measure these factors other than anxiety in the present study, or establish whether those participants with persistent depression or anxiety had symptoms which pre-dated the onset of IBD. Finally, we did not record whether patients had accessed psychological therapies during the study, which may explain some of the fluctuation in symptoms of anxiety and depression, although previous surveys have shown that access for patients with IBD to these is limited in the UK.[44]

Mood trajectories have been studied in the context of chronic disease, with a recent meta-analysis of over 60,000 patients with cancer, diabetes, and cardiovascular and liver disease demonstrating persistently abnormal anxiety and depression scores over a period of almost 4 years among one-in-eight patients following diagnosis.[45] Our study is, to our knowledge, the first to examine the stability of future mood according to such mood trajectories in IBD, and suggests that abnormal mood is even more stable over time in this

particular patient group, with over three-quarters of patients with persistently abnormal or worsening anxiety trajectories continuing to report symptoms of anxiety and over two-thirds with persistently abnormal or worsening depression trajectories reporting ongoing symptoms of depression in the subsequent 2 years. These findings suggest that, for patients with an established diagnosis of IBD reporting symptoms of anxiety or depression, unlike other chronic inflammatory conditions,[25, 26] these symptoms remain stable in the majority over time. Our findings support the notion that a single assessment of mood may be sufficient to diagnose common mental disorders in this context. An exception to this observation is patients with a new diagnosis, in whom abnormal anxiety trajectories predicted abnormal anxiety scores at 12 months, but not at 24 months, suggesting that in this group of patients, mood may be more fluctuant and reflect psychological adjustment to the disease state. Indeed, psychological adaptation has been reported in the context of chronic disease,[46] and similar improvements in anxiety scores have also been observed in patients with other chronic inflammatory disorders, including multiple sclerosis, in the 6 months following diagnosis.[47] The limited research conducted amongst IBD inception cohorts suggests a high prevalence of symptoms of a common mental disorder in this particular group of patients,[48, 49] and studies examining the risk factors for persistently abnormal mood in newly diagnosed patients may be key to implementing preventative strategies to mitigate subsequent high volume healthcare use.[46]

We have shown previously that persistently abnormal or worsening anxiety or depression trajectories were associated with increased healthcare utilisation in IBD.[24] However, data from the current study did not identify a relationship between these mood trajectories and subsequent adverse disease outcomes. These findings mirror those of a much smaller study of 32 patients with IBD,[50] which demonstrated that future adverse disease outcomes were not linked with mood fluctuations, and contradicts the findings of the wealth

of observational data suggesting the existence of brain-gut effects in IBD.[13, 14, 20, 21] As inflammatory and psychological burden have been proven to influence disease outcomes cumulatively in IBD,[13] it may be that studies adopting a more rigorous assessment of IBD activity are required to determine the role of mood trajectories on these outcomes. However, despite the large sample size, the number of patients with a persistently abnormal or worsening mood trajectory was relatively small and the study may be underpowered to detect such associations, particularly given the relatively short duration of follow-up in comparison with other studies.[13] Regardless, avoidance of adverse disease outcomes should not be the only consideration, and the consistent association between poor psychological health and reduced quality of life and increased healthcare utilisation is important to consider.[16, 24, 51, 52] Other factors that may be involved in fluctuations of mood include the emotional concerns of patients related to specific issues such as fatigue, urgency, fear of incontinence, or pain.[53-55]

Despite an abundance of observational data highlighting the high prevalence of symptoms of a common mental disorder in patients with IBD,[15] there remains a lack of consensus as to how we can address these symptoms appropriately within the constraints of routine care.[56] Policy makers with finite resources are faced with difficulty in this regard. Firstly, little is known regarding the longevity of these symptoms, or indeed if there is substantial fluctuation over time in a relapsing-remitting disease, particularly given the highest prevalence of symptoms of a common mental disorder appears to be during periods of disease activity.[15] Second, randomised controlled trials examining the efficacy of psychological therapies and gut-brain neuromodulators in IBD continue to recruit unselected patients without evidence of psychological co-morbidity, and show no clear benefit of such interventions, which means there is little evidence to support widespread uptake.[57] Our study adds value in this regard, by demonstrating that over two-thirds of patients with persistently abnormal or worsening mood trajectories, continued to experience symptoms of anxiety or

depression over a 2-year period. Validated questionnaires are simple cost-effective tools with a low time-resource burden, which could be utilised in everyday practice to identify symptoms of a common mental disorder in patients with IBD. This could then enable clinicians to allocate scarce psychological health resources to those most likely to benefit.[57] A similar strategy has been trialled across a range of chronic illnesses in secondary care for healthcare-related anxiety, with those identified with this condition being randomised to receive cognitive behavioural therapy (CBT) or treatment as usual; there were significant and sustained improvements in psychological health with CBT, although no difference in healthcare-related costs between groups.[58]

In conclusion poor psychological health, as determined by persistently abnormal or worsening anxiety and depression trajectories, remains unchanged amongst many patients with established IBD over a prolonged period. Although this study did not demonstrate an association between these trajectories and future adverse disease outcomes, we have previously demonstrated that they predict higher healthcare utilisation in this cohort of patients, and a wealth of data suggests poor psychological health negatively impacts quality of life, suggesting that poor psychological health exerts a negative influence on IBD. Further studies examining this issue in patients with IBD in other geographical regions would be informative. A clear consensus on screening and addressing psychological health in routine care is essential to address the unmet needs of a substantial proportion of patients with IBD.

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Supplementary Table 3.1. Baseline Characteristics of Patients According to Initial Anxiety or Depression Trajectories.

	Anxiety Trajectories				Depression Trajectories			
	Normal or improving (n=399)	**Fluctuating (n=268)**	**Abnormal or worsening (n=103)**	***p* value***	**Normal or improving (n=515)**	**Fluctuating (n=212)**	**Abnormal or worsening (n=50)**	***p* value***
Mean age in years at baseline (SD)	56.2 (16.7)	52.2 (15.8)	48.8 (15.8)	<0.001	54.4 (16.7)	53.4 (16.0)	53.9 (16.4)	0.16
Female sex (%)	183 (45.9)	170 (63.4)	64 (62.1)	<0.001	269 (52.2)	123 (58.0)	31 (62.0)	0.20
Married or co-habiting (%)	287 (72.5)	185 (69.5)	65 (63.7)	0.21	371 (72.7)	141 (66.5)	28 (57.1)	0.031
University graduate/professional (%)	149 (37.8)	105 (39.5)	43 (42.2)	0.71	213 (41.9)	73 (34.6)	11 (22.0)	0.008
Tobacco user (%)	24 (6.1)	18 (6.8)	10 (9.7)	0.43	27 (5.3)	19 (9.0)	6 (12.0)	0.065
Alcohol user (%)	283 (71.6)	192 (72.2)	70 (68.0)	0.71	375 (73.7)	145 (68.7)	29 (58.0)	0.041
IBD type (%)								
CD	171 (43.2)	119 (44.7)	45 (44.6)		217 (42.3)	95 (45.7)	25 (51.0)	
UC	197 (49.7)	131 (49.2)	48 (47.5)		263 (51.3)	98 (47.1)	20 (40.8)	
IBD-U	28 (7.1)	16 (6.0)	8 (7.9)	0.96	33 (6.4)	15 (7.2)	4 (8.2)	0.63

CD location (%)[†]								
Ileal	60 (33.3)	44 (36.4)	18 (40.0)		74 (32.7)	40 (41.2)	7 (28.0)	
Colonic	65 (36.1)	26 (21.5)	12 (26.7)		75 (33.2)	21 (21.6)	7 (28.0)	
Ileocolonic	55 (30.6)	51 (42.1)	15 (33.3)	0.07	77 (34.1)	36 (37.1)	11 (44.0)	0.24
Stricturing CD (%)	52 (13.1)	31 (11.7)	13 (12.9)	0.85	63 (12.3)	30 (14.4)	3 (6.1)	0.28
Penetrating CD (%)	16 (4.0)	27 (10.2)	5 (5.0)	0.005	27 (5.3)	19 (9.1)	3 (6.1)	0.16
Perianal CD (%)	20 (5.1)	16 (6.0)	10 (9.9)	0.19	26 (5.1)	15 (7.2)	6 (12.2)	0.099
Previous intestinal resection (%)	71 (17.9)	51 (19.2)	17 (16.7)	0.84	90 (17.5)	45 (21.5)	7 (14.3)	0.40
UC extent (%)[‡]								
Proctitis	59 (28.5)	38 (27.7)	14 (27.5)		76 (27.5)	30 (29.7)	8 (34.8)	
Left-sided	75 (36.2)	56 (40.9)	24 (47.1)		109 (39.5)	38 (37.6)	9 (39.1)	
Extensive	73 (35.3)	43 (31.4)	13 (25.5)	0.61	91 (33.0)	33 (32.7)	6 (26.1)	0.93
5-ASA use (%)	219 (55.3)	147 (55.3)	51 (50.5)	0.67	288 (56.1)	110 (52.9)	22 (44.9)	0.27
Immunomodulator use (%)	107 (27.0)	77 (28.9)	33 (32.7)	0.52	140 (27.3)	59 (28.4)	22 (44.9)	0.034
Biologic use (%)	82 (20.7)	55 (20.7)	27 (26.7)	0.39	104 (20.3)	46 (22.1)	14 (28.6)	0.38
Glucocorticosteroid use (%)	11 (2.8)	6 (2.3)	4 (4.0)	0.67	14 (2.7)	5 (2.4)	2 (4.1)	0.81
Antidepressant use (%)	48 (12.1)	52 (19.5)	29 (28.2)	<0.001	52 (10.1)	62 (29.2)	17 (34.0)	<0.001
Opiate use (%)	31 (7.8)	39 (14.6)	19 (18.4)	0.002	38 (7.4)	36 (17.0)	16 (32.0)	<0.001

Diagnosed with IBD in the last 12 months (%)	20 (5.1)	21 (8.0)	14 (13.7)	0.009	28 (5.5)	22 (10.5)	5 (10.0)	0.043
Self-reported a flare at baseline (%)	43 (10.9)	61 (22.9)	29 (28.2)	<0.001	62 (12.2)	55 (25.9)	15 (30.0)	<0.001
Active disease on HBI or SCCAI at baseline (%)	102 (25.8)	123 (46.2)	58 (56.3)	<0.001	145 (28.5)	106 (50.0)	35 (70.0)	<0.001
PHQ-12 somatoform symptom categories (%)								
Minimal	160 (43.4)	42 (16.5)	9 (9.8)		189 (32.2)	20 (10.3)	3 (7.0)	
Low	132 (35.8)	110 (43.3)	21 (22.8)		194 (40.2)	67 (34.5)	6 (14.0)	
Medium	65 (17.6)	21 (22.8)	37 (40.2)		84 (17.4)	79 (40.7)	17 (39.5)	
High	12 (3.3)	263 (36.8)	25 (27.2)	<0.001	15 (3.1)	28 (14.4)	17 (39.5)	<0.001
Mean SIBDQ score (SD)	56.3 (16.7)	52.2 (15.8)	48.8 (15.8)	<0.001	54.4 (16.7)	53.4 (16.0)	51.1 (15.2)	0.16

Chapter 4: Novel Symptom Clusters Predict Disease Impact and Healthcare Utilisation in Inflammatory Bowel Disease: Prospective Longitudinal Follow-up Study.

4.1 Summary

Background: Predicting adverse disease outcomes and high-volume users of healthcare amongst patients with inflammatory bowel disease (IBD) is difficult.

Aims: To use latent class analysis to create novel clusters of patients and to assess whether these predict outcomes during 6.5 years of longitudinal follow-up.

Methods: Baseline demographic features, disease activity indices, anxiety, depression, and somatoform symptom-reporting scores were recorded for 692 adults. Faecal calprotectin (FC) was analysed at baseline in 348 (50.3%) patients (<250mcg/g defined biochemical remission). Using baseline gastrointestinal and psychological symptoms, latent class analysis identified specific patient clusters. Rates of glucocorticosteroid prescription or flare, escalation, hospitalisation, or intestinal resection were compared between clusters using multivariate Cox regression.

Results: A three-cluster model was the optimum solution; 132 (19.1%) patients had below average gastrointestinal and psychological symptoms (cluster 1), 352 (50.9%) had average levels of gastrointestinal and psychological symptoms (cluster 2), and 208 (30.1%) had the highest levels of both gastrointestinal and psychological symptoms (cluster 3). Compared with cluster 1, cluster 3 had significantly increased risk of flare or glucocorticosteroid prescription (hazard ratio (HR) 2.13; 95% confidence interval (CI) 1.46-3.10), escalation (HR 1.92; 95% CI 1.34-2.76), a composite of escalation, hospitalisation, or intestinal resection (HR 2.05; 95% 1.45-2.88), or any of the endpoints of interest (HR 2.06; 95% CI 1.45-2.93). Healthcare utilisation was highest in cluster 3.

Conclusions: Novel model-based clusters identify patients with IBD at higher risk of adverse disease outcomes who are high volume users of healthcare.

4.2 Introduction

Inflammatory bowel disease (IBD), which encompasses Crohn's disease (CD) and ulcerative colitis (UC), affects an estimated 8.6 million people worldwide.[1] Typically, IBD follows a relapsing-remitting course, with symptoms of disease activity including abdominal pain, urgency, diarrhoea, and haematochezia. Although the exact aetiology remains unclear, a complex interplay between genetic and environmental factors is believed to trigger a cascade of alterations within the gut microbiome, resulting in enteric immune system dysregulation.[2, 3] IBD exerts a considerable socioeconomic burden in Western populations, with healthcare costs per person in the USA exceeding those for diabetes.[4] Healthcare expenditure is, in part, driven by the increasing use of biologics,[5] but hospitalisations and emergency department visits remain a substantial contributor.[6] In addition, the debilitating nature of symptoms generates indirect costs through restricted social interactions, impairment in work productivity, and development of functional disability.[7, 8]

One of the challenges faced by physicians is that symptom burden does not always reflect underlying disease activity in IBD.[9] Up to half of patients experience persistent abdominal pain despite quiescent disease,[10] and up to one-third of patients report symptoms compatible with irritable bowel syndrome (IBS), a common disorder of gut-brain interaction influenced by psychological health.[11] In addition, the prevalence of symptoms of common mental disorders, such as anxiety or depression, in patients with IBD is twice that of the general population, affecting up to half of patients during disease flares.[12] Irrespective of disease activity, psychological symptoms are associated with worse disease outcomes and increased healthcare utilisation,[13] with some studies suggesting that the annual costs for patients with IBD with a pre-existing mental health disorder are double that of those without.[5] Despite this, screening for common mental disorders is not integrated within routine IBD

care,[14] and even when such symptoms are identified, it is estimated that further action is taken in only half of cases.[15]

Incorporating psychological profiling into model-based clustering techniques in groups of patients with IBS, researchers have identified distinct and reproducible subgroups, or clusters, of patients based on the burden of gastrointestinal symptoms and psychological symptoms.[16, 17] To our knowledge, only one study has used this approach in patients with IBD, and the clusters derived were similar to those seen in IBS.[18] In IBS, membership of clusters with a higher burden of psychological symptoms is associated with higher healthcare utilisation and costs, irrespective of the burden of gastrointestinal symptoms.[17, 19] However, whether membership of a cluster with a high psychological or gastrointestinal symptom burden impacts disease outcomes or healthcare utilisation in patients with IBD is yet to be determined. This issue may be of relevance for healthcare organisations, where identifying patients at greatest risk of having a worse prognosis or being high volume users of care could allow resources, such as psychological therapies, to be offered to patient groups who are likely to benefit the most.

We hypothesised that model-based clustering, applying psychological symptom profiling, in addition to gastrointestinal symptom measures, would enable identification of distinct subgroups of patients with IBD, regardless of disease location, extent, or phenotype, and that membership of a cluster with a higher psychological symptom burden would be associated with worse disease outcomes and higher healthcare utilisation.

4.3 Methods

4.3.1 Participants and Setting

We recruited patients from IBD clinics based at St James's University Hospitals, Leeds, United Kingdom between November 2012 and June 2015. Eligible patients were aged ≥16 years with an established diagnosis of CD or UC, based on endoscopic, histological, and radiological findings. Participation involved completion of a baseline questionnaire. We, therefore excluded patients who were unable to understand written English, as well as patients with IBD-unclassified and those with a stoma, as reliable scoring systems are not available to assess disease activity accurately in the latter two groups of individuals. We undertook longitudinal follow-up between September 2014 and November 2021 (REC ref: 12/YH/0443/AM03), as described previously.[20] We reported study findings in accordance with the STROBE guidelines.[21]

4.3.2 Data Collection and Synthesis

4.3.2.1 Baseline Data

We recorded type of IBD, current IBD-related medications, history of a prior intestinal resection for IBD, and demographic data, including age, sex, marital status, ethnicity, educational level, and tobacco and alcohol use at baseline at the point of study enrolment. In addition, we collected data regarding anxiety or depression symptoms using the hospital anxiety and depression scale (HADS), with an abnormal score defined as ≥11, as per the original validation study,[22] and somatoform symptom-reporting using the validated patient health questionnaire-15 (PHQ-15) at baseline.[23]

We assessed IBD-related gastrointestinal symptoms at baseline using the Harvey-Bradshaw index (HBI) for patients with CD,[24] and the simple clinical colitis activity index

(SCCAI) for UC.[25] Patients were asked to provide a faecal calprotectin (FC) sample (Immundiagnostik, Blensheim, Germany) at the point of enrolment, which was sent for analysis. In line with local policy and international consensus,[26] biochemical remission at baseline was defined as an FC of <250mcg/g of stool.

4.3.2.2 Longitudinal Follow-up Data

To enable an objective measurement of disease activity, we reviewed participant's medical records during longitudinal follow-up. This was done by a single investigator (KMF), blinded to baseline questionnaire data. We extracted the following outcomes along with the date they occurred: flare of disease activity based on either a global assessment by a physician or need for a prescription for glucocorticosteroids, escalation of medical therapy due to uncontrolled IBD activity, hospitalisation due to uncontrolled IBD activity, or intestinal resection due to uncontrolled IBD activity. We also recorded the frequency of each of these. We did not include 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. Finally, to enable an assessment of overall healthcare utilisation, we recorded the frequency of IBD-related clinic appointments, and number of radiological and endoscopic investigations performed for IBD activity assessment.

4.3.3 Statistical Analysis

Due to a probable increased risk of the outcomes of interest, patients experiencing a flare at baseline were excluded from all analyses. We used LatentGOLD version 6.0 (Statistical Innovations, Belmont, MA, USA) to perform latent class analysis (LCA).[27] LCA applies structural equation modelling to enable identification of previously unobserved groups, referred to as latent classes, within multivariate data.[28] A statistical model is

postulated for the population from which the data sample is obtained, with the assumption that a mixture of underlying probability distributions generates the data.[29] The use of LCA for this purpose is model-based clustering, which is a flexible technique, enabling inclusion of multiple variables within the same model. Analysis is iterative, evaluating multiple solutions to determine the best output for any number of clusters.[29] Finally, robust statistical criteria are used to determine the best fit of the model, and the optimum number of clusters.[30] We used the Bayesian information criterion of the log-likelihood (BIC(LL)) for this purpose, selecting the cluster solution with the lowest BIC(LL) value as the best fit for the data. We have used this methodology previously to create clusters of patients with IBS.[16] Details of the variables at baseline used in the model, along with the ordinal scales, are provided in Supplementary Table 4.1. We included the following baseline variables in our model: HADS scores (normal, borderline abnormal, or abnormal), common components of the HBI or SCCAI (stool frequency, number of IBD-associated conditions, and general wellbeing), and responses to individual items from the PHQ-15. Using the cluster model with the lowest BIC(LL), we then calculated z-values for each cluster within that particular model by adjusting the cluster mean for each variable to the cohort mean and standard deviation for that variable, and then drew radar plots as a visual aid to compare the characteristics of each individual cluster.

We compared baseline characteristics of individuals in each cluster using a χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. To evaluate the influence of being in each cluster at baseline on healthcare utilisation we compared the frequency of each of flare of disease activity or glucocorticosteroid prescription, escalation of medical therapy, hospitalisation, or intestinal resection from longitudinal follow-up in each of the LCA clusters, using a χ^2 test. We then performed multivariate Cox regression analysis, controlling for all baseline characteristics, to establish if being in a particular cluster was an independent predictor for the occurrence of each of the

outcomes. We expressed these results as hazard ratios (HRs) with 95% confidence intervals (CIs). Given that our *a priori* hypothesis was there would be statistically significant differences between the clusters, and due to multiple comparisons, a 2-tailed P value of <0.01 was considered statistically significant for these analyses. We repeated this exercise for the subgroup of individuals who had a FC <250mcg/g at baseline. We also compared number of IBD-related appointments and investigations between clusters using one-way ANOVA. We performed statistical analyses using SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA).

4.4 Results

A total of 760 patients were recruited, with 692 (91.1%) providing complete clinical data at baseline to allow LCA, 348 (50.3%) of whom also supplied a baseline FC. Characteristics of those providing complete data and included in the LCA model, compared with those not included, are provided in Supplementary Table 4.2. The mean age of participants was 43.6 (SD 16.7 years, range 17 to 89 years), 382 (55.2%) were female, 647 (93.8%) were Caucasian, and 394 (56.9%) had CD. The number providing follow-up data ranged between 550 (79.5%) for need for glucocorticosteroids or flare of disease activity to 671 (97.0%) for intestinal resection.

4.4.1 Cluster Characteristics

The best LCA solution was obtained using a three-cluster model, as indicated by the point of convergence between the lowest BIC(LL) values for each cluster model. The three clusters each had distinct symptom profiles; cluster 1 consisted of 132 (19.1%) patients with below average gastrointestinal and psychological symptoms, cluster 2 352 (50.9%) patients with average levels of gastrointestinal symptoms and psychological symptoms, and cluster 3 208 (30.1%) patients with the highest levels of both gastrointestinal and psychological symptoms.

The symptom profiles for each cluster are provided in Figure 4.1 and baseline characteristics according to cluster in Table 4.1. At baseline, stool frequency was between 1 and 3 times per day in almost 95% of patients in cluster 1, only one patient reported their general wellbeing as poor, no patients reported being bothered by stomach pain a lot, and extraintestinal symptom-reporting was low. In cluster 2, at baseline, almost 35% of patients had a stool frequency above 1 to 3 times per day, 8% reported general wellbeing as poor or worse, 21% reported being bothered by stomach pain a lot, and extraintestinal symptom-

reporting was average other than for back pain, which was above average. In cluster 3, at baseline, almost 45% had a stool frequency above 1 to 3 times per day, more than 50% reported general wellbeing as poor or worse, over 60% reported being bothered by stomach pain a lot, and rates of extraintestinal symptom-reporting were extremely high for all symptoms.

Cluster 1 contained the lowest proportion of females, smokers, individuals reporting glucocorticosteroid use at baseline, and with a history of previous intestinal resection, and the highest proportion of alcohol users. There was also a trend towards cluster 1 having the lowest proportion of patients with CD. There were no significant differences between location, extent, or behaviour of IBD, or other IBD-related medication use at baseline. Mean FC at baseline was similar across all three clusters.

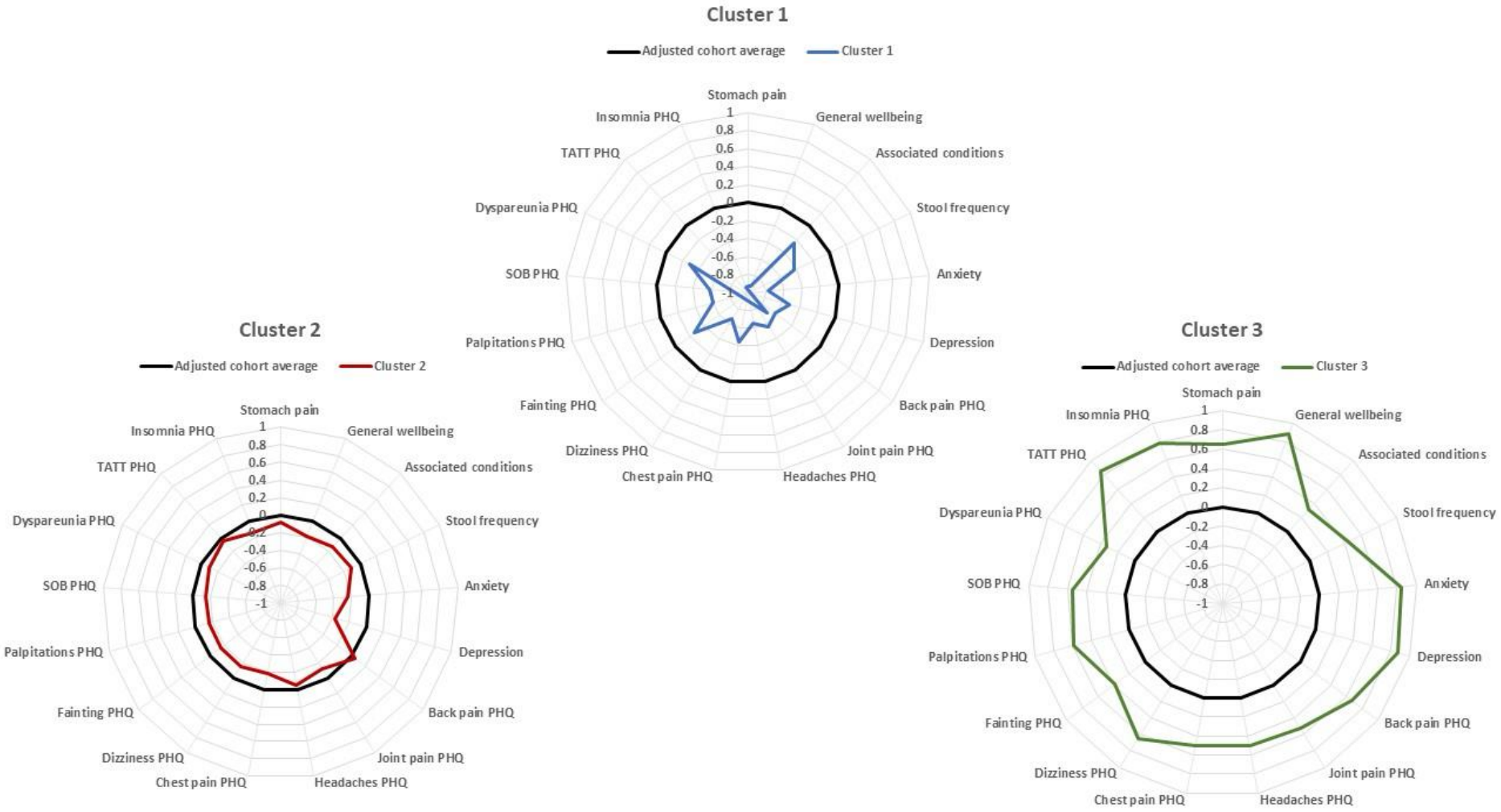
Table 4.1. Baseline Characteristics of Patients According to Cluster.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms (n = 132)	Cluster 2: Average levels of gastrointestinal and psychological symptoms (n = 352)	Cluster 3: Highest levels of gastrointestinal and psychological symptoms (n = 208)	*p* value*
Mean age in years at baseline (SD)	45.2 (19.1)	43.5 (16.7)	42.6 (14.9)	0.38
Female sex (%)	57 (43.2)	180 (51.1)	145 (69.7)	<0.001
Married or co-habiting (%)	73 (55.3)	229 (65.6)	122 (58.9)	0.074
University graduate/professional (%)	42 (31.8)	105 (30.1)	50 (24.4)	0.25
Tobacco user (%)	14 (10.6)	52 (14.8)	50 (24.3)	0.002
Alcohol user (%)	96 (72.7)	253 (72.1)	102 (49.5)	<0.001
CD (%)	66 (50.0)	193 (54.8)	135 (64.9)	0.013
CD location (%)				
Ileal	16 (24.2)	35 (18.1)	35 (25.9)	
Colonic	19 (28.8)	59 (30.6)	34 (25.2)	
Ileocolonic	31 (47.0)	99 (51.3)	66 (48.9)	0.49
Non-stricturing, non-penetrating CD (%)	54 (81.8)	163 (84.5)	107 (79.3)	0.11
Perianal CD (%)	8 (12.1)	24 (12.4)	5 (3.7)	0.020
UC extent (%)				
Proctitis	14 (21.2)	34 (21.5)	23 (31.1)	
Left-sided	29 (43.9)	79 (50.0)	29 (39.2)	
Extensive	23 (34.8)	45 (28.5)	22 (29.7)	0.38
5-ASA use (%)	64 (48.5)	170 (48.3)	92 (44.2)	0.61
Immunomodulator use (%)	44 (33.3)	136 (38.6)	69 (33.2)	0.33
Anti-TNFα use (%)	31 (23.5)	69 (19.6)	28 (13.5)	0.051
Glucocorticosteroid use (%)	7 (5.3)	35 (9.9)	34 (16.3)	0.004
Previous intestinal resection (%)	18 (13.6)	65 (18.5)	58 (27.9)	0.003
FC <250mcg/g at baseline (%)	45 (64.3)	104 (58.4)	62 (62.0)	0.66

General wellbeing at baseline (%)				
Very good	113 (85.6)	108 (30.7)	5 (2.4)	
Slightly below par	18 (13.6)	216 (61.4)	93 (44.7)	
Poor	1 (0.8)	27 (7.7)	79 (38.0)	
Very poor	0 (0.0)	1 (0.3)	21 (10.1)	
Terrible	0 (0.0)	0 (0.0)	10 (4.8)	<0.001
Stool frequency at baseline (%)				
1 – 3 times per day	124 (93.9)	268 (76.1)	118 (56.7)	
4 – 6 times per day	7 (5.3)	68 (19.3)	54 (26.0)	
7 – 9 times per day	1 (0.8)	12 (3.4)	16 (7.7)	
≥10 times per day	0 (0.0)	4 (1.1)	20 (9.6)	<0.001
Number of IBD-associated conditions at baseline (%)				
0	122 (92.4)	311 (88.4)	148 (71.2)	
1	9 (6.8)	34 (9.7)	50 (24.0)	
2	1 (0.8)	7 (2.0)	7 (3.4)	
3	0 (0.0)	0 (0.0)	3 (1.4)	<0.001
Stomach pain in the last 4 weeks (%)				
None	86 (65.2)	69 (19.6)	8 (3.8)	
A little	46 (34.8)	209 (59.4)	71 (34.1)	
A lot	0 (0.0)	74 (21.0)	129 (62.0)	<0.001

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

Figure 4.1. Profiles of the Three Latent Class Clusters Identified in 692 Patients with IBD.



