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TITLE PAGE

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

Short Title: Effect of Psychological Co-morbidity in IBD.

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Abbreviations:

ANOVA	analysis of variance
CD	Crohn's disease
CI	confidence interval
FC	faecal calprotectin
HADS	hospital anxiety and depression scale
HBI	Harvey-Bradshaw index
HR	hazard ratio
IBD	inflammatory bowel disease
PHQ-12	patient health questionnaire-12
RCT	randomised controlled trial

SCCAI	simple clinical colitis activity index
SF-36	medical outcomes study 36-item short form
UC	ulcerative colitis

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SUMMARY

Background: Psychological co-morbidity is more common in patients with inflammatory bowel disease (IBD), compared with the general population but little is known about the cumulative effect of increasing psychological burden on disease behaviour.

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

Methods: We collected complete demographic, symptom, and psychological co-morbidity data (anxiety, depression, and somatisation scores) at baseline from adults with IBD in biochemical remission (faecal calprotectin <250μg/g). Objective markers of disease activity, including glucocorticosteroid prescription or flare of disease activity, escalation of therapy, hospitalisation, or intestinal resection, were reviewed ≥2 years of follow-up. We performed multivariate Cox regression, controlling for patient characteristics and follow-up duration, to examine cumulative effect of psychological co-morbidities on subsequent IBD behaviour.

Results: Among 228 participants, 48 (22.0%) had one, 13 (6.0%) two, and nine (4.0%) three psychological co-morbidities at baseline. Following multivariate Cox regression analysis, glucocorticosteroid prescription or flare, and escalation of medical therapy, were significantly higher among those with two (hazard ratio (HR) = 3.18; 95% confidence interval (CI), 1.44-7.02, and HR = 2.48; 95% CI 1.03-5.93, respectively) or three (HR = 3.53; 95% CI 1.26-9.92, and HR = 8.19; 95% CI 2.88-23.23, respectively) psychological co-morbidities. Occurrence of at least one endpoint of interest, was significantly higher with increasing psychological co-morbidity (HR = 1.74; 95% CI 1.07-2.82 for one, 2.47; 95% CI 1.12-5.46 for two, and 4.93; 95% CI 1.84-13.17 for three psychological co-morbidities).

Conclusions: Individuals with IBD in biochemical remission experienced a worse disease course with increasing psychological co-morbidity at baseline.

Key Words: inflammatory bowel disease, anxiety, depression, somatisation, mood disorders, psychological co-morbidity

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions of the gastrointestinal tract which characteristically cycle through periods of relapse and remission. During episodes of flare, symptoms consistent with loose stool, abdominal pain, weight loss and bleeding per rectum predominate. The pathogenesis of inflammatory bowel disease (IBD) is thought to be a combination of genetic and environmental factors, combined with alterations in the intestinal microbiota and immunological dysregulation.[1, 2] There is also increasing evidence of communication via the brain-gut axis through stimulation of the autonomic and central nervous system combined with influences from the hypothalamic-pituitary-adrenal axis signalling a hormonal, neural and immune response.[3-5]

Although the impact of psychological factors in IBD is not fully understood, psychological co-morbidity is more common in patients with IBD, compared with the general population. A meta-analysis reported that symptoms of depression and anxiety are more common in women with IBD, compared with men, and those with CD, compared with UC. The pooled prevalence of anxiety or depression in IBD was 32% and 25% respectively, but this was as high as 58% and 39% during periods of disease activity.[6] Chronic mood disorders can lead to suppression of parasympathetic activity. For those with IBD with major depressive disorders this can lead to difficulty in achieving remission, and the need for early escalation of therapy.[7] An increasing number of large observational studies have reported independent associations between self-reported features of anxiety or depression and adverse outcomes in IBD, including higher rates of relapse of disease activity, hospitalisation, and escalation of therapy, as well as an increased risk of intestinal surgery.[8-12]

Most studies examining the impact of psychological disturbance in IBD have used self-reported measures, whereas a diagnosis of anxiety or depression requires persistent symptoms for a prolonged period in several domains. The International Classification of Disease 10th edition includes low energy, diminished appetite, and disturbed sleep as associated symptoms in the diagnostic criteria for depression, suggesting an overlap with features of somatisation. Recent studies have suggested that mood disorders can predate a diagnosis of IBD by several years, but those with coexistent somatic symptoms, rather than cognitive elements alone, appear to be at higher risk.[13, 14] This would suggest that somatisation, alongside mood disturbance, is more likely to result in an adverse disease course. A number of randomised controlled trials (RCTs) focusing on efficacy of psychological interventions in IBD have failed to show any effect on disease activity outcomes, despite improved mood scores.[15] Targeting patients with features of psychological co-morbidity, alongside persistent gastrointestinal symptoms, may be more likely to demonstrate that such an approach is beneficial.

