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TITLE PAGE

Title: Poor Correlation Between Clinical Disease Activity and Mucosal Inflammation, and the Role of Psychological Co-morbidity, in Inflammatory Bowel Disease.

Short running head: Symptoms, Inflammation, and Psychological Co-morbidity in IBD.

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Abbreviations:

5-ASA	5-aminosalicylates
BMI	body mass index
CI	confidence interval
CD	Crohn's disease
FC	fecal calprotectin
FGID	functional GI disorder
GI	gastrointestinal
HADS	hospital anxiety and depression scale
HBI	Harvey-Bradshaw index
IBD	inflammatory bowel disease

IBS	irritable bowel syndrome
NPV	negative predictive value
OR	odds ratio
PHQ	patient health questionnaire
PPV	positive predictive value
PROM	patient-reported outcome measure
SCCAI	simple clinical colitis activity index
TNFα	tumor necrosis factor-α
UC	ulcerative colitis

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ABSTRACT

Objectives: There is a move towards patient-reported outcome measures as endpoints in clinical trials of novel therapies for inflammatory bowel disease (IBD). However, the association between patient-reported symptoms and mucosal inflammation, and the influence of psychological factors, remains unclear. We examined this in a secondary care population.

Methods: Validated patient-reported disease activity indices were used to define clinically active disease in a cohort of 356 patients with ulcerative colitis (UC) or Crohn's disease (CD). A fecal calprotectin ≥250μg/g was used to define active mucosal inflammation. The hospital anxiety and depression scale (HADS) and patient health questionnaire (PHQ)-15 were used to assess for anxiety, depression, or somatization respectively. Logistic regression analysis was performed to determine the association between symptoms, mucosal inflammation, and psychological co-morbidity.

Results: Clinical disease activity was associated with mucosal inflammation in UC (odds ratio (OR) 3.36; 95% confidence interval (CI) 1.34-8.47), but not CD (OR 1.69; 95% CI 0.76-3.83). Depression in UC (OR 1.21 per 1-point increase in HADS; 95% CI 1.02-1.44), and somatization in UC (OR 1.17 per 1-point increase in PHQ-15; 95% CI 1.03-1.33) and CD (OR 1.31 per 1-point increase in PHQ-15; 95% CI 1.13-1.52) were associated with clinical disease activity. Overall, patient-reported symptoms yielded poor positive predictive values for mucosal inflammation in both CD and UC.

Conclusions: Patient-reported symptoms and the HBI were poor predictors of mucosal inflammation in CD. Psychological co-morbidity was associated with gastrointestinal symptom-reporting. A shift in the focus of IBD management towards one addressing both psychological and physical well-being is required.

What is current knowledge?

- The correlation between clinical disease activity indices and objective measures of mucosal inflammation in inflammatory bowel disease (IBD) may be poor.
- Despite this, there is a move towards patient-reported outcome measures (PROMs) as endpoints in clinical trials of novel therapies for IBD.
- Psychological co-morbidity is relatively common in inflammatory bowel disease (IBD) and is reported to be associated with clinically active disease and reduced quality of life.
- However, the impact of psychological co-morbidity on PROMs and mucosal inflammation is poorly described.

What is new here?

- Clinical disease activity indices yielded poor positive predictive values for mucosal inflammation in both Crohn's disease (CD) and ulcerative colitis (UC).
- Presence of depression in UC, and somatization in both UC and CD, were associated with an increased likelihood of reporting of the gastrointestinal symptoms that make up these activity indices.
- The existence of psychological co-morbidity in IBD was independent of mucosal inflammation defined by fecal calprotectin.
- Proposed clinical PROMs, such as rectal bleeding, abdominal pain, and altered stool frequency do not correlate with mucosal inflammation, and their utility as endpoints in clinical trials in IBD needs to be re-examined.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as the inflammatory bowel diseases (IBD), are chronic inflammatory disorders of the gastrointestinal (GI) tract, with a combined prevalence of 450 per 100,000 in Western populations, (1) and an increasing incidence for reasons that are incompletely understood. (2) The natural history of the condition is that of quiescent disease interspersed with flare-ups of disease activity, with current management strategies focused on reducing the inflammatory burden in patients with active disease, and attempting to maintain remission in those with inactive disease, in order to reduce total digestive damage. However, some patients experience symptoms in the absence of objective evidence of disease activity, with occult inflammation, visceral hypersensitivity altered mucosal permeability, and co-existent functional disease implicated as potential causes. (3-5)

