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TITLE PAGE

Title: Negative Effects on Psychological Health and Quality of Life of Genuine Irritable Bowel Syndrome-type Symptoms in Patients With Inflammatory Bowel Disease

Short "running" title: Irritable Bowel Syndrome-type Symptoms in Inflammatory Bowel Disease.

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Abbreviations:

5-ASA	5-aminosalicylates
ANOVA	analysis of variance
BMI	body mass index
CI	confidence interval
CD	Crohn's disease

FC	fecal calprotectin
GI	gastrointestinal
HADS	hospital anxiety and depression scale
HBI	Harvey-Bradshaw index
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
OR	odds ratio
PHQ	patient health questionnaire
SCCAI	simple clinical colitis activity index
SD	standard deviation
SF-36	short-form 36
TNFα	tumor necrosis factor-α
UC	ulcerative colitis

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ABSTRACT

Background & Aims: Symptoms compatible with irritable bowel syndrome (IBS) are common in patients with inflammatory bowel disease (IBD), but it is unclear whether this relates to occult IBD activity. We attempted to resolve this issue in a secondary care population using a cross-sectional study design.

Methods: We analyzed Rome III IBS symptoms; disease activity indices; and psychological, somatization, and quality of life data from 378 consecutive, unselected adult patients with IBD seen in clinics at St. James's University Hospital in Leeds, United Kingdom, from November 2012 through June 2015. Participants provided a stool sample for fecal calprotectin (FC) analysis; levels of ≥250 μg/g were used to define mucosal inflammation. Using symptom data and FC levels we identified 4 distinct groups of patients: those with true IBS-type symptoms (IBS-type symptoms with FC levels <250 μg/g, regardless of disease activity indices), quiescent IBD (no IBS-type symptoms with FC levels <250 μg/g, regardless of disease activity indices), occult inflammation (normal disease activity indices and FC levels ≥250 μg/g, regardless of IBS symptom status), or active IBD (abnormal disease activity indices with FC levels ≥250 μg/g, regardless of IBS symptom status). We compared characteristics between these groups.

Results: Fifty-seven of 206 patients with Crohn's disease (27.7%), and 34 of 172 patients with ulcerative colitis (19.8%) had true IBS-type symptoms. Levels of psychological co-morbidity and somatization were significantly higher among patients with true IBS-type symptoms than patients with quiescent IBD or occult inflammation. Quality of life levels were also significantly reduced compared with patients with quiescent disease or occult inflammation, and were similar to those of patients with active IBD. Using FC levels of ≥100

µg/g to define mucosal inflammation, we found a similar effect of IBS-type symptoms on psychological health and quality of life.

Conclusions: In a cross-sectional study, we identified a distinct group of patients with IBD and genuine IBS-type symptoms in the absence mucosal inflammation. These symptoms had negative effects on psychological wellbeing and quality of life—to the same degree as active IBD. New management strategies are required for this patient group.

KEY WORDS: irritable bowel syndrome, QOL, CD, UC, prevalence

The inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic disorders of the gastrointestinal (GI) tract, with a combined prevalence in Western populations as high as 450 per 100,000. [1] In contrast, irritable bowel syndrome (IBS) is a functional GI disorder, affecting 10-20% of individuals worldwide. [2] The etiology of these conditions is uncertain, although some of the proposed pathophysiological mechanisms, including dysregulation of the mucosal immune system and intestinal barrier dysfunction, may be shared. [3]

Given that CD and UC are lifelong conditions without cure, there is the potential for patients to be faced with many years of chronic GI symptoms and, as IBS is a highly prevalent condition, it is also plausible that a proportion of these symptoms may be secondary to co-existent IBS. A recent systematic review and meta-analysis of studies reporting IBS-type symptoms in IBD suggested an overall prevalence of between 35% and 44%. [4] However, among the 13 included studies, only two assessed for evidence of ongoing disease activity among those who reported these symptoms, [5, 6] using fecal calprotectin (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 genuine functional 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 biologics in patients with functional symptoms, when in fact other management strategies are required.

We have therefore examined this issue in a large cohort of IBD patients, 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. Our hypothesis was that there is a subset of IBD patients

with genuine IBS-type symptoms, and that these symptoms would impact negatively on 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.

METHODS

Participants and Setting

All individuals who participated had an established radiological, histological or endoscopic diagnosis of CD or UC. Unselected consecutive patients aged ≥16 years attending the IBD clinic at St. James's University Hospital, Leeds, United Kingdom, which serves a local population of 800,000 people, were approached about the study. Exclusion criteria were an inability to understand written English, a diagnosis of IBD-unclassified, isolated fistulizing peri-anal CD, or anyone with an end ileostomy or colostomy, due to the difficulties in assessing disease activity indices in these patients. At the clinic attendance, prior to the consultation with a gastroenterologist, individuals were presented with an information sheet explaining the nature of the study. Those who agreed to take part provided written informed consent at this visit. The study was approved by the local research ethics committee in November 2012, and data collection continued until June 2015. Data collection and synthesis are described in detail in the Supplementary Methods.

