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Article:

Fairbrass, KM orcid.org/0000-0002-5569-4762, Selinger, CP, Gracie, DJ et al. (1 more author) (2022) Prevalence and impact of Rome IV versus Rome III irritable bowel syndrome in patients with inflammatory bowel disease. *Neurogastroenterology & Motility*, 34 (5). e14256. ISSN 1350-1925

<https://doi.org/10.1111/nmo.14256>

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Accepted for publication 19th August 2021

TITLE PAGE

Title: Prevalence and Impact of Rome IV Versus Rome III Irritable Bowel Syndrome in Patients with Inflammatory Bowel Disease.

Short Title: Rome IV Versus Rome III in Patients with IBD.

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Abbreviations:	CD	Crohn's disease
	CI	confidence interval
	HADS	hospital anxiety and depression scale
	HBI	Harvey-Bradshaw index
	IBD	inflammatory bowel disease
	IBS	irritable bowel syndrome
	SCCAI	simple clinical colitis activity index
	SD	standard deviation
	UC	ulcerative colitis

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Writing Assistance: None

Author Contributions: KMF, DJG and ACF conceived and drafted the study. KMF collected all data. ACF analyzed the data. KMF and ACF interpreted the data. KMF, DJG and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

Data Transparency Statement: Data will be made available upon reasonable request from the corresponding author.

Word count: 3239

ABSTRACT

Background: Irritable bowel syndrome (IBS)-type symptoms are common in inflammatory bowel disease (IBD), but few studies have examined the prevalence and impact of IBS-type symptoms in IBD according to Rome IV criteria.

Methods: We collected demographic, symptom (Rome III, Rome IV, and clinical disease activity indices), psychological (anxiety, depression, and somatization), and quality of life data from 973 IBD patients. Medical records were reviewed to document disease type, extent/location, behavior, medical therapy, and antidepressant or opioid use. We compared characteristics of individuals with no IBS-type symptoms, Rome III IBS-type symptoms, and Rome IV IBS-type symptoms.

Key Results: In total, 302 (31.0%) patients met the Rome III criteria for IBS, and 172 (17.7%) met Rome IV criteria. Those with IBS-type symptoms were younger, more likely to be female, and had higher rates of antidepressant ($P=0.006$) or opioid use ($P=0.001$). Rome IV IBS-type symptoms were associated with symptoms of mood disorders, flare of disease activity, and lower quality of life scores ($P<0.001$ for all analyses). Compared with Rome III criteria, those with Rome IV IBS-type symptoms had significantly higher rates of anxiety ($P<0.001$), depression ($P=0.002$), and somatization ($P<0.001$), lower quality of life scores ($P<0.001$) and were more likely to have CD ($P=0.011$), with ileal distribution ($P=0.006$).

Conclusions & Inferences: Rome IV IBS-type symptoms are associated with increased psychological co-morbidity, lower quality of life scores, and higher rates of antidepressant or opioid use. This is a cohort potentially at risk of adverse clinical outcomes and should be a focus for future research.

Key words: characterization; anxiety; depression; Rome III; Rome IV

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic condition, with increasing global incidence and prevalence over the last 50 years.¹ The underlying pathophysiology is incompletely understood. However, immunological, neural, and hormonal dysregulation, alongside alterations in the microbiome, genetic and environmental factors are implicated. The natural history of IBD cycles through periods of remission and relapse, characterized by symptoms of abdominal pain, diarrhea, and hematochezia. Symptoms during flares of disease activity may overlap with those of functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), which is also characterized by abdominal pain and altered stool frequency or form. IBS affects between 5% and 10% of the general population,^{2,3} but prevalence of symptoms compatible with IBS in patients with IBD is up to three times higher.^{4,5} Even during periods of deep endoscopic and/or histological remission up to one-in-four patients report symptoms consistent with IBS.⁶