Although the evidence to support an impact of psychological co-morbidity on IBD activity is increasing, there is little published on the cumulative impact of multiple psychological co-morbidities on disease outcomes in IBD, unlike in functional gastrointestinal disorders, such as irritable bowel syndrome.[16] We aimed to examine the effect of increasing levels of psychological co-morbidity on subsequent IBD activity during longitudinal follow-up in patients in remission at study entry. Due to the potential confounding effects of psychological co-morbidity on gastrointestinal symptom-reporting, and therefore clinical disease activity indices,[17] we used a cohort of patients with confirmed biochemical remission at baseline.

METHODS

Participants and Setting

Between November 2012 to June 2015 patients aged ≥16 years with an established radiological, endoscopic or histological diagnosis of CD or UC were recruited into a cross-sectional study and sent a follow-up invitation 2 years later.[17] Patients with IBD-unclassified, end ileostomy, or colostomy were excluded due to potential inaccuracies in assessing clinical disease activity. Inability to understand written English was also an exclusion criterion. Longitudinal follow up was conducted between September 2014 to June 2017 (REC ref: 12/YH/0443). A follow-up questionnaire with consent form and patient information sheet was sent out to all those who responded to the baseline survey, with non-responders to postal questionnaires asked to participate during their scheduled outpatient appointments. Study findings were reported in accordance with the STROBE guidelines for reporting observational studies.[18]

Data Collection and Synthesis

As previously described, the date of original recruitment, IBD type, IBD-related medications and demographic data were recorded. At baseline and follow-up, symptoms of anxiety and depression were assessed with the hospital anxiety and depression scale (HADS),[19] and somatisation via the patient health questionnaire-12 (PHQ-12).[20] Quality of life was measured using the medical outcomes study 36-item short form (SF-36).[21]

As recommended in the original validation study, a HADS anxiety or depression score of ≥11 was classified as abnormal,[19] while somatisation severity was classified as high if the total

PHQ-12 was ≥13.[20] We used these data to categorise patients according to the total number of psychological co-morbidities they exhibited, from a possible total of three, including one or more of abnormal anxiety scores, abnormal depression scores, and high somatisation scores.

Clinical disease activity was measured using the Harvey-Bradshaw index (HBI) for CD,[22] and the simple clinical colitis activity index (SCCAI) for UC,[23] with a score of <5 used to define clinical remission in both, as recommended previously.[24, 25] Alongside this, patients provided a faecal calprotectin (FC) sample for analysis (Immundiagnostik, Blensheim, Germany) with biochemical remission defined as FC <250μg/g of stool, as supported by international consensus.[26]

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

Statistical Analysis

We compared the characteristics of those with no psychological co-morbidity at baseline to those with one, two, or three psychological co-morbidities. We used a χ^2 test for categorical

variables, an independent samples *t*-test for normally distributed continuous data, and the Mann-Whitney U test for non-parametric continuous data. For comparison across all four groups, a χ^2, one-way analysis of variance (ANOVA), or a Kruskal-Wallis ANOVA test were applied, as appropriate.

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

RESULTS

In total, 228 individuals provided complete HADS and PHQ-12 data at baseline and were in biochemical remission at study entry, with a FC ≤250μg/g. Of these, 218 (95.6%) participants provided complete data during longitudinal follow-up, with 48 (22.0%) participants reporting symptoms compatible with one, 13 (6.0%) two, and nine (4.1%) three psychological co-morbidities. Those with no psychological co-morbidity at baseline were significantly older (p = 0.001), and more likely to be in clinical remission at baseline (HBI or SCCAI score <5; p <0.001) (Table 1). There were no other significant differences according to other baseline characteristics including current medical therapy, IBD sub-type, disease extent, or disease distribution. Quality of life scores, according to the SF-36, were significantly lower across all domains with increasing number of psychological co-morbidities.