Statistical Analysis

We compared 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 somatization 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 cut off of <250μg/g of stool to define no evidence of mucosal inflammation we compared baseline demographic characteristics, HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatization between those with true 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, as well as across all four groups using a χ^2 test for categorical variables and a one-way analysis of variance (ANOVA) for continuous data. We repeated these comparisons between the same four categories, but using an FC of <100μg/g to define no evidence of mucosal inflammation (see Supplementary Results). 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 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 378 patients with IBD provided informed consent to participate and had complete data. Of these, 206 (54.5%) had confirmed CD and 172 (45.5%), UC. Characteristics of UC and CD patients are provided in Table 1. 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 Crohn's disease 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.

Effect of FC Analysis Using a Cut Off <250µg/g on Disease Activity Status and Characteristics of IBD patients with and without IBS-type Symptoms

Among the 206 CD patients, 57 (27.7%) were ultimately classified as having true 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 1). 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 had true IBS-type symptoms, whereas 31 (39.7%) of 78 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 true IBS-type symptoms and those with active disease, compared with the other two groups, and also more tobacco users among those with true IBS-type symptoms compared with those with quiescent CD, but no other differences in demographic characteristics (Table 2). Of note was that mean anxiety,

depression, and somatization scores were all significantly higher in CD with true 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 somatization in the CD with true 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 CD patients with true 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 disease.

Among the 172 UC patients, 34 (19.8%) were classified as true 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 2). 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 had true 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 somatization scores were all significantly higher in those with true 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 3). There were also significantly more patients who met criteria for anxiety, depression, or somatization in the group with true IBS-type symptoms than among those with either quiescent UC, or UC with occult inflammation. Mean quality of life scores were significantly lower in patients with true IBS-type symptoms compared with quiescent UC

patients 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. Again, quality of life scores were impaired to a similar degree to those with active UC.

DISCUSSION

This cross-sectional study has demonstrated an overall prevalence of IBS-type symptoms in outpatients with IBD of between 30% and 45%, with symptoms more commonly observed in patients with CD than UC. After utilizing FC analysis to minimize the likelihood of ongoing mucosal inflammation, approximately two-thirds of patients who met criteria for IBS were still felt to have genuine IBS-type symptoms, rather than occult inflammation or active disease, and between 26% and 41% of those who reported symptoms compatible with active disease were reclassified as having IBS-type symptoms. Among both CD and UC patients with true IBS-type symptoms there was substantial psychological co-morbidity, with the prevalence and severity of anxiety, depression, and somatization 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 CD and UC patients with quiescent disease or occult inflammation, and was of a similar magnitude to those with active disease. It may be that the presence of any GI symptoms in the absence of objective evidence of mucosal inflammation, including those incorporated in the clinical disease activity indices we used, is associated with poor psychological health and reduced quality of life, but this issue was not one our study aimed to examine.

Strengths of this study include the fact that we recruited a well-characterized group of consecutive unselected patients, collecting data on both presence of IBS-type symptoms and disease activity indices, as well as using FC as an objective quantitative measure of disease activity, in order to categorize patients in to those with true IBS-type symptoms, quiescent disease, occult inflammation, or active disease. FC is known to correlate well with endoscopic disease activity scores, [7] and more recently has been identified as a useful marker of small bowel inflammation in CD, when compared with magnetic resonance enterography.

[8] Our sample size of 378 patients is larger than previous studies examining this issue, [5, 6] and the fact that the study was conducted in a secondary care clinic, means that our results are likely to be generalizable to usual clinical practice. Finally, we used validated questionnaires to assess for presence of anxiety or depression, somatization, quality of life and the presence of IBS-type symptoms, albeit that the Rome III questionnaire has not been validated for use in patients with IBD. However, recent work from our group suggests that endorsement of these criteria correlates with higher clinical disease activity indices, which themselves appear to correlate with somatoform-type symptom reporting in both CD and UC. [9]

