The prevalence and impact of irritable bowel syndrome-type symptoms and psychological co-morbidity on inflammatory bowel disease

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INTELLECTUAL PROPERTY AND PUBLICATION STATEMENTS

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.

CHAPTER 1: Introduction.

- **Gracie DJ**, Ford AC. Letter: is there a bi-directional relationship between depression and IBD? *Aliment Pharmacol Ther*. 2014;40(2):213. The first author wrote the manuscript, following which it was critically reviewed by the remaining author.
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- **Gracie DJ**, Ford AC. Psychological Comorbidity and Inflammatory Bowel Disease Activity: Cause or Effect? *Clin Gastroenterol Hepatol*. 2016;14(7):1061-2. The first author wrote the manuscript, following which it was critically reviewed by the remaining author.
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- **Gracie DJ**, Ford AC. Editorial: challenging established perceptions of brain-gut interactions in functional gastrointestinal disorders - brain-gut, gut-brain, or both? *Aliment Pharmacol Ther*. 2016;44(8):899-900. The first author wrote the manuscript, following which it was critically reviewed by the remaining author.
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CHAPTER 3: Examining the relationship between clinical disease activity and mucosal inflammation, and the role of psychological co-morbidity, in IBD.

- **Gracie DJ**, Williams CJM, Sood R, Mumtaz S, Bholah MH, Hamlin PJ, Ford AC. Poor Correlation Between Clinical Disease Activity and Mucosal Inflammation, and the Role of Psychological Comorbidity, in Inflammatory Bowel Disease. *Am J Gastroenterol.* 2016;111(4):541-51. The first author collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.

CHAPTER 4: Assessing the relationship between the reporting of IBS-type symptoms, and psychological health and quality of life in patients with IBD.

- **Gracie DJ**, Williams CJM, Sood R, Mumtaz S, Bholah MH, Hamlin PJ, Ford AC. Negative Effects on Psychological Health and Quality of Life of Genuine Irritable Bowel Syndrome-type Symptoms in Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol.* 2017;15(3):376-384. The first author collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.
- **Gracie DJ**, Ford AC. Ongoing Symptoms in Ulcerative Colitis Patients in Remission: Irritable Bowel Syndrome or Gastrointestinal Symptoms in the Absence of Inflammation? *Inflamm Bowel Dis.* 2017;23(1):E4-E5. The first author collected the data, undertook all analyses, and wrote the manuscript,

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CHAPTER 5: Assessing the direction of brain-gut interactions in patients with IBD.

- **Gracie DJ**, Guthrie EA, Hamlin PJJ, Ford AC. Bi-directionality of Brain–Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2018;154(6):1635-1646. The first author collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.

CHAPTER 6: Describing the association between the reporting of IBS-type symptoms, and longitudinal disease activity, healthcare utilisation, psychological health, and quality of life in IBD.

- **Gracie DJ**, Hamlin PJ, Ford AC. The Longitudinal Impact of Genuine IBS-type Symptoms on Disease Activity, Healthcare Utilisation, Psychological Health, and Quality of Life in Inflammatory Bowel Disease. *Am J Gastroenterol*. 2018;113(5):702-712. The first author collected the data, undertook all analyses, and wrote the manuscript, following which it was critically reviewed by the remaining authors.

CHAPTER 7: Summarising the effect of psychological therapies on disease activity, psychological co-morbidity, and quality of life in IBD.

- **Gracie DJ**, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological co-morbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-

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

- Design of the study protocol
- Data collection
- Database construction
- Statistical analysis of data
- Drafting of all manuscripts. First author and guarantor of all published articles
- Design and drafting of thesis

The other members of the group, and their contributions, have been as follows:

- Assistance in study protocol design (ACF and PJH)
- Assistance in collecting data for the initial cross-sectional study and systematic review and meta-analysis (MHB, AJI, SM, RS and CJMW)
- Assistance in database construction (MHB, ACF and CJMW)
- Assistance in analysing data (ACF, EAG, PJH and AM-W)
- Critical review of drafted manuscripts for publication (ACF, EAG, PJH and AM-W)

ABSTRACT

Introduction: The brain-gut axis may influence disease outcomes in inflammatory bowel disease (IBD). Evidence supporting brain-gut axis activity would highlight a need for novel management strategies targeting this pathophysiological mechanism in IBD. The aim of this thesis was to examine these issues directly.

Methods: In simultaneous cross-sectional studies, the relationship between symptom-reporting, psychological co-morbidity, and disease activity, and the prevalence of irritable bowel syndrome (IBS)-type symptoms, as well as their association with impaired mood and quality of life, was assessed. In longitudinal follow-up, the temporal relationship between disease activity and psychological co-morbidity was examined to assess for the presence of brain-gut axis activity. The relationship between the reporting of IBS-type symptoms and the natural history of IBD was also assessed. A systematic review and meta-analysis of randomised controlled trials was conducted to investigate the efficacy of psychological therapies in IBD.

Results: The correlation between symptom-reporting and mucosal inflammation was poor. Symptom-reporting, but not mucosal inflammation, was associated with psychological co-morbidity. Baseline disease activity was associated with new-onset anxiety (odds ratio = 5.17; 95% confidence interval (CI) 1.35-19.8), and baseline anxiety was associated with new-onset disease flare (hazard ratio = 2.08; 95% CI 1.31-3.30), suggesting possible bi-directional brain-gut axis activity in IBD. IBS-type symptom-reporting was associated with psychological co-morbidity and poor quality of life, but reporting these symptoms was not associated with adverse longitudinal disease

activity outcomes. Psychological therapies were associated with short-term beneficial effects on depression and quality of life, but had no effect on disease activity.

Conclusions: Bi-directional brain-gut axis activity may influence the natural history of disease activity, and psychological wellbeing, in IBD. Patients reporting IBS-type symptoms exhibit psychological co-morbidity and reduced quality of life. Evidence supporting the use of psychological therapies in IBD is poor, but trials of these treatments in patients at risk of mood disorders may still prove beneficial.

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GLOSSARY OF TERMS

5-ASA	5-aminosalicylates
ANOVA	analysis of variance
APC	annual percentage change
BAM	bile acid malabsorption
BMI	body mass index
CBT	cognitive behavioural therapy
CD	Crohn's disease
CDAI	Crohn's disease activity index
CI	confidence interval
CRP	C-reactive protein
FC	faecal calprotectin
FGID	functional gastrointestinal disorder
FODMAP	fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
FMT	faecal microbiota transplantation
GI	gastrointestinal
GWAS	genome wide association study
HADS	hospital anxiety and depression scale
HBI	Harvey-Bradshaw index
HR	hazard ratio
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IL	interleukin
LPS	lipopolysaccharide

IQR	interquartile range
mRNA	messenger ribonucleic acid
NOD	nucleotide-binding oligomerisation domain-containing protein
NF-κB	nuclear factor kappa B
OR	odds ratio
PHQ	patient health questionnaire
PROM	patient-reported outcome measure
RNA	ribonucleic acid
RR	relative risk
SCCAI	simple clinical colitis activity index
SD	standard deviation
SF-36	short-form 36
SIBO	small intestinal bacterial overgrowth
SMD	standardised mean difference
TGF-β	transforming growth factor beta
Th	T helper cell
TNFα	tumour necrosis factor alpha
UC	ulcerative colitis

CHAPTER 1: Introduction

This chapter provides an overview of the medical history, epidemiology, pathophysiology, natural history, and conventional management of inflammatory bowel disease (IBD). A description of the current understanding of the relationship between gastrointestinal (GI) symptom-reporting, psychological co-morbidity, quality of life, and inflammatory activity in IBD, as well as a review of the current evidence base for alternative management strategies targeting mood disorders and irritable bowel syndrome (IBS)-type symptom-reporting in IBD will then be discussed. Deficits in the current understanding in these areas will be highlighted, which in turn will provide the rationale for conducting the work described within the latter chapters of this thesis.

1.1 Introduction to IBD

1.1.1 History of IBD

IBD, comprising Crohn's disease (CD) and ulcerative colitis (UC), is a collective term used to describe chronic inflammatory disorders of the GI tract. IBD presents with symptoms including diarrhoea, haematochezia, weight loss, and abdominal pain. The first description of chronic diarrhoeal illness dates as far back as ancient times, the aetiology of which was uncertain. Diarrhoea attributable to GI tract inflammation was first described in the 18th century, but the distinction between inflammatory and infective causes of diarrhoea remained uncertain due to the overwhelming incidence of cholera infection that was observed in Western populations during this time.

Sir Samuel Wilks authored a case report in 1859 in which the pathological findings of a case of acute dysentery were discussed. Here, a differential diagnosis of infective diarrhoea, poisoning, or an alternative non-infective inflammatory pathology,

akin to what may be considered IBD today, was discussed (Wilks, 1859). Subsequent to this, several additional cases were described in the latter half of the 19th century, after which time the term “ulcerative colitis” became integrated into common medical parlance (Hale-White, 1888). In 1909, during a symposium in which a selected sample of 177 cases of UC were discussed, pre-eminent medical professionals of the time discussed proposed risk factors, presenting symptoms, and potential treatments for UC (Allchin, 1909).

The recognition of a non-infective inflammatory pathology affecting the GI tract did not, however, provide a distinction between the two common forms of IBD that are recognised today. Despite previous medical practitioners noting pathology in the terminal ileum preceding this date (Wilks, 1859; Dalziel, 1913), a positive description of a GI disorder associated with pan-enteric inflammation, initially termed “regional enteritis”, but later taking the eponymous title used today, was not formally described until 1932 (Crohn et al., 1932). Here, the authors described a case series of patients with inflammatory ileitis affecting the terminal ileum, with evidence of the stricturing and fistulising/penetrating phenotypes that are recognised in CD today (Silverberg et al., 2005).

1.1.2 Pathophysiology of IBD

The aetiology of IBD is not fully understood. No unique pathophysiological mechanism has been identified that accounts for the development and propagation of either UC or CD. Instead, it is considered that a plethora of interacting factors combine to give rise to the typical phenotypic characteristics of IBD. These factors are likely to include, but are not limited to, dysregulation of enteric immunity, susceptible host genetics, alterations in the intestinal microbiome, and environmental factors. More

recently, in addition to this, psychological co-morbidity and stress have been recognised as potential additional contributory factors that may also be implicated in the pathogenesis of these diseases.

1.1.2.1 Dysregulation of enteric immunity

It is hypothesised that an abnormal immune response to the presence of pro-inflammatory gut microorganisms may be pivotal to the development of IBD. Traditionally, IBD has been considered a disorder characterised by dysregulation of adaptive immunity, with CD and UC considered T helper (Th) 1 and Th2-mediated disorders, respectively (Fuss et al., 1996). Despite this, disordered innate immune function is also likely to contribute to the development of these diseases. The innate immune system is the first line of defence against luminal pathogens, and comprises the intestinal barrier, and non-specific immune cells such as macrophages and dendritic cells. The function of each of these facets of innate immunity may be defective in IBD. Intestinal barrier dysfunction is characterised by increased paracellular permeability and reduced expression of tight junction proteins (Vivinus-Nebot et al., 2014). This, in turn, increases exposure to luminal pathogens, which is likely to contribute to the immune activation observed in IBD, via recognition of bacterial lipopolysaccharides (LPS).

The innate immune system is involved in the recognition of pathogenic antigens by immune cells including macrophages and dendritic cells, mediated by pattern recognition receptors such as trans-membrane Toll-like receptors and cytoplasmic nucleotide-binding oligomerisation domain-containing protein (NOD) like receptors, including NOD1 and NOD2. Innate immune cell activation results in an inflammatory cascade, mediated by nuclear factor kappa B (NF-κB), resulting in the production of pro-inflammatory cytokines and a disordered immune response including excessive Th1

responses (Watanabe et al., 2004), and inhibition of anti-inflammatory cytokines including interleukin (IL)-10 (Noguchi et al., 2009).

Adaptive immunity, involving both humoral and cell-mediated responses, differs from innate immunity, and is mediated via T cells. T cells interact with the innate immune system to produce an effective, long-lasting, individualised response to specific pathogens. Dysregulation of adaptive immunity in IBD results in an excessive immune response involving the inappropriate secretion of cytokines, leading to a pro-inflammatory state, which results in GI tract inflammation and ulceration. The role of T cells in the pathogenesis of IBD may differ between CD and UC. Th1-mediated interferon-γ expression in the mucosa of patients with CD is higher than that observed in patients with UC (Camoglio et al., 1998). In contrast, excessive Th2-mediated IL-5 and IL-13 release observed in UC is not typically seen in patients with CD (Heller et al., 2005). These findings have led to the assumption that CD and UC are Th1 and Th2-mediated diseases, respectively (Fuss et al., 1996).

Despite this, more recent opinion casts doubt on the simplicity of these binary associations. In addition to Th1 and Th2 activity, Th17 cells are also implicated in the pathogenesis of IBD. Their production is facilitated by IL-6 and transforming growth factor beta (TGF-β), and is enhanced by IL-23 (Zhou et al., 2007). Th17 cells are associated with the release of IL-17 and IL-21, which in turn results in the up regulation of IL-23 receptor expression, resulting in a positive feedback loop of pro-inflammatory cytokine release (McGovern and Powrie, 2007). The relative abundance of Th17 cells in the lamina propria of patients with IBD (Rovedatti et al., 2009), and the increased presence of IL-17 in the mucosa of patients with CD and UC when compared with healthy controls (Sugihara et al., 2010), supports the role of Th17 cells in the pathogenesis of IBD. IL-23 plays a key role in the crosstalk between innate and

adaptive immune responses in IBD. It is produced by activated dendritic cells of the innate immune system and, in addition to its role in the Th17 response described above, is responsible for the stimulation of innate immune cells to produce inflammatory cytokines, including IL-6 and tumour necrosis factor alpha (TNFα), which drive intestinal inflammation (McGovern and Powrie, 2007).

In addition to the propagation of pro-inflammatory immune pathways in IBD, dysfunction of anti-inflammatory homeostatic mechanisms is also likely to contribute to the development of active inflammation. Regulatory T cells are able to suppress the proliferation of naïve T helper cells, and produce anti-inflammatory cytokines including IL-10 and TGF-β (O'Garra and Vieira, 2004). However, defective TGF-β signalling, due to the up regulation of Smad7, inhibits regulatory T cell function, resulting in defective anti-inflammatory cytokine production in patients with IBD (Sedda et al., 2015). Inhibition of Smad7 has been the focus of clinical trials in IBD (Feagan et al., 2018), although its role in treatment algorithms is yet to be defined.

The combination of inappropriate immune activation, resulting in the production of pro-inflammatory cytokines including interferon-γ, IL-23, IL-17, and TNFα, and defective host anti-inflammatory mechanisms, results in the development of intestinal inflammation and the typical phenotypic characteristics observed in patients with active IBD.

1.1.2.2 Host genetics

Familial susceptibility to the development of IBD, particularly in twin studies, has led to the assumption that host genetics plays a role in the development of both CD and UC (Bengtson et al., 2010; Spehlmann et al., 2008). Despite this, the lack of an absolute association in the incidence of IBD between monozygotic twins confirms that

susceptible host genetics is only one contributory factor in the aetiology of IBD. Observational studies have described a greater association between the incidence of CD than UC within families (Spehlmann et al., 2008), and that the relative risk of developing IBD, when compared with the background population, is highest in monozygotic twins, followed by dizygotic twins, and then first-degree siblings (Bengtson et al., 2010).

Unlike disorders with classical Mendelian inheritance, no single gene has been identified that accounts for the development of either CD or UC. Instead, over 200 single nucleotide polymorphisms have been identified since the advent of genome wide association studies (GWAS) investigating genetics and IBD (Ye and McGovern, 2016). To date, the strongest genetic association is between CD and the presence of the caspase recruitment domain-containing protein 15 (CARD15)/NOD2 mutation on chromosome 16 (Hugot et al., 2001; Ogura et al., 2001). Other IBD risk variants have been identified including those involving the IL-23 receptor gene (Duerr et al., 2006). GWAS meta-analyses have identified at least 163 IBD risk loci, with significant cross over between CD and UC phenotypes (Jostins et al., 2012). A detailed description of the plethora of studies detailing the individual risk loci associated with IBD is beyond the scope of this thesis.

1.1.2.3 The intestinal microbiome

Typical microbiome changes in IBD include an increase in the relative abundance of pro-inflammatory species, a reduction in anti-inflammatory bacterial species such as *Faecalibacterium prausnitzii,* and a reduction in overall alpha bacterial diversity, when compared with healthy controls without IBD (Gevers et al., 2014). Notwithstanding the differences observed between IBD populations and healthy

controls, alterations in the microbiome have been observed between those with active and quiescent disease (Sepehri et al., 2007). Reduced abundance of *F. prausnitzii* has been observed in the mucosa-associated microbiome of some patients with CD following surgical resection for active disease, with these changes associated with higher rates of endoscopic recurrence at 6 months (Sokol et al., 2008). Furthermore, alterations in the mucosa-associated microbiome between inflamed and healthy areas of the GI tract in patients with an established diagnosis of CD have also been observed, thus supporting the association between alterations in the microbiome and disease activity in IBD (Gevers et al., 2014). Although the exact role of the microbiome in the development of intestinal inflammation in IBD is unknown, recognition of bacterial LPS, resulting in the aberrant immune activation that is described in more detail below, is thought to contribute. Whether susceptible host genetics has any influence on the microbiome profile in patients with IBD is uncertain, but individuals with an IBD-related genotype are more likely to display associated microbiome alterations, despite not displaying phenotypic characteristics of IBD (Imhann et al., 2018).

1.1.2.4 Environmental factors

Although the relationship between host genetics, enteric immunity, and the microbiome is likely to play a pivotal role in the aetiology of IBD, other environmental factors may also impact on the natural history of the disease. Tobacco smoking has a detrimental effect on the natural history of CD, with a significant increase in the odds of flare of disease activity, first surgery, flare of disease activity after first surgery, and the requirement for a second surgical resection observed in smokers when compared with non-smokers and ex-smokers (To et al., 2016b). In UC, tobacco smoking has traditionally been considered to impart beneficial effects on disease course, with the

onset of disease and flares of disease activity associated with smoking cessation (Harries et al., 1982; Calkins, 1989). However, trials of nicotine containing therapies have proved largely unsuccessful in UC (McGrath et al., 2004; Nikfar et al., 2010; Thomas et al., 1995; Thomas et al., 1996), and in meta-analyses of observational studies assessing the effect of tobacco smoking on the natural history of UC, results have been conflicting (Kuenzig et al., 2016; To et al., 2016a), thus casting doubt on the role of smoking in UC.

In addition to tobacco smoking, other environmental factors including urban dwelling (Soon et al., 2012), antibiotic use (Ungaro et al., 2014), lack of exercise (Sonnenberg, 1990; Khalili et al., 2013), and previous appendicectomy (Kaplan et al., 2008; Andersson et al., 2001; Myrelid et al., 2017) may also be implicated in the development of IBD.

1.1.2.5 Psychological factors

Psychological disorders, including anxiety, depression, and stress affect up to one-third of patients with IBD (Neuendorf et al., 2016). The mechanism by which these factors influence the development and natural history of IBD is uncertain, and forms a large part of the rationale for conducting the work which is described in this thesis. Studies conducted in functional gastrointestinal disorders (FGIDs) suggest that the relationship between GI symptom-reporting and mood disorders may be bi-directional (Koloski et al., 2012; Koloski et al., 2016), implicating brain-gut axis activity as a potential mediator of these relationships. Whether the same temporal relationship between disease activity and psychological co-morbidity exists in IBD is uncertain. A more detailed review of the proposed mechanisms by which psychological co-morbidity may negatively impact disease outcomes in IBD is provided later on.

1.1.3 Epidemiology of IBD

The global incidence and prevalence of IBD varies according to geographical locale and disease subtype. In a systematic review of 260 epidemiological studies conducted between 1920 and 2008 (Molodecky et al., 2012), the incidence and prevalence of UC and CD were reported separately for regions including Europe, Asia and the Middle East, and North America. In UC, the annual incidence was reported to range from 0.6 to 24.3 per 100,000 person-years in Europe, with a corresponding figure of 0 to 19.2 per 100,000 person-years in North America and 0.1 to 6.3 per 100,000 person years in Asia and the Middle East. In CD, the annual incidence was reported to range from 0.0 to 20.2 per 100,000 person-years in North America, with a corresponding figure for Europe, and Asia and the Middle East of 0.3 to 12.7 per 100,000 person-years, and 0.04 to 5.0 per 100,000 person-years, respectively. Data reported in the same study suggested that the overall prevalence of UC varied from 4.9 to 505 per 100,000 in Europe, 0.6 to 322 per 100,000 in North America and 4.9 to 168.3 per 100,000 in Asia and the Middle East. In CD, the overall prevalence was reported to vary from 0.6 to 322 per 100,000 in Europe, 16.7 to 318.5 per 100,000 in North America and 0.88 to 67.9 per 100,000 in Asia and the Middle East. There appeared to be no difference in the incidence or prevalence of IBD between male and female sex, and a peak age of onset occurred in the third decade of life. Overall, in studies that reported data over a minimum 10-year period, a temporal rise in the incidence of UC (annual percentage change (APC) 2.4% to 18.1%) and CD was observed (APC 1.2% to 23.3%), possibly due to an increase in urban dwelling (Soon et al., 2012), increased awareness of IBD, or greater use of colonoscopic and radiological investigations.

An update to this study, conducted by the same authors, including an additional 52 studies, demonstrated similar findings in Western populations (Ng et al., 2018b).

However, the inclusion of new epidemiological studies from the developing world provided a novel estimate of the prevalence of IBD in regions including Eastern Asia, South-eastern Asia, Western Asia, South America, and Africa where the reported prevalence (UC: 106.2 per 100,000; CD: 53.1 per 100,000) and incidence (UC: 6.76 per 100,000 person-years; CD: 8.40 per 100,000 person-years) of IBD was universally low. In keeping with the previous systematic review (Molodecky et al., 2012), the incidence of IBD was also noted to be increasing in developing countries, including Brazil (APC for CD 11.1% (95% confidence interval (CI) 4.8-17.8) and UC 14.9% (95% CI 10.4-19.6)) and Taiwan (APC for CD 4.0% (95% CI 1.0-7.1) and UC 4.8% (95% CI 1.8-8.0)).

1.1.4 The natural history of IBD

CD and UC are chronic GI disorders without cure. As a consequence, patients with IBD face a lifetime of disease with the need for long-term medical and surgical interventions, with the ultimate goal of minimising digestive damage. The natural history of IBD is that of quiescence interspersed with episodic flare-ups of disease activity. Such flare-ups may present with the development of new GI symptoms and/or new-onset inflammatory activity. Medical management of IBD has advanced in recent decades, such that the requirement for surgical intervention in both UC and CD has declined, particularly since the introduction of biological therapies. Current estimates suggest that the cumulative 5 year risk of surgery in CD is between 19.6% and 33.3%, with a corresponding figure of between 7.5% and 11.6% in UC (Rungoe et al., 2014; Frolkis et al., 2013). Furthermore, the risk of first surgery in CD may be reducing by up to 3.5% per year (Ma et al., 2017), and the risk of second surgery in CD is also reducing over time (Frolkis et al., 2014). Given the chronic nature of these diseases, there

remains a need for effective medical interventions that induce remission of active IBD, and effectively maintain remission in patients with quiescent disease.

1.1.5 Contemporary medical management of IBD

A combination of medical and surgical interventions form the basis of the management of patients with IBD. The aim of medical management is the maintenance of quiescent disease activity, the avoidance of glucorticosteroid therapy, and the avoidance of surgery. Pharmacological interventions in IBD target the putative pathophysiological mechanisms that contribute to the development and propagation of inflammatory activity. As described previously, a disordered immune response to a pro-inflammatory microbiome in genetically susceptible individuals may lead to the development of the phenotypic characteristics of IBD. The mainstay of contemporary pharmacological interventions in IBD, including glucocorticosteroid, 5-aminosalicylic acid (5-ASA), immunomodulators, and biological therapies, target the dysregulation of enteric immunity in order to impart their beneficial effects. Other interventions, including those seeking to modulate the pro-inflammatory microbiome in patients with IBD, such as probiotics, antibiotics, and faecal microbiota transplantation (FMT) have also been tested in IBD. A summary of the evidence base for these interventions is provided below.

1.1.5.1 Glucocorticosteroids

Glucocorticosteroids have formed the cornerstone of management of active IBD since the 1950s (Truelove and Witts, 1955; Lennard-Jones et al., 1960). The mechanism of action by which these drugs impart their anti-inflammatory effect is via cytoplasmic glucocorticoid receptor-mediated down regulation of NF-κB and activator protein-1,

both of which are potent transcription factors for many pro-inflammatory cytokines (Farrell and Kelleher, 2003). Since the publication of initial case series and uncontrolled trials of glucocorticosteroid therapy, conducted predominantly in patients with UC, several randomised controlled trials (RCT) assessing the effect of these drugs in IBD have been conducted. A systematic review and meta-analysis of RCTs seeking to clarify the evidence base for the use of glucocorticosteroids in IBD investigated the effect of glucocorticosteroids on the maintenance of disease remission and the induction of remission in active IBD (Ford et al., 2011b). The authors reported that there was likely to be a beneficial effect of glucocorticosteroid therapy over placebo for the induction of remission of active UC (relative risk (RR) of failure to achieve remission = 0.65; 95% CI 0.45-0.93) although the benefit was less clear in CD (RR of failure to achieve remission = 0.46; 95% CI 0.17-1.28), probably due to heterogeneity between the included studies. Adverse events were more common in patients receiving active treatment. Maintenance therapy with glucocorticosteroids is not recommended due to the well-documented systemic side effects of long-term treatment.

Due to its relatively favourable side-effect profile, budesonide is considered an alternative to standard glucocorticosteroid therapy in some instances in IBD. Several Cochrane reviews have sought to better elucidate its role in the management of IBD. These have reported that budesonide was inferior to standard glucocorticosteroids, but superior to placebo in the treatment of active CD (RR of achieving remission = 0.85, 95% CI 0.75-0.97 and RR of achieving remission = 1.93, 95% CI 1.37-2.73, respectively) (Rezaie et al., 2015), that budesonide-MMX® was superior to placebo in inducing clinical and endoscopic remission in patients with active UC (RR of achieving remission = 2.25; 95% CI 1.50-3.39), particularly in those with left sided disease (Sherlock et al., 2015), and that budesonide was not superior to placebo in the

maintenance of remission in quiescent CD at 3 months (RR of maintaining remission = 1.25; 95% CI 1.00-1.58) (Kuenzig et al., 2014).

1.1.5.2 5-aminosalicylic acids

Via their interaction with peroxisome proliferator-activated receptor gamma, 5-ASAs effectively reduce the expression of pro-inflammatory cytokines in UC, in part by the suppression of NF-κB, but potentially also by their interaction with lipoxygenase, cyclo-oxygenase, IL-1, IL-2, and TNFα (Iacucci et al., 2010). In a systematic review and meta-analysis of RCTs, these drugs were shown to be effective at maintaining remission in UC (RR of relapse versus placebo = 0.65; 95% CI 0.55-0.76), and for the treatment of mild-to-moderate active inflammation using oral preparations (RR of failure to achieve remission versus placebo = 0.79; 95% CI 0.73-0.85) (Ford et al., 2011a). In a further systematic review and meta-analysis, topical 5-ASAs were superior to placebo at maintaining remission in quiescent UC (RR of relapse = 0.60; 95% CI 0.49-0.73) (Ford et al., 2012b). Finally, combined topical and oral 5-ASA have been shown to be superior to oral 5-ASA monotherapy for the treatment of active UC (RR of failure to achieve remission = 0.65; 95% CI 0.47-0.91) (Ford et al., 2012a). 5-ASA use may also be associated with some chemoprotective effect against the onset of colitis-associated colorectal cancer (van Staa et al., 2005), although this assertion is disputed by others (Bernstein et al., 2011; Nguyen et al., 2012).

In contrast to UC, the evidence base for the use of 5-ASAs in the treatment of CD is less convincing. In a systematic review and meta-analysis of 22 RCTs, 5-ASAs were superior to placebo for the induction of remission of active CD (RR of failure to achieve remission = 0.89; 95% CI 0.80-0.99), but there was no benefit of 5-ASA over placebo for maintenance of remission in quiescent CD (RR of relapse versus placebo =

0.97; 95% CI 0.90-1.05) (Ford et al., 2011c). Despite this, the same authors did suggest there may be a role for mesalazine in the prevention of relapse of CD after surgically induced remission (RR of relapse versus placebo = 0.80; 95% CI 0.70-0.92) (Ford et al., 2011d).

1.1.5.3 Immunomodulators

Immunomodulators including thiopurines, methotrexate, and calcineurin inhibitors, such as tacrolimus and ciclosporin, have been trialled in patients with IBD. Their mechanisms of action are distinct, but focus on the inhibition of production of lymphocytes, or the inhibition of pro-inflammatory cytokine production.

Thiopurines are the most commonly prescribed immunomodulators in IBD. The efficacy of mercaptopurine, and its pro-drug azathioprine, has been investigated in several RCTs in both UC and CD. A systematic review and meta-analysis of RCTs investigating the efficacy of these drugs in IBD reported that their use as an intervention for the treatment of active disease was no better than placebo in CD (RR of induction of remission = 0.87; 95% CI 0.71-1.06) or UC (RR of remission = 0.85; 95% CI 0.71-1.01) (Khan et al., 2011a). In the same meta-analysis, the authors described a significant benefit of azathioprine therapy in the maintenance of remission of quiescent UC when data were pooled from three RCTs (RR of relapse versus placebo = 0.60; 95% CI 0.37-0.95). In CD, there appeared to be no overall benefit of thiopurines over placebo for the maintenance of remission in quiescent disease when data were pooled from two RCTs (RR of relapse = 0.64; 95% CI 0.43-1.23). However, when data from three withdrawal studies were assessed, there was an overall benefit (RR of relapse = 0.39; 95% CI 0.21-0.74) (Khan et al., 2011a). In the TOPPIC trial (Mowat et al., 2016), where the efficacy of mercaptopurine in the maintenance of remission in post-operative CD was compared

with placebo, there was no benefit of routine post-operative prophylaxis (HR for clinical recurrence = 0.54; 95% CI 0.27-1.06), other than in active smokers (HR for clinical recurrence = 0.13; 95% CI 0.04-0.46), where the deleterious effects of smoking (To et al., 2016b) appeared to be ameliorated.

A recent Cochrane review of RCTs investigating the effect of methotrexate as a therapeutic intervention in the treatment of refractory CD suggested that there may be a benefit of intramuscular methotrexate over placebo (McDonald et al., 2014), on the basis of the results from a single RCT (RR of failure to achieve remission = 0.75; 95% CI 0.61-0.93) (Feagan et al., 1995). Oral preparations were no more beneficial than placebo (RR of failure to achieve remission = 3.00; 95% CI 0.68-13.31). In the same meta-analysis, the combination of methotrexate and biological therapy was not found to be superior to biological therapy alone (McDonald et al., 2014). Two subsequent studies have been conducted that have advocated the use of methotrexate in refractory CD, but these studies had significant limitations, including a retrospective study design (Huang et al., 2017; Kopylov et al., 2016). A further Cochrane review of RCTs has reported on the efficacy of methotrexate as a maintenance treatment in CD (Patel et al., 2014). Here, intramuscular methotrexate was superior to placebo over 36 to 40 weeks of follow-up (RR of relapse = 1.67; 95% CI 1.05-2.67). The evidence base for the efficacy of methotrexate in UC is poorly quantified (Chande et al., 2014), and its use is not advocated by international consensus (Harbord et al., 2017).

The efficacy of calcineurin inhibitors, including tacrolimus and ciclosporin, has also been investigated in IBD. When compared with placebo, ciclosporin is an evidence-based treatment for glucocorticosteroid-refractory acute severe UC (Lichtiger et al., 1994), and its efficacy is equivalent to that of infliximab (Williams et al., 2016). However, there is a lack of evidence to support its use in the maintenance of remission

of quiescent UC, or in the treatment of CD. Topical tacrolimus has been shown to be effective in achieving clinical remission in patients with difficult-to-treat ulcerative proctitis (Lawrance et al., 2017), but its role as an oral treatment in both UC and CD is poorly defined (Gerich et al., 2013; Thin et al., 2013).

1.1.5.4 Biological therapies

Biological therapies form the mainstay of escalated medical treatment in IBD. Their use is advocated by international consensus for the management of both CD and UC (Gomollon et al., 2017; Harbord et al., 2017). At present, in the United Kingdom, the National Institute of Health and Care Excellence has approved the use of biological therapies including the anti-TNFα drugs infliximab, adalimumab, and golimumab (NICE, 2010; NICE, 2015a), the anti-integrin vedolizumab (NICE, 2015b; NICE, 2015c), and the IL-12/23p40 antagonist ustekinumab (NICE, 2017). Each of these drug classes has a distinct mechanism of action, but with the collective aim of modulating the disordered immune response that is observed in patients with IBD.

Infliximab has been shown to be an effective rescue therapy for active UC refractory to intravenous glucocorticosteroid therapy in a RCT including 45 patients (Jarnerot et al., 2005). Here, colectomy rates at 3 months were significantly lower in patients randomised to receive infliximab compared with placebo (7 (29%) of 24 versus 14 (66.7%) of 21; $P = 0.017$). The ACT 1 and ACT 2 RCTs of infliximab as a treatment for glucocorticosteroid-refractory active UC demonstrated improved clinical response when compared with placebo after 8 weeks (69% versus 37%; $P < 0.001$), which was sustained after 30 weeks of follow-up (Rutgeerts et al., 2005). In addition, the combination of azathioprine with infliximab has been shown to be superior to

infliximab monotherapy at achieving glucocorticosteroid-free remission after 16 weeks (31 (39.7%) of 78 versus 17 (22.1%) of 77; P = 0.017) (Panaccione et al., 2014).

The efficacy of adalimumab, an alternative anti-TNFα preparation administered subcutaneously, has been studied in the treatment of active UC, refractory to glucocorticosteroids and/or immunosuppressants. In the ULTRA 1 RCT, patients randomised to adalimumab therapy received induction doses of 160mg followed by 80mg at week 2, and 40mg every other week thereafter. These patients were more likely to achieve clinical remission at week 8 than those receiving placebo (18.5% versus 9.2%; P = 0.03) (Reinisch et al., 2011). In longitudinal follow-up over 52 weeks (ULTRA 2), adalimumab was also superior to placebo at maintaining clinical remission in UC (17.3% versus 8.5%; P = 0.004), with anti-TNFα naive patients more likely to respond than those with prior exposure (Sandborn et al., 2012b).

Golimumab, an alternative subcutaneously administered anti-TNFα drug, has also been trialled in patients with objectively confirmed glucocorticosteroid-refractory UC. The PURSUIT trial demonstrated that patients with moderate-to-severely active UC treated with golimumab had higher rates of clinical remission and mucosal healing following 6-week induction therapy than patients randomised to placebo (P ≤0.0001) (Sandborn et al., 2014a). The sustained response of 464 patients who responded to golimumab induction therapy at 6 weeks was evaluated after 54 weeks. Patients were randomised to 100mg every 4 weeks or placebo maintenance therapy. Here, the proportion of patients in clinical remission, and the proportion who had mucosal healing at week 54, was higher in patients randomised to receive active treatment than those receiving placebo (27.8% versus 15.6%; P = 0.004 and 42.4% and 26.6%; P = 0.002, respectively) (Sandborn et al., 2014b).

GEMINI 1 was a RCT of vedolizumab in endoscopically confirmed moderate-to-severe UC. Patients were randomised to receive vedolizumab 300mg or placebo at weeks 0 and 2, and were assessed for response at week 6. In terms of clinical response rate, defined as a reduction in Mayo score of three points and a decrease in score of 30% from baseline, a significant beneficial effect of vedolizumab therapy over placebo was identified at week 6 (47.1% versus 25.5%; P <0.001). Clinical remission rates at week 52, defined as a Mayo score ≤2 and no subscore >1, were also higher in patients randomised to receive vedolizumab maintenance therapy, either every 8 weeks or every 4 weeks, than placebo (41.8% versus 15.9%; P <0.001 and 44.8% versus 15.9%; P <0.001, respectively) (Feagan et al., 2013). This effect was greater in patients who were naïve to anti-TNFα therapy (Feagan et al., 2017).

As was the case in UC, infliximab was the first anti-TNFα therapy to be trialled in CD. In a RCT of infliximab as induction therapy in moderate-to-severe CD, a single infusion of 5mg per kilogram was superior to placebo in achieving a clinical response at 4 weeks (22 (81%) of 27 versus 4 (17%) of 24; P <0.001), which persisted at 12 weeks (Targan et al., 1997). The efficacy of maintenance infliximab therapy was assessed in the ACCENT 1 RCT (Hanauer et al., 2002). In this study, patients with active CD, who responded to an initial infusion of infliximab, were randomised to receive maintenance infliximab 5mg/kg or placebo at week 2, week 6, and at 8-weekly intervals thereafter. At week 30, clinical remission was maintained in a significantly greater proportion of patients treated with infliximab, when compared with placebo (44 (39%) of 113 vs. 23 (21%) of 110; P = 0.003). Investigators from the same study group also demonstrated a benefit of both induction and maintenance infliximab therapy over placebo in the management of fistulising CD (Present et al., 1999; Sands et al., 2004) The benefit of combined anti-TNFα and thiopurine therapy was assessed in the SONIC study

(Colombel et al., 2010). Here, the efficacy of infliximab, azathioprine, or combined infliximab and azathioprine was assessed. Glucocorticosteroid-free remission rates at 26 weeks were statistically significantly higher with combination therapy than with infliximab monotherapy (96 (56.8%) of 169 versus 75 (44.4%) of 169; P = 0.02), which in turn was more effective than azathioprine monotherapy (75 (44.4%) of 169 versus 51 (30.0%) of 170; P = 0.02).

In the CLASSIC-I trial, adalimumab monotherapy was trialled as a treatment for active CD. Patients included were anti-TNFα naïve. Clinical remission rates were significantly higher in those receiving adalimumab induction therapy (160mg week 0 and 80 mg week 2) when compared with placebo at 4 weeks (36% versus 12%; P = 0.001) (Hanauer et al., 2006). This effect appeared to be attenuated in patients previously exposed to anti-TNFα therapy (Sandborn et al., 2007). In the EXTEND study, the use of adalimumab maintenance treatment in CD over 12 months follow-up was assessed. All patients received 160mg/80mg induction therapy and then were randomised to either 40mg every other week, or placebo. Rates of mucosal healing and clinical remission were significantly higher in those treated with adalimumab, when compared with placebo at 52 weeks (24% versus 0%; P <0.001 and 33% versus 9%; P = 0.001, respectively) (Rutgeerts et al., 2012). Although not licensed for use in the UK, certolizumab pegol is an alternative anti-TNFα preparation that appears to be of benefit in both the induction and maintenance of remission in CD (Schreiber et al., 2005; Schreiber et al., 2007), particularly in those with objective inflammatory disease activity at randomisation.

In the GEMINI 2 RCT, the efficacy of the anti-integrin vedolizumab for the treatment of active CD, defined using clinical parameters and objective measures of inflammatory activity, was assessed (Sandborn et al., 2013). Here, vedolizumab therapy

was superior to placebo at achieving clinical remission at 6 weeks, although overall rates of remission were low (14.5% versus 6.8%; P = 0.02). Those who responded to induction therapy were then re-randomised to receive either placebo, vedolizumab 300mg every 4 weeks, or vedolizumab every 8 weeks. A greater proportion of patients receiving either vedolizumab every 4 weeks or every 8 weeks achieved clinical remission at 52 weeks when compared with placebo (39.0% versus 21.6%; P <0.001 and 36.4% versus 21.6%; P = 0.004, respectively) (Sandborn et al., 2013).

Ustekinumab an anti-IL-12/23p40 monoclonal antibody has also been trialled for the treatment of active CD that is refractory to anti-TNFα therapy (Sandborn et al., 2012a; Feagan et al., 2016). Two parallel RCTs (UNITI-1 and UNITI-2) were conducted to assess clinical response rates following induction therapy at week 6, and maintenance therapy at week 44. Clinical response rates at week 6 were significantly higher in patients receiving intravenous induction therapy with ustekinumab when compared with those receiving placebo (UNITI-1; P ≤0.003 and UNITI-2; P <0.001). Of those that responded to initial induction therapy who were then re-randomised to receive either ustekinumab every 8 weeks, ustekinumab every 12 weeks, or placebo remission rates at week 44 were higher in those receiving ustekinumab 8-weekly when compared with placebo (53.1% versus 35.9%; P = 0.005), and ustekinumab 12-weekly when compared with placebo (48.8% versus 35.9%; P = 0.04).

1.1.5.5 Faecal microbiota transplantation

Modification of the pro-inflammatory intestinal microbiota that is observed in patients with active IBD is the mechanism by which FMT is supposed to impart its beneficial effect on disease activity in IBD. Indeed, post-FMT faecal microbiome profiling in IBD populations has demonstrated that the microbiome post-transplant

mirrors that of the donor, rather than the host (Jacob et al., 2017). In a recent systematic review and meta-analysis of case reports, case series, cohort studies and RCTs, the efficacy of FMT in active UC and CD was reported (Paramsothy et al., 2017b). The majority of studies in UC, and all the studies in CD, were observational in nature. There were only four RCTs in patients with UC, which recruited a total of 277 patients (Moayyedi et al., 2015; Rossen et al., 2015; Paramsothy et al., 2017a; Costello et al., 2017). Formal meta-analysis of these studies revealed a potential benefit of FMT in UC (pooled OR of achieving clinical remission with FMT versus control = 2.89; 95% CI 1.36-6.13). Despite this, there was evidence of heterogeneity, and significant methodological differences in the study protocols, including different routes of faecal donor administration. Thus, at present, FMT remains an experimental intervention.

1.1.5.6 Probiotics and antibiotics

Probiotics are live microorganisms that confer a health benefit on the host. Their potential benefit in IBD is thought to arise via manipulation of the intestinal microbiome. Several RCTs have described the effect of probiotics, either as a single strain or as combined preparations, on disease activity in CD and UC, as well as for the maintenance of remission in patients with quiescent disease. Most recently, a systematic review and meta-analysis of RCTs reported that there was no effect of probiotics for the induction of remission of active CD, the maintenance of remission in quiescent CD, or the prevention of disease recurrence in post-operative CD (Derwa et al., 2017). The authors also noted that there was no overall benefit of probiotics in the treatment of active UC, but that when only RCTs of the combination probiotic VSL#3 were included, their appeared to be a benefit over placebo (RR of failure to achieve remission = 0.74; 95% CI 0.63-0.87). Furthermore, probiotics appeared to be of equivalent

efficacy to 5-ASA preparations for the maintenance of disease remission in quiescent UC (Derwa et al., 2017).

A systematic review and meta-analysis of RCTs investigating the use of antibiotics in the treatment of IBD reported that antibiotics may be of benefit in the treatment of both active UC and CD, but that significant heterogeneity was observed in these analyses (Khan et al., 2011b). Fewer studies have reported on the effect of antibiotic therapy on the maintenance of remission in quiescent IBD. Current international guidance does not support the use of antibiotics in IBD, apart from in the management of perianal CD, septic complication of penetrating CD, or in the treatment of small intestinal bacterial overgrowth (SIBO) (Gomollon et al., 2017; Harbord et al., 2017).

1.2 Symptom reporting in IBD

Traditional assessment of disease activity in IBD is centred upon the interpretation of patient-reported symptoms that are deemed likely to be attributable to active GI inflammation. Clinical decision-making is often made on these grounds, with recourse to ‘gold-standard’ investigations, including ileocolonoscopy and radiological investigations, reserved for patients who are deemed to have active disease on the basis of these symptoms. In clinical practice, as well as in clinical trials of novel therapies in IBD, clinical disease activity indices are routinely used to estimate disease activity. The use of the Crohn’s disease activity index (CDAI) and Harvey-Bradshaw index (HBI) are commonplace in CD, with equivalent indices including the Powell-Tuck index, Rachmilewitz clinical activity index, Mayo score, and simple clinical colitis index (SCCAI) adopted in UC.

The relationship between GI symptom-reporting and the presence of objectively quantified active mucosal inflammation has been previously investigated. Several authors have demonstrated that the correlation between GI symptom-reporting, captured using clinical disease activity indices, is suboptimal, particularly in CD. These indices, when compared with gold-standard investigations, perform inferiorly to objective markers of inflammation, including C-reactive protein (CRP) and faecal calprotectin (FC) (Falvey et al., 2015; af Bjorkesten et al., 2012; Sipponen et al., 2008; Jones et al., 2008; Schoepfer et al., 2009; Schoepfer et al., 2010; Targownik et al., 2015).

Accordingly, reliance on subjective measures of disease activity assessment, based on patient-reported symptoms, may have implications for the long-term management of patients with IBD. In a cross-sectional study of 150 patients with CD and 126 patients with UC, where the attending physician was blinded to FC results, physician decision-making made on the basis of clinical parameters alone, was recorded. Here, 31% of patients who underwent escalation of medical therapy and 60% of patients who were referred for endoscopic or radiological investigations, did not have a FC >250µg/g (Derwa et al., 2018). The authors also reported that more than one-in-three patients with a FC >250µg/g received neither escalation of medical therapy nor referral for investigations to objectively determine inflammatory activity (Derwa et al., 2018). Although, in the latter instance, the benefit of a treat-to-target approach towards the management of patients with IBD has yet to be determined (Sandborn et al., 2014c; Bryant et al., 2014; D'Haens et al., 2014), these data highlight the inherent inconsistencies associated with clinical decision-making in IBD, when made on the basis of patient-reported symptoms alone. This is of particular relevance at the current time as the US Food and Drug Administration have recently advocated the use of

patient-reported outcome measures (PROMs) as end points in trials of novel therapeutic interventions in IBD (Williet et al., 2014).

1.2.1 Symptom reporting in the absence of inflammation in IBD

Given that the correlation between symptom-reporting and objectively confirmed mucosal inflammation is poor, factors other than inflammatory activity are likely to contribute to the generation of GI symptoms in IBD. The presence of symptoms in the absence of inflammation has often been attributed to co-existent irritable bowel syndrome (IBS), which is reported to affect up to 35% of patients with clinically quiescent IBD (Halpin and Ford, 2012). In contrast to IBD, IBS is a highly prevalent condition, with a worldwide population prevalence of between 10% and 20% (Lovell and Ford, 2012). The cardinal features of IBS are those of a change in bowel habit in the presence of abdominal pain or discomfort. Patients are subtyped according to the predominant stool pattern they report: IBS with diarrhoea, IBS with constipation, or mixed IBS, if stool pattern fluctuates between the two. IBS is a FGID, without any known organic explanation. The condition is diagnosed using symptom-based diagnostic criteria, with the current gold-standard being either the Rome III (Longstreth et al., 2006) or Rome IV criteria (Mearin et al., 2016). Recent evidence suggests that the accuracy of these in predicting the presence of IBS is only modest (Ford et al., 2013), but may be improved with additional history and simple laboratory investigations (Sood et al., 2016).

1.2.2 The overlap between IBS and IBD

Symptoms associated with a flare of disease activity in IBD may include abdominal discomfort, alteration in bowel habit towards looser stools, and rectal

bleeding. Traditional management dictates that a change in symptoms in individuals with IBD should prompt an assessment of disease activity, via clinical disease activity scoring systems such as the SCCAI in UC (Walmsley et al., 1998) or HBI in CD (Harvey and Bradshaw, 1980). The results of these clinical disease activity indices are then combined with serum and/or faecal biomarkers of disease activity, including CRP and FC, as well as endoscopic visualisation of the colonic mucosa, with histopathological interpretation of biopsy specimens, or appropriate radiological investigations.

These investigations may aid the decision-making process, in terms of the need to modify or escalate pharmacotherapy. However, when patients present with lower GI symptoms in the absence of biochemical, radiological, endoscopic, and histopathological evidence of disease activity, the clinician is faced with a dilemma regarding further management, as this then raises the possibility of either subclinical inflammatory activity, or co-existent IBS in a patient with known IBD. Escalation of therapy in this situation may be advocated by some experts, but the use of immunomodulator therapies or biological agents is not without the risk of adverse events (Williams et al., 2014; Ford and Peyrin-Biroulet, 2013; Beaugerie et al., 2009; Peyrin-Biroulet et al., 2011) and, in the case of biological therapies, carries with it significant financial implications. In addition, in clinical trials, patients with IBD without objective evidence of disease activity often do not respond to these agents as well as those with definitive evidence of active inflammation (Reinisch et al., 2012; Colombel et al., 2010; Schreiber et al., 2005).