4.4.2 Glucocorticosteroid Prescription or Flare of Disease Activity

A total of 294 (53.5%) of 550 patients across all three clusters required a prescription for glucocorticosteroids or had a flare of disease activity during a mean follow-up of 4.0 years (range 7 days to 8.7 years). Likelihood was lowest in cluster 1 with below average levels of both gastrointestinal and psychological symptoms (40.0%) and was significantly higher in both clusters 2 (52.8%) and 3 (66.0%) than cluster 1, and in cluster 3 versus cluster 2 (Table 4.2). More than 80% of patients requiring a prescription for glucocorticosteroids or experiencing a flare were in clusters 2 and 3. The mean number of prescriptions for glucocorticosteroids or flares during follow-up was significantly higher in clusters 2 and 3.

Following multivariate Cox regression, controlling for all baseline data and using cluster 1 as the reference cluster, the increase in likelihood of prescription for glucocorticosteroids or flare remained significant in cluster 3 (HR = 2.13; 95% CI 1.46 to 3.10, $p<0.001$) (Table 4.2 and Figure 4.2). Younger age was also independently associated with reduced likelihood of flare or need for glucocorticosteroids (HR per year= 0.98; 95% CI 0.97 to 0.99, $p<0.001$) and UC with a higher likelihood (HR = 1.60; 95% CI 1.15 to 2.21, $p=0.005$). Results were similar when only individuals with an FC <250mcg/g were considered in the analysis (HR for cluster 3 versus cluster 1 = 3.63; 95% CI 1.83 to 7.22, $p<0.001$ (Supplementary Table 4.3), and were also similar for those with CD and UC (Supplementary Tables 4.4 and 4.5).

Table 4.2. Clinical Outcomes of Patients According to Cluster at Baseline.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms (n = 132)	Cluster 2: Average levels of gastrointestinal and psychological symptoms (n = 352)	*p* value*	Cluster 3: Highest levels of gastrointestinal and psychological symptoms (n = 208)	*p* value*	*p* value†	*p* value‡
Glucocorticosteroids/flare (%) (% of all glucocorticoids/flares)	48/120 (40.0) (16.3)	151/286 (52.8) (51.4)	0.019	95/144 (66.0) (32.3)	<0.001	0.009	<0.001
Multivariate HR for glucocorticosteroids/flare (95% CI)	1.00 (reference)	1.50 (1.07 – 2.09)	0.019	2.13 (1.46 – 3.10)	<0.001	N/A	<0.001
Mean number of glucocorticosteroids/flares (SD)	0.98 (1.52)	1.50 (1.80)	0.002	1.81 (1.72)	<0.001	0.048	<0.001
Escalation (%) (% of all escalations)	51/125 (40.8) (15.5)	172/308 (55.8) (52.3)	0.005	106/174 (60.9) (32.2)	0.001	0.28	0.002
Multivariate HR for escalation (95% CI)	1.00 (reference)	1.61 (1.17 – 2.22)	0.003	1.92 (1.34 – 2.76)	<0.001	N/A	0.001
Mean number of escalations (SD)	0.74 (1.10)	1.17 (1.29)	<0.001	1.19 (1.20)	0.001	0.80	0.002
Hospitalisation (%) (% of all hospitalisations)	23/129 (17.8) (13.9)	71/339 (20.9) (43.0)	0.45	71/199 (35.7) (43.0)	<0.001	<0.001	<0.001
Multivariate HR for hospitalisation (95% CI)	1.00 (reference)	1.07 (0.66 – 1.72)	0.79	1.61 (0.97 – 2.68)	0.064	N/A	0.048
Mean number of hospitalisations (SD)	0.26 (0.72)	0.29 (0.70)	0.67	0.54 (0.90)	0.002	0.001	<0.001
Intestinal resection (%) (% of all intestinal resections)	11/129 (8.5) (13.4)	33/339 (9.7) (40.2)	0.69	38/203 (18.7) (46.3)	0.011	0.003	0.003
Multivariate HR for intestinal resection (95% CI)	1.00 (reference)	0.98 (0.49 – 1.98)	0.96	1.70 (0.82 – 3.56)	0.16	N/A	0.10

Mean number of intestinal resections (SD)	0.11 (0.38)	0.10 (0.31)	0.83	0.19 (0.41)	0.056	0.006	0.011
Escalation, hospitalisation, or intestinal resection (%) (% of all escalations, hospitalisations, or intestinal resections)	56/125 (44.8) (15.9)	179/308 (58.1) (50.7)	0.012	118/173 (68.2) (33.4)	<0.001	0.029	<0.001
Multivariate HR for escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	1.51 (1.11 – 2.05)	0.009	2.05 (1.45 – 2.88)	<0.001	N/A	<0.001
Glucocorticosteroids/flare, escalation, hospitalisation, or intestinal resection (%) (% of all glucocorticosteroids/flares, escalations, hospitalisations, or intestinal resections)	57/120 (47.5) (17.1)	174/286 (60.8) (52.1)	0.013	103/143 (72.0) (30.8)	<0.001	0.022	<0.001
Multivariate HR for glucocorticosteroids/flare, escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	1.48 (1.09 – 2.01)	0.012	2.06 (1.45 – 2.93)	<0.001	N/A	<0.001

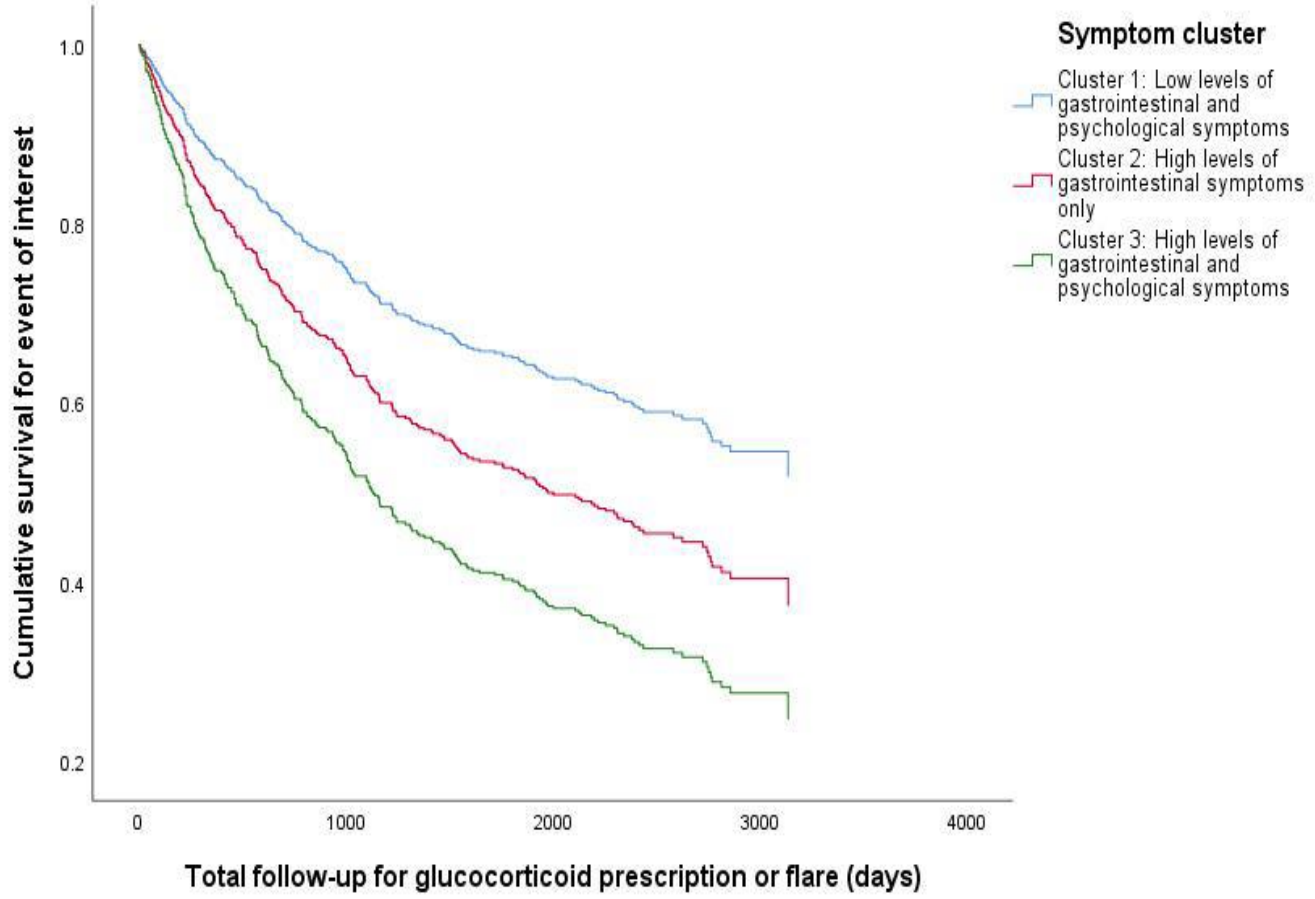
*χ^2 for comparison of categorical data or independent samples *t*-test for comparison of continuous data or hazard ratios vs. cluster 1.

†χ^2 for comparison of categorical data or independent samples *t*-test for comparison of continuous data vs. cluster 2.

‡χ^2 for comparison of categorical data or one-way ANOVA for comparison of continuous data or hazard ratios across all three groups.

N/A; not applicable.

Figure 4.2. Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity According to Baseline Cluster.



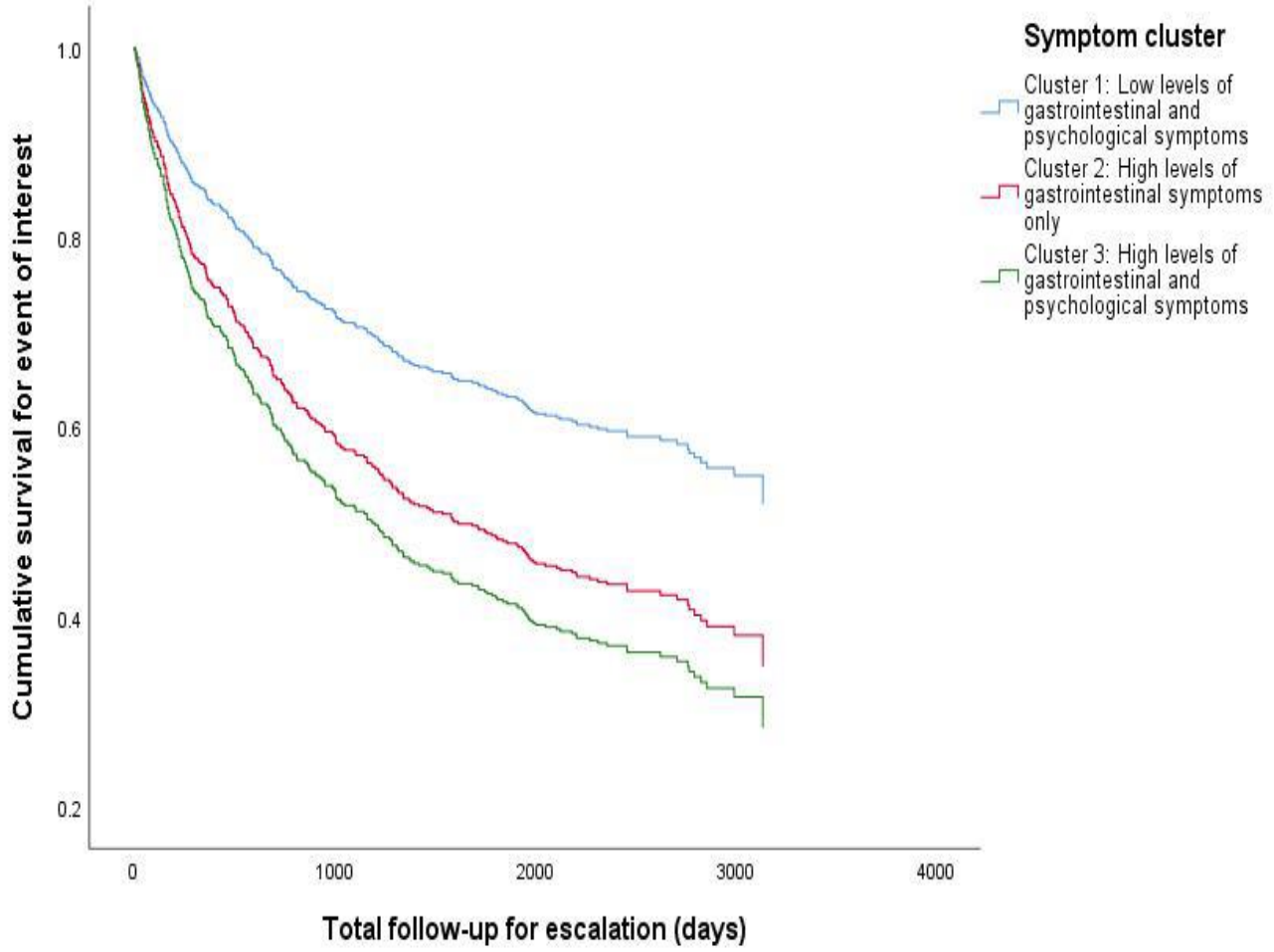
4.4.3 Escalation of Medical Therapy Due to Uncontrolled IBD Activity

Of the 607 patients providing complete data, 329 (54.2%) required escalation of medical therapy during a mean follow-up of 3.8 years (range 4 days to 8.7 years). Likelihood was lowest in cluster 1 with below average levels of both gastrointestinal and psychological symptoms (40.8%) and was significantly higher in both clusters 2 (55.8%) and 3 (60.9%) than cluster 1 (Table 4.2). Again, more than 80% of patients requiring escalation were in clusters 2 and 3. The mean number of escalations during follow-up was significantly higher in clusters 2 and 3 versus cluster 1.

After multivariate Cox regression, likelihood of escalation was significantly higher in cluster 2 than cluster 1 (HR= 1.61; 95% CI 1.17 to 2.22, p=0.003) and again highest in cluster

3 (HR= 1.92; 95% CI 1.34 to 2.76, p<0.001) (Table 4.2 and Figure 4.3). 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 (HR = 0.98; 95% CI 0.97 to 0.99, p<0.001) and glucocorticosteroid use at baseline an increased likelihood (HR= 1.66; 95% CI 1.17 to 2.35, p=0.005). Again, results were similar when only those with an FC <250mcg/g were included in the analysis (HR for cluster 3 versus cluster 1 = 3.48; 95% CI 1.69 to 7.19, p=0.001) (Supplementary Table 4.3). There was no significant difference in likelihood of escalation according to cluster in patients with CD, but in those with UC cluster 3 had a significantly higher likelihood of escalation (Supplementary Tables 4.4 and 4.5).

Figure 4.3. Survival Analysis for Occurrence of Escalation of Medical Therapy due to Uncontrolled IBD Activity According to Baseline Cluster.



4.4.4 Hospitalisation Due to Uncontrolled IBD Activity

A total of 165 (24.7%) of 667 patients were hospitalised due to uncontrolled IBD activity during a mean follow-up of 5.4 years (range 2 days to 8.7 years). The likelihood of hospitalisation was significantly higher in both cluster 2 (20.9%) and cluster 3 (35.7%) compared with cluster 1 (17.8%), and in cluster 3 versus cluster 2 (Table 4.2). Again, over 80% of individuals hospitalised were in clusters 2 or 3. The mean number of hospitalisations during follow-up was significantly higher in clusters 2 and 3 versus cluster 1, and significantly higher in cluster 3 versus cluster 2.

Following multivariate Cox regression, there was no significant difference in likelihood of hospitalisation between clusters (Table 4.2). Results were similar when only individuals with an FC <250mcg/g, CD, or UC were considered in the analysis (Supplementary Tables 4.3 to 4.5).

4.4.5 Intestinal Resection Due to Uncontrolled IBD Activity

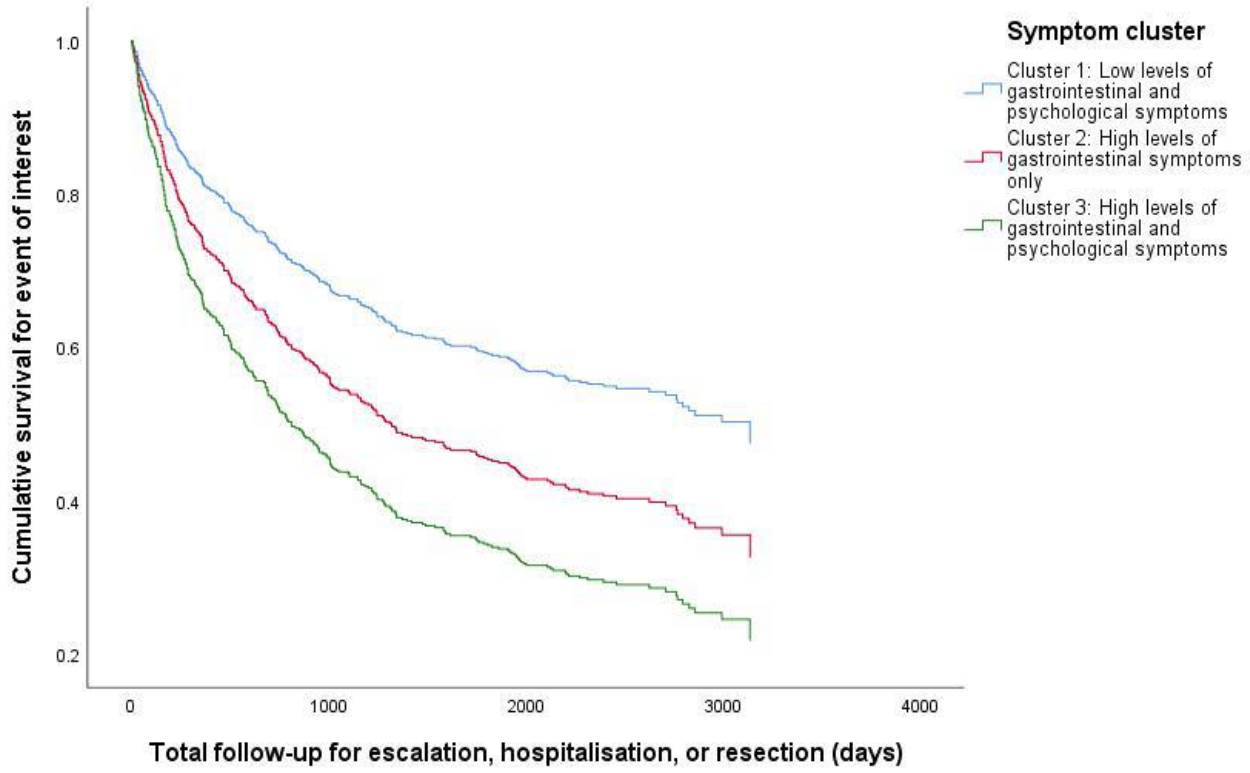
Overall, 82 (12.2%) of 671 patients underwent intestinal resection due to uncontrolled IBD activity during a mean follow-up of 6.0 years (range 4 days to 8.7 years). The likelihood of intestinal resection was higher in cluster 3 (18.7%) than both cluster 1 (8.5%) and cluster 2 (9.7%) but was only significantly higher than cluster 2 (Table 4.2). Again, over 80% of individuals undergoing intestinal resection were in clusters 2 or 3. The mean number of intestinal resections was significantly higher in cluster 3 than cluster 1.

After multivariate Cox regression the differences in likelihood of intestinal resection between the three clusters failed to reach statistical significance (Table 4.2). There were also no statistical differences between the clusters for likelihood of intestinal resection when limiting the analysis to patients with an FC <250mcg/g, those with CD, or those with UC (Supplementary Tables 4.3 to 4.5).

4.4.6 Escalation, Hospitalisation, or Intestinal Resection Due to Uncontrolled IBD Activity

In total, 353 (58.3%) of 606 patients experienced one or more of these endpoints during longitudinal follow-up (Table 4.2). Cluster 1 had the lowest proportion of events (44.8%), followed by cluster 2 (58.1%), and then cluster 3 (68.2%). Likelihood was only significantly higher in cluster 3 than cluster 1 (Table 4.2). Following multivariate Cox regression those in both cluster 2 (HR = 1.51; 95% CI 1.11 to 2.05, p=0.009) and cluster 3 (HR= 2.05; 95% CI 1.45 to 2.88, p<0.001) were more likely to experience one or more of escalation, hospitalisation, or intestinal resection than cluster 1 (Figure 4.4). Results were similar for those with an FC <250mcg/g (Supplementary Table 4.3), but among those with CD or UC only cluster 3 had a significantly higher likelihood of escalation, hospitalisation, or intestinal resection (Supplementary Tables 4.4 and 4.5).

Figure 4.4. Survival Analysis for Occurrence of Escalation of Medical Therapy, Hospitalisation, or Intestinal Resection due to Uncontrolled IBD Activity According to Baseline Cluster.



4.4.7 Any Endpoint

Overall, 334 (60.8%) of 549 patients experienced one or more of the four endpoints during longitudinal follow-up (Table 4.2). Again, cluster 1 had the lowest likelihood (47.5%), followed by cluster 2 (60.8%), and cluster 3 (72.0%). Only cluster 3 had a significantly higher likelihood of one or more of these endpoints than cluster 1. Following multivariate Cox regression analysis, again only individuals in cluster 3 had a significantly higher likelihood of experiencing one or more of these endpoints (HR = 2.06; 95% CI 1.45 to 2.93, p<0.001) than cluster 1. When only those with an FC <250mcg/g were considered in the analysis both cluster 2 and 3 had a significantly higher likelihood of any event than cluster 1 (Supplementary Table 4.3), but when IBD type was considered only cluster 3 had a significantly higher likelihood of experiencing any event in CD or UC (Supplementary Tables 4.4 and 4.5).

4.4.8 Healthcare Utilisation During Longitudinal Follow-up

Mean number of IBD helpline calls and clinic appointments with a gastroenterologist were significantly higher in both clusters 2 and 3 than cluster 1, and were highest in cluster 3, although not significantly higher than in cluster 2 (Table 4.3). There was also a significant increase in mean number of radiological investigations for IBD in cluster 3 compared with both clusters 1 and 2, but no statistically significant difference between clusters 1 and 2. Finally, mean number of endoscopic investigations was significantly higher in clusters 2 and 3, when compared with cluster 1, but there was no statistical difference between clusters 2 and 3.

Table 4.3. Healthcare Utilisation of Patients According to Cluster at Baseline.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms (n = 132)	Cluster 2: Average levels of gastrointestinal and psychological symptoms (n = 352)	*p* value*	Cluster 3: Highest levels of gastrointestinal and psychological symptoms (n = 208)	*p* value*	*p* value†	*p* value‡
Mean number of clinic appointments with a gastroenterologist (SD)	6.57 (5.36)	9.59 (6.49)	<0.001	10.76 (6.37)	<0.001	0.041	<0.001
Mean number of IBD helpline calls (SD)	3.12 (4.82)	5.07 (6.72)	0.001	5.85 (7.18)	<0.001	0.21	0.001
Mean number of radiological investigations related to IBD activity (SD)	0.60 (1.20)	0.83 (1.39)	0.080	1.34 (1.72)	<0.001	<0.001	<0.001
Mean number of endoscopic investigations related to IBD activity (SD)	0.57 (0.83)	0.96 (1.12)	<0.001	1.02 (1.18)	<0.001	0.56	<0.001

*Independent samples *t*-test for comparison of continuous data vs. cluster 1.

†Independent samples *t*-test for comparison of continuous data vs. cluster 2.

‡One-way ANOVA for comparison of continuous data across all three groups.

4.5 Discussion

We have established the feasibility of subgrouping beyond conventional measures of disease location, phenotype, and disease activity in a large, well-characterised, cohort of patients with IBD. Furthermore, we examined the effects of cluster membership on disease outcomes and healthcare utilisation. To the best of our knowledge, this is the first study to do so in IBD. We identified three unique clusters, each with distinct characteristics, derived from a combination of gastrointestinal symptoms and psychological symptoms at baseline, including anxiety, depression, and somatoform symptom-reporting. Cluster 1 was characterised by below average gastrointestinal and psychological symptoms at baseline, cluster 2 by average levels of gastrointestinal symptoms and psychological symptoms at baseline, and cluster 3 by the highest levels of both gastrointestinal and psychological symptoms at baseline. Among these, members of cluster 3 were most likely to report increased stool frequency and stomach pain and to have undergone previous intestinal resection. However, there were no other significant differences in disease characteristics or activity between the clusters at baseline, including FC levels in a subset of patients. Disease outcomes and healthcare utilisation were significantly impacted by cluster membership; over 80% of all disease endpoints occurring amongst members of clusters 2 and 3, both with a higher gastrointestinal symptom burden. However, cluster 3, the cluster with the highest psychological symptom burden, had both the greatest proportion of patients with each of the disease endpoints and the highest levels of healthcare utilisation. After controlling for all baseline data, membership of cluster 3 was associated with a significantly higher risk of disease flare or glucocorticosteroid prescription, treatment escalation, a composite of escalation, hospitalisation, or resection, and of reaching any of the adverse disease outcomes of interest, compared with cluster 1. The strength of these associations increased further when only patients in biochemical remission at baseline were considered in the analysis.

Being the sole provider of care to these patients, together with the use of electronic records, means the likelihood that the endpoints of interest have been captured accurately during the study period is maximised. These patients were seen in secondary care and are, therefore, likely to be generalisable to many other patients with IBD in the UK healthcare system. Our inclusion of multiple measures of IBD activity at baseline, some of which are less likely to be subject to over-reporting by participants, and blinding the assessor to baseline data, enabled an objective assessment of adverse disease outcomes and markers of healthcare utilisation during longitudinal follow up. Use of multivariate Cox regression, controlling for other baseline data, ensured that any associations observed relating to these outcomes are likely to be independent. It has been suggested that disease activity indices based on symptoms, such as the HBI and SCCAI, are subject to over-reporting in patients with somatoform behaviour.[9] Therefore, in addition to our primary analyses, we used FC as a marker of activity in a subset of patients, to compare the effects of cluster membership amongst only patients in biochemical remission at baseline, which further strengthens our findings.

We did not validate the LCA model externally on another dataset and the three-cluster solution may, therefore, not perform as well when applied to other cohorts. As the study ran alongside routine clinical care, study participants were treated by several physicians with potentially different interpretations of patient-reported symptoms and, thus, some of the more subjective endpoints may be subject to inter-observer variation. For similar reasons, we could not mandate endoscopic assessment at baseline in all patients, hence our attempt to collect a baseline FC sample from patients. Only half of patients provided this, which may impact the reliability of analyses in this group, particularly for less frequent outcomes. Although we used an FC <250mcg/g to define biochemical remission, in line with international consensus, we accept that this cut off has a lower sensitivity for active disease than lower thresholds and

may, therefore, overestimate the proportion of patients in remission.[26, 31] Additionally, despite all electronic patient records being reviewed by a single assessor, blinded to baseline data, health records could contain documentation relating to a previous common mental disorder or co-existing functional disorder. We were unable to remove this potential element of bias when assessing endpoints. We hypothesised that membership of a cluster with a higher psychological symptom burden would be associated with worse disease outcomes, but the rate of hospitalisation or intestinal resection, although numerically higher in cluster 3, were not significantly different from cluster 1. This could relate to a lack of power to detect these rarer endpoints. Finally, the study was not an inception cohort, so we cannot exclude the possibility that those in cluster 3 already had experienced a worse disease course and, therefore, had higher levels of psychological symptoms as a result. This may mean that the association between higher levels of psychological symptoms and adverse disease outcomes is due to confounding and, in truth, relates to a more aggressive disease course to the point of study enrolment.

Psychological co-morbidity is highly prevalent alongside other chronic diseases, and distinct subgroups of patients, including one or more characterised by an increased psychological symptom burden, have been identified in cohorts of patients with multiple sclerosis,[32] breast cancer,[33] and heart failure.[34] However, to our knowledge, only one other group have attempted to incorporate measures of psychological health to establish the presence of such clusters in patients with IBD.[18] In this study, three of the clusters mirrored the symptom profiles we observed. However, Conley *et al.* identified the presence of a fourth cluster characterised by low levels of gastrointestinal symptoms and high levels of psychological symptoms. These variations in the number and specific characteristics of the clusters are, of course, inevitable when different variables are used to generate the model and underscore the importance of scrutinizing which are used. It is important to point out that

stool frequency, which is regarded as a fundamental symptom of IBD, was not one of the variables used in the study by Conley *et al*. Despite the differences in the number and specific characteristics of the clusters, baseline characteristics of the clusters in our study were comparable with those of the corresponding clusters, with females and tobacco users being more likely to belong to a cluster with the highest psychological symptom burden. This is perhaps not surprising, given that female sex is consistently associated with higher levels of psychological co-morbidity in IBD,[12] and tobacco use is linked with worsening disease outcomes in CD,[35] which in our study had the highest association with membership to cluster 3.

With a mean follow up duration of 6.5 years, we have been able to capture several measures of healthcare utilisation and demonstrate that model-based clustering can be used to identify subgroups of patients with IBD who are likely to be higher utilisers of healthcare, in addition to being more likely to experience adverse disease outcomes. Furthermore, membership of cluster 3, with the highest gastrointestinal and psychological symptom burden, was associated with the greatest healthcare utilisation, and increased frequency of adverse disease outcomes, despite an FC at baseline similar to that of individuals in clusters 1 and 2. This work, therefore, adds to an expanding body of evidence that psychological co-morbidity is a fundamental influence on disease activity in IBD,[36, 37] and a major contributor to healthcare utilisation.[13, 37-39]

Previous research has suggested that the presence of symptoms of anxiety or depression in patients with IBD may be more detrimental to the natural history of the disease than mucosal inflammation.[38] In the present study, those in cluster 3, who had the highest gastrointestinal and psychological symptom burden, including extraintestinal symptom-reporting, had higher rates of all the endpoints of interest, and a significantly higher rate of composites of these endpoints, as well as higher healthcare utilisation. The magnitude of

these associations increased when only those with an FC <250mcg/g were included in the analyses. Despite this, psychological health is not considered a treatment target in IBD,[40] and access to psychological services for many patients with IBD remains limited.[41, 42] Some studies have demonstrated that addressing psychological health in routine care reduces emergency department visits, hospitalisations, and glucocorticosteroids prescriptions in patients with IBD.[36, 37, 39] A previous meta-analysis of randomised controlled trials found that psychological therapies produced short-term improvements in anxiety, depression, and quality of life scores in IBD.[43] However, any benefit during subsequent follow-up was observed only for depression scores. In a meta-analysis of observational studies, including over 30,000 patients with IBD, the prevalence of mood disorders was highest during times of disease activity,[12] yet most trials examining the effect of psychological therapies in IBD have been conducted in unselected patients with quiescent disease and no psychological co-morbidity.[43]

With finite funding and resources available, effective integration of psychological care in routine IBD practice is not possible without clear guidance to direct physicians as to how to screen for psychological co-morbidities, and which patients to select for psychological therapies. The clusters we observed may serve to detect patients with a high gastrointestinal and psychological symptom burden, who are more likely to experience a poor prognosis and who are high volume users of medical care. Application of the clusters in clinical practice could, therefore, serve to identify not only patients more likely to experience an aggressive disease course in whom early intervention with immunosuppressants or biologics may be warranted, but also patients whose natural history is more likely to be indolent, and who could have therapy de-escalated or be followed up less frequently in outpatient clinic. However, as this was not an inception cohort, this is somewhat speculative. The former group of individuals could represent a population in whom psychological

therapies may be effective. Future research should first look to establish the external validity of the clusters we describe in different cohorts of patients with IBD and, if replicated, prospective trials could then compare psychological therapies with usual care to assess if cluster membership can be used to predict response.