The presence of IBS-type symptoms in IBD has clinical implications, and there is no clear consensus as to how to manage them.⁷ In patients with IBD in clinical remission, with a normal fecal calprotectin, the presence of these symptoms does not appear to have any deleterious effects on natural history of the disease, in terms of increased risk of escalation of therapy, hospitalization, or intestinal resection related to uncontrolled IBD activity.⁸ However, in this patient group IBS-type symptoms are associated with increased likelihood of consultation, repeated investigation, and psychological co-morbidity, and lead to impairments in quality of life of a similar magnitude to IBD patients with confirmed disease activity.⁸⁻¹⁰

In 2016 the Rome IV criteria for IBS were published,¹¹ with validation studies demonstrating that these are more specific for a diagnosis of IBS, compared with Rome III.^{12,13}

The Rome IV criteria are more stringent than Rome III. The term abdominal discomfort was removed from the definition of IBS, and the frequency at which abdominal pain must occur was increased to at least once weekly. This reduces the number of healthy individuals falsely labelled as having IBS in population-based studies.^{3, 13} However, evidence suggests that these criteria select a cohort of patients with IBS with more severe symptoms and higher levels of psychological co-morbidity.^{14, 15}

A recent meta-analysis examining the prevalence of IBS-type symptoms in patient with IBD in remission identified 27 studies examining this issue,⁵ but only two used the Rome IV criteria,^{16, 17} compared with 16 using Rome III. Although there appeared to be little difference in the prevalence of IBS-type symptoms between the Rome III and Rome IV criteria in this meta-analysis, estimated at 33.5% and 29.6% respectively, both studies using the Rome IV criteria were small, each recruiting less than 150 patients. Given that fewer patients with IBS meet the Rome IV criteria, and those that do have more severe symptoms and higher levels of psychological co-morbidity,^{14, 15} we postulated that prevalence of IBS-type symptoms in patients with IBD would be lower using the Rome IV criteria, but that those who did report symptoms would have worse psychological health and quality of life. We therefore examined this issue in a large group of patients with IBD.

MATERIALS AND METHODS

Participants and Setting

All patients aged >16 years, with an established histological, endoscopic, or radiological diagnosis of Crohn's disease (CD), ulcerative colitis (UC), or IBD-unclassified (IBD-U) attending IBD clinics between 2017-2020, at St James' University Hospital in Leeds, a tertiary referral hospital serving a population of over 800,000 people, were sent a postal invitation to participate. The postal invitation included an individual web-link to an online participant information sheet, consent form, and questionnaire. All patients were offered the option of a paper version of these documents if they preferred. This cross-sectional survey represents baseline data collected as part of an on-going longitudinal study approved by the Wales Research Ethics Committee in February 2020 (REC ref: 20/WA/0044).

Data Collection and Synthesis

We recorded the initial date of recruitment and demographic data, which included sex, age, marital status, ethnicity, educational level, and lifestyle factors, including tobacco and alcohol use. Clinical disease activity was assessed using the Harvey-Bradshaw index (HBI) for CD,¹⁸ and the simple clinical colitis activity index (SCCAI) for UC,¹⁹ with a score of <5 used to define remission, as recommended previously.^{20,21} Symptoms of anxiety or depression were captured using the hospital anxiety and depression scale (HADS),²² somatization data through the patient health questionnaire-12 (PHQ-12),²³ and quality of life data via the health survey short IBD questionnaire (SIBDQ).²⁴ The total HADS score for either anxiety or depression ranges from 0 to 21. Severity was classified as normal (score 0-7), borderline (score 8-10), or abnormal (score >11), as previously recommended.²² The PHQ-12 is derived from the PHQ-15,²⁵

and scores range from 0 to 24. We categorized severity into high (total PHQ-12 ≥ 13), medium (8-12), low (4-7), or minimal (≤ 3). IBS-type symptoms were recorded using the Rome III and IV questionnaires.^{13, 26} The presence of IBS-type symptoms was defined according to the scoring algorithms recommended by the questionnaires. Electronic medical records were accessed to verify IBD type (CD, UC, or IBD-unclassified) and extent of disease, as well as prior IBD-related intestinal resection. Current IBD-related medication use, including 5-aminosalicylates (5-ASAs), immunosuppressants, biologic therapies, or glucocorticosteroids, was recorded, as well as use of antidepressant drugs or opioids. All authors had access to the study data, reviewed and approved the final manuscript.