Given that both IBS and IBD are chronic diseases, which may present with similar symptoms, and that individuals with IBS are often diagnosed on symptom grounds alone using an imperfect gold-standard (Ford et al., 2013), there is the potential

for a missed diagnosis of IBD in patients thought to have IBS. Indeed, the rate of incident IBD diagnoses in patients with an existing diagnosis of IBS is over five times that of the background non-IBS population (Canavan et al., 2014). It is also possible that alternative organic, non-inflammatory pathology such as bile acid malabsorption (BAM), or SIBO could also affect patients with quiescent IBD, leading to a mis-diagnosis of lower GI symptoms as co-existent IBS. This is particularly relevant to patients with CD with a stenosing phenotype, or those having undergone prior intestinal resection (Gracie et al., 2012; Aziz et al., 2015; Ford et al., 2009a; Chachu and Osterman, 2016; Rana et al., 2013). Furthermore, some individuals with IBS, particularly those with a post-infectious aetiology, have been shown to display evidence of low-grade mucosal inflammation (Sundin et al., 2014; Chadwick et al., 2002; Barbara et al., 2004; Barbara et al., 2007), suggesting that this may be a contributing factor in the development of these symptoms in patients with IBD. This has led to some experts proposing that the classical view that IBS and IBD are mutually exclusive conditions, falling either side of a functional-organic divide, is too simplistic. Instead a biopsychosocial model of 'IBD-IBS' has been put forward (Long and Drossman, 2010), although this approach remains controversial.

1.2.3 Proposed aetiology of IBS-type symptoms in IBD

Given that there is a several-fold increase in the prevalence of IBS-type symptoms in IBD compared with the background population (Halpin and Ford, 2012; Lovell and Ford, 2012), it follows that patients with IBD who display these symptoms may share common risk factors for their development with the IBS population. To date, the aetiology of IBS is unclear, but is thought to arise from a combination of psychological, as well as organic pathologies. An increasing body of evidence

suggesting that the cause of IBS is multifactorial has superseded the classical view of IBS as a centrally driven condition. There is now a realisation that low-grade mucosal inflammation (Ford and Talley, 2011), an altered microbiome (Kassinen et al., 2007), increased intestinal permeability (Marshall et al., 2004), and genetic factors contribute to its development (Ek et al., 2015), all of which are common to IBD, as described above.

1.2.3.1 Mucosal inflammation, dysbiosis, intestinal permeability, and visceral hypersensitivity

Mucosal inflammation is the hallmark of IBD. However, recent advances in the understanding of the aetiology of IBS suggest subclinical mucosal inflammation and increased mucosal barrier permeability may play a role in the development of symptoms. Studies have demonstrated increased levels of circulating pro-inflammatory cytokines in the peripheral blood (McKernan et al., 2011; Keohane et al., 2010), and intestinal mucosa of patients with IBS (Chadwick et al., 2002; Ford and Talley, 2011), when compared with controls. The exact cause of this inflammation is uncertain, but may be related to an alteration in the gut microbiome, with evidence of a dysbiosis in IBS, and a relative abundance of pro-inflammatory species compared with healthy individuals without IBS (Lee and Lee, 2014).

The advent of 16s ribosomal ribonucleic acid (RNA) gene sequencing has provided a specific and relatively inexpensive method of studying microbial diversity in the gut, and with it further investigation of the association of altered gut microbial composition in various GI diseases including IBS (Hong and Rhee, 2014), IBD (Walujkar et al., 2014), and colorectal cancer (Akin and Tozun, 2014). The mechanism by which gut microbes may be able to affect intestinal permeability, thus propagating

symptoms compatible with IBS, is complex but dysregulation of the enteric nervous system in response to an altered microbiome, as is observed in IBD, has been proposed as a cause (Zhou et al., 2009; Camilleri et al., 2012).

It is suggested that dysbiosis is associated with an increase in the expression of Toll-like receptors in the intestinal epithelium, which are responsible for the recognition of bacterial LPS (Brint et al., 2011). This, in combination with the presence of pro-inflammatory bacterial species, induces activation of the enteric nervous system, resulting in mucosal inflammation, altered expression of tight junction proteins (Piche et al., 2009), epithelial barrier dysfunction, increased mucosal permeability, and consequent visceral hypersensitivity and stimulation of the brain-gut axis. Moreover, the complex interactions between gut microbes, the enteric nervous system, and the brain-gut axis has also been implicated in the development of stress, anxiety, and depression in patients with IBS (Mayer et al., 2014), with some evidence to suggest this interplay may also affect the prevalence of psychological illness, even in individuals without any evidence of GI disease (Vitetta et al., 2014).

One could assume, therefore, that distinct alterations in the microbiome would be observed in patients with IBD with quiescent inflammatory activity who report IBS-type symptoms. This topic is poorly described, yet in one study attempting to investigate this matter, there was no significant difference in the differential abundance of bacterial taxa or alpha diversity, and little difference in beta diversity, between patients with asymptomatic quiescent IBD and those who reported IBS-type symptoms (Shutkever et al., 2018). Despite this, the authors conceded that the lack of observable difference in the faecal microbiota between these groups could have been secondary to unmeasured confounding, which may have resulted from the concomitant use of medications, including proton pump inhibitors and antibiotics. The study also failed to

address the potential impact of the mucosa-associated microbiome, and any role that the proteome or metabolome may have had on the development of these symptoms.

The potential role of subclinical inflammatory activity in the aetiology of IBS-type symptoms in IBD has been investigated in a prospective case-control study of patients with IBS or quiescent IBD, including 31 patients with CD and 18 patients with UC, and healthy controls undergoing ileocolonoscopy. Biopsy specimens were taken and questionnaires completed to assess the severity of IBS-type symptoms in all participants (Vivinus-Nebot et al., 2014). These biopsies were assessed for pro-inflammatory cell infiltrates, including mast cells, intraepithelial lymphocytes, and eosinophils, as well as immunohistochemistry for CD-117 and CD-3. Colonic paracellular permeability and TNFα levels were quantitatively assessed. Messenger RNA (mRNA) expression of tight junction proteins ZO-1, a-catenin, and occludin were also measured. The authors demonstrated an increase in paracellular permeability in patients with IBD with IBS-type symptoms, compared with those without, and reported that paracellular permeability in patients with IBS was comparable to those with quiescent IBD with IBS-type symptoms, whereas paracellular permeability in patients with quiescent IBD without IBS-type symptoms was similar to that of controls. The presence of IBS-type symptoms was associated with increased paracellular permeability and reduced tight junction protein mRNA expression universally. Mast cell infiltrates were higher in patients with IBS, CD, and UC versus controls, but intraepithelial lymphocytes were demonstrated in higher numbers in all IBD groups, including those reporting IBS-type symptoms, versus IBS and controls. This suggests that subclinical inflammation is implicated in the aetiology of these symptoms, especially as TNFα mRNA expression were higher in the subgroup of IBD patients who reported IBS-type

symptoms compared to those who did not, albeit that no associated increase in TNFα protein expression was identified.

The chronic recurrent mucosal inflammation characteristic of IBD may also lead to visceral afferent hypersensitivity. This could, in turn, lead to symptoms compatible with IBS via abnormal neuronal responses causing hyperalgesia and allodynia, together with abnormal local reflexes, resulting in altered GI motility and secretion. Evidence to support this comes from a rat model of colitis (La et al., 2003) and, more recently, a barostat study conducted among patients with UC in remission (van Hoboken et al., 2011). Here, a positive correlation between rectal perception thresholds and IBS-type symptoms was observed when compared with healthy controls. Furthermore, in patients reporting IBS-type symptoms, an increased number of mast cells were observed in the colonic mucosa, with a higher percentage of these mast cells in close proximity to nerve fibres, a finding previously described in patients with IBS (Barbara et al., 2004).

1.2.3.2 Psychological co-morbidity and the brain-gut axis

Several observational studies have highlighted an association between the reporting of IBS-type symptoms and psychological co-morbidity and poor quality of life in patients with IBD (Simren et al., 2002; Ansari et al., 2008; Barratt et al., 2011; Bryant et al., 2011; Farrokhyar et al., 2006; Minderhoud et al., 2004; Piche et al., 2010). Stress, anxiety, and depression are common in both IBS and IBD (Whitehead et al., 2002; Graff et al., 2009; Henningsen et al., 2003; Panara et al., 2014; Neuendorf et al., 2016). However, the effect of psychological co-morbidity on the natural history of these conditions remains controversial. Prior understanding of the cause of these conditions led healthcare professionals to assume that IBS was a centrally-mediated process, and IBD a condition largely restricted to the GI tract. However, evidence now exists to

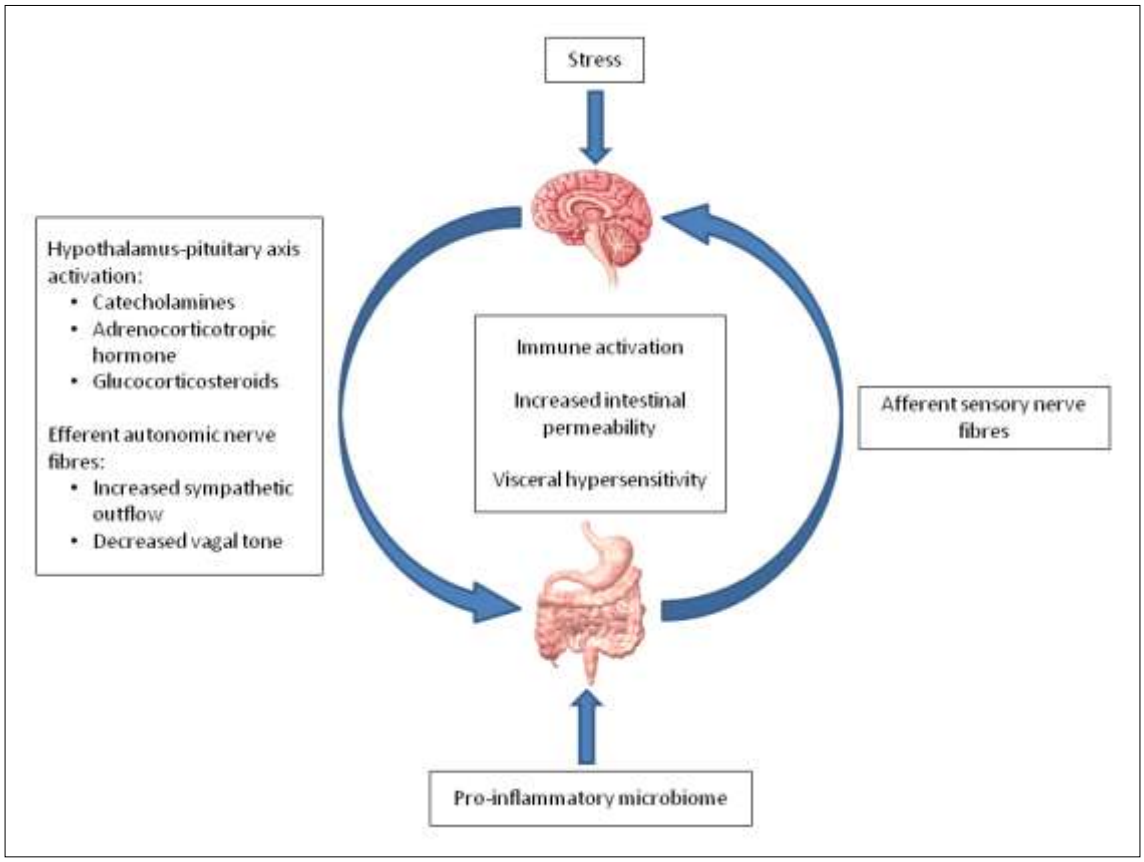
suggest that the relationship between stress and flares of disease activity in the two conditions may be more complex, and that the presence of psychological co-morbidity is associated with increased symptom severity or flares of disease activity in both (Lackner et al., 2013; Shah et al., 2014; Mittermaier et al., 2004).

A proposed explanation is that psychological co-morbidity results in a 'stress response', which may contribute to worse outcomes in these conditions. This stress response results from a complex interaction between different interconnected parts of the brain including the hypothalamus, amygdala, and hippocampus. Communication between these areas results in activation of the hypothalamus-pituitary axis. In response to stressful stimuli, adrenocorticotropic-releasing hormone is secreted from the hypothalamus. This stimulates the production of adrenocorticotropic hormone from the anterior pituitary gland, resulting in increased secretion of glucocorticosteroids from the zona fasciculata of the adrenal cortex. The impact of hypothalamus-pituitary activity may include direct effects of adrenocorticotropic hormone on the GI tract, such as increased intestinal permeability, which has been observed in murine models of stress (Santos et al., 1999). In addition, increased sympathetic autonomic activity associated with stressful stimuli is associated with enhanced secretion of catecholamines, including adrenaline and noradrenaline, from the adrenal medulla. The combination of increased catecholamine secretion, and increased sympathetic outflow is postulated to impart pro-inflammatory effects on the GI tract via stimulation of mast cells and macrophages, with inflammatory cytokines mediating these effects (Johnson et al., 2005). In contrast, the vagus nerve is thought to have a direct anti-inflammatory role, via cholinergic inhibition of pro-inflammatory cytokines (Matteoli and Boeckxstaens, 2013), but these parasympathetic responses are diminished during the stress response.

In addition to the involvement of neuroendocrine pathways, which may be enhanced by stressful stimuli, afferent sensory nerve fibres are involved in the propagation of painful stimuli in a gut to brain direction. The aetiology of visceral hypersensitivity is uncertain, but may involve abnormal enteric immune system activation in response to exposure to luminal bacterial LPS, arising secondary to increased colonic permeability, as described previously. In terms of response to visceral pain, perception is thought to involve the spinothalamic, spinoreticular and spinomesencephalic tracts (Drossman, 2004). Interestingly, the central co-ordinating centre for each of these pathways involves the limbic system, which also serves to mediate emotional responses, supporting the theory that psychological as well as physiological pathology contributes to the development of functional GI symptoms in IBS and IBD. This interaction between descending and ascending autonomic nerves, the enteric nervous system, neuroendocrine pathways, and the intestinal microbiome is referred to as the brain-gut axis (Jones et al., 2006b).

Figure 1 provides an illustrative description of the proposed neuro-hormonal pathways involved in the brain-gut axis.

Figure 1: Proposed neurohormonal pathways of the brain-gut axis



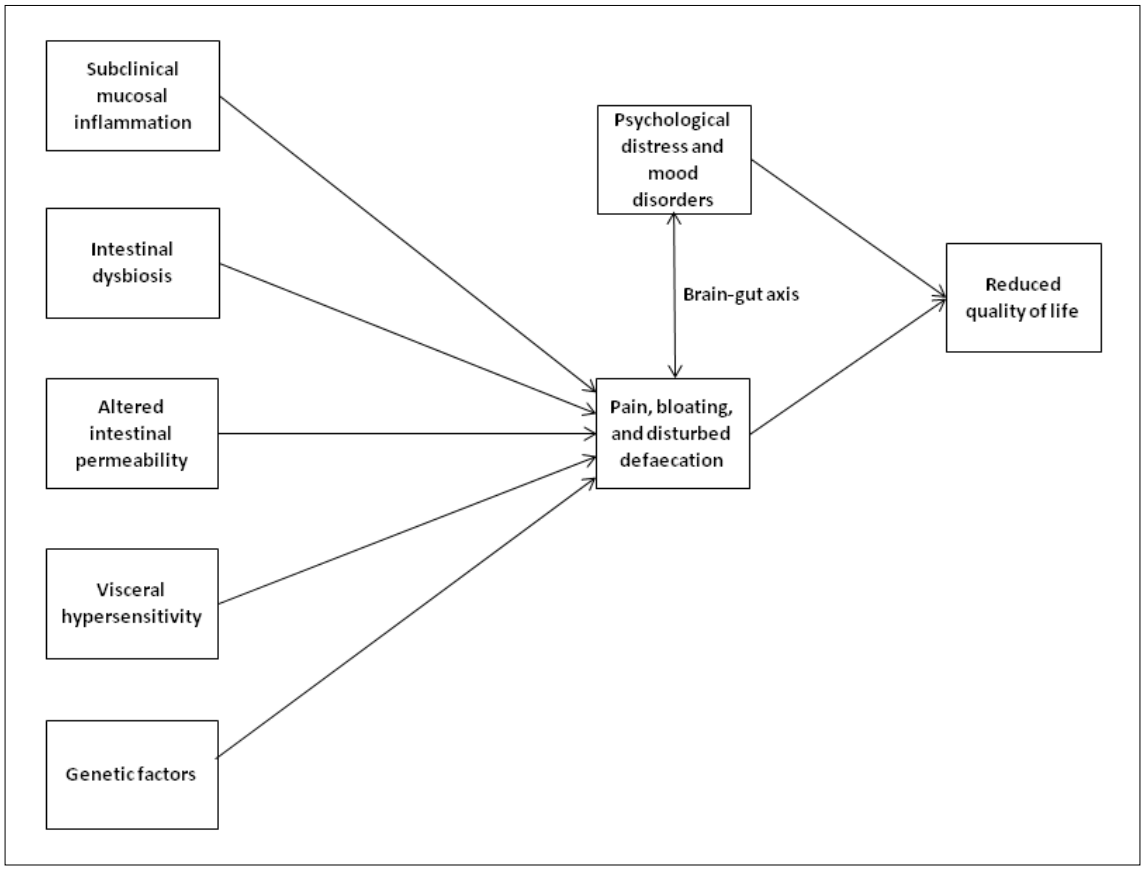
It follows that psychological health, stress, anxiety and depression symptoms, and visceral hypersensitivity are inter-related and, therefore, that mood may influence the generation and perception of symptoms. Longitudinal follow-up studies have suggested that there is a higher risk of developing anxiety or depression in people without mood disorders who report GI symptoms compatible with IBS at baseline, but also an increased likelihood of asymptomatic people who demonstrate anxiety or depression at baseline developing GI symptoms *de novo* (Koloski et al., 2012). This bi-directional effect of the brain-gut pathway seen in FGIDs raises the possibility that the relationship between brain and gut may also be bi-directional in IBD, and that co-existent anxiety or depression, if unrecognised or untreated, may have a role in the generation of symptoms compatible with IBS in such patients.

Evidence to support a bi-directional relationship between the brain and gut in IBD comes mainly from animal models. Mice with chronic GI inflammation develop behavioural changes akin to mood disorders in humans (Bercik et al., 2010). Studies have demonstrated that, in murine models of quiescent colitis, the induction of depression can reactivate inflammation of the colonic mucosa (Ghia et al., 2009), which can be attenuated by the administration of antidepressant drugs, and that this is mediated via interference with the inhibition of pro-inflammatory macrophage activity by the vagus nerve (Ghia et al., 2008). In humans, there is some evidence to suggest that acute psychological stress induces the production of pro-inflammatory cytokines in the serum and mucosa of patients with UC (Mawdsley et al., 2006). Small retrospective studies of the effect of psychological counselling or antidepressants have been conducted in patients with UC and CD acting as their own controls before and after the institution of these interventions, and have demonstrated fewer relapses of disease activity, less utilisation of glucocorticosteriods, and requirement for fewer endoscopic

investigations following their introduction (Goodhand et al., 2012a; Wahed et al., 2010). In addition, in a recent study patients with IBD demonstrated an improvement in overall depression scores following the commencement of anti-TNFα or immunomodulator therapy for active disease (Horst et al., 2015).

Figure 2 provides an illustrative description of the proposed factors that may contribute to the development of IBS-type symptoms, and the role of the brain-gut axis, in IBD.

Figure 2: Proposed aetiology of IBS-type symptoms in patients with IBD



1.2.4 Prevalence of IBS-type symptom-reporting in IBD, and deficits in current understanding of their aetiology

A recent systematic review and meta-analysis, which pooled data from 13 cross-sectional surveys and case-control studies, estimated that around one-in-three patients with UC, and almost half of patients with CD reported symptoms compatible with IBS (Halpin and Ford, 2012). When compared with healthy controls, the odds for reporting IBS-type symptoms in patients with IBD felt to be in clinical remission was 4.39 (95 % CI 2.24-8.61). However, 11 of the 13 studies included failed to utilise a quantitative measure of mucosal inflammation to define remission of disease activity prior to assessing for the presence of IBS-type symptoms. Thus, whether symptom-reporting in these studies was secondary to occult inflammatory activity, or the presence of genuine IBS-type symptoms is unknown. To complicate matters further, in the two studies that did seek to assess for mucosal inflammation (Berrill et al., 2013; Keohane et al., 2010), results were conflicting. In one cross-sectional survey of patients with IBD in clinical remission, significantly higher levels of FC were observed among those who reported symptoms compatible with IBS, compared with those without (Keohane et al., 2010). However, in another study of similar design (Berrill et al., 2013), there was no difference in median FC levels between those who reported IBS-type symptoms and those who did not, suggesting that subclinical inflammation was not the cause of IBS-types symptoms in this cohort of patients.

Since the publication of this systematic review and meta-analysis, two further studies have also addressed this issue, and reported that IBS-type symptom-reporting was not secondary to occult inflammatory activity (Jonefjall et al., 2013; Henriksen et al., 2018). However, in the majority of these studies, participant numbers were small, or were restricted to patients with UC only, and neither of these studies examined the

effect of IBS-type symptom-reporting on the natural history of IBD. Therefore, there remains a need for large-scale studies of the prevalence of IBS-type symptom-reporting in both UC and CD, where disease activity is assessed objectively, and where longitudinal follow-up is performed. These requirements provide the rationale for conducting the work that is presented in Chapters 4 and 6 of this thesis.

1.3 The impact of mood in IBD

Psychological co-morbidity, including anxiety and depression, is common in patients with IBD, with observational studies reporting a prevalence of up to 35% (Neuendorf et al., 2016). The impact of these mood disorders in IBD may be several-fold. Distinct from any potential adverse impact upon disease activity outcomes, it is proposed that the presence of psychological disease may affect adherence to medical therapy (Goodhand et al., 2013), and also impact the frequency of investigation requesting and clinic attendance, which may be ameliorated by the administration of antidepressants (Goodhand et al., 2012a).

The relationship between mood and disease activity in IBD is uncertain. Cross-sectional studies alluding to an association between psychological co-morbidity and adverse disease activity outcomes fail to address the critical question regarding the temporal relationship between the two. As described earlier, interactions between psychological wellbeing and disease activity are likely to be mediated by brain-gut interactions that have the potential to act in a brain-to-gut direction, a gut-to-brain direction, or both. Evidence to support bi-directional relationships between mood and GI disorders is based on the findings of studies in patients with FGIDs (Koloski et al., 2012; Koloski et al., 2016). Here, antecedent mood disorders in asymptomatic individuals were associated with the development of subsequent GI symptoms, and GI

symptom-reporting was associated with the development of *de novo* psychological co-morbidity over both short-term (Koloski et al., 2012), and long-term follow-up (Koloski et al., 2016). However, evidence to support a similar phenomenon in IBD is, to date, lacking.

1.3.1 The impact of mood on disease activity in IBD

In a systematic review and meta-analysis of observational studies reporting the impact of psychological co-morbidity on disease outcomes in IBD, Alexakis *et al.* suggested that, when data were pooled from four longitudinal studies, including a total of 314 patients in clinical remission at baseline (Bitton et al., 2008; Bitton et al., 2003; Langhorst et al., 2013; Levenstein et al., 2000), depression was not associated with flare of disease activity during longitudinal follow-up (hazard ratio (HR) = 1.04, 95% CI 0.97-1.12) (Alexakis et al., 2017). Although only four studies were included in formal meta-analysis, the authors identified an additional seven studies (North et al., 1991; Mittermaier et al., 2004; Mardini et al., 2004; Persoons et al., 2005; Mikocka-Walus et al., 2008; Camara et al., 2011; Mikocka-Walus et al., 2016), five of which reported a significant association between antecedent mood disorders and adverse longitudinal disease activity outcomes (Mittermaier et al., 2004; Mikocka-Walus et al., 2016; Persoons et al., 2005; Mardini et al., 2004; Camara et al., 2011). In addition to these, a large registry-based observational study, not included in the aforementioned systematic review, supports the assertion that psychological co-morbidity may negatively impact longitudinal disease activity outcomes (Gaines et al., 2016).

A major limiting factor in the examination of the temporal relationship between mood disorders and longitudinal disease activity in all studies conducted to date is the lack of objective quantification of inflammatory activity. Of the 12 studies identified

above, nine described the impact of pre-existing psychological co-morbidity, including depression, anxiety, perceived stress, or a stressful life event on longitudinal disease outcomes using clinical disease activity indices as the sole determinant of disease activity (Mittermaier et al., 2004; Mikocka-Walus et al., 2016; Persoons et al., 2005; Gaines et al., 2016; Mardini et al., 2004; Bitton et al., 2008; Camara et al., 2011; Mikocka-Walus et al., 2008; North et al., 1991). The remaining three studies (Levenstein et al., 2000; Bitton et al., 2003; Langhorst et al., 2013) used a combination of clinical disease activity indices and endoscopic assessment to describe the longitudinal association between stress and depression over short-term follow-up in a combined study population of only 213 patients with UC.

The lack of large observational studies where objective measures of inflammation are utilised to confirm remission of disease activity, and in which the impact of mood disorders on longitudinal disease activity outcomes is assessed, particularly in patients with CD, highlights the deficiencies in understanding of the temporal relationship between disease activity and psychological co-morbidity in IBD. Further longitudinal studies addressing these deficiencies are required to resolve this uncertainty.

1.3.2 The impact of disease activity on mood in IBD

Three longitudinal studies have sought to investigate gut-brain interactions in IBD (Panara et al., 2014; Lix et al., 2008; Porcelli et al., 1996). Of these, two (Panara et al., 2014; Porcelli et al., 1996) described a detrimental impact of antecedent disease activity on subsequent psychological wellbeing, with an increased incidence of new-onset anxiety and depression during longitudinal follow-up ranging from 6 months to 8 years. In the third study, the authors described an association between disease activity

and subsequent reduced quality of life, but no impact upon development of anxiety or depression (Lix et al., 2008). In combination, these data provide some evidence for the existence of gut-brain interactions in IBD. However, as previously described, inherent limitations in the design of these studies impacts the confidence with which these relationships can be accepted. Two of the three studies based their assessment of baseline disease activity on clinical measures only (Lix et al., 2008; Porcelli et al., 1996), and the third used a retrospective case note review in order to determine the presence of inflammatory activity, and its impact on longitudinal outcomes (Panara et al., 2014).

1.3.3 Bi-directional brain-gut interactions in IBD

Sexton *et al.* conducted a longitudinal follow-up study of 369 patients with IBD conducted over a period of 6 months (Sexton et al., 2017). Here, the authors described the relationship between perceived stress, symptom-reporting, and longitudinal disease activity using baseline and 3-monthly serial FC measurement. Following multivariate regression analysis to adjust for confounding variables, their results supported the existence of a bi-directional relationship between clinical disease activity and perceived stress in CD. However, no temporal relationship between inflammatory activity, as defined by FC levels, and perceived stress was identified.

1.3.4 Brain-gut interactions in IBD: more questions than answers?

Despite the plethora of observational studies attempting to delineate brain-gut interactions in IBD, these relationships remain poorly defined. Flaws in the design of several of the previously published works limit the validity of the current evidence in this field. Addressing this deficiency in current understanding is important for several

reasons. Firstly, any potential association between psychological co-morbidity and subsequent adverse disease activity outcomes would prompt a review of the management of mood in IBD, particularly as evidence-based management strategies are, to date, lacking (Timmer et al., 2011; Mikocka-Walus et al., 2006; Macer et al., 2017; Knowles et al., 2013). Secondly, the identification of a bi-directional relationship between disease activity and psychological co-morbidity, which is known to adversely affect quality of life, would support the need for an integrated model of care combining simultaneous management of psychological health and inflammatory activity in patients with IBD.

Thus, studies that deconstruct the mélange of potentially interconnected relationships between active mucosal inflammation, GI symptom-reporting, which may be secondary to genuine inflammatory activity, a co-existent FGID or somatoform behaviour, and psychological co-morbidity are required before the true relationship between mood and inflammatory activity in IBD can be confidently described. To address these deficiencies, a cross-sectional study independently assessing the association between inflammatory activity defined using FC, and clinical/symptomatic disease activity defined using clinical disease activity indices, with the presence of anxiety, depression, and somatisation was conducted, and is described in Chapter 3. Furthermore, a prospective longitudinal study assessing the temporal relationship between inflammatory activity, symptom-reporting, psychological co-morbidity, and longitudinal disease activity outcomes is required to further delineate potential bi-directional relationships in IBD. These deficiencies will be addressed in the study described in Chapter 5.

1.4 Treatment of IBS-type symptoms and psychological co-morbidity in IBD

In patients without IBD, a confirmed diagnosis of IBS is associated with more sickness-related absences from work than those without bowel symptoms (Drossman et al., 1993). IBS costs almost $1 billion in direct costs and another $50 million in indirect costs per year (Everhart and Ruhl, 2009). Furthermore, patients with IBS consume >50% more health care resources than matched controls without IBS (Inadomi et al., 2003). All of these factors suggest that proactive treatment of IBS-type symptoms in IBD may also be required. In IBS, the evidence base for effective therapies has been summarised previously (Ford et al., 2014a). Soluble fibre, antispasmodics, antidepressants, psychological therapies, and probiotics all appear to be of some benefit (Moayyedi et al., 2014; Ford et al., 2014c; Ford et al., 2014b; Ford et al., 2008). As described previously, subclinical mucosal inflammation, an abnormal microbiome, and disordered brain-gut axis activity may be implicated in the development of IBS-type symptoms and psychological co-morbidity in IBD. Thus, the use of immunomodulators, probiotics, FMT, antidepressants, and psychological therapies may also be beneficial in the treatment of IBS-type symptoms in IBD. A summary of the current evidence base for the treatment of IBS-type symptoms and psychological co-morbidity in patients with IBD is described below.

1.4.1 Conventional IBD treatment

As described earlier, several RCTs investigating the effect of various medications, including glucocorticosteroids, 5-ASAs, immunomodulators, and biological therapies, have been conducted in IBD. However, end-points in these studies have focused exclusively on their effect on disease activity, largely using clinical disease activity indices. Although none of these studies has reported the efficacy of such

treatments on the management of IBS-type symptoms specifically, three RCTs of biological therapy have commented on the lack of efficacy of these treatments in symptomatic patients with IBD who did not have objective evidence of inflammatory activity at randomisation (Reinisch et al., 2012; Colombel et al., 2010; Schreiber et al., 2005). These findings suggest that conventional medical treatments targeting disordered enteric immunity are not effective in the management of symptomatic patients in whom the inflammatory burden is limited, akin to the situation seen in patients reporting IBS-type symptoms.

The proposed pathophysiological mechanisms by which psychological co-morbidity and inflammatory activity may be inter-related are discussed above. Mood disorders are associated with increased circulating pro-inflammatory cytokines and CRP (Howren et al., 2009), suggesting that treatment with immunosuppressants may impart beneficial effects on mood, independent of their effects on inflammatory activity. In IBD, prior observational studies of patients with CD and UC newly commenced on either anti-TNFα therapy or vedolizumab have demonstrated improved depression scores and better sleep following treatment (Horst et al., 2015; Stevens et al., 2017). Despite these findings being of interest, neither of these studies accounted for the potential confounding effect of glucocorticosteroid tapering on mood in their analyses, nor were there any data presented to suggest an additional benefit of these drugs on mood, other than that associated with an improvement in inflammatory activity.

1.4.2 Manipulation of the intestinal microbiome

The microbiome-gut-brain axis has been implicated in the development of disease activity and psychological co-morbidity. Manipulation of the intestinal microbiome is, therefore, an attractive target for therapeutic interventions in IBD.

Probiotics may be effective for the treatment of persistent GI symptoms (Ford et al., 2014c) and depression (Pinto-Sanchez et al., 2017) in IBS. Their use has also been examined in IBD in a recent systematic review and meta-analysis of RCTs (Derwa et al., 2017), where their efficacy in the treatment of active disease and maintenance of quiescent disease was limited. However, none of the RCTs included in this systematic review and meta-analysis sought to determine the effect of probiotics on either mood or IBS-type symptom-reporting in patients with IBD. In non-IBD populations, the effect of probiotics on mood has been studied in a meta-analysis of 10 RCTs (Ng et al., 2018a). Here, the authors concluded that there was a lack of evidence to support the use of probiotics in the treatment of depressive symptoms, and that the inclusion of studies of depressed and non-depressed populations in the same analyses, as well as the use of varying strains and treatment regimens of probiotic, limited the validity of their findings.

FMT is an experimental intervention in IBD. Its use in the treatment of IBS-type symptoms in IBD has not been evaluated. However, in an observational study of FMT in patients with IBS, active treatment was associated with improved depression scores, which were observed in association with an improvement in faecal bacterial diversity, measured using the Shannon index (Kurokawa et al., 2018). Overall, there are a lack of controlled studies of FMT in both IBS and IBD to support its use outside the setting of clinical trials. Despite this, in the only RCT of FMT in IBS (Johnsen et al., 2018), there was a significant improvement in IBS symptom severity in patients treated with FMT, when compared with a placebo of the patient's own faeces, at 3-month follow-up suggesting that further RCTs may be worthwhile.

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) is recommended for the treatment of IBS. FODMAPs are

osmotically active fermentable carbohydrates, the ingestion of which results in increased luminal water and gas volume (Staudacher et al., 2014), leading to the perception of pain, but only in selected patients with visceral hypersensitivity (Major et al., 2017). The low FODMAP diet is also associated with alterations in bacterial diversity, specifically the abundance of *Bifidobacteria* (Halmos et al., 2015). In a systematic review and meta-analysis of studies assessing the efficacy of a low FODMAP diet in the treatment of IBS, significant improvements in symptom severity and quality of life were associated with active treatment, when compared with a normal diet (Schumann et al., 2018). Only one of these studies assessed the impact of a low FODMAP diet on anxiety and depression, with no benefit observed. In three of the nine randomised trials included in this meta-analysis, the effect of a low FODMAP diet on the intestinal microbiome was assessed (McIntosh et al., 2017; Staudacher et al., 2012; Staudacher et al., 2017). A reduction in the abundance of *Bifidobacteria* was observed in association with an improvement in symptom severity after treatment. However, the reduction in *Bifidobacteria* abundance observed in patients on a low FODMAP diet appears to be able to be reversed by concomitant probiotic consumption, without attenuating the effect of the diet on IBS symptom severity, suggesting its effect may be independent of any associated alteration in *Bifidobacteria* abundance (Staudacher et al., 2017). Although the effect of the low FODMAP diet on mood in IBS is uncertain, a RCT published since the aforementioned systematic review and meta-analysis, examined its effect on IBS symptom severity, psychological wellbeing, and quality of life. The authors reported a significant improvement in quality of life and anxiety scores, in addition to beneficial effects on IBS symptom severity, after 4 weeks of treatment (Eswaran et al., 2017).

The use of a low FODMAP diet in patients with IBD reporting IBS-type symptoms is, to date, poorly described. In a randomised controlled open-label trial of 89 patients with IBD, who also fulfilled the Rome III criteria for IBS, participants were randomised to a low FODMAP or normal diet. The investigators reported higher rates of improvement in IBS-type symptom severity and quality of life in patients receiving the low FODMAP diet, when compared with those eating a normal diet ($P = 0.02$ and $P < 0.001$, respectively) (Pedersen et al., 2017). In a further randomised, double blind, placebo controlled, cross-over, re-challenge trial of patients with IBD with functional symptoms who had previously responded to a low FODMAP diet, 32 participants were randomly allocated to a series of 3-day fermentable carbohydrate challenges, during which time symptom severity and stool output was assessed (Cox et al., 2017). Pain ($P = 0.004$), bloating ($P = 0.002$), flatulence ($P = 0.004$), and faecal urgency scores ($P = 0.014$) were all significantly higher on day 3 of fructan challenge (FODMAP) compared with day 3 of glucose challenge (control). Although these studies, and other observational studies, investigating the relationship between FODMAPs and IBS-type symptom-reporting in patients with IBD (Maagaard et al., 2016; Gearry et al., 2009; Testa et al., 2018; Prince et al., 2016) highlight a potential role for the low FODMAP diet in their treatment, the lack of large-scale RCTs limits the applicability of these findings to clinical practice. Further RCTs investigating the efficacy of this intervention on symptom severity, quality of life, and psychological co-morbidity are required before its use can be advocated in IBD.

1.4.3 Antidepressants

The proposed mechanisms by which these drugs may impart beneficial effects in IBD are twofold. These include the induction of vagus nerve-mediated anti-

inflammatory effects (Ghia et al., 2008), but also a potential direct effect on pro-inflammatory cytokines that may arise via action of the NF-κB and nitric oxide pathways, which are both implicated in the aetiology of IBD (Rahimi et al., 2012).

Tricyclic antidepressants and selective serotonin reuptake inhibitors are more effective than placebo in treating IBS (Ford et al., 2014b). However, their efficacy in IBD is less well-described. A systematic review of studies reporting the efficacy of antidepressant medications in the maintenance and induction of remission of IBD was published in 2006 (Mikocka-Walus et al., 2006). The review included six case reports, one non-randomised open-label study, and one letter that, collectively, reported beneficial effects of bupropion, paroxetine, amitriptyline, and phenelezine. However, the studies were small, and all except one was conducted in patients with CD. An updated systematic review, including an additional eight studies, has been conducted by the same authors (Macer et al., 2017). These studies were again largely retrospective and observational in design, with only one RCT involving a total of 35 patients included (Daghaghzadeh et al., 2015). Overall, a beneficial effect of antidepressants on disease activity was observed in 12 of 15 studies, and an improvement in depression and anxiety scores was reported in eight of nine studies reporting these outcomes. Despite this, the authors concluded that a lack of RCTs assessing the effect of these drugs on longitudinal disease outcomes, mood, and quality of life meant that estimating the efficacy of these drugs in IBD was not possible.

Since the publication of this systematic review, an additional pilot RCT of fluoxetine in the treatment of IBD has been conducted (Mikocka-Walus et al., 2017). The authors reported that fluoxetine was not superior to placebo in the maintenance of disease remission, or treatment of psychological wellbeing, albeit in a small sample of

only 26 patients. As a result, the study was unlikely to be sufficiently powered to detect a difference in these outcomes.

Only one study has reported the efficacy of tricyclic antidepressants in patients with IBD reporting ongoing symptoms in the absence of objectively quantified inflammatory activity (Iskandar et al., 2014). It is important to point out that patients in this retrospective study were not screened formally using validated questionnaires to confirm whether or not they met symptom-based criteria for IBS. Despite this, outcomes, which were based on self-reported symptom severity using a Likert scale, appeared to be good, with at least a moderate improvement in 60% of patients with IBD, with a better response observed in patients with UC compared with CD. Symptom response in patients with IBD was similar to that observed in a control group of patients with IBS.

1.4.4 Psychological therapy

In addition to antidepressants, psychological therapies have also been shown to be beneficial in IBS (Ford et al., 2014c). These include cognitive behavioural therapy (CBT) and gut-directed hypnotherapy, both of which are recommended by national guidelines for the management of IBS (Ford et al., 2014a; Spiller et al., 2007). However, definitive evidence supporting the use of psychological therapies as an effective treatment in IBD, particularly in those reporting IBS-type symptoms is lacking, with only one study conducted, which recruited just 27 patients with IBS-type symptoms among a total study population of 66 (Berrill et al., 2014).

A Cochrane review has investigated the efficacy of psychotherapy, patient education, and relaxation techniques in IBD (Timmer et al., 2011). Outcomes assessed included health-related quality of life, coping, emotional status, and disease activity. In

total 21 studies were included, but there was no clear benefit identified for any of the psychological interventions in adults with IBD, for any of the outcomes of interest. Another systematic review of 16 studies of psychological interventions, including stress management, psychodynamically informed therapy, CBT, and hypnosis assessed their effects on anxiety and depression, quality of life, and IBD activity. CBT and psychodynamically informed therapy appeared beneficial for anxiety and depression, but had no effect on disease activity, whereas hypnotherapy, used in two studies, demonstrated a beneficial effect on disease activity, but not anxiety, depression, or quality of life (Knowles et al., 2013).

Since the publication of the Cochrane review by Timmer *et al.* in 2011, several additional RCTs of psychological therapies in IBD have been conducted (McCombie et al., 2016; Mikocka-Walus et al., 2015; Keefer et al., 2012; Schoultz et al., 2015; Jedel et al., 2014; Keefer et al., 2013; Berrill et al., 2014; Boye et al., 2011; Mizrahi et al., 2012; Vogelaar et al., 2011; Vogelaar et al., 2014). These individual studies have examined the effect of CBT, hypnotherapy, solution focussed therapy, and stress management on outcomes including disease activity, anxiety, depression, perceived stress, and quality of life.

Five RCTs have studied the effect of CBT on disease activity, psychological wellbeing and quality of life in patients with IBD (Keefer et al., 2012; Berrill et al., 2014; Mikocka-Walus et al., 2015; Schoultz et al., 2015; McCombie et al., 2016). Overall, no beneficial effect on disease activity was observed in any of these studies. Positive effects on quality of life were reported in three studies (Keefer et al., 2012; McCombie et al., 2016; Mikocka-Walus et al., 2015), but with no effect over treatment as usual in the remaining two RCTs (Berrill et al., 2014; Schoultz et al., 2015). Similarly, evidence for the impact of these interventions on psychological wellbeing is

conflicting, with two studies reporting a benefit (Keefer et al., 2012; Schoultz et al., 2015), but not the other three (Berrill et al., 2014; McCombie et al., 2016; Mikocka-Walus et al., 2015).

Only two RCTs have considered the effect of hypnotherapy on disease outcomes in IBD (Mizrahi et al., 2012; Keefer et al., 2013). Results were again conflicting with one study reporting a beneficial effect on psychological wellbeing and quality of life, but not disease activity (Mizrahi et al., 2012), and the other an increased likelihood of remaining in clinical remission, but no effect on quality of life or psychological factors (Keefer et al., 2013). Two RCTs, conducted by the same authors, have investigated the efficacy of solution focussed therapy in IBD (Vogelaar et al., 2011; Vogelaar et al., 2014). These studies demonstrated a beneficial effect on fatigue and quality of life, but not disease activity or psychological wellbeing. Finally, two RCTs have investigated the use of stress management in the treatment of IBD (Boye et al., 2011; Jedel et al., 2014). These studies reported a beneficial effect on quality of life, but no effect on disease activity or psychological wellbeing.

As described, a significant number of additional RCTs of psychological therapies have been conducted since the Cochrane review was performed in 2011 (Timmer et al., 2011). In this study, the authors included quasi-randomised and non-randomised studies in their analysis, thus limiting the quality and reliability of the data presented. Furthermore, a prospective study assessing patient attitudes towards treatment of mood disorders in IBD reported that psychological therapies were preferred to antidepressants, with 60% of patients with IBD receiving psychological therapy recommending its use, compared with a corresponding figure of 30% for patients treated with antidepressants (Mikocka-Walus and Andrews, 2016). Taken in combination, the methodological deficiencies of the previous meta-analysis, the

availability of new RCTs of psychological therapies in IBD, and the patient preference for psychological intervention ahead of antidepressant therapy in the treatment of mood disorders in IBD provides the rationale for conducting a methodologically robust, contemporaneous, systematic review and meta-analysis of RCTs of psychological therapies in IBD. Such a study would provide a summary of the current evidence base of the use of psychological therapies for the treatment of disease activity, psychological co-morbidity, and quality of life in IBD. It is for this reason that the systematic review and meta-analysis described in Chapter 7 was performed.

CHAPTER 2: Aims and objectives

The aims of this thesis are to explore the relationship between GI symptom-reporting, including those symptoms meeting criteria for IBS, inflammatory activity, and psychological wellbeing and quality of life in patients with IBD, to describe the impact of these relationships on longitudinal disease activity outcomes, and to provide a summary of the efficacy of psychological therapies as a therapeutic intervention in IBD. These aims are addressed in the following pieces of work:

2.1 Examining the relationship between clinical disease activity and mucosal inflammation, and the role of psychological co-morbidity, in IBD

The correlation between the presence of mucosal inflammation and GI symptom-reporting is poor (Targownik et al., 2015). Despite this, as previously described, traditional assessment of IBD activity is centred on the interpretation of patient-reported symptoms, with invasive endoscopic and radiological investigations performed in those where diagnostic uncertainty persists. Although the relationship between symptom-reporting and mucosal inflammation has been investigated previously, the association between psychological co-morbidity on symptom-reporting has not previously been studied in IBD. This deficiency was addressed by performing a cross-sectional study of secondary care patients with confirmed IBD, in which clinical disease activity indices, FC and psychological data were collected. The aim of this study was to describe the relationship between GI symptom-reporting and the presence of mucosal inflammation in IBD, and to assess whether the presence of psychological co-morbidity including anxiety, depression, or somatisation influenced this relationship.

2.2 Assessing the relationship between the reporting of IBS-type symptoms, and psychological health and quality of life in patients with IBD

The reporting of IBS-type symptoms in patients with clinically quiescent IBD is as high as 35% (Halpin and Ford, 2012). The aetiology of these symptoms is uncertain, with some authors suggesting they arise secondary to occult inflammatory activity, and others disputing this. In IBD, the correlation between GI symptom-reporting and mucosal inflammation is poor. Thus, attributing GI symptoms to co-existent IBS is not possible without the use of an objective marker of intestinal inflammation. The presence of psychological co-morbidity including anxiety, depression, or somatisation, and reduced quality of life, is commonly observed in patients with IBS, highlighting the potential role of the brain-gut axis in the development of this clinical syndrome. Whether a similar association between IBS-type symptom-reporting, and the presence of psychological co-morbidity and reduced quality of life exists in IBD populations is uncertain. Previous investigators have attempted to describe this relationship. However, few of these have sought to quantify inflammatory activity before applying diagnostic criteria for IBS, and none have investigated the relationship between IBS-type symptom-reporting and somatoform behaviour. The aims of the study described in Chapter 4 were to provide an assessment of the prevalence of genuine IBS-type symptom-reporting in patients with CD and UC, and to assess the association between the presence of genuine IBS-type symptoms and anxiety, depression, somatisation, and quality of life.

2.3 Assessing the direction of brain-gut interactions in patients with IBD

The relationship between GI symptom-reporting and psychological co-morbidity in IBS is well-established, and appears to be bi-directional (Koloski et al., 2012; Koloski et al., 2016). In keeping with this, therapeutic interventions targeting disordered brain-gut activity are evidence based in IBS (Ford et al., 2014b). The prevalence of psychological co-morbidity in IBD is high, yet the impact of anxiety and depression on longitudinal disease activity outcomes remains uncertain. Previous authors have attempted to describe a temporal relationship between psychological factors and disease activity in IBD, but many are confounded by limitations including a reliance on symptom-reporting as the sole determinant of disease activity, a small sample size, exclusion of patients with CD, and a failure to assess whether any potential relationship between the brain and the gut in IBD may be bi-directional. Thus, the aim of Chapter 5 was to simultaneously examine for the presence of both brain-to-gut and gut-to-brain interactions in a single study population of patients with IBD. In order to fulfil this aim, the association between anxiety or depression at study entry, in patients with quiescent disease at baseline, with subsequent disease activity outcomes, including flare of disease activity or need for glucocorticosteroid prescription, escalation of medical therapy, hospitalisation, and intestinal resection was investigated during longitudinal follow-up. Simultaneously, the association between baseline active disease, in patients with normal anxiety and depression scores at baseline, and the risk of developing subsequent anxiety or depression was also assessed longitudinally.

2.4 Describing the association between the reporting of IBS-type symptoms, and longitudinal disease activity, healthcare utilisation, psychological health, and quality of life in IBD

Although the reporting of IBS-type symptoms occurs in up to 35% of patients with clinically quiescent IBD (Halpin and Ford, 2012), the association between the reporting of these symptoms and longitudinal disease outcomes has not been studied before. The association between IBS-type symptom-reporting, and the presence of psychological co-morbidity and poor quality of life is described in Chapter 4. When taken in conjunction with the association that psychological co-morbidity may have with adverse longitudinal disease activity outcomes described in Chapter 5, it is possible that the reporting of IBS-type symptoms in IBD may also be associated with a deleterious impact on longitudinal disease outcomes, particularly if these symptoms relate to occult disease activity, as some investigators have proposed (Keohane et al., 2010; Vivinus-Nebot et al., 2014). A longitudinal follow-up study was therefore conducted with the aim of assessing disease activity outcomes including flare of disease activity or the need for glucorticosteroid prescription, escalation of medical therapy, hospitalisation or intestinal resection over a minimum follow-up period of 2 years. An additional aim of this study was to assess whether the association between IBS-type symptom-reporting and psychological co-morbidity and poor quality of life observed at baseline persisted over time, and to determine whether the reporting of these symptoms was associated with increased healthcare utilisation.

2.5 Summarising the effect of psychological therapies on disease activity, psychological co-morbidity, and quality of life in IBD

The association between psychological co-morbidity and adverse disease activity outcomes in IBD is discussed in Chapter 5. These issues potentially highlight the need for an integrated approach to the management of IBD, which incorporates the management of inflammatory activity with that of psychological wellbeing. Psychological therapy and antidepressants are evidence-based interventions in the management of other chronic GI disorders whose pathophysiology may also involve brain-gut axis dysregulation (Ford et al., 2014b). It follows that these interventions may also have beneficial effects in IBD. Indeed, the use of antidepressants in IBD was the subject of a recent systematic review which reported potential benefits for these drugs, but also highlighted that a lack of RCTs meant that their use could not be advocated strongly (Macer et al., 2017). In addition, the role of psychological therapies in IBD was the subject of a Cochrane systematic review and meta-analysis in 2011 (Timmer et al., 2011). However, methodological weaknesses in this study, as well as the publication of several additional RCTs since 2011, means that its findings may be out-dated. An updated systematic review and meta-analysis was therefore conducted with the aim of providing a thorough and contemporaneous review of the role of psychological therapies in IBD, with a focus on their potential effects on disease activity, psychological co-morbidity, and quality of life.