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Supplementary Table 4.1. Baseline Variables Used in the Latent Class Analysis.

Measurement	Variable	Scale Used	Rationale for Inclusion
IBD activity at baseline (simple clinical colitis activity index for UC/Harvey-Bradshaw index for CD)	Stool frequency	0 – One to three times per day 1 – Four to six times per day 2 – Seven to nine times per day 3 – More than 10 times per day	The Harvey-Bradshaw index for CD, and simple clinical colitis activity index for UC, are validated scoring tools used to assess IBD activity clinically. As both CD and UC were included in this study, only the parameters which are included in both scoring tools were used. Abdominal pain is not captured by the simple clinical colitis activity index, so we used the stomach pain question from the PHQ-15.
	Extracolonic features (IBD-associated conditions)	0 – None 1 – One feature 2 – Two features 3 – Three features	
	General wellbeing	0 – Very well 1 – Below par 2 – Poor 3 – Very poor 4 – Terrible	
Mood disorder at baseline (hospital anxiety and depression scale)	Anxiety or depression	0 – Normal (score 0 – 7) 1 – Borderline abnormal (score 8 – 10) 2 – Abnormal (score ≥11)	The hospital anxiety and depression scale is a validated tool for measuring anxiety and depression. In both categories scores of 0-7 normal, 8-10 borderline abnormal, and ≥11 abnormal. Studies have demonstrated the bidirectional effects of the gut brain axis, and mood disorders may affect the natural history of IBD.
Somatoform-symptom reporting at baseline (patient health questionnaire-15)	Stomach pain Back pain Arm, leg, or joint pain Headaches Chest pain Dizziness Fainting spells Heart pounding/racing Shortness of breath Pain/problems during intercourse Feeling tired or low in energy Trouble sleeping	0 – Never 1 – A little 2 – A lot	Somatoform-symptom reporting is associated with disorders of gut-brain interaction (DGBI), including irritable bowel syndrome. Up to one quarter of patients with IBD who are in remission, have symptoms compatible with a DGBI. The patient health questionnaire-15 is a validated tool used to measure somatoform-symptom reporting levels in patients with chronic medical conditions.

Supplementary Table 4.2. Comparison of Those Included in the Latent Class Analysis Compared with Those Not Included.

	Included in the Latent Class Analysis Model (n = 692)	Not Included in the Latent Class Analysis Model (n = 68)	*p* value*
Mean age in years at baseline (SD)	43.6 (16.7)	49.0 (17.4)	0.010
Female sex (%)	382 (55.2)	39 (57.4)	0.73
Married or co-habiting (%)	424 (61.6)	32 (49.2)	0.051
University graduate/professional (%)	197 (28.7)	11 (17.5)	0.056
Tobacco user (%)	116 (16.8)	15 (22.7)	0.23
Alcohol user (%)	451 (65.5)	45 (66.2)	0.91
CD (%)	394 (56.9)	45 (66.2)	0.14
CD location (%)			
Ileal	86 (21.8)	11 (24.4)	
Colonic	112 (28.4)	16 (35.6)	
Ileocolonic	196 (49.7)	18 (40.0)	0.45
Non-stricturing, non-penetrating CD (%)	324 (82.2)	39 (86.7)	0.68
Perianal CD (%)	37 (9.4)	6 (13.3)	0.40
UC extent (%)			
Proctitis	71 (23.8)	6 (26.1)	
Left-sided	137 (46.0)	10 (43.5)	
Extensive	90 (30.2)	7 (30.4)	0.96
5-ASA use (%)	326 (47.1)	34 (50.0)	0.65
Immunomodulator use (%)	249 (36.0)	18 (26.5)	0.12
Anti-TNFα use (%)	128 (18.5)	14 (20.6)	0.67
Glucocorticosteroid use (%)	76 (11.0)	5 (7.4)	0.36
Previous intestinal resection (%)	141 (20.4)	21 (30.9)	0.04
FC <250mcg/g at baseline (%)	211 (60.6)	20 (54.1)	0.44

Supplementary Table 4.3. Clinical Outcomes of Patients in Biochemical Remission (FC <250mcg/g) According to Cluster at Baseline.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms (n = 43)	Cluster 2: Average levels of gastrointestinal and psychological symptoms (n = 99)	*p* value*	Cluster 3: Highest levels of gastrointestinal and psychological symptoms (n = 60)	*p* value*	*p* value†
Multivariate HR for glucocorticosteroids/flare (95% CI)	1.00 (reference)	2.43 (1.28 – 4.62)	0.007	3.63 (1.83 – 7.22)	<0.001	0.001
Multivariate HR for escalation (95% CI)	1.00 (reference)	2.87 (1.48 – 5.58)	0.002	3.48 (1.69 – 7.19)	0.001	0.002
Multivariate HR for hospitalisation (95% CI)	1.00 (reference)	3.69 (0.83 – 16.5)	0.088	3.67 (0.76 – 17.8)	0.11	0.22
Multivariate HR for intestinal resection (95% CI)	1.00 (reference)	2.64 (0.31 – 22.7)	0.38	2.33 (0.23 – 23.6)	0.48	0.68
Multivariate HR for escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	2.74 (1.41 – 5.31)	0.003	3.87 (1.90 – 7.88)	<0.001	0.001
Multivariate HR for glucocorticosteroids/flare, escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	2.40 (1.29 – 4.46)	0.005	3.94 (2.02 – 7.69)	<0.001	<0.001

*For comparison of hazard ratios with cluster 1.

†For comparison of hazard ratios across all three groups.

Table 4.4. Clinical Outcomes of Patients with Crohn's Disease According to Cluster at Baseline.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms (n = 66)	**Cluster 2: Average levels of gastrointestinal and psychological symptoms (n =183)**	***p* value ***	**Cluster 3: Highest levels of gastrointestinal and psychological symptoms (n = 128)**	***p* value***	***p* value †**
Multivariate HR for glucocorticosteroids/flare (95% CI)	1.00 (reference)	1.39 (0.88 – 2.19)	0.16	2.30 (1.38 – 3.85)	0.002	0.003
Multivariate HR for escalation (95% CI)	1.00 (reference)	1.43 (0.94 – 2.16)	0.094	1.62 (1.01 – 2.59)	0.046	0.13
Multivariate HR for hospitalisation (95% CI)	1.00 (reference)	1.18 (0.63 – 2.22)	0.60	1.73 (0.89 – 3.35)	0.11	0.14
Multivariate HR for intestinal resection (95% CI)	1.00 (reference)	0.88 (0.40 – 1.94)	0.75	1.37 (0.59 – 3.18)	0.47	0.35
Multivariate HR for escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	1.44 (0.96 – 2.16)	0.076	1.93 (1.23 – 3.02)	0.004	0.016
Multivariate HR for glucocorticosteroids/flare, escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	1.44 (0.96 – 2.16)	0.075	1.96 (1.23 – 3.11)	0.004	0.017

*For comparison of hazard ratios with cluster 1.

†For comparison of hazard ratios across all three groups.

Supplementary Table 4.5. Clinical Outcomes of Patients with Ulcerative Colitis According to Cluster at Baseline.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms (n = 63)	**Cluster 2: Average levels of gastrointestinal and psychological symptoms (n = 148)**	***p* value***	**Cluster 3: Highest levels of gastrointestinal and psychological symptoms (n = 71)**	***p* value***	***p* value†**
Multivariate HR for glucocorticosteroids/flare (95% CI)	1.00 (reference)	1.57 (0.94 – 2.63)	0.83	1.90 (1.05 – 3.44)	0.035	0.099
Multivariate HR for escalation (95% CI)	1.00 (reference)	1.87 (1.12 – 3.12)	0.017	2.37 (1.33 – 4.23)	0.004	0.013
Multivariate HR for hospitalisation (95% CI)	1.00 (reference)	0.89 (0.42 – 1.89)	0.76	1.32 (0.59 – 2.95)	0.50	0.49
Multivariate HR for intestinal resection (95% CI)	1.00 (reference)	2.17 (0.42 – 11.2)	0.36	3.54 (0.68 – 18.3)	0.13	0.30
Multivariate HR for escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	1.66 (1.02 – 2.70)	0.043	2.29 (1.32 – 4.00)	0.003	0.014
Multivariate HR for glucocorticosteroids/flare, escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	1.47 (0.89 – 2.42)	0.13	2.29 (1.28 – 4.08)	0.005	0.019

*For comparison of hazard ratios with cluster 1.

†For comparison of hazard ratios across all three groups.

Chapter 5: Cumulative Impact of Clinical Disease Activity, Biochemical Activity, and Psychological Health on the Natural History of Inflammatory Bowel Disease During 8 Years of Longitudinal Follow-up.

5.1 Summary

Background: Common mental disorders, including anxiety and depression, are prevalent in patients with inflammatory bowel disease (IBD), and may be associated with adverse outcomes. However, whether increasing psychological co-morbidity, in combination with disease activity, exerts a cumulative effect on prognosis is uncertain.

Aims: To assess this in a longitudinal follow-up study.

Methods: We collected baseline demographic and IBD-related information, clinical activity using disease activity scores, and biochemical activity using calprotectin. Patients were grouped according to presence or absence of disease activity. Patients in remission or with active disease were sub grouped according to presence or absence of symptoms of a common mental disorder at baseline. We recorded occurrence of adverse outcomes over 8.1 years, comparing their occurrence across subgroups using Cox regression.

Results: Among 717 participants with clinical activity data and 187 with clinical and biochemical activity data, rates of adverse outcomes increased with both disease activity and increasing psychological co-morbidity. Rates of flare or glucocorticosteroid prescription, escalation, or death were higher with clinical activity (HR 2.89; 95% CI 1.68-4.93 and 2.52; 95% CI 1.55-4.10, and 6.97; 95% CI 2.43-20.0, respectively) or clinical and biochemical activity (HR 7.26; 95% CI 2.86-18.5, 3.62; 95% CI 1.59-8.25, and 57.3; 95% CI 7.58-433, respectively) and two common mental disorders. Rates of hospitalisation (HR 6.20; 95% CI 1.88-20.4) or hospitalisation and/or intestinal resection (HR 7.46; 95% CI 2.41-23.2) were higher with clinical and biochemical activity and two common mental disorders.

Conclusion: Psychological co-morbidity and active disease have a cumulative adverse impact on IBD prognosis.

5.2 Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic immune mediated disorders of the gastrointestinal tract, collectively termed inflammatory bowel disease (IBD). Mucosal inflammation, the hallmark of disease activity, is associated with debilitating symptoms, loss of work productivity, and significant morbidity.[1,2] Prompt recognition and treatment of inflammatory activity is, therefore, the cornerstone of current treatment.[3] The development of advanced medical therapies and cost effective non-invasive biomarkers, such as faecal calprotectin (FC), coincide with a reduction in the frequency of IBD-related surgeries in Western populations, despite an overall rise in prevalence of IBD throughout the last two decades.[4,5] However, although the inflammatory burden is of paramount importance in IBD, substantial healthcare utilisation and high out-of-pocket expenses incurred by patients continue to contribute to an increasing socioeconomic burden.[6-10] In light of the aforementioned developments to improve management of inflammatory aspects of the disease, this suggests other factors influence the natural history of IBD.

Adverse psychological health influences disease outcomes and healthcare utilisation negatively in the context of chronic illness, including chronic obstructive pulmonary disease, ischaemic heart disease, and type 2 diabetes.[11-13] Similar effects are apparent in IBD, with symptoms of a common mental disorder, such as anxiety or depression, associated with future disease flares, escalation of medical therapy, hospitalisation, IBD-related surgeries, and an attenuated response to biologics.[14-18] Psychological health also appears to be a driver of increased healthcare utilisation,[19-23] with a Crohn's and Colitis Foundation initiative highlighting that patients with IBD and one or more co-existing common mental disorders generate double the annual healthcare costs of patients without co-existing common mental disorders.[23] Of particular relevance, the prevalence of common mental disorders in IBD is significantly higher than in the general population.[24] One-quarter of patients experience

symptoms of depression, and almost one-third symptoms of anxiety, which increase further during periods of disease activity, affecting almost 50% of patients.[25]

In ischaemic heart disease, psychological stress influences the development of myocardial ischaemia to a similar magnitude to conventional exercise-induced stress, with the two exerting a cumulative effect.[13] This suggests psychological health may be of equal importance to physical factors in the context of chronic disease. Given the proportion of patients with IBD exhibiting symptoms of a common mental disorder, these findings bring in to question the lack of consensus regarding their identification and appropriate management in routine care.[26] However, a meta-analysis of over 9000 patients with IBD demonstrated that gut-brain interactions in IBD are bi-directional.[19] This highlights an inherent deficit in existing research examining brain-gut effects; failure to consider co-existent inflammatory burden, which could be the true driver of adverse disease outcomes in these patients.[14-17]

To date, only one study, to our knowledge, has considered the influence of psychological health in conjunction with inflammatory burden.[27] This reported a cumulative impact of co-existent poor psychological health and active disease on adverse disease outcomes in IBD, including flare, escalation of medical therapy, and mortality. The strength of these associations was similar when disease activity was confirmed biochemically, suggesting genuine brain-gut effects on the natural history of IBD. A cumulative impact on rarer, but more objective, adverse disease outcomes, including hospitalisation or intestinal resection, was not shown, and a longer duration of follow-up may be required to assess this. Furthermore, whether increasing psychological co-morbidity, in combination with disease activity, exerts a cumulative effect on adverse disease outcomes is uncertain We, therefore, examined this issue in a large cohort of patients with established IBD during an average of 8 years of follow-up.

5.3 Methods

5.3.1 Participants and Setting

Consecutive patients with an established diagnosis of CD or UC based on endoscopic, histological, or radiological findings were invited to participate in a cross-sectional survey conducted at Leeds Teaching Hospitals NHS Trust between November 2012 and June 2015.[28] Because participation required completion of a baseline questionnaire, patients who were unable to understand written English were excluded. Due to a lack of reliable scoring tools to assess clinical disease activity amongst patients with IBD-unclassified, end ileostomies, or colostomies, these individuals were also excluded. Prospective longitudinal follow-up of all individuals was conducted between September 2014 and October 2023 (REC ref: 12/YH/0443/AM03). Study findings were reported in line with the STROBE guidelines.[29]

5.3.2 Data Collection and Synthesis

The date of study recruitment, type of IBD, and all IBD-related medications were recorded at baseline in addition to demographic data, including age, sex, and lifestyle factors. In addition, we collected data regarding psychological health, including the presence of symptoms of anxiety or depression using the hospital anxiety and depression scale (HADS), with a HADS-anxiety or HADS-depression score of ≥11 considered abnormal, as suggested by the original validation study.[30] Somatoform symptom-reporting was recorded via the patient health questionnaire-15 (PHQ-15).[31] We measured clinical disease activity at baseline using the Harvey-Bradshaw index (HBI) for CD,[32] and the simple clinical colitis activity index (SCCAI) for UC.[33] A score of <5 was used to define clinical remission in both, as has been suggested previously.[32,34] All participants were asked to provide a FC sample for analysis (Immundiagnostik, Blensheim, Germany), with biochemical remission defined as a

FC of <100mcg/g of stool, as supported by international consensus,[35] in our main analysis. However, we also used a FC of <250mcg/g in a sensitivity analysis.

Participants' medical records were reviewed by two investigators (KMF and CR), both of whom were blinded to baseline questionnaire data to enable objective assessment of disease activity, during longitudinal follow-up. The following adverse disease outcomes, along with their date of occurrence, were collected: flare of disease activity, based on a physician's global assessment, or a prescription for glucocorticosteroids; escalation of medical therapy due to uncontrolled IBD activity, hospitalisation due to uncontrolled IBD activity; intestinal resection due to uncontrolled IBD activity; a composite of either hospitalisation or intestinal resection due to uncontrolled IBD activity (using the first of these events to occur to calculate the time to event); and death. Outcomes occurring within 30 days of recruitment were excluded, to minimise any potential association between presence of a common mental disorder or disease activity at baseline and an impending adverse disease outcome. Alterations made to medical therapy without evidence of uncontrolled IBD activity (e.g., changes made as the result of therapeutic drug monitoring), or surgery for isolated perianal CD, were not included as endpoints. Given the duration of follow-up in the study, it is entirely possible that patients were either lost to follow-up or moved region and had the care of their IBD taken over by another centre. In these instances, if the event(s) of interest had already occurred this did not present any issues. However, where the event(s) of interest had not occurred at the point the patient was lost to follow-up they were censored, with the event categorised as having not occurred, at the last point of follow-up in our clinic.

5.3.3 Statistical Analysis

Individuals were classified at baseline according to both clinical disease activity and psychological health. Participants were categorised in to one of five groups: clinical

remission (HBI or SCCAI <5) without symptoms of a common mental disorder (HADS-anxiety and HADS-depression score <11), clinical remission with symptoms of a common mental disorder (HADS-anxiety or HADS-depression score ≥11), clinical activity (HBI or SCCAI ≥5) without symptoms of a common mental disorder, clinical activity with symptoms of one common mental disorder (HADS-anxiety or HADS-depression score ≥11), or clinical activity with symptoms of two common mental disorders (HADS-anxiety and HADS-depression score ≥11). This exercise was then repeated for the subgroup of patients who provided a baseline FC sample to create a further five groups: combined clinical and biochemical remission (FC <100mcg/g) without symptoms of a common mental disorder, combined clinical and biochemical remission with symptoms of a common mental disorder, combined clinical and biochemical activity (FC ≥100mcg/g) without symptoms of a common mental disorder, combined clinical and biochemical activity with symptoms of one common mental disorder, and finally combined clinical and biochemical activity with symptoms of two common mental disorders. For these analyses those with any discrepancy between clinical and biochemical data (e.g., clinical remission but biochemical activity) were excluded from the analysis. We performed a sensitivity analysis with a FC of <250mcg/g used to define biochemical remission and ≥250mcg/g used to define biochemical activity.

To assess the impact of baseline clinical or biochemical activity and symptoms of a common mental disorder on disease outcomes we compared the rates of each of the adverse disease outcomes of interest (flare of disease activity or glucocorticosteroid prescription, escalation of therapy, hospitalisation, intestinal resection, a composite of the two most stringent adverse disease outcomes including only hospitalisation or intestinal resection, or death) between the five groups using a χ^2 test during longitudinal follow-up. Multivariate Cox regression analysis, controlling for all baseline characteristics including age, sex, marital status, tobacco and alcohol intake, educational level, type of IBD, IBD-related medications,

and level of somatoform symptom-reporting according to the PHQ-15, was performed to identify independent predictors of each of the adverse disease outcomes of interest. A 2-tailed *P*-value of <0.01 was considered statistically significant due to multiple comparisons. Results were expressed as hazard ratios (HR) with a 95% confidence interval (CI). SPSS for Windows version 29.0 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses.

5.4 Results

A total of 760 individuals were recruited, with 717 (94.3%) providing complete clinical activity data at baseline (mean age at baseline 44.0 years, 395 (55.1%) female, 411 (57.3%) CD). A total of 384 (50.5%) of the 760 patients provided a baseline FC measurement, of whom 187 (26.1%) were either in clinical and biochemical remission or had clinical and biochemical activity at baseline (mean age at baseline 49.8 years, 104 (55.6%) female, 96 (51.3%) CD) using an FC of <100mcg/g. Using an FC of <250mcg/g, 205 (27.0%) patients were either in clinical and biochemical remission or had clinical and biochemical activity at baseline. For the 717 patients providing complete clinical activity data at baseline, the number with longitudinal follow-up data ranged from 565 (78.8%) for flare of disease activity or need for glucocorticosteroids to 702 (97.9%) for death, with a mean follow-up in all patients of 8.1 years. Patients with both clinical disease activity and increasing psychological co-morbidity were significantly less likely to consume alcohol and significantly more likely to report high levels of somatoform symptom-reporting (Table 5.1). The remaining baseline characteristics were similar between groups, including type of IBD, IBD-related medication use, and location, behaviour, or extent of disease. Among 187 patients providing a baseline FC and being in clinical and biochemical remission or having clinical and biochemical activity at baseline, the number with longitudinal follow-up data ranged from 148 (79.1%) for flare of disease activity or need for glucocorticosteroids to 182 (97.3%) for death, with a mean follow-up in all patients of 8.3 years. Patients with combined clinical and biochemical activity and increasing psychological co-morbidity were significantly more likely to smoke tobacco and report high levels of somatoform symptoms (Supplementary Table 5.1).

Table 5.1. Baseline Patient Characteristics According to Both Clinical Disease Activity and Symptoms of a Common Mental Disorder at Baseline.

	Clinical Remission		**Clinical Activity**			
	No symptoms of a common mental disorder (n=338)	**Symptoms of a common mental disorder (n=85)**	**No symptoms of a common mental disorder (n=172)**	**Symptoms of a common mental disorder (n=73)**	**Symptoms of two common mental disorders (n=49)**	***P* value***
Mean age (SD)	45.6 (18.3)	43.5 (15.1)	43.4 (15.7)	39.6 (13.4)	42.5 (15.7)	0.12
Female sex (%)	166 (49.1)	48 (56.5)	102 (59.3)	47 (64.4)	32 (65.3)	0.029
Married or cohabiting (%)	206 (61.3)	50 (60.2)	109 (64.1)	47 (64.4)	25 (51.0)	0.54
University graduate/ professional (%)	107 (32.0)	20 (24.1)	50 (29.2)	15 (20.5)	9 (18.4)	0.11
Tobacco user (%)	49 (14.5)	10 (12.0)	29 (16.9)	18 (25.0)	15 (30.6)	0.013
Alcohol user (%)	234 (69.2)	53 (63.1)	118 (69.0)	43 (59.7)	17 (34.7)	<0.001
CD (%)	183 (54.1)	50 (58.8)	104 (60.5)	42 (57.5)	32 (65.3)	0.49
CD location (%)						
Ileal (%)	37/183 (20.2)	11/50 (22.0)	20/104 (19.2)	14/42 (33.3)	9/32 (28.1)	
Colonic (%)	61/183 (33.3)	16/50 (32.0)	24/104 (23.1)	7/42 (16.7)	10/32 (31.3)	

Ileocolonic (%)	85/183 (46.4)	23/50 (46.0)	60/104 (57.7)	21/42 (50.0)	13/32 (40.6)	0.21
Non-stricturing, non-penetrating CD (%)	157/183 (85.8)	39/50 (78.0)	86/104 (82.7)	31/42 (73.8)	26/32 (81.3)	0.43
Perianal disease (%)	15/183 (8.2)	5/50 (10.0)	14/104 (13.5)	4/42 (9.5)	2/32 (6.3)	0.63
UC extent (%)						
Proctitis	36/155 (23.2)	12/35 (34.3)	14/68 (20.6)	8/31 (25.8)	3/17 (17.6)	
Left-sided	74/155 (47.7)	13/35 (37.1)	30/68 (44.1)	14/31 (45.2)	10/17 (58.8)	
Extensive	45/155 (29.0)	10/35 (28.6)	24/68 (35.3)	9/31 (29.0)	5/17 (23.5)	0.84
5-aminosalicylate use (%)	169 (50.0)	39 (45.9)	81 (47.1)	34 (46.6)	18 (36.7)	0.52
Immunomodulator use (%)	121 (35.8)	27 (31.8)	64 (37.2)	28 (38.4)	14 (28.6)	0.73
Biologic use (%)	68 (20.1)	18 (21.2)	30 (17.4)	12 (16.4)	6 (12.2)	0.63
Glucocorticosteroid use (%)	27 (8.0)	9 (10.6)	25 (14.5)	7 (9.6)	9 (1 8.4)	0.080
High levels of somatoform symptom-reporting on PHQ-15 (%)	15 (4.5)	19 (24.7)	35 (21.3)	37 (54.4)	29 (64.4)	<0.001
FC <100µg/g	83/182 (45.6)	16/44 (36.4)	31/77 (40.3)	7/34 (20.6)	12/27 (44.4)	0.092

*One-way analysis of variance for comparison of continuous data, χ^2 for comparison of categorical data across all four groups.

5.4.1 Flare of Disease Activity or Need for Glucocorticosteroid Prescription

A total of 306 (54.2%) of 565 patients experienced a flare of disease activity or required a prescription for glucocorticosteroids during a mean follow-up of 5.0 years in all 565 patients, with a median time to flare or glucocorticosteroid prescription of 1.8 years. Those with clinical activity at baseline and symptoms of one or two common mental disorders at baseline had the highest rates of flare or glucocorticosteroid prescription (60.4% and 78.1%, respectively, P=0.0070 for trend, Table 5.2). Following multivariate Cox regression, the likelihood of flare or glucocorticosteroid prescription was significantly higher in participants with symptoms of one or two common mental disorders at baseline (HR 2.06; 95% CI 1.30 to 3.26, P=0.0020, and HR 2.89; 95% CI 1.68 to 4.93, P<0.001, Table 5.2 and Figure 5.1a). Younger age (HR per year 0.98; 95% CI 0.97 to 0.99, P<0.001) was associated with a reduced likelihood, and UC (HR 1.55; 95% CI 1.12 to 2.15, P=0.0080) and glucocorticosteroid use at baseline (HR 1.93; 95% CI 1.26 to 2.96, P=0.0030) an increased likelihood, of flare or glucocorticosteroid prescription.

When only patients in clinical and biochemical remission or having clinical and biochemical activity at baseline were considered, 84 (56.8%) of 148 patients experienced a flare of disease activity or required a glucocorticosteroid prescription during a mean follow-up of 5.3 years. Again, patients with clinical and biochemical activity and symptoms of two common mental disorders at baseline had the highest rates of flare or glucocorticosteroid prescription (87.5%, P=0.0080 for trend, Table 5.3). After multivariate Cox regression, the likelihood of a flare of disease activity or receiving a prescription for glucocorticosteroids remained highest in participants with clinical and biochemical disease activity and symptoms of two common mental disorders at baseline (HR 7.26; 95% CI 2.86 to 18.5, P<0.001, Table 5.3 and Figure 5.1b), but the rate was also significantly higher in those with clinical and biochemical disease activity and no symptoms of a common mental disorder at baseline (HR

3.54; 95% CI 1.82 to 6.89, *P*<0.001) and those with clinical and biochemical disease activity and symptoms of one common mental disorder at baseline (HR 3.09; 1.39 to 6.87, *P*<0.01). Sensitivity analyses with a FC of <250mcg/g used to define biochemical remission and ≥250mcg/g to define biochemical activity are provided in Supplementary Table 5.2.