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

Glucocorticosteroid Prescription or Flare of Disease Activity

Of the 218 patients in biochemical remission at baseline, 81 (37.2%) required a prescription of glucocorticosteroids or reported a flare of disease activity during a mean of 858.5 days of longitudinal follow-up. Of these, 37 (45.7%) had at least one psychological co-morbidity at baseline, with an increased risk of glucocorticosteroid prescription or flare compared with those with no psychological co-morbidity at baseline (p = 0.004; Table 2). Following multivariate Cox regression analysis controlling for baseline data, rates of glucocorticosteroid prescription or flare were significantly higher among those with either two (HR = 3.18; 95% CI,

1.44 to 7.02) or three (HR = 3.53; 95% CI 1.26 to 9.92) psychological co-morbidities (Figure 1). There was no impact of sex, type of IBD, or IBD-related medications in Cox regression analysis.

Escalation of Medical Therapy due to Disease Activity

In total 73 (33.5%) of the 218 patients required escalation of therapy for IBD activity during a mean follow-up of 882.6 days. Of these, 33 (45.2%) had at least one psychological co-morbidity. The proportion of patients requiring escalation increased according to number of psychological co-morbidities ($p = 0.01$; Table 2). Following multivariate Cox regression analysis, again presence of two (HR = 2.48; 95% CI 1.03 to 5.93) or three (HR = 8.19; 95% CI 2.88 to 23.23) psychological co-morbidities was significantly associated with escalation of medical therapy (Figure 2), but there was no impact of sex, type of IBD, or IBD-related medications.

Hospitalisation or Intestinal Resection due to Active IBD

The numbers of patients requiring hospitalisation or intestinal resection during the study period were smaller. Overall, 19 (8.7%) patients required hospitalisation and seven (3.2%) intestinal resection during a mean of 1064.7 and 1100.9 days of follow-up respectively. Among those hospitalised, 10 (52.6%) had at least one psychological co-morbidity at baseline ($p = 0.04$; Table 2). Among those requiring intestinal resection four (57.1%) had at least one psychological co-morbidity at baseline. However, there was no association between number of psychological co-morbidities at baseline and need for hospitalisation or intestinal resection after multivariate Cox regression, and no impact of sex, type of IBD, or IBD-related medications.

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

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

In total, 95 (43.6%) patients experienced one or more of the four endpoints of interest. Using a composite endpoint of the occurrence of any of these four outcomes there were significantly higher rates of one or more of these endpoints occurring among those with one (p = 0.003) or two (p = 0.02) psychological co-morbidities at baseline, compared with those with none (Table 2). After multivariate Cox regression analysis, increasing psychological co-morbidity at baseline was significantly associated with the occurrence of one or more of the four outcomes of interest (HR = 1.74; 95% CI 1.07 to 2.82 for one psychological co-morbidity, HR = 2.47; 95% CI 1.12 to 5.46 for two, and HR = 4.93; 95% CI 1.84 to 13.17 for three psychological co-morbidities) (Figure 3). There was no impact of sex, type of IBD, or IBD-related medications in Cox regression analysis.

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

Of the 218 patients included at baseline, 78 (35.8%) required escalation, hospitalisation, or intestinal resection due to active IBD, and 35 (44.9%) of these had at least one psychological co-morbidity at baseline. There was an increasing likelihood of one or more of these endpoints occurring with increasing numbers of psychological co-morbidities at baseline (p = 0.01; Table 2). After multivariate Cox regression analysis, there was no significant increase in likelihood of

any of these events of interest among patients with one or two psychological co-morbidities at baseline, but those with three psychological co-morbidities were more likely to need to escalate therapy, require hospitalisation, or undergo intestinal resection during the study period (HR = 5.92; 95% CI 2.12 to 16.52) (Figure 4). There was no impact of sex, type of IBD, or IBD-related medications in Cox regression analysis.