CHAPTER 3: Examining the relationship between clinical disease activity and mucosal inflammation, and the role of psychological co-morbidity, in IBD

3.1 Introduction

Although considered primary GI disorders, CD and UC are associated with significant psychological co-morbidity. Anxiety or depression is reported to affect up to one-in-three patients with IBD (Tribbick et al., 2015; Walker et al., 2008; Fuller-Thomson et al., 2015). Furthermore, recent observational data from longitudinal studies suggest that mood disorders, including anxiety and depression, may be associated with adverse disease outcomes and reduced quality of life (Kappelman et al., 2014). However, many studies designed to investigate these issues have used clinical disease activity indices to assess disease activity, rather than gold-standard investigations such as ileocolonoscopy or small bowel imaging, or faecal biomarkers of intestinal inflammation to assess disease activity. As a result, given that the correlation between these tools and objective measures of inflammation may be variable, (Falvey et al., 2015; af Bjorkesten et al., 2012; Sipponen et al., 2008; Jones et al., 2008; Schoepfer et al., 2010) the implication of their results is uncertain.

Whether psychological co-morbidity affects clinical disease outcomes has important implications for clinical practice. A clearer understanding of whether psychological health is associated with increasing inflammatory burden, or just the reporting of functional symptoms attributable to the GI tract in general, may aid clinical decision-making, which is suboptimal when made on the basis of patient-reported symptoms alone (Derwa et al., 2018). In the former instance, this may dictate the need for escalation of conventional therapies, but in the latter situation where the aetiology of these symptoms is unclear, and where evidence suggests that the efficacy of these treatments is suboptimal, (Colombel et al., 2010; Schreiber et al., 2005; Reinisch et al., 2012) other management strategies may be required. This is particularly relevant at the

present time, as the US Food and Drug Administration are moving towards PROMs as a measure of efficacy in clinical trials of novel therapies for IBD (Williet et al., 2014).

A large cross-sectional study of patients with IBD was therefore conducted to attempt to resolve these uncertainties. Patient-reported clinical disease activity indices and FC, as measures of clinically active disease and mucosal inflammation respectively, and psychological data regarding anxiety, depression, and somatisation, were recorded. The hypothesis was that symptomatic disease activity would be associated with the presence of psychological co-morbidity, independent of inflammatory burden.

3.2 Methods

3.2.1 Participants and setting

Patients aged 16 and over, with an established radiological, histological, or endoscopic diagnosis of CD or UC attending the IBD clinic at St. James's University Hospital, Leeds, United Kingdom, a tertiary referral hospital serving a population of over 800,000 people were approached about the study. Included participants were both consecutive and unselected. Due to difficulty in assessing disease activity indices, patients with an end ileostomy or colostomy were excluded, as were those with a diagnosis of inflammatory bowel disease unclassified, isolated fistulising peri-anal CD, or any individual with an inability to understand written English. Prior to their consultation with a gastroenterologist, individuals were provided with an information sheet explaining the nature of the study. Those who agreed to take part gave written informed consent at this visit. The study received approval from the local research ethics committee in November 2012 (REC ref: 12/YH/0443), and data collection ceased in June 2015.

3.2.2 Data collection and synthesis

3.2.2.1 Demographic data and disease characteristics

Demographic data including gender, age, ethnicity, marital status, educational level, tobacco and alcohol use, weight (in kilograms), and height (in metres), which were used to calculate body mass index (BMI), were collected from all participants. Medication history, including current use of 5-ASAs, glucocorticosteroids, immunosuppressants, or anti-TNFα therapy, disease location or distribution, as defined by the Montreal classification (Silverberg et al., 2005), and any previous intestinal resection related to CD were also recorded.

3.2.2.2 Assessment of patient-reported IBD activity and mucosal inflammation

Patient-reported IBD activity was assessed using HBI for CD (Harvey and Bradshaw, 1980), and the SCCAI for UC (Walmsley et al., 1998), with a score ≥5 used to define clinically active disease for both, as previously recommended (Vermeire et al., 2010; Jowett et al., 2003). In addition, participants were asked to report whether, in their own opinion, they were attending with a flare of disease activity. Those who agreed to participate were asked to provide stool for quantitative FC analysis within 1 week of inclusion, as an objective marker of mucosal inflammation. This has a reported sensitivity and specificity of 93.5% and 79.2% respectively for predicting mucosal inflammation identified at ileocolonoscopy (Loitsch et al., 2010). A cut off of ≥250µg/g of stool was used to define the presence of active disease, in line with the European Crohn's and Colitis Organisation consensus on the use of FC to measure disease activity (Rogler et al., 2013), as other investigators have employed (Targownik et al., 2015; D'Haens et al., 2012; Lin et al., 2014). The FC level was measured using an enzyme-

linked immunosorbent assay (ELISA) (Immundiagnostik AG, Bensheim, Germany), as per manufacturer's instructions. Internal inter-assay coefficient of variation was 8.3% (low) to 9.4% (high).

3.2.2.3 Reference standard used to define presence of IBS-type symptoms

IBS-type symptoms were assessed via the Rome III criteria (Longstreth et al., 2006), according to the scoring algorithm incorporated within the Rome III diagnostic questionnaire for the adult FGIDs. IBS-type symptoms were defined as present when an individual reported abdominal discomfort or pain with a frequency of at least 2 or 3 days per month over the last 3 months, with the onset of discomfort at least 6 months previously, associated with two or more of the following: an improvement of pain or discomfort with the passage of stool, more or less frequent bowel movements, or looser or firmer stools.

3.2.2.4 Definition of anxiety or depression

The presence of either anxiety or depression was assessed using the hospital anxiety and depression scale (HADS) (Zigmond and Snaith, 1983). This 14-item questionnaire consists of seven questions screening for the presence of anxiety symptoms, and seven for depression symptoms, with a 4-point response for each item, ranging from 0 to 3. The total possible score on the HADS ranges from a minimum of 0 to a maximum of 21 for both anxiety and depression. Severity was categorised, according to total HADS score, into normal (total HADS depression or anxiety score 0-7), borderline normal (8-10), and abnormal (≥11) (Zigmond and Snaith, 1983).

3.2.2.5 Definition of somatisation severity

Somatisation data were collected using the patient health questionnaire-15 (PHQ-15), which is derived from the validated full PHQ (Spitzer et al., 1999; Spitzer et al., 2000). This questionnaire enquires about the presence of 15 somatic symptoms (or symptom clusters) over the last 4 weeks, which are thought to contribute to >90% of physical complaints reported in the outpatient environment (Kroenke et al., 1990). Each individual was asked to rate the severity of each symptom as "not bothered at all" (scored as 0), "bothered a little" (scored as 1), or "bothered a lot" (scored as 2). The total PHQ-15 score ranges from a minimum of 0 to a maximum of 30. Somatisation severity was categorised, using the total PHQ-15 score, into high (total PHQ-15 ≥15), medium (10-14), low (5-9), and minimal (≤4) levels of somatisation severity (Kroenke et al., 2002).

3.2.3 Statistical analysis

Demographic data, disease characteristics, medication use, presence or absence of symptoms meeting the Rome III criteria for IBS, disease activity indices, FC levels, and anxiety, depression, and somatisation data were compared between patients with CD and UC using a χ^2 test for categorical variables and an independent samples *t*-test for continuous data.

In order to assess the relationship between clinical disease activity indices, mucosal inflammation, IBS-type symptoms, and psychological factors, a comparison of baseline demographic and disease-related characteristics, the presence of symptoms fulfilling the Rome III criteria for IBS, the presence of a self-reported flare of disease activity, anxiety, depression, and somatisation scores, and the presence of anxiety, depression, or somatisation was conducted between patients with CD and UC

separately, and dichotomised into those with or without clinically active symptomatic disease, using a total HBI or SCCAI cut off of ≥5 for CD and UC respectively, or those with and without active mucosal inflammation, using a FC cut off of ≥250μg/g of stool. A χ^2 test was used to compare categorical variables and an independent samples *t*-test for continuous data. Independent risk factors for clinically active symptomatic disease defined according to HBI or SCCAI, or active mucosal inflammation according to FC, were determined for all patients with CD and UC separately by performing multivariate logistic regression to control for all other demographic and disease-related characteristics, presence of symptoms fulfilling the Rome III criteria for IBS, the presence of a self-reported flare of disease activity, and anxiety, depression, and somatisation scores.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a total HBI or SCCAI score ≥5, and the individual symptom items included within each scoring system, as well as the presence of Rome III IBS-type symptoms, a self-reported flare of disease activity, abnormal HADS anxiety or depression scores, or high levels of somatisation were calculated in terms of predicting mucosal inflammation using a FC of ≥250μg/g, in order to assess the extent to which clinical disease activity indices, IBS symptoms, a self-reported flare of disease activity, and psychological co-morbidity were indicative of objective evidence of disease activity.

Due to multiple comparisons, a 2-tailed P value of <0.01 was considered to be statistically significant for all analyses, and the results of multivariate logistic regression were expressed as odds ratios (ORs) with 99% confidence intervals (CIs). All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

3.3 Results

In total, 356 (44.6%) of 799 patients who initially consented to participate had complete HBI or SCCAI, Rome III, HADS and PHQ-15 data, and returned a sample for FC analysis. Of these, 191 (53.7%) had confirmed CD and 165 (46.3%) UC. In terms of baseline demographic characteristics, patients with CD were significantly more likely to smoke, less likely to be prescribed 5-ASAs, more likely to be prescribed immunomodulator or anti-TNFα therapy, and fulfil Rome III criteria for IBS than patients with UC. There were no other statistically significant differences between those with CD and UC (Table 1).

Table 1: Characteristics of patients with CD and UC

	Crohn's disease (n = 191)	Ulcerative colitis (n = 165)	P value*
Mean age in years (SD)	46.7 (16.6)	51.2 (16.3)	0.01
Female gender (%)	119 (62.3)	89 (53.9)	0.11
Married or co-habiting (%)	118 (61.8)	119 (72.1)	0.04
University/postgraduate (%)	50 (26.3)	48 (29.4)	0.51
Mean BMI (SD)	26.3 (5.6)	27.1 (5.7)	0.20
Tobacco user (%)	40 (20.9)	7 (4.2)	<0.001
Alcohol user (%)	121 (63.4)	110 (66.7)	0.51
Crohn's disease location (%)			
Ileal	43 (22.5)	N/A†	
Colonic	62 (32.5)	N/A†	
Ileocolonic	86 (45.0)	N/A†	N/A†
Crohn's disease behaviour (%)			
Non-stricturing, non-penetrating	163 (85.3)	N/A†	
Stricturing	21 (13.1)	N/A†	
Penetrating	7 (3.7)	N/A†	N/A†
Perianal Crohn's disease present (%)	16 (8.4)	N/A†	N/A†
Ulcerative colitis extent (%)			
Proctitis	N/A†	45 (27.3)	
Left sided	N/A†	74 (44.8)	
Extensive	N/A†	46 (27.9)	N/A†
5-ASA use (%)	53 (27.7)	131 (79.4)	<0.001
Immunomodulator use (%)	88 (46.1)	34 (20.6)	<0.001
Anti-TNFα use (%)	52 (27.2)	4 (2.4)	<0.001
Glucocorticosteroid use (%)	21 (11.0)	17 (10.3)	0.83
Previous intestinal resection (%)	62 (32.5)	N/A†	N/A†
Rome III IBS criteria fulfilled (%)	86 (45.0)	49 (29.7)	0.003

Mean HBI/SCCAI (SD)	4.3 (3.5)	4.0 (3.2)	N/A†
HBI/SCCAI ≥5 (%)	69 (36.1)	66 (40.0)	0.45
Self-reported flare (%)	42 (22.0)	51 (30.9)	0.06
Mean FC (SD)	468 (777)	541 (922)	0.43
FC ≥250µg/g (%)	73 (38.2)	65 (39.4)	0.82
Mean HADS anxiety score (SD)	7.5 (4.6)	7.2 (4.9)	0.49
HADS anxiety categories (%)			
Normal	102 (53.4)	93 (56.4)	
Borderline abnormal	39 (20.4)	32 (19.4)	
Abnormal	50 (26.2)	40 (24.2)	0.85
Mean HADS depression score (SD)	5.0 (4.2)	4.7 (4.3)	0.49
HADS depression categories (%)			
Normal	139 (72.8)	134 (81.2)	
Borderline abnormal	32 (16.8)	11 (6.7)	
Abnormal	20 (10.5)	20 (12.1)	0.01
Mean PHQ-15 somatisation score (SD)	10.3 (4.7)	9.0 (5.2)	0.02
PHQ-15 somatisation categories (%)			
Mild	20 (10.5)	33 (20.0)	
Low	64 (33.5)	49 (29.7)	
Medium	72 (37.7)	52 (31.5)	
High	35 (18.3)	31 (18.8)	0.08

*Independent samples *t*-test for continuous data, and χ^2 for categorical data.

†N/A; not applicable.

3.3.1 Characteristics of patients with IBD according to the presence or absence of clinically active disease

Of the 191 patients with CD, 69 (36.1%) had clinically active disease, with an HBI ≥5. These patients were more likely to have had a previous intestinal resection, fulfil Rome III criteria for IBS, self-report a flare of disease activity, and have higher mean HADS anxiety, HADS depression, and PHQ-15 scores, as well as higher anxiety, depression, and somatisation severity (Table 2). There was no difference in mean FC, or the proportion of patients with an elevated FC, between those with clinically active or quiescent disease.

Of the 165 patients with UC, 66 (40.0%) had clinically active disease. These participants were also more likely to self-report a flare of disease activity, have higher mean HADS anxiety, HADS depression, and PHQ-15 scores, and higher anxiety, depression, and somatisation severity. In patients with UC mean FC (857µg/g vs. 333µg/g), and the proportion of patients with an elevated FC, were significantly higher in those with clinically active disease (Table 2).

After multivariate logistic regression, higher PHQ-15 scores were associated with clinically active disease in CD. Self-reported flare was associated with clinically active disease in UC (Table 3).

Table 2: Relationship between elevated patient-reported disease activity indices (HBI or SCCAI ≥5) and personal and disease characteristics in CD and UC

	Crohn's disease (n = 191)			Ulcerative colitis (n = 165)		
	HBI <5 (n = 122)	**HBI ≥5 (n = 69)**	**P value***	**SCCAI <5 (n = 99)**	**SCCAI ≥5 (n = 66)**	**P value***
Mean age in years (SD)	46.5 (17.6)	47.1 (14.7)	0.82	53.4 (17.0)	47.9 (14.7)	0.03
Female gender (%)	68 (55.7)	51 (73.9)	0.01	53 (53.5)	36 (54.5)	0.90
Married or co-habiting (%)	74 (60.7)	44 (63.8)	0.67	75 (75.8)	44 (66.7)	0.20
University/postgraduate (%)	36 (29.8)	14 (20.3)	0.15	29 (29.9)	19 (28.8)	0.88
Mean BMI (SD)	25.8 (5.3)	27.2 (6.0)	0.12	26.5 (5.5)	28.0 (5.8)	0.10
Tobacco user (%)	22 (18.0)	18 (26.1)	0.19	3 (3.0)	4 (6.1)	0.34
Alcohol user (%)	79 (64.8)	42 (60.9)	0.59	68 (68.7)	42 (63.6)	0.50
Crohn's disease location (%)						
Ileal	20 (16.4)	23 (33.3)		N/A†	N/A†	
Colonic	46 (37.7)	16 (23.2)		N/A†	N/A†	
Ileocolonic	56 (45.9)	30 (43.5)	0.01	N/A†	N/A†	N/A†

Crohn's disease behaviour (%)						
Non-stricturing, non-penetrating	110 (90.2)	53 (76.8)		N/A†	N/A†	
Structuring	9 (7.4)	12 (17.4)		N/A†	N/A†	
Penetrating	3 (2.5)	4 (5.8)	0.04	N/A†	N/A†	N/A†
Perianal Crohn's disease present (%)	9 (7.4)	7 (10.1)	0.51	N/A†	N/A†	N/A†
Ulcerative colitis (%)						
Proctitis	N/A†	N/A†		31 (31.3)	14 (21.2)	
Left sided	N/A†	N/A†		42 (42.4)	32 (48.5)	
Extensive	N/A†	N/A†	N/A†	26 (26.3)	20 (30.3)	0.36
5-ASA use (%)	36 (29.5)	17 (24.6)	0.47	79 (79.8)	52 (78.8)	0.88
Immunomodulator use (%)	54 (44.3)	34 (49.3)	0.50	18 (18.2)	16 (24.2)	0.35
Anti-TNFα use (%)	35 (28.7)	17 (24.6)	0.55	1 (1.0)	3 (4.5)	0.15
Glucocorticosteroid use (%)	12 (9.8)	9 (13.0)	0.50	7 (7.1)	10 (15.2)	0.09
Previous intestinal resection (%)	29 (23.8)	33 (47.8)	0.001	N/A†	N/A†	N/A†
Rome III IBS criteria fulfilled (%)	38 (31.1)	48 (69.6)	<0.001	22 (22.2)	27 (40.9)	0.01
Self-reported flare (%)	18 (14.8)	24 (34.8)	0.001	16 (16.2)	35 (53.0)	<0.001
Mean FC (SD)	508 (885)	397 (535)	0.28	333 (556)	857 (1235)	0.002

FC ≥250µg/g (%)	45 (36.9)	28 (40.6)	0.61	31 (31.3)	34 (51.5)	0.009
Mean HADS anxiety score (SD)	6.5 (4.4)	9.2 (4.5)	<0.001	5.8 (4.2)	9.2 (5.2)	<0.001
HADS anxiety categories (%)						
Normal	75 (61.5)	27 (39.1)		64 (64.6)	29 (43.9)	
Borderline abnormal	25 (20.5)	14 (20.3)		21 (21.2)	11 (16.7)	
Abnormal	22 (18.0)	28 (40.6)	0.002	14 (14.1)	26 (39.4)	0.001
Mean HADS depression score (SD)	4.0 (3.7)	6.8 (4.3)	<0.001	3.2 (3.0)	7.0 (5.1)	<0.001
HADS depression categories (%)						
Normal	99 (81.1)	40 (58.0)		91 (91.9)	43 (65.2)	
Borderline abnormal	16 (13.1)	16 (23.2)		5 (5.1)	6 (9.1)	
Abnormal	7 (5.7)	13 (18.8)	0.001	3 (3.0)	17 (25.8)	<0.001
Mean PHQ-15 somatisation score (SD)	8.6 (4.3)	13.4 (3.9)	<0.001	7.2 (5.0)	11.8 (4.3)	<0.001
PHQ-15 somatisation categories (%)						
Mild	20 (16.4)	0 (0.0)		31 (31.3)	2 (3.0)	
Low	55 (45.1)	9 (13.0)		35 (35.4)	14 (21.2)	
Medium	35 (28.7)	37 (53.6)		25 (25.3)	27 (40.9)	
High	12 (9.8)	23 (33.3)	<0.001	8 (8.1)	23 (34.8)	<0.001

*Independent samples *t*-test for continuous data, and χ^2 for categorical data. †N/A; not applicable.

Table 3: Relationship between elevated patient-reported disease activity indices (HBI or SCCAI ≥5) and personal and disease characteristics in CD and UC after logistic regression

	Crohn's disease and HBI ≥5 OR (99% CI)	Ulcerative colitis and SCCAI ≥5 OR (99% CI)
Female gender	1.06 (0.34-3.32)	0.63 (0.17-2.35)
Age (per year)	1.00 (0.97-1.04)	0.98 (0.95-1.02)
Married or co-habiting	1.93 (0.64-5.78)	0.35 (0.09-1.28)
University/postgraduate	1.33 (0.35-5.06)	0.66 (0.17-2.55)
BMI (per unit)	1.05 (0.96-1.15)	1.04 (0.94-1.16)
Tobacco use	1.34 (0.34-5.26)	3.95 (0.20-77.9)
Alcohol use	1.23 (0.40-3.79)	1.70 (0.44-6.61)
5-ASA use	0.79 (0.21-3.02)	1.13 (0.27-4.81)
Immunomodulator use	1.35 (0.47-3.81)	1.74 (0.41-7.43)
Anti-TNFα use	0.92 (0.28-3.04)	1.55 (0.04-66.0)
Glucocorticosteroid use	1.13 (0.23-5.64)	0.80 (0.13-4.98)
Previous intestinal resection	2.63 (0.86-8.06)	N/A*
Rome III IBS criteria fulfilled	2.46 (0.86-7.03)	1.25 (0.32-4.85)
Self-reported flare	1.21 (0.36-4.03)	4.83 (1.37-17.1)
FC ≥250µg/g	1.77 (0.58-5.39)	3.11 (0.94-10.3)
Anxiety (per 1-point change on HADS anxiety score)	0.95 (0.81-1.11)	0.94 (0.77-1.13)
Depression (per 1-point change on HADS depression score)	1.04 (0.86-1.25)	1.21 (0.97-1.52)
Somatisation (per 1-point change on PHQ-15 score)	1.31 (1.08-1.60)	1.17 (0.97-1.52)

*N/A; not applicable

3.3.2 Characteristics of patients with IBD according to presence or absence of mucosal inflammation

In total, 73 (38.2%) patients with CD and 65 (39.4%) with UC were classified as having evidence of mucosal inflammation, with an FC ≥250μg/g. Patients with UC with mucosal inflammation had higher mean SCCAI scores, and a greater proportion of patients had clinically active disease, with an SCCAI ≥5. There were no other differences in baseline demographics, disease characteristics, or the prevalence of psychological co-morbidity between those with and without mucosal inflammation in either CD or UC (Table 4).

After multivariate logistic regression, higher somatisation scores (per 1-point increase in total PHQ-15 score) were negatively associated with mucosal inflammation in CD, and clinically active disease, with an SCCAI ≥5, was positively associated with mucosal inflammation in UC (Table 5).

Table 4: Relationship between elevated FC ≥250 µg/g and personal and disease characteristics in CD and UC

	Crohn's disease (n = 191)			Ulcerative colitis (n = 165)		
	FC <250µg/g (n = 118)	**FC ≥250µg/g (n = 73)**	**P value***	**FC <250µg/g (n = 100)**	**FC ≥250µg/g (n = 65)**	**P value***
Mean age in years (SD)	45.0 (15.6)	49.5 (17.8)	0.07	51.4 (16.0)	51.0 (17.0)	0.90
Female gender (%)	70 (59.3)	49 (67.1)	0.28	58 (58.0)	31 (47.7)	0.19
Married or co-habiting (%)	71 (60.2)	47 (64.4)	0.56	71 (71.0)	48 (73.8)	0.69
University/postgraduate (%)	33 (28.0)	17 (23.6)	0.51	29 (29.0)	19 (30.2)	0.87
Mean BMI (SD)	25.9 (5.6)	27.0 (5.5)	0.19	26.4 (5.1)	28.2 (6.4)	0.06
Tobacco user (%)	25 (21.2)	15 (20.5)	0.92	3 (3.0)	4 (6.2)	0.33
Alcohol user (%)	77 (65.3)	44 (60.3)	0.49	70 (70.0)	40 (61.5)	0.26
Crohn's disease location (%)						
Ileal	22 (18.6)	21 (28.8)		N/A†	N/A†	
Colonic	44 (37.3)	18 (24.7)		N/A†	N/A†	
Ileocolonic	52 (44.1)	34 (46.6)	0.12	N/A†	N/A†	N/A†

Crohn's disease behaviour (%)						
Non-stricturing, non-penetrating	103 (87.3)	60 (82.2)		N/A†	N/A†	
Stricturing	9 (7.6)	12 (16.4)		N/A†	N/A†	
Penetrating	6 (5.1)	1 (1.4)	0.08	N/A†	N/A†	N/A†
Perianal Crohn's disease present (%)	10 (8.5)	6 (8.2)	0.95	N/A†	N/A†	N/A†
Ulcerative colitis extent (%)						
Proctitis	N/A†	N/A†		27 (27.0)	18 (27.7)	
Left sided	N/A†	N/A†		48 (48.0)	26 (40.0)	
Extensive	N/A†	N/A†	N/A†	25 (25.0)	21 (32.3)	0.52
5-ASA use (%)	37 (31.4)	16 (21.9)	0.16	81 (81.0)	50 (76.9)	0.53
Immunomodulator use (%)	59 (50.0)	29 (39.7)	0.17	21 (21.0)	13 (20.0)	0.88
Anti-TNFα use (%)	39 (33.1)	13 (17.8)	0.02	3 (3.0)	1 (1.5)	0.55
Glucocorticosteroid use (%)	10 (8.5)	11 (15.1)	0.16	9 (9.0)	8 (12.3)	0.50
Previous intestinal resection (%)	40 (33.9)	22 (30.1)	0.59	N/A†	N/A†	N/A†
Rome III IBS criteria fulfilled (%)	54 (45.8)	32 (43.8)	0.80	33 (33.0)	16 (24.6)	0.25
Mean HBI/SCCAI (SD)	4.1 (3.5)	4.5 (3.6)	0.54	3.3 (2.7)	4.9 (3.6)	0.003
HBI/SCCAI ≥5 (%)	41 (34.7)	28 (38.4)	0.61	32 (32.0)	34 (52.3)	0.009

Self-reported flare (%)	24 (20.3)	18 (24.7)	0.48	25 (25.0)	26 (40.0)	0.04
Mean HADS anxiety score (SD)	7.5 (4.8)	7.5 (4.4)	0.91	7.5 (5.2)	6.6 (4.5)	0.24
HADS anxiety categories (%)						
Normal	62 (52.5)	40 (54.8)		54 (54.0)	39 (60.0)	
Borderline abnormal	24 (20.3)	15 (20.5)		19 (19.0)	13 (20.0)	
Abnormal	32 (27.1)	18 (24.7)	0.93	27 (27.0)	13 (20.0)	0.59
Mean HADS depression score (SD)	4.8 (4.0)	5.4 (4.4)	0.30	4.8 (4.6)	4.6 (3.9)	0.83
HADS depression categories (%)						
Normal	88 (74.6)	51 (69.9)		81 (81.0)	53 (81.5)	
Borderline abnormal	20 (16.9)	12 (16.4)		7 (7.0)	4 (6.2)	
Abnormal	10 (8.5)	10 (13.7)	0.52	12 (12.0)	8 (12.3)	0.98
Mean PHQ-15 somatisation score (SD)	10.6 (5.0)	10.0 (4.2)	0.40	9.1 (5.4)	8.9 (4.9)	0.78
PHQ-15 somatisation categories (%)						
Mild	15 (12.7)	5 (6.8)		20 (20.0)	13 (20.0)	
Low	35 (29.7)	29 (39.7)		29 (29.0)	20 (30.8)	
Medium	42 (35.6)	30 (41.1)		30 (30.0)	22 (33.8)	
High	26 (22.0)	9 (12.3)	0.14	21 (21.0)	10 (15.4)	0.83

*Independent samples *t*-test for continuous data, and χ^2 for categorical data. †N/A; not applicable.

Table 5: Relationship between FC≥250 µg/g and personal and disease characteristics in CD and UC after logistic regression

	Crohn's disease and FC ≥250µg/g OR (99%CI)	Ulcerative colitis and FC ≥250µg/g OR (99%CI)
Female gender	1.81 (0.68-4.84)	0.62 (0.21-1.85)
Age (per year)	1.01 (0.98-1.04)	0.99 (0.95-1.02)
Married or co-habiting	0.89 (0.35-2.26)	1.34 (0.44-4.06)
University/postgraduate	0.85 (0.28-2.56)	1.13 (0.35-3.68)
BMI (per unit)	1.04 (0.96-1.13)	1.05 (0.96-1.15)
Tobacco use	1.01 (0.29-3.44)	1.63 (0.12-22.4)
Alcohol use	0.98 (0.37-2.57)	0.43 (0.14-1.30)
5-ASA use	0.38 (0.12-1.17)	0.67 (0.20-2.23)
Immunomodulator use	0.49 (0.19-1.26)	0.90 (0.27–2.99)
Anti-TNFα use	0.56 (0.19-1.67)	0.32 (0.008-12.5)
Glucocorticosteroid use	2.75 (0.60-12.6)	0.78 (0.15-4.04)
Previous intestinal resection	0.70 (0.25-1.92)	N/A*
Rome III IBS criteria fulfilled	1.11 (0.42-2.94)	0.69 (0.20-2.38)
Self-reported flare	1.87 (0.59-5.86)	1.86 (0.57-6.06)
HBI/SCCAI ≥5	1.69 (0.58-4.95)	3.36 (1.00-11.3)
Anxiety (per 1-point change on HADS anxiety score)	1.00 (0.87-1.16)	0.95 (0.81-1.12)
Depression (per 1-point change on HADS depression score)	1.10 (0.94-1.29)	0.97 (0.80-1.18)
Somatisation (per 1-point change on PHQ-15 score)	0.85 (0.73-0.997)	0.97 (0.84-1.12)

*N/A; not applicable

3.3.3 Performance of HBI, self-reported flare, Rome III criteria, and psychological factors in predicting mucosal inflammation in CD

The sensitivity, specificity, PPV, and NPV of the individual symptom items of the HBI, an HBI ≥5, presence of the Rome III criteria for IBS, self-report of a flare of disease activity, and presence of anxiety, depression, or somatisation in predicting mucosal inflammation in CD are reported in Table 6. Although the individual HBI symptom items demonstrated good specificity generally, ranging between 66.1% for ≥3 stools per day and 97.5% for the presence of abdominal mass, the corresponding sensitivity scores were poor (4.1% to 34.2%). As a result, the PPV of these, and total HBI score ≥5, was generally poor, between 35.9% and 50.0%. Reporting symptoms compatible with Rome III-defined IBS, a self-reported flare, and the presence of anxiety or depression were no worse than either the individual symptoms items of the HBI, or a total HBI score ≥5, at predicting mucosal inflammation.

3.3.4 Performance of SCCAI, self-reported flare, Rome III criteria, and psychological factors in predicting mucosal inflammation in UC

In patients with UC the performance of the SCCAI was broadly similar to self-reported flare at predicting mucosal inflammation, with increasing daytime or nocturnal stool frequency the most specific symptom items, and urgency the most sensitive (Table 7). In terms of the PPV, the Rome III criteria were inferior to both SCCAI and self-reported flare at predicting mucosal inflammation, although the 95% CIs overlapped, as were the presence of abnormal HADS anxiety, abnormal HADS depression, or high somatisation severity.

Table 6: Sensitivity, specificity, positive, and negative predictive values of patient-reported clinical disease activity indices, self-reported flare of disease activity, Rome III criteria for IBS, and psychological factors in predicting mucosal inflammation in CD

	FC ≥250 (n = 73)	FC <250 (n = 118)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95%CI)	NPV (95% CI)
Poor or very poor general health (%)	18 (24.7)	26 (22.0)	24.7 (15.6-36.4)	78.0 (69.2-84.9)	40.9 (26.7-56.7)	62.6 (54.2-70.3)
Moderate or severe abdominal pain (%)	15 (20.5)	24 (20.3)	20.5 (12.3-31.9)	79.7 (71.1-86.3)	38.5 (23.8-55.3)	61.8 (53.6-69.5)
≥3 stools/day (%)	25 (34.2)	40 (33.9)	34.2 (23.8-46.4)	66.1 (56.7-74.4)	38.5 (26.9-51.4)	61.9 (52.8-70.3)
Abdominal mass (%)	3 (4.1)	3 (2.5)	4.1 (1.1-12.3)	97.5 (92.2-99.3)	50.0 (14.0-86.1)	62.2 (54.7-69.1)
≥1 associated condition (%)	14 (19.2)	25 (21.2)	19.2 (11.3-30.4)	78.8 (70.1-85.6)	35.9 (21.7-52.9)	61.2 (52.9-68.9)
≥2 associated conditions (%)	3 (4.1)	4 (3.4)	4.1 (1.1-12.3)	96.6 (91.0-98.9)	42.9 (11.8-79.8)	62.0 (54.5-68.9)

HBI ≥5 (%)	28 (38.4)	41 (34.7)	38.4 (27.4-50.5)	65.3 (55.9-73.6)	40.6 (29.1-53.1)	63.1 (53.9-71.5)
Rome III IBS criteria fulfilled (%)	32 (43.8)	54 (45.8)	43.8 (32.4-55.9)	54.2 (44.8-63.4)	37.2 (27.2-48.4)	61.0 (50.9-70.2)
Self-reported flare (%)	18 (24.7)	24 (20.3)	24.7 (15.6-36.4)	79.7 (71.1-86.3)	42.9 (28.1-58.9)	63.1 (54.8-70.7)
Abnormal HADS anxiety score (%)	18 (24.7)	32 (27.1)	24.7 (15.6-36.4)	72.9 (63.8-80.5)	50.0 (23.3-50.9)	61.0 (52.4-69.0)
Abnormal HADS depression score (%)	10 (13.7)	10 (8.5)	13.7 (7.1-24.2)	91.5 (84.6-95.6)	50.0 (27.9-72.2)	63.2 (55.4-70.3)
High PHQ-15 somatisation severity (%)	9 (12.3)	26 (22.0)	12.3 (6.1-22.6)	78.0 (69.2-84.9)	25.7 (13.1-43.6)	59.0 (50.8-66.7)

Table 7: Sensitivity, specificity, positive, and negative predictive values of patient-reported clinical disease activity indices, self-reported flare of disease activity, Rome III criteria for IBS, and psychological factors in predicting mucosal inflammation in UC

	FC ≥250 (n = 65)	FC<250 (n = 100)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95%CI)	NPV (95% CI)
≥4 stools/day (%)	31 (47.7)	21 (21.0)	47.7 (35.3-60.4)	79.0 (69.5-86.3)	59.6 (45.1-72.7)	69.9 (60.5-78.0)
≥7 stools/day (%)	11 (16.9)	6 (6.0)	16.9 (9.1-28.7)	94.0 (86.9-97.5)	64.7 (38.6-84.7)	63.5 (55.2-71.2)
≥1 stool/night (%)	29 (44.6)	22 (22.0)	44.6 (32.5-57.4)	78.0 (68.4-85.4)	56.9 (42.3-70.4)	68.4 (59.0-76.6)
≥4 stools/night (%)	2 (3.1)	3 (3.0)	3.1 (0.5-11.7)	97.0 (90.9-99.2)	40.0 (7.3-83.0)	60.6 (52.6-68.2)
Any degree of urgency (%)	51 (78.5)	63 (63.0)	78.5 (66.2-87.3)	37.0 (27.7-47.3)	44.7 (35.5-54.3)	72.6 (58.0-83.7)
Rectal bleeding (%)	39 (60.0)	52 (52.0)	60.0 (47.1-71.7)	48.0 (38.0-58.2)	42.9 (32.7-53.7)	64.9 (52.8-75.4)

Poor general wellbeing or worse (%)	11 (16.9)	12 (12.0)	16.9 (9.1-28.7)	88.0 (79.6-93.4)	47.8 (27.4-68.9)	62.0 (53.4-69.9)
≥1 associated condition (%)	8 (12.3)	13 (13.0)	12.3 (5.8-23.4)	87.0 (78.4-92.6)	38.1 (19.0-61.3)	60.4 (51.9-68.4)
≥2 associated conditions (%)	0 (0.0)	3 (3.0)	Unable to estimate	97.0 (90.9-99.2)	Unable to estimate	59.9 (51.9-67.4)
SCCAI ≥5 (%)	34 (52.3)	32 (32.0)	52.3 (39.7-64.7)	68.0 (57.8-76.8)	51.5 (39.0-63.9)	68.7 (58.5-77.4)
Rome III IBS criteria fulfilled (%)	16 (24.6)	33 (33.0)	24.6 (15.1-37.1)	67.0 (56.8-75.9)	32.7 (20.4-47.7)	57.8 (48.2-66.8)
Self-reported flare (%)	26 (40.0)	25 (25.0)	40.0 (28.3-52.9)	75.0 (65.2-82.9)	51.0 (36.8-65.1)	65.8 (56.2-74.3)
Abnormal HADS anxiety score (%)	13 (20.0)	27 (27.0)	20.0 (11.5-32.1)	73.0 (63.0-81.2)	32.5 (19.1-49.2)	58.4 (49.2-67.0)
Abnormal HADS depression score (%)	8 (12.3)	12 (12.0)	12.3 (5.8-23.4)	88.0 (79.6-93.4)	40.0 (20.0-63.6)	60.7 (52.2-68.6)
High PHQ-15 somatisation severity (%)	10 (15.4)	21 (21.0)	15.4 (8.0-26.9)	79.0 (69.5-86.3)	32.3 (17.3-51.5)	59.0 (50.1-67.3)

3.4 Discussion

These results have demonstrated that patient-reported clinical disease activity indices are only modest predictors of mucosal inflammation in UC, and do not predict mucosal inflammation in CD. In addition, these activity indices were no more accurate in predicting mucosal inflammation than patient self-report of a flare of disease activity. In univariate analysis, more severe psychological co-morbidity was observed in clinically active IBD, but was not significantly associated with the presence of mucosal inflammation. The individual symptom items that make up the HBI performed suboptimally when used to predict intestinal inflammation, with reasonable specificity, but low sensitivity, and poor PPVs. In UC, urgency or rectal bleeding were the most sensitive, and high daytime or nocturnal stool frequency the most specific items of the SCCAI, although PPVs for predicting mucosal inflammation were still modest.

Strengths of this study include the large, well-characterised group of consecutive, unselected patients with IBD who provided complete patient-reported clinical data, and the use of FC as an objective measure of intestinal inflammation. Patients were recruited from a secondary care population, thereby increasing the generalisability of these findings to usual clinical practice. The use of validated questionnaires for the assessment of symptomatic disease activity in CD and UC (Walmsley et al., 1998; Harvey and Bradshaw, 1980), IBS symptoms (Longstreth et al., 2006; Ford et al., 2013), anxiety and depression (Zigmond and Snaith, 1983), and somatisation (Spitzer et al., 1999; Spitzer et al., 2000) is another strength. Specifically, the HADS is a measure of anxiety and depression symptoms that is widely used in clinical research. Its major strength over other measures of depression including the Beck depression inventory is its ease of administration and length, particularly in a questionnaire study such as this where responder fatigue may influence the rate of

missing data. However, the use of HADS has been criticised by some, as it may fail to capture somatic symptoms of depression that could be identified using other measures of depression such as the PHQ-9. Accepting this deficiency, a further strength of this study was that PHQ-15 somatisation data were collected to address this potential shortcoming directly.

Although FC was used as an objective measure of mucosal inflammation, a weakness is that, due to the observational nature of this study, with recruitment taking place alongside usual clinical care, gold-standard investigations for the assessment of disease activity, including ileocolonoscopy, histological assessment of ileal and colonic mucosal biopsies, and small bowel imaging were not undertaken. The use of a FC cut off value of ≥250μg/g of stool to define the presence of active inflammation, although supported by previous authors and an international consensus statement (Targownik et al., 2015; Rogler et al., 2013; D'Haens et al., 2012; Lin et al., 2014), may be criticised by some. In addition, although FC is thought to be representative of endoscopic disease activity indices (D'Haens et al., 2012), its utility as a marker of active small bowel inflammation in CD is uncertain, with one study assessing its correlation with magnetic resonance enterography suggesting equivalence (Cerrillo et al., 2015), another supporting its use, but proposing greater accuracy when used to identify colonic over small bowel inflammation (Stawczyk-Eder et al., 2015), and a third reporting poor correlation with video capsule endoscopy in the identification of significant small bowel inflammation (Kopylov et al., 2015).

Also of note is that a greater proportion of patients with CD with a total HBI score ≥5 had isolated small bowel disease than those who did not, suggesting that disease location may influence the generation of symptoms or, given that there was no association between this variable and biochemical disease activity, that FC

underestimates small bowel inflammatory burden. Furthermore, in the absence of radiological assessment of the small bowel, it may be that hitherto undiagnosed fibrostenotic small bowel disease contributed to the development of symptoms in patients with small bowel disease. In clinical practice, this may then be falsely attributed to functional disease on the basis of a normal FC. To address these potential confounding factors directly, a sensitivity analysis in which the 43 patients isolated ileal Crohn's disease were excluded, was conducted. There remained no significant difference in the proportion of patients with, and without clinically active CD with evidence of mucosal inflammation defined by FC ≥250µg/g (17 (46%) of 46 vs. 35 (34.3%) of 102, P = 0.76), and no significant association between those with and without clinical disease activity and mean FC (407µg/g vs. 505µg/g, P = 0.51), reinforcing the lack of association between total HBI scores and mucosal inflammation in ileocolonic and colonic CD.

Both IBS-type symptoms and a history of previous intestinal resection were associated with symptomatically active CD. Although IBS-type symptoms in patients with no evidence of mucosal inflammation could be considered to be due to genuine co-existent functional symptoms, previous intestinal resection may be associated with alternative, non-inflammatory, organic diagnoses such as SIBO or BAM (Gracie et al., 2012; Greco et al., 2015). This may have led to an overestimate of the prevalence of functional symptoms in this subgroup of patients.

Several studies have assessed the diagnostic accuracy of patient-reported clinical disease activity indices at predicting inflammatory burden in IBD (af Bjorkesten et al., 2012; Sipponen et al., 2008; Jones et al., 2008; Schoepfer et al., 2010), however few have attempted to delineate the relationship between symptoms, inflammation, and their relationship with psychological wellbeing. Most recently, Targownik *et al.* assessed the

utility of the HBI, Powell-Tuck Index, and Manitoba IBD Index at predicting active IBD using a FC cut off of ≥250 μg/g of stool in 478 patients with IBD, and the association between symptoms, inflammatory burden, and perceived stress (Targownik et al., 2015). In keeping with the findings described here, there was no association between patient-reported clinical disease activity and mucosal inflammation in CD, and only a modest relationship between the two in UC. In addition, perceived stress was associated with clinically active disease, but not active mucosal inflammation. Goodhand *et al.* described the relationship between disease activity, depression, anxiety, and perceived stress in 103 UC and 101 patients with CD, compared with 124 healthy volunteers (Goodhand et al., 2012b). In this study, mean anxiety and depression scores were higher in both patients with CD and UC, and active inflammation was associated with depression, but not anxiety, in UC. Another study conducted among 162 patients with IBD examined the association between active disease, the presence of co-existent FGIDs, mood disorders, and quality of life using validated questionnaires (Bryant et al., 2011). The authors reported significantly higher depression scores and lower quality of life scores in those with symptoms compatible with a co-existent FGID, regardless of the presence of active inflammatory disease. Although these studies reported the relationship between psychological health, mucosal inflammation, and IBD-related symptoms (Targownik et al., 2015; Goodhand et al., 2012b), or the relationship between physician's global assessment of disease activity, functional symptoms, and psychological co-morbidity (Bryant et al., 2011), they did not incorporate all of these in a large single cohort of patients as has been described here.

This study has important clinical implications, as the data suggest that patient-reported symptoms in IBD are associated with significant psychological co-morbidity, with abnormal HADS anxiety scores observed in roughly 40% of all patients with IBD

with clinical disease activity indices ≥5, and abnormal HADS depression scores in one-in-four patients with UC with a SCCAI ≥5. The association between somatisation and clinically active IBD, but not mucosal inflammation, suggests that the reporting of the symptom items that make up these clinical disease activity indices may be due to somatoform-type behaviour or co-existent functional disease in a subset of patients, rather than being secondary to genuine mucosal inflammation or extra-intestinal manifestations of IBD. Furthermore, the lack of any association between psychological co-morbidity and inflammatory activity casts doubt on a role of the brain-gut axis in the pathogenesis of IBD, which has been championed by some. This emphasises the importance of conducting prospective, longitudinal studies examining the temporal relationship between inflammatory activity and psychological co-morbidity in IBD, such as that described in Chapter 5.

These findings highlight the disparity between patient-reported symptoms and objective assessments of IBD activity, and reinforce the requirement for careful consideration before escalation of conventional IBD therapies, or making judgments concerning the effectiveness of novel therapies, on the basis of clinical disease activity indices alone. Moreover, the finding that a simple dichotomous patient opinion as to whether their disease was active or not was as effective as both the HBI in CD, and the SCCAI in UC, at predicting mucosal inflammation in this study further highlights that the use of these indices as a sole determinant of disease activity or drug efficacy is not desirable. The move toward PROMs, in conjunction with biomarkers of inflammation and endoscopic indices, in the assessment of outcomes in IBD clinical trials aims to address these inconsistencies (Williet et al., 2014; Peyrin-Biroulet et al., 2015). To date, proposed clinical PROMs, include rectal bleeding and alteration in stool frequency in UC (Jairath et al., 2015), and abdominal pain, stool frequency, and general well-being

in CD (Khanna et al., 2015). However, based on these data, these outcomes have only modest PPVs when used to assess mucosal inflammation, and have been shown to correlate poorly with mucosal healing in UC in other studies (Jharap et al., 2015), casting doubt on their utility in this setting.

In summary, these findings support the assertions of previous authors in suggesting patient-reported clinical disease activity indices are not associated with mucosal inflammation in CD, and are only modestly associated with mucosal inflammation in UC, suggesting that the move towards PROMs in clinical trials of novel IBD therapies may need to be re-examined. Psychological co-morbidity, specifically somatisation in CD, was associated with the reporting of the symptoms that make up these indices. Although these data suggest that objective biochemical measures of inflammatory activity should form the basis of disease activity assessment, ideally as a point-of-care test, the association between GI symptoms, in the absence of disease activity, and psychological co-morbidity highlights the need for a paradigm shift in the management of some patients away from one focused solely on physical well-being. This reinforces the requirement for further assessment of psychological therapies or antidepressants, and the identification of novel treatments for the significant proportion of patients with IBD who suffer from associated psychological co-morbidity. Studies assessing such therapies are scarce with disappointing results (Timmer et al., 2011; Macer et al., 2017), which supports the requirement for a contemporaneous review of the efficacy of these treatments, as is described in Chapter 7.

CHAPTER 4: Assessing the relationship between the reporting of IBS-type symptoms, and psychological health and quality of life in patients with IBD

4.1 Introduction

Drawing on the conclusions of Chapter 3, there is clear evidence of a disparity between inflammatory activity and symptom-reporting in IBD, which may be influenced by mood. The explanation for this disparity is uncertain, but co-existent IBS-type symptom-reporting has been implicated as one potential cause. Pooled data from a systematic review and meta-analysis of studies reporting the prevalence of IBS-type symptoms in IBD suggested that these symptoms affect between 35% and 44% of patients (Halpin and Ford, 2012). However, among the 13 included studies, only two assessed for evidence of ongoing disease activity among those who reported these symptoms (Keohane et al., 2010; Berrill et al., 2013), using objective measures of intestinal inflammation, such as FC. The number of included patients in both studies was relatively small, and the results were conflicting.

This issue has important implications for clinical practice, as there may be considerable difficulty in distinguishing IBS-type symptoms in IBD from those secondary to ongoing occult inflammation, due to the lack of immediate access to the results of diagnostic tests to differentiate between the two in the outpatient clinic. This could result in unnecessary invasive endoscopic investigations or inappropriate escalation of therapy to either immunosuppressants or biological therapies in patients with functional symptoms, when in fact other management strategies are required (Derwa et al., 2018).

This issue has therefore been examined in a large cross-sectional study of patients with IBD, using FC as an objective measure of disease activity, and the Rome III criteria for IBS, in order to assess the true magnitude of this problem. The hypothesis was that there is a subset of patients with IBD with genuine IBS-type symptoms, and that these symptoms may be associated with poor psychological health and quality of

life which, if proven, may serve as a mandate for treatment trials in this challenging group of patients in order to resolve continuing uncertainty surrounding how best to manage them.

4.2 Methods

4.2.1 Participants and setting

This was as described in Chapter 3. In brief, unselected and consecutive patients aged 16 and over, with an established diagnosis of CD or UC attending the IBD clinic at St. James's University Hospital, Leeds, were approached about the study. Patients with an end ileostomy or colostomy were excluded, as were those with a diagnosis of inflammatory bowel disease unclassified, isolated fistulising peri-anal CD, or any individual with an inability to understand written English. Those who agreed to take part gave written informed consent at this visit. The study received approval from the local research ethics committee in November 2012 (REC ref: 12/YH/0443), and data collection ceased in June 2015.

4.2.2 Data collection and synthesis

4.2.2.1 Demographic data and disease characteristics

This was as described in Chapter 3, with demographic data including gender, age, ethnicity, marital status, educational level, tobacco and alcohol use, weight, height and BMI collected from all participants. Medication history, including current use of 5-ASAs, glucocorticosteroids, immunosuppressants, or anti-TNFα therapy, disease

location or distribution, and any previous intestinal resection related to CD were also recorded.