Although considered primary GI disorders, CD and UC are associated with significant psychological co-morbidity. Anxiety or depression is reported to affect up to one-in-three patients with IBD. (6-8) Furthermore, recent observational data from longitudinal studies suggest that mood disorders, including anxiety and depression, may be associated with adverse disease outcomes and reduced quality of life. (9) However, many studies designed to investigate these issues have used clinical disease activity indices to assess disease activity, rather than gold-standard investigations such as ileocolonoscopy or small bowel imaging, or fecal biomarkers of intestinal inflammation and, given that the correlation between these tools and objective measures of inflammation may be variable, (10-14) the implication of these results is uncertain.

Whether psychological co-morbidity affects clinical disease outcomes has important implications for clinical practice. A clearer understanding of whether psychological health is associated with increasing inflammatory burden, or just the reporting of symptoms

attributable to the GI tract in general, may aid clinical decision making. In the former instance, this may dictate the need for escalation of conventional therapies, but in the latter situation where the etiology of these symptoms is unclear, and where evidence suggests that the efficacy of these treatments is sub-optimal, (15) other management strategies may be required. This is particularly relevant at the present time, as the US Food and Drug Administration are moving towards patient-reported outcome measures (PROMs) as a measure of efficacy in clinical trials of novel therapies for IBD. (16)

We have therefore conducted a large cross-sectional study of IBD patients, and collected patient-reported clinical disease activity indices and fecal calprotectin (FC), as measures of clinically active disease and mucosal inflammation respectively, in order to better understand the relationship between the two, as well as the interplay of these with functional symptoms and psychological health. Our hypothesis was that symptomatic disease activity would be associated with the presence of psychological co-morbidity, independent of inflammatory burden. If proven, these data may act as a caution against the current prevailing opinion with respect to PROMs in clinical trials in IBD, and also serve as a mandate for future studies to assess the longitudinal effects of mood disorders on the natural history of IBD, suggesting the need for a paradigm shift in the management of IBD patients away from one focused solely on physical well-being.

METHODS

Participants and Setting

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

Data Collection and Synthesis

Demographic Data and Disease Characteristics

Demographic data including gender, age, ethnicity, marital status, educational level, tobacco and alcohol use, weight (in kilograms) and height (in meters), which were used to calculate body mass index (BMI), were collected from all participants. Medication history, including current use of 5-aminosalicylates (5-ASAs), glucocorticosteroids, immunosuppressants, or anti-tumor necrosis factor (TNF)-α therapy, disease location and behavior for CD, or distribution for UC, as defined by the Montreal classification, (17) and any previous intestinal resection related to CD were also recorded.

Assessment of Patient-reported IBD Activity and Mucosal Inflammation

Patient-reported IBD 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 ≥5 used to define clinically active disease for both, as previously recommended. (20, 21) In addition, participants were asked to report whether, in their own opinion, they were attending with a flare of disease activity. Those who agreed to participate were asked to provide stool for quantitative FC analysis (Immundiagnostik, Bensheim, Germany) within one week of inclusion, as an objective marker of mucosal inflammation. This has a reported sensitivity and specificity of 93.5% and 79.2% respectively for predicting mucosal inflammation identified at ileocolonoscopy. (22) We used a cut off of ≥250µg/g of stool to define the presence of active disease, in line with the European Crohn's and Colitis Organization consensus on the use of FC to measure disease activity, (23) as other investigators have employed. (24-26)

Reference Standard Used to Define Presence of Irritable Bowel Syndrome (IBS)-type Symptoms

IBS-type symptoms were assessed via the Rome III criteria, (27) according to the scoring algorithm incorporated within the Rome III diagnostic questionnaire for the adult functional GI disorders. IBS-type symptoms were defined as present when an individual reported abdominal discomfort or pain with a frequency of at least 2 or 3 days per month over the last 3 months, with the onset of discomfort at least 6 months previously, associated with two or more of the following: an improvement of pain or discomfort with the passage of stool, more or less frequent bowel movements, or looser or firmer stools.