Figure 5.1a. Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity According to Clinical Disease Activity Status and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

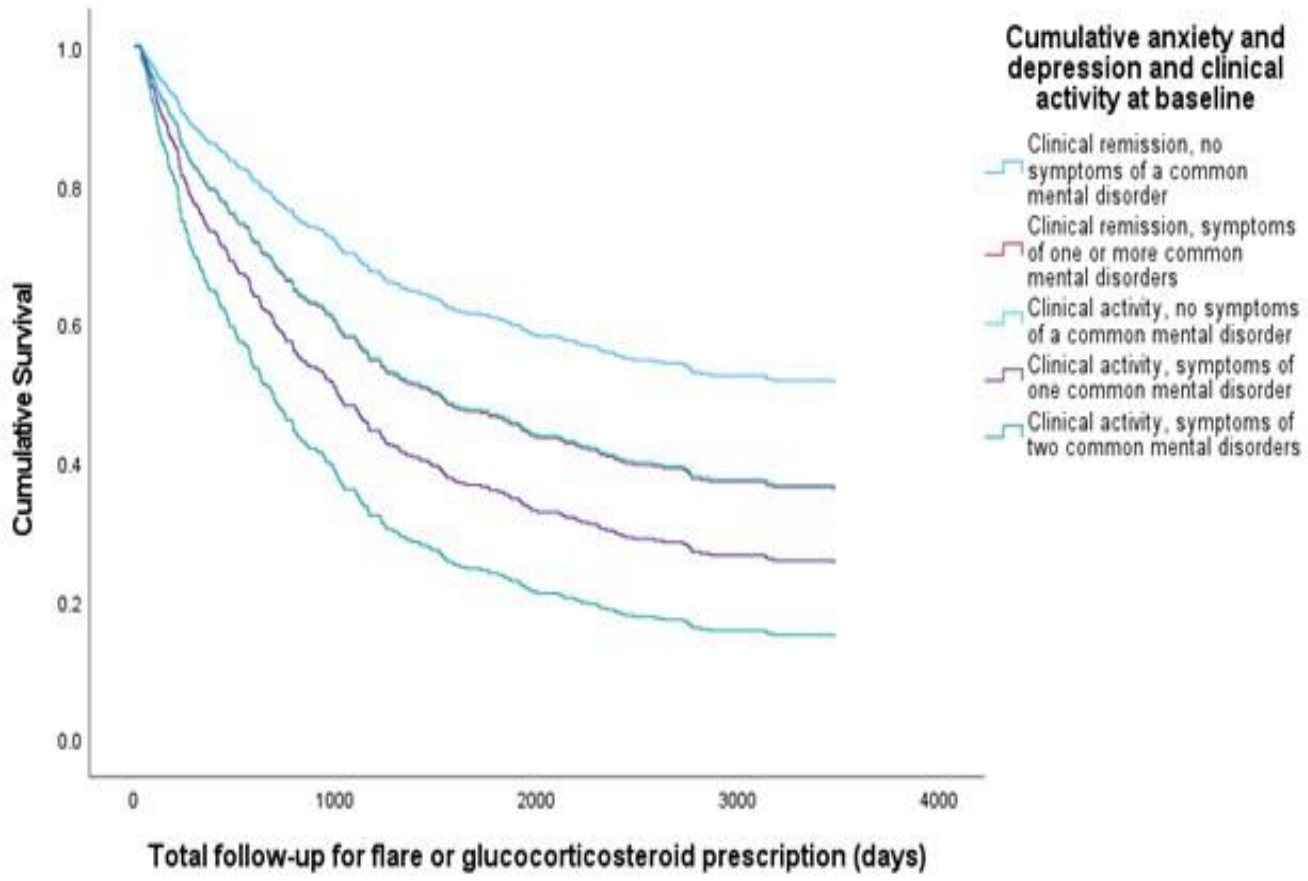


Table 5.2. Adverse Disease Outcomes in Patients According to Clinical Disease Activity Status and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Clinical Remission		Clinical Activity			
	No symptoms of a common mental disorder	**Symptoms of a common mental disorder**	**No symptoms of a common mental disorder**	**Symptoms of a common mental disorder**	**Symptoms of two common mental disorders**	***P* value**
Flare of disease activity or glucorticosteroid prescription (%)	145/298 (48.7)	45/75 (60.0)	59/110 (53.6)	32/50 (64.0)	25/32 (78.1)	0.0070*
Multivariate HR for flare of disease activity or glucorticosteroid prescription (95% CI)	1.00 (reference)	1.54 (1.06-2.23)	1.52 (1.10-2.10)	2.06 (1.30-3.26)†	2.89 (1.68-4.93)†	<0.001
Escalation of medical therapy due to uncontrolled IBD activity (%)	157/307 (51.1)	47/78 (60.3)	79/134 (59.0)	32/56 (57.1)	29/38 (76.3)	0.034*
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.43 (1.00-2.05)	1.45 (1.09-1.94)	1.33 (0.86-2.06)	2.52 (1.55-4.10)†	0.0020

Hospitalisation due to uncontrolled IBD activity (%)	67/326 (20.6)	26/82 (31.7)	44/168 (26.2)	25/69 (36.2)	17/43 (39.5)	0.0070*
Multivariate HR for hospitalisation due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.45 (0.86-2.42)	1.37 (0.92-2.05)	1.50 (0.88-2.56)	1.53 (0.82-2.83)	0.38
Intestinal resection due to uncontrolled IBD activity (%)	27/326 (8.3)	12/82 (14.6)	24/170 (14.1)	17/71 (23.9)	10/46 (21.7)	0.0020*
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.12 (0.48-2.63)	1.70 (0.94-3.07)	2.41 (1.17-4.97)	1.88 (0.84-4.22)	0.14
Hospitalisation or intestinal resection (%)	67/326 (20.6)	26/82 (31.7)	46/170 (27.1)	26/70 (37.1)	19/44 (43.2)	0.0020*
Multivariate HR for hospitalisation or intestinal resection (95% CI)	1.00 (reference)	1.47 (0.88-2.46)	1.40 (0.94-2.09)	1.57 (0.93-2.65)	1.79 (0.99-3.23)	0.22
Death (%)	34/331 (10.3)	6/82 (7.3)	6/170 (3.5)	3/71 (4.2)	8/48 (16.7)	0.011*
Multivariate HR for death (95% CI)	1.00 (reference)	1.58 (0.59-4.27)	0.60 (0.23-1.61)	2.11 (0.45-9.77)	6.97 (2.43-20.0)†	0.0030

*For comparison across all four groups.

†$P<0.001$ versus reference category.

Table 5.3. Adverse Disease Outcomes in Patients According to Combined Clinical and Biochemical Disease Activity Status, using an FC<100mcg/g or ≥100mcg/g, and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Combined clinical and biochemical remission		Combined clinical and biochemical activity			
	No symptoms of a common mental disorder	**Symptoms of a common mental disorder**	**No symptoms of a common mental disorder**	**Symptoms of a common mental disorder**	**Symptoms of two common mental disorders**	***P* value**
Flare of disease activity or glucorticosteroid prescription (%)	35/79 (44.3)	11/16 (68.8)	17/24 (70.8)	14/21 (66.7)	7/8 (87.5)	0.019*
Multivariate HR for flare of disease activity or glucorticosteroid prescription (95% CI)	1.00 (reference)	1.95 (0.93-4.07)	3.54 (1.82-6.89)‡	3.09 (1.39-6.87)†	7.26 (2.86-18.5)‡	<0.001
Escalation of medical therapy due to uncontrolled IBD activity (%)	36/79 (45.6)	10/16 (62.5)	25/31 (80.6)	13/21 (61.9)	8/10 (80.0)	0.0080*
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.51 (0.70-3.24)	3.82 (2.17-6.73)‡	1.93 (0.88-4.23)	3.62 (1.59-8.25)‡	<0.001
Hospitalisation due to uncontrolled IBD activity (%)	11/79 (13.9)	2/16 (12.5)	12/46 (26.1)	8/25 (32.0)	5/13 (38.5)	0.094*

Multivariate HR for hospitalisation due to uncontrolled IBD activity (95% CI)	1.00 (reference)	0.88 (0.19-4.18)	1.80 (0.72-4.50)	3.19 (1.12-9.09)	6.20 (1.88-20.4)†	0.027
Intestinal resection due to uncontrolled IBD activity (%)	2/79 (2.5)	0/16 (0.0)	6/46 (13.0)	5/25 (20.0)	3/15 (15.0)	0.013*
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	N/A	4.68 (0.88-24.9)	7.54 (1.14-51.0)	7.18 (0.92-56.2)	0.29
Hospitalisation or intestinal resection (%)	11/79 (13.9)	2/16 (12.5)	12/46 (26.1)	8/25 (32.0)	6/14 (42.9)	0.052*
Multivariate HR for hospitalisation or intestinal resection (95% CI)	1.00 (reference)	0.93 (0.20-4.40)	1.86 (0.74-4.65)	3.38 (1.19-9.58)	7.46 (2.41-23.2)‡	0.0080
Death (%)	11/80 (13.8)	0/16 (0.0)	2/46 (4.3)	2/25 (8.0)	4/15 (26.7)	0.061*
Multivariate HR for death (95% CI)	1.00 (reference)	N/A	0.83 (0.16-4.42)	33.6 (3.83-294)†	57.3 (7.58-433)‡	<0.001

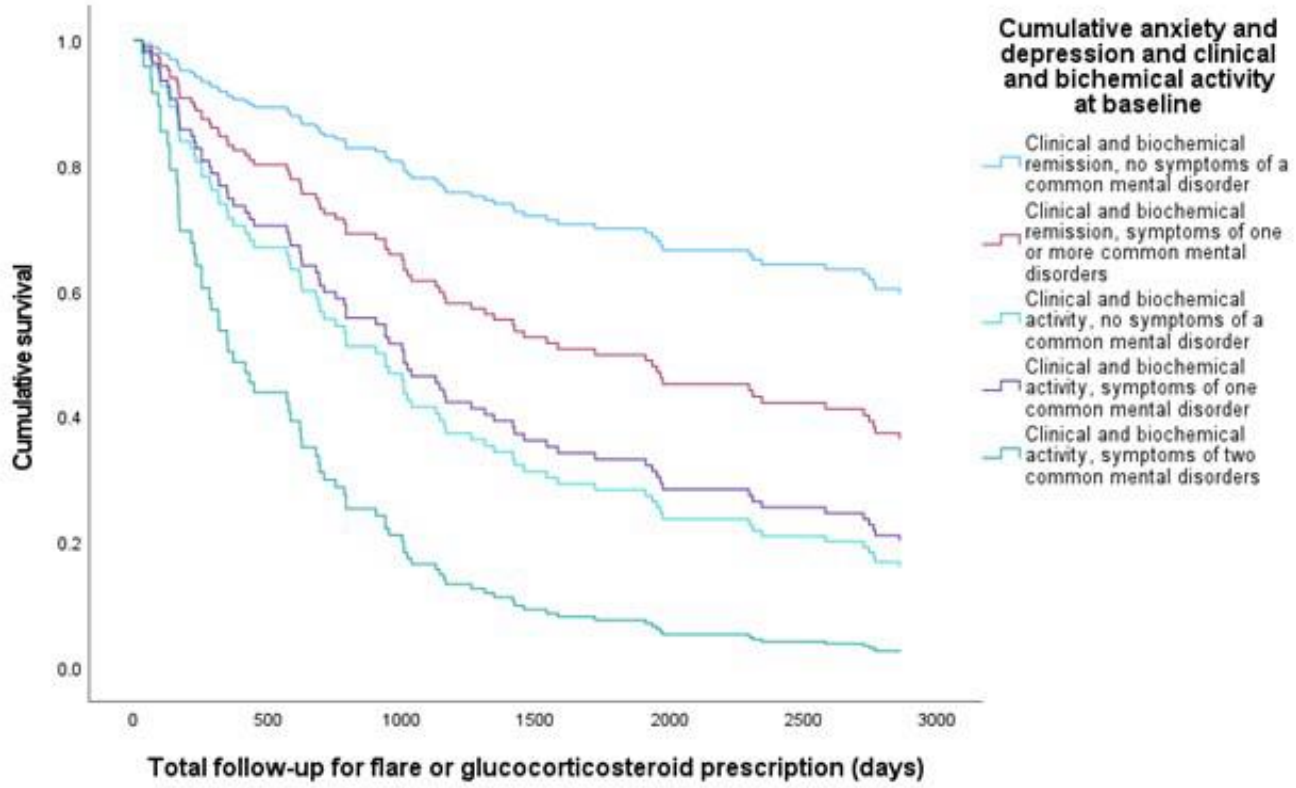
N/A; no events, HR not estimable.

*For comparison across all four groups.

†P<0.01 versus reference category.

‡P<0.001 versus reference category.

Figure 5.1b. Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity According to Combined Clinical and Biochemical Disease Activity Status and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.



5.4.2 Escalation of Medical Therapy due to Uncontrolled IBD Activity

A total of 344 (56.1%) of 613 patients required escalation of medical therapy due to uncontrolled IBD activity during a mean follow-up of 4.9 years in all 613 patients, with a median time to escalation of 1.6 years. Rates of escalation were highest (76.3%) in patients with clinical disease activity and symptoms of two common mental disorders at baseline (P=0.034 for trend, Table 5.2). After multivariate Cox regression, the likelihood of requiring escalation of medical therapy due to uncontrolled IBD activity was significantly higher in patients with clinical disease activity with symptoms of two common mental disorders at baseline (HR 2.52; 95% CI 1.55 to 4.10, P<0.001, Table 5.2 and Figure 5.2a). Younger age (HR per year 0.98; 95% CI 0.97 to 0.99, P<0.001) was associated with a reduced likelihood

of requiring escalation of medical therapy and baseline glucocorticosteroid use (HR 1.70; 95% CI 1.18 to 2.46, *P*=0.0040) an increased likelihood.

When only patients in clinical and biochemical remission or having clinical and biochemical activity at baseline were considered, 92 (58.6%) patients required escalation of medical therapy during a mean follow-up of 5.1 years in all 157 patients. Rates of escalation due to uncontrolled IBD activity during longitudinal follow-up were highest in those with clinical and biochemical disease activity and no symptoms of a common mental disorder and those with clinical and biochemical disease activity and symptoms of two common mental disorders (80.6% and 80.0%, respectively, Table 5.3 and Figure 5.2b). Following multivariate Cox regression, the likelihood of requiring escalation of medical therapy due to uncontrolled IBD activity remained significant in those with clinical and biochemical disease activity at baseline with no symptoms of a common mental disorder (HR 3.82; 95% CI 2.17 to 6.73, *P*<0.001, Table 5.3) and those with biochemical disease activity and symptoms of two common mental disorders (HR 3.62; 95% CI 1.59 to 8.25, *P*<0.001). Sensitivity analyses with a FC of <250mcg/g used to define biochemical remission and ≥250mcg/g to define biochemical activity are provided in Supplementary Table 5.2.

Figure 5.2a. Survival Analysis for Escalation of Medical Therapy Due to Uncontrolled IBD Activity According to Clinical Disease Activity Status and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

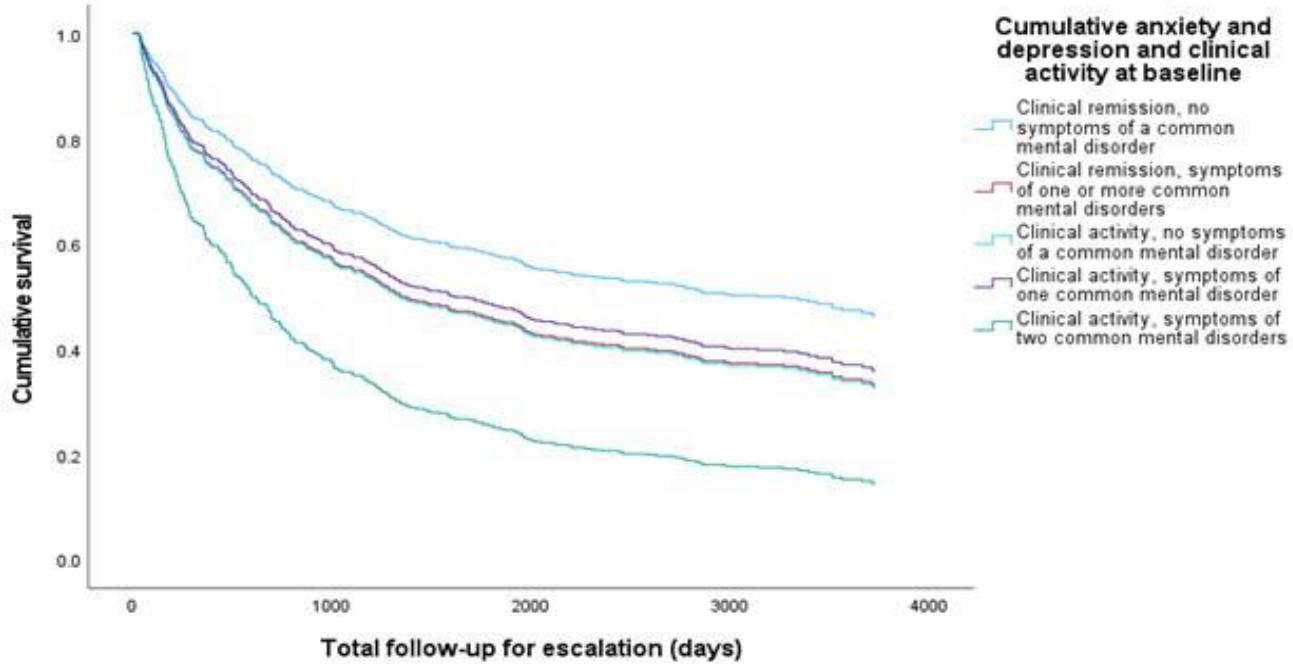
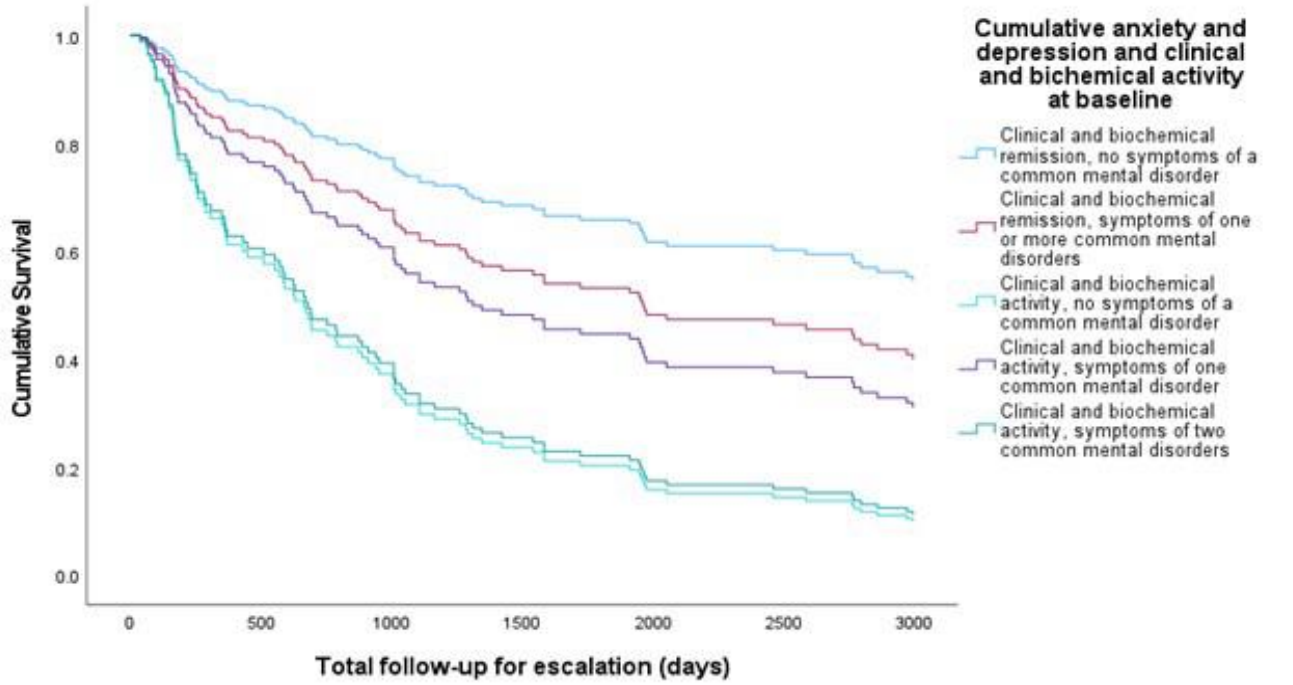


Figure 5.2b. Survival Analysis for Escalation of Medical Therapy Due to Uncontrolled IBD Activity According to Combined Clinical and Biochemical Disease Activity Status and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.



5.4.3 Hospitalisation Due to Uncontrolled IBD Activity

In total, 179 (26.0%) of 688 patients were hospitalised due to uncontrolled IBD activity during a mean follow-up of 7.0 years in all patients, with a median time to hospitalisation of 2.3 years. Rates of hospitalisation were significantly higher in those with clinical disease activity and symptoms of one or two common mental disorders at baseline (36.2% and 39.5%, respectively, $P<0.007$ for trend, Table 5.2). However, the likelihood of requiring hospitalisation was not significantly higher in any of the groups after multivariate Cox regression, although it remained highest in those with clinical disease activity and symptoms of one or two common mental disorders at baseline ($P=0.38$ for trend, Table 5.2). Younger age was associated with a reduced likelihood of hospitalisation (HR per year 0.98; 95% CI 0.97 to 0.99, $P<0.001$), as was alcohol consumption (HR 0.55; 95% CI 0.40 to 0.76, $P<0.001$), and 5-aminosalicylate use at baseline (HR 0.59; 95% CI 0.39 to 0.87, $P=0.0090$). Glucocorticosteroid use at baseline was associated with an increased likelihood of hospitalisation (HR 1.92; 95% CI 1.27 to 2.92, $P=0.0020$).

When only patients in clinical and biochemical remission or having clinical and biochemical activity at baseline were considered, 38 (21.2%) of 179 patients required hospitalisation during a mean follow-up of 7.5 years in all patients. Rates of hospitalisation due to uncontrolled IBD activity were highest in those with clinical and biochemical disease activity and symptoms of one (32.0%) or two (38.5%) common mental disorders (Table 5.3). Following multivariate Cox regression, the likelihood of requiring hospitalisation due to uncontrolled IBD activity was significantly higher only in patients with clinical and biochemical disease activity and symptoms of two common mental disorders at baseline (HR 6.20; 95% CI 1.88 to 20.4, $P=0.0030$). Sensitivity analyses with a FC of <250mcg/g used to define biochemical remission and ≥250mcg/g to define biochemical activity are provided in Supplementary Table 5.2.

5.4.4 Intestinal Resection Due to Uncontrolled IBD Activity

In total, 90 (12.9%) of 695 patients required intestinal resection due to uncontrolled IBD activity during a mean follow-up of 7.9 years in all patients, and a median time to intestinal resection of 2.5 years. Rates of intestinal resection were highest in patients with clinical activity and symptoms of one or two common mental disorders (23.9% and 21.7%, respectively, *P*=0.0020 for trend, Table 5.2). Following multivariate Cox regression, the likelihood of requiring intestinal resection due to uncontrolled IBD activity was not significantly different between the groups (*P*=0.14 for trend, Table 5.2). Glucocorticosteroid use was the only factor associated with an increased likelihood of requiring intestinal resection (HR 2.27; 95% CI 1.28 to 4.01, *P*=0.0050).

When only patients in clinical and biochemical remission or having clinical and biochemical activity at baseline were considered, 16 (8.8%) of 181 patients required intestinal resection during a mean follow-up of 8.3 years in all patients. Rates of intestinal resection were highest in patients with disease activity and symptoms of one or two common mental disorders (20.0% and 15.0%, respectively, Table 5.3). However, after multivariate Cox regression, the likelihood of requiring intestinal resection was not significantly different between the groups, although it remained highest in those with clinical disease activity and symptoms of one or two common mental disorders at baseline (*P*=0.29 for trend, Table 5.3). Sensitivity analyses with a FC of <250mcg/g used to define biochemical remission and ≥250mcg/g to define biochemical activity are provided in Supplementary Table 5.2.

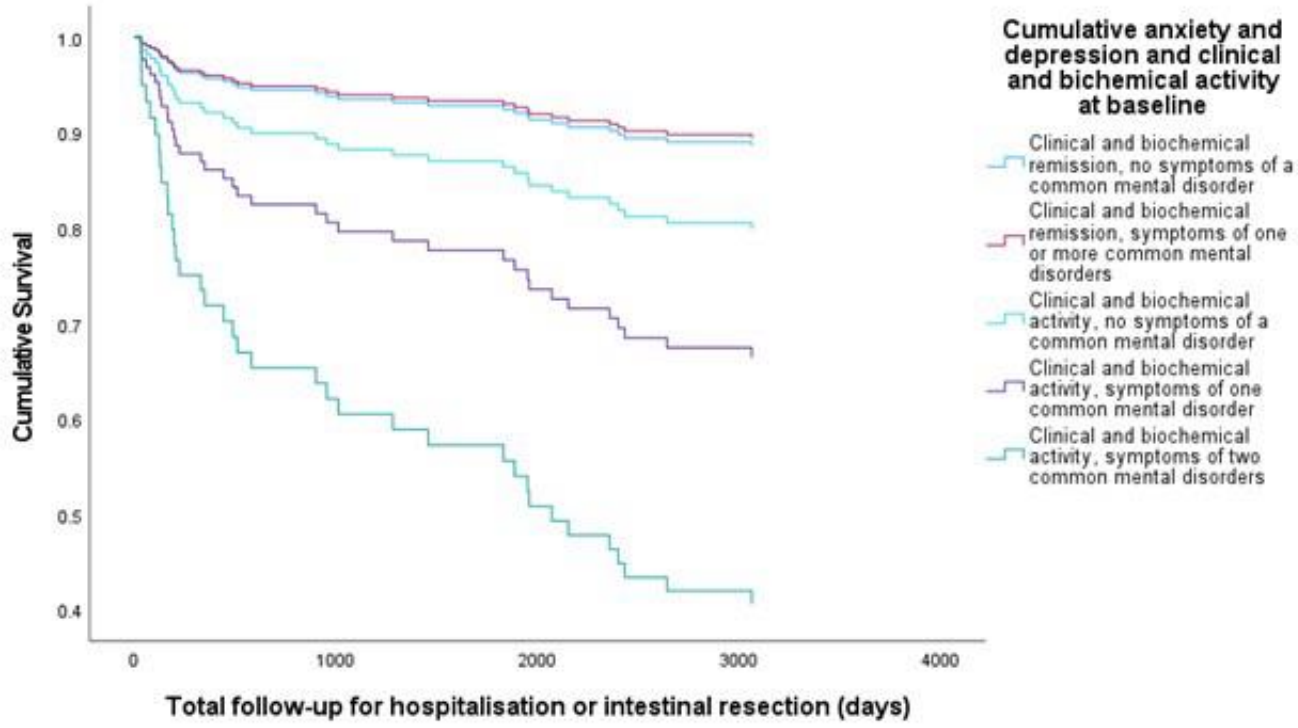
5.4.5 Hospitalisation or Intestinal Resection Due to Uncontrolled IBD Activity

In total 184 (26.6%) of 692 patients were hospitalised or required intestinal resection due to uncontrolled IBD activity during a mean follow-up of 7.0 years in all patients, with a median time to hospitalisation or intestinal resection of 2.3 years. Patients with clinical

disease activity and symptoms of one or two common mental disorders had the highest rates (37.1% and 43.2%, respectively, P=0.0020 for trend, Table 5.2). After multivariate Cox regression, however, there was no statistically significant difference between the groups, although the rate remained highest in those with clinical disease activity and symptoms of two common mental disorders (HR 1.79; 95% CI 0.99 to 3.23). Younger age (HR per year 0.98; 95% CI 0.97 to 0.99, P<0.001) alcohol consumption (HR 0.55; 95% CI 0.40 to 0.75, P<0.001), and 5-aminosalicylate use at baseline (HR 0.57; 95% CI 0.39 to 0.85, P=0.0060) were associated with a reduced likelihood of hospitalisation or intestinal resection, and glucocorticosteroid use at baseline (HR 1.99; 95% CI 1.32 to 2.99, P<0.001) an increased likelihood.

When only patients in clinical and biochemical remission or having clinical and biochemical activity at baseline were considered, 39 (21.7%) of a total of 180 patients were hospitalised or required intestinal resection due to uncontrolled IBD activity during a mean follow-up of 7.5 years in all patients. Rates were highest in patients with clinical and biochemical disease activity and symptoms of one or two common mental disorders (32.0% and 42.9%, respectively). Following multivariate Cox regression, patients with clinical and biochemical disease activity and symptoms of two common mental disorders were significantly more likely to require hospitalisation or intestinal resection due to uncontrolled IBD activity (HR 7.46; 95% CI 2.41 to 23.2, P<0.001) (Figure 5.3). Sensitivity analyses with a FC of <250mcg/g used to define biochemical remission and ≥250mcg/g to define biochemical activity are provided in Supplementary Table 5.2.

Figure 5.3. Survival Analysis for Hospitalisation or Intestinal Resection Due to Uncontrolled IBD Activity According to Combined Clinical and Biochemical Disease Activity Status and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.



5.4.6 All-cause Mortality

Of 702 patients, a total of 57 (8.1%) died during a mean longitudinal follow-up of 8.8 years in all patients, with a median time to death of 5.3 years. Patients with clinical activity and symptoms of two common mental disorders had the highest rates of death (16.7%), but this did not reach statistical significance (P=0.011 for trend, Table 5.2). However, following multivariate Cox regression, mortality rates were significantly higher in this group of patients (HR 6.97; 95% CI 2.43 to 20.0, P<0.001, Table 5.2). Increasing age was the only other baseline characteristic associated with an increased risk of death (HR per year 1.12; 95% CI 1.09 to 1.15, P<0.001).

When only patients in clinical and biochemical remission or having clinical and biochemical activity at baseline were considered, 19 (10.4%) of 182 patients died during a

mean longitudinal follow-up of 8.9 years in all patients. Mortality was highest in patients with clinical and biochemical disease activity and symptoms of two common mental disorders (26.7%), but this was not statistically significant (P=0.061 for trend, Table 5.3). However, after multivariate Cox regression, mortality was significantly higher in patients with clinical and biochemical disease activity and symptoms of either one (HR 33.6; 95% CI 3.83 to 294, P=0.0020, Table 5.3) or two common mental disorders (HR 57.3; 95% CI 7.58 to 433) (P<0.001, Table 5.3). Sensitivity analyses with a FC of <250mcg/g used to define biochemical remission and ≥250mcg/g to define biochemical activity are provided in Supplementary Table 5.2.

5.5 Discussion

This longitudinal follow-up study has examined the cumulative impact of clinical disease activity, clinical and biochemical activity, and psychological health on adverse disease outcomes in patients with IBD over a mean follow-up of more than 8 years. Not only were the absolute numbers of almost all the events of interest numerically higher in those with clinical disease activity and symptoms of at least one common mental disorder at baseline, but also increasing psychological burden, as defined by the presence of symptoms of two common mental disorders, was associated with the highest number of adverse disease outcomes in most of our analyses. Even after controlling for all baseline characteristics, individuals with clinical disease activity and symptoms of two common mental disorders were significantly more likely to experience a flare or need for glucocorticosteroid prescription or escalation of medical therapy due to uncontrolled IBD activity and had higher all-cause mortality. Furthermore, individuals with clinical and biochemical activity and symptoms of two common mental disorders were significantly more likely to experience a flare or need for glucocorticosteroid prescription, escalation of medical therapy, hospitalisation, a composite of hospitalisation or intestinal resection, or death. Results were broadly similar when we used a FC of <250mcg/g to define biochemical remission and ≥250mcg/g to define biochemical activity, although it should be pointed out that this threshold is debated, and it would also lead to more individuals with potential biochemical activity being assigned to the biochemical remission categories, which may bias the results of the study towards the null hypothesis.

As we are the sole provider of IBD-related care to all recruited participants, and with access to the involved individuals' electronic medical records, it is likely that we have captured most of the adverse disease outcomes occurring among these patients. Investigators assessing adverse disease outcomes were blinded to participants' baseline questionnaire data

to minimise bias when assessing occurrence of the endpoints of interest during longitudinal follow-up. Performing multivariate Cox regression analysis to control for all baseline demographic and IBD-related data, as well as somatoform symptom-reporting, means our findings are unlikely to be confounded by these other potential influencers of adverse disease outcomes. Even though our unit conforms to recommendations to seek definitive evidence of disease activity prior to any escalation of medical therapy,[36] flare of disease activity and, to a lesser extent, escalation of medical therapy are more contingent on patient-reported outcome measures, which introduce a degree of subjectivity and could be influenced by patient over-reporting.[28,37] Definitions of what constitutes a flare may also vary between centres. The sample size and the extended follow-up period of the study mean that the chance of rarer, but more objective, events of interest occurring during follow-up was maximised. Finally, various cut-offs are applied in clinical practice to determine biochemical disease activity, but our use of a FC of <100mcg/g of stool to define biochemical remission has a greater sensitivity than higher cut-offs. This means the likelihood of overestimating the number of patients in remission at baseline is much less likely, and the outcomes observed are more likely to be genuinely due to the combined effects of disease activity and adverse psychological health.[38] The cumulative impact of mood and disease activity on the more objective disease outcomes, including hospitalisation or intestinal resection, and death, identified in these analyses, therefore, underscores the importance of brain-gut effects in IBD.