4.2.2.2 Assessment of IBD activity

Assessment of IBD activity was performed using the HBI for CD (Harvey and Bradshaw, 1980), and the SCCAI for UC (Walmsley et al., 1998), with a score <5 used to define clinical remission for both, as previously recommended (Vermeire et al., 2010; Jowett et al., 2003). In addition, at their clinic visit participants were asked to provide stool for quantitative FC analysis, as an objective marker of mucosal inflammation, within 7 days of study entry. A cut off of <250µg/g of stool was used in the primary analysis to define no evidence of mucosal inflammation, in line with the European Crohn's and Colitis Organisation consensus on the use of FC to measure disease activity (Rogler et al., 2013), as other investigators have employed (Targownik et al., 2015; D'Haens et al., 2012; Lin et al., 2014), but using <100µg/g in a secondary analysis

4.2.2.3 Reference standard used to define the presence of IBS-type symptoms

This was as described in Chapter 3. IBS-type symptoms were defined as present when an individual reported abdominal discomfort or pain with a frequency of at least 2 or 3 days per month over the last 3 months, with the onset of discomfort at least 6 months previously, associated with two or more of the following: an improvement of pain or discomfort with the passage of stool, more or less frequent bowel movements, or looser or firmer stools (Longstreth et al., 2006).

4.2.2.4 Definition of disease activity and the presence of IBS-type symptoms

Using a combination of disease activity indices, presence or absence of symptoms compatible with Rome III-defined IBS, and FC levels, patients with UC or CD were categorised into four subgroups. Those who fulfilled the Rome III criteria for IBS and had a FC <250μg/g were defined as having IBS-type symptoms, regardless of disease activity indices. Those who did not fulfil the Rome III criteria for IBS and had a FC <250μg/g were defined as having quiescent disease, regardless of disease activity indices. Those with normal disease activity indices and a FC ≥250μg/g were defined as having occult inflammation, regardless of IBS symptom status. Finally, those with abnormal disease activity indices with a FC ≥250μg/g were defined as having active disease, regardless of whether or not they fulfilled the Rome III criteria for IBS. In sensitivity analysis, patients were categorised in an identical manner using a FC of <100μg/g or ≥100μg/g.

4.2.2.5 Definition of anxiety or depression

This was as described in Chapter 3, with the presence of either anxiety or depression assessed using the HADS (Zigmond and Snaith, 1983). Severity was categorised, according to total HADS score, into normal (total HADS depression or anxiety score 0-7), borderline normal (8-10), and abnormal (≥11) (Zigmond and Snaith, 1983).

4.2.2.6 Definition of somatisation severity

This was as described in Chapter 3. Somatisation data were collected using the PHQ-15 (Kroenke et al., 2002), and severity categorised into high (total PHQ-15 ≥15),

medium (10-14), low (5-9), and minimal (≤4) levels of somatisation severity (Kroenke et al., 2002).

4.2.2.7 Assessment of quality of life

The medical outcomes study 36-item short-form (SF-36) health survey, a validated questionnaire used to assess physical and mental health status, was used to make an assessment of health-related quality of life (McHorney et al., 1993). This comprises 36 questions which are grouped into eight health domains (physical functioning, role limitations due to physical health, role limitations due to emotional health, energy or fatigue, emotional well-being, social functioning, pain, and general health). Patients were asked to complete the questionnaire giving responses to each question from zero to one hundred, from which a mean score for each health domain was calculated, with higher scores indicating more favourable health-related quality of life.

4.2.3 Statistical analysis

Comparison of baseline demographic characteristics, prevalence of IBS-type symptoms, disease activity, HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatisation was performed between patients with CD and UC using a χ^2 test for categorical variables, and an independent samples *t*-test for continuous data.

After classification of disease activity and IBS-type symptom status using a FC <250µg/g of stool to define no evidence of mucosal inflammation, baseline demographic characteristics, HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatisation were compared between those

reporting IBS-type symptoms and the other three groups of patients individually (quiescent disease, occult inflammation, or active disease) using a χ^2 test for categorical variables, and an independent samples *t*-test for continuous data. These comparisons were repeated across all four groups using a χ^2 test for categorical variables, and a one-way analysis of variance (ANOVA) for continuous data. Where continuous data were not normally distributed, equivalent non-parametric tests including the Mann-Whitney U test and Kruskal-Wallis analysis of variance were applied. These analyses were then repeated but using an FC of <100µg/g to define no evidence of mucosal inflammation. Due to multiple comparisons a 2-tailed P value of <0.01 was considered to be statistically significant for all analyses. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

4.3 Results

4.3.1 Baseline demographics

In total, 378 (47.3%) of 799 patients who initially consented to participate in the study provided complete Rome III questionnaire and clinical disease activity data, and returned a faecal sample for FC analysis. Of these, 206 (54.5%) had confirmed CD and 172 (45.5%), UC. Characteristics of patients with CD and UC are provided in Table 8. There were 144 (38.1%) patients with IBD who reported symptoms compatible with IBS, 92 (44.7%) with CD and 52 (30.2%) with UC (P = 0.004). In terms of disease activity, 128 (62.1%) of those with CD had an HBI <5, and 103 (59.9%) of those with UC had an SCCAI <5. Patients with CD were slightly younger, more likely to smoke, less likely to be using 5-ASAs, more likely to be using immunosuppressants or anti-

TNFα drugs, and scored lower in some domains of the SF-36, such as energy/fatigue, pain, and general health than those with UC.

Table 8: Characteristics of patients with CD and UC

	Crohn's disease (n = 206)	Ulcerative colitis (n = 172)	P value*
Mean age in years (SD)	47.1 (16.6)	51.9 (16.4)	0.005
Female gender (%)	126 (61.2)	93 (54.1)	0.16
Married or co-habiting (%)	127 (61.7)	122 (70.9)	0.07
University graduate/professional (%)	54 (26.2)	49 (28.5)	0.57
Mean BMI (SD)	26.4 (5.6)	27.1 (5.7)	0.22
Tobacco user (%)	43 (20.9)	8 (4.7)	<0.001
Alcohol user (%)	128 (62.1)	115 (66.9)	0.37
5-ASA use (%)	59 (28.6)	137 (79.7)	<0.001
Immunomodulator use (%)	93 (45.1)	37 (21.5)	<0.001
Anti-TNFα use (%)	57 (27.7)	4 (2.3)	<0.001
Glucocorticosteroid use (%)	21 (10.2)	18 (10.5)	0.93
Previous intestinal resection (%)	70 (34.0)	N/A†	N/A†
Rome III IBS criteria fulfilled (%)	92 (44.7)	52 (30.2)	0.004
In remission on HBI or SCCAI (%)	128 (62.1)	103 (59.9)	0.66
Mean HADS anxiety score (SD)	7.7 (4.6)	7.2 (5.0)	0.35
HADS anxiety categories (%)			
Normal	106 (51.5)	95 (55.2)	
Borderline abnormal	42 (20.4)	33 (19.2)	
Abnormal	58 (28.2)	44 (25.6)	0.76
Mean HADS depression score (SD)	5.2 (4.2)	4.7 (4.3)	0.28
HADS depression categories (%)			
Normal	147 (71.4)	139 (80.8)	
Borderline abnormal	34 (16.5)	11 (6.4)	
Abnormal	25 (12.1)	21 (12.2)	0.01
Mean PHQ-15 somatisation score (SD)	10.3 (4.7)	9.0 (5.2)	0.012

PHQ-15 somatisation categories (%)			
Mild	20 (9.7)	34 (19.8)	
Low	65 (31.6)	49 (28.5)	
Medium	74 (35.9)	52 (30.2)	
High	35 (17.0)	31 (18.0)	0.05
Median SF-36 quality of life score (IQR)			
Physical functioning	85.0 (55.0-95.0)	90.0 (70.0-100.0)	0.13
Role limitations physical health	50.0 (0.0-100.0)	75.0 (0.0-100.0)	0.04
Role limitations emotional problems	100.0 (33.3-100.0)	100.0 (33.3-100.0)	0.73
Energy/fatigue	40.0 (20.0-60.0)	50.0 (30.0-70.0)	0.006
Emotional well-being	68.0 (52.0-84.0)	72.0 (56.0-84.0)	0.14
Social functioning	75.0 (37.5-87.5)	75.0 (50.0-100.0)	0.05
Pain	67.5 (33.8-80.0)	67.5 (45.0-90.0)	0.002
General health	40.0 (25.0-60.0)	55.0 (40.0-75.0)	<0.001

*Independent samples t-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for categorical data.

†N/A; not applicable.

4.3.2 Effect of FC analysis using a cut off <250µg/g on disease activity status and characteristics of patients with IBD with and without IBS-type symptoms

Among the 206 patients with CD, 57 (27.7%) were ultimately classified as having IBS-type symptoms based on a cut off <250µg/g, 69 (33.5%) as quiescent CD, 49 (23.8%) as CD with occult inflammation, and 31 (15.0%) as active CD (Figure 3). Therefore, after FC analysis, 57 (62.0%) of 92 patients who met criteria for IBS had no evidence of active disease or occult inflammation and were classified as having IBS-type symptoms. Thirty-one (39.7%) of 78 patients with an HBI ≥5 had genuinely active disease, and 32 (41.0%) were reclassified as having IBS-type symptoms.

There were significantly more females among those with IBS-type symptoms and those with active disease, compared with the other two groups, and also more tobacco users among those with IBS-type symptoms compared with those with quiescent CD, but no other differences in demographic characteristics (Table 9). Of note was that mean anxiety, depression, and somatisation scores were all significantly higher in patients with CD with IBS-type symptoms compared with patients with either quiescent CD, or CD with occult inflammation, but were similar to those in patients with active CD. There were also more patients who met criteria for somatisation in the CD with IBS-type symptoms group than those with either quiescent CD, or CD with occult inflammation, but an almost identical proportion among those with active CD. Quality of life scores across all eight domains of the SF-36 were impaired among those patients with CD reporting IBS-type symptoms, compared with those with quiescent CD, or occult inflammation, and in several instances these differences were statistically significant, with scores impaired to a similar degree to that seen in patients with active CD.

Figure 3: Disease activity and IBS symptom status for patients with CD using a cut off <250µg/g

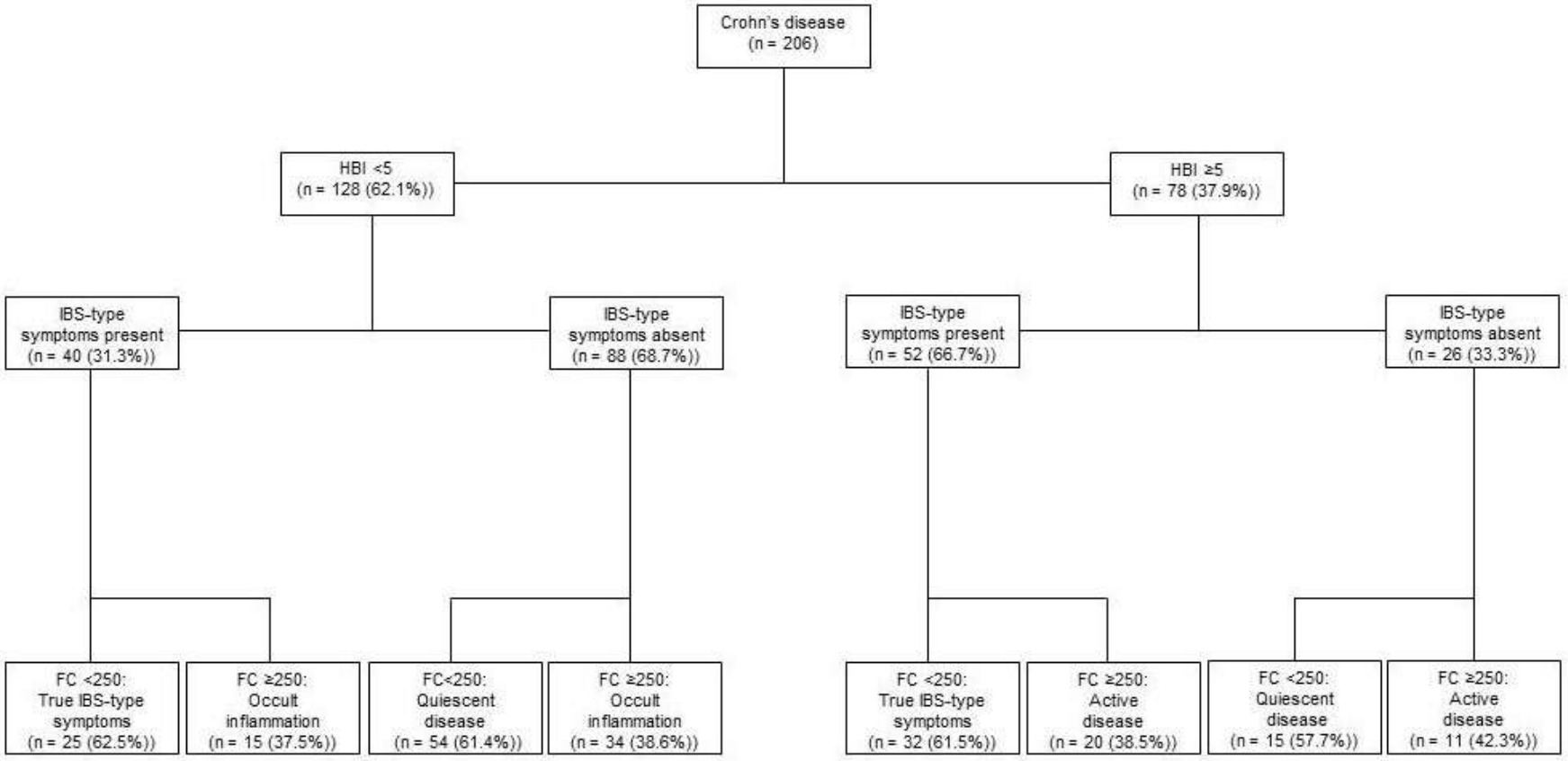


Table 9: Disease activity status and characteristics of patients with CD after FC analysis using a cut off <250µg/g

	CD with IBS-type symptoms (n = 57)	Quiescent CD (n = 69)	P value*	CD with occult inflammation (n = 49)	P value*	Active CD (n = 31)	P value*	P value†
Mean age in years (SD)	45.5 (15.3)	45.3 (16.2)	0.92	49.3 (19.2)	0.27	50.4 (15.3)	0.16	0.34
Female gender (%)	44 (77.2)	30 (43.5)	<0.001	29 (59.2)	0.05	23 (74.2)	0.75	0.001
Married or co-habiting (%)	32 (56.1)	45 (65.2)	0.39	28 (57.1)	0.99	22 (71.0)	0.26	0.49
University graduate/professional (%)	14 (24.6)	21 (30.4)	0.59	11 (22.4)	0.98	8 (25.8)	0.99	0.81
Mean BMI (SD)	25.6 (5.5)	26.4 (5.6)	0.45	26.6 (5.7)	0.40	27.4 (5.3)	0.15	0.56
Tobacco user (%)	18 (31.6)	8 (11.6)	0.006	10 (20.4)	0.19	7 (22.6)	0.37	0.06
Alcohol user (%)	38 (66.7)	42 (60.9)	0.57	28 (57.1)	0.31	20 (64.5)	0.84	0.78
Crohn's disease location (%)								
Ileal	13 (22.8)	10 (14.5)		13 (26.5)		12 (38.7)		
Colonic	21 (36.8)	24 (34.8)		14 (28.6)		5 (16.1)		
Ileocolonic	23 (40.4)	35 (50.7)	0.38	22 (44.9)	0.66	14 (45.2)	0.09	0.14

Crohn's disease behaviour (%)								
Non-stricturing, non-penetrating	48 (84.2)	61 (88.4)		43 (87.8)		23 (74.2)		
Stricturing	6 (10.5)	4 (5.8)		5 (10.2)		7 (22.6)		
Penetrating	3 (5.3)	4 (5.8)	0.62	1 (2.0)	0.68	1 (3.2)	0.30	0.29
Perianal Crohn's disease present (%)	4 (7.0)	6 (8.7)	0.73	3 (6.1)	0.85	3 (9.7)	0.66	0.93
5-ASA use (%)	20 (35.1)	21 (30.4)	0.58	13 (26.5)	0.34	5 (16.1)	0.06	0.29
Immunomodulator use (%)	31 (54.4)	30 (43.5)	0.22	18 (36.7)	0.07	14 (45.2)	0.41	0.33
Anti-TNFα use (%)	18 (31.6)	23 (33.3)	0.83	8 (16.3)	0.07	8 (25.8)	0.57	0.19
Glucocorticosteroid use (%)	4 (7.0)	6 (8.7)	0.73	8 (16.3)	0.13	3 (9.7)	0.66	0.42
Previous intestinal resection (%)	24 (42.1)	22 (31.9)	0.24	11 (22.4)	0.03	13 (41.9)	0.99	0.13
Mean HADS anxiety score (SD)	9.1 (4.4)	6.7 (4.8)	0.004	6.5 (4.0)	0.002	9.3 (4.6)	0.84	0.001
HADS anxiety categories (%)								
Normal	21 (36.8)	42 (60.9)		31 (63.3)		12 (38.7)		
Borderline abnormal	15 (26.3)	11 (15.9)		10 (20.4)		6 (19.4)		
Abnormal	21 (36.8)	16 (23.2)	0.03	8 (16.3)	0.02	13 (41.9)	0.76	0.03
Mean HADS depression score (SD)	6.3 (3.7)	4.1 (4.3)	0.003	4.4 (3.9)	0.01	7.2 (4.4)	0.33	<0.001

HADS depression categories (%)								
Normal	37 (64.9)	54 (78.3)		39 (79.6)		17 (54.8)		
Borderline abnormal	11 (19.3)	10 (14.5)		6 (12.2)		7 (22.6)		
Abnormal	9 (15.8)	5 (7.2)	0.20	4 (8.2)	0.24	7 (22.6)	0.62	0.15
Mean PHQ-15 score (SD)	12.7 (4.6)	8.8 (4.6)	0.005	8.2 (3.3)	0.002	12.6 (4.2)	0.92	<0.001
PHQ-15 somatisation categories (%)								
Mild	1 (1.8)	14 (21.5)		5 (11.1)		0 (0.0)		
Low	12 (21.8)	23 (35.4)		24 (53.3)		6 (20.7)		
Medium	25 (45.5)	19 (29.2)		16 (35.6)		14 (48.3)		
High	17 (30.9)	9 (13.8)	0.001	0 (0.0)	<0.001	9 (31.0)	0.90	<0.001

Median SF-36 quality of life score (IQR)								
Physical functioning	80.0 (50.0-90.0)	92.5 (66.3-100.0)	0.005	85.0 (55.0-100.0)	0.17	67.5 (27.5-95.0)	0.41	0.01
Role limitations physical health	25.0 (0.0-75.0)	87.5 (25.0-100.0)	<0.001	75.0 (25.0-100.0)	0.004	12.5 (0.0-100.0)	1.00	0.001
Role limitations emotional problems	66.7 (0.0-100.0)	100.0 (33.3-100.0)	0.01	100.0 (41.7-100.0)	0.05	100.0 (0.0-100.0)	0.41	0.06
Energy/fatigue	35.0 (20.0-50.0)	50.0 (22.5-70.0)	0.01	50.0 (30.0-65.0)	0.06	25.0 (10.0-40.0)	0.09	0.001
Emotional well-being	64.0 (48.0-76.0)	76.0 (60.0-88.0)	<0.001	64.0 (52.0-88.0)	0.36	56.0 (44.0-78.0)	0.56	0.003
Social functioning	50.0 (37.5-75.0)	75.0 (50.0-100.0)	0.004	81.3 (56.9-100.0)	0.001	50.0 (37.5-75.0)	0.83	<0.001
Pain	45.0 (32.5-68.8)	77.5 (50.0-90.0)	<0.001	67.5 (45.0-90.0)	<0.001	42.5 (22.5-57.5)	0.31	<0.001
General health	35.0 (25.0-50.0)	50.0 (35.0-75.0)	<0.001	45.0 (25.0-60.0)	0.04	30.0 (15.0-40.0)	0.28	<0.001
Mean FC (SD)	89.6 (62.7)	88.4 (62.9)	0.91	1200 (1105)	<0.001	907 (671)	<0.001	<0.001

*Independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for comparison of categorical data vs. CD with IBS-type symptoms.

†One way ANOVA for normally distributed continuous data, Kruskal-Wallis analysis of variance for non-parametric data, and χ^2 for comparison of categorical data across all four groups.

Among the 172 patients with UC, 34 (19.8%) were classified as having IBS-type symptoms based on a cut off <250µg/g, 68 (39.5%) as quiescent UC, 34 (19.8%) as UC with occult inflammation, and 36 (20.9%) as active UC (Figure 4). Therefore, after FC analysis, 34 (65.4%) of 52 patients who met criteria for IBS had no evidence of active disease or occult inflammation and were classified as having IBS-type symptoms, whereas 36 (52.2%) of 69 with an SCCAI ≥5 had genuinely active disease, and 18 (26.1%) were reclassified as having IBS-type symptoms.

There were no differences in demographic characteristics between the four groups, but mean anxiety, depression, and somatisation scores were all significantly higher in those reporting IBS-type symptoms, compared with those with either quiescent UC, or occult inflammation, and anxiety scores were also significantly higher than in those with active UC (Table 10). There were also significantly more patients who met criteria for anxiety, depression, or somatisation in the group with IBS-type symptoms than among those with either quiescent UC, or UC with occult inflammation. Median quality of life scores were significantly lower in patients with IBS-type symptoms compared with patients with quiescent UC for all domains of the SF-36 except physical functioning, and all domains except physical functioning, role limitations due to physical health, and energy/fatigue when compared with UC with occult inflammation. As was observed in the analyses for patients with CD, quality of life scores in patients with UC reporting IBS-type symptoms were impaired to a similar degree to those with active UC.

Figure 4: Disease activity and IBS symptom status for patients with UC using a cut off <250µg/g

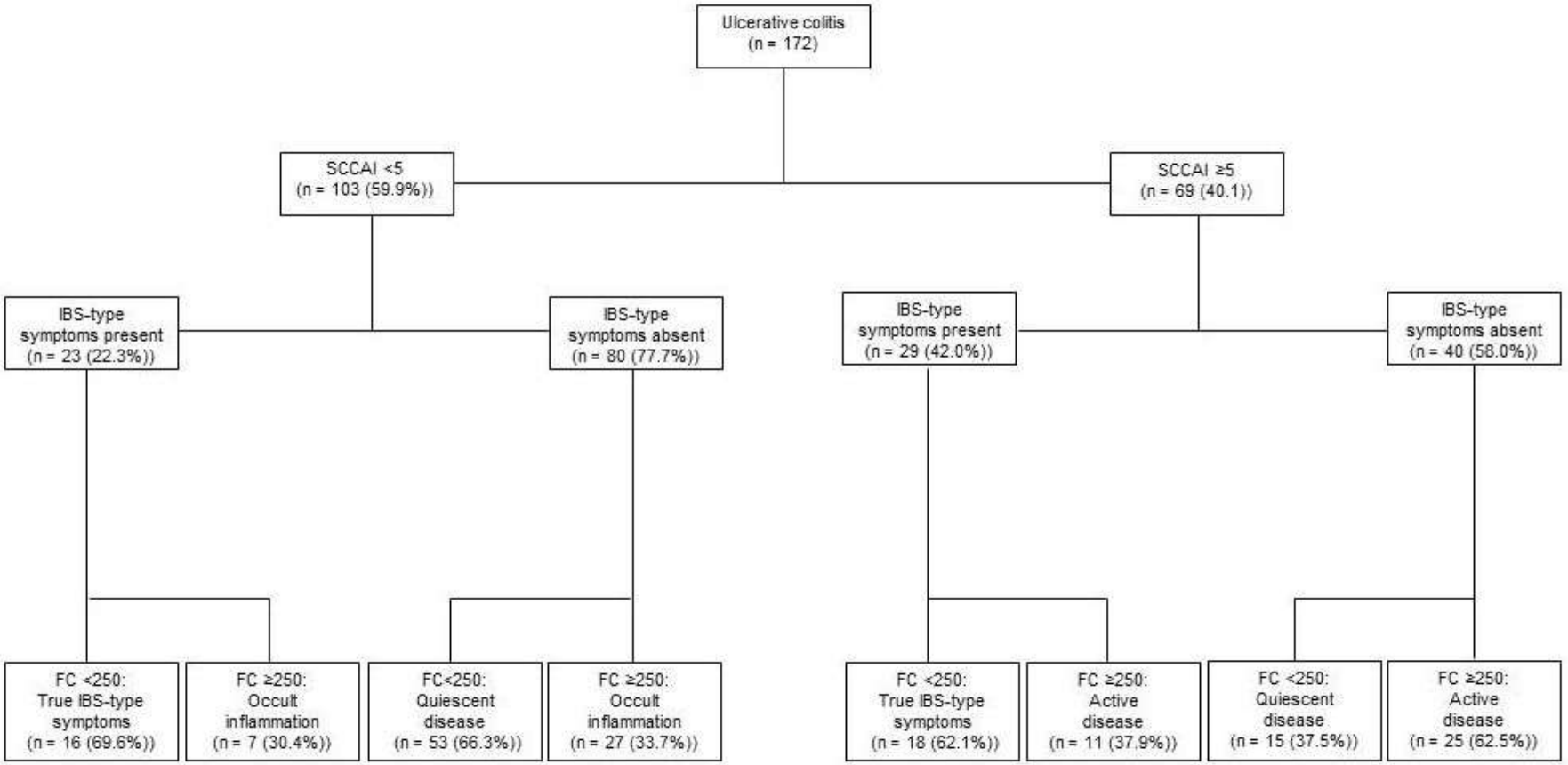


Table 10: Disease activity status and characteristics of patients with UC after FC analysis using a cut off <250µg/g

	UC with IBS-type symptoms (n = 34)	Quiescent UC (n = 68)	P value*	UC with occult inflammation (n = 34)	P value*	Active UC (n = 36)	P value*	P value†
Mean age in years (SD)	48.3 (14.4)	53.6 (16.8)	0.10	54.8 (17.0)	0.09	49.6 (16.8)	0.73	0.25
Female gender (%)	20 (58.8)	40 (58.8)	1.0	14 (41.2)	0.15	19 (52.8)	0.61	0.36
Married or co-habiting (%)	25 (73.5)	46 (67.6)	0.70	26 (76.5)	0.99	25 (69.4)	0.91	0.80
University graduate/professional (%)	10 (29.4)	20 (29.4)	1.0	8 (23.5)	0.78	11 (30.6)	0.99	0.95
Mean BMI (SD)	26.8 (5.6)	26.1 (4.8)	0.58	28.8 (7.3)	0.21	27.6 (5.4)	0.53	0.15
Tobacco user (%)	1 (2.9)	2 (2.9)	1.0	3 (8.8)	0.29	2 (5.6)	0.59	0.53
Alcohol user (%)	22 (64.7)	49 (72.1)	0.45	24 (70.6)	0.604	20 (55.6)	0.44	0.36
Ulcerative colitis extent (%)								
Proctitis	11 (32.4)	17 (25.0)		11 (32.4)		8 (22.2)		
Left-sided	15 (44.1)	33 (48.5)		13 (38.2)		15 (41.7)		
Extensive	8 (23.5)	18 (26.5)	0.74	10 (29.4)	0.83	13 (36.1)	0.45	0.83
5-ASA use (%)	30 (88.2)	53 (77.9)	0.21	27 (79.4)	0.32	27 (75.0)	0.16	0.54
Immunomodulator use (%)	7 (20.6)	16 (23.5)	0.74	6 (17.6)	0.76	8 (22.2)	0.87	0.92

Anti-TNFα use (%)	2 (5.9)	1 (1.5)	0.21	0 (0.0)	0.15	1 (2.8)	0.52	0.40
Glucocorticosteroid use (%)	5 (14.7)	5 (7.4)	0.24	3 (8.8)	0.45	5 (13.9)	0.92	0.59
Mean HADS anxiety score (SD)	11.2 (5.1)	5.8 (4.3)	<0.001	5.8 (4.4)	<0.001	7.5 (4.6)	0.003	<0.001
HADS anxiety categories (%)								
Normal	9 (26.5)	45 (66.2)		22 (64.7)		19 (52.8)		
Borderline abnormal	7 (20.6)	13 (19.1)		7 (20.6)		6 (16.7)		
Abnormal	18 (52.9)	10 (14.7)	<0.001	5 (14.7)	0.002	11 (30.6)	0.07	0.001
Mean HADS depression score (SD)	7.9 (5.1)	3.2 (3.4)	<0.001	3.0 (2.5)	<0.001	6.2 (4.2)	0.13	<0.001
HADS depression categories (%)								
Normal	21 (61.8)	62 (91.2)		32 (97.0)		24 (66.7)		
Borderline abnormal	4 (11.8)	3 (4.4)		0 (0.0)		4 (11.1)		
Abnormal	9 (26.5)	3 (4.4)	0.001	1 (3.0)	0.002	8 (22.2)	0.90	0.001
Mean PHQ-15 somatisation score (SD)	12.9 (4.3)	7.3 (5.0)	<0.001	6.5 (4.6)	<0.001	10.9 (4.4)	0.07	<0.001
PHQ-15 somatisation categories (%)								
Mild	1 (3.0)	19 (28.4)		12 (37.5)		2 (5.9)		
Low	5 (15.2)	24 (35.8)		12 (37.5)		8 (23.5)		
Medium	13 (39.4)	17 (25.4)		7 (21.9)		15 (44.1)		
High	14 (42.4)	7 (10.4)	<0.001	1 (3.1)	< 0.001	9 (26.5)	0.52	<0.001

Median SF-36 quality of life score (IQR)								
Physical functioning	80.0 (65.0-95.0)	90.0 (77.5-100.0)	0.05	92.5 (65.0-100.0)	0.33	77.5 (55.0-95.0)	0.69	0.06
Role limitations physical health	25.0 (0.0-96.9)	100.0 (50.0-100.0)	<0.001	100.0 (18.8-100.0)	0.02	25.0 (0.0-100.0)	0.92	<0.001
Role limitations emotional problems	50.0 (0.0-100.0)	100.0 (66.7-100.0)	<0.001	100.0 (91.7-100.0)	0.001	66.7 (0.0-100.0)	0.25	<0.001
Energy/fatigue	40.0 (22.5-50.0)	55.0 (40.0-70.0)	0.001	50.0 (40.0-70.0)	0.02	30.0 (20.0-60.0)	0.83	0.001
Emotional well-being	58.0 (36.0-75.0)	76.0 (60.0-90.0)	<0.001	76.0 (68.0-84.0)	0.001	64.0 (56.0-84.0)	0.08	<0.001
Social functioning	62.5 (43.8-87.5)	87.5 (62.5-100.0)	0.003	100.0 (68.8-100.0)	0.001	50.0 (37.5-75.0)	0.13	<0.001
Pain	45.0 (32.5-73.8)	80.0 (65.6-97.5)	<0.001	90.0 (57.5-100.0)	<0.001	57.5 (45.0-75.0)	0.13	<0.001
General health	45.0 (30.0-57.5)	60.0 (43.8-85.0)	0.003	70.0 (47.5-78.8)	0.001	45.0 (26.3-60.0)	0.95	<0.001
Mean FC (SD)	93.7 (70.5)	80.0 (59.2)	0.34	854 (714)	<0.001	1611 (1340)	<0.001	<0.001

*Independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for comparison of categorical data vs. UC with IBS-type symptoms.

†One way ANOVA for normally distributed continuous data, Kruskal-Wallis analysis of variance for non-parametric data, and χ^2 for comparison of categorical data across all four groups.

4.3.3 Effect of FC analysis using a cut off <100µg/g on disease activity status and characteristics of patients with IBD with and without IBS-type symptoms

Results of comparisons between the four CD and UC groups using a FC cut off <100µg/g to define no evidence of mucosal inflammation were similar in terms of the magnitude of the differences in anxiety, depression, somatisation, and quality of life scores seen among those with both IBS-type symptoms and active disease, although due to a reduction in the size of the group of individuals with IBS-type symptoms there were fewer statistically significant differences (Tables 11 and 12). When analyses using this cut off were repeated for all patients with IBD combined, the differences in psychological co-morbidity and quality of life in those with IBS-type symptoms became statistically significant once more (Table 13).

Table 11: Disease activity status and characteristics of patients with CD after FC analysis using a cut off <100µg/g

	CD with IBS-type symptoms (n = 37)	Quiescent CD (n = 49)	P value*	CD with occult inflammation (n = 74)	P value*	Active CD (n = 46)	P value*	P value†
Mean age in years (SD)	48.3 (14.6)	44.8 (17.2)	0.32	47.5 (18.0)	0.81	47.9 (15.6)	0.90	0.75
Female gender (%)	28 (75.7)	21 (42.9)	0.002	45 (60.8)	0.12	32 (69.6)	0.54	0.009
Married or co-habiting (%)	21 (58.3)	33 (67.3)	0.39	42 (56.8)	0.88	21 (67.4)	0.40	0.53
University graduate/professional (%)	9 (24.3)	16 (32.7)	0.40	16 (21.9)	0.78	13 (28.3)	0.69	0.59
Mean BMI (SD)	25.5 (6.0)	25.7 (4.9)	0.83	26.5 (5.9)	0.39	27.5 (5.2)	0.12	0.35
Tobacco user (%)	11 (29.7)	5 (10.2)	0.02	16 (21.6)	0.35	11 (23.9)	0.55	0.14
Alcohol user (%)	26 (70.3)	30 (61.2)	0.38	45 (60.8)	0.33	27 (60.0)	0.33	0.75
Crohn's disease location (%)								
Ileal	9 (24.3)	8 (16.3)		16 (21.6)		15 (32.6)		
Colonic	17 (45.9)	17 (34.7)		22 (29.7)		8 (17.4)		
Ileocolonic	11 (29.7)	24 (49.0)	0.19	36 (48.6)	0.14	23 (50.0)	0.02	0.09
5-ASA use (%)	15 (40.5)	14 (28.6)	0.25	23 (31.1)	0.32	7 (15.2)	0.009	0.08

Crohn's disease behaviour (%)								
Non stricturing, non penetrating	33 (89.2)	44 (89.8)		64 (86.5)		34 (73.9)		
Stricturing	3 (8.1)	2 (4.1)		8 (10.8)		9 (19.6)		
Penetrating	1 (2.7)	3 (6.1)	0.57	2 (2.7)	0.90	3 (6.5)	0.22	0.23
Perianal Crohn's disease present (%)	2 (5.4)	3 (6.1)	0.89	7 (9.5)	0.46	4 (8.7)	0.57	0.84
Immunomodulator use (%)	22 (59.5)	20 (40.8)	0.09	31 (41.9)	0.08	20 (43.5)	0.15	0.28
Anti-TNFα use (%)	9 (24.3)	14 (28.6)	0.66	20 (27.0)	0.76	14 (30.4)	0.54	0.94
Glucocorticosteroid use (%)	4 (10.8)	3 (6.1)	0.43	10 (13.5)	0.69	4 (8.7)	0.75	0.59
Previous intestinal resection (%)	13 (35.1)	13 (26.5)	0.39	20 (27.0)	0.38	24 (52.2)	0.12	0.02
Mean HADS anxiety score (SD)	8.0 (3.9)	6.3 (4.4)	0.06	7.0 (4.7)	0.24	10.0 (4.5)	0.04	<0.001
HADS anxiety categories (%)								
Normal	17 (45.9)	31 (63.3)		44 (59.5)		14 (30.4)		
Borderline abnormal	10 (27.0)	8 (16.3)		14 (18.9)		10 (21.7)		
Abnormal	10 (27.0)	10 (20.4)	0.26	16 (21.6)	0.39	22 (47.8)	0.15	0.01
Mean HADS depression score (SD)	5.6 (3.9)	3.6 (4.2)	0.03	4.8 (3.9)	0.27	7.3 (4.1)	0.06	<0.001

HADS depression categories (%)								
Normal	27 (73.0)	40 (81.6)		56 (75.7)		24 (52.2)		
Borderline abnormal	5 (13.5)	6 (12.2)		12 (16.2)		11 (23.9)		
Abnormal	5 (13.5)	3 (6.1)	0.48	6 (8.1)	0.65	11 (23.9)	0.15	0.04
Mean PHQ-15 somatisation score (SD)	11.7 (4.5)	8.8 (4.4)	0.004	8.9 (4.3)	0.003	13.1 (4.3)	0.19	0.001
PHQ-15 somatisation categories (%)								
Mild	1 (2.9)	11 (23.4)		8 (11.6)		0 (0.0)		
Low	11 (31.4)	15 (31.9)		32 (46.4)		7 (16.3)		
Medium	14 (40.0)	15 (31.9)		22 (31.9)		23 (53.5)		
High	9 (25.7)	6 (12.8)	0.05	7 (10.1)	0.06	13 (30.2)	0.26	<0.001

Median SF-36 score quality of life (IQR)								
Physical functioning	82.5 (61.3-91.3)	92.5 (66.3-100.0)	0.04	85.0 (65.0-100.0)	0.22	65.0 (30.0-92.5)	0.10	0.003
Role limitations physical health	25.0 (0.0-100.0)	87.5 (6.3-100.0)	0.02	75.0 (25.0-100.0)	0.02	25.0 (0.0-75.0)	0.76	0.003
Role limitations emotional problems	100.0 (0.0-100.0)	100.0 (75.0-100.0)	0.05	100.0 (33.3-100.0)	0.41	66.7 (0.0-100.0)	0.66	0.05
Energy/fatigue	35.0 (25.0-50.0)	50.0 (31.3-70.0)	0.07	50.0 (23.8-65.0)	0.33	25.0 (10.0-45.0)	0.009	<0.001
Emotional well-being	68.0 (60.0-78.0)	80.0 (60.0-88.0)	0.01	66.0 (52.0-88.0)	0.71	56.0 (44.0-72.0)	0.08	0.003
Social functioning	62.5 (37.5-87.5)	75.0 (50.0-100.0)	0.14	75.0 (50.0-100.0)	0.14	50.0 (34.4-62.5)	0.05	0.001
Pain	45.0 (32.5-70.0)	77.5 (50.0-90.0)	0.003	70.0 (45.0-90.0)	0.001	43.8 (30.0-57.5)	0.35	<0.001
General health	35.0 (25.0-60.0)	60.0 (35.0-75.0)	0.005	50.0 (25.0-60.0)	0.15	30.0 (15.0-35.0)	0.02	<0.001
Mean FC (SD)	50.4 (18.2)	55.3 (25.7)	0.30	849 (1025)	<0.001	669 (649)	<0.001	<0.001

*Independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for comparison of categorical data vs. CD with IBS-type symptoms.

†One way ANOVA for normally distributed continuous data, Kruskal-Wallis analysis of variance for non-parametric data, and χ^2 for comparison of categorical data across all four groups.

Table 12: Disease activity status and characteristics of patients with UC after FC analysis using a cut off <100µg/g

	UC with IBS-type symptoms (n = 19)	Quiescent UC (n = 48)	P value*	UC with occult inflammation (n = 55)	P value*	Active UC (n = 50)	P value*	P value†
Mean age in years (SD)	44.5 (14.1)	54.5 (17.4)	0.02	53.3 (16.7)	0.03	50.7 (15.5)	0.12	0.13
Female gender (%)	10 (52.6)	26 (54.2)	0.91	30 (54.5)	0.89	27 (54.0)	0.92	0.99
Married or co-habiting (%)	14 (73.7)	29 (60.4)	0.31	44 (80.0)	0.56	35 (70.0)	0.76	0.18
University graduate/professional (%)	6 (31.6)	13 (27.1)	0.71	16 (30.2)	0.91	14 (28.6)	0.81	0.98
Mean BMI (SD)	26.7 (5.3)	26.4 (5.0)	0.86	27.1 (6.5)	0.78	27.8 (5.6)	0.44	0.67
Tobacco user (%)	1 (5.3)	1 (2.1)	0.49	3 (5.6)	0.96	3 (6.0)	0.91	0.79
Alcohol user (%)	12 (63.2)	34 (70.8)	0.54	39 (70.9)	0.53	30 (60.0)	0.81	0.59
Ulcerative colitis extent (%)								
Proctitis	8 (42.1)	11 (22.9)		20 (36.4)		8 (16.0)		
Left-sided	7 (36.8)	25 (52.1)		21 (38.2)		23 (46.0)		
Extensive	4 (21.1)	12 (25.0)	0.28	14 (25.5)	0.89	19 (38.0)	0.06	0.14
5-ASA use (%)	19 (100.0)	36 (75.0)	0.02	45 (81.8)	0.05	37 (74.0)	0.01	0.08
Immunomodulator use (%)	3 (15.8)	16 (33.3)	0.15	7 (12.7)	0.74	11 (22.0)	0.57	0.08

Anti-TNFα use (%)	0 (0.0)	0 (0.0)	-	1 (1.8)	0.55	3 (6.0)	0.28	0.20
Glucocorticosteroid use (%)	2 (10.5)	3 (6.3)	0.55	6 (10.9)	0.96	7 (14.0)	0.70	0.66
Mean HADS anxiety score (SD)	10.8 (5.5)	6.0 (4.3)	0.002	6.0 (4.8)	0.002	8.5 (4.6)	0.11	<0.001
HADS anxiety categories (%)								
Normal	5 (26.3)	31 (64.6)		37 (67.3)		22 (44.0)		
Borderline abnormal	5 (26.3)	12 (25.0)		7 (12.7)		9 (18.0)		
Abnormal	9 (47.4)	5 (10.4)	0.002	11 (20.0)	0.008	19 (38.0)	0.39	0.002
Mean HADS depression score (SD)	7.3 (5.5)	3.5 (3.4)	0.01	3.2 (3.2)	0.005	6.6 (4.5)	0.65	<0.001
HADS depression categories (%)								
Normal	15 (78.9)	43 (89.6)		49 (90.7)		32 (64.0)		
Borderline abnormal	0 (0.0)	3 (6.3)		2 (3.7)		6 (12.0)		
Abnormal	4 (21.1)	2 (4.2)	0.06	3 (5.6)	0.11	12 (24.0)	0.25	0.005
Mean PHQ-15 somatisation score (SD)	11.8 (4.2)	7.3 (4.8)	0.001	7.5 (5.7)	0.001	11.2 (4.3)	0.56	<0.001
PHQ-15 somatisation categories (%)								
Mild	1 (5.3)	13 (27.7)		18 (34.0)		2 (4.3)		
Low	4 (21.1)	20 (42.6)		15 (28.3)		10 (21.3)		
Medium	8 (42.1)	8 (17.0)		15 (28.3)		21 (44.7)		
High	6 (31.6)	6 (12.8)	0.01	5 (9.4)	0.02	14 (29.8)	1.0	<0.001

Median SF-36 quality of life score (IQR)								
Physical functioning	85.0 (65.0-100.0)	90.0 (75.0-100.0)	0.48	95.0 (70.0-100.0)	0.52	75.0 (55.0-95.0)	0.19	0.02
Role limitations physical health	50.0 (0.0-100.0)	100.0 (50.0-100.0)	0.05	100.0 (50.0-100.0)	0.19	25.0 (0.0-100.0)	0.24	<0.001
Role limitations emotional problems	66.7 (0.0-100.0)	100.0 (66.7-100.0)	0.03	100.0 (66.7-100.0)	0.06	66.7 (0.0-100.0)	0.99	0.005
Energy/fatigue	50.0 (32.5-57.5)	55.0 (40.0-70.0)	0.09	50.0 (40.0-75.0)	0.16	30.0 (20.0-60.0)	0.16	<0.001
Emotional well-being	68.0 (42.0-78.0)	76.0 (60.0-88.0)	0.11	80.0 (60.0-92.0)	0.03	64.0 (53.0-80.0)	0.71	0.04
Social functioning	75.0 (50.0-100.0)	87.5 (62.5-100.0)	0.22	87.5 (62.5-100.0)	0.17	50.0 (25.0-75.0)	0.01	<0.001
Pain	62.5 (45.5-80.0)	80.0 (60.0-90.0)	0.03	90.0 (57.5-100.0)	0.02	56.3 (45.0-70.0)	0.60	<0.001
General health	52.5 (36.3-66.3)	60.0 (41.3-83.8)	0.13	70.0 (45.0-80.0)	0.03	45.0 (27.5-57.5)	0.28	<0.001
Mean FC (SD)	40.2 (22.6)	46.4 (19.9)	0.31	589 (654)	<0.001	1198 (1307)	<0.001	<0.001

*Independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for comparison of categorical data vs. UC with IBS-type symptoms.

†One way ANOVA for normally distributed continuous data, Kruskal-Wallis analysis of variance for non-parametric data, and χ^2 for comparison of categorical data across all four groups.

Table 13: Disease activity status and characteristics of all patients with IBD after FC analysis using a cut off <100µg/g

	IBD with IBS-type symptoms (n = 56)	Quiescent IBD (n = 97)	P value*	IBD with occult inflammation (n = 129)	P value*	Active IBD (n = 96)	P value*	P value†
Mean age in years (SD)	47.0 (14.4)	49.6 (17.9)	0.32	50.0 (17.6)	0.23	49.3 (15.5)	0.35	0.73
Female gender (%)	38 (67.9)	47 (48.5)	0.02	75 (58.1)	0.21	59 (61.5)	0.43	0.10
Married or co-habiting (%)	35 (63.6)	62 (63.9)	0.97	86 (66.7)	0.69	66 (68.8)	0.52	0.88
University graduate/professional (%)	15 (26.8)	29 (29.9)	0.68	32 (25.4)	0.84	27 (28.4)	0.83	0.89
Mean BMI (SD)	25.9 (5.8)	26.1 (4.9)	0.83	26.8 (6.2)	0.35	27.7 (5.4)	0.07	0.17
Tobacco user (%)	12 (21.4)	6 (6.2)	0.005	19 (14.8)	0.27	14 (14.6)	0.28	0.05
Alcohol user (%)	38 (67.9)	64 (66.0)	0.81	84 (65.1)	0.72	57 (60.0)	0.33	0.75
5-ASA use (%)	34 (60.7)	50 (51.5)	0.27	68 (52.7)	0.32	44 (45.8)	0.08	0.36
Immunomodulator use (%)	25 (44.6)	36 (37.1)	0.36	38 (29.5)	0.05	31 (32.3)	0.13	0.21
Anti-TNFα use (%)	9 (16.1)	14 (14.4)	0.79	21 (16.3)	0.97	17 (17.7)	0.80	0.94
Glucocorticosteroid use (%)	6 (10.7)	6 (6.2)	0.32	16 (12.4)	0.74	11 (11.5)	0.89	0.47
Mean HADS anxiety score (SD)	9.0 (4.7)	6.1 (4.3)	<0.001	6.6 (4.8)	0.002	9.2 (4.6)	0.79	<0.001

HADS anxiety categories (%)								
Normal	22 (39.3)	62 (63.9)		81 (62.8)		36 (37.5)		
Borderline abnormal	15 (26.8)	20 (20.6)		21 (16.3)		19 (19.8)		
Abnormal	19 (33.9)	15 (15.5)	0.007	27 (20.9)	0.01	41 (42.7)	0.47	<0.001
Mean HADS depression score (SD)	6.2 (4.5)	3.6 (3.8)	<0.001	4.1 (3.7)	0.003	6.9 (4.3)	0.31	<0.001
HADS depression categories (%)								
Normal	42 (75.0)	83 (85.6)		105 (82.0)		56 (58.3)		
Borderline abnormal	5 (8.9)	9 (9.3)		14 (10.9)		17 (17.7)		
Abnormal	9 (16.1)	5 (5.2)	0.08	9 (7.0)	0.16	23 (24.0)	0.11	<0.001
Mean PHQ-15 somatisation score (SD)	11.8 (4.4)	8.0 (4.7)	<0.001	8.3 (5.0)	<0.001	12.1 (4.4)	0.69	<0.001
PHQ-15 somatisation categories (%)								
Mild	2 (3.7)	24 (25.5)		26 (21.3)		2 (2.2)		
Low	15 (27.8)	35 (37.2)		47 (38.5)		17 (18.9)		
Medium	22 (40.7)	23 (24.5)		37 (30.3)		44 (48.9)		
High	15 (27.8)	12 (12.8)	0.001	12 (9.8)	0.001	27 (30.0)	0.57	<0.001

Median SF-36 quality of life score (IQR)								
Physical functioning	85.0 (65.0-100.0)	90.0 (73.8-100.0)	0.03	90.0 (65.0-100.0)	0.14	75.0 (45.0-95.0)	0.07	<0.001
Role limitations physical health	25.0 (0.0-100.0)	100.0 (50.0-100.0)	0.001	75.0 (25.0-100.0)	0.005	25.0 (0.0-100.0)	0.44	<0.001
Role limitations emotional problems	100.0 (0.0-100.0)	100.0 (66.7-100.0)	0.004	100.0 (33.3-100.0)	0.06	66.7 (0.0-100.0)	0.68	<0.001
Energy/fatigue	45.0 (26.3-53.8)	55.0 (40.0-70.0)	0.005	50.0 (30.0-70.0)	0.06	30.0 (15.0-45.0)	0.01	<0.001
Emotional well-being	68.0 (55.0-77.0)	76.0 (60.0-88.0)	0.006	72.0 (56.0-88.0)	0.06	64.0 (48.0-80.0)	0.43	0.001
Social functioning	75.0 (50.0-87.5)	87.5 (56.3-100.0)	0.02	87.5 (62.5-100.0)	0.03	50.0 (25.0-75.0)	0.002	<0.001
Pain	55.0 (32.5-77.5)	77.5 (57.5-90.0)	<0.001	77.5 (49.4-90.0)	<0.001	53.8 (32.5-67.5)	0.60	<0.001
General health	45.0 (25.0-60.0)	60.0 (40.0-75.0)	0.001	55.0 (35.0-75.0)	0.01	35.0 (20.0-50.0)	0.06	<0001
Mean FC (SD)	46.9 (20.2)	50.9 (23.3)	0.27	738 (892)	<0.001	941 (1070)	<0.001	<0.001

*Independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for comparison of categorical data vs. IBD with IBS-type symptoms.