Given that this was a cross-sectional study, an obvious weakness is that causality cannot be implied by our results. Furthermore, one-in-three CD patients had undergone intestinal resection previously and, given that bile acid diarrhea or small intestinal bacterial overgrowth may occur as a result of surgery, [10, 11] and that there is overlap between the symptoms of these conditions and those of IBS, [12, 13] it is possible that we have overestimated the prevalence of IBS. In addition, gold-standard investigations for IBD activity, including small bowel imaging and ileocolonoscopy were not performed routinely as the study was conducted within usual clinical practice. This means that we cannot exclude the fact that there was ongoing mucosal inflammation or, in those with CD, occult fibrostenotic small bowel disease in some individuals who met criteria for IBS, although no difference in disease behavior was observed across the four groups. However, only 24% of included patients with CD and IBS-type symptoms had isolated small bowel disease, and even when we used a FC cut off <100µg/g, 18% of those with CD, and 11% of those with UC still had true IBS-type symptoms. There were fewer statistically significant differences between groups when a FC cut off <100µg/g was used, although this was likely due to a reduction in the size of the groups of individuals with either true IBS-type symptoms or quiescent disease. When analyses using this cut off were repeated for CD and UC patients together, the differences in

psychological co-morbidity and quality of life in those with IBS-type symptoms became statistically significant once again. The lack of a control group meant that we could not compare the impact of IBS-type symptoms on psychological health and quality of life in patients with IBD to that in patients with confirmed IBS. Finally, we did not collect data delineating the brain-gut constructs involved in the generation of IBS-type symptoms in patients with IBD, which may have allowed exploration of the mechanisms by which these symptoms occur.

Several studies have investigated the prevalence of IBS-type symptoms in patients with IBD, and their association with psychological co-morbidity. However, only two, to our knowledge, have utilized an objective measure of mucosal inflammation. [5, 6] Keohane et al. assessed the prevalence of IBS-type symptoms, and their impact on quality of life and depression scores in 106 IBD patients, and found that 60% of CD and 39% of UC patients in clinical remission met the Rome II criteria for IBS. [5] Quality of life scores were lower, and depression scores higher in UC, but not CD, patients 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 true IBS. In contrast, Berrill et al. recruited 169 IBD patients, and reported that 32% of those in clinical remission reported IBS-type symptoms, again with higher anxiety and depression scores in the IBS group, [6] with no differences in FC levels between those with and without IBS-type symptoms, but only 61 patients returned a stool sample. Whilst our findings suggest a similar prevalence of IBS-type symptoms in patients in clinical remission, these studies did not use FC levels to define a genuine subset of IBD patients with true IBS-type symptoms, nor were they large enough to explore the characteristics of this group. In addition, given that the mean FC levels we observed in UC and CD patients with true IBS-

type symptoms were very similar to those with quiescent disease, our findings do not support occult disease activity as the sole cause of these symptoms.

The etiology of functional symptoms in IBD remains uncertain, and is likely to be multi-factorial. Higher levels of peripheral and mucosal pro-inflammatory cytokines have been demonstrated in IBS patients,[14] and it may be that in IBD a low-grade inflammation, distinct from that of overt disease activity, leads to activation of the enteric nervous system, epithelial barrier dysfunction, increased mucosal permeability, visceral hypersensitivity, and activation of the brain-gut axis, resulting in the generation of IBS-type symptoms. The cause of this ongoing low-grade inflammation could be perturbations in the intestinal microbiome, with a relative abundance of pro-inflammatory bacterial species having been previously described in IBS. [15] Activation of the brain-gut axis may also be responsible for the development of psychological co-morbidity. However, whether this arises de novo, as a consequence of IBS-type symptoms, or whether functional symptoms arise secondary to pre-existing anxiety and depression is unclear. Evidence to support a bi-directional relationship between the brain and gut has been described in animal models of disease, where mice with chronic GI inflammation develop behavioral changes similar to mood disorders in humans, [16] and inducing depression in murine models of quiescent colitis results in reactivation of disease, [17] which may be attenuated by the administration of antidepressant medication. [18] Our data provide support for the same bi-directional effect in humans. Those with IBS-type symptoms and those with active disease had higher levels of anxiety, depression, and somatization 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, disease activity, and presence of IBS-type symptoms will be needed to prove this hypothesis.

Our study has 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 true IBS-type symptoms is likely to occur. Secondly, although escalation of conventional immunosuppressant and biological therapies has been advocated previously in these patients, [3] current data do not support the efficacy of such drugs when objective evidence of disease activity is lacking. [19] In addition, this approach may be expensive and could expose patients to potential unnecessary risks associated with these therapies. [20, 21] Despite this, there is a paucity of evidence for alternative approaches in this group of patients, and controlled trials of psychological and pharmacological therapies, including antidepressants, as well as manipulation of the intestinal microbiota by probiotics or fecal microbial transfer may be required.

In summary, genuine IBS-type symptoms in IBD are common, and are associated with higher levels of anxiety, depression, and somatization, and reduced quality of life. Previous investigators have suggested that functional symptoms in IBD are secondary to occult disease activity. However, our study has identified a distinct group of patients with ongoing GI symptoms in the absence of objective evidence of disease activity, and demonstrates that the presence of these symptoms impacts negatively on both psychological wellbeing and quality of life, to the same degree as 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.