Conducting the study alongside routine clinical care introduces some weaknesses. Despite every effort to eliminate bias, existing documentation could not be redacted from participant's medical records prior to review. It is, therefore, possible that assessors may have seen evidence of an existing diagnosis of a common mental disorder, which could have influenced interpretation of more subjective endpoints. Similarly, participants were managed by several different physicians throughout the study, which introduces a degree of

interobserver variation. For instance, there are likely to be differing thresholds assigned to the more subjective endpoints of interest in clinical practice. Participants' medical records were reviewed by two different assessors during longitudinal follow-up, which could also introduce a degree of interobserver variation, although pre-defined criteria for each of the adverse disease outcomes were adhered to by both assessors. Inferring a diagnosis of a common mental disorder using the HADS questionnaire responses from a single point in time, rather than performing a clinical assessment to establish a formal diagnosis, could be criticised for being overly simplistic. However, this would have been infeasible given the sample size. In addition, in a recent study examining trajectories of HADS anxiety or depression scores in patients with IBD, only 10% of patients with abnormal scores at baseline had an improvement during longitudinal follow-up.[20] This suggests a single assessment may be stable in the majority of patients with IBD. Only half of patients provided baseline FC samples, and, because of our stringent definition of clinical and biochemical remission or activity, these analyses may be inadequately powered or give imprecise results, as reflected by the wide 95% CIs. Therefore, some of the results, particularly those for all-cause mortality, should be interpreted with caution. We did not collect data on other drugs that may influence activity or prognosis of IBD, such as opioids or non-steroidal anti-inflammatory drugs.[39] Finally, repeat FC measurements were not performed during longitudinal follow-up to assess changes in disease activity. However, this was infeasible with an average follow-up of 8.1 years, and the fluctuating course of IBD is both unlikely to have been a reliable determinant of overall disease activity and to add to the study considering the objective adverse disease outcomes we examined.

These results confirm our findings from two of our previous studies but add to them. First, we have demonstrated previously that adverse psychological health at baseline influences the natural history of IBD negatively, and to a similar degree to inflammatory

burden.[27] Second, we have also shown that, among patients with IBD in biochemical remission, there is a cumulative effect of psychological co-morbidity at baseline on the likelihood of adverse disease outcomes.[14] The current study examines the impact of both the presence and the degree of psychological co-morbidity at baseline on these endpoints according to both clinical and clinical and biochemical disease activity. Compared with existing studies examining brain-gut and gut-brain effects in IBD,[19] this study has one of the longest periods of follow-up, and utilised markers of biochemical remission to determine baseline disease activity, alongside traditional clinical disease activity indices. The existing body of research examining brain-gut effects in IBD demonstrates an association between symptoms of a common mental disorder and future adverse disease outcomes.[17,40-42] However, most prior studies have delineated patients only by measures of psychological health,[19] and have not assessed whether there is a cumulative impact of disease activity, which is also a driver of morbidity and is, in itself, associated with a higher prevalence of symptoms of a common mental disorder.[25]

The sole use of clinical disease activity indices to determine underlying inflammatory activity is another inherent flaw of many existing studies examining brain-gut effects in IBD.[19] These correlate poorly with underlying mucosal inflammation and are now considered to constitute low value care when used in isolation.[28,36,37] An exception to this is a study by Mules *et al.*,[43] the results of which are in contrast to those from our study. The authors demonstrated that symptoms of psychological illness at baseline were associated with an increased symptom burden in IBD, but not with endoscopic or biochemical disease activity, or the development of subsequent disease activity, as determined by a repeat FC at 6 months. However, like many others studies in the field,[19] the duration of follow-up was short and the number of included patients relatively small. Other groups have reported that severity in IBD can be characterised by other factors beyond inflammation,[44] incorporating baseline

medications and some blood results, and this can be used to predict prognosis.[45-47] Finally, most studies examining brain-gut or gut-brain interactions are performed in established cohorts of patients with IBD.[19] This means that patients may have already experienced an adverse disease course, which could have impacted their psychological health. Any future association between psychological health and prognosis may, therefore, arise due to confounding. Inception cohorts that assess psychological health at the time of a diagnosis of IBD will be required to disentangle this complex relationship.

The importance of inflammatory burden in IBD is undisputed. However, the observation that psychological health appears not only to affect disease outcomes to a similar magnitude to disease activity, but also has a cumulative effect alongside disease activity, challenges the absence of psychological health as a treatment target.[3] Given the consistent association between disease activity and poor psychological health in IBD, considering both the inflammatory and psychological burden of the disease is key, particularly as treatment of the two may differ considerably. Brain-gut behavioural therapies are effective in irritable bowel syndrome.[48,49] They may have optimal efficacy in IBD when delivered to selected patients with evidence of pre-existing psychological co-morbidity,[50] which is of particular relevance to healthcare systems with finite resources, as the blanket use of psychological therapies is probably unrealistic. Our results suggest that the impact of adverse psychological health is greatest in patients with disease activity, yet only four randomised controlled trials (RCTs) have evaluated the role of such therapies in the context of active IBD, and none recruited patients with evidence of psychological co-morbidity.[51-54] To integrate a biopsychosocial model of care in routine IBD practice successfully requires further assessment of these treatments in this particular group of patients. Similarly, neuromodulators have a good evidence base in disorders of gut-brain interaction. [55-58] However, there is a lack of RCTs in IBD, and although they appear to demonstrate positive effects in treating

psychological and somatic symptoms, limited conclusions can be made regarding their influence on the disease course.[59] This should be a priority area for future IBD research, particularly given the favourable safety profile seen in similar RCTs conducted in irritable bowel syndrome.[55]

In summary, our study demonstrates that, even when stringent and objective assessments are applied to determine underlying disease activity, genuine brain-gut effects are apparent in IBD. Not only does adverse psychological health appear to influence the natural history of the disease to a similar magnitude to inflammatory activity, but also this is cumulative, with patients with symptoms of more than one common mental disorder at the greatest risk of future adverse disease outcomes. That most of these endpoints were not significantly higher in patients with active disease alone highlights alternative therapeutic targets in IBD, which do not feature in current guidelines but, if utilised correctly, have the potential to improve outcomes for some patients. Given the prevalence of common mental disorders among patients with IBD, our findings suggest that focusing solely on the inflammatory aspects of UC or CD will result in unmet needs among a substantial proportion of patients and may contribute to adverse disease outcomes. There are ever expanding options to identify and treat persistent mucosal inflammation, but strategies to identify and manage co-existing poor psychological health are also needed, if we are to provide holistic care for patients with IBD.

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Supplementary Table 5.1. Baseline Patient Characteristics According to Both Combined Clinical and Biochemical Disease Activity and Symptoms of a Common Mental Disorder at Baseline.

	Combined Clinical and Biochemical Remission		Combined Clinical and Biochemical Activity			
	No symptoms of a common mental disorder (n=83)	**Symptoms of a common mental disorder (n=16)**	**No symptoms of a common mental disorder (n=46)**	**Symptoms of a common mental disorder (n=27)**	**Symptoms of two common mental disorders (n=15)**	***P* value***
Mean age (SD)	50.9 (18.0)	45.8 (14.1)	51.8 (15.4)	45.4 (14.2)	50.2 (18.2)	0.44
Female sex (%)	39 (47.0)	10 (62.5)	26 (56.5)	21 (77.8)	8 (53.3)	0.084
Married or cohabiting (%)	54 (65.1)	12 (75.0)	33 (71.7)	20 (74.1)	8 (53.3)	0.57
University graduate/ professional (%)	28 (33.7)	5 (31.3)	13 (28.9)	8 (29.6)	4 (26.7)	0.97
Tobacco user (%)	8 (9.6)	1 (6.3)	2 (4.3)	8 (29.6)	4 (26.7)	0.0070
Alcohol user (%)	54 (65.1)	14 (87.5)	32 (71.1)	16 (59.3)	5 (33.3)	0.023
CD (%)	42 (50.6)	11 (68.8)	21 (45.7)	13 (48.1)	9 (60.0)	0.54
CD location (%) Ileal (%)	6/42 (14.3)	2/11 (18.2)	5/21 (23.8)	7/13 (53.8)	2/9 (22.2)	

Colonic (%) Ileocolonic (%)	18/42 (42.9) 18/42 (42.9)	7/11 (63.6) 2/11 (18.2)	5/21 (23.8) 11/21 (52.4)	1/13 (7.7) 5/13 (38.5)	2/9 (22.2) 5/9 (55.6)	0.033
Non-stricturing, non-penetrating CD (%)	40/42 (95.2)	9/11 (81.8)	17/21 (81.0)	8/13 (61.5)	7/9 (77.8)	0.015
Perianal disease (%)	2/42 (4.8)	0/11 (0.0)	3/21 (14.3)	0/13 (0.0)	1/9 (11.1)	0.35
UC extent (%) Proctitis Left-sided Extensive	 9/41 (22.0) 19/41 (46.3) 13/41 (31.7)	 2/5 (40.0) 3/5 (60.0) 0/5 (0.0)	 5/25 (20.0) 11/25 (44.0) 9/25 (36.0)	 2/14 (14.3) 7/14 (50.0) 5/14 (35.7)	 1/6 (16.7) 4/6 (66.7) 1/6 (16.7)	0.84
5-aminosalicylate use (%)	44 (53.0)	8 (50.0)	24 (52.2)	12 (44.4)	6 (40.0)	0.86
Immunomodulator use (%)	31 (37.3)	5 (31.3)	16 (34.8)	9 (33.3)	3 (20.0)	0.78
Biologic use (%)	13 (15.7)	3 (18.8)	10 (21.7)	6 (22.2)	1 (6.7)	0.66
Glucocorticosteroid use (%)	2 (2.4)	1 (6.3)	8 (17.4)	2 (7.4)	1 (6.7)	0.047
High levels of somatoform symptom-reporting on PHQ-15 (%)	5 (6.0)	3 (20.0)	5 (11.9)	13 (50.0)	7 (50.0)	<0.001

*One-way analysis of variance for comparison of continuous data, χ^2 for comparison of categorical data across all four groups.

Supplementary Table 5.2. Adverse Disease Outcomes in Patients According to Combined Clinical and Biochemical Disease Activity Status, using an FC<250mcg/g or ≥250mcg/g, and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline.

	Combined clinical and biochemical remission		Combined clinical and biochemical activity			
	No symptoms of a common mental disorder	**Symptoms of a common mental disorder**	**No symptoms of a common mental disorder**	**Symptoms of a common mental disorder**	**Symptoms of two common mental disorders**	***P* value**
Flare of disease activity or glucorticosteroid prescription (%)	48/109 (44.0)	18/29 (62.1)	11/15 (73.3)	9/10 (90.0)	3/4 (75.0)	0.010*
Multivariate HR for flare of disease activity or glucorticosteroid prescription (95% CI)	1.00 (reference)	1.82 (0.98-3.40)	3.61 (1.66-7.81)†	6.33 (2.31-17.3)‡	3.87 (1.05-14.3)	<0.001
Escalation of medical therapy due to uncontrolled IBD activity (%)	49/109 (45.0)	18/29 (62.1)	18/22 (81.8)	8/10 (80.0)	5/6 (83.3)	0.0030*
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.79 (0.98-3.26)	3.87 (2.07-7.23)‡	2.48 (0.94-6.52)	5.07 (1.83-14.1)†	<0.001
Hospitalisation due to uncontrolled IBD activity (%)	17/109 (15.6)	6/29 (20.7)	9/37 (24.3)	6/14 (42.9)	2/9 (22.2)	0.18*

Multivariate HR for hospitalisation due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.44 (0.53-3.93)	1.39 (0.57-3.38)	5.67 (1.85-17.4)†	3.23 (0.65-16.1)	0.042
Intestinal resection due to uncontrolled IBD activity (%)	4/109 (3.7)	2/29 (6.9)	4/37 (10.8)	4/14 (28.6)	3/11 (27.3)	0.0030*
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.53 (0.25-9.38)	2.46 (0.52-11.5)	13.2 (2.55-67.9)†	15.31 (2.42-96.8)†	0.0090
Hospitalisation or intestinal resection (%)	17/109 (15.6)	6/29 (20.7)	9/37 (24.3)	6/14 (42.9)	3/10 (30.0)	0.15*
Multivariate HR for hospitalisation or intestinal resection (95% CI)	1.00 (reference)	1.46 (0.54-3.98)	1.42 (0.58-3.45)	5.89 (1.94-17.8)†	5.05 (1.27-20.1)	0.015
Death (%)	16/111 (14.4)	1/29 (3.4)	1/37 (2.7)	2/14 (14.3)	4/11 (36.4)	0.017*
Multivariate HR for death (95% CI)	1.00 (reference)	0.79 (0.09-6.73)	0.35 (0.05-2.79)	7.25 (1.30-40.3)	10.3 (2.27-46.5)†	0.0070

*One-way analysis of variance for comparison of continuous data, χ^2 for comparison of categorical data across all four groups.

Chapter 6: Effectiveness of Psychological Therapies in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis.

6.1 Summary

Background: There is increasing evidence for an influence of the gut-brain axis on the natural history of inflammatory bowel disease (IBD). Psychological therapies may, therefore, have beneficial effects in IBD but previous data are conflicting. We updated our previous systematic review and meta-analysis to assess whether inclusion of more randomised controlled trials (RCTs) demonstrated any beneficial effects and to examine whether this varied by treatment modality.

Methods: We searched MEDLINE, EMBASE, EMBASE Classic, PsychINFO, and the Cochrane central register of controlled trials from 1st January 2016 to 30th April 2023. RCTs published in any language recruiting patients ≥16 years with IBD comparing psychological therapy with control intervention or treatment as usual were eligible. We pooled dichotomous data to obtain relative risks (RR) of inducing remission in active disease, or preventing relapse of quiescent disease, with 95% confidence intervals (CI). We pooled continuous data to estimate standardised mean differences (SMD) in disease activity indices, anxiety, depression, stress, and quality of life scores with 95% CIs.

Findings: The updated literature search identified a total of 469 citations. Of 25 eligible RCTs, none were at low risk of bias. Only four trials recruited patients with active disease, and incomplete data reporting meant effect on disease activity indices could not be ascertained. However, quality of life scores were significantly higher with active therapy in these four RCTs after treatment completion (309 patients, SMD 0.68; 95% CI 0.09 to 1.26) but with heterogeneity between studies (I^2 = 82%). In quiescent disease, RR of relapse of disease activity was not reduced with psychological therapy (10 RCTs, 861 patients, 0.83; 95% CI 0.62 to 1.12), again with significant heterogeneity between studies (I^2 = 60%), and the funnel plot suggested evidence of publication bias or other small study effects (Egger test, p=0.046). However, anxiety (13 RCTs, 1088 patients, SMD -0.23; 95% CI -0.36 to -0.09, I^2 =

18%), depression (15 RCTs, 1189 patients, SMD -0.26; 95% CI -0.38 to -0.15, I^2 = 2%), and stress (11 RCTs, 813 patients, SMD -0.22; 95% CI -0.42 to -0.03 I^2 = 47%) scores were significantly lower, and quality of life scores (16 RCTs, 1080 patients, SMD 0.31; 95% CI = 0.16 to 0.46 I^2 = 30%) significantly higher with psychological therapy at treatment completion. This benefit persisted up to final follow-up for depression scores. Effects were strongest in trials of third wave therapies and in RCTs recruiting patients with impaired psychological health, fatigue, or reduced quality of life at baseline.

Interpretation: Psychological therapies have beneficial effects on anxiety, depression, stress, and quality of life scores, but not disease activity.

6.2 Introduction

Inflammatory bowel disease (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), is a chronic gastrointestinal condition with increasing prevalence across North America and Europe.[1] The course of IBD is typically one of flares of disease activity interspersed with periods of disease quiescence. Several factors are implicated in its development, including dysbiosis, reduced integrity of the intestinal barrier, and immune dysfunction within the gut. The gut and brain communicate through the gut-brain axis, and it is increasingly recognised that this bi-directional communication system may play a pivotal role not only in the psychological health of patients with the condition,[2] but also in the prognosis of IBD.[3] Patients with ongoing disease activity are more likely to develop new onset symptoms of depression or anxiety than those whose disease is quiescent,[4,5] and patients with coexistent symptoms of anxiety or depression appear to be more likely to experience adverse disease outcomes than patients without such symptoms.[4-6] Once psychological symptoms develop they appear to be persistent or fluctuating for the majority, with few patients with IBD experiencing complete resolution.[7]

However, whether treatments directed at the gut-brain axis, such as psychological therapies, can influence disease activity or psychological health in IBD is unclear. Although there have been multiple randomised controlled trials (RCTs) examining the effect of interventions including cognitive behavioural therapy and gut-directed hypnotherapy in IBD, many are small and underpowered, have high rates of loss to follow-up, study differing endpoints, including anxiety, depression, stress, or quality of life, and demonstrate conflicting results. We previously assessed this issue systematically,[8] identifying all trials published up to 2016. Meta-analysis of these RCTs did not demonstrate any benefit of psychological therapies in the longer term for either IBD activity or psychological health. However, only 14 trials were included in this meta-analysis, which contained less than 1200 patients.

In the intervening years, there have been multiple RCTs conducted. We, therefore, updated our previous systematic review and meta-analysis of psychological therapies in IBD. We aimed to assess whether psychological therapy had any impact on disease activity, psychological symptoms, including anxiety, depression, or stress scores, or health-related quality of life.

6.3 Methods

6.3.1 Search Strategy and Selection Criteria

We searched the medical literature, including MEDLINE, EMBASE, EMBASE Classic, PsychINFO, and the Cochrane central register of controlled trials (from 1st January 2016 to 30th April 2023) to update our previous meta-analysis on this subject.[8] In addition, we hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2022 to identify trials published only in abstract form. We did not search trial registries. Finally, we performed a recursive search of the bibliographies of all eligible articles.

We defined eligible studies as those including patients (≥16 years of age) with an endoscopic, histological, or radiologically confirmed diagnosis of IBD, reporting the effect of psychological therapy of any modality, when compared with control or treatment as usual, on outcomes including disease activity, depression, anxiety, perceived stress, or quality of life. Only RCTs were eligible for inclusion. The eligibility criteria were defined *a piori* (see appendix page 1).

The literature search was performed by two investigators (CR and ACF) using the terms: *cognitive therapy, psychotherapy, behaviour therapy, relaxation techniques, mindfulness*, *meditation*, or *hypnosis* (both as medical subject headings (MeSH) and free text terms), and the following free text terms: *behavioural therapy*, *relaxation therapy*, *mindfulness meditation*, *psychotherapy*, or *hypnotherapy*. These terms were combined using the set operator AND with studies identified using the terms: *Crohn disease*, *inflammatory bowel disease*, *colitis*, *ileitis*, or *ulcerative colitis* (both as MeSH and free text terms), and *Crohn$ disease* or *regional enteritis* (as free text terms). We applied no language restrictions to the search. Two investigators (CR and ACF) evaluated all abstracts

identified, independently. We obtained potentially relevant papers and evaluated them in more detail, using pre-designed forms, to assess eligibility independently according to the pre-defined criteria. We translated foreign language papers, where required. We resolved disagreements between investigators by discussion.

6.3.2 Data Analysis

Dichotomous outcomes assessed were the effect of psychological therapy versus control in terms of failure to achieve remission in active IBD, or to prevent relapse of disease activity in quiescent IBD. We extracted data for these endpoints at the final point of trial follow-up, to maximise the number of events in the analysis. Continuous outcomes assessed included the effect of psychological therapies versus control on clinical disease activity indices, anxiety scores, depression scores, stress scores, or quality of life scores. Trials were analysed separately according to whether they recruited patients with IBD with clinically active disease at the time of randomisation, or predominantly patients whose disease was quiescent. As the effect of psychological therapies on mood and quality of life may be greatest immediately after completion of therapy, we extracted data for these endpoints both at the point of completion of therapy, and at the final point of follow-up. Where studies did not report these types of data but were otherwise eligible for inclusion in the meta-analysis, we attempted to contact the original investigators to obtain supplementary dichotomous or continuous data. In three of these trials, we were successful.[9-11]

Data extraction was carried out by two investigators independently (CR and ACF), using a Microsoft excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, US) as dichotomous outcomes (remission or failure of remission in active IBD, and relapse or no relapse of disease activity in quiescent IBD), or mean disease activity indices, anxiety scores, depression scores, stress score, or quality of life scores, along with a standard deviation (SD).

For dichotomous outcomes, we extracted data as intention-to-treat analyses, wherever trial reporting allowed this, with all dropouts assumed to be treatment failures (i.e., failed to achieve remission in active IBD trials, or disease activity relapsed in quiescent IBD trials). For other outcomes, mean scores and SDs after psychological therapy or control could only be recorded for those who provided complete data. In addition, the following data were recorded for each trial: type of psychological therapy used, country, setting (primary, secondary, or tertiary care-based), number of centres, number of sessions of psychological therapy administered, duration of therapy, and duration of follow-up. We also recorded the handling of the control arm in each trial.

We used the Cochrane risk of bias tool to assess this at the study level.[12] Two investigators (CR and ACF) performed this independently. We resolved disagreements by discussion. We recorded the method used to generate the randomisation schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data for any of the endpoints of interest, and whether there was evidence of selective reporting of outcomes.

We measured the degree of agreement between the two investigators, in terms of judging study eligibility, using a Kappa statistic. We pooled all data using a random effects model,[13] in order to give a more conservative estimate of the effect of psychological therapies on disease outcomes in IBD. For dichotomous outcomes, we expressed the impact of psychological therapies as a relative risk (RR) of failure to achieve remission with 95% confidence intervals (CI) with intervention versus control in trials of therapy for active IBD, or a RR of relapse of disease activity in trials of therapy for quiescent IBD. Where psychological therapies appeared more effective than control in IBD, we planned to calculate the number needed to treat (NNT), along with 95% CIs, using the formula NNT = 1 / (control

event rate x (1 – RR)). For continuous data, including effect on disease activity indices, psychological wellbeing scores, and quality of life scores, we summarised the effect of psychological therapies using a standardised mean difference (SMD) and 95% CIs. An SMD of 0.2 can be considered to represent a small effect, 0.5 a moderate effect, and 0.8 a large effect.[14]

We conducted subgroup analyses including only trials using the same modality of psychological therapy, where sufficient RCTs existed, to assess whether the effect was stronger for any particular treatment modality. This was only possible for cognitive behavioural therapy (CBT) (i.e., therapy emphasising thoughts and beliefs in understanding and changing behaviour and emotional responses) and so-called third wave psychological approaches. The latter have evolved from CBT and focus on the process of change and how a person relates to internal experiences. They include acceptance, mindfulness, and value-focused approaches.[15] We also conducted subgroup analyses according to whether trials recruited selected groups of patients with IBD, such as those with anxiety, depression, stress, fatigue, or reduced quality of life, as we hypothesised that these patients may be more likely to experience a benefit of psychological therapies, compared with unselected patients.

We assessed heterogeneity between studies using both the χ^2 test, with a P value <0.10 used to define a significant degree of heterogeneity, and the I^2 statistic. The I^2 ranges between 0% and 100%, with values of 25% to 49% considered low, 50% to 74% moderate, and ≥75% high heterogeneity.[16] We used Review Manager version 5.4.1 (The Cochrane Collaboration 2020) to generate Forest plots of pooled RRs and SMDs with 95% CIs, as well as funnel plots. We assessed these, if there were a sufficient number (≥10) of studies included in the meta-analysis,[17] for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test.[18]

6.4 Results

The updated literature search identified a total of 469 citations of which, after title and abstract review, we deemed 46 potentially relevant and assessed them further for eligibility (Figure 6.1). Of these, we excluded 35 for various reasons leaving 11 new eligible studies,[9-11,19-26] to be pooled with the existing 14 studies eligible for inclusion in the prior version of the meta-analysis.[27-40] Agreement between reviewers for eligibility assessment was excellent (Kappa statistic = 0.83). Detailed characteristics of the 25 eligible RCTs are provided in Table 6.1; for risk of bias across all trials see appendix page 2. None of the trials were at low risk of bias. Four of the RCTs were conducted only in patients with active IBD,[9,25,30,31] 18 in patients with IBD in remission,[10,11,19,23,24,26-29,32-40] and three in mixed populations of patients, but in whom the majority were in remission.[20-22] We pooled trials together in individual analyses according to the data reported within them but excluded the latter three trials in sensitivity analyses.

Ten trials used third wave therapies, such as mindfulness or acceptance and commitment therapy,[9-11,20,23-26,34,37] eight trials used CBT,[19,21,22,30,32,33,35,36] two trials solution focused therapy,[39,40] one trial psychodynamic therapy,[29] one trial gut-directed hypnotherapy,[38] one trial guided imagery,[31] one trial stress management, [27] and one trial a combination of multiple therapies.[28] Only nine RCTs recruited specific populations of patients, rather than unselected patients with IBD. Four recruited patients with fatigue,[19,26,39,40] two patients with increased stress levels,[20,24] one patients with depression,[10] one patients with reduced quality of life scores,[21] and one patients with either increased stress levels or reduced quality of life scores.[11]

Figure 6.1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.

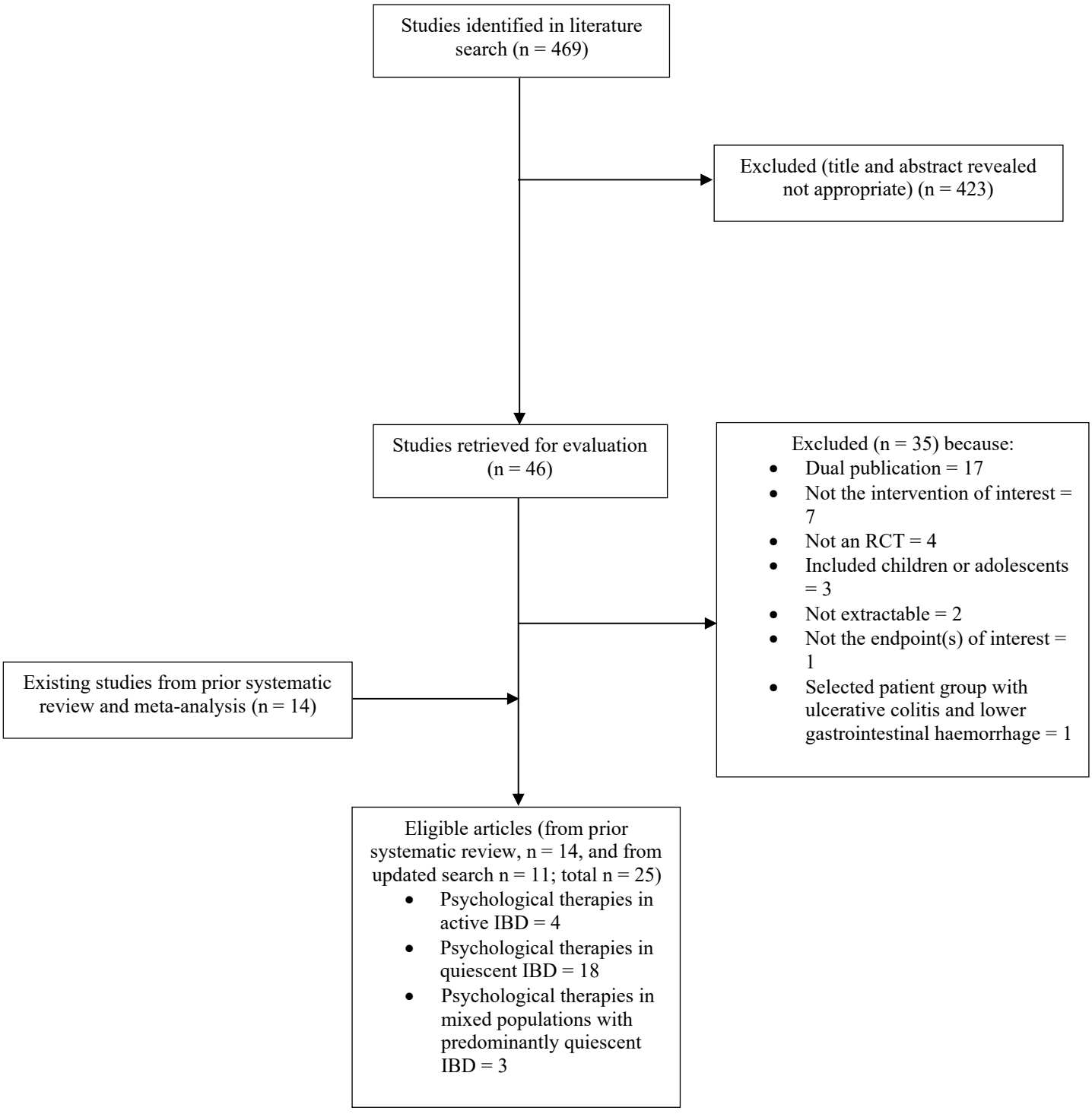


Table 6.1. Characteristics of the Included Studies.