Statistical Analysis

The proportions of patients reporting symptoms that meeting criteria for either Rome III or Rome IV IBS were calculated. Characteristics between those with no IBS-type symptoms, and those that fulfilled criteria for either Rome III or Rome IV IBS were compared across all three groups using Pearson's χ^2 test for categorical data and one-way analysis of variance (ANOVA) for continuous data. For comparison of only those with Rome III or Rome IV IBS-type symptoms, Pearson's χ^2 test was applied to categorical data, and an independent students *t*-test for continuous data. Due to multiple comparisons, a 2-tailed P value of <0.01 was considered statistically significant. All statistical analyses were performed using SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 4823 patients were contacted, of whom 973 (20.2%) responded to our invitation and provided complete baseline data for these analyses. The mean age of included patients was 52.2 years (age range 17-93 years), 530 (54.5%) were female, 888 (91.3%) white Caucasian, and 436 (44.8%) had CD. Among these 973 individuals, 302 (31.0%) had IBS-type symptoms as defined by the Rome III criteria, and 172 (17.7%) met the Rome IV criteria. All 172 patients with Rome IV IBS-type symptoms also met the Rome III criteria (the Rome IV cohort), and 130 fulfilled only the Rome III criteria (the Rome III cohort).

Characteristics of Individuals with IBS-type Symptoms Meeting Either the Rome III or IV Criteria Versus Individuals with No IBS-type Symptoms

Patients meeting either the Rome III or IV criteria for IBS-type symptoms were significantly younger ($P<0.001$) and more likely to be female ($P<0.001$) (Table 1). Those with Rome III IBS-type symptoms were more likely to drink alcohol than those without IBS-type symptoms ($P=0.001$), and those with Rome IV IBS-type symptoms less likely to be married or co-habiting ($P=0.003$). Antidepressant or opioid use was more common in those with either Rome III or Rome IV IBS-type symptoms compared with those without ($P=0.006$ and $P=0.001$ respectively), but there were no significant differences in the proportions of patients receiving IBD-related drugs.

Those with Rome IV IBS-type symptoms were more likely to self-report they were having a flare of their IBD currently ($P<0.001$) and were more likely to have clinically active disease according to the HBI or SCCAI ($P<0.001$) than those without IBS-type symptoms.

Among 588 patients in clinical remission, 58 (9.9%) reported Rome IV IBS-type symptoms and

79 (13.4%) Rome III, meaning that among those in remission according to the HBI or SCCAI 137 (23.3%) reported IBS-type symptoms. They also had significantly higher mean HADS anxiety or depression scores and higher PHQ-12 scores, and significantly higher proportions had abnormal HADS anxiety or depression scores or had higher levels of somatization severity ($P = <0.001$ for all analyses), compared with those without IBS-type symptoms. Finally, those with Rome IV IBS-type symptoms had significantly lower quality of life scores according to the SIBDQ than those without ($P < 0.001$).

Characteristics of Individuals with IBS-type Symptoms Meeting the Rome IV Criteria Compared with the Rome III Criteria