Definition of Anxiety or Depression

The presence of either anxiety or depression was assessed using the hospital anxiety and depression scale (HADS). (28) This 14-item questionnaire consists of seven questions screening for the presence of anxiety symptoms, and seven for depression symptoms, with a 4-point response for each item, ranging from 0 to 3. The total possible score on the HADS ranges from a minimum of 0 to a maximum of 21 for both anxiety and depression. Severity was categorized, according to total HADS score, into normal (total HADS depression or anxiety score 0-7), borderline normal (8-10), and abnormal (≥11). (28)

Definition of Somatization Severity Using the Patient Health Questionnaire-15 (PHQ-15)

Somatization data were collected using the PHQ-15, which is derived from the validated full PHQ. (29, 30) This questionnaire enquires about the presence of 15 somatic symptoms (or symptom clusters) over the last 4 weeks, which are thought to contribute to >90% of physical complaints reported in the outpatient environment. (31) Each individual was asked to rate the severity of each symptom as "not bothered at all" (scored as 0), "bothered a little" (scored as 1), or "bothered a lot" (scored as 2). The total PHQ-15 score ranges from a minimum of 0 to a maximum of 30. Somatization severity was categorized, using the total PHQ-15 score, into high (total PHQ-15 ≥15), medium (10-14), low (5-9) and minimal (≤4) levels of somatization severity,

Statistical Analysis

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

In order to assess the relationship between clinical disease activity indices, mucosal inflammation, functional symptoms, and psychological factors we compared baseline demographic and disease-related characteristics, the presence of symptoms fulfilling the Rome III criteria for IBS, the presence of a self-reported flare of disease activity, anxiety, depression, and somatization scores, and the presence of anxiety, depression, or somatization between CD and UC patients separately, and dichotomized into those with or without clinically active symptomatic disease, using a total HBI or SCCAI cut off of ≥5 for CD and UC respectively, or those with and without active mucosal inflammation, using a FC cut off of ≥250μg/g of stool. We conducted sensitivity analyses using an elevated cut-off of ≥7 on the HBI or SCCAI to define clinically active disease for both CD and UC. A χ^2 test was used to compare categorical variables and an independent samples t-test for continuous data. Independent risk factors for clinically active symptomatic disease defined according to HBI or SCCAI, or active mucosal inflammation according to FC, were determined for all patients with CD and UC separately by performing multivariate logistic regression to control for all other demographic and disease-related characteristics, presence of symptoms fulfilling the Rome III criteria for IBS, the presence of a self-reported flare of disease activity, and anxiety, depression, and somatization scores.

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

Due to multiple comparisons, a 2-tailed P value of <0.01 was considered to be statistically significant for all analyses, and the results of multivariate logistic regression were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

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

Characteristics of IBD Patients According to Presence or Absence of Clinically Active Disease

Of the 191 CD patients, 69 (36.1%) had clinically active disease, with an HBI ≥5. These patients were more likely to have had a previous intestinal resection, fulfill Rome III criteria for IBS, self-report a flare of disease activity, and have higher mean HADS anxiety, HADS depression, and PHQ-15 scores, as well as higher anxiety, depression, and somatization severity (Table 2). Mean FC results were generally lower in those with clinically active disease (397µg/g vs. 508µg/g), and there was no difference in the proportion of patients with an elevated FC.

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

After multivariate logistic regression, a previous intestinal resection, fulfilling the Rome III criteria for IBS, and higher PHQ-15 scores were associated with clinically active disease in CD. Self-reported flare, FC ≥250µg/g, higher HADS depression scores and higher total PHQ-15 scores were associated with clinically active disease in UC (Table 3).

When an HBI of ≥7 was used to define clinically active CD, the proportion of patients with a FC ≥250µg/g was almost identical in those with and without clinically active disease (16 (38.1%) of 42 vs. 57 (38.3%) of 149; P = 0.99), and mean FC values remained lower among those with clinically active disease (354µg/g vs. 500µg/g; P = 0.28). After multivariate logistic regression analysis there remained no association between clinically active disease, with an HBI ≥7, and FC ≥250µg/g (OR = 1.24; 95% CI 0.46 to 3.33).