Study	Participants and Setting	Active Intervention	Handling of the Control Arm	Duration of Follow-up	Outcomes Studied (% of Patients Providing Complete Data)
Jantschek 1998 [29]	108 patients with CD from 4 tertiary care centres in Germany	10 sessions of psychodynamic psychotherapy over 12 months	Standardised drug therapy including tapered prednisolone and sulfasalazine	24 months	Relapse of disease activity: Crohn's disease activity index, but no threshold specified (100) Psychological wellbeing: Beck depression inventory and state-trait anxiety (75.0) Quality of life: IBD-Q (73.1)
Smith 2002 [27]*	100 patients (50 with CD, 50 with UC) from 1 tertiary care centre in the UK	3 to 6-monthly sessions of stress management and attention control therapy over 12 months	Routine clinical follow-up	12 months	Clinical disease activity indices: modified Crohn's disease activity index (100) Psychological wellbeing: hospital anxiety and depression scale (100)

Langhorst 2007 [28]	60 patients with UC recruited via public advertisement in Germany	Weekly sessions of stress reduction, stress management, dietary recommendations, and mindfulness over 10 weeks	Usual medical care	12 months	Relapse of disease activity: Rachmilewitz clinical activity index >5 (100) Clinical disease activity indices: Rachmilewitz clinical activity index (93.3) Psychological wellbeing: brief symptom inventory for anxiety (93.3) Quality of life: IBD-Q (93.3)
Boye 2011[30]	114 patients with IBD from 4 tertiary care centres in Norway and Germany	3 group sessions, followed by weekly individual sessions for 6 to 9 weeks, and up to 3 booster sessions of psychoeducation and relaxation, with cognitive behavioural therapy-based sessions, over 12 months	Treatment as usual	18 months	Remission of disease activity: Harvey-Bradshaw index or Rachmilewitz clinical activity index ≤1 (100) Clinical disease activity indices: Harvey-Bradshaw index or Rachmilewitz clinical activity index (100) Quality of life: IBD-Q (100)
Vogelaar 2011[39]†	40 patients with CD with fatigue from 1 tertiary care centre in the Netherlands	5 sessions of solution focused therapy, or 10 sessions of problem-solving therapy, over 3 months	Treatment as usual	6 months	Clinical disease activity indices: Crohn's disease activity index (57.5) Psychological wellbeing: hospital anxiety and depression scale (57.5) Quality of life: IBD-Q (57.5)

Keefer 2012 [32]	28 patients with CD from 1 tertiary care centre in the USA	Weekly sessions of project-management, including cognitive behavioural therapy and social learning theory, over 6 weeks	Treatment as usual	8 weeks	Psychological wellbeing: perceived stress questionnaire (100) Quality of life: IBD-Q (100)
Mizrahi 2012 [31]	56 patients with IBD from 1 tertiary care centre in Israel	3 sessions of relaxation training and guided imagery over 5 weeks	Waiting list control	5 weeks	Psychological wellbeing: state-trait anxiety, and visual analogue scales for depression and stress (69.6) Quality of life: IBD-Q (69.6)
Keefer 2013 [38]	54 patients with UC from 1 tertiary care centre in the USA	Weekly sessions of gut-directed hypnotherapy over 7 weeks	Attention control	12 months	Relapse of disease activity: Self-report, Mayo score >2, or escalation of therapy (100) Psychological wellbeing: perceived stress questionnaire (92.6) Quality of life: IBD-Q and short-form-12 (92.6)
Berrill 2014 [33]	66 patients with IBD from 2 tertiary care centres in the UK	6 sessions of multi-convergent therapy, including mindfulness meditation and cognitive behavioural therapy, over 16 weeks	Standard medical therapy	12 months	Relapse of disease activity: Harvey-Bradshaw index ≥5 or simple clinical colitis activity index ≥3 (100) Psychological wellbeing: perceived stress questionnaire (77.3) Quality of life: IBD-Q (89.4)

Jedel 2014 [34]	55 patients with UC from 1 tertiary care centre, and the greater Chicago area, in the USA	Weekly sessions of mindfulness-based stress reduction, including sitting meditation, body scans, yoga postures, and awareness of personal reactions to everyday events, over 8 weeks	Attention control	12 months	Relapse of disease activity: ulcerative colitis disease activity index >2 (100) Clinical disease activity indices: ulcerative colitis disease activity index (92.7) Psychological wellbeing: Beck depression inventory, state-trait anxiety, and perceived stress questionnaire (92.7) Quality of life: IBD-Q (92.7)
Vogelaar 2014 [40]	98 patients with IBD with fatigue from 2 tertiary care centres in the Netherlands	6 sessions of solution focused therapy over 3 months, with a booster session at month 6	Treatment as usual	9 months	Clinical disease activity indices: Crohn's disease activity index or Rachmilewitz clinical activity index (91.8) Psychological wellbeing: hospital anxiety and depression scale (91.8) Quality of life: IBD-Q and short-form-36 (91.8)

Mikocka-Walus 2015 [35]	174 patients with IBD from 2 tertiary care centres in Australia	Weekly sessions of face-to-face or internet-delivered cognitive behavioural therapy over 10 weeks	Standard care	12 months	Relapse of disease activity: Crohn's disease activity index ≥150 or simple clinical colitis activity index ≥3 (100) Clinical disease activity indices: Crohn's disease activity index or simple clinical colitis activity index (40.8) Psychological wellbeing: hospital anxiety and depression scale, state-trait anxiety, and COPE questionnaire (60.9) Quality of life: short-form-36 (60.9)
Schoultz 2015 [37]	44 patients with IBD from outpatient gastroenterology clinics in two national health boards in Scotland, UK	Weekly sessions of mindfulness-based cognitive therapy, including body scan, sitting and walking meditation, mindful stretching, and cognitive behavioural exercises, over 8 weeks	Waiting list control	6 months	Clinical disease activity indices: Crohn's disease activity index or simple clinical colitis activity index (52.3) Psychological wellbeing: Beck depression inventory and state-trait anxiety (54.5) Quality of life: IBD-Q (54.5)

McCombie 2016 [36]	199 patients with IBD from secondary and tertiary care centres, as well as support groups, in New Zealand	8 sessions of computerised cognitive behavioural therapy over 12 weeks	Treatment as usual	6 months	Clinical disease activity indices: Harvey-Bradshaw index or simple clinical colitis activity index (55.3) Psychological wellbeing: hospital anxiety and depression scale and perceived stress questionnaire (58.8) Quality of life: IBD-Q and short-form-12 (58.8)
Bennebroek Evertsz 2017 [21]	118 patients with IBD with reduced quality of life from four secondary and tertiary care centres in the Netherlands	8 sessions of cognitive behavioural therapy over 8 weeks	Waiting list control	14 weeks	Psychological wellbeing: hospital anxiety and depression scale and perceived stress questionnaire (81.4) Quality of life: IBD-Q (81.4)
Artom 2019 [19]	31 patients with IBD with fatigue from one tertiary care centre in the UK	8 sessions of cognitive behavioural therapy by telephone over 8 weeks	Self-help sheet	12 months	Clinical disease activity indices: Harvey-Bradshaw index or simple clinical colitis activity index (71.0) Psychological wellbeing: patient health questionnaire-9 and generalised anxiety disorder-7 (81.4) Quality of life: IBD-Q (81.4)

Wynne 2019 [11]	122 patients with IBD with increased stress or a reduced quality of life from one tertiary care centre in Ireland	8 sessions of acceptance and commitment therapy over 8 weeks	Standard care	20 weeks	Relapse of disease activity: self-report (100) Clinical disease activity indices: short Crohn's disease activity index or short Mayo score (64.8) Psychological wellbeing: depression anxiety stress scale-21 (64.8) Quality of life: short health scale (64.8)
Hunt 2019 [22]	140 patients with IBD recruited online and in-person via one tertiary care centre in the USA	Cognitive behavioural therapy self-help book over 6 weeks	Waiting list control	6 weeks	Clinical disease activity indices: Harvey-Bradshaw index (62.1) Psychological wellbeing: Beck depression inventory and state-trait anxiety (62.1) Quality of life: SIBD-Q (62.1)
Bernabeu 2021 [20]	120 patients with IBD with increased stress from one tertiary care centre in Spain	8 sessions of multicomponent (elements of cognitive behavioural therapy, mindfulness, and acceptance and commitment therapy) group psychological therapy over 8 weeks	Treatment as usual	8 weeks	Relapse of disease activity: self-report (100) Clinical disease activity indices: Crohn's disease activity index or partial Mayo score (100) Psychological wellbeing: hospital anxiety and depression scale and perceived stress questionnaire (100) Quality of life: IBD-Q (100)

Ewais 2021 [10]	64 patients with IBD with depression from one tertiary care centre in Australia	8 sessions of mindfulness-based cognitive behavioural therapy over 8 weeks	Waiting list control	20 weeks	Psychological wellbeing: depression anxiety stress scale-21 (64.1) Quality of life: SIBD-Q (59.4)
Goren 2022 [9]	139 patients with CD recruited from multiple secondary and tertiary care centres in Israel	7 sessions of cognitive behavioural therapy and mindfulness-based stress reduction with daily exercise over 3 months	Waiting list control	3 months	Clinical disease activity indices: Harvey-Bradshaw index (83.5) Quality of life: SIBD-Q (83.5)
Jedel 2022 [23]	43 patients with UC from one tertiary care centre in the USA	8 sessions of mindfulness/mindfulness-based stress reduction over 8 weeks	Attention control	12 months	Relapse of disease activity: ulcerative colitis disease activity index >2 (100) Clinical disease activity indices: ulcerative colitis disease activity index (88.4) Psychological wellbeing: Beck depression inventory, state-trait anxiety, and perceived stress questionnaire (88.4) Quality of life: IBD-Q (88.4)

Peerani 2022 [24]	101 patients with IBD with increased stress from four tertiary care centres in Canada	Online stress reduction intervention over 12 weeks	Standard care	12 weeks	Relapse of disease activity: need for prednisone or escalation to a biologic (100) Clinical disease activity indices: partial Mayo score (100) Psychological wellbeing: hospital anxiety and depression scale and perceived stress questionnaire (100) Quality of life: SIBD-Q (100)
Xi 2022 [25]	40 patients with IBD from one tertiary care centre in China	Mindfulness meditation over 3 months	Conventional nursing methods	3 months	Psychological wellbeing: self-rating anxiety scale (100) Quality of life: IBD-Q (100)
Bredero 2023 [26]	113 patients with IBD with fatigue from one tertiary care centre in the Netherlands	Weekly sessions of mindfulness-based cognitive therapy, including group meditation, cognitive behavioural exercises, psycho-education, and daily homework over 8 weeks	Waiting list control	3 months	Psychological wellbeing: Beck depression inventory and generalised anxiety disorder-7 (100) Quality of life: IBD-Q (100)

*Smith 2002 [27] provided all outcomes data for those with CD (Smith 2002a) and those with UC (Smith 2002b) separately.

†Vogelaar 2011[39] compared solution focused therapy (Vogelaar 2011a) and problem-solving therapy (Vogelaar 2011b) with treatment as usual.

6.4.1 Effect of Psychological Therapy in Patients with Active IBD

6.4.1.1 Effect of Psychological Therapy on Disease Activity in Patients with Active IBD

Of the four trials including patients with IBD with ongoing active disease,[9,25,30,31] only one reported dichotomous data concerning the effect of psychological therapy in inducing remission of active IBD.[30] In total, 12 (21.1%) of 57 patients undergoing psychological therapy entered clinical remission, compared with 2 (3.5%) of 57 patients in the control group, after 18 months of follow-up. Only one trial reported effect of psychological therapy on disease activity indices in 116 patients,[9] with significantly lower disease activity indices in patients assigned to active therapy (median 4.00 (IQR 2.00-5.00)) versus those allocated to control (7.00 (IQR 4.50-9.00)).

6.4.1.2 Effect of Psychological Therapy on Anxiety, Depression, Stress, and Quality of Life Scores in Patients with Active IBD

Two RCTs reported on the effect of psychological therapy on anxiety scores in 79 patients with active IBD.[25,31] There was no benefit in favour of active therapy (SMD = -1.04; 95% CI -2.46 to 0.39). Only one trial reported on impact of psychological therapy on depression or stress scores,[31] meaning formal meta-analysis was not possible. All four RCTs reported the effect of psychological therapy on quality of life scores in 309 patients.[9,25,30,31] Overall, quality of life scores were significantly higher after completion of therapy in those assigned to active treatment (SMD = 0.68; 95% CI 0.09 to 1.26, p=0.02) (see appendix page 3), but with significant heterogeneity between studies (I^2 = 82%).

6.4.2 Effect of Psychological Therapy in Patients with Quiescent IBD

6.4.2.1 Effect of Psychological Therapy on Disease Activity in Patients with Quiescent IBD

In total, there were 10 RCTs reporting dichotomous data concerning the effect of psychological therapy on relapse rates in patients with quiescent IBD. One trial included patients with CD,[29] four RCTs patients with UC,[23,28,34,38] and five trials patients with IBD.[11,20,24,33,35] Overall, 166 (37.5%) of 443 patients treated with psychological therapy experienced a relapse of disease activity, compared with 155 (37.1%) of 418 patients in the control group. Compared with control, the RR of relapse of disease activity in all patients with IBD treated with psychological therapy was 0.83 (95% CI 0.62 to 1.12) (Figure 6.2). There was significant heterogeneity between studies (I^2 = 60%), and the funnel plot suggested evidence of publication bias or other small study effects (Egger test, p=0.046). There was no effect according to type of IBD (Figure 6.2).

Thirteen RCTs reported data on the effect of psychological therapy on disease activity indices in 1015 patients with IBD at completion of therapy.[11,19,20,22-24,27,28,34-37,40] Nine trials assessed impact on disease activity indices in CD,[11,19,20,24,27,35-37,40] 12 in UC,[11,19,20,23,24,27,28,34-37,40] and one in IBD.[22] There was no significant difference in disease activity indices among those treated with psychological therapy, compared with those in the control group, at completion of therapy (SMD = -0.01; 95% CI -0.13 to 0.12) (see appendix page 4 and Table 6.2), with no evidence of heterogeneity between studies (I^2 = 0%). There was also no effect of psychological therapies on disease activity indices according to group of patients studied (see appendix page 5). Excluding the two trials that included a mixed population of patients did not affect the significance of the pooled result (SMD = -0.08; 95% CI -0.22 to 0.05).[20,22] Results were similar when the 11 trials, containing 663 patients, reporting effect on disease activity indices at last point of follow-up were pooled (SMD = -0.03; 95% CI -0.18 to 0.12, I^2

= 0%) (see appendix page 5 and Table 6.2).[11,19,23,27,28,34-37,39,40] There were sufficient data to pool trials of CBT and third wave therapies; neither had a significant impact on disease activity indices (Table 6.3). Similarly, there was no effect in trials that recruited selected or unselected groups of patients (Table 6.4).

Figure 6.2. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control in Preventing Relapse in Patients with Quiescent IBD at the Final Point of Follow-up.

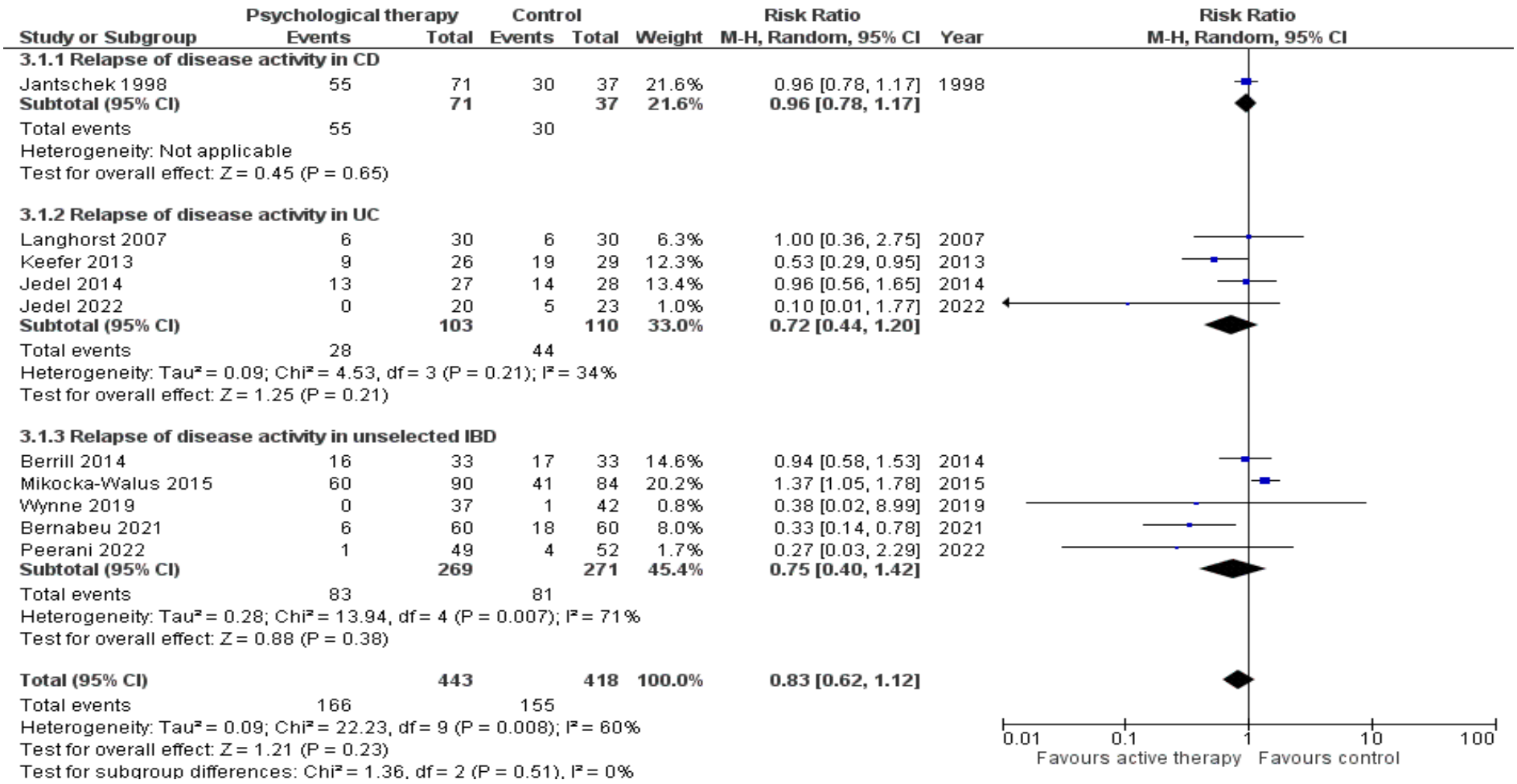


Table 6.2. Effect of Psychological Therapy on Clinical Disease Activity Indices and Anxiety, Depression, Stress, and Quality of Life Scores in Patients with Quiescent IBD.

	Number of trials	Number of patients	SMD for Effect of Psychological Therapies (95% confidence interval)	*p* value for the difference	I^2 (*p* value for χ^2)
Disease activity indices					
At completion of therapy	13	1015	-0.01 (-0.13 to 0.12)	0.91	0% (0.93)
At final point of follow-up	11	663	-0.03 (-0.18 to 0.12)	0.71	0% (0.91)
Anxiety scores					
At completion of therapy	13	1088	-0.23 (-0.36 to -0.09)	<0.001	18% (0.26)
At final point of follow-up	9	700	-0.17 (-0.34 to 0.01)	0.06	20% (0.25)
Depression scores					
At completion of therapy	15	1189	-0.26 (-0.38 to -0.15)	<0.001	2% (0.43)
At final point of follow-up	12	856	-0.16 (-0.30 to -0.03)	0.02	0% (0.94)
Stress scores					
At completion of therapy	11	813	-0.22 (-0.42 to -0.03)	0.03	47% (0.04)
At final point of follow-up	9	551	-0.18 (-0.40 to 0.04)	0.11	38% (0.12)
Quality of life scores					
At completion of therapy	16	1080	0.31 (0.16 to 0.46)	<0.001	30% (0.13)
At final point of follow-up	14	773	0.13 (-0.02 to 0.29)	0.08	8% (0.36)

SMD; standardised mean difference.

Table 6.3. Effect of CBT or Third Wave Therapies on Clinical Disease Activity Indices and Anxiety, Depression, Stress, and Quality of Life Scores in Patients with Quiescent IBD.

	Number of trials	Number of patients	SMD for Effect of Psychological Therapies (95% confidence interval)	*p* value for the difference	I^2 (*p* value for χ^2)
Disease activity indices					
At completion of therapy with CBT	4	360	0.07 (-0.14 to 0.18)	0.50	0% (0.60)
At final point of follow-up with CBT	3	203	-0.05 (-0.34 to 0.23)	0.72	0% (0.98)
At completion of therapy with third wave	6	412	-0.04 (-0.24 to 0.15)	0.66	0% (0.79)
At final point of follow-up with third wave	4	168	-0.07 (-0.39 to 0.24)	0.64	11% (0.35)
Anxiety scores					
At completion of therapy with CBT	5	465	-0.17 (-0.42 to 0.09)	0.20	43% (0.13)
At final point of follow-up with CBT	2	204	-0.10 (-0.45 to 0.26)	0.59	44% (0.18)
At completion of therapy with third wave	5	379	-0.27 (-0.50 to -0.04)	0.02	16% (0.31)
At final point of follow-up with third wave	4	263	-0.15 (-0.48 to 0.19)	0.40	43% (0.16)
Depression scores					
At completion of therapy with CBT	5	466	-0.24 (-0.45 to -0.03)	0.03	21% (0.28)
At final point of follow-up with CBT	2	204	-0.20 (-0.46 to 0.07)	0.15	0% (0.47)
At completion of therapy with third wave	7	454	-0.36 (-0.55 to -0.17)	<0.001	0% (0.59)
At final point of follow-up with third wave	6	338	-0.26 (-0.47 to -0.04)	0.02	0% (0.90)

Stress scores					
At completion of therapy with CBT	4	333	-0.01 (-0.35 to 0.34)	0.98	54% (0.09)
At final point of follow-up with CBT	4	300	-0.13 (-0.39 to 0.14)	0.35	20% (0.29)
At completion of therapy with third wave	6	430	-0.39 (-0.61 to -0.17)	<0.001	18% (0.29)
At final point of follow-up with third wave	4	201	-0.39 (-0.71 to -0.06)	0.02	23% (0.27)
Quality of life scores					
At completion of therapy with CBT	6	435	0.34 (0.08 to 0.60)	<0.001	37% (0.16)
At final point of follow-up with CBT	4	216	0.33 (-0.08 to 0.73)	0.11	41% (0.17)
At completion of therapy with third wave	6	372	0.37 (0.16 to 0.57)	<0.001	0% (0.45)
At final point of follow-up with third wave	5	259	0.20 (-0.06 to 0.46)	0.13	6% (0.37)

SMD; standardised mean difference

Table 6.4. Effect of Psychological Therapy on Clinical Disease Activity Indices and Anxiety, Depression, Stress, and Quality of Life Scores in Selected and Unselected Patients with Quiescent IBD.

	Number of trials	Number of patients	SMD for Effect of Psychological Therapies (95% confidence interval)	*p* value for the difference	I^2 (*p* value for χ^2)
Disease activity indices					
At completion of therapy in selected patients	5	409	-0.06 (-0.26 to 0.14)	0.55	0% (0.79)
At final point of follow-up in selected patients	4	204	0.05 (-0.23 to 0.33)	0.71	0% (0.68)
At completion of therapy in unselected patients	8	606	0.03 (-0.13 to 0.19)	0.73	0% (0.84)
At final point of follow-up in unselected patients	7	459	-0.07 (-0.25 to 0.12)	0.49	0% (0.86)
Anxiety scores					
At completion of therapy in selected patients	7	546	-0.37 (-0.54 to -0.21)	<0.001	0% (0.55)
At final point of follow-up in selected patients	5	338	-0.21 (-0.44 to 0.01)	0.06	6% (0.38)
At completion of therapy in unselected patients	6	542	-0.07 (-0.24 to 0.09)	0.39	0% (0.56)
At final point of follow-up in unselected patients	4	362	-0.11 (-0.39 to 0.17)	0.44	41% (0.15)

Depression scores					
At completion of therapy in selected patients	7	546	-0.43 (-0.60 to -0.26)	<0.001	0% (0.50)
At final point of follow-up in selected patients	5	338	-0.18 (-0.39 to 0.03)	0.10	0% (0.79)
At completion of therapy in unselected patients	8	643	-0.12 (-0.28 to 0.03)	0.12	0% (0.92)
At final point of follow-up in unselected patients	7	518	-0.15 (-0.33 to 0.02)	0.09	0% (0.82)
Stress scores					
At completion of therapy in selected patients	4	341	-0.45 (-0.74 to -0.17)	0.002	39% (0.18)
At final point of follow-up in selected patients	2	112	-0.62 (-1.00 to -0.24)	0.002	0% (0.69)
At completion of therapy in unselected patients	7	472	-0.07 (-0.28 to 0.14)	0.54	21% (0.27)
At final point of follow-up in unselected patients	7	439	-0.08 (-0.29 to 0.12)	0.43	12% (0.34)
Quality of life scores					
At completion of therapy in selected patients	6	464	0.44 (0.26 to 0.63)	<0.001	0% (0.57)
At final point of follow-up in selected patients	5	271	0.08 (-0.16 to 0.31)	0.52	0% (0.95)
At completion of therapy in unselected patients	10	616	0.21 (0.01 to 0.42)	0.04	35% (0.13)
At final point of follow-up in unselected patients	9	502	0.18 (-0.06 to 0.43)	0.14	42% (0.09)

SMD; standardised mean difference

6.4.2.2 Effect of Psychological Therapy on Anxiety, Depression, Stress, and Quality of Life Scores in Patients with Quiescent IBD

Thirteen RCTs provided data on the effect of psychological therapy on anxiety scores in IBD at completion of therapy,[10,11,19-24,27,28,35,36,40] and nine at the final point of follow-up.[10,11,23,26,27,35,36,39,40] At completion of therapy, when data were pooled from a total of 1088 patients, anxiety scores were significantly lower in those assigned to a psychological therapy (SMD = -0.23; 95% CI -0.36 to -0.09) (Figure 6.3 and Table 6.2). There was no heterogeneity between the included RCTs (I^2 = 18%). The effect was similar when the three trials recruiting a mixed population of patients were excluded from the analysis (SMD = -0.20; 95% CI -0.36 to -0.05).[20-22] The significant difference in anxiety scores did not persist at the last point of follow-up in 700 patients (SMD = -0.17; 95% CI = -0.34 to 0.01) (see appendix page 6 and Table 6.2). Subgroup analysis in trials of CBT or third wave therapies demonstrated that third wave therapies had a significant impact on anxiety scores, but this was only at completion of therapy (Table 6.3). The effect on anxiety scores was only seen in trials recruiting selected patients, and this was only seen at completion of therapy (Table 6.4).

Fifteen RCTs examined the effect of psychological therapy on depression scores in IBD at end of therapy,[10,11,19-24,27,29,34-37,40] and 12 at the final point of follow-up.[10,11,23,26,27,29,34-37,39,40] Data were available for 1189 patients at completion of therapy, with a significant reduction in depression scores for those treated with psychological therapy compared with control (SMD = -0.26; 95% CI -0.38 to -0.15) (Figure 6.4 and Table 6.2), and no heterogeneity between studies (I^2 = 2%). Removing the three studies with a mixed population of patients had no effect on the pooled result (SMD = -0.28; 95% CI -0.41 to -0.15).[20-22] At the final point of follow-up, when data were pooled from 856 patients, the effect on depression scores persisted (SMD = -0.16; 95% CI -0.30 to -0.03), with no heterogeneity (I^2 = 0%) (see appendix page 7 and Table 6.2). Subgroup analysis in trials of CBT or third wave

therapies demonstrated that both CBT and third wave therapies had a significant impact on depression scores at completion of therapy, but this was only present at final point of follow-up for third wave therapies (Table 6.3). Again, the effect on depression scores was only seen in trials recruiting selected patients, and this was only seen at completion of therapy (Table 6.4).

Eleven RCTs reported data on the effect of psychological therapy on stress scores in IBD, when compared with control, at completion of therapy,[10,11,20,23,24,32-36,38] and nine at the final point of follow-up.[10,11,23,32-36,38] When data were pooled at the end of therapy, psychological therapy led to a reduction in stress scores in 813 patients (SMD = -0.22; 95% CI -0.42 to -0.03) (see appendix page 8 and Table 6.2), with borderline moderate heterogeneity between studies (I^2 = 47%). At the final point of follow-up, when data were available for 551 patients, there was no longer a beneficial effect of psychological therapies compared with control (SMD = -0.18; 95% CI -0.40 to 0.04) (see appendix page 9 and Table 6.2). A significant effect on stress scores was only demonstrated in trials of third wave therapies, and this persisted to the final point of follow-up (Table 6.3). The effect on stress scores was only seen in trials recruiting selected patients, and this persisted to the final point of follow-up (Table 6.4).

Sixteen RCTs reported data on the effect of psychological therapy on quality of life in IBD at completion of therapy,[10,19-24,28,29,32-34,36-38,40] and 14 at the final point of follow-up.[10,19,23,26,28,29,32-34,36-40] There was a significant improvement in IBD-specific quality of life at completion of therapy, when data were pooled from 1080 patients (SMD = 0.31; 95% CI = 0.16 to 0.46) (Figure 6.5 and Table 6.2), with low heterogeneity between studies (I^2 = 30%). Exclusion of the three studies recruiting a mixed population of patients had no impact on the pooled result (SMD = 0.34; 95% CI 0.17 to 0.52).[20-22] However, at the final point of follow-up in 773 patients the effect of psychological therapies on quality of life was no longer

significant (SMD = 0.13; 95% CI -0.02 to 0.29) (see appendix page 10 and Table 6.2). A significant improvement in quality of life scores was seen in trials of both CBT and third wave therapies at completion of therapy, but this did not persist to the final point of follow-up with either (Table 6.3). An improvement in quality of life anxiety scores was seen in trials recruiting both selected and unselected patients, but was strongest in selected patients and did not persist to the final point of follow-up (Table 6.4).

Figure 6.3. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Anxiety Scores in Patients with Quiescent IBD at Completion of Therapy.