Patients fulfilling the criteria for Rome IV IBS-type symptoms were less likely to drink alcohol than those meeting the Rome III criteria ($P < 0.001$), and there was a trend towards them being more likely to have CD ($P = 0.011$) (Table 1). Among those with CD, Rome IV IBS-type symptoms were significantly more frequent in those with ileal disease ($P = 0.006$). There were no other significant differences in demographic or disease characteristics, IBD-related drugs, or antidepressant or opioid use. However, those with Rome IV IBS-type symptoms were more likely to self-report a current flare of disease activity ($P < 0.001$), and to have active disease according to the HBI or SCCAI ($P < 0.001$). Mean HADS anxiety and depression scores were significantly higher among those with Rome IV IBS-type symptoms ($P < 0.001$), and prevalence of abnormal HADS anxiety and depression scores was also higher ($P < 0.001$ and $P = 0.002$, respectively). Mean PHQ-12 scores were significantly higher ($P < 0.001$), and the proportion with high levels of somatization severity was significantly higher ($P < 0.001$). Finally, SIBDQ scores

were significantly lower among those with Rome IV IBS-type symptoms compared with those with Rome III ($P < 0.001$).

DISCUSSION

To our knowledge, this is the first study examining prevalence and characteristics of Rome IV IBS-type symptoms, compared with Rome III, in patients with IBD. In keeping with the current literature,⁵ almost one third of this cohort self-reported IBS-type symptoms compatible with the Rome III criteria. Notably, more than half of these patients also fulfilled the Rome IV criteria for IBS, requiring a higher frequency of abdominal pain to meet these latter criteria. Those with IBS-type symptoms according to both Rome IV and III criteria were more likely to be female and were younger, those with Rome III IBS were more likely to drink alcohol, and those with Rome IV IBS were less likely to be married or co-habiting. Although there were no differences in IBD-related drugs between those who did and did not report IBS-type symptoms, those with IBS-type symptoms were more likely to be taking antidepressants, and those with Rome IV IBS-type symptoms were more likely to be prescribed opioids. Rome IV IBS-type symptoms were reported more frequently by CD patients compared with UC. Conversely, Rome III-type symptoms were more frequent in UC patients. Rates of self-report of a current flare of IBD activity were higher among those with Rome IV IBS-type symptoms, and a significantly greater number of patients with Rome IV IBS-type symptoms had active disease according to clinical indices. However, even among patients in clinical remission according to the HBI or SCCAI, one-in-four reported either Rome IV or Rome III IBS-type symptoms, although prevalence was lower with Rome IV at 9.9%, compared with 13.4% with Rome III. Finally, as has been observed among patients with IBS, there were significantly higher depression, anxiety, and somatization scores among those with Rome IV IBS-type symptoms, and significantly lower quality of life scores. These associations with psychological co-morbidity and reduced quality of life highlight the impact of these symptoms on patients with IBD.

We performed unselected recruitment from a large cohort of patients seen in our IBD clinics, so the results of this study are likely to be generalizable to other patients seen in secondary or tertiary centers. By using an online questionnaire to collect data, we ensured that data capture was complete for most variables of interest. In addition, we accessed electronic medical records to verify type of IBD, and extent, location, and behavior of disease, as well as prior IBD-related surgery. We used validated questionnaires to assess clinical disease activity specifically for those with UC or CD, and used the Rome III and IV criteria for IBS side-by-side, rather than approximating one or other definition, as some studies in IBS have done.¹⁴ We also used validated measures of psychological co-morbidities including anxiety, depression, and somatization, as well as quality of life scores.

One of the main limitations is the lack of an objective measure of IBD activity, such as a fecal calprotectin, meaning that the presence of IBS-type symptoms could relate to ongoing disease activity. Future studies to corroborate our findings, which use biochemical or endoscopic markers of disease activity, are therefore required. However, we, and others, have previously shown that clinical disease activity indices correlate poorly with objective markers of inflammation,^{9, 27} particularly in CD. Even in studies that have used a fecal calprotectin to confirm mucosal remission, up to one-in-three patients reported IBS-type symptoms,⁵ and when histological remission was used it was one-in-four patients.⁶ Those self-reporting a flare of symptoms, and with active disease according to clinical indices were significantly more likely to meet Rome IV criteria for IBS. Features of clinical disease activity endorsed potentially overlap the self-reporting of IBS-type symptoms. This would be particularly relevant to patients with CD, where disease activity in this study was measured using the HBI, which includes assessment of abdominal pain, and may correlate with the more frequent nature of abdominal pain required

to meet Rome IV criteria. Irrespective of this, our reported prevalence of IBS-type symptoms is comparable to that found within the IBD population in remission.⁵ Although the number of patients recruited into the study was large, we are unable to ascertain if they are representative of our entire population of patients with IBD, and we cannot exclude the fact that there may have been responder bias, with those more likely to report these symptoms, or to have co-existent psychological morbidity, being more motivated to take part.