When an SCCAI of ≥7 was used to define clinically active UC, there remained a significantly higher proportion of patients with clinically active disease who had evidence of mucosal inflammation (22 (68.8%) of 32 vs. 43 (32.2%) of 133; P <0.001), and mean FC remained significantly higher among those with clinically active disease (1080µg/g vs. 409µg/g; P <0.001). After multivariate logistic regression analysis clinically active UC remained associated with mucosal inflammation (OR = 10.9; 95% CI 2.93 to 40.8).

Characteristics of IBD Patients According to Presence or Absence of Mucosal Inflammation

In total, 73 (38.2%) patients with CD and 65 (39.4%) with UC were classified as having evidence of mucosal inflammation, with an FC ≥250µg/g. UC patients with mucosal inflammation had higher mean SCCAI scores, and a greater proportion of patients had clinically active disease, with an SCCAI ≥5. There were no other differences in baseline

demographics, disease characteristics, or the prevalence of psychological co-morbidity between those with and without mucosal inflammation in either CD or UC (Table 4).

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

Performance of HBI, Self-reported Flare, Rome III Criteria, and Psychological Factors in Predicting Mucosal Inflammation in CD.

The sensitivity, specificity, PPV and NPV of the individual symptom items of the HBI, an HBI ≥5, presence of the Rome III criteria for IBS, self-report of a flare of disease activity, and presence of anxiety, depression, or somatization in predicting mucosal inflammation in CD are reported in Supplementary Table 1. Although the individual HBI symptom items demonstrated good specificity generally, ranging between 66.1% for ≥3 stools per day and 97.5% for the presence of abdominal mass, the corresponding sensitivity scores were poor (4.1% to 34.2%). As a result, the PPV of these, and total HBI score ≥5, was generally poor, between 35.9% and 50.0%. Reporting symptoms compatible with Rome III-defined IBS, a self-reported flare, and the presence of anxiety or depression were no worse than either the individual symptoms items of the HBI, or a total HBI score ≥5, at predicting mucosal inflammation.

Performance of SCCAI, Self-reported Flare, Rome III Criteria, and Psychological Factors in Predicting Mucosal Inflammation in UC.

In patients with UC the performance of the SCCAI was broadly similar to self-reported flare at predicting mucosal inflammation, with increasing daytime or nocturnal stool frequency the most specific symptom items, and urgency the most sensitive (Supplementary Table 2). In terms of the PPV, the Rome III criteria were inferior to both SCCAI and self-reported flare at predicting mucosal inflammation, although the 95% CIs overlapped, as were the presence of abnormal HADS anxiety, abnormal HADS depression, or high somatization severity.

DISCUSSION

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

Strengths of this study include the large, well-characterized group of consecutive, unselected IBD patients who provided complete patient-reported clinical data, and our use of FC as an objective measure of intestinal inflammation. Moreover, these patients were recruited from a secondary care population, thereby increasing the generalizability of our findings to usual clinical practice. Our use of validated questionnaires for the assessment of symptomatic disease activity in CD and UC, (18, 19) IBS symptoms, (27, 32) anxiety and depression, (28) and somatization (29, 30) is another strength.

Although FC was used as an objective measure of mucosal inflammation, a weakness is that, in our observational study design, with recruitment taking place alongside usual clinical care, gold-standard investigations for the assessment of disease activity, including ileocolonoscopy, histological assessment of ileal and colonic mucosal biopsies, and small bowel imaging were not undertaken. Our use of a FC cut off value of ≥250μg/g of stool to define the presence of active inflammation, although supported by previous authors and an

international consensus statement, (23-26) may be criticized by some. In addition, although FC is thought to be representative of endoscopic disease activity indices, (25) its utility as a marker of active small bowel inflammation in CD is uncertain, with one study assessing its correlation with magnetic resonance enterography suggesting equivalence, (33) another supporting its use, but proposing greater accuracy when used to identify colonic over small bowel inflammation, (34) and a third reporting poor correlation with video capsule endoscopy in the identification of significant small bowel inflammation. (35)

Also of note is that a greater proportion of CD patients with a total HBI score ≥5 had isolated small bowel disease than those who did not, suggesting that disease location may influence the generation of symptoms or, given that there was no association between this variable and biochemical disease activity, that FC underestimates small bowel inflammatory burden. Furthermore, in the absence of radiological assessment of the small bowel, it may be that hitherto undiagnosed fibrostenotic small bowel disease contributed to the development of symptoms. In clinical practice this may then be falsely attributed to functional disease on the basis of a normal FC. However, in a subgroup analysis, when the 43 patients with isolated ileal disease were excluded, there remained no significant difference in the proportion of patients with, and without clinically active CD with evidence of mucosal inflammation defined by FC ≥ 250µg/g (17 (46%) of 46 vs. 35 (34.3%) of 102, P = 0.76), and no significant association between those with and without clinical disease activity and mean FC (407µg/g vs. 505µg/g, P = 0.51), reinforcing the lack of association between total HBI scores and mucosal inflammation in ileocolonic and colonic CD.