†One way ANOVA for normally distributed continuous data, Kruskal-Wallis analysis of variance for non-parametric data, and χ^2 for comparison of categorical data across all four groups.

4.4 Discussion

After utilising FC as an objective measure of IBD activity, this cross-sectional study has demonstrated an overall prevalence of IBS-type symptom-reporting in outpatients with IBD of 27.7% in CD and 19.8% in UC. Among both patients with CD and UC with IBS-type symptoms there was substantial psychological co-morbidity, with the prevalence and severity of anxiety, depression, and somatisation all higher than among patients with either quiescent disease or occult inflammation. In addition, the reduction in quality of life associated with the presence of these symptoms was consistently greater than that observed in patients with CD and UC with quiescent disease or occult inflammation, and was of a similar magnitude to those with active disease.

Many of the strengths of this study, including the use of validated questionnaires, the generalisability of its findings, and the use of quantitative measures of intestinal inflammation are in keeping with those described in Chapter 3, and are not re-discussed here. Specific strengths of this study include its sample size of 378 patients, which is larger than any previous study examining the prevalence of IBS-type symptom-reporting in IBD, and the fact that it was not restricted to the study of patients with UC alone (Keohane et al., 2010; Berrill et al., 2013; Jonefjall et al., 2016; Henriksen et al., 2018).

Given that this was a cross-sectional study, an obvious weakness is that causality cannot be implied by these results. Furthermore, one-in-three patients with CD had undergone intestinal resection previously and, given that BAM or SIBO may occur as a result of surgery (Gracie et al., 2012; Greco et al., 2015), and that there is overlap between the symptoms of these conditions and those of IBS (Ford et al., 2009a; Aziz et al., 2015), it is possible that the reported prevalence of IBS-type symptoms has been

overestimated. The reliance on FC as the sole determinant of inflammatory activity, rather than "gold-standard" endoscopic and radiological investigations, could also be considered a weakness for two reasons. Firstly, in CD, patients with occult fibrostenotic disease, who may report symptoms that are not related to intestinal inflammation, but who may not have IBS, could have been falsely categorised as reporting these symptoms. Secondly, occult inflammatory activity could have been missed. However, even when a FC cut off <100µg/g was used, 18% of those with CD, and 11% of those with UC still reported IBS-type symptoms. There were fewer statistically significant differences between groups when a FC cut off <100µg/g was used, but this was likely to be secondary to a reduction in the size of the groups of individuals with either IBS-type symptoms or quiescent disease. When analyses using this cut off were repeated for all patients with CD and UC combined, the differences in psychological co-morbidity and quality of life in those with IBS-type symptoms became statistically significant once more.

Several studies have investigated the prevalence of IBS-type symptoms in patients with IBD, and their association with psychological co-morbidity. However, only four have utilised an objective measure of mucosal inflammation (Berrill et al., 2013; Keohane et al., 2010; Henriksen et al., 2018; Jonefjall et al., 2016). Keohane *et al.* assessed the prevalence of IBS-type symptoms, and their impact on quality of life and depression scores in 106 patients with IBD, and found that 60% of CD and 39% of patients with UC in clinical remission met the Rome II criteria for IBS (Keohane et al., 2010). Quality of life scores were lower, and depression scores higher in UC, but not in patients with CD with IBS-type symptoms versus those without. However, FC levels were significantly higher among patients meeting Rome II criteria, suggesting that the mechanism for these symptoms was occult inflammation, rather than genuine IBS. In

contrast, Berrill *et al.* recruited 169 patients with IBD, and reported that 32% of those in clinical remission reported IBS-type symptoms, again with higher anxiety and depression scores in the IBS group, with no differences in FC levels between those with and without IBS-type symptoms, but only 61 patients returned a stool sample (Berrill et al., 2013).

Subsequent to these studies Jonefjäll *et al.* reported a prevalence of IBS-type symptom-reporting of 18% in patients with UC in deep remission, defined using a flexible sigmoidoscopy or FC <200µg/g of stool. No significant difference in median FC level between patients in deep remission with, and without, IBS-type symptoms was reported, yet IBS-type symptom-reporting was consistently associated with anxiety, depression, and poor quality of life (Jonefjall et al., 2016). Finally, Henriksen *et al.* reported a prevalence of IBS-type symptoms of between 27% and 29% in 260 patients with UC who underwent colonoscopy or FC testing, and that this figure was unaffected by the presence, or absence, of inflammatory activity (Henriksen et al., 2018). The authors made no comment on the association between these symptoms and psychological health or quality of life. Taken into context with the findings of the present study, where no difference in mean FC level was observed between patients reporting IBS-type symptoms, and those defined as having quiescent disease, these studies refute the assertion that occult inflammatory activity is the sole cause of IBS-type symptom-reporting in patients with IBD.

The aetiology of functional symptoms in IBD remains uncertain and is likely to be multi-factorial, as was discussed earlier. The association between IBS-type symptom-reporting and psychological co-morbidity, but not inflammatory activity that is described in this and other studies (Berrill et al., 2013; Jonefjall et al., 2016; Henriksen et al., 2018), suggests that brain-gut interactions may contribute to the

development of these symptoms. Here, patients with IBS-type symptoms and those with active disease had higher levels of anxiety, depression, and somatisation compared with those with quiescent disease or occult inflammation. In the former group, this suggests a brain-gut direction of effect with psychological co-morbidity leading to the generation of functional GI symptoms, and in the latter group a gut-brain direction of effect with active inflammation leading to psychological symptoms. However, longitudinal studies examining the relationship between psychological health, inflammatory activity, and GI symptom-reporting are required before this hypothesis can be proven. This deficiency in understanding, in combination with the findings presented in Chapter 3, provides further rationale for conducting the longitudinal follow-up studies that are described in Chapters 5 and 6.

These findings have important implications for clinical practice. Firstly, IBS-type symptoms are common and, with the increased use of biomarkers such as FC, to monitor disease activity, the emergence of a cohort of patients with IBS-type symptoms without evidence of mucosal inflammation is likely to occur. Secondly, although escalation of conventional immunosuppressant and biological therapies has been advocated previously in these patients (Vivinus-Nebot et al., 2014), current data does not support the efficacy of such drugs when objective evidence of disease activity is lacking (Colombel et al., 2010; Schreiber et al., 2005; Reinisch et al., 2012). In addition, this approach may be expensive and could expose patients to potential unnecessary risks associated with these therapies (Ford and Peyrin-Biroulet, 2013; Lichtenstein et al., 2012). Despite this, there is a paucity of evidence for alternative approaches in this group of patients, which further supports the need for novel treatments options addressing psychological wellbeing in patients with IBD, and provides the rationale for

conducting the systematic review and meta-analysis of RCTs of psychological therapies in IBD described in Chapter 7.

In summary, genuine IBS-type symptoms in IBD are common, and are associated with higher levels of anxiety, depression, and somatisation, and reduced quality of life. This study has identified a distinct group of patients with ongoing GI symptoms in the absence of objective evidence of disease activity. The presence of these symptoms is associated with impaired psychological wellbeing and quality of life, to a similar degree to that observed in patients with active disease. The cause of these symptoms is uncertain, as is their effect on the natural history of IBD, and further longitudinal studies examining the relationship between disease activity, IBS-type symptoms, and psychological co-morbidity are warranted.

CHAPTER 5: Assessing the direction of brain-gut interactions in patients with IBD

5.1 Introduction

Mood disorders, such as anxiety or depression, are observed more commonly in patients with IBD than in healthy individuals (Panara et al., 2014; Graff et al., 2009; Fuller-Thomson and Sulman, 2006; Mittermaier et al., 2004; Goodhand et al., 2012b), and are associated with GI symptom-reporting as illustrated in Chapters 3 and 4. However, the direction of the relationship between the gut and brain in IBD is unclear. In people with FGIDs, longitudinal studies suggest that there is a higher risk of developing anxiety or depression in people without mood disorders who report GI symptoms at baseline, but also an increased likelihood of asymptomatic people who demonstrate anxiety or depression at baseline developing GI symptoms *de novo* (Koloski et al., 2012; Koloski et al., 2016). This raises the possibility that the relationship between brain and gut may also be bi-directional in IBD. Hence, co-existent anxiety or depression, if unrecognised or untreated, may have deleterious effects on the subsequent natural history and prognosis of IBD, while untreated or refractory disease activity may have implications for future psychological health.

These are important issues because patients with quiescent IBD may be at a lower risk of relapse if co-existing mood disorders are identified and treated. This in turn may lead to a more benign disease course, with a reduced need for subsequent escalation of medical therapy, hospitalisation, or surgery. Conversely, patients with active IBD may be at risk of developing potentially treatable mood disorders, which are known to negatively affect quality of life, as described in Chapter 4. The aim of this longitudinal follow-up study, conducted over a minimum of 2 years, was to investigate the possibility that brain-gut interactions in IBD may be bi-directional. On the basis of previous research, where a bi-directional relationship between the brain and gut has been identified in FGIDs (Koloski et al., 2012; Koloski et al., 2016), the hypothesis was

that the same relationships would exist between anxiety and depression, and disease activity in IBD. Confirmation of a bi-directional relationship between mood and disease activity would reinforce the need for the integration of therapies targeting inflammatory activity with novel interventions aiming to improve psychological wellbeing in patients with IBD, including psychological therapies, addressed in Chapter 7.

5.2 Methods

5.2.1 Participants and setting

Individuals recruited into the cross-sectional study described in Chapters 3 and 4 were sent a postal invitation to participate in a longitudinal follow-up study, after a minimum interval of 2 years had elapsed. All patients had an established radiological, histological, or endoscopic diagnosis of CD or UC, and were aged ≥16 years at the time of baseline recruitment. Exclusion criteria were an inability to understand written English, a diagnosis of IBD-unclassified, and anyone with an end ileostomy or colostomy, due to the difficulties in assessing disease activity indices in these patients. The follow-up postal invitation included a written information sheet explaining the nature of the study, a consent form, and a questionnaire similar to that completed at baseline. If no response to the initial invitation to participate was received, a second questionnaire was sent. In order to maximise response rates, non-responders to the postal invitation into the study were also contacted at their scheduled outpatient clinic appointments during the study period. The longitudinal follow-up study was approved by the local research ethics committee in September 2014 (REC ref: 12/YH/0443), and data collection continued until June 2017. Study findings were reported in accordance with the STROBE guidelines for reporting observational studies (von Elm et al., 2008).

5.2.2 Data collection and synthesis

Date of recruitment into the original cross-sectional survey, demographic data, type of IBD, medications, Rome III IBS symptom data (Longstreth et al., 2006), somatisation data, captured using the PHQ-15 (Kroenke et al., 2002), and FC (Immundiagnostik, Bensheim, Germany) were recorded at baseline, as described in Chapters 3 and 4. In total, 401 (50.2%) of 799 patients provided a stool sample for FC analysis at baseline.

5.2.2.1 Longitudinal objective assessment of IBD activity

This was performed both at baseline and follow-up using the HBI for CD (Harvey and Bradshaw, 1980), and SCCAI for UC (Walmsley et al., 1998), with a score ≥5 used to define clinical disease activity for both, as previously recommended (Vermeire et al., 2010; Jowett et al., 2003). Objective assessment of disease activity during longitudinal follow-up was made by detailed case note review by a sole investigator (DJG), blinded to the baseline questionnaire data. The case notes of each patient included at baseline were assessed for the following clinical endpoints, with the date of each endpoint recorded, where applicable: glucorticosteroid prescription or flare of disease activity identified by physician's global assessment, escalation of medical therapy due to uncontrolled disease activity, hospitalisation secondary to objectively confirmed IBD activity, and intestinal resection. Escalation of medical therapy in response to therapeutic drug monitoring, but in the absence of inflammatory activity, was not included as an endpoint, nor was surgical intervention for isolated perianal CD.

5.2.2.2 Definition of normal and abnormal anxiety and depression scores

This was as described in Chapters 3 and 4, with the presence of either anxiety or depression again assessed using the HADS (Zigmond and Snaith, 1983), and severity categorised as previously described (Zigmond and Snaith, 1983).

5.2.3 Statistical analysis

All baseline data between those who responded to the follow-up questionnaire and those who did not were compared using a χ^2 test for categorical variables, and an independent samples *t*-test for continuous data.

To assess for the presence of a gut-to-brain interaction during longitudinal follow-up, the proportion of patients with new-onset abnormal anxiety or depression scores (i.e. normal HADS scores at baseline, but above threshold HADS anxiety or depression scores at follow-up) was compared according to baseline IBD activity. HBI or SCCAI scores ≥5 were used to define active disease at baseline, but a sensitivity analysis was also performed in patients with biochemical evidence of IBD activity at baseline (FC ≥250μg/g). To assess for the presence of a brain-to-gut interaction during longitudinal follow-up, the proportion of patients with clinically quiescent disease at baseline (defined by HBI or SCCAI scores <5) who subsequently developed one of the objective measures of disease activity detailed above, was compared according to the presence of either abnormal HADS anxiety or depression scores at baseline. Furthermore, the relationship between the presence of clinical disease activity at follow-up (defined by HBI or SCCAI scores ≥5) and the presence of baseline psychological co-morbidity was also assessed in patients with HBI or SCCAI scores <5 at baseline, dichotomised into those with and without abnormal HADS anxiety or depression scores at baseline. Again sensitivity analysis, where only those in clinical remission and with

no biochemical evidence of IBD activity at baseline (FC <250µg/g) were considered as having quiescent disease, were conducted for all these analyses. Proportions were compared using a χ^2 test. A 2-tailed P value of 0.05 was considered to be statistically significant for all these analyses.

Independent predictors of the development of abnormal anxiety or depression scores at the point of questionnaire follow-up in those with normal scores at baseline were determined by performing multivariate logistic regression analysis to control for baseline demographic characteristics, type of IBD, medications, presence or absence of Rome III IBS-type symptoms, and somatisation severity. Similarly, multivariate Cox regression analysis was performed to indentify independent predictors of any of the clinical disease activity endpoints of interest during longitudinal follow-up in those with quiescent disease at baseline. A 2-tailed P value of <0.05 was considered to be statistically significant, and the results were expressed as ORs or HRs with 95% CIs. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

5.3 Results

In total, 405 (50.7%) of 799 patients included in the initial cross-sectional survey consented to participate and returned a follow-up questionnaire. Of these, 239 (59.0%) had CD and 166 (41.0%) UC. Participants who returned the follow-up questionnaire were older, more likely to be married or co-habiting, and were more likely to fulfil the Rome III criteria for IBS. There were no other differences in baseline characteristics, including disease activity, defined by either FC or clinical disease activity indices, or psychological co-morbidity, between responders and non-responders (Table 14).

Table 14: Baseline demographic, disease-related, and psychological characteristics of responders and non-responders to the follow-up questionnaire

	Follow-up questionnaire responder (n = 405)	**Follow-up questionnaire non-responder (n = 394)**	**P value***
Mean age in years (SD)	46.8 (16.4)	41.0 (16.4)	<0.001
Female gender (%)	234 (57.8)	205 (52.0)	0.10
Caucasian ethnicity (%)	386 (95.8)	359 (92.1)	0.03
Married or co-habiting (%)	265 (65.6)	217 (55.9)	0.005
University/postgraduate (%)	112 (28.0)	111 (28.7)	0.83
Mean BMI (SD)	26.6 (5.5)	26.1 (5.5)	0.26
Tobacco user (%)	65 (16.1)	71 (18.1)	0.46
Alcohol user (%)	264 (65.5)	254 (64.6)	0.80
Crohn's disease (%)	239 (59.0)	220 (55.8)	0.36
5-ASA use (%)	189 (46.7)	185 (47.0)	0.94
Immunomodulator use (%)	153 (37.8)	133 (33.8)	0.24
Anti-TNFα use (%)	85 (21.0)	67 (17.0)	0.15
Glucocorticosteroid use (%)	44 (10.9)	39 (9.9)	0.66
Rome III IBS criteria fulfilled (%)	166 (41.5)	128 (33.3)	0.02
HBI/SCCAI <5 (%)	229 (58.9)	214 (58.0)	0.81
FC <250µg/g (%)	152 (62.8)	89 (56.0)	0.17
HADS anxiety categories (%)			
Normal	215 (53.6)	207 (53.4)	
Borderline abnormal	82 (20.4)	76 (19.6)	
Abnormal	104 (25.9)	105 (27.1)	0.92

HADS depression categories (%)			
Normal	306 (76.3)	292 (74.7)	
Borderline abnormal	47 (11.7)	52 (13.3)	
Abnormal	48 (12.0)	47 (12.0)	0.79
PHQ-15 somatisation categories (%)			
Mild	52 (13.5)	66 (17.6)	
Low	126 (32.7)	113 (30.2)	
Medium	132 (34.3)	119 (31.8)	
High	75 (19.5)	76 (20.3)	0.41

*Independent samples *t*-test for continuous data, and χ^2 for categorical data.

5.3.1 Association between baseline disease activity and the development of abnormal anxiety scores during longitudinal follow-up

There were 192 patients with normal HADS anxiety and depression scores at baseline, and 22 (11.5%) of these developed abnormal anxiety scores at the point of follow-up. Of these 22, 11 (50.0%) had evidence of clinical disease activity at baseline, compared with 46 (27.1%) of the 170 patients who did not develop abnormal anxiety scores (P = 0.03; Table 15). Following multivariate logistic regression analysis, clinical disease activity remained significantly associated with the development of abnormal anxiety scores (OR = 5.17; 95% CI 1.35-19.8). In sensitivity analysis, when FC ≥250μg/g was used to define baseline disease activity, there was no association between this and abnormal anxiety scores (P = 0.80; Table 15), and this was confirmed following logistic regression analysis (OR = 2.38; 95% CI 0.14-41.0).

5.3.2 Association between baseline disease activity an development of abnormal depression scores during longitudinal follow-up

Of the 192 patients with normal HADS anxiety and depression scores at baseline, only three (1.6%) developed abnormal depression scores during follow-up. There was no significant association between baseline disease activity and the development of abnormal depression scores (Table 15), and too few patients developing abnormal depression scores to perform logistic regression analysis. Sensitivity analysis for abnormal depression scores could not be performed, because none of the three patients provided FC at baseline.

Table 15: Relationship between the presence of IBD activity at baseline and subsequent development of abnormal anxiety or depression scores, among patients with normal anxiety and depression scores at baseline

	Normal follow-up HADS anxiety score	**Abnormal follow-up HADS anxiety score**	**P value**	**Normal follow-up HADS depression score**	**Abnormal follow-up HADS depression score**	**P value**
HBI/SCCAI ≥5 (%)	46/170 (27.1)	11/22 (50.0)	0.03	56/189 (29.6)	1/3 (33.3)	0.89
FC ≥250µg/g (%)	45/112 (40.2)	4/9 (44.4)	0.80	49/121 (40.5)	0/0 (0)	N/A

5.3.3 Association between baseline abnormal anxiety scores and development of disease activity during longitudinal follow-up

5.3.3.1 Glucorticosteroid prescription or flare of disease activity

Of 388 patients with clinically quiescent disease at baseline, 128 (33.0%) required a prescription of glucocorticosteroids or developed a flare of disease activity over a mean length of follow-up of 838 days (SD ± 436 days). Of these 128, 35 (27.3%) had abnormal anxiety scores at baseline, compared with 38 (14.6%) of the 260 patients who did not (P = 0.003; Table 16). When only need for glucocorticosteroids was considered, there were 22 (30.6%) of 72 patients requiring a glucocorticosteroid prescription with abnormal anxiety scores at baseline, compared with 51 (16.1%) of 316 not requiring a glucocorticosteroid prescription (P = 0.005). Following multivariate Cox regression analysis, baseline abnormal anxiety scores were associated with glucocorticosteroid prescription or a flare of disease activity (HR = 2.08; 95% CI 1.31-3.30; Table 17 and Figure 5). In sensitivity analysis, abnormal baseline anxiety scores remained associated with need for glucocorticosteroid prescription or flare of disease activity (P = 0.02; Table 18), and this was also the case following Cox regression analysis (HR = 2.29; 95% CI 1.03-5.07).

Table 16: Relationship between the presence of abnormal anxiety or depression scores at baseline, and subsequent development of IBD activity, among patients with IBD in clinical remission at baseline

	Glucorticosteroid prescription or flare of disease activity			Escalation of medical therapy in response to uncontrolled disease activity			Hospitalisation due to disease activity			Intestinal resection			Clinical disease activity		
	No	**Yes**	**P Value**	**No**	**Yes**	**P value**	**No**	**Yes**	**P Value**	**No**	**Yes**	**P value**	**No**	**Yes**	**P value**
Abnormal baseline anxiety score (%)	38/260 (14.6)	35/128 (27.3)	0.003	37/255 (14.5)	38/148 (25.7)	0.005	59/365 (16.2)	17/58 (29.3)	0.02	69/401 (17.2)	7/22 (31.8)	0.08	32/179 (17.9)	11/47 (23.4)	0.39
Abnormal baseline depression score (%)	13/259 (5.0)	4/128 (3.1)	0.39	13/254 (5.1)	5/148 (3.4)	0.42	16/364 (4.4)	5/58 (8.6)	0.17	18/400 (4.5)	3/22 (13.6)	0.06	6/178 (3.4)	6/47 (12.8)	0.01

Table 17: Independent predictors of subsequent IBD activity following multivariate Cox regression analysis, among patients with IBD in clinical remission at baseline

	Glucorticosteroid prescription or flare of disease activity		Escalation of medical therapy in response to uncontrolled disease activity		Hospitalisation due to disease activity		Intestinal resection		Clinical disease activity	
	Hazard ratio (95% CI)	**P value**	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**
Female sex	0.82 (0.56-1.22)	0.33	0.89 (0.62-1.29)	0.53	1.12 (0.63-1.98)	0.70	1.13 (0.43-2.98)	0.81	2.55 (1.15-5.65)	0.02
Age (per year)	0.96 (0.95-0.98)	<0.001	0.97 (0.96-0.98)	<0.001	0.97 (0.94-0.99)	0.002	0.96 (0.91-1.00)	0.06	0.99 (0.97-1.02)	0.55
Married or co-habiting	1.10 (0.73-1.66)	0.64	1.49 (1.01-2.21)	0.05	1.22 (0.67-2.24)	0.52	0.58 (0.20-1.65)	0.31	1.00 (0.49-2.06)	1.00
Tobacco use	1.28 (0.72-2.27)	0.40	0.97 (0.56-1.66)	0.90	1.66 (0.79-3.50)	0.19	1.52 (0.44-5.18)	0.51	1.90 (0.81-4.47)	0.14

Alcohol use	0.60 (0.40-0.91)	0.02	0.74 (0.51-1.08)	0.12	0.45 (0.25-0.81)	0.008	1.14 (0.38-3.46)	0.82	0.74 (0.36-1.52)	0.41
University/postgraduate education	1.12 (0.73-1.71)	0.61	1.10 (0.74-1.63)	0.65	0.76 (0.38-1.51)	0.43	0.90 (0.30-2.71)	0.85	0.75 (0.30-1.84)	0.53
BMI (per unit)	1.04 (1.00-1.07)	0.03	1.02 (0.99-1.06)	0.24	1.03 (0.98-1.08)	0.28	1.06 (0.97-1.17)	0.20	0.99 (0.93-1.06)	0.77
Crohn's disease	0.54 (0.32-0.90)	0.02	0.79 (0.49-1.28)	0.35	0.68 (0.29-1.57)	0.36	0.41 (0.04-4.15)	0.45	1.39 (0.58-3.30)	0.46
5-ASA use at baseline	1.06 (0.65-1.72)	0.82	0.97 (0.61-1.54)	0.90	0.60 (0.28-1.31)	0.20	0.15 (0.02-1.39)	0.10	1.20 (0.54-2.66)	0.65
Immunosuppressant use at baseline	1.15 (0.77-1.73)	0.49	0.73 (0.50-1.08)	0.12	1.60 (0.87-2.94)	0.13	1.25 (0.47-3.29)	0.66	0.56 (0.28-1.14)	0.11
Anti-TNFα use at baseline	0.90 (0.52-1.54)	0.70	1.33 (0.83-2.14)	0.24	1.36 (0.66-2.80)	0.40	1.31 (0.48-3.55)	0.60	0.79 (0.32-1.90)	0.59
Glucorticosteroid use at baseline	1.81 (0.96-3.42)	0.07	2.56 (1.51-4.32)	<0.001	2.91 (1.46-5.78)	0.002	1.09 (0.26-4.60)	0.91	1.48 (0.46-4.83)	0.51
Presence of Rome III IBS-type symptoms at baseline	1.17 (0.77-1.78)	0.45	1.30 (0.88-1.91)	0.18	1.36 (0.74-2.50)	0.32	1.09 (0.38-3.11)	0.88	1.52 (0.74-3.10)	0.25

Abnormal anxiety scores at baseline	2.08 (1.31-3.30)	0.002	1.82 (1.19-2.80)	0.006	1.59 (0.77-3.31)	0.21	1.62 (0.50-5.26)	0.42	0.88 (0.35-2.16)	0.77
Abnormal depression scores at baseline	0.72 (0.24-2.10)	0.54	0.86 (0.33-2.27)	0.77	0.79 (0.22-2.84)	0.72	0.68 (0.07-7.06)	0.75	0.82 (0.22-3.13)	0.78
High level of somatisation at baseline	0.63 (0.30-1.30)	0.21	0.72 (0.36-1.44)	0.36	1.07 (0.44-2.59)	0.88	2.04 (0.49-8.42)	0.33	1.01 (0.34-3.03)	0.98

Figure 5: Survival plot for glucocorticosteroid prescription or flare of disease activity between patients with and without anxiety at baseline

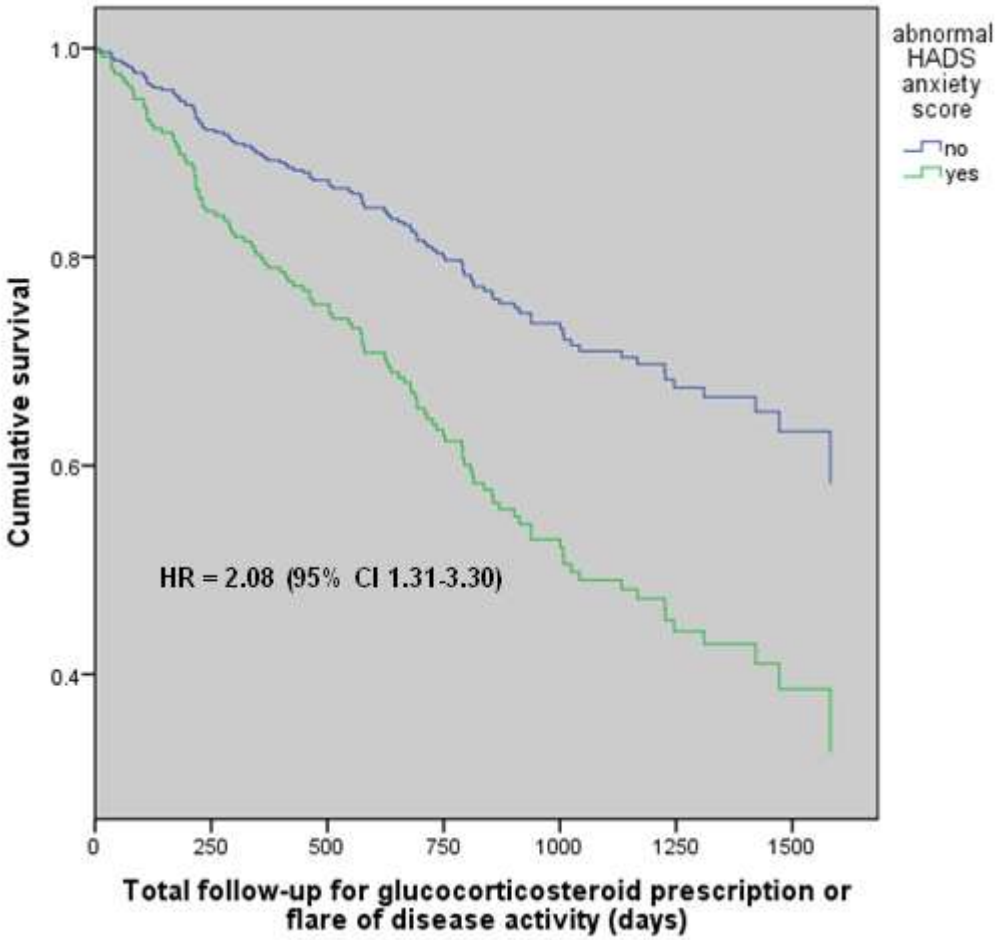


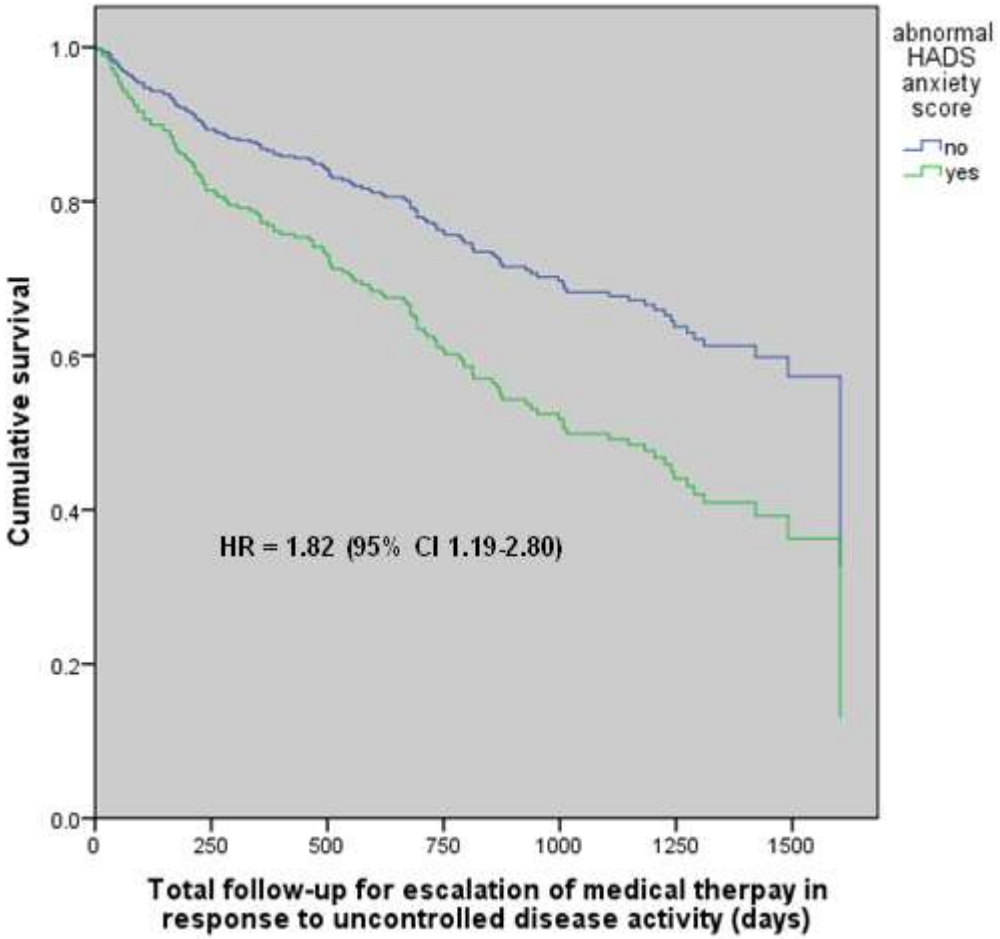
Table 18: Relationship between presence of abnormal anxiety or depression scores at baseline, and subsequent development of IBD activity, among patients with IBD in both clinical and biochemical remission at baseline

	Glucocorticosteroid prescription or flare of disease activity			Escalation of medical therapy in response to uncontrolled disease activity			Hospitalisation due to disease activity			Intestinal resection			Clinical disease activity		
	No	**Yes**	**P Value**	**No**	**Yes**	**P value**	**No**	**Yes**	**P Value**	**No**	**Yes**	**P value**	**No**	**Yes**	**P value**
Abnormal baseline anxiety score (%)	14/97 (14.4)	14/46 (30.4)	0.02	14/98 (14.3)	14/45 (31.1)	0.02	23/130 (17.7)	5/13 (38.5)	0.07	26/139 (18.7)	2/4 (50.0)	0.12	14/80 (17.5)	8/16 (50.0)	0.005
Abnormal baseline depression score (%)	4/97 (4.1)	1/46 (2.2)	0.55	4/98 (4.1)	1/45 (2.2)	0.57	5/130 (3.8)	0/13 (0)	0.47	5/139 (3.6)	0/4 (0)	0.70	1/80 (1.3)	4/16 (25.0)	<0.001

5.3.3.2 Escalation of medical therapy due to uncontrolled disease activity

Of 403 patients with clinically quiescent disease at baseline, 148 (36.7%) underwent escalation of medical therapy in response to uncontrolled IBD activity over a mean length of follow-up of 807 days (SD ± 454 days). Of these 148, 38 (25.7%) had abnormal anxiety scores at baseline compared with 37 (14.5%) of 255 patients who did not undergo escalation of medical therapy (P = 0.005; Table 16). Following multivariate Cox regression analysis, baseline abnormal anxiety scores were associated with escalation of medical therapy (HR = 1.82; 95% CI 1.19-2.80; Table 17 and Figure 6). In sensitivity analysis, abnormal baseline anxiety scores remained associated with escalation of medical therapy (P = 0.02; Table 18), and this persisted following Cox regression analysis (HR = 2.43; 95% CI 1.13-5.20).

Figure 6: Survival plot for escalation of medical therapy in response to uncontrolled IBD between patients with and without anxiety at baseline



5.3.3.3 Hospitalisation due to IBD activity

Of 423 patients with clinically quiescent disease at baseline, 58 (13.7%) were hospitalised as a result of objectively quantified IBD activity over a mean length of follow-up of 979 days (SD ± 414 days). Of these 58, 17 (29.3%) patients had an abnormal baseline anxiety score, compared with 59 (16.2%) of 365 patients who were not hospitalised (P = 0.02; Table 16). Following multivariate Cox regression analysis, baseline abnormal anxiety score was no longer associated with hospitalisation (HR = 1.59; 95% CI 0.77-3.31; Table 17). In sensitivity analysis, there was no association between baseline abnormal anxiety scores and hospitalisation (Table 18).

5.3.3.4 Intestinal resection

Of 423 patients with clinically quiescent disease at baseline, 22 (5.2%) underwent intestinal resection over a mean length of follow-up of 1032 days (SD ± 384 days). Of these, seven (31.8%) had abnormal baseline anxiety scores compared with 69 (17.2%) of 401 patients who did not undergo intestinal resection (P = 0.08; Table 16). Following multivariate Cox regression analysis, baseline abnormal anxiety scores were not associated with intestinal resection (HR = 1.62; 95% CI 0.50-5.26; Table 17). In sensitivity analysis, there remained no association between baseline abnormal anxiety scores and intestinal resection (Table 18).

5.3.3.5 Clinical disease activity

Of 226 patients with clinically quiescent disease at baseline (defined as baseline HBI or SCCAI score <5), 47 (20.8%) reported symptoms consistent with clinical disease activity (defined as HBI or SCCAI score ≥5) over a mean length of follow-up of 935 days (SD ± 187 days). Of these, 11 (23.4%) had abnormal baseline anxiety scores,

compared with 32 (17.9%) of 179 who did not report symptoms consistent with clinical disease activity (P = 0.39; Table 16). Following Cox regression analysis, there remained no association between abnormal anxiety scores at baseline and the development of clinically active IBD (HR = 0.88; 95% CI 0.35-2.16, Table 17). In sensitivity analysis, when only patients in clinical remission with FC <250µg/g at baseline were included, abnormal baseline anxiety scores were associated with the development of clinically active IBD (P = 0.005; Table 18). There were too few patients to perform Cox regression analysis.

5.3.4 Association between baseline abnormal depression scores and development of disease activity during longitudinal follow-up

5.3.4.1 Glucocorticosteroid prescription or flare of disease activity

Of the 128 patients requiring a prescription for glucocorticosteroids or developing a flare of disease activity, four (3.1%) had abnormal depression scores at baseline, compared with 13 (5.0%) of the 259 patients who did not (P = 0.39; Table 16). There remained no association following multivariate Cox regression analysis (HR = 0.72; 95% CI 0.24-2.10; Table 17), or in sensitivity analysis (Table 18).

5.3.4.2 Escalation of medical therapy due to uncontrolled disease activity

Of 148 patients undergoing escalation of medical therapy, five (3.4%) had abnormal depression scores at baseline compared with 13 (5.1%) of 254 patients who did not undergo escalation (P = 0.42; Table 16). Following multivariate Cox regression analysis, there was no association between escalation of medical therapy and abnormal

depression scores at baseline (HR = 0.86; 95% CI 0.33-2.27; Table 17), and in sensitivity analysis (Table 18).

5.3.4.3 Hospitalisation due to IBD activity

Among the 58 patients hospitalised, five (8.6%) had abnormal baseline depression scores, compared with 16 (4.4%) of 364 patients who were not hospitalised (P = 0.17; Table 16). There was no association between abnormal depression scores at baseline and hospitalisation following multivariate Cox regression analysis (HR = 0.79; 95% CI 0.22-2.84; Table 17), or in sensitivity analysis (Table 18).

5.3.4.4 Intestinal resection

Of 22 patients undergoing intestinal resection, three (13.6%) had abnormal baseline depression scores compared with 18 (4.5%) of 400 patients who did not undergo resection (P = 0.06; Table 16). Following Cox regression analysis, there was no association between baseline abnormal depression scores and intestinal resection (HR = 0.68; 95% CI 0.07-7.06; Table 17), and this remained the case in sensitivity analysis (Table 18).

5.3.4.5 Clinical disease activity

Six (12.8%) of 47 patients reporting symptoms consistent with clinically active disease had abnormal baseline depression scores, compared with six (3.4%) of 178 who did not report symptoms (P = 0.01; Table 16). However, this association was lost following Cox regression analysis (HR = 0.82; 95% CI 0.22-3.13; Table 17). In sensitivity analysis, abnormal depression scores were associated with development of

clinically active IBD (P <0.001; Table 18). There were too few patients to perform Cox regression analysis.

5.4 Discussion

Building on the data presented in Chapters 3 and 4, this longitudinal follow-up study has demonstrated that bi-directional brain-gut axis interactions appear to exist in patients with IBD. Evidence for a gut-to-brain interaction is provided by the development of new-onset abnormal anxiety scores in patients with clinically active IBD, but no psychological co-morbidity at baseline. A brain-to-gut interaction is highlighted by the relationship between antecedent psychological co-morbidity and the subsequent development of objective markers of disease activity both in patients in clinical remission and, in sensitivity analysis, asymptomatic patients without evidence of biochemical IBD activity at baseline. These findings are novel, as previous studies examining the temporal relationship between psychological co-morbidity and disease activity have addressed either gut-brain, or brain-gut interactions, alone rather than describing both simultaneously, as is presented here.

This data set comprising almost 800 patients with complete clinical data at baseline, over 400 of whom provided longitudinal follow-up questionnaire data, is larger than the only other study that has sought to describe these relationships in IBD (Sexton et al., 2017). Performing Cox regression analysis allowed the determination of independent baseline predictors of subsequent new-onset psychological co-morbidity, and new-onset disease activity, after adjusting for other variables, including total duration of follow-up in all patients. The definition of normal and abnormal anxiety and depression scores at baseline and follow-up used in this study is a further strength. Here, only the association between definitely abnormal HADS anxiety and depression scores

at baseline with longitudinal disease activity was assessed, rather than including those with borderline scores at baseline. Similarly, only patients with definitely normal HADS scores at baseline who subsequently developed definitely abnormal scores *de novo* in longitudinal follow-up were classified as developing the psychological endpoints of interest. Excluding patients with borderline abnormal HADS scores from these definitions ensured that the most conservative estimate of the bi-directional relationship between disease activity and psychological co-morbidity over time was reported. Additionally, sensitivity analyses, assessing the association between impaired mood and longitudinal disease outcomes in patients in clinical remission with no biochemical evidence of IBD activity at baseline, meant that the potential confounding effect of occult inflammation was controlled for.

Limitations of this study include the inability to collect FC data on all patients included in the initial cross-sectional survey. This meant that, although a sensitivity analysis incorporating baseline inflammatory activity was performed, the principle gut-to-brain findings were based on clinical indices, rather than objectively quantified inflammatory activity at baseline. As a result, these analyses were performed in smaller numbers of patients. This meant that for longitudinal outcomes, including abnormal depression scores, hospitalisation, and intestinal resection, there were too few cases with the outcome of interest to perform Cox regression, despite some of these outcomes trending towards significance in univariate analysis. In keeping with this theme, although longitudinal disease activity endpoints were collected on the basis of objectively defined criteria, there is the possibility that some of these endpoints, such as escalation of therapy, were reached based on symptoms, rather than true inflammatory activity. However, in this UK-based study population, where decisions to escalate to biologic therapy are made solely on definite evidence of inflammatory activity, in line

with National Institute for Health and Care Excellence guidelines (NICE, 2010; NICE, 2015a), the impact of this potential confounding factor is likely to be limited. The lack of serial FC measurement may also be perceived as a weakness, but this was compensated for by using objective clinical markers of the natural history of IBD in the brain-to-gut analyses, rather than clinical disease activity indices alone. A further limitation was that longitudinal data collection was performed on only two occasions during the study period, with data analysed at a group level. Thus, given that the relationship between disease activity and psychological distress is likely to be complex, and that individualistic psychological factors other than those reported here may influence this relationship, these findings may be less robust than assumed. Supporting this, a recent within-subject study, using vector autoregressive modelling, with multiple time points for individual patients post-myocardial infarction has shown a range of different complex interactions between psyche and soma (Rosmalen et al., 2012). This kind of personalised response has yet to be delineated in IBD, but may underlie the aggregated data outcomes reported here. Finally, the use of HADS scores as a marker of anxiety or depression could be criticised as, although these are widely used, their psychometric properties have been challenged by some experts (Coyne and van Sonderen, 2012). In addition, the HADS does not collect data concerning somatic depressive symptoms, such as anhedonia, change in appetite, and irritability, which have been shown to be associated with biomarkers of inflammation (van Dooren et al., 2016), and may also explain the relatively low prevalence of abnormal depression scores observed in this study.

Several previous studies investigating the temporal relationship between disease activity and mood in IBD have used clinical indices as the sole determinant of longitudinal disease activity (Mittermaier et al., 2004; Persoons et al., 2005; Mikocka-

Walus et al., 2016; Gaines et al., 2016; Mardini et al., 2004; Lix et al., 2008; Porcelli et al., 1996). In doing so, as illustrated by the findings of Chapter 3, the authors only provide evidence of a relationship between psychological co-morbidity and subjective symptom-reporting, which does not distinguish their findings from those previously described in patients with FGIDs (Koloski et al., 2012; Koloski et al., 2016). In this study population, a baseline abnormal anxiety score was significantly associated with the development of flare or glucocorticosteroid prescription, escalation of medical therapy, and hospitalisation. However, there was no consistent association between baseline anxiety scores and subsequent development of clinical disease activity, suggesting that the longitudinal objective disease activity endpoints used in this study are likely to reflect the presence of genuine inflammatory activity, rather than subjective symptom-reporting alone. This is further supported by the fact that there was no significant association between high levels of somatoform-type behaviour and the longitudinal disease activity endpoints used.

The findings of Chapter 3 go some way to deconstructing the complex relationship between inflammatory activity, GI symptom-reporting, and psychological co-morbidity in IBD. Added to that, in Chapter 4, the identification of a well-characterised group patients with IBD with co-existent IBS-type symptoms, who suffer from anxiety and depression to the same degree as patients with overt inflammatory activity, provided the rationale for conducting the longitudinal study that is presented here. Although this study helps delineate the temporal relationship between symptom-reporting, psychological co-morbidity, and inflammatory activity by its identification of bi-directional brain-gut interactions, it fails to address the potential impact of co-existent IBS-type symptom-reporting on longitudinal disease activity outcomes, specifically. In this study, following multivariate Cox regression analysis, fulfilling the Rome III

criteria at baseline was not associated with any of the four objective outcomes used to assess longitudinal disease activity (Table 17), nor was it associated with the development of new-onset psychological co-morbidity (OR = 2.29; 95% CI 0.57-9.20). However, this study did not aim to address this issue specifically, as the methodology described in Chapter 4 that successfully identified IBS-type symptom-reporters, was not adopted. This lack in understanding of the impact of IBS-type symptom-reporting on longitudinal disease activity outcomes is important, as these symptoms affect one-in-four patients with IBD, and treatment options for these patients are not evidence-based. The study described in Chapter 6 aims to resolve these uncertainties.

To summarise the findings of this study, bi-directional brain-gut axis interactions appear to exist in patients with IBD. Patients with normal anxiety scores at baseline and clinically active disease had over five times the odds of developing abnormal anxiety scores during follow-up, when compared with patients in clinical remission. Similarly, patients with quiescent disease activity at baseline, but abnormal anxiety scores, had two-fold higher rates of flare of disease activity or need for glucocorticosteroids, and escalation of therapy. An acceptance of the existence of brain-gut axis activity in IBD, and its influence on disease course, has important implications for future management strategies. Evidence supporting the use of psychological therapies and antidepressants in IBD is poor (Macer et al., 2017; Timmer et al., 2011), and in the latter instance outdated. Thus, these findings underline the need for the development of a novel approaches towards IBD management, away from one that focuses solely on the management of inflammatory activity, to one that integrates this with the need for proactive management of psychological wellbeing.

CHAPTER 6: Describing the association between the reporting of IBS-type symptoms, and longitudinal disease activity, healthcare utilisation, psychological health, and quality of life in IBD

6.1 Introduction

As described in Chapter 4, IBS-type symptom-reporting in IBD is common, and is associated with considerable psychological co-morbidity and reduced quality of life. Until now, the majority of studies that have drawn attention to the prevalence and impact of IBS-type symptoms in patients with IBD have been cross-sectional in nature (Berrill et al., 2013; Keohane et al., 2010; Jonefjall et al., 2016; Henriksen et al., 2018). Thus, the relationship between reporting these symptoms and the longer-term natural history and prognosis of IBD patients remains uncertain.

The aim of this study was to address this issue in a longitudinal follow-up study of the patients who were recruited into the cross-sectional study described in Chapter 4. Specifically, the aims were to assess the relationship between reporting IBS-type symptoms at study entry and subsequent disease activity, healthcare utilisation, psychological well-being, and quality of life during a minimum follow-up period of 2 years. The results described in Chapter 5 have shown that, following multivariate Cox regression analysis, in patients with quiescent disease at baseline, fulfilling the Rome III criteria for IBS was not associated with adverse longitudinal disease activity outcomes. This, in conjunction with the results of RCTs that have indirectly assessed the efficacy of biological therapy for the treatment of these patients, and found it to be poor (Schreiber et al., 2005; Colombel et al., 2010; Reinisch et al., 2012) helped to inform the hypothesis for this study, which was that these symptoms are not due to occult inflammatory activity, and that there would be no association between IBS-type symptom-reporting and adverse longitudinal disease activity outcomes.

6.2 Methods

6.2.1 Participants and setting

Individuals recruited into the cross-sectional study described in Chapter 4 were included in this longitudinal follow-up study. Participants were sent a follow-up postal invitation to participate as outlined in Chapter 5. The longitudinal follow-up study was approved by the local research ethics committee in September 2014 (REC ref: 12/YH/0443), and data collection continued until June 2017. Study findings were reported in accordance with the STROBE guidelines for observational studies (von Elm et al., 2008).

6.2.2 Data collection and synthesis

Date of recruitment into the original cross-sectional survey, demographic data, type of IBD, medication use for IBD, Rome III IBS symptom data, anxiety and depression data, somatisation data, quality of life data, and FC (Immundiagnostik, Bensheim, Germany) were recorded at baseline, as described in Chapter 3.

6.2.2.1 Definition of disease activity and presence of IBS-type symptoms

This was as described in Chapter 4. Sensitivity analysis, using a FC <100µg/g stool to define quiescent disease, was again performed.

6.2.2.2 Definition of anxiety or depression

This was as described in Chapters 3, 4, and 5, and for these reasons is not reported in detail here. The presence of either anxiety or depression was assessed using

the HADS (Zigmond and Snaith, 1983), with severity categorised as previously described (Zigmond and Snaith, 1983).

6.2.2.3 Definition of somatisation severity

This was as described in Chapters 3 and 4, with somatisation data collected using the PHQ-15 (Kroenke et al., 2002), and severity categorised into high (total PHQ-15 ≥15), medium (10-14), low (5-9), and minimal (≤4) levels of somatisation severity (Kroenke et al., 2002).

6.2.2.4 Assessment of quality of life

This was as described in Chapter 4. In brief, quality of life data were collected using the SF-36 health survey (McHorney et al., 1993). Patients were asked to complete the questionnaire giving responses to each question from zero to one hundred, from which a mean score for each health domain of the SF-36 was calculated, with higher scores indicating more favourable health-related quality of life.