The differences in baseline demographic characteristics seen in our cohort, although not all statistically significant, are comparable with larger non-IBD cohorts.^{15, 28} We observed a significant proportion of those without IBS-type symptoms were either married or co-habiting compared to those with Rome III or Rome IV IBS-type symptoms. The social support network offered through positive relationships is beneficial to both physical and mental health.²⁹ With studies showing quality relationships can reduce symptoms of common mental disorders, lower stress levels and blood pressure.³⁰ This positive feedback loop and suppression of sympathetic activity enables control of the neuroendocrine, immune response described by the brain-gut axis, which remains a key feature in the development of functional gastrointestinal disorders.

The magnitude of the decrease in prevalence of Rome IV IBS-type symptoms, compared with Rome III, is comparable to observations from the general population.^{3, 31} Of note, in those with and without IBS-type symptoms, there were no significant differences in IBD-related drugs, including immunosuppressant and glucocorticosteroid use. This would suggest that making treatment decisions based on symptoms alone, unless there is evidence of occult activity, is unlikely to benefit these symptoms.³²⁻³⁴ Nonetheless, management of IBS-type symptoms, rather than occult inflammation, poses a clinical challenge. Given that IBS-type symptoms overlap closely with those of a flare, unsurprisingly this cohort are more likely to present to secondary

care, undergo more investigations, and are likely to incur increased healthcare costs.⁸ In addition, those with Rome IV-type symptoms, who report more severe abdominal pain, were more likely to be prescribed opioids compared with those with Rome III IBS-type symptoms, or those without IBS-type symptoms at all. Chronic opioid use is common in IBD, with studies demonstrating associations with increased healthcare use, mood disorders, prior gastrointestinal surgery, IBD activity, and mortality.^{35, 36} There is no evidence that opioids significantly improve pain or quality of life scores in patients with IBD.³⁷ Their association with IBS-type symptoms in the current study is therefore concerning and highlights the need for evidence-based management strategies for IBS-type symptoms in patients with IBD.^{7, 38}

Among those with CD, we found Rome IV IBS-type symptoms were reported more frequently, compared with UC. A recent meta-analysis reported that IBS-type symptoms were more frequently reported in patients with CD in remission,⁵ although only one of these studies used the Rome IV criteria.¹⁷ This contrasts with our findings, where those meeting the Rome III criteria for IBS were more likely to have UC. Extent of UC did not seem to affect the likelihood of reporting IBS-type symptoms in general, or meeting Rome III versus Rome IV criteria, whereas those with ileal CD were more likely to meet Rome IV criteria. This may be partly explained by the higher prevalence of pain found in those with ileal CD compared to colonic CD or UC.³⁷ Active small bowel disease is not easily identified by investigations such as endoscopy or fecal calprotectin, therefore the higher prevalence of IBS-type symptoms in this group may reflect occult disease activity. With ileal resection becoming increasingly accepted as a cost effective and valid treatment option in this subgroup,³⁹ reporting these symptoms may reflect other organic conditions arising due to surgery, such as adhesions, small intestinal bacterial overgrowth, or bile acid diarrhea.^{40, 41} However, there was no association between previous

surgery and likelihood of reporting IBS-type symptoms. Similarly, there appeared to be no association between reporting IBS-type symptoms and a fistulizing or stricturing phenotype or perianal involvement. However, numbers in some of these subgroup analyses were small and potentially underpowered to detect any significant differences.