DISCUSSION

This longitudinal study supports other existing literature suggesting that psychological co-morbidity is independently linked to future adverse outcomes in patients with IBD in remission. As previously described,[6, 27] one-in-three of the patients with IBD in biochemical remission in this study self-reported symptoms consistent with at least one psychological co-morbidity at baseline. Importantly, we were able to demonstrate a cumulative impact of number of psychological co-morbidities on subsequent disease behaviour. Those with more than one psychological co-morbidity had a significantly higher risk of glucocorticosteroid prescription or flare of disease activity, as well as a need to escalate therapy due to poorly controlled IBD activity. Using a composite of any of the four outcomes of interest the same pattern was observed, and even when the more subjective glucocorticosteroid prescription or flare of disease activity was omitted, the results of our analysis remained the same. The results of this study underline the need to integrate a holistic biopsychosocial care model into the management of patients with IBD.

We recruited an unselected cohort of patients via their routine outpatient appointments and therefore our findings are likely to be representative to the many patients with IBD in remission. We used a stringent definition of remission, according to FC results at study entry, to remove any influence of ongoing occult inflammation, and control for the potential relationship between clinical disease activity indices, which rely on patient report, and psychological co-morbidity on our results. An FC of ≥250μg/g is accepted by expert opinion as an appropriate level to detect a flare of IBD activity and supported by international consensus.[26] In Cox regression analyses, we adjusted for all baseline characteristics, including age, sex, marital status, educational level, type of IBD, and use of glucocorticosteroids, immunomodulators and

anti-TNF therapy. We were also conservative in our criteria for defining presence of psychological co-morbidity, only classifying those with definitely abnormal HADS scores as having evidence of psychological co-morbidity.

Nevertheless, there are some limitations. Although patients were in biochemical remission at study entry, this does not exclude the fact that they may have had severe disease at some point prior to recruitment, and that this has led to psychological co-morbidity. In this case, it may be that it is the continuing impact of the severity of disease prior to study entry, rather than psychological co-morbidity, that is affecting the natural history of the disease adversely. The study also relied on evidence of psychological co-morbidity measured at a single time point, and via self-report, which is not a definitive diagnosis of a common mental disorder. Psychological disorders have the potential to fluctuate in severity over time, but persistently abnormal mood scores, such as those seen in major depressive disorder, may be associated with higher disease activity scores, poorer quality of life, and lower rates of remission.[28] The limited time points examined in this longitudinal study may not take into account potential variations in symptoms of psychological co-morbidity over time, which might help better characterise a particularly high risk group of patients.

Due to the stringent criteria for inclusion, the number of patients eligible for inclusion was relatively small, and the study is likely underpowered for some of the less frequently occurring endpoints. Despite this, when all four endpoints of interest were combined, or when escalation due to disease activity, hospitalisation, and intestinal resection were considered, there remained a cumulative effect of increasing psychological co-morbidity on adverse disease outcomes. Flare and glucocorticosteroid prescription events were the most common occurrences. A flare of disease activity based on a physician's global assessment could be influenced by the

subjective nature of self-reported gastrointestinal symptoms without evidence of ongoing inflammation, and an association between psychological co-morbidity and gastrointestinal symptom-reporting *per se* has been recognised in several studies.[12, 29, 30] Escalation of therapy based on clinical indices alone, particularly in those with mood disorders, has not been shown to alter long-term outcomes in IBD.[7, 31] Previous research from our group supports this, with no evidence of an association between the reporting of symptoms compatible with irritable bowel syndrome in patients with IBD in remission, and future adverse clinical outcomes during longitudinal follow-up.[32]

Functional gastrointestinal disorders are common in patients with IBD, with a prevalence of symptoms compatible with irritable bowel syndrome in up to 25% despite histological or endoscopic evidence of remission,[33] which is much higher than in the general population.[34] Anxiety and depression are also more prevalent in patients with IBD with irritable bowel syndrome-type symptoms,[35, 36] and may pre-date symptom onset.[37] The brain-gut axis incorporates a bi-directional effect; as psychological co-morbidity increases, so does the likelihood of developing gastrointestinal symptoms in the future.[38] Conversely persistent IBD activity is associated with future development of psychological co-morbidity.[8] Although both psychological therapies and gut-brain neuromodulators are beneficial in patients with IBS,[39] the evidence for their use in IBD is not as conclusive. In a meta-analysis of 14 RCTs there appeared to be some short-term benefit on depression scores from psychological therapies, however this effect waned over time.[15] Despite this, there are few RCTs examining the efficacy of gut-brain neuromodulators in IBD on mood disorders, although there have been some encouraging results from observation and retrospective studies.[40] One of the reasons for lack of convincing efficacy observed in trials to date may be the recruitment of unselected patients with IBD, rather than

focusing on only those with evidence of psychological co-morbidity. A recent retrospective analysis of those undergoing major abdominal surgery in relation to IBD, highlighted a significant association to those patients with a pre-existing established diagnosis of anxiety or depression,[41] supporting the bi-directional influence of the brain-gut axis. The objective endpoints highlighted in our study, further support this theory that increased psychological burden independently increase the risk of occult inflammation over time.