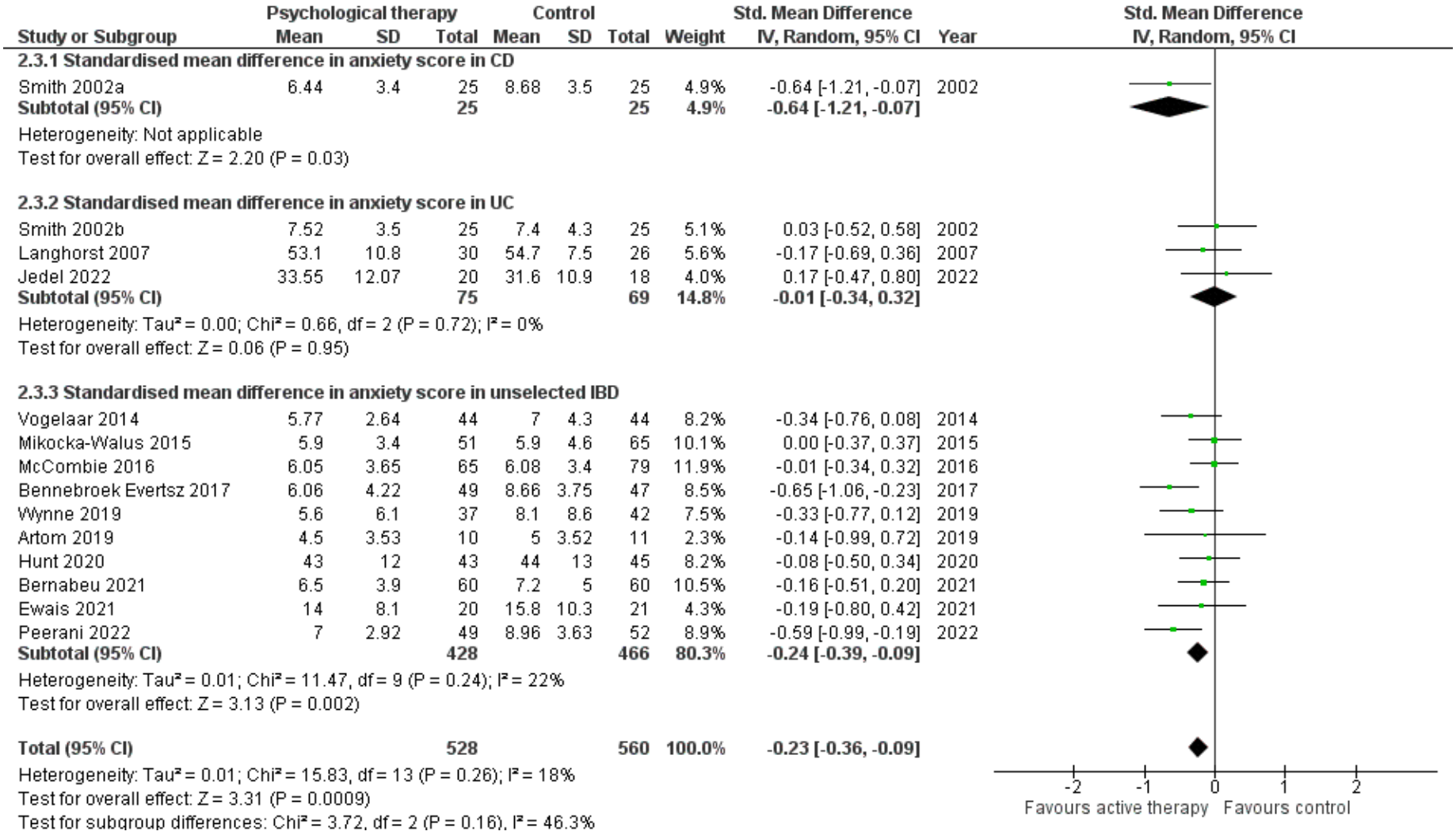


Figure 6.4. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Depression Scores in Patients with Quiescent IBD at Completion of Therapy.

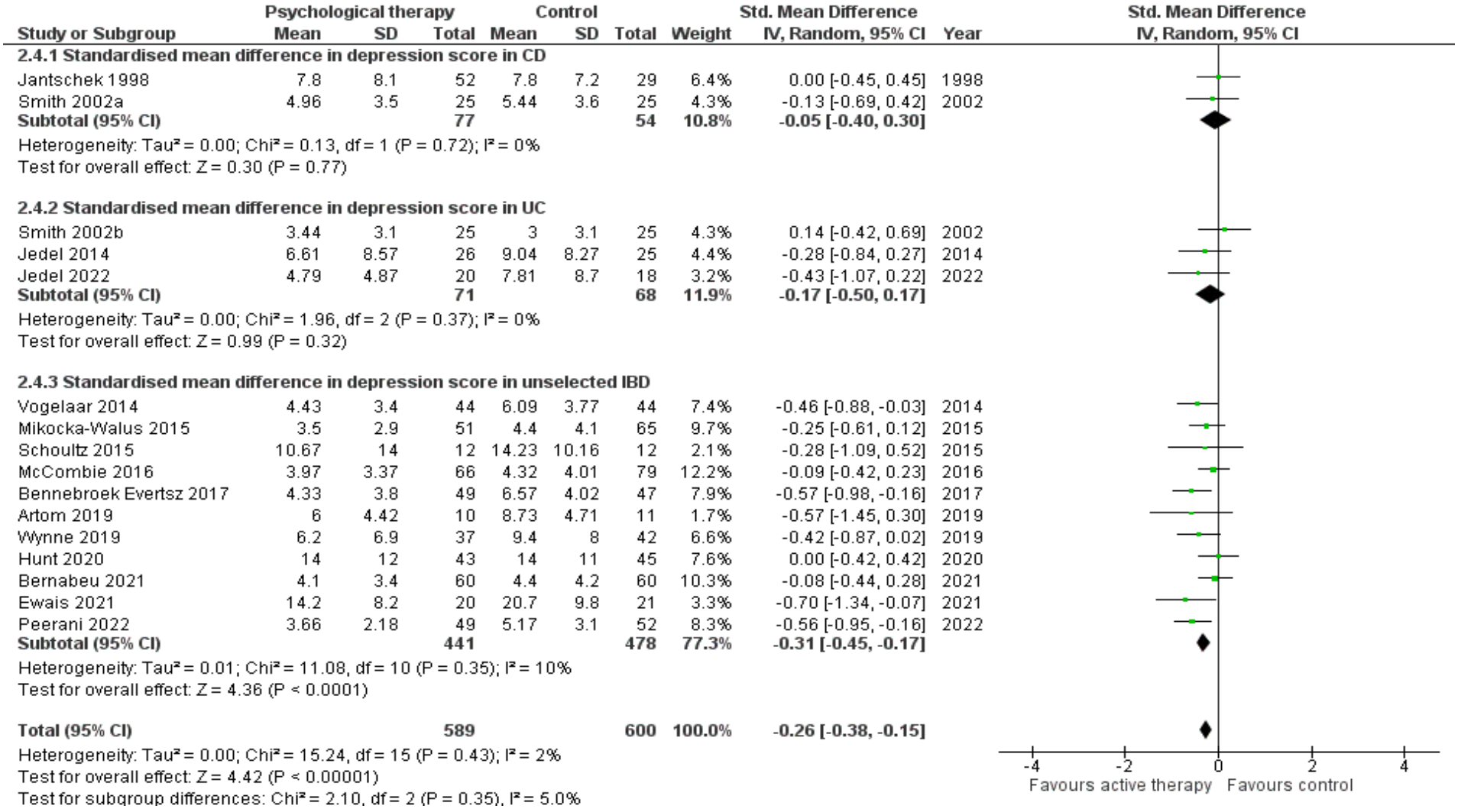
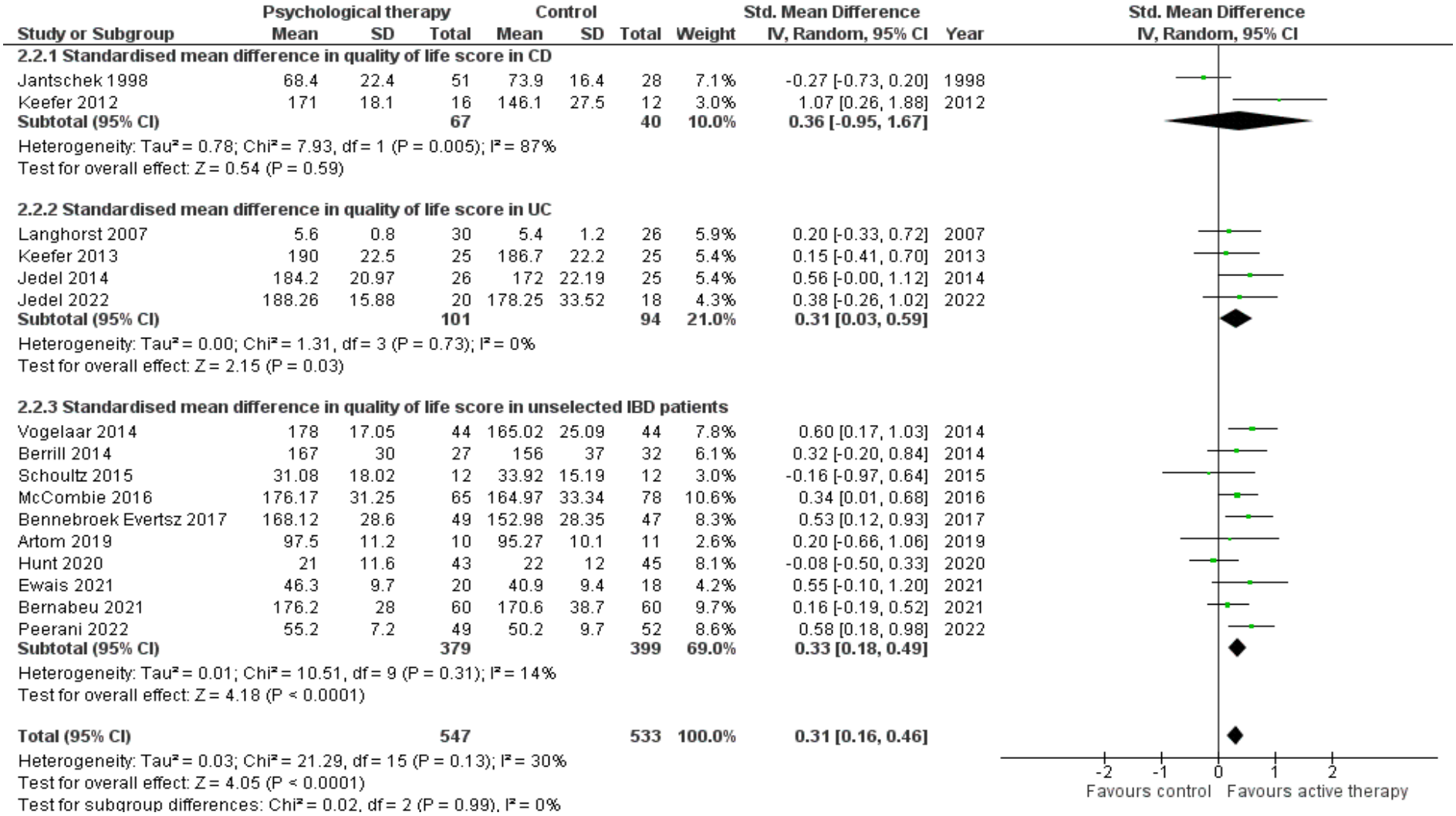


Figure 6.5. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Quality of Life Scores in Patients with Quiescent IBD at Completion of Therapy.



6.5 Discussion

We present findings from an updated systematic review and meta-analysis, examining the effects of psychological therapies on disease activity indices, disease relapse, psychological health, and quality of life in IBD. To date, only one study has examined the effect of psychological therapy on clinically active disease,[9] preventing any formal conclusions as to their effect in terms of inducing remission. The limited number of trials in patients with active disease also precluded formal meta-analysis to examine their effects on psychological health, other than anxiety scores, where no benefit was demonstrated. There was no impact of psychological therapies on the risk of relapse of disease activity or clinical disease activity indices in patients with quiescent IBD. In terms of other endpoints, however, psychological therapies when considered together led to short-term improvements in anxiety, depression, and stress scores in patients in remission and, in the case of the effect on depression scores this persisted to the last point of follow-up. Most of the effect sizes observed were small, but some were in the moderate range. When we performed subgroup analysis, only third wave therapies were associated with significant effects on anxiety and stress scores at completion of therapy, but both CBT and third wave therapies led to improvements in depression scores at this point in time. Third wave therapies were also associated with improvements in depression and stress scores at final follow-up. Anxiety, depression, and stress scores only improved in trials recruiting selected groups of patients in whom psychological therapy might be expected to have the most benefit. Quality of life scores improved with psychological therapies after completion of treatment for both patients with active and quiescent disease, with CBT and third wave therapies, and in selected and unselected patients, although this was no longer significant at the last point of follow-up. We found no significant differences regarding the effects of psychological therapies between patients with CD and UC.

The number of eligible trials since the previous version of this meta-analysis has increased considerably, with data from an additional 11 studies since our last review.[8] Other strengths include the independent eligibility assessment and data extraction done in duplicate, our use of a random effects model in the analyses, to give a more conservative estimate of the effect of psychological therapies in IBD, and the subgroup analyses according to modality of psychological treatment and whether patients were those who could be expected to be more likely to respond to psychological therapy, rather than unselected patients with IBD. We used an intention-to-treat analysis for dichotomous outcomes, with all patients lost to follow-up presumed to be treatment failures. We also extracted data separately, wherever possible, according to type of IBD, and performed analyses separately according to disease activity at the time of recruitment, which enabled accurate interpretation of the effects of psychological therapies in these separate patient populations. Furthermore, we contacted authors of the original studies to obtain supplementary data, maximising the number of studies eligible for inclusion.

Limitations arise particularly in the subgroup of patients with clinically active IBD, where the small number of studies precludes, for the most part, any meaningful conclusions being drawn. Furthermore, there was significant heterogeneity between these trials in our analysis of effect on quality of life scores. None of the trials were at low risk of bias, largely because blinding in trials of psychological therapy is logistically difficult. Of the 24 studies included, only two trials were reported as being double-blind.[23,34] In addition, many of the trials that reported continuous data only provided results for patients that completed the treatment course, which may mean that the benefit of psychological therapies in IBD has been overestimated. Our pooling of individual RCT's together to consider the effect of psychological therapy as one entity, despite studies recruiting different patient groups, adopting different protocols including the type of psychological intervention administered,

method of delivery, duration of treatment, and frequency of sessions, could be criticised. However, we attempted to address this, to some extent, performing separate analyses for CBT and third wave therapies, as well as patient group. Nevertheless, there are limitations in comparing CBT with third wave therapies, since the latter are derived from CBT,[41] although they feature certain new constructs, such as acceptance or mindfulness. In addition, classic CBT studies tend to be older while third wave could be considered the new 'improved' CBT. We were unable to compare CBT with any other therapies as too few trials were available. This is an important gap in the literature. It would be of great practical interest to gastro-psychologists to know if there are indeed any differences in efficacy between more traditional, and longer, approaches, such as psychodynamic therapy, and briefer therapies, such as CBT. Finally, given the multitude of pharmacological treatments with an established efficacy to treat IBD, the fact that few studies detailed alterations in medication, or treatment escalation, throughout the study period could present a significant confounding factor when considering the effectiveness of psychological therapies, particularly in patients with active disease.

For functional gastrointestinal disorders, where gut-brain axis communication is considered to be a fundamental driver of symptom burden, psychological therapies have an established role in reducing both the symptoms of anxiety and depression, and physical symptom burden.[42-44] Symptoms compatible with functional bowel disorders are reported by up to one-third of patients with quiescent IBD,[45-47] and evidence from a meta-analysis of more than 9000 patients highlights that gut-brain axis interactions also contribute to the natural history of IBD.[5] However, only two eligible RCT reported that they recruited patients with "functional" symptoms, which met criteria for irritable bowel syndrome, in patients with quiescent disease,[22,33] and only one reported a subgroup analysis examining this issue.[33] Furthermore, the presence of psychological co-morbidity in IBD contributes to both adverse

disease outcomes and increased healthcare utilisation,[3-7] which is particularly relevant given the prevalence of psychological co-morbidity in patients with IBD compared with the general population.[2] Studies have previously demonstrated that screening for psychological co-morbidity is feasible in clinical practice,[48] and national guidelines acknowledge that psychological therapies have a role in IBD management,[49] but there remains a lack of official guidance as to which patients to refer for psychological therapies, and when. This may be due, in part, to uncertainty regarding their effectiveness, with individual studies demonstrating promising results, but previous meta-analyses failing to demonstrate more than non-sustained improvements in quality of life and depression.[8,50] The findings from this meta-analysis demonstrate, however, that some psychological therapies, particularly third wave therapies, may be associated with sustained improvements in psychological health and quality of life, particularly in patients with abnormal psychological health, fatigue, or impaired quality of life at baseline. This supports a role for such therapies in clinical practice.

Perhaps disappointing, is that despite the fact that psychological co-morbidity in IBD is most prevalent during periods of disease activity,[2,7] or in patients with quiescent disease with co-existing symptoms compatible with a functional bowel disorder,[45,46] there were very few RCTs examining the effects of psychological therapies in these populations. Furthermore, most trials assessing psychological therapies in quiescent disease have been conducted in unselected patients with IBD, irrespective of psychological health, despite there being evidence for a benefit in this distinct group of patients, particularly in paediatric populations.[48,51,52] This means it is unlikely these will demonstrate a major benefit, and this hypothesis was supported by the results of our subgroup analyses. Even if they were of benefit in unselected patients, IBD services simply do not have the funding, or resources, to provide access to such therapies for all patients. It is, therefore, imperative that future RCTs focus on assessing the impact of psychological therapies in patients who exhibit higher levels

of psychological symptoms at study entry or patients with IBS-type symptoms in the presence of biochemical or mucosal remission, as well as others at risk of poorer outcomes such as people reporting significant levels of pain or fatigue, who are more likely to benefit.

In summary, the findings of this systematic review and meta-analysis demonstrate the efficacy of psychological therapies in providing short-term improvements in anxiety, depression, stress, and quality of life scores in patients with IBD, but not disease activity indices in patients with either active or quiescent disease or preventing relapse of disease activity in patients in remission. Third wave therapies appeared to exert the strongest effect, and this benefit persisted longer-term for depression and stress scores with this treatment modality. However, further prospective trials assessing the efficacy of these therapies in patients who are most likely to benefit are needed to enable formal guidelines to be developed to aid clinicians in the selection of patients for psychological therapy in clinical settings.

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Supplementary Table 6.1. Eligibility Criteria.

Randomised controlled trials.
Patients aged ≥16 years with a confirmed diagnosis of IBD, according to endoscopic, histological, or radiological criteria.
Compared psychological therapies with a control, including a physician's "usual management", symptom monitoring, or supportive therapy.
Reported a dichotomous assessment of failure of remission in active disease or relapse of disease activity in quiescent disease, or a continuous assessment of clinical disease activity, anxiety, depression, stress, or quality of life.

Supplementary Table 6.2. Assessment of Risk of Bias of Included Studies.

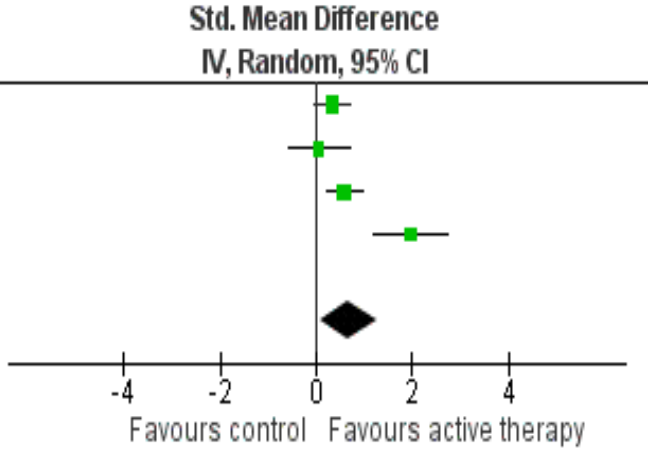
Study and Year	Method of Generation of Randomisation Schedule Stated?	Method of Concealment of Treatment Allocation Stated?	Blinding?	No Evidence of Incomplete Outcomes Data?	No Evidence of Selective Reporting of Outcomes?	Overall Assessment
Jantschek 1998 [1]	Unclear	Low	High	High	Low	High
Smith 2002 [2]	Unclear	Unclear	High	Low	Low	High
Langhorst 2007 [3]	Unclear	Unclear	High	Low	Low	High
Boye 2011[4]	Low	Low	High	High	Low	High
Vogelaar 2011[5]	Low	Unclear	High	High	Low	High
Keefer 2012 [6]	Low	Unclear	High	High	Low	High
Mizrahi 2012 [7]	Unclear	Unclear	High	High	Low	High
Keefer 2013 [8]	Low	Yes	High	Low	Low	High
Berrill 2014 [9]	Low	Unclear	High	High	Low	High
Jedel 2014 [10]	Low	Low	Low	High	Low	High
Vogelaar 2014[11]	Low	Unclear	High	Low	Low	High
Mikocka-Walus 2015 [12]	Low	Unclear	High	High	Low	High
Schoultz 2015 [13]	Low	Unclear	High	High	Low	High
McCombie 2016 [14]	Low	Unclear	High	High	Low	High
Bennebroek Evertsz 2017 [15]	Low	Low	High	High	Low	High
Artom 2019 [16]	Low	Low	High	High	Low	High
Wynne 2019 [17]	Low	Low	High	High	Low	High
Hunt 2019 [18]	Low	Low	High	High	Low	High
Bernabeu 2021 [19]	Low	Unclear	High	Low	Low	High
Ewais 2021 [20]	Low	Low	High	High	Low	High
Goren 2022 [21]	Low	Unclear	High	High	Low	High
Jedel 2022 [22]	Low	Low	Low	High	Low	High
Peerani 2022 [23]	Low	Low	High	Low	Low	High
Xi 2022 [24]	Low	Unclear	High	Low	Low	High
Bredero 2023 [25]	Low	Low	High	Low	Low	High

Supplementary Figure 6.1. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Quality of Life Scores in Patients with Active IBD at Completion of Therapy.

	Psychological therapy			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Boye 2011	173	25.1	57	164.1	27.2	57	28.2%	0.34 [-0.03, 0.71]	2011
Mizrahi 2012	177	28.62	18	175.48	20.53	21	23.2%	0.06 [-0.57, 0.69]	2012
Goren 2022	47.93	9.66	55	41.64	11.41	61	28.1%	0.59 [0.22, 0.96]	2022
Xi 2022	166.72	14.3	20	140.28	11.97	20	20.5%	1.97 [1.20, 2.73]	2022
Total (95% CI)			**150**			**159**	**100.0%**	**0.68 [0.09, 1.26]**	

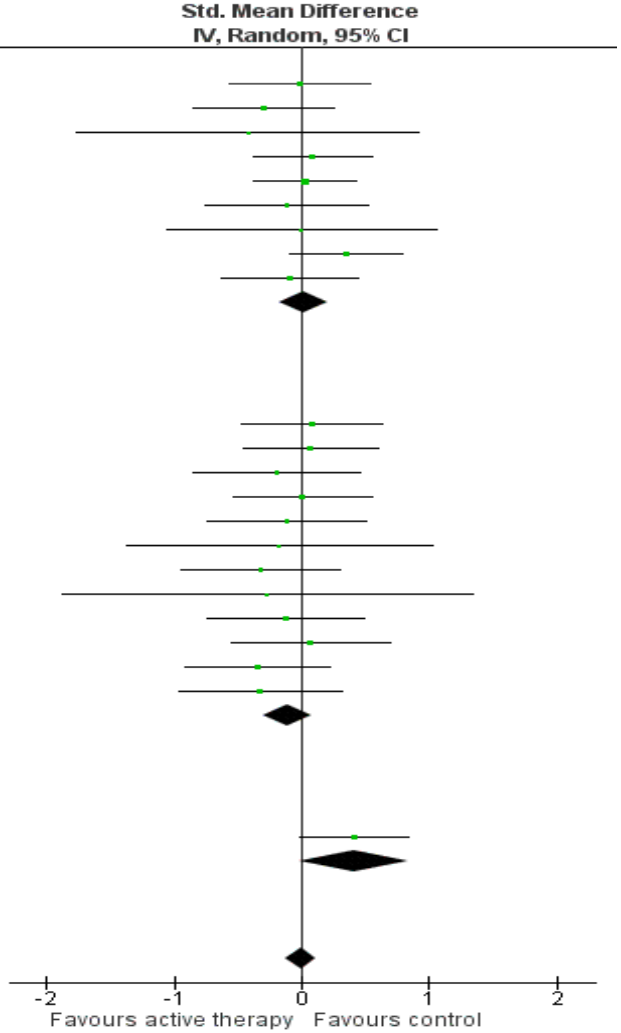
Heterogeneity: Tau² = 0.28; Chi² = 16.67, df = 3 (P = 0.0008); I² = 82%

Test for overall effect: Z = 2.27 (P = 0.02)

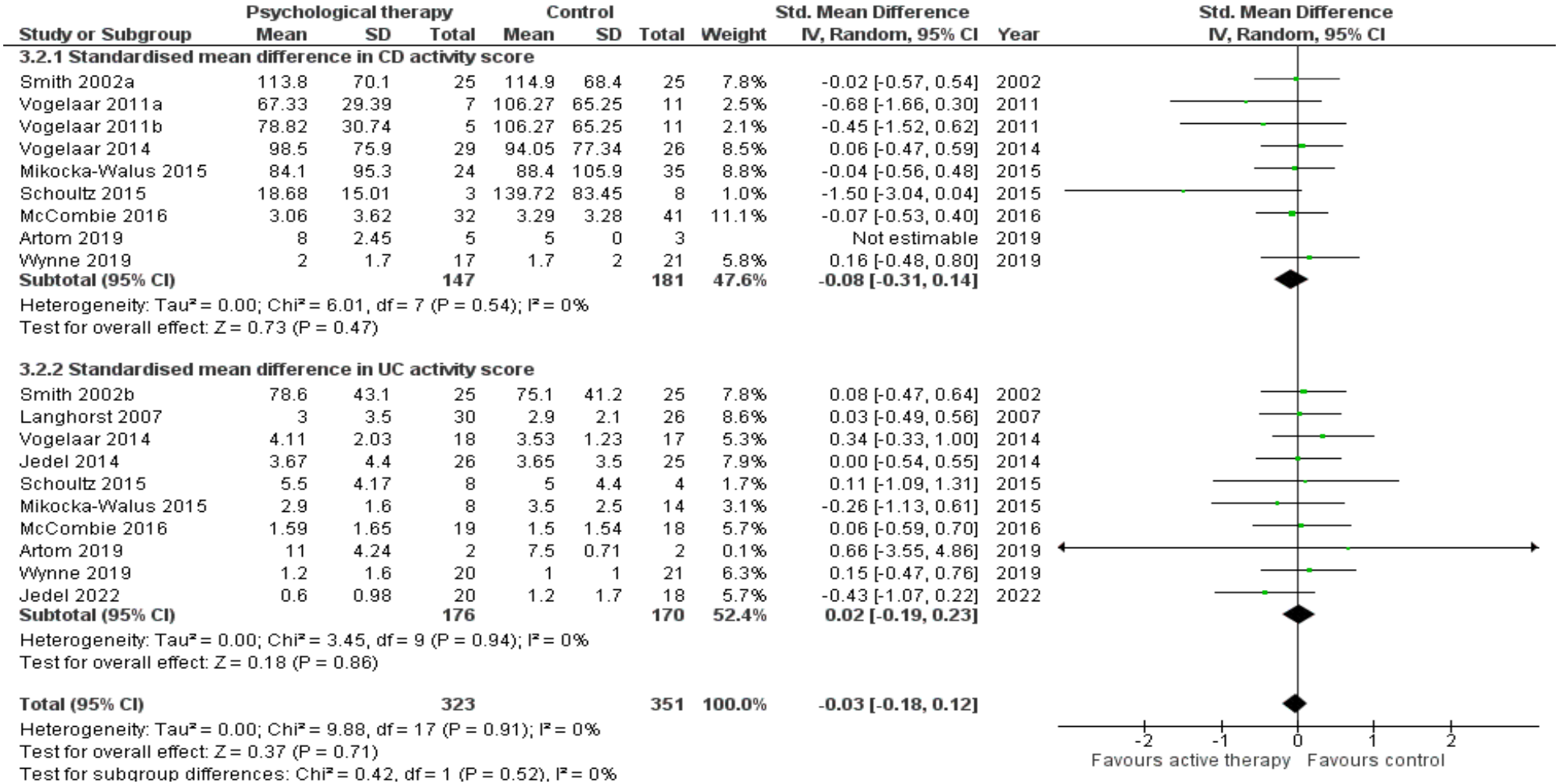


Supplementary Figure 6.2. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Disease Activity Indices in Patients with Quiescent IBD at Completion of Therapy.