6.2.2.5 Longitudinal objective assessment of IBD activity

As in Chapter 5, objective assessment of disease activity during longitudinal follow-up was made by detailed case note review by a sole investigator (DJG), blinded to baseline questionnaire data. The case notes of each patient included at baseline were assessed for the following clinical endpoints, with the date of each endpoint recorded, where applicable: glucorticosteroid prescription or flare of disease activity identified by physician's global assessment, escalation of medical therapy due to uncontrolled disease activity, hospitalisation secondary to objectively confirmed IBD activity, and intestinal resection. Escalation of medical therapy in response to therapeutic drug monitoring, but

in the absence of inflammatory activity, was not included as an endpoint, nor was surgical intervention for isolated perianal CD.

6.2.2.6 Longitudinal assessment of healthcare utilisation

Case note review was undertaken to determine the number of clinical encounters during follow-up. Specifically, the number of IBD-related clinic appointments, the number of IBD helpline telephone calls made in order to obtain IBD specialist nurse advice regarding disease management, and the number of radiological and endoscopic investigations performed for assessment of disease activity were recorded. Radiological investigations included computerised tomography imaging, magnetic resonance imaging, or small bowel meal. Imaging for the assessment of isolated perianal disease in CD was not included, due to the limited utility of FC as a marker of perianal disease activity. Endoscopic investigations performed for the assessment of IBD activity including flexible sigmoidoscopy, colonoscopy, or wireless capsule endoscopy were recorded. Planned therapeutic endoscopic procedures, and those requested as part of IBD-related colorectal cancer surveillance, were not included.

6.2.2.7 Longitudinal assessment of psychological health and quality of life

Responses to the follow-up questionnaire, administered after a minimum of 2 years, were used to assess for the presence of anxiety, depression, somatisation, and to measure quality of life, using the same instruments previously described.

6.2.3 Statistical analysis

Baseline demographic, disease-related, and psychological data for all patients with IBD included at baseline was compared between patients with CD and UC. After

classification of disease activity and IBS symptom status, baseline demographic characteristics, HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatisation was compared between patients with IBD reporting IBS-type symptoms and the other three groups of patients individually (quiescent disease, occult inflammation, or active disease), using a χ^2 test for categorical variables, and an independent samples *t*-test for continuous data. Comparisons across all four groups were performed using a χ^2 test for categorical variables, and a one-way ANOVA for continuous data. Where continuous data were not normally distributed, equivalent non-parametric tests including the Mann-Whitney U test and Kruskal-Wallis analysis of variance were applied. The same comparisons were made between these groups for each of the four objective disease activity outcomes and the three measures of healthcare utilisation during longitudinal follow-up. Similarly, follow-up HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatisation at follow-up were compared between the four groups to determine the relationship between IBS-type symptom-reporting and psychological health and quality of life over time. Due to multiple comparisons in all these analyses, a 2-tailed P-value of <0.01 was considered statistically significant.

Independent predictors of the occurrence of any of the objective disease activity outcomes of interest were determined by performing multivariate Cox regression analysis to control for all baseline demographic characteristics, baseline IBD activity category, medications, and the presence or absence of baseline abnormal anxiety or depression scores, or high somatisation scores. The results were expressed as HRs with 99% CIs. Sensitivity analysis using a FC <100µg/g to define those who reported IBS-type symptoms was also performed. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

6.3 Results

6.3.1 Baseline demographic characteristics

In total, 360 (95.2%) of 378 patients included in the initial cross-sectional survey had available follow-up disease activity data after case note review. Of these, 200 (55.6%) had CD and 160 (44.4%) UC. At baseline, patients with CD were more likely to smoke, to use immunomodulator therapy and anti-TNFα drugs, but less likely to use 5-ASAs, when compared with those with UC ($P < 0.001$ for all) (Table 19). There was no difference in the proportion of patients who were defined as having IBS-type symptoms, quiescent disease, occult inflammation, or active disease, and no difference in levels of anxiety, depression, or somatisation between patients with CD and UC at baseline. Patients with CD had lower mean SF-36 quality of life scores at baseline for energy/fatigue ($P = 0.005$), pain ($P = 0.002$), and general health ($P < 0.001$) than patients with UC.

Table 19: Baseline characteristics of patients with CD and UC

	Crohn's disease (n = 200)	**Ulcerative colitis (n = 160)**	**P Value***
Mean age in years (SD)	47.3 (16.7)	51.8 (16.5)	0.01
Female gender (%)	124 (62.0)	89 (55.6)	0.22
Married or co-habiting (%)	125 (62.8)	115 (71.9)	0.07
University graduate/professional (%)	52 (26.1)	48 (30.6)	0.35
Mean BMI (SD)	26.4 (5.6)	27.2 (5.7)	0.19
Tobacco user (%)	43 (21.5)	8 (5.0)	<0.001
Alcohol user (%)	122 (61.3)	106 (66.3)	0.33
5-ASA use (%)	56 (28.0)	130 (81.3)	<0.001
Immunomodulator use (%)	91 (45.5)	36 (22.5)	<0.001
Anti-TNFα use (%)	56 (28.0)	3 (1.9)	<0.001
Glucocorticosteroid use (%)	21 (10.5)	18 (11.3)	0.82
Disease category (%)			
IBS-type symptoms	54 (27.0)	31 (19.4)	
Quiescent disease	69 (34.5)	64 (40.0)	
Occult inflammation	47 (23.5)	31 (19.4)	
Active disease	30 (15.0)	34 (21.3)	0.14
Mean HADS anxiety score (SD)	7.6 (4.7)	7.0 (4.9)	0.01
HADS anxiety categories (%)			
Normal	105 (52.5)	92 (57.5)	
Borderline abnormal	39 (19.5)	30 (18.8)	
Abnormal	56 (28.0)	38 (23.8)	0.59
Mean HADS depression score (SD)	5.2 (4.3)	4.6 (4.2)	0.19
HADS depression categories (%)			
Normal	142 (71.0)	130 (81.8)	
Borderline abnormal	33 (16.5)	10 (6.3)	
Abnormal	25 (12.5)	19 (11.9)	0.01

Mean PHQ-15 score (SD)	10.3 (4.7)	8.9 (5.1)	0.23
PHQ-15 somatisation categories (%)			
Mild	20 (10.6)	32 (20.8)	
Low	63 (33.5)	46 (29.9)	
Medium	70 (37.2)	48 (31.2)	
High	35 (18.6)	28 (18.2)	0.07
Median SF-36 quality of life score (IQR)			
Physical functioning	85.0 (51.3-95.0)	90.0 (70.0-100.0)	0.05
Role limitations physical health	50.0 (0.0-100.0)	75.0 (0.0-100.0)	0.05
Role limitations emotional problems	100.0 (33.3-100.0)	100.0 (33.3-100.0)	0.68
Energy/fatigue	40.0 (20.0-60.0)	50.0 (30.0-70.0)	0.005
Emotional well-being	68.0 (52.0-84.0)	72.0 (60.0-88.0)	0.10
Social functioning	75.0 (37.5-87.5)	75.0 (50.0-100.0)	0.05
Pain	67.5 (32.5-80.0)	67.5 (45.0-90.0)	0.002
General health	40.0 (25.0-60.0)	55.0 (40.0-75.0)	<0.001
Mean FC (SD)	482 (785)	574 (945)	0.31

*Independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for comparison of categorical data.

6.3.2 Characteristics of patients with IBD with and without IBS-type symptoms

Based on FC results, Rome III IBS-type symptom status, and clinical disease activity indices at baseline, the 360 patients with IBD included in longitudinal follow-up were divided into four groups at study entry as follows: 85 (23.6%) had IBS-type symptoms, 133 (36.9%) had quiescent disease, 78 (21.7%) had occult inflammation, and 64 (17.8%) had active disease. Assessment of baseline demographic and disease characteristics, psychological data, and quality of life data across the four groups was unchanged from that previously reported in Chapter 4. In brief, patients reporting true IBS-type symptoms were more likely to be female and to smoke than patients with quiescent disease (P = 0.002 for both), but there were no other differences. Mean baseline anxiety, depression, and somatisation scores were significantly higher, and quality of life scores significantly lower, in patients with IBS-type symptoms when compared with patients with quiescent disease or occult inflammation, but were equivalent to those observed in patients with active disease.

6.3.3 Association between reporting IBS-type symptoms at baseline and disease activity during longitudinal follow-up

During longitudinal follow-up, patients reporting IBS-type symptoms at baseline were no more likely to receive a glucocorticosteroid prescription or experience a flare of disease activity, require escalation of medical therapy in response to uncontrolled IBD activity, be hospitalised, or undergo intestinal resection than patients with quiescent disease or occult inflammation at baseline (Table 20). However, patients with active disease at baseline were more likely to receive a glucocorticosteroid prescription or experience a flare of disease activity, or require escalation of medical therapy in response to uncontrolled IBD activity, than patients reporting IBS-type symptoms at

baseline, and compared with all three of the other patient groups. There was also a non-significant trend towards patients with active disease being more likely to require hospitalisation or intestinal resection, compared with the other three groups (P = 0.01 and P = 0.02, respectively). Sensitivity analyses using a FC <100µg/g to define those who reported IBS-type symptoms as having IBD with IBS-type symptoms are provided in Table 21. The lack of any association between presence of IBS-type symptoms at baseline and subsequent disease activity remained consistent.

Table 20: Association between reporting IBS-type symptoms at baseline and objective markers of disease activity during longitudinal follow-up, after FC analysis using cut off <250µg/g

	IBD with IBS-type symptoms (n = 85)	Quiescent IBD (n = 133)	P value*	IBD with occult inflammation (n = 78)	P value*	Active IBD (n = 64)	P value*	P value†
Glucocorticosteroid prescription or flare of disease activity (%)	36 (42.4)	43 (32.3)	0.13	29 (37.2)	0.50	45 (70.3)	0.001	<0.001
Escalation of medical therapy in response to uncontrolled IBD activity (%)	32 (37.6)	42 (31.6)	0.36	27 (34.6)	0.69	44 (68.8)	<0.001	<0.001
Hospitalisation due to disease activity (%)	10 (11.8)	11 (8.3)	0.39	9 (11.5)	0.96	16 (25.0)	0.04	0.01
Intestinal resection (%)	5 (5.9)	4 (3.0)	0.30	3 (3.8)	0.55	9 (14.1)	0.09	0.02

*χ^2 for comparisons vs. IBD with IBS-type symptoms.

†χ^2 for comparison across all four groups.

Table 21: Association between reporting IBS-type symptoms at baseline and objective markers of disease activity during longitudinal follow-up, after FC analysis using cut off <100µg/g

	IBD with IBS-type symptoms (n = 54)	Quiescent IBD (n = 95)	P value*	IBD with occult inflammation (n = 122)	P value*	Active IBD (n = 89)	P value*	P value†
Glucocorticosteroid prescription or flare of disease activity (%)	23 (42.6)	28 (29.5)	0.11	45 (36.9)	0.47	57 (64.0)	0.01	<0.001
Escalation of medical therapy in response to uncontrolled IBD activity (%)	19 (35.2)	27 (28.4)	0.39	43 (35.2)	0.99	56 (62.9)	0.001	<0.001
Hospitalisation due to disease activity (%)	3 (5.6)	6 (6.3)	0.85	16 (13.1)	0.14	21 (23.6)	0.005	0.001
Intestinal resection (%)	1 (1.9)	1 (1.1)	0.68	7 (5.7)	0.25	12 (13.5)	0.02	0.002

*χ^2 for comparisons vs. IBD with IBS-type symptoms.

†χ^2 for comparison across all four groups.

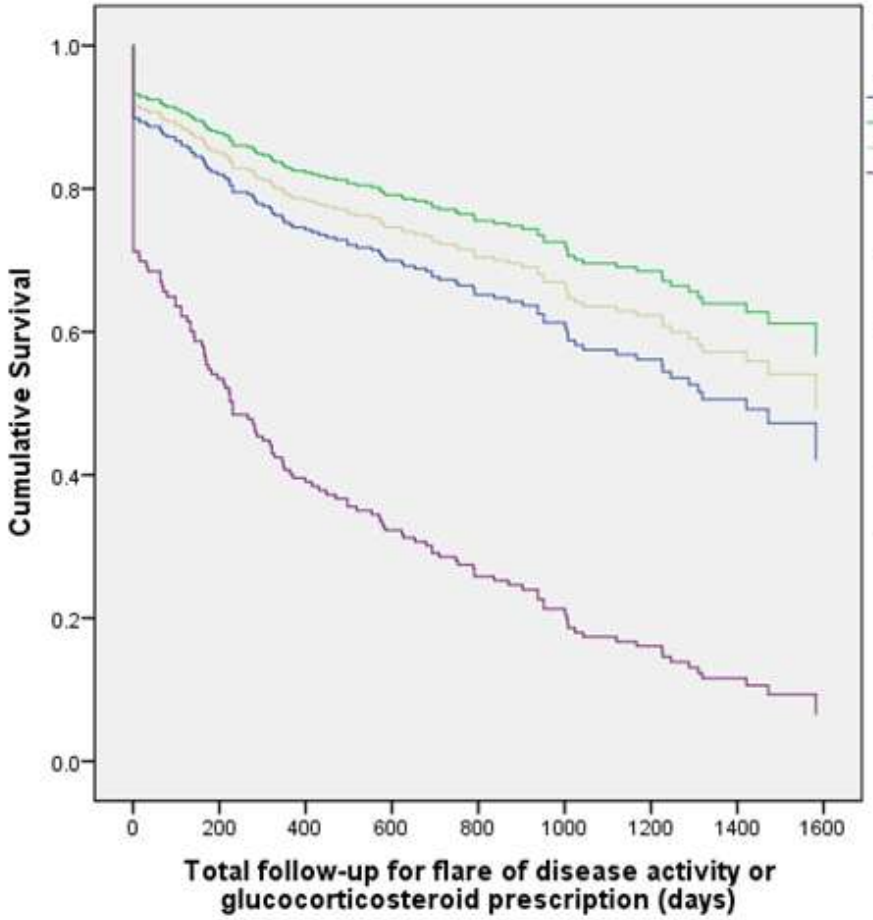
Following multivariate Cox regression analysis, during a mean length of follow-up of 754 days (SD ± 517), patients reporting IBS-type symptoms had a similar likelihood of requiring a glucocorticosteroid prescription or experiencing a flare of disease activity to those with quiescent disease (HR = 0.66; 99% CI 0.35-1.24) or occult inflammation (HR = 0.82; 99% CI 0.39-1.71) at baseline (Table 22 and Figure 7). However, this endpoint was significantly more likely in patients with active disease at baseline (HR = 3.16; 99% CI 1.65-6.07). Similarly, over a mean length of follow-up of 773 days (SD ± 505), when compared with patients reporting IBS-type symptoms at baseline, need for escalation of medical therapy in response to uncontrolled IBD activity was significantly higher in patients with active disease at baseline (HR = 3.24; 99% CI 1.70-6.20). However, the likelihood of this event was similar in patients with IBS-type symptoms and those with quiescent disease (HR = 0.80; 99% CI 0.41-1.55) or occult inflammation (HR = 0.87; 99% CI 0.39-1.91) (Table 22 and Figure 8). There were no differences in need for hospitalisation, over a mean length of follow-up of 1019 days (SD ± 430), or intestinal resection, over a mean length of follow-up of 1073 days (SD ± 1117), when patients with IBS-type symptoms were compared with those with quiescent disease, occult inflammation, or active disease at baseline (Table 22 and Figures 9 and 10, respectively). Sensitivity analyses using a FC <100µg/g revealed similar findings (Table 23).

Table 22: Baseline independent predictors of objective markers of disease activity during longitudinal follow-up

	Glucorticosteroid prescription or flare of disease activity		Escalation of medical therapy in response to uncontrolled IBD activity		Hospitalisation due to disease activity		Intestinal resection	
	Hazard ratio (99% CI)	P value	Hazard ratio (99% CI)	P value	Hazard ratio (99% CI)	P value	Hazard ratio (99% CI)	P value
Female sex	1.05 (0.64-1.72)	0.79	0.91 (0.54-1.54)	0.66	0.85 (0.34-2.08)	0.64	1.89 (0.36-9.80)	0.32
Age (per year)	0.97 (0.96-0.99)	<0.001	0.98 (0.96-0.99)	<0.001	0.98 (0.95-1.01)	0.07	0.99 (0.94-1.04)	0.66
Married or co-habiting	0.92 (0.57-1.48)	0.64	1.52 (0.88-2.63)	0.05	1.32 (0.51-3.40)	0.46	0.70 (0.18-2.83)	0.52
Tobacco use	0.37 (0.15-0.94)	0.006	0.69 (0.32-1.48)	0.22	0.71 (0.18-2.86)	0.53	1.61 (0.31-8.25)	0.45
Alcohol use	1.04 (0.63-1.71)	0.83	0.95 (0.57-1.60)	0.80	0.64 (0.26-1.58)	0.20	0.30 (0.07-1.30)	0.04
University/postgraduate education	0.96 (0.57-1.59)	0.82	0.89 (0.52-1.54)	0.59	0.81 (0.28-2.35)	0.62	1.36 (0.25-7.54)	0.64
Body mass index (per unit)	1.01 (0.98-1.06)	0.35	1.03 (0.99-1.07)	0.07	1.05 (0.98-1.12)	0.10	1.02 (0.91-1.14)	0.64
Crohn's disease	0.66 (0.37-1.76)	0.06	0.69 (0.38-1.26)	0.11	1.12 (0.37-3.42)	0.79	1.09 (0.17-7.06)	0.90
5-ASA use	1.29 (0.72-2.31)	0.26	1.10 (0.60-1.99)	0.69	0.67 (0.23-2.01)	0.35	0.44 (0.07-2.58)	0.23
Immunosuppressant use	0.85 (0.51-1.41)	0.40	0.56 (0.32-0.98)	0.007	1.30 (0.52-3.23)	0.46	1.04 (0.24-4.46)	0.94
Anti-TNFα use	0.81 (0.38-1.76)	0.49	1.05 (0.49-2.24)	0.86	1.49 (0.46-4.83)	0.39	7.41 (1.41-33.9)	0.002

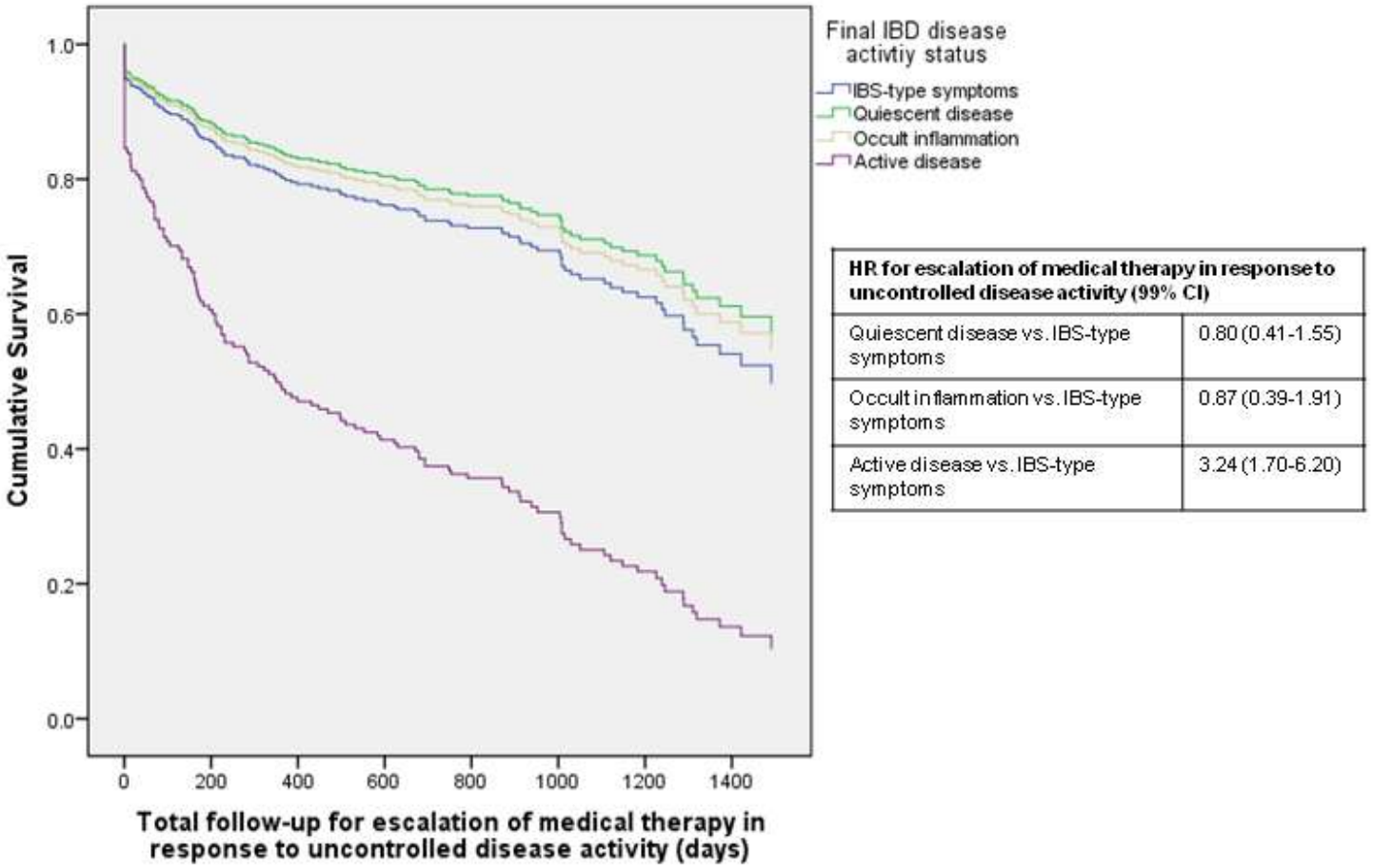
Glucorticosteroid use	2.40 (1.30-4.42)	<0.001	1.86 (0.97-3.57)	0.01	2.47 (0.89-6.87)	0.02	2.76 (0.38-20.31)	0.19
Disease category								
IBS-type symptoms	Reference	N/A	Reference	N/A	Reference	N/A	Reference	N/A
Quiescent disease	0.66 (0.35-1.24)	0.09	0.80 (0.41-1.55)	0.38	0.57 (0.17-1.97)	0.24	0.63 (0.08-4.88)	0.56
Occult inflammation	0.82 (0.39-1.71)	0.49	0.87 (0.39-1.91)	0.64	0.75 (0.19-3.05)	0.60	0.58 (0.05-6.73)	0.56
Active disease	3.16 (1.65-6.07)	<0.001	3.24 (1.70-6.20)	<0.001	2.03 (0.66-6.25)	0.11	2.82 (0.51-15.5)	0.12
Abnormal anxiety score	1.12 (0.64-1.96)	0.61	1.30 (0.73-2.31)	0.24	1.73 (0.65-4.57)	0.15	2.13 (0.45-10.1)	0.21
Abnormal depression score	1.46 (0.70-3.03)	0.19	1.60 (0.76-3.37)	0.11	1.73 (0.53-5.68)	0.24	1.19 (0.18-7.95)	0.82
High somatisation score	0.73 (0.38-1.42)	0.22	0.94 (0.48-1.84)	0.82	0.73 (0.22-2.37)	0.49	1.21 (0.21-6.96)	0.78

Figure 7: Survival plot of the association between reporting IBS-type symptoms and flare of disease activity or glucocorticosteroid prescription



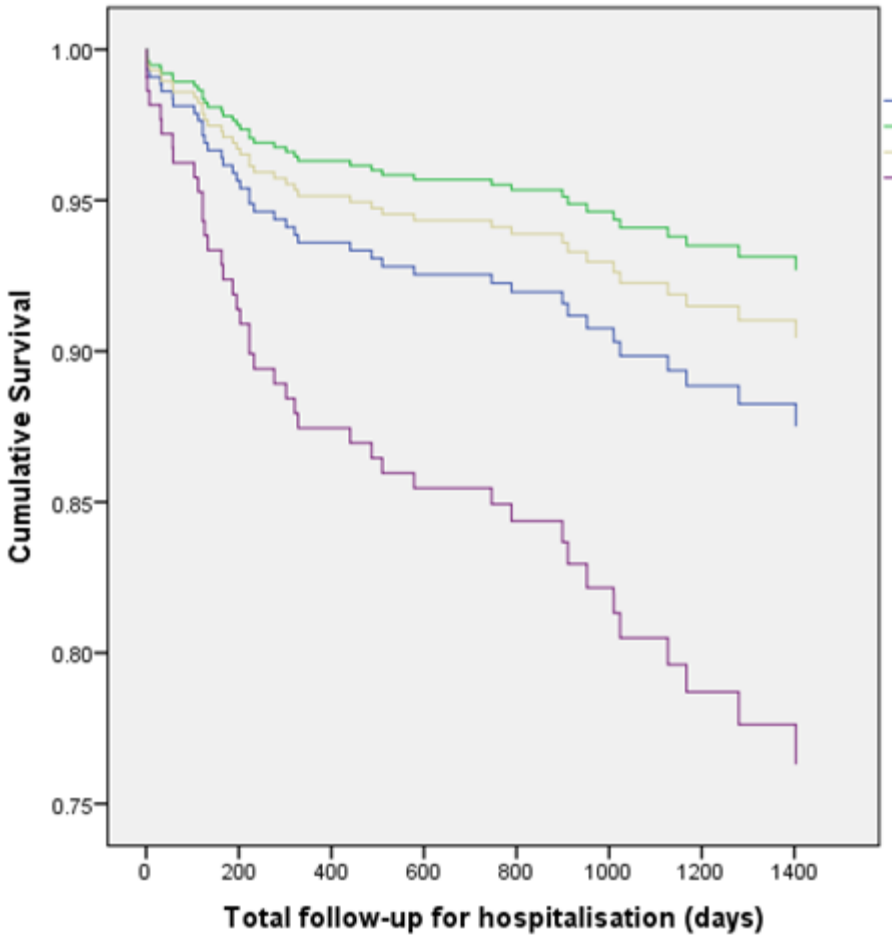
HR for flare of disease activity or glucocorticosteroid prescription (99% CI)	
Quiescent disease vs. IBS-type symptoms	0.66 (0.35-1.24)
Occult inflammation vs. IBS-type symptoms	0.82 (0.39-1.77)
Active disease vs. IBS-type symptoms	3.16 (1.65-6.07)

Figure 8: Survival plot of the association between reporting IBS-type symptoms and escalation of medical therapy in response to uncontrolled IBD



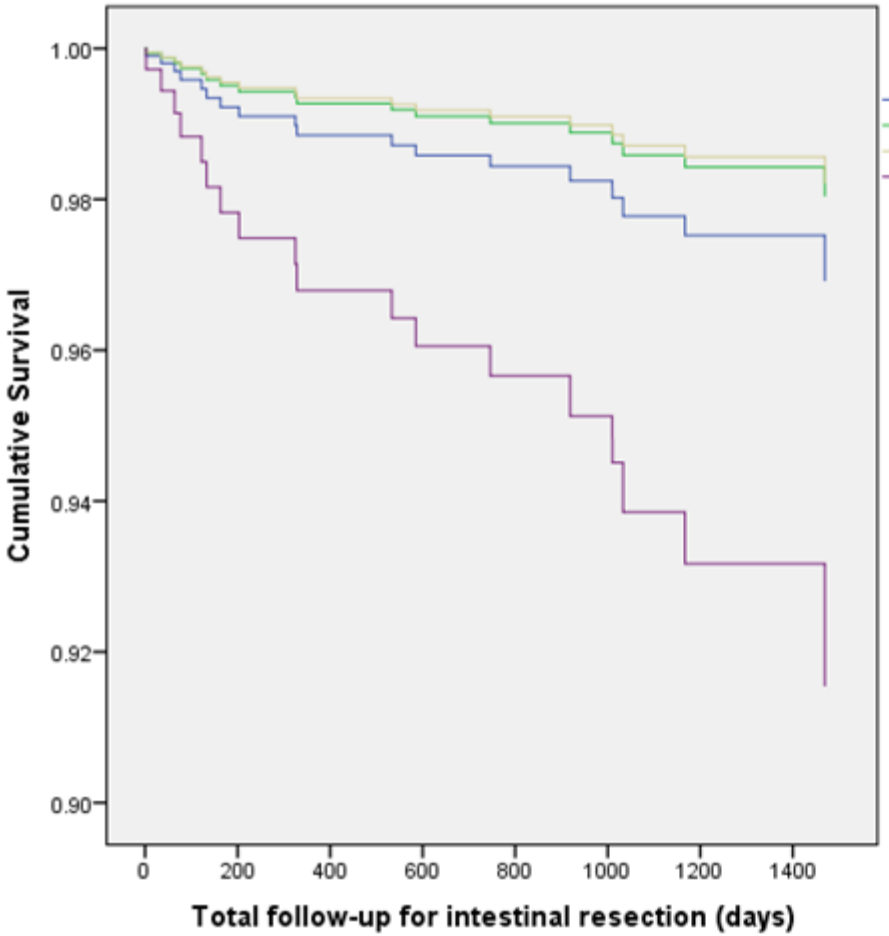
HR for escalation of medical therapy in response to uncontrolled disease activity (99% CI)	
Quiescent disease vs. IBS-type symptoms	0.80 (0.41-1.55)
Occult inflammation vs. IBS-type symptoms	0.87 (0.39-1.91)
Active disease vs. IBS-type symptoms	3.24 (1.70-6.20)

Figure 9: Survival plot of the association between reporting IBS-type symptoms and hospitalisation



HR for hospitalisation (99% CI)	
Quiescent disease vs. IBS-type symptoms	0.57 (0.17-1.97)
Occult inflammation vs. IBS-type symptoms	0.75 (0.19-3.05)
Active disease vs. IBS-type symptoms	2.03 (0.66-6.25)

Figure 10: Survival plot of the association between reporting IBS-type symptoms and intestinal resection



HR for intestinal resection (99% CI)	
Quiescent disease vs. IBS-type symptoms	0.63 (0.08-4.88)
Occult inflammation vs. IBS-type symptoms	0.58 (0.05-6.73)
Active disease vs. IBS-type symptoms	2.82 (0.51-15.5)

Table 23: Baseline IBS-type symptom status as a predictor of objective markers of disease activity during longitudinal follow-up, after FC analysis using a cut off <100µg/g

	Glucorticosteroid prescription or flare of disease activity		Escalation of medical therapy in response to uncontrolled IBD activity		Hospitalisation due to disease activity		Intestinal resection	
	Hazard ratio (99% CI)	**P value**	**Hazard ratio (99% CI)**	**P value**	**Hazard ratio (99% CI)**	**P value**	**Hazard ratio (99% CI)**	**P value**
Disease category								
IBS-type symptoms	Reference	N/A	Reference	N/A	Reference	N/A	Reference	N/A
Quiescent disease	0.61 (0.28-1.33)	0.10	0.81 (0.35-1.87)	0.51	1.06 (0.15-7.33)	0.94	Unable to estimate	0.96
Occult inflammation	0.77 (0.37-1.58)	0.34	0.88 (0.40-1.95)	0.68	1.99 (0.36-11.1)	0.30	3.40 (0.18-63.4)	0.28
Active disease	2.64 (1.30-5.36)	<0.001	3.03 (1.44-6.38)	<0.001	4.38 (0.83-23.1)	0.02	9.19 (0.51-166)	0.05

6.3.4 Association between reporting IBS-type symptoms and healthcare utilisation during longitudinal follow-up

When compared with patients reporting IBS-type symptoms at baseline during a mean length of follow-up of 1073 days (SD ± 1117), there was no difference in the median number of investigations performed or clinics attended when compared with patients with quiescent disease, occult inflammation, or active disease at baseline (Table 24). Patients reporting IBS-type symptoms made fewer IBD helpline telephone calls than patients with active disease (P = 0.007; Table 24), but no difference was observed when IBS-type symptom reporters were compared with patients with quiescent disease or occult inflammation. When the same comparisons were made across all four groups, an overall difference in the number of investigations performed (P = 0.004; Table 24), clinic attendances (P = 0.002; Table 24), and helpline calls made (P <0.001; Table 24) was observed, which may have been related to increased healthcare utilisation in patients with active disease.

Table 24: Association between reporting IBS-type symptoms and healthcare utilisation during longitudinal follow-up

	IBD with IBS-type symptoms (n = 85)	Quiescent IBD (n = 133)	P value*	IBD with occult inflammation (n = 78)	P value*	Active IBD (n = 64)	P value*	P value†
Median number of investigations (IQR)	1.0 (0.0-2.0)	1.0 (0.0-1.0)	0.04	1.0 (0.0-1.3)	0.21	1.0 (1.0-2.0)	0.24	0.004
Median number of clinic appointments (IQR)	6.0 (3.5-10.0)	5.0 (3.0-7.5)	0.06	6.0 (3.0-8.0)	0.16	7.5 (5.0-11.0)	0.12	0.002
Median number of helpline calls (IQR)	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.30	0.0 (0.0-2.0)	0.51	1.0 (0.0-3.0)	0.007	<0.001

*Mann-Whitney U test for comparisons vs. IBD with IBS-type symptoms.

†Kruskal-Wallis analysis of variance for comparison across all four groups.

6.3.5 Association between reporting IBS-type symptoms and psychological health and quality of life during longitudinal follow-up

228 (63.3%) of 360 patients returned a follow-up questionnaire and therefore provided anxiety, depression, somatisation, and quality of life data after a minimum follow-up period of 2 years. There were no significant differences in baseline characteristics between patients with IBD who did, and did not, return a follow-up questionnaire (Table 25). During longitudinal follow-up (mean duration 928 days (SD ± 198)), patients reporting IBS-type symptoms at baseline had significantly higher mean anxiety, depression, and somatisation scores when compared with patients with quiescent disease at baseline (Table 26). These were also generally higher than among patients with occult inflammation at baseline, although not statistically significant, but were similar to those in patients with active disease at baseline.

Follow-up quality of life scores across all eight domains of the SF-36 were impaired among those reporting IBS-type symptoms at baseline, compared with those with either quiescent disease or occult inflammation, and in several instances these differences were statistically significant. The degree of impairment of quality of life during longitudinal follow-up was similar among patients reporting IBS-type symptoms and those with active disease at baseline.

Table 25: Baseline characteristics of patients with and without follow-up questionnaire data

	No follow-up questionnaire returned (n = 132)	**Follow-up questionnaire returned (n = 228)**	**P value***
Mean age in years (SD)	47.0 (17.7)	50.7 (16.0)	0.04
Female gender (%)	71 (53.8)	142 (62.3)	0.11
Married or co-habiting (%)	84 (63.6)	156 (68.7)	0.32
University graduate/professional (%)	34 (26.0)	66 (29.3)	0.49
Mean BMI (SD)	26.6 (5.0)	26.8 (6.0)	0.83
Tobacco user (%)	16 (12.1)	35 (15.4)	0.39
Alcohol user (%)	79 (59.8)	149 (65.6)	0.27
Crohn's disease (%)	67 (50.8)	133 (58.3)	0.16
Disease category (%)			
IBS-type symptoms	21 (15.9)	64 (28.1)	
Quiescent disease	54 (40.9)	79 (34.6)	
Occult inflammation	28 (21.2)	50 (21.9)	
Active disease	29 (22.0)	35 (15.4)	0.04
5-ASA use (%)	69 (52.3)	117 (51.3)	0.86
Immunomodulator use (%)	43 (32.6)	84 (36.8)	0.41
Anti-TNFα use (%)	15 (11.4)	44 (19.3)	0.05
Glucocorticosteroid use (%)	17 (12.9)	22 (9.6)	0.34
Mean HADS anxiety score (SD)	7.7 (5.1)	7.2 (4.6)	0.38
HADS anxiety categories (%)			
Normal	74 (56.1)	123 (53.9)	
Borderline abnormal	23 (17.4)	46 (20.2)	
Abnormal	35 (26.5)	59 (25.9)	0.81
Mean HADS depression score (SD)	5.3 (4.4)	4.7 (4.2)	0.25

HADS depression categories (%)			
Normal	93 (70.5)	179 (78.9)	
Borderline abnormal	22 (16.7)	21 (9.3)	
Abnormal	17 (12.9)	27 (11.9)	0.10
Mean PHQ-15 score (SD)	9.8 (4.9)	9.6 (5.0)	0.69
PHQ-15 somatisation categories (%)			
Mild	22 (17.3)	30 (14.0)	
Low	32 (25.2)	77 (35.8)	
Medium	46 (36.2)	72 (33.5)	
High	27 (21.3)	36 (16.7)	0.21
Median SF-36 quality of life score (IQR)			
Physical functioning	85.0 (55.0-100.0)	90.0 (65.0-100.0)	0.84
Role limitations physical health	50.0 (0.0-100.0)	75.0 (0.0-100.0)	0.05
Role limitations emotional problems	100.0 (0.0-100.0)	100.0 (33.3-100.0)	0.05
Energy/fatigue	42.5 (25.0-65.0)	45.0 (27.5-65.0)	0.57
Emotional well-being	68.0 (52.0-84.0)	72.0 (56.0-84.0)	0.56
Social functioning	62.5 (50.0-100.0)	75.0 (50.0-100.0)	0.23
Pain	67.5 (45.0-90.0)	67.5 (45.0-90.0)	0.56
General health	45.0 (30.0-70.0)	50.0 (30.0-70.0)	0.81
Mean FC (SD)	544 (893)	510 (841)	0.73

*Independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for comparison of categorical data.

Table 26: Association between reporting IBS-type symptoms and psychological health and quality of life during longitudinal follow-up

	IBD with IBS-type symptoms (n = 64)	Quiescent IBD (n = 79)	P value*	IBD with occult inflammation (n = 50)	P value*	Active IBD (n = 35)	P value*	P value†
Mean HADS anxiety score (SD)	9.2 (4.8)	6.4 (5.1)	0.001	7.4 (5.0)	0.05	7.7 (4.2)	0.13	0.008
HADS anxiety categories (%)								
Normal	23 (35.9)	49 (62.8)		27 (54.0)		18 (51.4)		
Borderline abnormal	12 (18.8)	11 (14.1)		12 (24.0)		9 (25.7)		
Abnormal	29 (45.3)	18 (23.1)	0.005	11 (22.0)	0.03	8 (22.9)	0.09	0.02
Mean HADS depression score (SD)	6.8 (4.9)	4.2 (4.0)	0.001	4.8 (4.1)	0.02	6.2 (4.7)	0.57	0.003
HADS depression categories (%)								
Normal	38 (59.4)	61 (78.2)		37 (74.0)		21 (60.0)		
Borderline abnormal	14 (21.9)	11 (14.1)		7 (14.0)		7 (20.0)		
Abnormal	12 (18.8)	6 (7.7)	0.04	6 (12.0)	0.26	7 (20.0)	0.97	0.20
Mean PHQ-15 score (SD)	12.4 (5.2)	8.0 (5.4)	<0.001	9.8 (6.3)	0.02	10.8 (4.7)	0.14	<0.001

PHQ-15 somatisation categories (%)								
Mild	4 (6.5)	21 (28.4)		10 (20.0)		2 (6.3)		
Low	14 (22.6)	28 (37.8)		14 (28.0)		11 (34.4)		
Medium	26 (41.9)	16 (21.6)		17 (34.0)		11 (34.4)		
High	18 (29.0)	9 (12.2)	<0.001	9 (18.0)	0.10	8 (25.0)	0.67	0.003
Median SF-36 score (IQR)								
Physical functioning	75.0 (50.0-90.0)	90.0 (70.0-100.0)	<0.001	85.0 (57.5-95.0)	0.16	85.0 (47.5-95.0)	0.23	0.003
Role limitations physical health	37.5 (0.0-81.3)	100.0 (50.0-100.0)	<0.001	75.0 (0.0-100.0)	0.26	75.0 (0.0-100.0)	0.11	<0.001
Role limitations emotional problems	100.0 (0.0-100.0)	100.0 (66.7-100.0)	0.04	100.0 (33.3-100.0)	0.57	100.0 (33.3-100.0)	0.51	0.22
Energy/fatigue	35.0 (20.0-50.0)	55.0 (30.0-73.8)	<0.001	40.0 (25.0-65.0)	0.16	35.0 (11.3-55.0)	1.00	0.001
Emotional well-being	58.0 (48.0-72.0)	72.0 (57.0-92.0)	<0.001	76.0 (58.0-84.0)	0.007	64.0 (56.0-84.0)	0.05	0.001
Social functioning	62.5 (37.5-87.5)	87.5 (50.0-100.0)	<0.001	75.0 (50.0-100.0)	0.02	75.0 (37.5-93.8)	0.32	0.003
Pain	61.3 (32.5-67.5)	77.5 (56.9-90.0)	0.001	68.8 (55.6-87.5)	0.01	67.5 (42.5-80.0)	0.42	0.005
General health	30.0 (20.0-50.0)	50.0 (35.0-73.8)	<0.001	50.0 (30.0-65.0)	0.01	32.5 (23.8-55.0)	0.60	<0.001

*Independent samples *t*-test for normally distributed continuous data, Mann-Whitney U test for non-parametric data, and χ^2 for comparison of categorical data vs. IBD with IBS-type symptoms.

†One way ANOVA for normally distributed continuous data, Kruskal-Wallis analysis of variance for non-parametric data, and χ^2 for comparison of categorical data across all four groups.

6.4 Discussion

This longitudinal follow-up study has demonstrated that the reporting of IBS-type symptoms in patients with objectively confirmed quiescent IBD is not associated with adverse disease activity outcomes, but is associated with a long-term to impairment of mood and quality of life. Although the reporting of these symptoms does not appear to affect longitudinal disease activity, suggesting that they are not related to occult inflammation, their association with impaired psychological well-being and quality of life highlights the importance of these findings.

The association between the reporting of IBS-type symptoms and psychological co-morbidity and reduced quality of life has been described in previous studies, (Berrill et al., 2013; Jonefjall et al., 2016; Keohane et al., 2010) as well as in Chapter 4, but no study, to date, has attempted to address the impact of these symptoms on longitudinal outcomes in IBD. Specifically, this is the first study to examine the relationship between IBS-type symptom-reporting and subsequent IBD activity, using objective endpoints, and to provide data on healthcare utilisation in these patients, as well as the durability of the association between the reporting of these symptoms and psychological co-morbidity and poor quality of life over time.

Strengths of this study, including its large sample size, the generalisability of its findings, the use of validated questionnaires, and the use of Cox regression analysis to identify independent predictors of longitudinal disease activity, are in keeping with those reported in previous chapters. The stratification of patients into those with IBS-type symptoms, quiescent disease, occult inflammation, and active disease is a further strength as it permitted independent assessment of the longitudinal association between baseline inflammatory activity and GI symptom-reporting, and objective measures of disease activity, healthcare use, psychological well-being, and quality of life over time.

Finally, objective longitudinal disease activity assessment data were collected blinded to baseline disease activity and psychological data, therefore eliminating researcher confirmation bias.

Limitations of this study include the sample size and length of follow-up. Following Cox regression analysis, there was no statistically significant difference in the need for hospitalisation or intestinal resection when patients reporting IBS-type symptoms were compared with those with active disease at baseline. Despite this, in univariate analysis, the absolute proportion of patients fulfilling these endpoints was higher in those defined as having active disease at baseline. This is likely to be secondary to the relatively low event rate for these variables and, if the sample size had been larger, or follow-up continued for a longer period of time, these comparisons may have become statistically significant. The contentious nature of a FC cut off of ≥250μg/g used in these analyses has been addressed in previous chapters. For this reason, sensitivity analysis was performed using a threshold of ≥100μg/g to define mucosal inflammation, and the findings remained consistent.

The assessment of quality of life and psychological well-being in longitudinal follow-up was based on questionnaire responses at a single point in time after a minimum of 2 years. Because of this, no comment on the consistency of the association between baseline IBS-type symptom-reporting and psychological well-being and poor quality of life over multiple points of follow-up can be made. However, in sensitivity analysis, patients reporting IBS-type symptoms who had abnormal anxiety scores at baseline were more likely to continue to report abnormal anxiety scores at longitudinal follow-up than those who did not (16 (64.0%) of 25 vs. 13 (33.3%) of 39; P = 0.02). Similar findings were also true for those with IBS-type symptoms and abnormal baseline depression scores (9 (69.2%) of 13 vs. 3 (5.9%) of 51; P <0.001), and high

baseline somatisation scores (12 (54.5%) of 22 vs. 5 (13.5%) of 37; P = 0.001). This suggests that, in susceptible individuals, the association between IBS-type symptoms and psychological co-morbidity is likely to be durable. Finally, due to the low event rate for some of the longitudinal disease activity outcomes, and the attrition rate associated with administering postal follow-up questionnaires for longitudinal psychological and quality of life, data on patients with IBD dichotomised into those with UC and CD were not presented.

Only one other study has attempted to address the longitudinal impact of IBS-type symptom-reporting in IBD (Jonefjall et al., 2013). This study reported data from an inception cohort of 94 patients with UC followed up annually over a 3-year period. In keeping with the findings from this study, the authors describe an association between IBS-type symptom-reporting in patients with objectively confirmed quiescent disease, and poor psychological well-being and quality of life over time. However, the impact of IBS-type symptom-reporting on longitudinal disease activity, or healthcare utilisation, was not addressed. In addition, the study population was relatively small, and excluded patients with CD. A relationship between IBS-type symptom-reporting and healthcare utilisation has been described in another study (Abdalla et al., 2017), but this was cross-sectional in design, relied on patient recall of healthcare interactions over the preceding year, rather than accurate prospective data collection, and did not examine effects on investigation requesting.

The aetiology of IBS-type symptom-reporting in patients with IBD remains uncertain. The role of subclinical mucosal inflammation is debated, with some authors suggesting it is likely to be central to the development of these symptoms (Vivinus-Nebot et al., 2014; Keohane et al., 2010), although the findings reported in Chapter 4 and those of other investigators refute this (Jonefjall et al., 2013; Berrill et al., 2013;

Henriksen et al., 2018). Increased colonic mucosal pro-inflammatory cell infiltrates, and increased mucosal TNFα mRNA protein expression have been described in patients reporting IBS-type symptoms (Vivinus-Nebot et al., 2014). In keeping with this, raised serum levels of pro-inflammatory cytokines, including IL-1β, IL-6, IL-13, IL-10, and IL-8 have also been observed in patients reporting IBS-type symptoms (Jonefjall et al., 2016). Despite this, in the same study, there was no difference in median FC levels between patients who did, and who did not, report IBS-type symptoms, although again an association between IBS-type symptom-reporting and psychological co-morbidity was observed.

Studies identifying antecedent gastroenteritis as a risk factor for the subsequent development of IBS in non-IBD populations have led to the suggestion that post-inflammatory dysmotility and visceral hypersensitivity may contribute to the development of chronic GI symptoms (Thabane et al., 2007). Whether this concept is transferrable to the IBD population is unclear, particularly as the extent and severity of inflammation at the time of first presentation does not appear to be associated with the subsequent development of IBS-type symptoms following mucosal healing in IBD (Jonefjall et al., 2015). These findings, in conjunction with the lack of association between objective longitudinal disease activity outcomes and IBS-type symptom-reporting described here, cast further doubt on the role of subclinical inflammation in the aetiology of these symptoms.

The description of a distinct subgroup of patients with occult GI inflammation who have objective evidence of inflammatory activity, but who do not report GI symptoms, further supports this. When compared with patients with occult inflammatory activity, the greater consistency with which psychological co-morbidity was associated with IBS-type symptom-reporting suggests that brain-gut axis activation,

rather than the presence of subclinical mucosal inflammation, could be central to the development of these symptoms. However, this hypothesis remains speculative, particularly as, despite the high prevalence of psychological co-morbidity associated with the reporting of these symptoms, and the potential existence of bi-directional brain-gut interactions in IBD described in Chapter 5, no association between adverse longitudinal disease activity outcomes was observed in patients reporting IBS-type symptoms in this study. Reasons for this could include the fact that, although the prevalence of abnormal HADS anxiety (35 (43.8%) of 85) and depression scores (16 (18.9%) of 85) in patients reporting IBS-type symptoms at baseline was high, 47 (55.3%) of 85 patients reporting IBS-type symptoms had neither abnormal HADS anxiety nor abnormal HADS depression scores at baseline. This suggests that implicating abnormal brain-gut interactions as the sole factor responsible for their development may be too simplistic.

The findings of this study highlight a distinct group of patients with occult inflammation who display evidence of ongoing mucosal inflammation, yet do not report symptoms consistent with active disease. A surprising finding was that, in these cases, no deleterious effect on longitudinal disease activity was observed. The reason for this is uncertain, and is in conflict with previously published data (D'Inca et al., 2008; Naismith et al., 2014; Turvill, 2014). However, these studies used different levels of FC to define occult inflammation at baseline than that described here, and failed to exclude patients reporting IBS-type symptoms from their analyses, which may have confounded longitudinal disease activity assessment made on the basis of patient reported symptoms.