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TABLES

Table 1: Characteristics of Patients with CD and UC.

	CD (n = 206)	**UC (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
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
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 score (SD)	10.3 (4.7)	9.0 (5.2)	0.012

PHQ-15 somatization 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
Mean SF-36 score (SD)			
Physical functioning	73.1 (29.5)	79.0 (24.2)	0.04
Role limitations physical health	52.4 (43.4)	61.5 (42.8)	0.05
Role limitations emotional problems	67.5 (43.2)	70.0 (41.4)	0.57
Energy/fatigue	41.2 (23.7)	48.7 (23.5)	0.004
Emotional well-being	66.5 (19.9)	69.0 (21.5)	0.27
Social functioning	65.5 (29.3)	71.1 (28.7)	0.07
Pain	59.6 (26.6)	67.9 (25.9)	0.002
General health	43.9 (22.6)	54.6 (24.4)	<0.001

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

†N/A; not applicable.

Table 2: Disease Activity Status and Characteristics of CD Patients After FC Analysis Using a Cut Off <250µg/g.

	CD with true IBS (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
CD 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
CD behavior (%)								
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
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
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 somatization 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
Mean SF-36 score (SD)								
Physical functioning	70.8 (26.2)	78.5 (29.8)	0.13	74.6 (29.0)	0.49	62.5 (32.9)	0.24	0.09
Role limitations physical health	36.8 (40.1)	65.2 (41.3)	<0.001	61.5 (41.9)	0.003	39.2 (44.9)	0.81	<0.001
Role limitations emotional problems	55.2 (45.9)	75.3 (40.2)	0.01	73.6 (40.1)	0.03	63.4 (45.8)	0.42	0.05
Energy/fatigue	36.6 (21.5)	48.3 (25.4)	0.009	45.4 (22.5)	0.06	28.3 (19.6)	0.09	0.001
Emotional well-being	62.2 (17.9)	73.0 (19.9)	0.002	66.6 (20.0)	0.26	60.3 (20.3)	0.66	0.005
Social functioning	56.4 (28.5)	70.7 (31.3)	0.008	75.4 (23.6)	<0.001	55.6 (27.7)	0.91	0.001
Pain	50.5 (22.5)	67.5 (29.2)	<0.001	68.1 (21.2)	<0.001	45.5 (24.5)	0.35	<0.001
General health	37.0 (19.8)	53.2 (23.0)	<0.001	46.8 (22.5)	0.02	31.0 (16.1)	0.13	<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 continuous data, and χ^2 for comparison of categorical data vs. CD with true IBS.

†One way ANOVA for continuous data, and χ^2 for comparison of categorical data across all four groups.

Table 3: Disease Activity Status and Characteristics of UC Patients After FC Analysis Using a Cut Off <250µg/g.

	UC with true IBS (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
UC 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

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
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 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 somatization 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

Mean SF-36 score (SD)								
Physical functioning	74.8 (26.6)	84.5 (19.7)	0.08	78.1 (27.3)	0.63	73.4 (25.7)	0.82	0.11
Role limitations physical health	41.8 (41.3)	77.3 (36.4)	<0.001	67.6 (42.9)	0.02	43.6 (43.0)	0.86	<0.001
Role limitations emotional problems	47.9 (44.8)	79.6 (36.7)	0.001	82.4 (36.0)	0.001	60.0 (42.6)	0.26	<0.001
Energy/fatigue	38.3 (21.6)	57.0 (22.2)	<0.001	52.7 (21.5)	0.02	38.6 (22.7)	0.95	<0.001
Emotional well-being	56.0 (22.7)	73.9 (19.7)	<0.001	74.7 (18.7)	0.001	66.6 (21.2)	0.06	<0.001
Social functioning	62.1 (28.6)	78.7 (26.4)	0.007	84.8 (20.2)	<0.001	51.8 (28.0)	0.14	<0.001
Pain	52.2 (24.1)	74.9 (25.2)	<0.001	78.1 (23.9)	<0.001	59.7 (22.0)	0.19	<0.001
General health	45.0 (20.0)	60.6 (24.4)	0.001	62.2 (25.1)	0.003	45.7 (22.7)	0.89	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 continuous data, and χ^2 for comparison of categorical data vs. UC with true IBS.

†One way ANOVA for continuous data, and χ^2 for comparison of categorical data across all four groups.

Figure 1: Disease Activity and IBS Symptom Status for CD Patients Using a Cut Off <250µg/g.

Figure 2: Disease Activity and IBS Symptom Status for UC Patients Using a Cut Off <250µg/g.