Both IBS-type symptoms and a history of previous intestinal resection were associated with symptomatically active CD. Although IBS-type symptoms in patients with no evidence of mucosal inflammation could be considered to be due to genuine co-existent

functional symptoms, previous intestinal resection may be associated with alternative, non-inflammatory, organic diagnoses such as small intestinal bacterial overgrowth or bile acid diarrhea. (36, 37) This may have led to an overestimate of the prevalence of functional symptoms in this sub-group of patients.

Several studies have assessed the diagnostic accuracy of patient-reported clinical disease activity indices at predicting inflammatory burden in IBD, (11-14) however few have attempted to delineate the relationship between symptoms, inflammation, and their relationship with psychological wellbeing. Most recently, Targownik et al., (24) assessed the utility of the HBI, Powell-Tuck Index and Manitoba IBD Index at predicting active IBD using a FC cut off of ≥250 μg/g of stool in 478 IBD patients, and the association between symptoms, inflammatory burden, and perceived stress. In keeping with our findings, there was no association between patient-reported clinically active disease and mucosal inflammation in CD, and only a modest relationship between the two in UC. In addition, perceived stress was associated with clinically active disease, but not active mucosal inflammation. Goodhand et al., (38) described the relationship between disease activity, depression, anxiety, and perceived stress in 103 UC and 101 CD patients, compared with 124 healthy volunteers. In this study, mean anxiety and depression scores were higher in both CD and UC patients, and active inflammation was associated with depression, but not anxiety, in UC. Another study conducted among 162 patients with IBD examined the association between active inflammatory disease, the presence of co-existent functional gastrointestinal disorders (FGIDs), mood disorder, and quality of life using validated questionnaires. (39) The authors reported significantly higher depression scores and lower quality of life scores in those with symptoms compatible with a co-existent FGID, regardless of the presence of active inflammatory disease. However, although these studies reported the relationship between psychological health, mucosal inflammation, and IBD-related symptoms, (24, 38) or

the relationship between physician's global assessment of disease activity, functional symptoms, and psychological co-morbidity, (39) they did not incorporate all of these in a large single cohort of patients.

Our study has important clinical implications, as the data suggest that patient-reported symptoms in IBD are associated with significant psychological co-morbidity, with abnormal HADS anxiety scores observed in roughly 40% of all IBD patients with disease activity indices ≥5, and abnormal HADS depression scores in one-in-four UC patients with a SCCAI ≥5. The association between somatization and clinically active IBD, but not mucosal inflammation, suggests that the reporting of the symptom items that make up these clinical disease activity indices in a subset of patients may be due to somatoform-type behavior, or co-existent functional disease, rather than being secondary to genuine mucosal inflammation or extra-intestinal manifestations of IBD. Whether this impacts on clinical practice, with a resultant increase in referrals to associated specialties for management of presumed extra-intestinal manifestations of IBD, such as inflammatory arthropathy, is uncertain as the only previous study to examine somatization in adult patients with IBD did not report these data. (40)

Our findings highlight the disparity between patient-reported symptoms and objective assessments of IBD activity, regardless of the cut-off used to define active disease, and reinforce the requirement for careful consideration before escalation of conventional IBD therapies, or making judgments concerning the effectiveness of novel therapies, on the basis of clinical disease activity indices alone. Moreover, the finding that a simple dichotomous patient opinion as to whether their disease was active or not was as effective as both the HBI in CD, and the SCCAI in UC, at predicting mucosal inflammation in our study further highlights that the use of these indices as a sole determinant of disease activity or drug efficacy is not desirable. The move toward PROMs, in conjunction with biomarkers of

inflammation and endoscopic indices, in the assessment of outcomes in IBD clinical trials aims to address these inconsistencies. (16, 41) However, to date, proposed clinical PROMs, include rectal bleeding and alteration in stool frequency in UC, (42) and abdominal pain, stool frequency, and general well-being in CD, (43) which based on our findings have only modest PPVs when used to assess mucosal inflammation, and have been shown to correlate poorly with mucosal healing in UC in other studies. (44)