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

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Table 1: Baseline Characteristics of Patients According to Number of Psychological Co-morbidities at Baseline.

	No psychological co-morbidity (n = 148)	**One psychological co-morbidity (n = 48)**	***p* value***	**Two psychological co-morbidities (n = 13)**	***p* value***	**Three psychological co-morbidities (n = 9)**	***p* value***	***p* value****
Mean age in years (SD)	51.5 (17.0)	41.7 (11.8)	<0.001	42.4 (15.1)	0.06	45.8 (13.6)	0.33	0.001
Female sex (%)	82 (55.4)	30 (62.5)	0.39	10 (76.9)	0.13	7 (77.8)	0.19	0.25
BMI (SD)	26.2 (5.1)	26.1 (5.6)	0.88	25.8 (4.8)	0.78	26.89 (8.4)	0.83	0.98
Married or co-habiting (%)	103 (69.6)	32 (66.7)	0.70	9 (69.2)	0.98	2 (22.2)	0.003	0.03
Caucasian ethnicity (%)	143 (96.6)	48 (100)	0.20	13 (100)	0.50	8 (88.9)	0.24	0.23
University graduate/professional (%)	47 (31.8)	13 (27.1)	0.54	3 (6.3)	0.52	1 (11.1)	0.19	0.53
Tobacco user (%)	16 (10.8)	7 (14.6)	0.48	4 (30.8)	0.04	2 (22.2)	0.297	0.18
Alcohol user (%)	99 (66.9)	33 (68.8)	0.86	8 (61.5)	0.67	4 (44.4)	0.159	0.52
CD (%)	82 (55.4)	30 (62.5)	0.39	8 (61.5)	0.67	3 (33.3)	0.197	0.41
CD distribution (%)								
Ileal	11/82 (13.4)	10/30 (33.3)		1/8 (12.5)		1/3 (33.3)		
Colonic	34/82 (41.5)	8/30 (26.7)		4/8 (50.0)		1/3 (33.3)		
Ileocolonic	37/82 (45.1)	12/30 (40.0)	0.05	3/8 (37.5)	0.89	1/3 (33.3)	0.62	0.32

CD behavior (%)								
Non-stricturing, non-penetrating	75/82 (91.5)	24/30 (80.0)		7/8 (87.5)		2/3 (66.7)		
Stricturing	4/82 (4.9)	4/30 (13.3)		0/8		0/3		
Penetrating	3/82 (3.7)	2/30 (6.7)	0.23	1/8 (12.5)	0.43	1/3 (33.3)	0.06	0.17
Perianal CD (%)	7/82 (8.5)	2/30 (6.7)	0.75	0/8	0.39	0/3	0.60	0.79
Previous intestinal resection in CD (%)	26/82 (31.7)	10/30 (33.3)	0.870	3/8 (37.5)	0.738	2/3 (66.7)	0.206	0.65
UC extent (%)								
Proctitis	16/65 (24.6)	6/18 (33.3)		2/5 (40.0)		3/6 (50.0)		
Left-sided	34/65 (52.3)	9/18 (50.0)		1/5 (20.0)		2/6 (33.3)		
Extensive	15/65 (23.1)	3/18 (16.7)	0.71	2/5 (40.0)	0.38	1/6 (16.7)	0.40	0.67
5-ASA use (%)	84 (56.8)	22 (45.8)	0.19	5 (38.5)	0.20	7 (77.8)	0.22	0.17
Immunomodulator use (%)	53 (35.8)	20 (41.7)	0.47	4 (30.8)	0.72	2 (22.2)	0.41	0.67
Anti-TNFα use (%)	28 (18.9)	14 (29.2)	0.13	2 (15.4)	0.75	0	0.15	0.17
Glucocorticosteroid use (%)	9 (6.1)	6 (12.5)	0.146	2 (15.4)	0.202	2 (22.2)	0.065	0.18
HBI/SCCAI <5 (%)	107 (74.8)	27 (57.4)	0.02	6 (46.2)	0.03	0	<0.001	<0.001
Median FC (IQR)	57.6 (40.5-97.2)	83 (40.4-126.6)	0.19	178 (47.4-207.1)	0.03	69.3 (31.5-100.2)	0.96	0.112
Median HADS anxiety score (IQR)	5 (2-7)	12 (11-14)	<0.001	15 (12-17)	<0.001	18 (12-20)	<0.001	<0.001