Once again, this study has shown that the presence of IBS-type symptoms in IBD is associated with low mood scores, somatization, and poor quality of life. Previous studies have suggested the impact of these symptoms is equivalent to those associated with active disease.^{9, 10} Within the general population, symptoms in keeping with Rome IV functional gastrointestinal disorders are associated with increased levels of somatization and healthcare costs, and reduced quality of life.⁴² People with IBS who meet Rome IV criteria also report more severe symptoms, and higher levels of anxiety and depression than those who meet Rome III criteria.¹⁵ We have shown these findings translate into the IBD population; those with Rome IV IBS-type symptoms had greater psychological co-morbidity and lower quality of life. Several longitudinal studies have demonstrated significant links between mood disorders and increased risk of flare, glucocorticosteroid use, escalation of therapy, and trends towards an increased risk of hospitalization and intestinal surgery.⁴³⁻⁴⁶ Although there is good evidence for a benefit of neuromodulators and psychological therapies in improving symptoms in patients with IBS,⁴⁷ any equivalent benefit of these treatments in patients with IBD is unclear.^{48, 49} Whether this subgroup of patients with IBD who report Rome IV, rather than Rome III, IBS-type symptoms have higher healthcare needs and clinical costs, and whether the association with psychological co-morbidity impacts on the natural progression of disease is not able to be ascertained from this study and should be the subject of future research.

This is, to our knowledge, the largest study to examine the prevalence of IBS-type symptoms in patients with IBD and the first to compare characteristics of those meeting Rome IV criteria with Rome III. Those meeting Rome IV criteria were more likely to have CD, to use opioids, to meet clinical criteria for disease activity, to have abnormal anxiety, depression, and somatization scores, and to have lower quality of life scores. This suggests the presence of IBS-type symptoms has significant clinical implications, and that the burden of these symptoms increases when the Rome IV criteria, rather than Rome III, are used to define their presence. Despite the lack of evidence-based management strategies for these patients we would suggest that, given the observed association with low mood scores, reduced quality of life, and antidepressant and opioid use, clinicians should be screening their patients with IBD in remission for the presence of IBS-type symptoms to try to improve outcomes in this patient group. Patients with IBD meeting Rome IV criteria for IBS and with abnormal mood scores also represent an ideal cohort for future research into the effects of neuromodulators and psychological therapies in IBD.

Grant support: None

Disclosures: KMF: none. CPS: none. DJG: none. ACF: none.

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Table 1: Baseline Characteristics of Patients According to Rome Criteria for IBS-type Symptoms.

	No IBS-type symptoms (n=671)	Rome III IBS-type symptoms (n=130)	Rome IV IBS-type symptoms (n=172)	P Value Across All Three Groups*	P Value Rome III IBS vs. Rome IV IBS**
Mean age (SD)	53.4 (16.7)	51.7 (16.1)	47.8 (16.3)	<0.001	0.041
Female sex (%)	334 (49.8)	79 (61.7)	117 (68.4)	<0.001	0.23
Married or co-habiting (%)	484 (72.7)	93 (71.5)	102 (59.3)	0.003	0.028
White Caucasian (%)	617 (92.0)	119 (91.5)	152 (88.4)	0.32	0.64
University or postgraduate education (%)	246 (37.0)	64 (49.2)	68 (40.0)	0.032	0.11
Smoker (%)	42 (6.3)	7 (5.4)	18 (10.5)	0.12	0.11
Alcohol use (%)	484 (72.7)	110 (85.3)	112 (65.9)	0.001	<0.001
Type of IBD (%)					
CD	288 (43.2)	53 (40.8)	95 (56.2)		
UC	336 (50.5)	71 (54.6)	63 (37.3)		
IBD-U	42 (6.3)	6 (4.6)	11 (6.5)	0.017	0.011
CD location † (%)					
Ileal	81 (28.1)	12 (22.6)	42 (44.7)		
Colonic	100 (34.7)	19 (35.8)	17 (18.1)		
Ileocolonic	107 (37.2)	22 (41.5)	35 (37.2)	0.011	0.006