This study provides data on an emerging cohort of patients with IBD with distinct needs. The lack of association between IBS-type symptom-reporting and

objective longitudinal disease activity outcomes may explain the limited efficacy of traditional pharmacological therapies in these patients (Colombel et al., 2010; Schreiber et al., 2005; Reinisch et al., 2012). Evidence-based management strategies for the treatment of IBS exist (Ford et al., 2014c; Ford et al., 2014b; Ford et al., 2009b; Ford et al., 2008), but are of unproven benefit in IBD. Trials of alternative therapies, including psychological therapies (Timmer et al., 2011), probiotics (Derwa et al., 2017), and antidepressants (Mikocka-Walus et al., 2017; Macer et al., 2017) have been conducted in patients with IBD but the results have been disappointing, and as will be described in Chapter 7, few have addressed the treatment of IBS-type symptoms in IBD specifically. In the UK, there has been a recent call from the Health Technology Assessment Programme of the National Institute for Health Research for a trial of therapies for ongoing diarrhoea and abdominal pain in patients with stable UC, which may help to address this deficit in current knowledge.

This work highlights the existence of a distinct group of patients with IBD who report IBS-type symptoms in the absence of inflammatory activity, and that reporting these symptoms is associated with long-term psychological co-morbidity and poor quality of life, but not adverse inflammatory disease activity outcomes. The consistent association between psychological co-morbidity and IBS-type symptom-reporting over time, and the lack of any equivalent relationship with mucosal inflammation, suggests that activation of the brain-gut axis, rather than subclinical inflammatory activity, could be contributory to the development of these symptoms. Future trials of therapies targeting disordered brain-gut axis activity in this specific group of patients with IBD may therefore be helpful.

CHAPTER 7: Summarising the effect of psychological therapies on disease activity, psychological co-morbidity, and quality of life in IBD

7.1 Introduction

As illustrated in Chapter 4, psychological co-morbidity in IBD is associated with both symptom-reporting and inflammatory activity. The results described in Chapter 5 highlight the potential role of bi-directional brain-gut interactions in the aetiology of disease activity in IBD. These brain-gut interactions have been studied in other chronic GI disorders, including IBS, where the relationship between GI symptom-reporting and psychological co-morbidity is well-established (Fond et al., 2014), and where the direction of effect may also be bi-directional (Koloski et al., 2012; Koloski et al., 2016).

RCTs of psychological therapies, such as CBT or hypnotherapy, have been conducted in IBS and meta-analyses of these studies have demonstrated that they are effective treatments (Ford et al., 2009b; Ford et al., 2014b). However, whether these therapies are also effective in IBD is unclear. A systematic review and meta-analysis published in 2011 suggested that these interventions were possibly of benefit in adolescents with IBD, but not adults (Timmer et al., 2011). However, the authors included quasi-randomised and non-randomised studies in their analysis, and there have been numerous additional studies published in the intervening years (McCombie et al., 2016; Mikocka-Walus et al., 2015; Keefer et al., 2012; Schoultz et al., 2015; Jedel et al., 2014; Keefer et al., 2013; Berrill et al., 2014; Boye et al., 2011; Mizrahi et al., 2012; Vogelaar et al., 2011; Vogelaar et al., 2014). Therefore an updated systematic review and meta-analysis examining the efficacy of psychological therapies in IBD, with particular emphasis on their effects on disease activity indices, psychological wellbeing, including anxiety, depression, and perceived stress, and quality of life was conducted.

7.2 Methods

7.2.1 Search strategy and study selection

A literature search of MEDLINE, EMBASE, EMBASE Classic, PsychINFO, and the Cochrane central register of controlled trials (from 1947 to September 2016) was carried out to identify studies investigating the effects of psychological therapies in IBD. Eligible studies had to include patients (≥16 years of age) with an endoscopic, histological, or radiologically confirmed diagnosis of IBD, and report 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, which were defined *a priori*, are summarised in Table 27.

Table 27: Eligibility criteria for study inclusion

- 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, psychological co-morbidity*, or quality of life.

***** Eligible studies could assess psychological co-morbidity via measurement of anxiety (including state and trait anxiety), depression, or perceived stress.

The literature search was performed using the terms: *cognitive therapy*, *psychotherapy*, *behaviour therapy*, *relaxation techniques*, *mindfulness*, *meditation*, or *hypnosis* (both as medical subject headings and free text terms), and the following free text terms: *behavioural therapy*, *relaxation therapy*, *mindfulness meditation*, or *hypnotherapy*. These terms were combined using the Boolean set operator AND with studies identified using the terms: *Crohn disease*, *inflammatory bowel disease*, *colitis*, *ileitis*, or *ulcerative colitis* (both as medical subject headings and free text terms), and *Crohn$ disease* or *regional enteritis* (as free text terms). There were no language restrictions applied to the search and any foreign articles were translated. All titles and abstracts identified by the search were assessed for inclusion, and a recursive search of the bibliographies of selected articles was carried out. Two investigators judged eligibility on the selected articles independently, using pre-designed eligibility forms, and a third investigator resolved any disagreements.

7.2.2 Outcome assessment

Dichotomous outcomes assessed were the efficacy of psychological therapies versus control in terms of failure to achieve remission in active IBD, or to prevent relapse of disease activity in quiescent IBD. Data were extracted for these endpoints at the final point of trial follow-up, in order to maximise the number of events in the analysis. Continuous outcomes assessed included the efficacy of psychological therapies versus control, in terms of effect on clinical disease activity indices, anxiety scores, depression scores, perceived 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 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, data were extracted for these endpoints both at 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, the original investigators were contacted in order to obtain supplementary dichotomous or continuous data. This was obtained in six of these trials (Vogelaar et al., 2011; Vogelaar et al., 2014; Berrill et al., 2014; McCombie et al., 2016; Keefer et al., 2012; Keefer et al., 2013).

7.2.3 Data extraction

Data extraction was carried out by two investigators independently, 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 scores, mean psychological wellbeing scores, or mean quality of life scores, and SD. As most RCTs recruited patients with IBD, rather than only patients with CD, or only patients with UC, studies were pooled to examine the effect of psychological therapies in IBD overall, rather than according to disease type individually. For dichotomous outcomes, data were extracted as an intention-to-treat analysis, wherever trial reporting allowed this, with all drop-outs assumed to be treatment failures (i.e. failed to achieve remission in active IBD trials, or disease activity relapsed in quiescent IBD trials). However, due to high drop-out rates in some trials, a sensitivity analysis was performed using a per protocol analysis. For the secondary outcomes, mean scores and SD after psychological therapies or control were recorded only for those who provided complete data, in order not to overestimate the efficacy of psychological therapies in IBD.

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. Handling of the control arm in each trial was also recorded.

The evidence base for psychological interventions in the management of depression and anxiety is greatest for CBT (APS, 2010). A subgroup analysis was therefore conducted including only trials using CBT, to assess whether the effect was stronger for this treatment modality.

7.2.4 Assessment of risk of bias

This was conducted by two investigators in accordance with guidance published in the Cochrane handbook (Higgins and Green, 2011). Any disagreement was resolved by discussion. Risk of bias was assessed by recording the methods used to generate the randomisation schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, what proportion of subjects completed follow-up, whether an intention-to-treat analysis was extractable, and whether there was evidence of selective reporting of outcomes.

7.2.5 Data synthesis and statistical analysis

The degree of agreement between the two investigators, in terms of judging study eligibility, was measured using a Kappa statistic. For dichotomous outcomes the impact of psychological therapies was expressed as a RR of failure to achieve remission, with 95% CIs, with intervention versus control in trials of therapy for active IBD, or RR of relapse of disease activity in trials of therapy for quiescent IBD. Where psychological therapies appeared more effective than control in IBD, the number

needed to treat, along with 95% CIs, using the formula number needed to treat = 1/ (control event rate x (1-RR)) was calculated. For continuous data, including effect on disease activity indices, psychological wellbeing scores, and quality of life scores, the impact of psychological therapies was summarised using a standardised mean difference (SMD) and 95% CIs.

Heterogeneity between studies was assessed using the I^2 statistic with a cut off of 50% (Higgins et al., 2003), and the χ^2 test with a P value <0.10, as the threshold to define a statistically significant degree of heterogeneity. All data were pooled using a random effects model (DerSimonian and Laird, 1986), in order to give a more conservative estimate of the effect of psychological therapies on disease outcomes in IBD. Review Manager version 5.3 (RevMan for Windows 2014, the Nordic Cochrane Centre, Copenhagen, Denmark) was used to generate Forest plots of pooled RRs and SMDs with 95% CIs, as well as funnel plots. These were assessed, if there were a sufficient number (≥10) of studies included in the meta-analysis (Sterne et al., 2011), for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test (Egger et al., 1997).

7.3 Results

7.3.1 Search outcomes

The literature search identified a total of 1,824 citations of which, after title and abstract review, 46 were deemed potentially relevant and were assessed further for eligibility (Figure 11). Of these, a further 32 were excluded for various reasons leaving 14 studies eligible for data extraction (Smith et al., 2002; Langhorst et al., 2007; Jantschek et al., 1998; Boye et al., 2011; Mizrahi et al., 2012; Keefer et al., 2012; Berrill

et al., 2014; Jedel et al., 2014; Mikocka-Walus et al., 2015; McCombie et al., 2016; Schoultz et al., 2015; Keefer et al., 2013; Vogelaar et al., 2011; Vogelaar et al., 2014). Agreement between reviewers for eligibility assessment was excellent (Kappa statistic = 0.91). Detailed study characteristics are provided in Table 28, and risk of bias across all studies is reported in Table 29.

Figure 11: Flow diagram of assessment of studies identified in the systematic review and meta-analysis

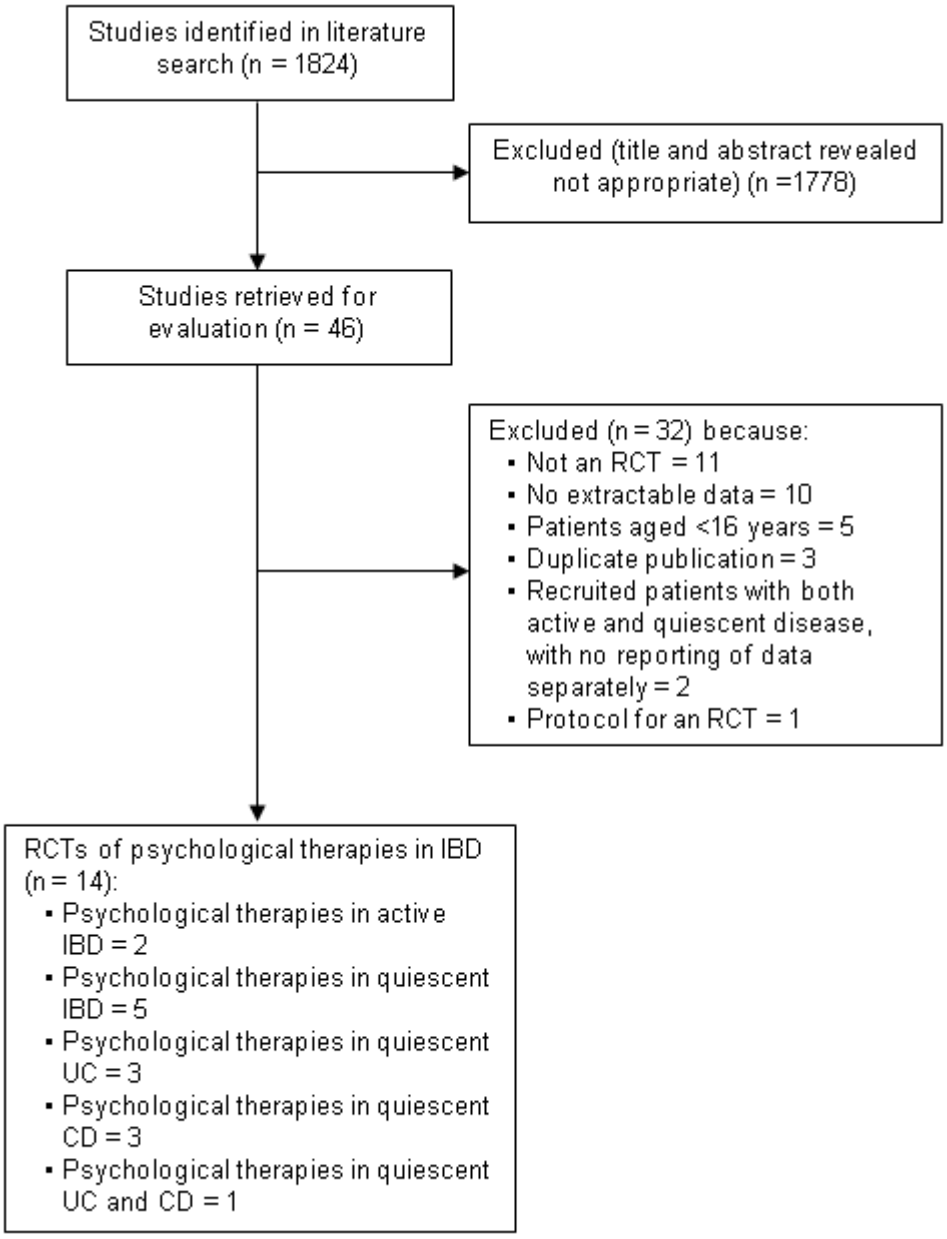


Table 28: Characteristics of included studies

Study	Participants and setting	Active intervention	Handling of the control arm	Duration of follow-up	Outcomes studied (% of patients providing complete data)
Jantschek 1998	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: CDAI, 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*	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 CDAI (100) Psychological wellbeing: HADS (100)

Langhorst 2007	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	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: HBI or Rachmilewitz clinical activity index <4 (100) Clinical disease activity indices: HBI or Rachmilewitz clinical activity index (100) Quality of life: IBD-Q (100)

Vogelaar 2011†	40 patients with CD 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: CDAI (57.5) Psychological wellbeing: HADS (57.5) Quality of life: IBD-Q (57.5)
Keefer 2012	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	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	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	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: HBI ≥5 or SCCAI ≥3 (100) Psychological wellbeing: perceived stress questionnaire (77.3) Quality of life: IBD-Q (89.4)

Jedel 2014	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	98 patients with IBD 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: CDAI or Rachmilewitz clinical activity index (91.8) Psychological wellbeing: HADS (91.8) Quality of life: IBD-Q and SF-36 (91.8)

Mikocka-Walus 2015	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: CDAI≥150 or SCCAI ≥3 (100) Clinical disease activity indices: CDAI or SCCAI (40.8) Psychological wellbeing: HADS, state-trait anxiety, and COPE questionnaire (60.9) Quality of life: SF-36 (60.9)
Schoultz 2015	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: CDAI or SCCAI (52.3) Psychological wellbeing: Beck depression inventory and state-trait anxiety (54.5) Quality of life: IBD-Q (54.5)

McCombie 2016	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: HBI or SCCAI (55.3) Psychological wellbeing: HADS and perceived stress questionnaire (58.8) Quality of life: IBD-Q and short-form-12 (58.8)

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

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

Table 29: Assessment of risk of bias of included studies

	Method of randomisation	Concealment of allocation	Level of blinding	Follow-up rate ≥90%	Intention-to-treat analysis extractable	Evidence of selective reporting of outcomes	Risk of bias
Jantschek 1998	No	Yes	Investigator	No	Yes	No	High
Smith 2002	No	No	Unblinded	Yes	Yes	No	High
Langhorst 2007	No	No	Unblinded	Yes	Yes	No	High
Boye 2011	Yes	Yes	Investigator	No	Yes	No	High
Vogelaar 2011	Yes	No	Unblinded	No	Yes	No	High
Keefer 2012	Yes	No	Unblinded	No	No	No	High
Mizrahi 2012	No	No	Unblinded	No	Yes	No	High
Keefer 2013	Yes	Yes	Investigator	Yes	Yes	No	High
Berrill 2014	Yes	No	Unblinded	No	Yes	No	High
Jedel 2014	Yes	Yes	Double	No	Yes	No	High
Vogelaar 2014	Yes	No	Investigator	Yes	Yes	No	High
Mikocka-Walus 2015	Yes	No	Unblinded	No	Yes	No	High
Schoultz 2015	Yes	No	Unblinded	No	Yes	No	High
McCombie 2016	Yes	No	Unblinded	No	Yes	No	High

7.3.2 Effect of psychological therapies on disease activity, psychological wellbeing, and quality of life in patients with active IBD

Only two of the 14 RCTs eligible for inclusion included patients with IBD with ongoing active disease (Mizrahi et al., 2012; Boye et al., 2011). Only one of these studies reported dichotomous data concerning the efficacy of psychological therapy in the induction of remission of active IBD (Boye et al., 2011). 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.

In terms of effect on other outcomes, including change in clinical disease activity indices (Boye et al., 2011), depression (Mizrahi et al., 2012), anxiety (Mizrahi et al., 2012), and perceived stress scores (Mizrahi et al., 2012), each of these were only reported in one RCT, and therefore formal meta-analysis was not possible. Psychological therapy was not associated with an improvement in any of these outcomes, when compared with control, in patients with active IBD. Both studies assessed the effect of psychological therapies on quality of life in a total of 153 patients with IBD. Here, the SMD in quality of life score at the final point of follow-up was not significantly different (0.27; 95% CI -0.05 to 0.59).

7.3.3 Effect of psychological therapies on disease activity, psychological wellbeing, and quality of life in patients with quiescent IBD

Twelve of the 14 eligible RCTs assessed these outcomes in patients with IBD who had quiescent disease at randomisation (Jantschek et al., 1998; Smith et al., 2002; Langhorst et al., 2007; Keefer et al., 2012; Keefer et al., 2013; Berrill et al., 2014; Jedel et al., 2014; Mikocka-Walus et al., 2015; Schoultz et al., 2015; McCombie et al., 2016; Vogelaar et al., 2011; Vogelaar et al., 2014). Four of these presented data in patients

with CD (Jantschek et al., 1998; Smith et al., 2002; Keefer et al., 2012; Vogelaar et al., 2011), four in patients with UC (Smith et al., 2002; Langhorst et al., 2007; Keefer et al., 2013; Jedel et al., 2014), and five in patients with IBD (Mikocka-Walus et al., 2015; McCombie et al., 2016; Schoultz et al., 2015; Berrill et al., 2014; Vogelaar et al., 2014). Results from all analyses in patients with quiescent IBD are summarised in Table 30.

Table 30: Effect of psychological therapies on disease activity, psychological wellbeing, and quality of life in patients with quiescent IBD

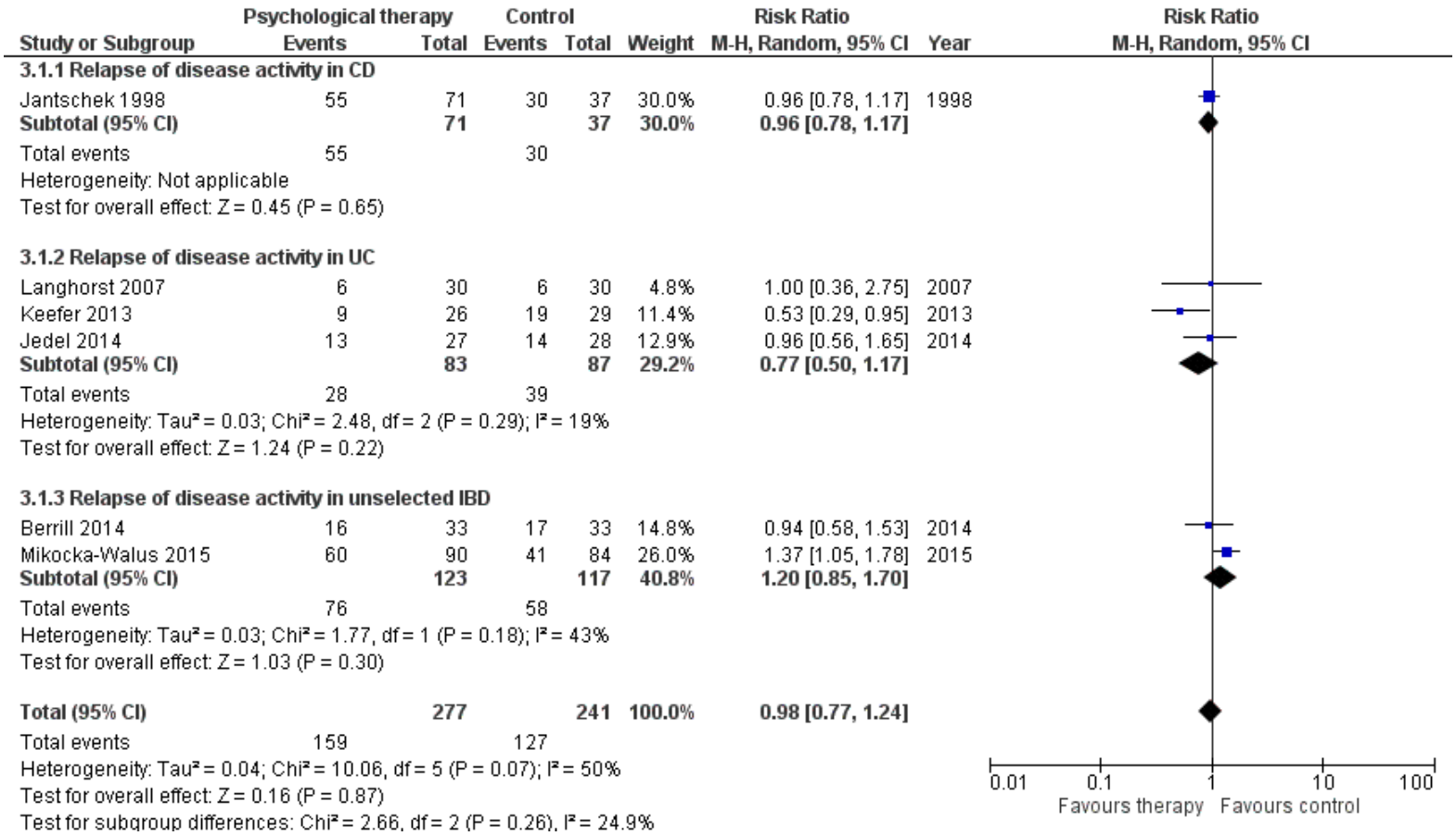
	Number of trials	Number of patients	Summary statistic for effect of psychological therapies (95% CI)	P value for the difference	I^2 (P value)
Preventing relapse of IBD (RR)	6	518	0.98 (0.77 to 1.24)	0.87	50% (0.07)
Clinical disease activity indices (SMD)	8	534	-0.03 (-0.20 to 0.14)	0.73	0% (0.87)
Anxiety scores (SMD)					
At completion of therapy	5	504	-0.14 (-0.33 to 0.04)	0.13	7% (0.37)
At final point of follow-up	5	437	-0.18 (-0.39 to 0.04)	0.10	17% (0.30)
State anxiety scores (SMD)					
At completion of therapy	3	217	-0.14 (-0.41 to 0.14)	0.33	0% (0.66)
At final point of follow-up	3	207	-0.04 (-0.32 to 0.24)	0.76	0% (0.62)
Trait anxiety scores (SMD)					
At completion of therapy	3	191	-0.16 (-0.44 to 0.13)	0.28	0% (0.80)
At final point of follow-up	3	181	0.05 (-0.25 to 0.34)	0.75	0% (0.48)
Depression scores (SMD)					
At completion of therapy	7	605	-0.17 (-0.33 to -0.01)	0.04	0% (0.76)
At final point of follow-up	8	593	-0.11 (-0.27 to 0.05)	0.17	0% (0.93)

Perceived stress scores (SMD)					
At completion of therapy	6	434	-0.07 (-0.31 to 0.18)	0.59	34% (0.18)
At final point of follow-up	6	401	-0.10 (-0.33 to 0.13)	0.40	22% (0.27)
Quality of life scores (SMD)					
At completion of therapy	9	578	0.30 (0.07 to 0.52)	0.01	42% (0.09)
At final point of follow-up	10	577	0.15 (-0.05 to 0.34)	0.14	22% (0.24)

7.3.3.1 Effect of psychological therapies in preventing relapse of quiescent IBD

In total, there were six RCTs reporting dichotomous data concerning the effect of psychological therapies on relapse rates in quiescent IBD. One study included patients with CD (Jantschek et al., 1998), three studies included patients with UC (Jedel et al., 2014; Keefer et al., 2013; Langhorst et al., 2007), and two included patients with IBD (Berrill et al., 2014; Mikocka-Walus et al., 2015). Overall, 159 (57.4%) of 277 patients treated with psychological therapy experienced a relapse of disease activity, compared with 127 (52.7%) of 241 patients in the control group. Compared with control, the RR of relapse of disease activity in all patients with IBD treated with psychological therapies was 0.98 (95% CI 0.77 to 1.24) (Figure 12). There was significant heterogeneity between studies (I^2 = 50%, P = 0.07), but too few studies to assess for publication bias. When the effect of psychological therapies on relapse of disease activity was studied according to whether trials recruited patients with CD, patients with UC, or patients with IBD there remained no effect of psychological therapies at final point of follow-up (Figure 12). Per protocol analysis did not reveal any beneficial effect of psychological therapies on disease relapse (RR = 0.86; 95% CI 0.71 to 1.05), but there was no heterogeneity between studies (I^2 = 0%, P = 0.46).

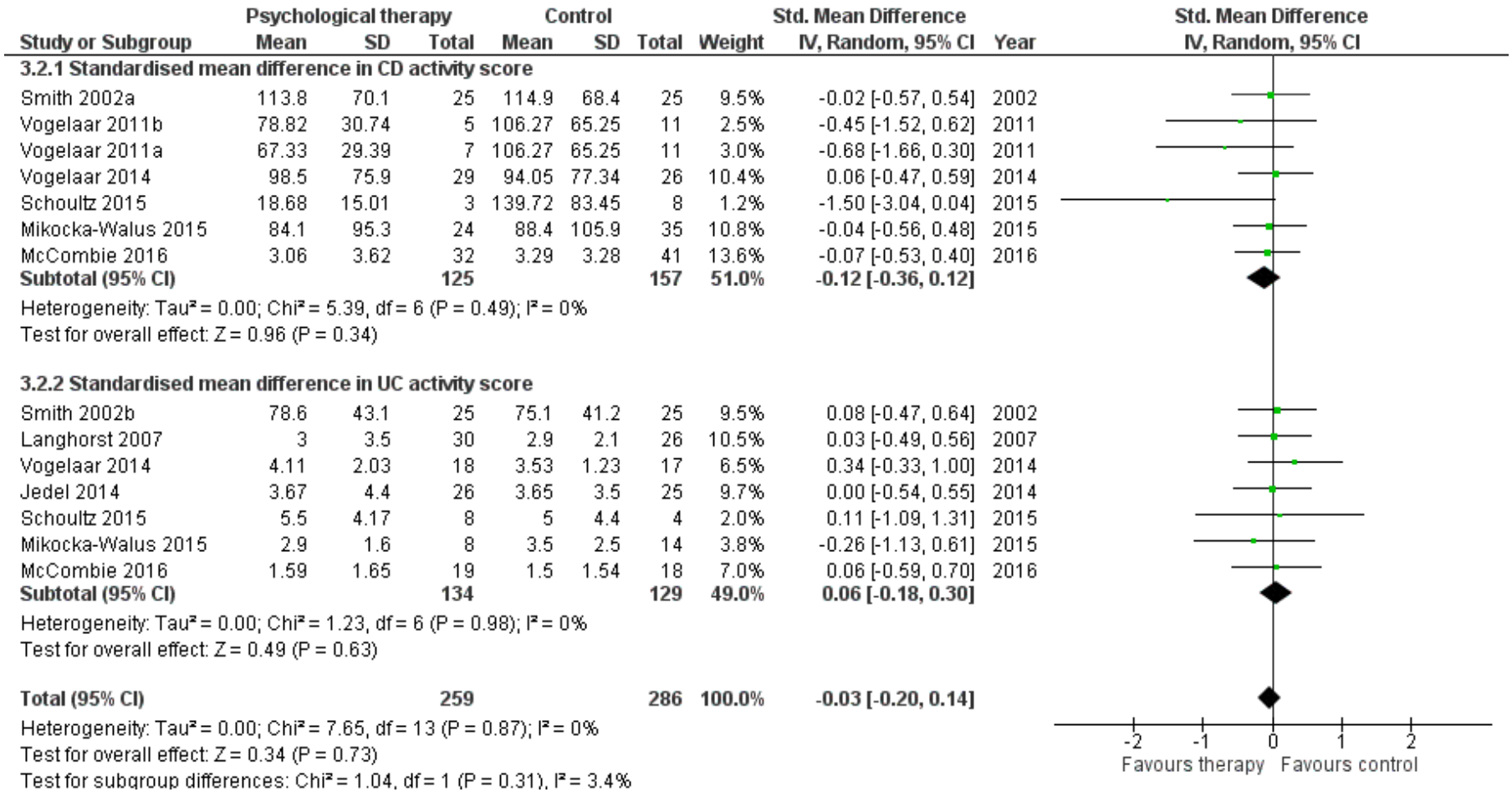
Figure 12: Forest plot of RCTs reporting the effect of psychological therapies vs. control in preventing relapse of quiescent IBD at the final point of follow-up



7.3.3.2 Effect of psychological therapies on clinical disease activity indices in IBD

Eight RCTs reported data on the effect of psychological therapies on disease activity indices in patients with IBD at the final point of follow-up. Six RCTs assessed impact on disease activity indices in CD (McCombie et al., 2016; Mikocka-Walus et al., 2015; Schoultz et al., 2015; Smith et al., 2002; Vogelaar et al., 2011; Vogelaar et al., 2014), and seven in UC (Langhorst et al., 2007; McCombie et al., 2016; Mikocka-Walus et al., 2015; Schoultz et al., 2015; Smith et al., 2002; Jedel et al., 2014; Vogelaar et al., 2014). There was no significant difference in disease activity indices among those treated with psychological therapies, compared with those in the control group, at the final point of follow-up (SMD = -0.03; 95% CI -0.20 to 0.14) (Figure 13), with no evidence of heterogeneity between studies (I^2 = 0%, P = 0.87). Again, there were too few studies to assess for publication bias. There was also no effect of psychological therapies on disease activity indices among only patients with CD, or only patients with UC (Figure 13).

Figure 13: Forest plot of RCTs reporting the effect of psychological therapies vs. control on disease activity indices in quiescent IBD at the final point of follow-up



7.3.3.3 Effect of psychological therapies on anxiety scores in IBD

Five studies provided data on the effect of psychological therapies on anxiety scores in IBD at the end of therapy (Smith et al., 2002; Langhorst et al., 2007; Vogelaar et al., 2014; Mikocka-Walus et al., 2015; McCombie et al., 2016), and five at the final point of follow-up (Mikocka-Walus et al., 2015; McCombie et al., 2016; Smith et al., 2002; Vogelaar et al., 2011; Vogelaar et al., 2014). At completion of therapy, when data were pooled from a total of 504 patients, there was no effect of psychological therapies on anxiety scores (SMD = -0.14; 95% CI -0.33 to 0.04) (Figure 14). There was no heterogeneity between the included RCTs (I^2 = 7%, P = 0.37), and too few studies to assess for publication bias. At the last point of follow-up, there was still no effect of psychological therapies on anxiety scores in 437 patients (SMD = -0.18; 95% CI = -0.39 to 0.04) (Figure 15). There was also no effect of psychological therapies on state (Jantschek et al., 1998; Schoultz et al., 2015; Mikocka-Walus et al., 2016) or trait (Jedel et al., 2014; Schoultz et al., 2015; Mikocka-Walus et al., 2016) anxiety scores in three trials at either completion of therapy, or at final point of follow-up (Figures 16-19).

Figure 14: Forest plot of RCTs reporting the effect of psychological therapies vs. control on anxiety scores in quiescent IBD at the completion of therapy

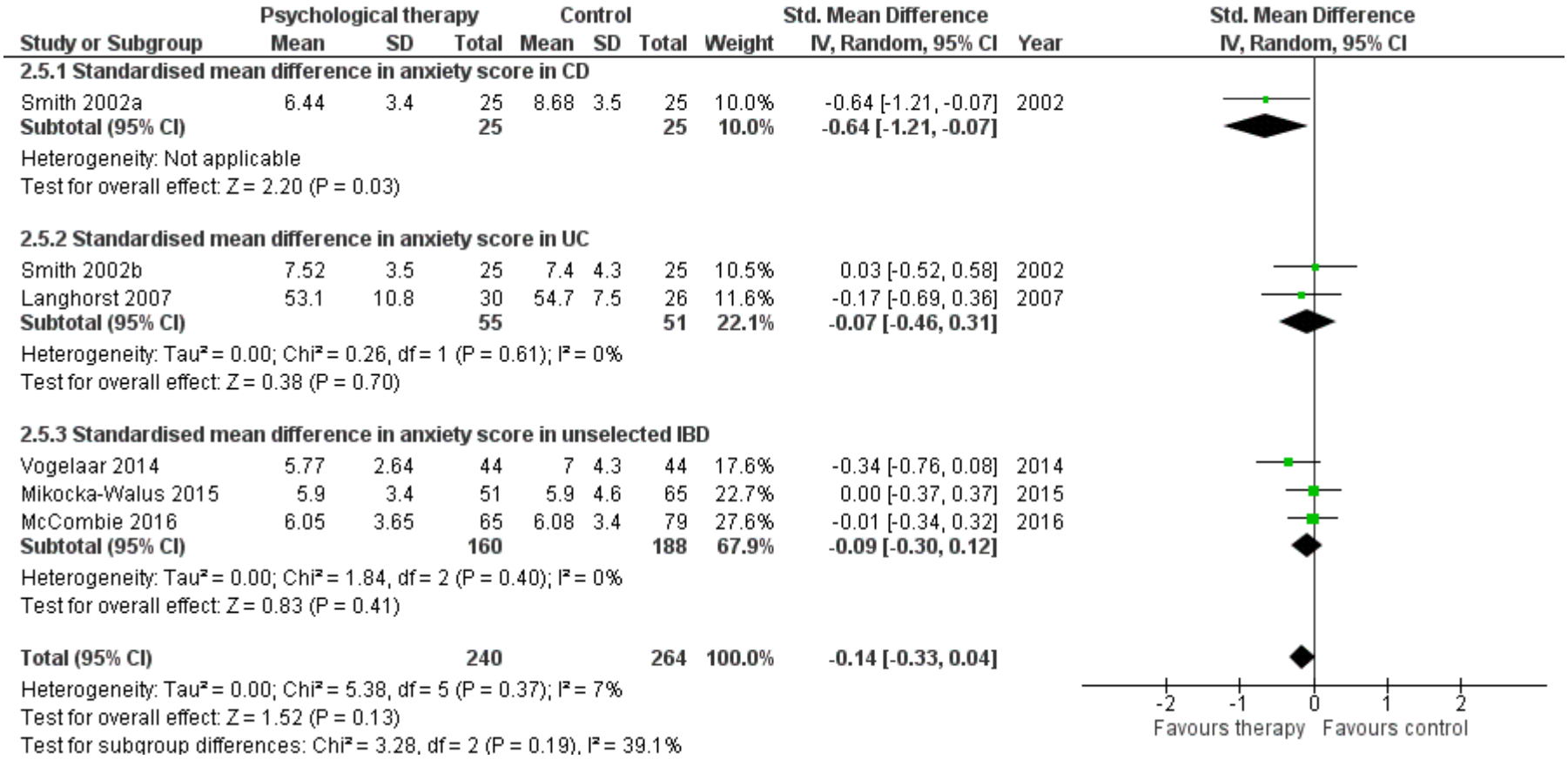


Figure 15: Forest plot of RCTs reporting the effect of psychological therapies vs. control on anxiety scores in quiescent IBD at the final point of follow-up

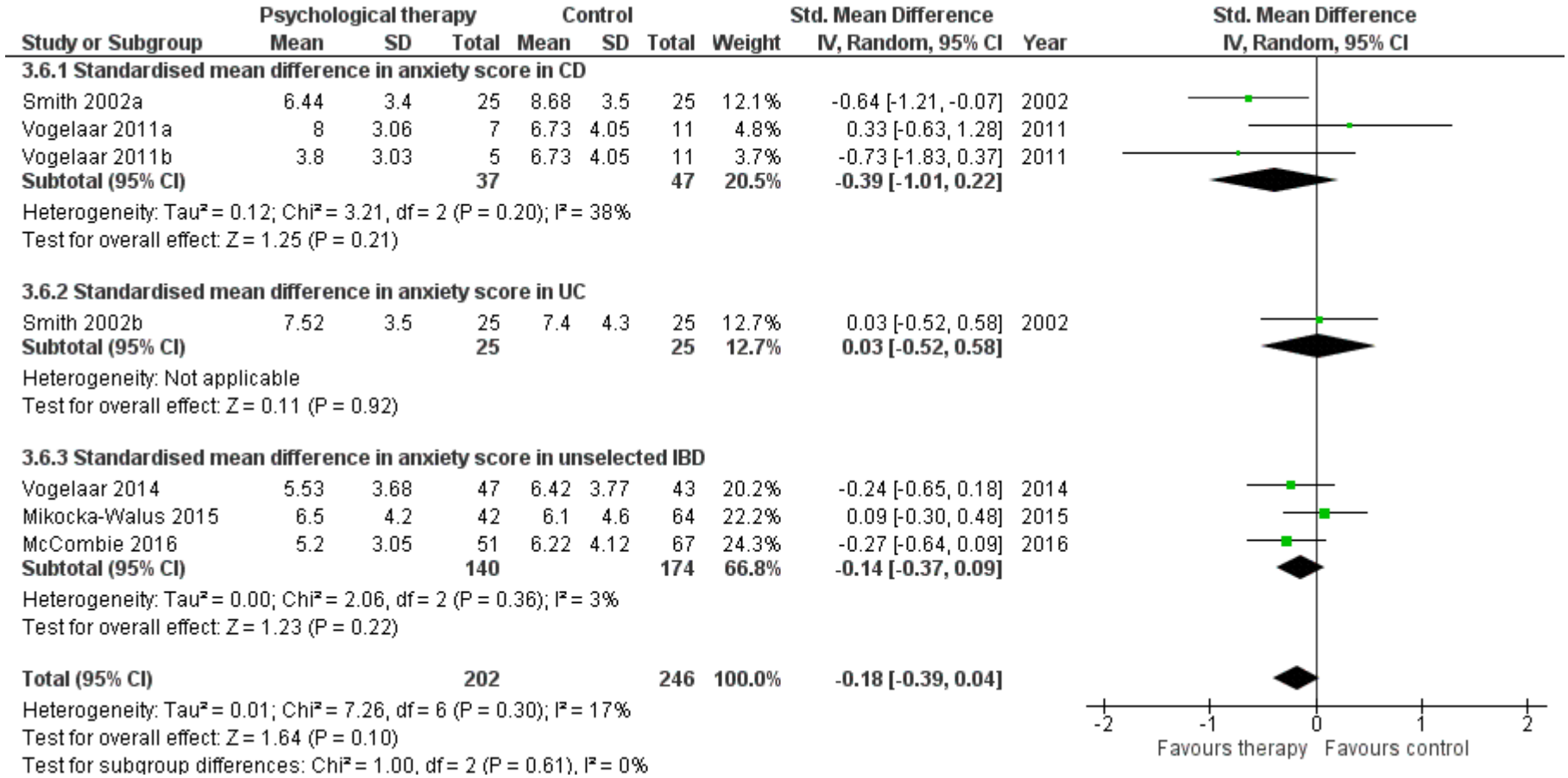


Figure 16: Forest plot of RCTs reporting the effect of psychological therapies vs. control on state anxiety scores in quiescent IBD at completion of therapy

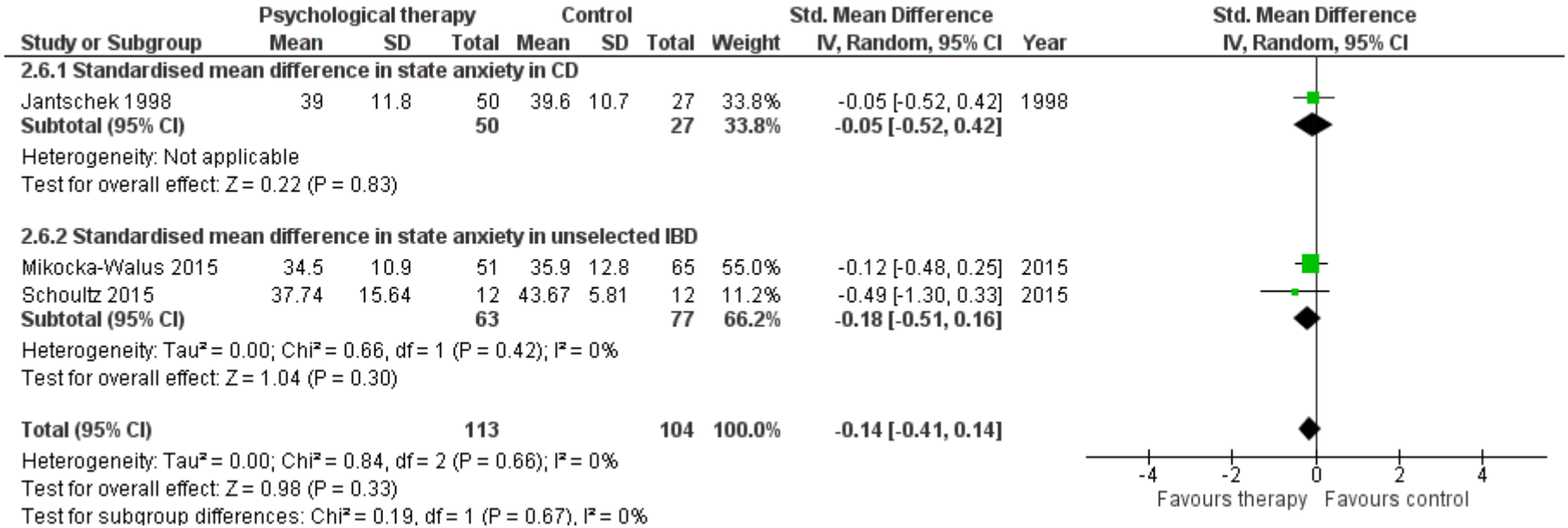


Figure 17: Forest Plot of RCTs reporting the effect of psychological therapies vs. control on state anxiety scores in quiescent IBD at the final point of follow-up

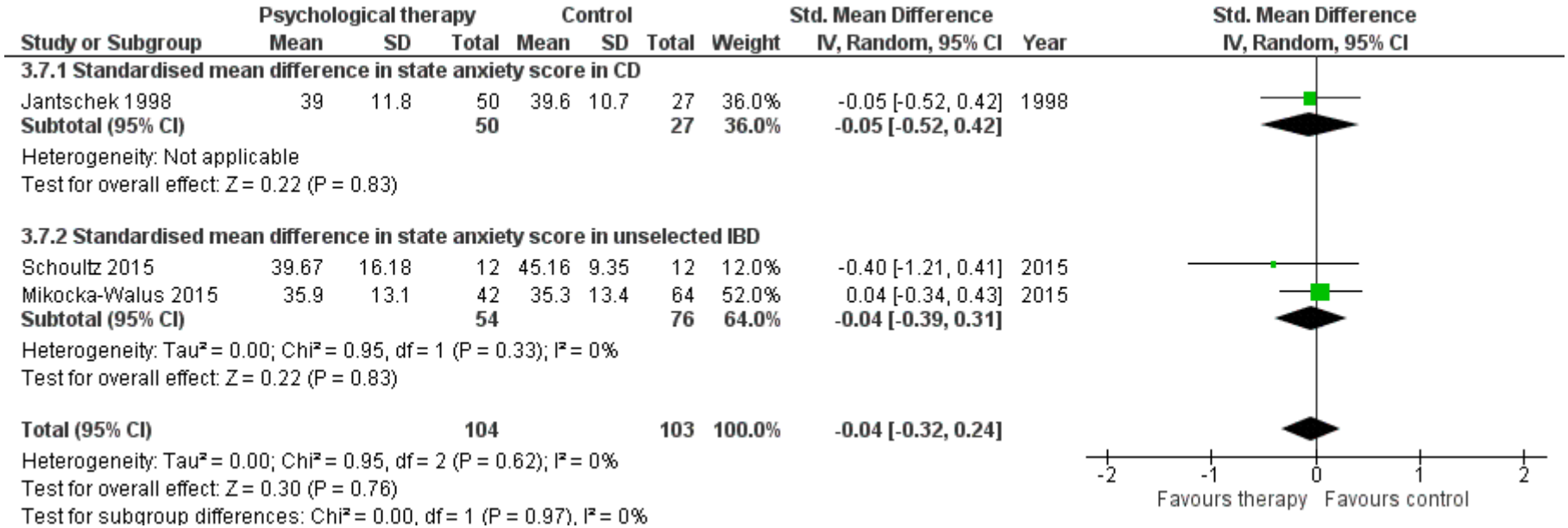


Figure 18: Forest plot of RCTs reporting the effect of psychological therapies vs. control on trait anxiety scores in quiescent IBD at completion of therapy

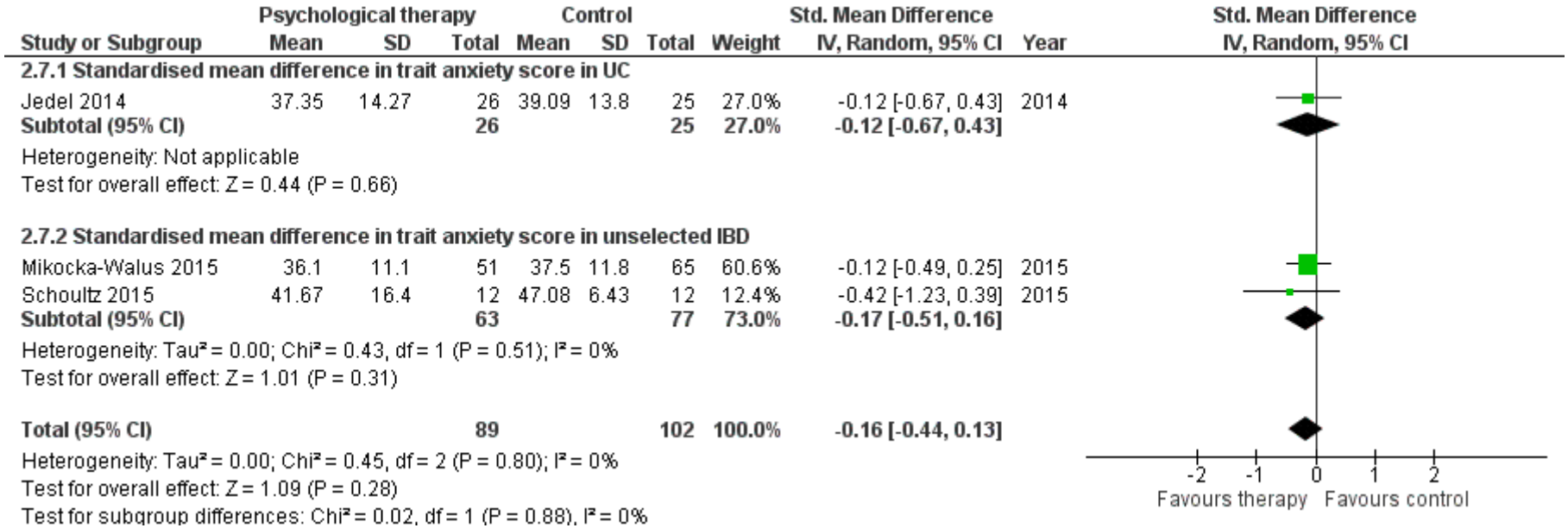
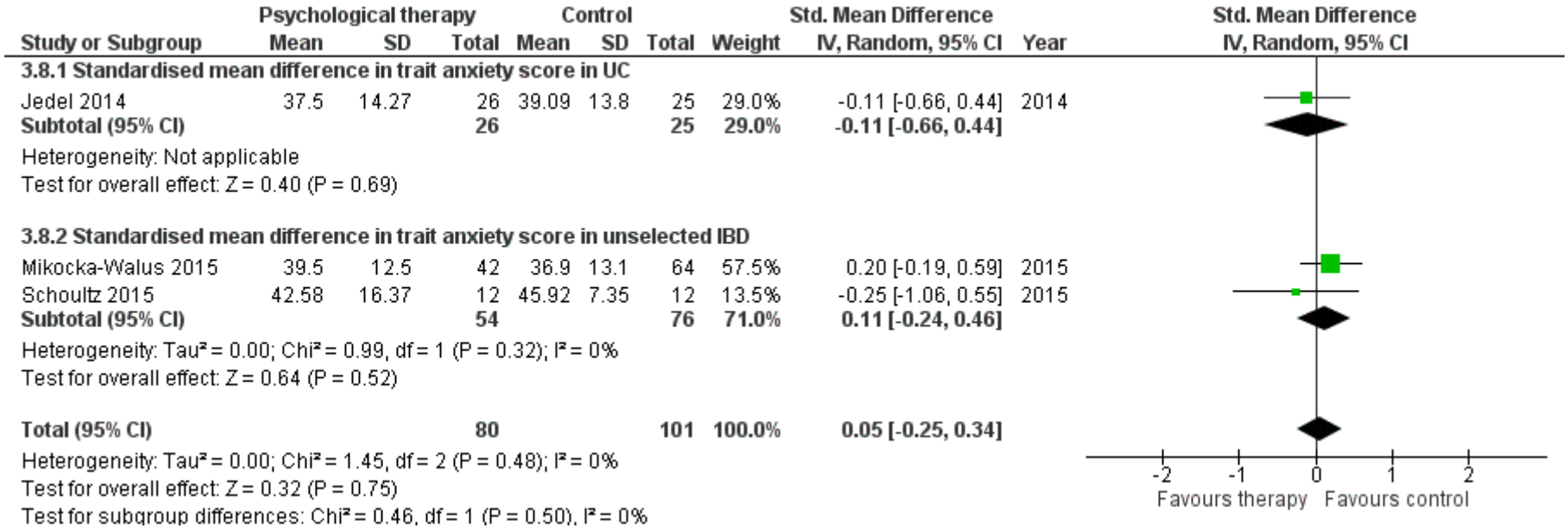


Figure 19: Forest plot of RCTs reporting the effect of psychological therapies vs. control on trait anxiety scores in quiescent IBD at the final point of follow-up



7.3.3.4 Effect of psychological therapies on depression scores in IBD

Seven studies examined the effect of psychological therapies on depression scores in IBD at end of therapy (Jantschek et al., 1998; Smith et al., 2002; Jedel et al., 2014; Mikocka-Walus et al., 2015; McCombie et al., 2016; Schoultz et al., 2015; Vogelaar et al., 2014), and eight at the final point of follow-up (Vogelaar et al., 2011; Vogelaar et al., 2014; Jantschek et al., 1998; Smith et al., 2002; Jedel et al., 2014; Schoultz et al., 2015; Mikocka-Walus et al., 2015; McCombie et al., 2016). Data were available for 605 patients at completion of therapy, with a SMD in depression scores for those treated with psychological therapies compared with control of -0.17 (95% CI -0.33 to -0.01, P = 0.04) (Figure 20), with no heterogeneity between studies (I^2 = 0%, P = 0.76). Again there were too few studies to assess for publication bias. This beneficial effect on depression scores was only seen in RCTs that recruited patients with IBD (Figure 20). At the final point of follow-up, when data were pooled from 593 patients, the effect on depression scores was no longer evident (SMD = -0.11; 95% CI -0.27 to 0.05), with no heterogeneity (I^2 = 0%, P = 0.93) (Figure 21). There were too few studies to assess for publication bias.