Anxiety categories (%)								
Normal	117 (79.1)	3 (6.3)		0		0		
Borderline abnormal	31 (20.9)	8 (16.7)		0		0		
Abnormal	0	37 (77.1)	<0.001	13 (100)	<0.001	9 (100)	<0.001	<0.001
Median HADS depression score (IQR)	2(1-4)	7 (5-9)	<0.001	11 (9-16)	0.001	14 (12.5-17.5)	<0.001	<0.001
Depression categories (%)								
Normal	142 (95.9)	25 (52.1)		2 (15.4)		0		
Borderline abnormal	6 (4.1)	19 (39.6)		2 (15.4)		0		
Abnormal	0	4 (8.3)	<0.001	9 (69.2)	<0.001	9 (100)	<0.001	<0.001
Median PHQ-12 score (IQR)	5 (3-8)	9 (6-12)	<0.001	11 (11-13.5)	<0.001	14 (13.3-16.5)	<0.001	<0.001
PHQ-12 somatisation categories (%)								
Mild	46 (31.1)	3 (6.3)		0		0		
Low	64 (43.2)	15 (31.3)		2 (15.4)		0		
Medium	38 (25.7)	23 (47.9)		7 (53.8)		0		
High	0	7 (14.6)	<0.001	4 (30.8)	<0.001	9 (100)	<0.001	<0.001

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

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

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

Table 2: Clinical Outcomes of Patients According to Number of Psychological Co-morbidities at Baseline.

	No psychological co-morbidity (n = 148)	**One psychological co-morbidity (n = 47)**	***p* value***	**Two psychological co-morbidities (n = 13)**	***p* value***	**Three psychological co-morbidities (n = 9)**	***p* value***	***p* value****
Individual disease activity outcomes (%)								
Flare (n = 81)	44 (29.7)	23 (48.9)	0.02	9 (69.2)	0.004	5 (55.6)	0.10	0.004
Escalation (n = 73)	40 (27)	20 (42.6)	0.05	7 (53.8)	0.04	6 (66.7)	0.01	0.01
Hospitalisation (n = 19)	9 (6.1)	8 (17.0)	0.02	0 (0.0)	0.36	2 (22.2)	0.07	0.04
Resection (n = 7)	3 (2.0)	4 (8.5)	0.04	0 (0.0)	0.60	0 (0.0)	0.67	0.13
Composite disease activity outcomes (%)								
Flare, escalation, hospitalisation, or resection (n = 95)	52 (35.1)	28 (59.6)	0.003	9 (69.2)	0.02	6 (66.7)	0.06	0.002
Escalation, hospitalisation, or resection (n = 78)	43 (29.1)	22 (46.8)	0.02	7 (53.8)	0.06	6 (66.7)	0.02	0.01

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

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

Figure 1. Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity According to Number of Psychological Co-morbidities at Baseline.

Figure 2. Survival Analysis for Occurrence of Escalation of Medical Therapy due to Disease Activity According to Number of Psychological Co-morbidities at Baseline.

Figure 3. Survival Analysis for Occurrence of Glucocorticosteroid Prescription or Flare of Disease Activity, Escalation of Medical Therapy due to Disease Activity, Hospitalisation, or Intestinal Resection due to Active IBD According to Number of Psychological Co-morbidities at Baseline.

Figure 4. Survival Analysis for Occurrence Escalation of Medical Therapy due to Disease Activity, Hospitalisation, or Intestinal Resection due to Active IBD According to Number of Psychological Co-morbidities at Baseline.