Stricturing CD[†] (%)	86 (29.9)	12 (22.6)	26 (27.4)	0.53	0.55
Penetrating CD[†] (%)	47 (16.3)	10 (18.9)	14 (14.7)	0.51	0.81
Perianal CD[†] (%)	44 (15.3)	10 (18.9)	15 (15.8)	0.63	0.81
UC extent[‡] (%)					
Proctitis	95 (29.3)	22 (33.8)	18 (30.0)		
Left-sided	116 (35.8)	23 (35.4)	26 (43.3)		
Extensive	113 (34.9)	20 (30.8)	16 (26.7)	0.66	0.67
Previous intestinal resection for IBD (%)	142 (21.3)	30 (23.1)	36 (21.3)	0.90	0.71
Antidepressant use (%)	92 (13.7)	31 (23.8)	34 (19.8)	0.006	0.39
Opioid use (%)	60 (9.0)	18 (13.8)	33 (19.2)	0.001	0.22
5-ASA use (%)	355 (53.3)	65 (50.0)	75 (44.4)	0.11	0.33
Immunosuppressant use (%)	180 (27.0)	31 (23.8)	52 (30.8)	0.40	0.19
Anti-TNFα use (%)	97 (14.6)	20 (15.4)	33 (19.5)	0.28	0.35
Vedolizumab use (%)	21 (3.2)	6 (4.6)	5 (3.0)	0.67	0.45
Current glucocorticosteroid use (%)	19 (2.9)	3 (2.3)	7 (4.1)	0.60	0.38
Current flare of IBD (%)	88 (13.2)	20 (15.4)	66 (38.4)	<0.001	<0.001
Active disease according to HBI or SCCAI (%)	204 (31.1)	47 (37.3)	111 (65.7)	<0.001	<0.001

HADS anxiety score categories (%)					
Normal	420 (64.1)	64 (50.4)	55 (32.5)		
Borderline abnormal	135 (20.6)	37 (29.1)	43 (25.4)		
Abnormal	100 (15.3)	26 (20.5)	71 (42.0)	<0.001	<0.001
Mean HADS anxiety score (SD)	6.1 (4.2)	7.5 (3.9)	9.5 (4.7)	<0.001	<0.001
HADS depression score categories (%)					
Normal	542 (82.0)	94 (73.4)	91 (53.8)		
Borderline abnormal	74 (11.2)	21 (16.4)	44 (26.0)		
Abnormal	45 (6.8)	13 (10.2)	34 (20.1)	<0.001	0.002
Mean HADS depression score (SD)	4.0 (3.8)	5.1 (3.8)	7.2 (4.2)	<0.001	<0.001
Level of PHQ-12 somatization severity (%)					
Minimal	237 (38.2)	21 (17.1)	9 (5.8)		
Low	223 (36.0)	56 (45.5)	47 (30.3)		
Medium	119 (19.2)	34 (27.6)	65 (41.9)		
High	41 (6.6)	12 (9.8)	34 (21.9)	<0.001	<0.001
Mean PHQ-12 somatization score (SD)	5.5 (4.2)	7.1 (3.8)	9.3 (4.1)	<0.001	<0.001
Mean SIBDQ score (SD)	54.7 (11.7)	49.1 (9.8)	38.8 (11.2)	<0.001	<0.001

*P value for one-way analysis of variance for continuous data and Pearson χ^2 for comparison of categorical data.

**P value for independent samples *t*-test for continuous data and Pearson χ^2 for comparison of categorical data.

† n = 288 with no IBS-type symptoms, 53 with Rome III IBS-type symptoms, and 95 with Rome IV IBS-type symptoms

‡ n = 324 with no IBS-type symptoms, 65 with Rome III IBS-type symptoms, and 60 with Rome IV IBS-type symptoms

GRAPHICAL ABSTRACT