Figure 20: Forest plot of RCTs reporting the effect of psychological therapies vs. control on depression scores in quiescent IBD at completion of therapy

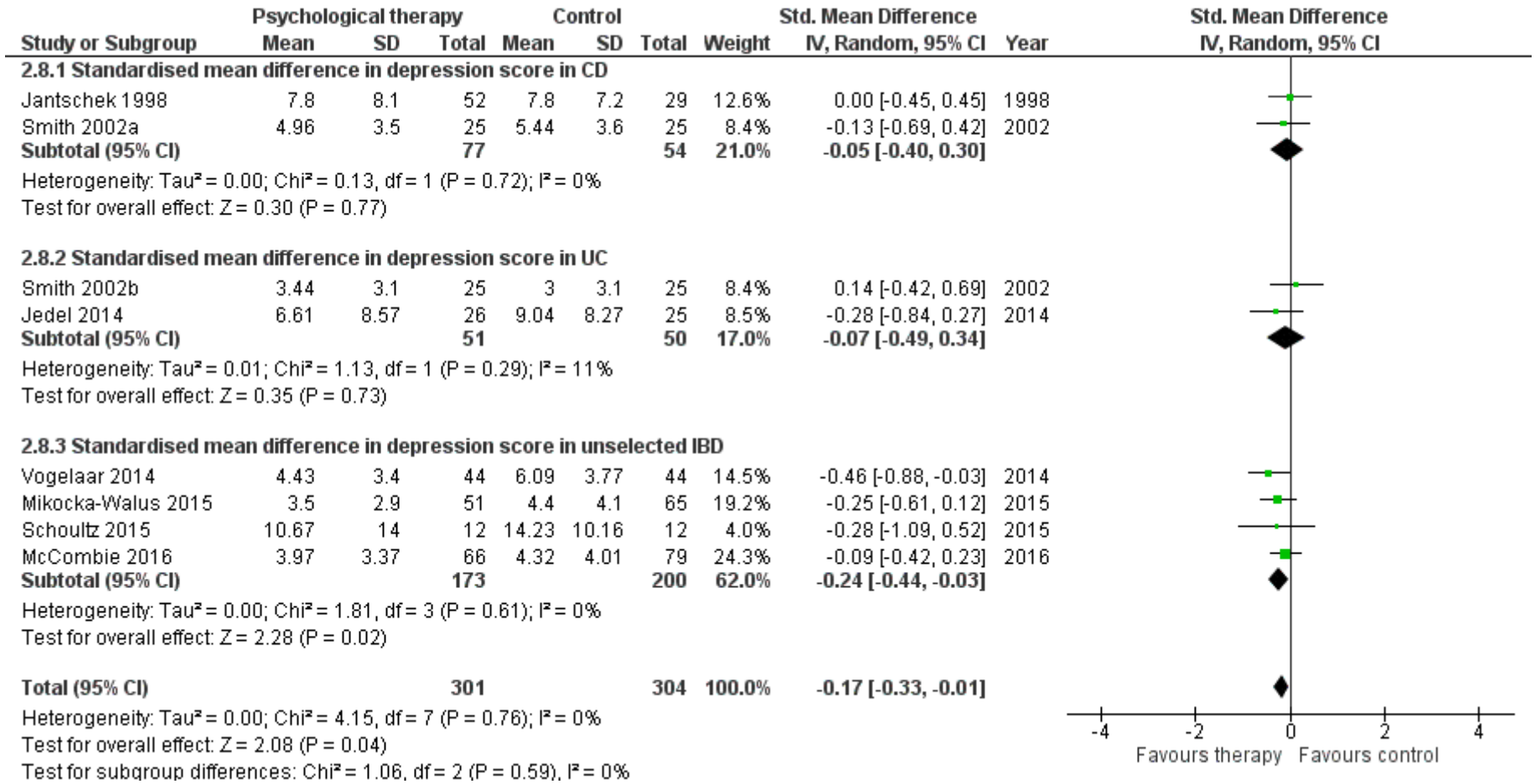
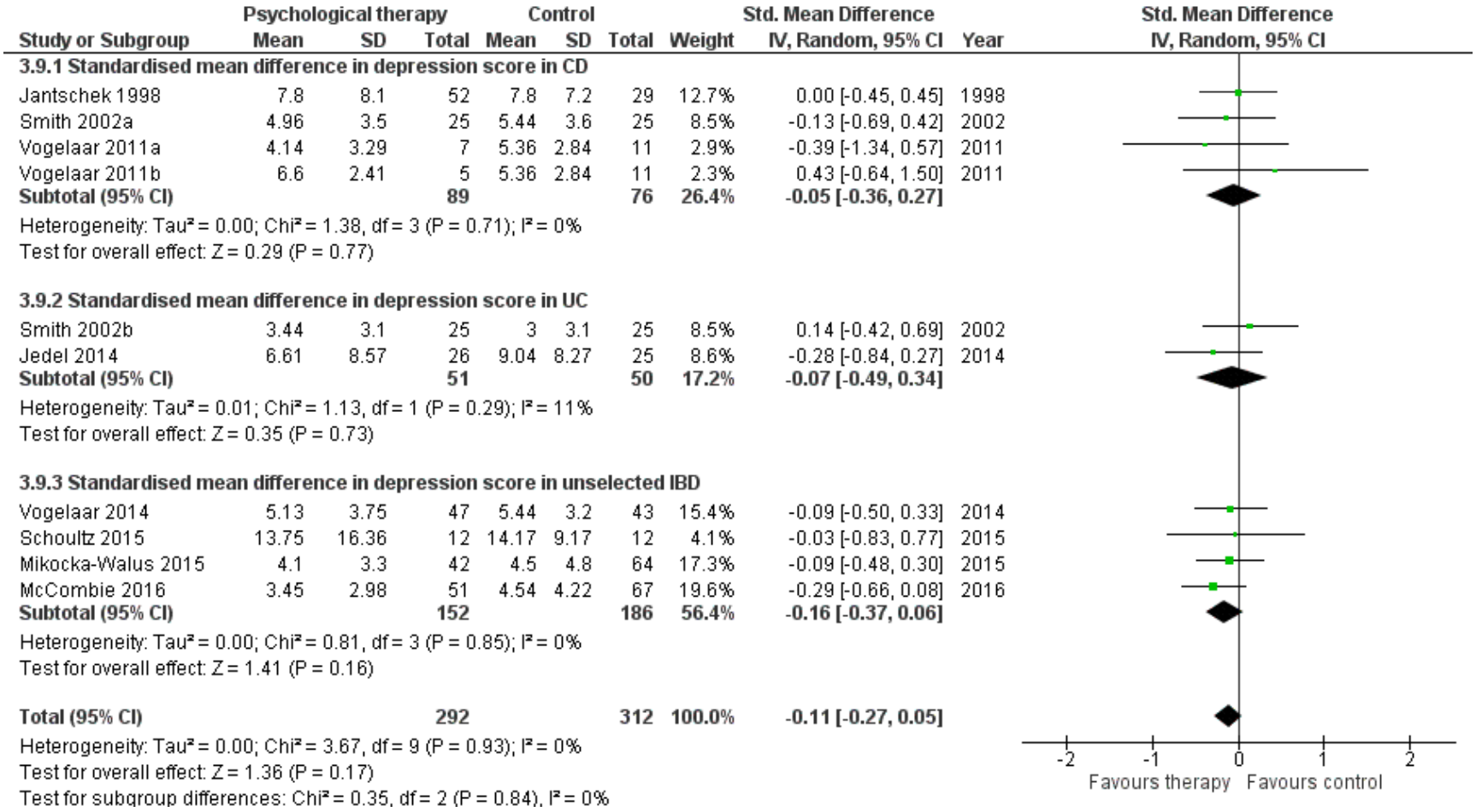


Figure 21: Forest plot of RCTs reporting the effect of psychological therapies vs. control on depression scores in quiescent IBD at the final point of follow-up



7.3.3.5 Effect of psychological therapies on perceived stress scores in IBD

Six RCTs reported data on the effect of psychological therapies on perceived stress score in IBD, when compared with control (Keefer et al., 2012; Keefer et al., 2013; Jedel et al., 2014; Berrill et al., 2014; Mikocka-Walus et al., 2015; McCombie et al., 2016). When data were pooled at the end of therapy, psychological therapies had no effect on perceived stress scores in 434 patients (SMD = -0.07; 95% CI -0.31 to 0.18) (Figure 22), with no heterogeneity between studies (I^2 = 34%, P = 0.18). At the final point of follow-up, when data were available for 401 patients, there was still no beneficial effect of psychological therapies compared with control (SMD in perceived stress scores = -0.10; 95% CI -0.33 to 0.13) (Figure 23), again with no heterogeneity noted between included studies (I^2 = 22%, P = 0.27). There were too few studies to assess for publication bias in both these analyses. Again, there were no effects noted according to whether studies recruited patients with CD only, patients with UC only, or patients with IBD.

Figure 22: Forest plot of RCTs reporting the effect of psychological therapies vs. control on perceived stress scores in quiescent IBD at completion of therapy

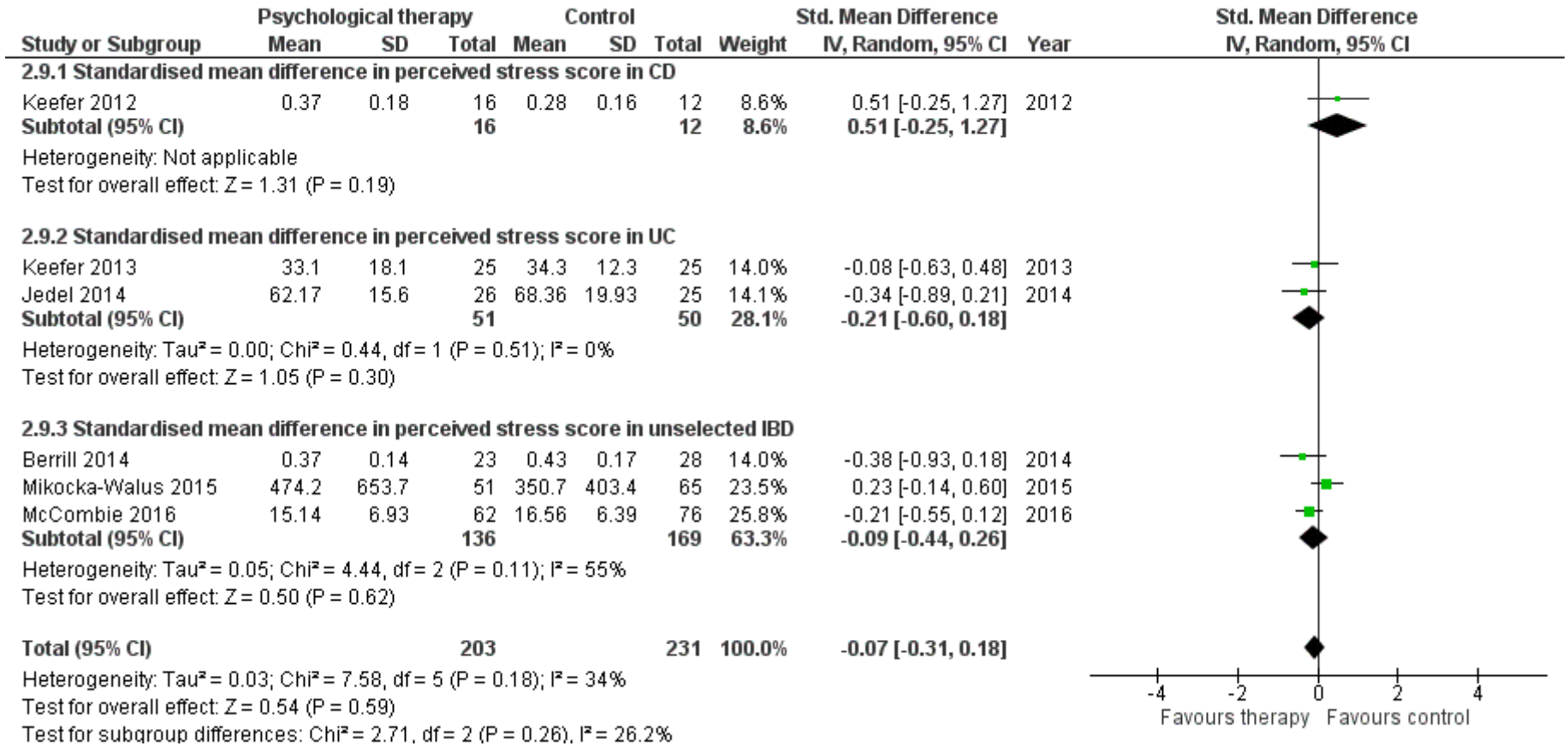
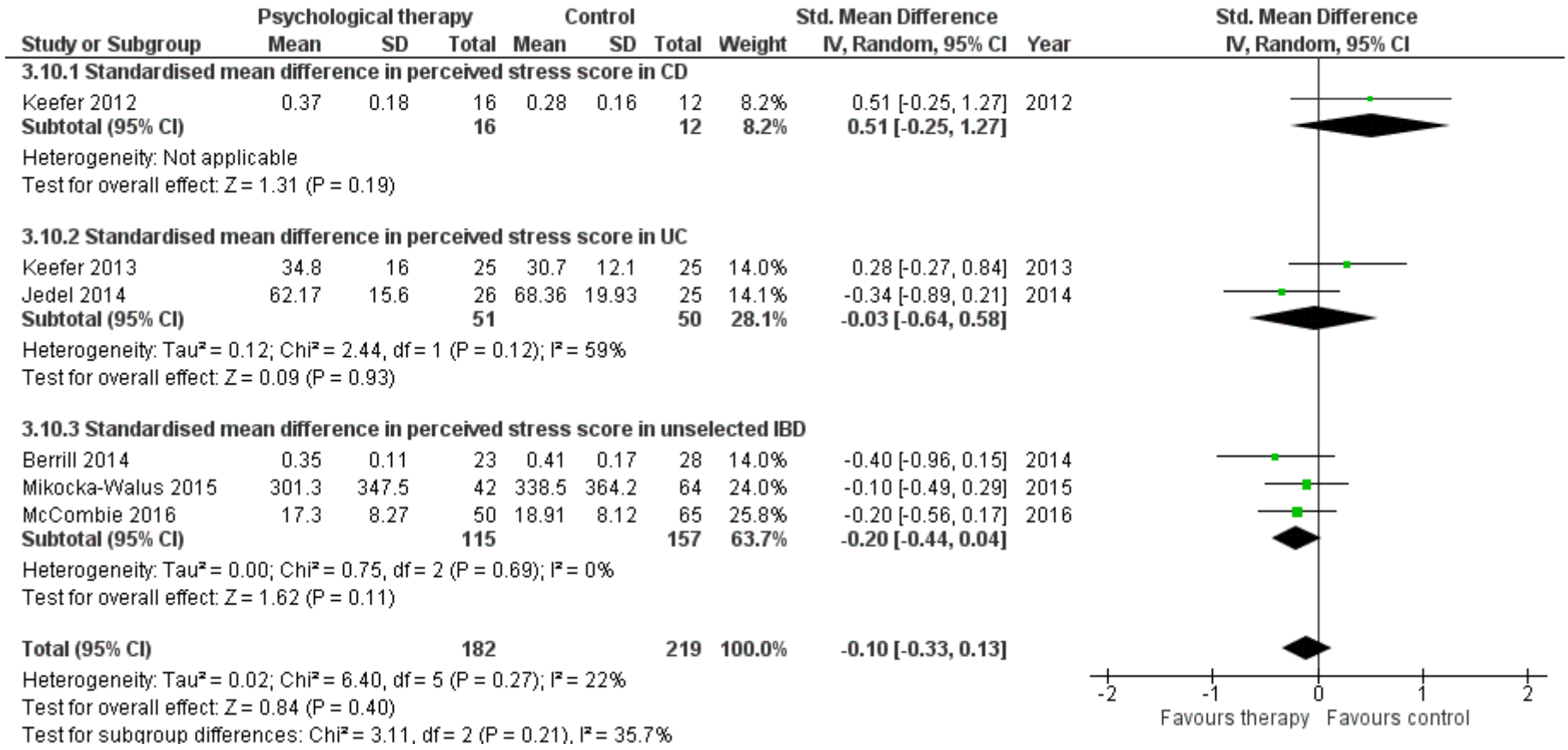


Figure 23: Forest plot of RCTs reporting the effect of psychological therapies vs. control on perceived stress scores in quiescent IBD at the final point of follow-up



7.3.3.6 Effect of psychological therapies on quality of life in IBD

Eleven studies reported data on the effect of psychological therapies on quality of life in IBD (Jantschek et al., 1998; Keefer et al., 2012; Langhorst et al., 2007; Keefer et al., 2013; Jedel et al., 2014; Berrill et al., 2014; Vogelaar et al., 2014; Vogelaar et al., 2011; Schoultz et al., 2015; McCombie et al., 2016; Mikocka-Walus et al., 2015). Nine of these RCTs assessed effects on IBD-specific quality of life at end of therapy (Jantschek et al., 1998; Langhorst et al., 2007; Keefer et al., 2012; Berrill et al., 2014; Keefer et al., 2013; Jedel et al., 2014; Schoultz et al., 2015; McCombie et al., 2016; Vogelaar et al., 2014), and 10 at the final point of follow-up (Vogelaar et al., 2011; Vogelaar et al., 2014; Jantschek et al., 1998; Keefer et al., 2012; Keefer et al., 2013; Langhorst et al., 2007; Jedel et al., 2014; Berrill et al., 2014; Schoultz et al., 2015; McCombie et al., 2016). In addition, four trials examined effect on physical quality of life or mental quality of life separately (Keefer et al., 2013; Mikocka-Walus et al., 2015; McCombie et al., 2016; Vogelaar et al., 2014), both at end of therapy and at the final point of follow-up. There was a significant improvement in IBD-specific quality of life at the end of therapy, when data were pooled from 578 patients (SMD 0.30; 95% CI = 0.07 to 0.52, P = 0.01) (Figure 24). There was borderline heterogeneity observed between the included studies (I^2 = 42%, P = 0.09), but too few studies to assess for publication bias. When the effect of psychological therapies on IBD-specific quality of life was studied according to whether trials recruited patients with CD, patients with UC, or patients with IBD there was only a benefit observed among patients with IBD at the end of therapy (SMD = 0.37; 95% CI 0.15 to 0.59, P = 0.001) (Figure 24). Any beneficial effect of psychological therapies on IBD-specific quality of life at completion of therapy was lost by the final point of follow-up. When data were pooled from 577 patients there were no differences in IBD-specific quality of life (SMD = 0.15; 95% CI -

0.05 to 0.34) (Figure 25). There was no heterogeneity between studies (I^2 = 22%, P = 0.24), and no evidence of publication bias (Egger test, P = 0.44).

When compared with control, psychological therapies had no effect on physical quality of life or mental quality of life at completion of therapy in 399 patients (SMD = 0.17; 95% CI -0.03 to 0.37 and SMD = 0.15; 95% CI -0.05 to 0.34, respectively). There was no evidence of heterogeneity between studies in these analyses although with only four RCTs, power to detect this would be limited. At final point of follow-up in 363 patients there was no difference in physical (SMD = 0.02; 95% CI = -0.19 to 0.23) or mental quality of life (SMD = 0.05; 95% CI = -0.22 to 0.32) when those receiving psychological therapies were compared with control, with no heterogeneity noted for either outcome. There were too few studies to assess for publication bias in all these analyses.

Figure 24: Forest plot of RCTs reporting the effect of psychological therapies vs. control on quality of life scores in quiescent IBD at the completion of therapy

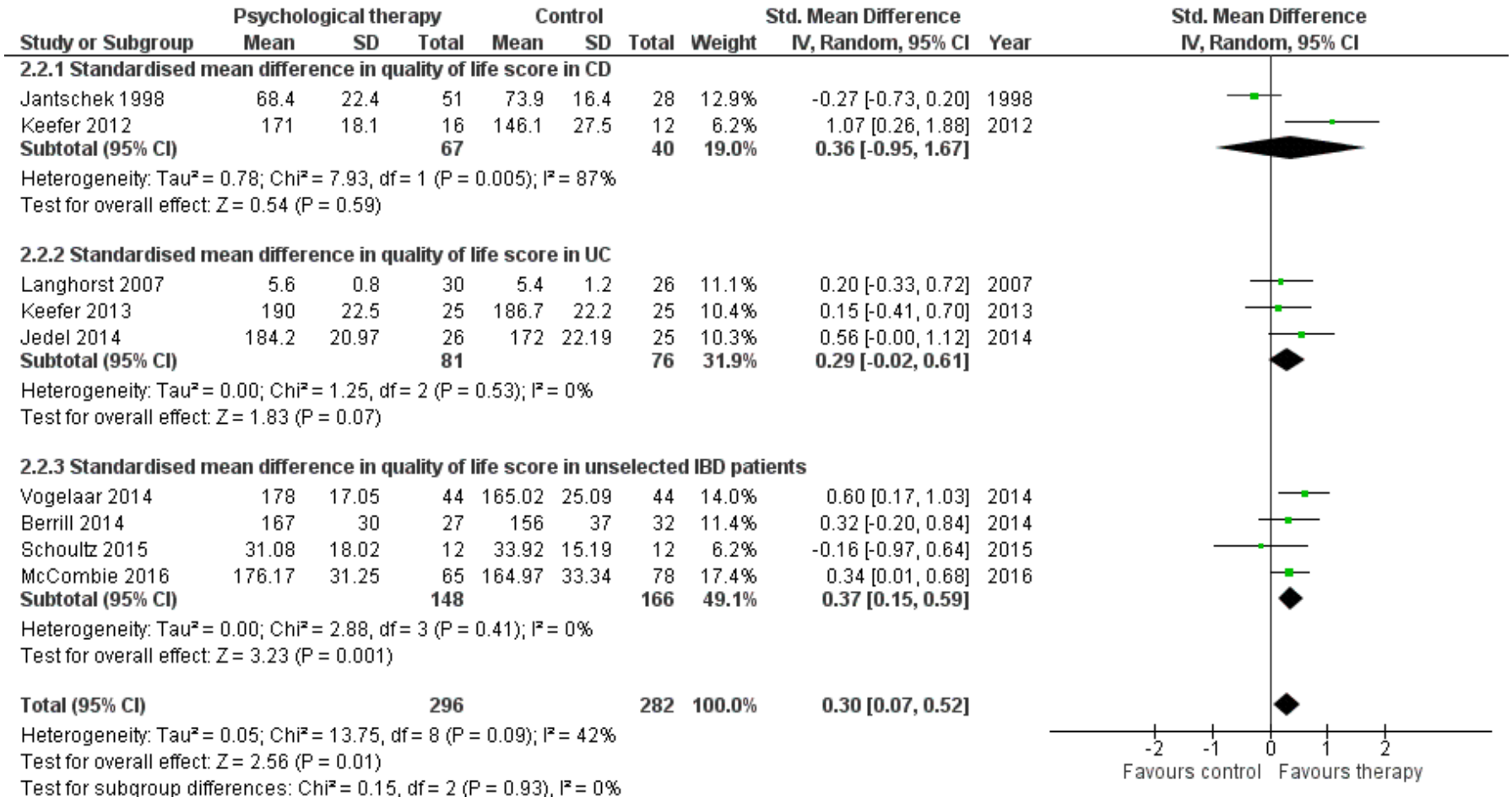
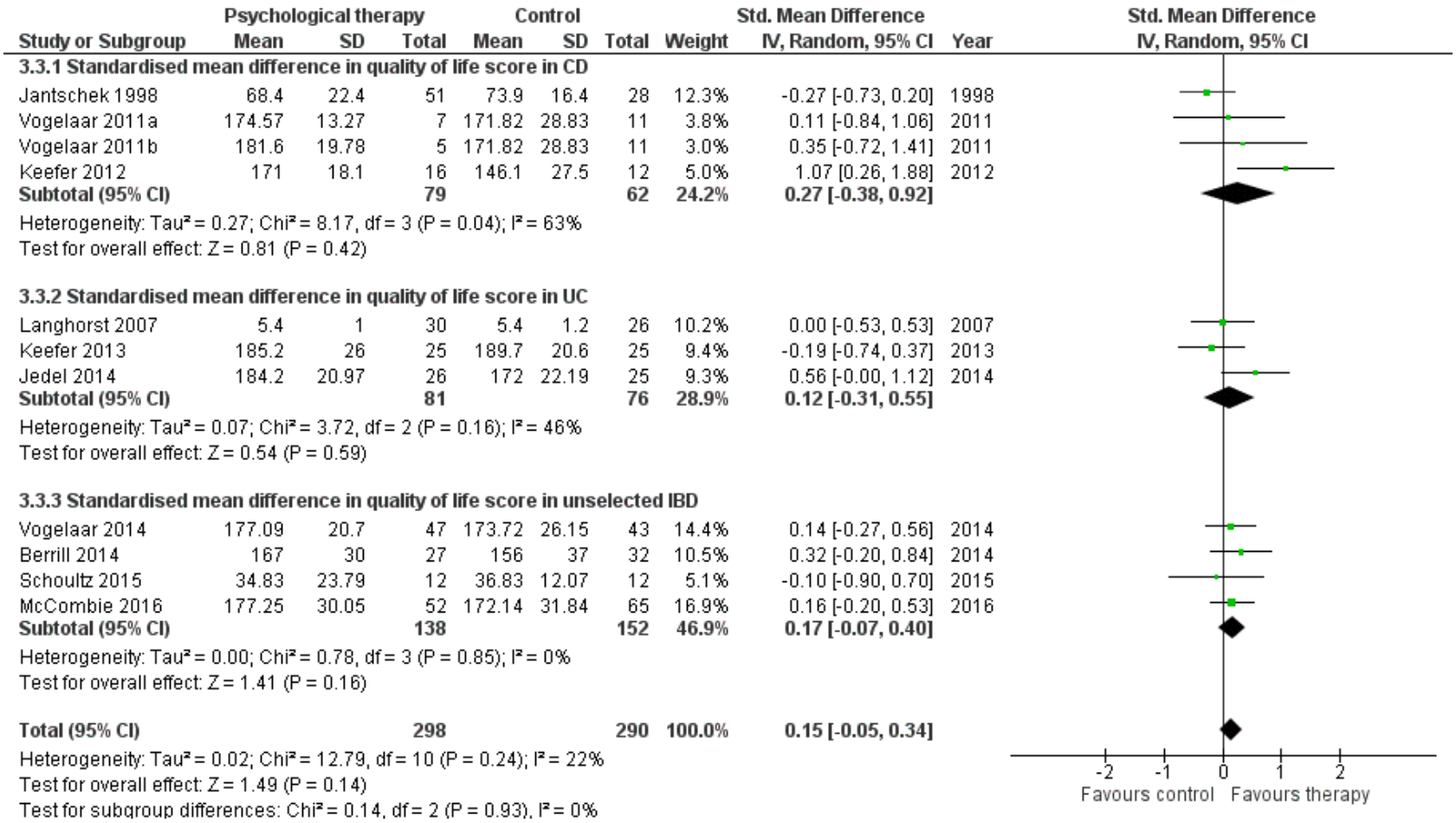


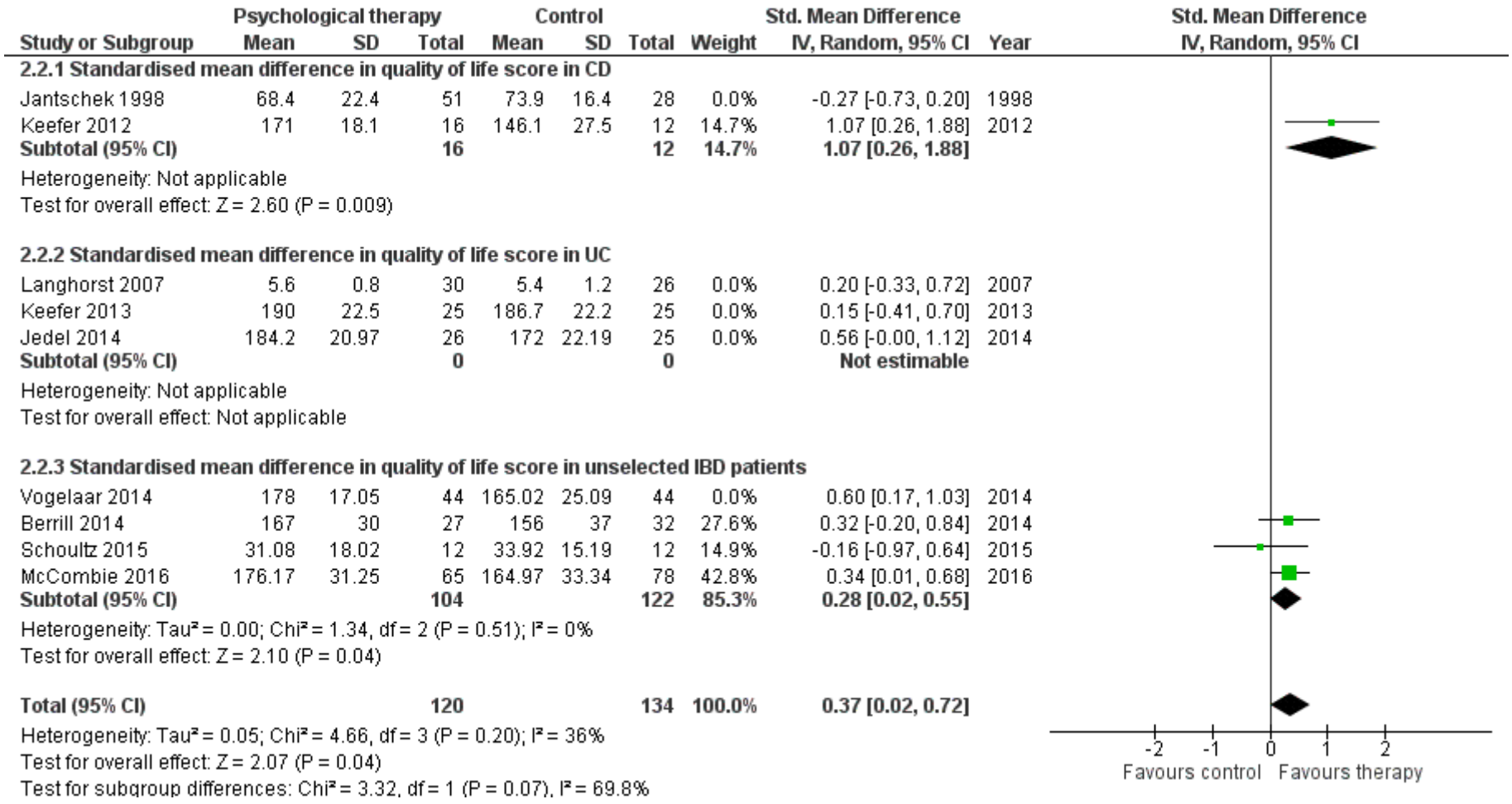
Figure 25: Forest plot of RCTs reporting the effect of psychological therapies vs. control on quality of life scores in quiescent IBD at the final point of follow-up



7.3.3.7 Effect of CBT in preventing relapse of quiescent IBD, and effect on clinical disease activity indices, anxiety scores, depression scores, perceived stress scores, and quality of life in IBD

Five studies (Keefer et al., 2012; Berrill et al., 2014; Mikocka-Walus et al., 2015; Schoultz et al., 2015; McCombie et al., 2016), including 511 patients with IBD, reported data on the effect of CBT on one or more of these endpoints. There was a significant improvement in quality of life at the end of therapy, when data were pooled from 254 patients (SMD = 0.37; 95% CI 0.02 to 0.72; Figure 26), although this beneficial effect was lost at the final point of follow-up. There was no other significant effect of CBT on disease activity indices, anxiety or depression scores, or perceived stress scores when compared with control therapy.

Figure 26: Forest plot of RCTs reporting the effect of CBT vs. control on quality of life scores in quiescent IBD at completion of therapy



7.4 Discussion

This systematic review and meta-analysis has demonstrated that psychological therapies may provide a limited, short-term improvement in depression scores and quality life in patients with clinically quiescent IBD, but that these effects appear to be lost over time. The beneficial effect on quality of life was greater when only RCTs that used CBT, which is thought to have the best evidence for efficacy in the management of anxiety and depression (APS, 2010), were included in the analysis. Otherwise, psychological therapies did not appear to improve either clinical disease indices or psychological outcomes in IBD. There did not appear to be any benefits of psychological therapies according to type of IBD. Furthermore, there was no significant effect on most measurements of mood, either at the point where psychological therapies had just been completed, or during extended follow-up. Part of this lack of benefit may have arisen from a lack of sensitivity or specificity of the instruments used to detect changes in mood, as well as failure by the majority of trials to recruit only patients who had abnormal levels of psychological health, when compared with the general IBD population.

Strengths of this study include the rigorous methodology adopted. Several of the RCTs included in the 2011 Cochrane review (Timmer et al., 2011) addressing this issue did not fulfil the inclusion criteria for various reasons. These included a lack of randomisation (Grootenhuis et al., 2009; Freyberger et al., 1985), recruitment of patients with both active and quiescent disease, with no reporting of data separately for these distinct groups of patients (Milne et al., 1986), being conducted in an adolescent population (Szigethy et al., 2007), redundant publication (Elsenbruch et al., 2005), or providing no extractable data (Garcia-Vega and Fernandez-Rodriguez, 2004). Every effort was made to contact the authors of potentially eligible studies, where

dichotomous or continuous data of interest were not available in the published manuscript. Data extraction was performed on the basis of intention-to-treat analysis, with all patients lost to follow-up assumed to be treatment failures, for dichotomous endpoints such as remission or relapse of disease activity, in order to avoid overestimation of the effect of the active intervention. Pooling of data was performed using a random effects model, in order to give a more conservative estimate of the effect of psychological therapies in IBD. A further strength of this study is the number of participants included. This systematic review and meta-analysis included a number of additional studies (Mikocka-Walus et al., 2015; McCombie et al., 2016; Berrill et al., 2014; Boye et al., 2011; Keefer et al., 2013; Vogelaar et al., 2011; Vogelaar et al., 2014), and almost three times more participants than were included in the Cochrane review published by Timmer *et al.* in 2011. Analyses according to the subtype of IBD was also conducted, in order to assess whether there was any benefit of psychological therapies in either CD or UC separately. Lastly, a subgroup analysis to investigate the effect of CBT alone was conducted, as this has the best evidence for use in anxiety and depression (APS, 2010).

There are limitations to this meta-analysis, which arise mainly from the relatively small number of studies available for analysis, and their risk of bias. Although there was no significant heterogeneity seen in the majority of the endpoints studied, there was significant heterogeneity between RCTs reporting on the effect of psychological therapies on relapse of disease activity in quiescent IBD. In addition, all the identified trials were at high risk of bias, due to the lack of adequate blinding, with only one trial employing a double-blind design (Jedel et al., 2014). This is often a problem with studies of psychological therapies, although there is the potential to blind assessors to therapy. However, only four of the identified studies performed this

(Jantschek et al., 1998; Keefer et al., 2013; Boye et al., 2011; Vogelaar et al., 2014). The included studies employed various methods of handling the control arms, which may mean that pooling the data from them could be viewed as inappropriate. The fact that duration of follow-up was not uniform between eligible studies may also mean that a significant benefit of psychological therapies, which is perhaps time-dependent, has been overlooked. Individual trials also used differing types, formats, durations, and intensities of psychological therapy, which may have led to a lack of benefit when all studies were pooled together. However, when only the five RCTs that used CBT were considered in the analysis, there was still no effect on disease activity indices, anxiety or depression scores, or perceived stress scores. Finally, the eligible trials included in these analyses span an 18-year period, during which the management of IBD has been revolutionised by the advent of biological therapies. The fact that increasing use of these drugs in more recent studies may have had an impact on the findings of this meta-analysis cannot, therefore, be excluded.

These findings are in keeping with those previously published in adult IBD populations (Timmer et al., 2011). Other than a significant improvement in depression and quality of life scores immediately following the cessation of therapy, no statistically significant benefit of these interventions in IBD was identified. Despite this, psychological therapies have been shown to be effective in the treatment of other chronic disorders, including IBS, functional dyspepsia, and non-cardiac chest pain (Ford et al., 2014b; Orive et al., 2015; Jones et al., 2006a). The majority of the RCTs included in this meta-analysis were conducted in patients in clinical remission. Only two studies examined the effect of psychological therapies in active disease (Mizrahi et al., 2012; Boye et al., 2011). However, as described in Chapters 4 and 6, often the greatest psychological burden is seen in patients with active disease, or those with IBS-type

symptoms, suggesting it is these subgroups of patients who may benefit most from these types of treatment. Only one RCT, which conducted a subgroup analysis assessing the effect of multi-convergent therapy on disease activity and quality of life in patients with IBD reporting IBS-type symptoms, has considered this issue (Berrill et al., 2014). In this study, quality of life scores in those receiving multi-convergent therapy were significantly improved, when compared with control after 4 months of follow-up, and remained higher during the entire 12 months of the study, although this difference was no longer statistically significant. Furthermore, disease activity scores were also generally lower among those assigned to psychological therapy throughout the entire 12 months of the study. Finally, none of the included RCTs investigated the effect of psychological interventions in patients with IBD with pre-existing depression or anxiety, despite there being evidence for a benefit in this distinct group of patients, particularly in paediatric populations (Szigethy et al., 2007; Thompson et al., 2012; Szigethy et al., 2004).

In addition to the outcomes addressed in this systematic review and meta-analysis, fatigue is now recognised as an increasing problem in people with IBD, and is more prevalent than in the general population, affecting up to 40% of patients (Romberg-Camps et al., 2010; Jelsness-Jorgensen et al., 2011b). Furthermore, fatigue may be associated with depression and reduced quality of life, independent of disease activity (Cohen et al., 2014; Jelsness-Jorgensen et al., 2011a). To date, only two of the studies identified sought to investigate the effect of psychological therapies in this particular subgroup of patients with IBD (Vogelaar et al., 2014; Vogelaar et al., 2011), randomising patients in clinical remission with raised fatigue scores to receive solution focused therapy, problem solving therapy, or treatment as usual. In the larger of these two studies (Vogelaar et al., 2014), significant improvements in fatigue scores and

quality of life were observed after 3 months of follow-up in the intervention group, suggesting psychological therapies may be beneficial in this particular population.

The findings of the observational studies that have been conducted in Chapters 3 to 6 highlight a high prevalence of psychological co-morbidity in IBD. The relationship between psychological co-morbidity and poor quality of life that is described in Chapters 4 and 6, its longitudinal association with IBS-type symptom-reporting, combined with the deleterious impact that symptoms of anxiety may have on subsequent disease activity, reinforces the need for evidence-based management strategies that address mood disorders in IBD. This systematic review and meta-analysis suggests that psychological therapies, and CBT in particular, may be of limited short-term benefit in terms of improvements in depression and quality of life in patients with IBD. However, despite the inclusion of several hundred patients in most of the analyses conducted, no beneficial effect of psychological therapies on disease activity, or other measures of psychological health, including anxiety or stress was identified.

Despite this, there remains a need for further investigation of the utility of these interventions, particularly in those patients who are more likely to suffer from co-existent psychological distress or fatigue. In addition, with the increasing use of faecal biomarkers of intestinal inflammation, such as FC, as a means of assessing disease activity objectively, it is likely that increasing numbers of patients with IBD with no objective evidence of disease activity who report IBS-type symptoms will be identified. This distinct cohort of patients also have unmet needs, in terms of therapy, and are often difficult to manage. Trials assessing the effects of psychological therapies, which use an adequate number of therapy sessions, have a sufficient duration of follow-up, use blinded assessors for endpoint assessment, and focus on the efficacy of CBT in these patients would therefore also be welcome.

CHAPTER 8: Conclusions

The diagnosis and management of IBD has evolved significantly in recent decades. Observational studies assessing disease outcomes in IBD have demonstrated a decline in the incidence of surgery, presumably secondary to the development of novel therapeutic agents during this time (Frolkis et al., 2013; Frolkis et al., 2014). Despite this, the complex nature of IBD, characterised by its uncertain aetiology, highlights that current available treatments remain suboptimal in some groups of patients. The focus of contemporary medical intervention is almost exclusively centred upon the treatment of inflammatory activity, via management of disordered intestinal immunity, despite the myriad of proposed aetiological factors that are likely to contribute to the development of disease activity in IBD.

Psychological co-morbidity is acknowledged as a potential contributor to the development of IBD, and to the propagation of disease activity. To date, studies that have sought to describe the relationship between mood and disease activity in IBD have failed to account for the presence or absence of inflammatory activity because they have used clinical disease activity indices as their sole measure of disease burden. Deconstructing the complex relationships between symptom-reporting, inflammatory activity, psychological co-morbidity and co-existent IBS-type symptoms in IBD is important for several reasons. Firstly, in clinical practice, aside from their poor correlation with objectively quantified inflammation, reliance on patient-reported symptoms to define disease activity fails to account for potential co-existent FGIDs or somatoform behaviour, which may result in inappropriate investigation requesting, or escalation of medical therapy (Derwa et al., 2018). Secondly, in observational research studies addressing the relationship between disease activity and psychological co-morbidity, and in trials of therapeutic interventions aimed at improving psychological and disease activity outcomes, the potential for confounding is considerable. Therefore,

before an accurate assessment of the influence of mood on disease activity can be made, clarification of these relationships is required. This thesis has attempted to address these shortcomings in understanding by presenting data from five distinct, but inter-related pieces of work. Broad themes running throughout include the relationship between mood, symptom-reporting, and inflammatory activity, the relationship between IBS-type symptom-reporting, psychological co-morbidity, and quality of life, as well as a review of the current evidence base for the use of psychological therapies in IBD.

Previous researchers have highlighted limitations of the use of clinical disease activity indices in identifying inflammatory activity in IBD (af Bjorkesten et al., 2012; Sipponen et al., 2008; Targownik et al., 2015). However, none had sought to address the potential impact of anxiety, depression, or somatisation on these relationships. Therefore, a cross-sectional study, using FC as an objective marker of intestinal inflammation, was performed to clarify these uncertainties. This confirmed that clinical disease activity indices were poor predictors of mucosal inflammation, and that psychological co-morbidity was associated with symptom-reporting, but not inflammatory activity, in IBD.

The results of this study subsequently informed the design of the longitudinal follow-up study that was conducted to assess how the relationship between mood, symptom-reporting, and inflammatory activity evolved over time. Here, the successful identification of bi-directional brain-gut axis activity in IBD was novel. These findings provide a mandate for further research investigating the benefit of treatments targeting mood disorders in IBD, not only because these are independently associated with detrimental effects on quality of life (Maunder, 2005), but also because effectively addressing co-existent mood disorders in IBD may have beneficial effects on longitudinal inflammatory activity.

The second theme presented concerns the identification of patients with IBD who report IBS-type symptoms, and their association with impaired psychological wellbeing and quality of life. In a cross-sectional study using novel methodology incorporating clinical disease activity indices, the Rome III criteria for IBS, and FC as an objective marker of inflammatory activity, patients with IBD were divided into four distinct groups: quiescent IBD, IBD with IBS-type symptom, occult inflammatory IBD, and active IBD. Here, a distinct group of patients who report persistent symptoms in the absence of objectively determined inflammatory activity was identified. Affecting one-in-four patients with IBD, the prevalence of IBS-type symptom-reporting was lower than that previously described in a meta-analysis of observational studies (Halpin and Ford, 2012). Psychological co-morbidity and poor quality of life were both associated with IBS-type symptom-reporting, to a significantly greater degree than was observed in patients with quiescent disease or occult inflammation, but to an equivalent extent to patients with overt active IBD.

These findings highlight the need for evidence-based management strategies for these patients. Furthermore, given the potential role of the brain-gut axis in the generation of these symptoms, and the apparent influence of brain-gut axis activity on longitudinal disease outcomes in IBD described above, this study also emphasised the need for longitudinal assessment of the impact of IBS-type symptom-reporting on disease activity, psychological wellbeing, and quality of life. The findings of the study conducted to investigate these issues suggested that, although IBS-type symptom-reporting was not associated with adverse disease activity outcomes, its association with psychological co-morbidity and poor quality of life was robust over extended follow up.

Each of the four observational studies were conducted in order to address an unmet need, in terms of effective therapeutic interventions for the management of mood

disorders and IBS-type symptoms in IBD. Given the identification of bi-directional brain-gut interactions in IBD, such interventions have the potential to positively impact the natural history of IBD, but also mediate the detrimental effect of mood disorders on quality of life. For this reason an updated systematic review and meta-analysis of RCTs assessing the efficacy of psychological therapies in IBD was conducted. Although limited beneficial effects of psychological therapies on quality of life and depression were reported, the most promising of which was seen with CBT, methodological weaknesses in the included studies limit the validity of these findings. On the basis of this review, psychological therapies had no impact on disease activity in IBD, but again clinical disease activity indices were the sole measure of disease activity outcomes in these trials. Furthermore, the inclusion of patients without anxiety or depression at baseline is likely to have limited the effect of these interventions.

The work undertaken in this thesis has also informed the generation of novel hypotheses, which may provide opportunities for future research. As described in the systematic review and meta-analysis of RCTs of psychological therapies in IBD, the results of these interventions are disappointing. However, a review of the efficacy of psychological therapies and antidepressants in IBD, in a selected group of patients who suffer from mood disorders, or who report IBS-type symptoms, may yield results that are more positive. The aetiology of IBS-type symptom-reporting in IBD is uncertain. In this study population, less than 50% of patients reporting these symptoms had abnormal HADS anxiety or depression scores, suggesting that factors other than psychological health are likely to have an impact on the reporting of these symptoms. Investigating the role of the intestinal microbiome in the generation of these symptoms, for example, may provide a biological target for trials of future therapeutic interventions. A criticism of the longitudinal study describing bi-directional brain-gut interactions in IBD was that

the collection of data, which was conducted at only two time points and at group, rather than individual, level was too simplistic. Personalised research identifying complex relationships between psyche and soma has been studied in patients following myocardial infarction (Rosmalen et al., 2012), but to date this has not been explored in IBD. Finally, in addition to defining a specific group of patients who report IBS-type symptoms, a second group of hitherto poorly characterised patients with occult inflammatory activity was also identified. In longitudinal follow-up, these patients tend not to suffer adverse disease activity outcomes, despite having evidence of inflammatory activity equivalent to those with overt active symptomatic IBD at baseline. Although the efficacy of a treat-to-target approach to the management of IBD is not evidence-based (Sandborn et al., 2014c), further characterisation of this group of patients may still be worthwhile.

In summary, this thesis has addressed the relationship between GI symptom-reporting, psychological co-morbidity, and inflammatory activity in a large secondary care cohort of patients with IBD. A well-characterised group of patients who report IBS-type symptoms has been identified, and a robust association between the reporting of these symptoms and impaired psychological health and quality of life has been described. The identification of potential bi-directional brain-gut interactions in IBD provides a therapeutic target for rigorous RCTs of treatments addressing mood disorders in these patients, which are, to date, lacking.

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