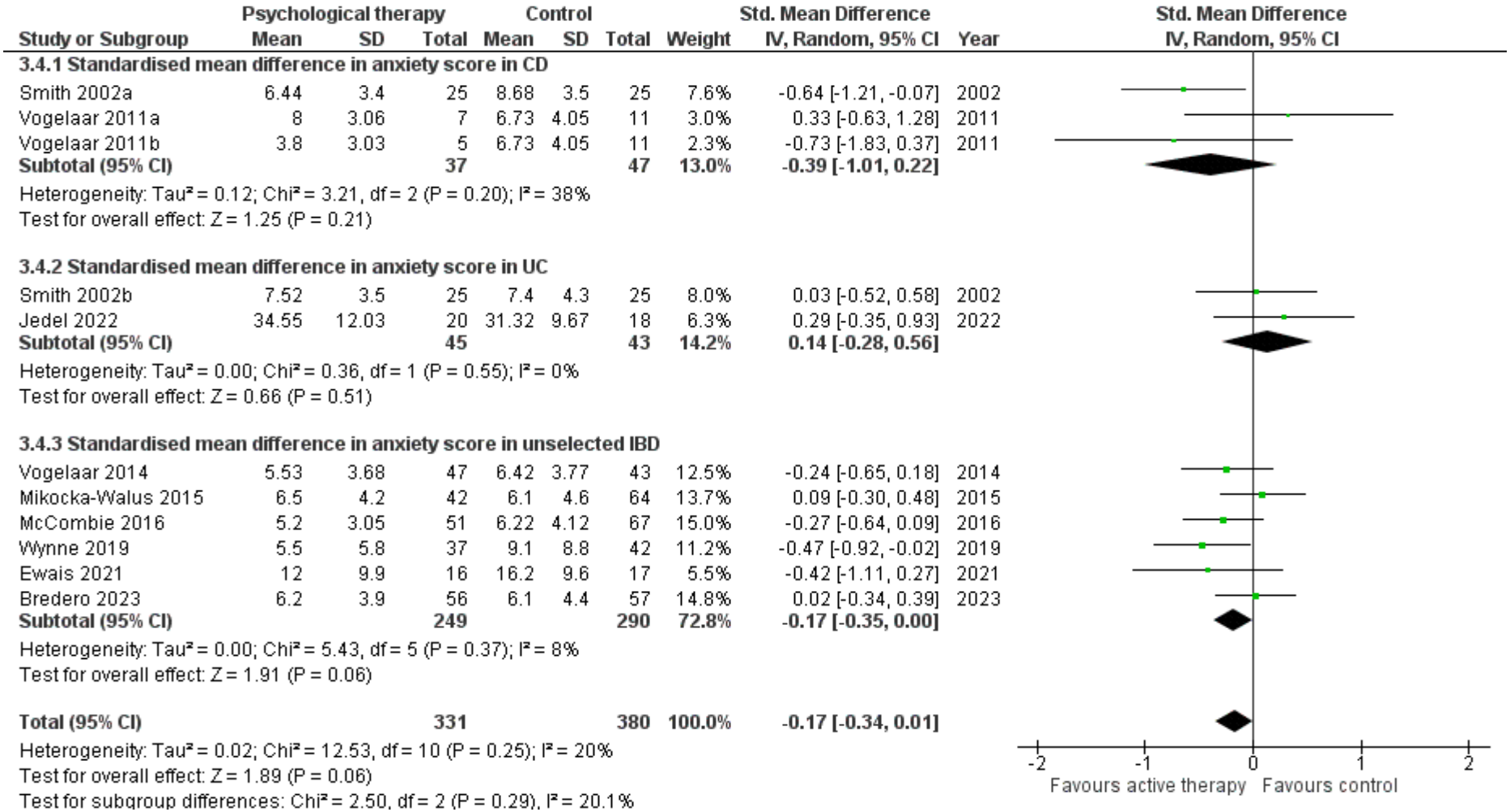
Study or Subgroup	Psychological therapy Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
2.1.1 Standardised mean difference in CD activity score									
Smith 2002a	113.8	70.1	25	114.9	68.4	25	5.0%	-0.02 [-0.57, 0.54]	2002
Vogelaar 2014	79.45	58.39	27	97.71	60.65	24	5.0%	-0.30 [-0.86, 0.25]	2014
Schoultz 2015	69	86.16	3	101.88	66.69	8	0.9%	-0.42 [-1.77, 0.92]	2015
Mikocka-Walus 2015	91.3	90.3	33	83.2	92.2	39	7.2%	0.09 [-0.38, 0.55]	2015
McCombie 2016	3.88	4.01	43	3.77	3.96	53	9.5%	0.03 [-0.37, 0.43]	2016
Wynne 2019	1.9	1.6	17	2.1	1.8	21	3.8%	-0.11 [-0.75, 0.53]	2019
Artom 2019	5.5	6.05	8	5.5	4.46	6	1.4%	0.00 [-1.06, 1.06]	2019
Bernabeu 2021	131	111.2	43	97.3	72.9	37	7.9%	0.35 [-0.09, 0.79]	2021
Peerani 2022	4.2	3.7	25	4.5	2.8	28	5.3%	-0.09 [-0.63, 0.45]	2022
Subtotal (95% CI)			**224**			**241**	**45.9%**	**0.02 [-0.17, 0.20]**	
Heterogeneity: Tau² = 0.00; Chi² = 4.27, df = 8 (P = 0.83); I² = 0%									
Test for overall effect: Z = 0.18 (P = 0.86)									
2.1.2 Standardised mean difference in UC activity score									
Smith 2002b	78.6	43.1	25	75.1	41.2	25	5.0%	0.08 [-0.47, 0.64]	2002
Langhorst 2007	2.9	2.8	30	2.7	2.6	26	5.6%	0.07 [-0.45, 0.60]	2007
Vogelaar 2014	3.88	1.67	16	4.2	1.58	20	3.6%	-0.19 [-0.85, 0.47]	2014
Jedel 2014	3.67	4.4	26	3.65	3.5	25	5.1%	0.00 [-0.54, 0.55]	2014
Mikocka-Walus 2015	3.5	1.8	16	3.7	1.6	26	4.0%	-0.12 [-0.74, 0.51]	2015
Schoultz 2015	3.88	3.4	8	4.5	3	4	1.1%	-0.17 [-1.38, 1.03]	2015
McCombie 2016	1.45	2.95	20	2.45	3.15	20	4.0%	-0.32 [-0.95, 0.30]	2016
Artom 2019	4	2.83	2	4.5	1.22	6	0.6%	-0.27 [-1.88, 1.34]	2019
Wynne 2019	1.1	1.7	20	1.3	1.5	21	4.1%	-0.12 [-0.74, 0.49]	2019
Bernabeu 2021	1.47	2.4	17	1.3	2.3	23	3.9%	0.07 [-0.56, 0.70]	2021
Peerani 2022	0.8	1.1	24	1.3	1.7	24	4.7%	-0.34 [-0.91, 0.23]	2022
Jedel 2022	0.48	1.07	20	0.9	1.44	18	3.8%	-0.33 [-0.97, 0.31]	2022
Subtotal (95% CI)			**224**			**238**	**45.4%**	**-0.11 [-0.29, 0.07]**	
Heterogeneity: Tau² = 0.00; Chi² = 3.05, df = 11 (P = 0.99); I² = 0%									
Test for overall effect: Z = 1.17 (P = 0.24)									
2.1.3 Standardised mean difference in IBD activity score									
Hunt 2020	8.95	5.5	43	7.05	3.5	45	8.6%	0.41 [-0.01, 0.83]	2020
Subtotal (95% CI)			**43**			**45**	**8.6%**	**0.41 [-0.01, 0.83]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.90 (P = 0.06)									
Total (95% CI)			**491**			**524**	**100.0%**	**-0.01 [-0.13, 0.12]**	
Heterogeneity: Tau² = 0.00; Chi² = 12.34, df = 21 (P = 0.93); I² = 0%									
Test for overall effect: Z = 0.11 (P = 0.91)									
Test for subgroup differences: Chi² = 5.02, df = 2 (P = 0.08), I² = 60.2%									



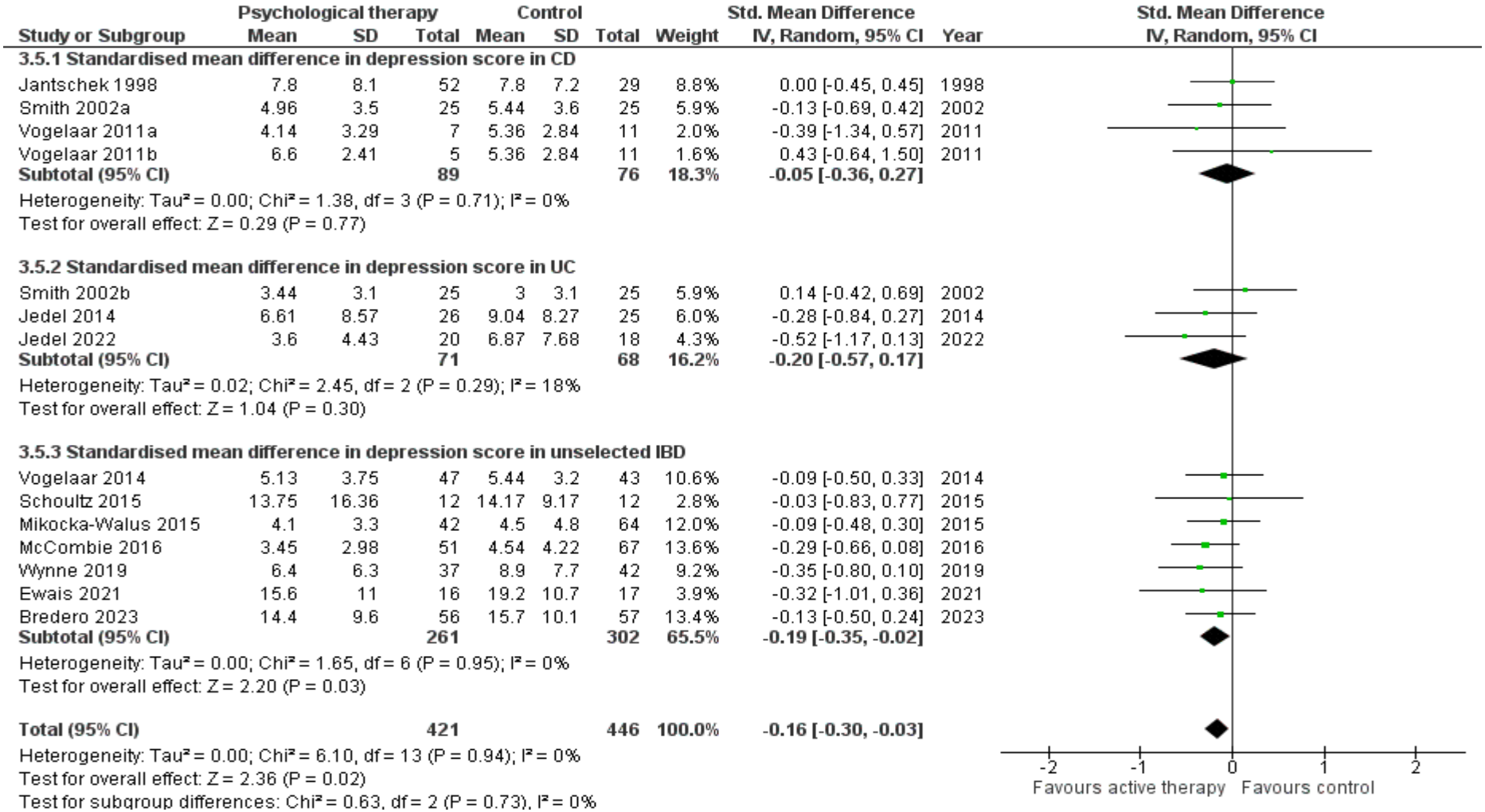
Supplementary Figure 6.3. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Disease Activity Indices in Patients with Quiescent IBD at the Final Point of Follow-up.



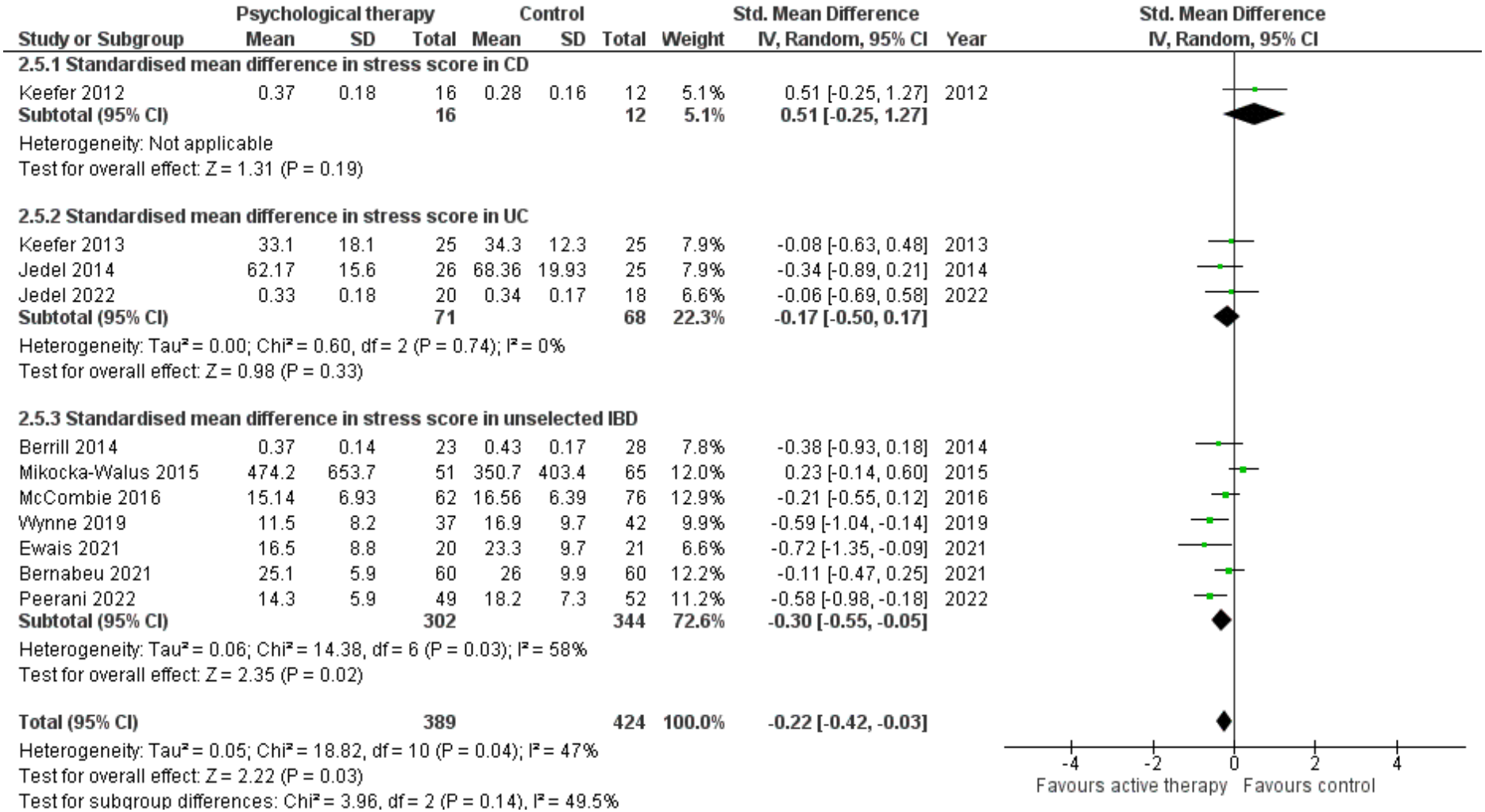
Supplementary Figure 6.4. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Anxiety Scores in Patients with Quiescent IBD at the Final Point of Follow-up.



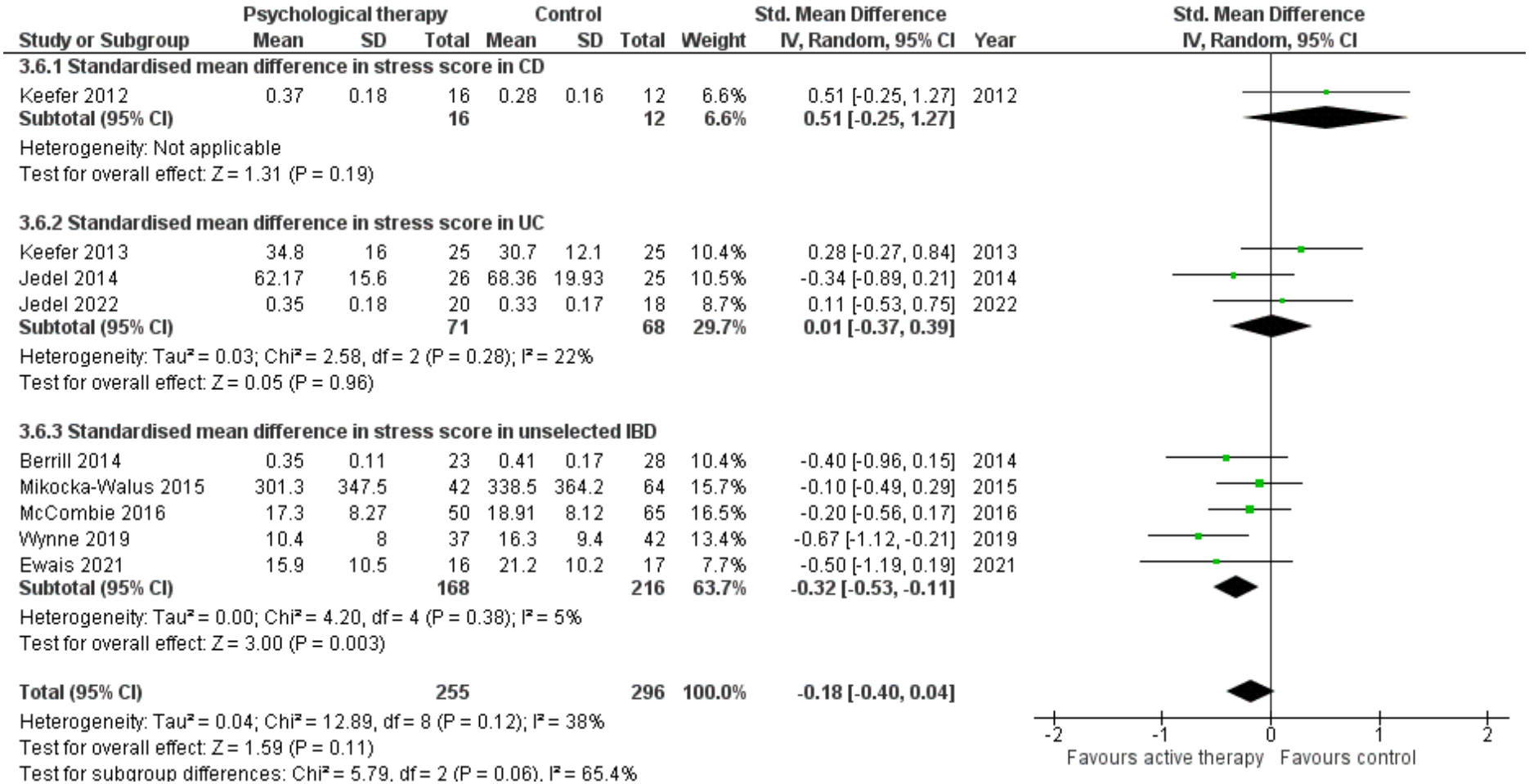
Supplementary Figure 6.5. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Depression Scores in Patients with Quiescent IBD at the Final Point of Follow-up.



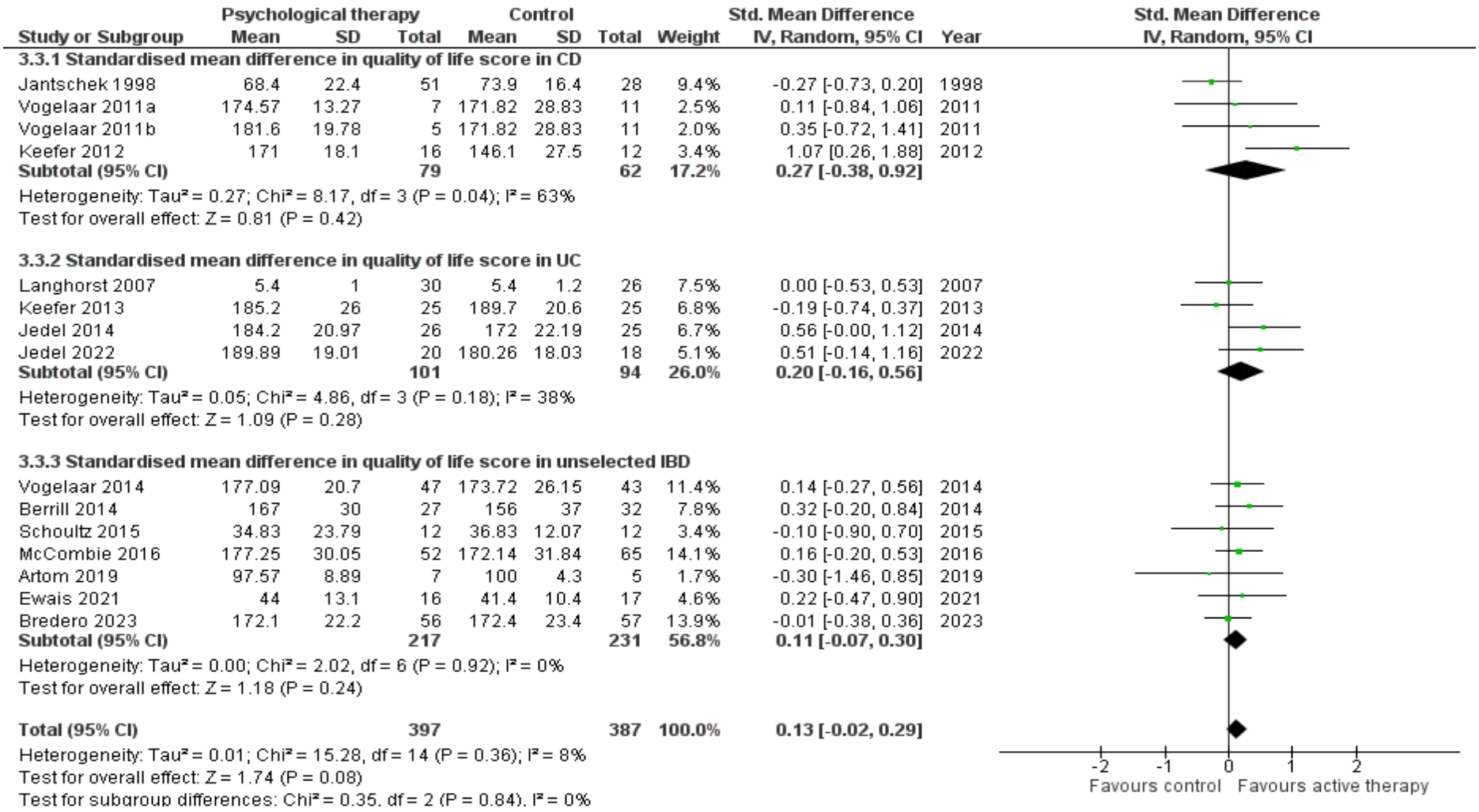
Supplementary Figure 6.6. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Stress Scores in Patients with Quiescent IBD at Completion of Therapy.



Supplementary Figure 6.7. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Stress Scores in Patients with Quiescent IBD at the Final Point of Follow-up.



Supplementary Figure 6.8. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Quality of Life Scores in Patients with Quiescent IBD at the Final Point of Follow-up.



Chapter 7: Discussion

The turn of the 21st century has brought with it substantial medical advances in IBD, including the implementation of the non-invasive faecal biomarker FC to reliably delineate disease activity without the need for endoscopic evaluation, and the introduction of a multitude of advanced therapies with proven efficacy in treating the inflammatory aspect of the disease.[1-5] Associated declines in the number of IBD-related surgeries and mortality certainly attest to the success of these developments.[6-8] However, healthcare utilisation trends remain stable and the cost of IBD continues to rise, suggesting that the conventional model of IBD care does not address all the key aspects of the disease.[9-12] Higher than expected placebo response rates have been observed across RCTs examining novel therapies in IBD, which are considerably lower when objective measures of disease activity are adopted, and poor psychological health may be a potential driver of this discrepancy.[13-15] Furthermore, observational studies also highlight that the relationship between clinical disease activity indices, which are reliant on patient-reported outcome measures, and underlying inflammatory activity is discordant, with the former overestimating disease activity, particularly in individuals with poor psychological health.[15, 16]

The high prevalence of poor psychological health in patients with IBD, and its apparent adverse effects on disease outcomes, healthcare utilisation, and quality of life highlights bi-directional gut-brain axis effects and underscores the importance of addressing psychological health in routine care, moving more towards a biopsychosocial model.[16-19] However, although poor psychological health is highly prevalent in IBD, a consensus has yet to be reached as to how, and who, to screen for the presence of symptoms of anxiety and depression in routine clinical care.[20] Studies examining the prevalence of these symptoms are also restricted to cohorts of patients with established disease, which raises questions as to whether the high prevalence of poor psychological health in IBD is a result of genuine gut-brain communications or, as some researchers suggest, a response to having already

experienced an adverse disease course.[21] The fluctuating nature of IBD makes it difficult to discriminate the former from the latter, and most existing studies examine psychological health at a single time point in patients with established IBD.[17] Furthermore, much of the data pertaining to brain-gut effects in IBD is conducted using clinical disease activity scores in isolation, and therefore the results may be inaccurate for the reasons mentioned above.[17, 18] Studies examining the influence of disease activity and psychological health on long-term disease outcomes using objective measurements of the former are lacking. The combination of finite healthcare resources and a lack of evidence to guide clinicians as to when to offer psychological health screening, and whom to offer gut-brain axis-directed therapies to, likely contribute to the sole focus of medical management in IBD being the control of inflammatory activity.

Through the production of five distinct chapters, this thesis has explored the prevalence of symptoms of anxiety and depression amongst patients newly diagnosed with IBD, determining that these symptoms most likely arise from genuine gut-brain axis mediated effects, rather than a previous adverse disease course. The persistence of poor psychological health during follow-up of patients with IBD is highlighted, with a focus on the detrimental impact this has on the natural history of IBD and drawing attention to screening methods in routine clinical care, and the potential of gut-brain axis-directed therapies as adjunctive treatments for affected patients. The following sections will summarise the findings of the individual published chapters and provide a commentary to unify them as a single body of work

7.1 Summary of Chapter 2: Prevalence and Predictors of Symptoms of Anxiety or Depression at Diagnosis in Patients with Inflammatory Bowel Disease: An Inception Cohort.

There are few studies reporting on the prevalence of poor psychological health in newly diagnosed patients with IBD, and disentangling the role of gut-brain axis mediated interactions on poor psychological health from the effects of a preceding adverse disease on psychological health course is challenging in patients with established disease. This prospective cross-sectional study recruited patients at the point of receiving a diagnosis of IBD, all of whom had objectively confirmed disease activity. This study identified that the prevalence of symptoms of anxiety and depression was almost 40% in newly diagnosed patients, and most patients did not have a pre-existing mental health diagnosis. Furthermore, as participants were recruited prior to escalation or failure of medical therapy, or intestinal resection, a preceding adverse disease course was not possible. The findings that symptoms of anxiety and depression are highly prevalent at the point of diagnosis suggests genuine gut-brain effects, which may influence the subsequent disease course and strengthens the conclusions of the remaining chapters of this thesis regarding gut-brain axis mediated interactions.

7.2 Summary of Chapter 3: Persistence of Symptoms of Anxiety and Depression in Inflammatory Bowel Disease: A Longitudinal Follow-Up Study.

Psychological health is not a continuum and mood exhibits substantial fluctuations over time in the general population.[22] The findings of existing studies examining the role of the gut-brain axis in IBD, including the work presented in the chapters of this thesis, are largely based on single assessments of mood and could, therefore, be inaccurate. This study addressed this issue by collating assessments of mood at 3-monthly intervals over a 12-month

period to establish mood trajectories in a large cohort of patients with IBD. The effect of these mood trajectories on subsequent mood over a 2-year period was then examined. The finding that poor psychological health, as determined by a persistently abnormal or worsening trajectory of anxiety or depression, is a persistent issue for many patients over a prolonged period of longitudinal follow-up suggests that the psychological health of patients with IBD cannot be overlooked in routine care. Furthermore, it highlights that a single assessment of mood is sufficient in most patients to identify subsequent poor psychological health. This study also highlights that screening tools could be implemented in routine clinical care to identify patients with IBD who are suffering with concurrent poor psychological health.

7.3 Summary of Chapter 4: Novel Symptom Clusters Predict Disease Impact and Healthcare Utilisation in Inflammatory Bowel Disease: Prospective Longitudinal Follow-up Study.

Utilising model-based clustering techniques in a large cohort of patients, applying a combination of gastrointestinal and psychological symptoms, including measures of anxiety, depression, and somatoform symptom-reporting, this longitudinal follow-up study established the feasibility of subgrouping patients with IBD beyond conventional assessments of disease location, phenotype, or activity. Three unique clusters were derived: cluster 1 demonstrated below average gastrointestinal and psychological symptoms; cluster 2 had average levels of gastrointestinal and psychological symptoms; and cluster 3 had the highest levels of both gastrointestinal and psychological symptoms. During the longitudinal follow-up period, patients in cluster 3, with the highest psychological and gastrointestinal symptom burden, demonstrated the highest levels of healthcare utilisation and a significantly higher risk of disease flare or glucocorticosteroid prescription, treatment escalation, and a composite of

escalation, hospitalisation, or intestinal resection, compared with those in cluster 1 with the lowest level of these symptoms. They also had the greatest likelihood of experiencing any of the adverse disease outcomes of interest, compared with those in cluster 1. These findings suggest that when co-existing in individuals with active disease, poor psychological health has consequences for both individuals with IBD, in terms of their disease course, and healthcare services, in terms of cost and resource use.

7.4 Summary of Chapter 5: Cumulative Impact of Clinical Disease Activity, Biochemical Activity, and Psychological Health on the Natural History of Inflammatory Bowel Disease During 8 Years of Longitudinal Follow-up.

This study examined the cumulative impact of disease activity and poor psychological health on disease outcomes in IBD over an 8-year longitudinal follow-up period and determined that, in patients with evidence of disease activity, increasing psychological burden, as defined by the presence of symptoms of both anxiety and depression, was associated with a significantly increased risk of adverse disease outcomes, including a flare or need for glucocorticosteroid prescription and a higher all cause-mortality. Due to the potential for over-reporting of symptoms in patients with poor psychological health, a subgroup analysis of patients with combined clinical and biochemical disease activity was also conducted. This strengthened the findings, with individuals with clinical and biochemical activity and symptoms of two common mental disorders being significantly more likely to experience a flare or need for glucocorticosteroid prescription, escalation of medical therapy, hospitalisation, a composite of hospitalisation or intestinal resection, or death. The findings of this study highlight the long-term negative effects of poor psychological health in IBD and

draw attention to the gut-brain axis as a potential alternative therapeutic target in these patients.

7.5 Summary of Chapter 6: Effectiveness of Psychological Therapies in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis.

As alluded to in the introductory chapter of this thesis, there are a paucity of data pertaining to the efficacy of gut-brain axis-directed therapies in patients with evidence of poor psychological health. In healthcare systems with finite resources, psychological therapies are time consuming and necessitate the recruitment of additional allied healthcare professionals to deliver them. It is, therefore, important to understand which patients are likely to benefit from such interventions. This meta-analysis examined the efficacy of these therapies, determining that psychological therapies, and particularly third-wave therapies, may lead to sustained improvements in psychological health and quality of life. Subgroup analyses in trials recruiting patients with evidence of pre-existing poor psychological health were performed, including symptoms of fatigue, or impaired quality of life, with a clearer benefit evident in these patient groups. In healthcare systems with finite resources it is likely to be unrealistic to offer all patients with IBD access to psychological therapies. The subgroup analysis, therefore, highlights the importance of screening for poor psychological health to enable appropriate resource allocation to patients who are most likely to benefit from such interventions.

7.6 Conclusions

In summary, the work undertaken in this thesis underscores the high prevalence of symptoms of anxiety and depression in patients with IBD and confirms that poor

psychological health affects individuals newly diagnosed with the disease prior to the development of disease-related complications, and to a similar magnitude seen in those with established disease. This suggests genuine gut-brain effects in IBD. Furthermore, the persistence of abnormal mood has been confirmed over an 8-year period in a large group of patients, which coupled with the negative impacts on healthcare utilisation and disease outcomes also highlights the presence of brain-gut effects in IBD. This work, therefore, support bi-directional gut-brain axis communication in IBD and underscores the importance of moving toward a biopsychosocial model of care, with routine screening for poor psychological health and referral of such patients for consideration of adjunctive therapies directed at the gut-brain axis. Such a shift in management strategy is likely to address the currently unmet needs of a substantial proportion of patients.

7.7 Future Directions

In demonstrating the high prevalence of poor psychological health at the outset of a diagnosis of IBD, and subsequent deleterious effects these symptoms have on the disease course in established cohorts of patients with IBD, this thesis strengthens the mandate for IBD care to shift towards a biopsychosocial model of care. However, gaps in understanding remain regarding the role of the gut-brain axis in IBD. Future studies should look to examine the potential negative effects of brain-gut communications in newly diagnosed patients over a prolonged follow-up period, which if demonstrated may serve as a call for the need to assess and address poor psychological health proactively at the outset of the disease to mitigate against future complications. It is also imperative that future RCTs examining the role of psychological therapies and gut-brain neuromodulators in IBD do so amongst patients with

evidence of poor psychological health, to enable a determination of their efficacy in this patient group.

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