In summary, our findings support the assertions of previous authors in suggesting patient-reported clinical disease activity indices are not associated with mucosal inflammation in CD, and are only modestly associated with mucosal inflammation in UC, suggesting that the move towards PROMs in clinical trials of novel IBD therapies may need to be re-examined. In addition, psychological co-morbidity, specifically depression in UC and somatization in UC and CD, were associated with the reporting of the symptoms that make up these indices. Although these data suggest that objective biochemical measures of inflammatory activity should form the basis of disease activity assessment, ideally as a point-of care-test, the association between GI symptoms, in the absence of disease activity, and psychological co-morbidity highlights the need for a paradigm shift in the management of some patients away from one focused solely on physical well-being. This reinforces the requirement for further assessment of the efficacy of alternative treatment options, such as psychological therapies or antidepressants, and the identification of novel treatments in a subset of IBD patients with associated psychological co-morbidity, especially as studies assessing such therapies, to date, are scarce with disappointing results. (45-47)

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Guarantor of the article: DJG is guarantor.

Specific author contributions: DJG, CJMW, RS, SM, MHB, PJH, and ACF conceived and drafted the study. DJG, CMJW, SM, MHB, and RS collected all data. DJG, PJH, and ACF analyzed and interpreted the data. DJG, PJH, and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

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Table 1. Characteristics of Included Crohn's Disease and Ulcerative Colitis Patients.

	Crohn's disease (n = 191)	**Ulcerative colitis (n = 165)**	**P value***
Mean age in years (SD)	46.7 (16.6)	51.2 (16.3)	0.01
Female gender (%)	119 (62.3)	89 (53.9)	0.11
Married or co-habiting (%)	118 (61.8)	119 (72.1)	0.04
University/postgraduate (%)	50 (26.3)	48 (29.4)	0.51
Mean BMI (SD)	26.3 (5.6)	27.1 (5.7)	0.20
Tobacco user (%)	40 (20.9)	7 (4.2)	<0.001
Alcohol user (%)	121 (63.4)	110 (66.7)	0.51
Crohn's disease location (%)			
Ileal	43 (22.5)	N/A†	
Colonic	62 (32.5)	N/A†	
Ileocolonic	86 (45.0)	N/A†	N/A†
Crohn's disease behavior (%)			
Non-stricturing, non-penetrating	164 (85.9)	N/A†	
Stricturing	20 (10.5)	N/A†	
Penetrating	7 (3.7)	N/A†	N/A†
Perianal Crohn's disease present (%)	16 (8.4)	N/A†	N/A†
Ulcerative colitis extent (%)			
Proctitis	N/A†	45 (27.3)	
Left sided	N/A†	74 (44.8)	
Extensive	N/A†	46 (27.9)	N/A†
5-ASA use (%)	53 (27.7)	131 (79.4)	<0.001
Immunomodulator use (%)	88 (46.1)	34 (20.6)	<0.001
Anti TNF-α use (%)	52 (27.2)	4 (2.4)	<0.001
Glucocorticosteroid use (%)	21 (11.0)	17 (10.3)	0.83
Previous intestinal resection (%)	62 (32.5)	N/A†	N/A†
Rome III IBS criteria fulfilled (%)	86 (45.0)	49 (29.7)	0.003

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

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

†N/A; not applicable

Table 2. Relationship Between Elevated Patient-reported Disease Activity Indices (HBI or SCCAI ≥5) and Personal and Disease Characteristics in Crohn's Disease and Ulcerative Colitis.

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

Crohn's disease behavior (%)						
Non-stricturing, non-penetrating	109 (90.1)	54 (78.3)		N/A†	N/A†	
Stricturing	9 (7.4)	11 (15.9)		N/A†	N/A†	
Penetrating	3 (2.5)	4 (5.8)	0.08	N/A†	N/A†	N/A†
Perianal Crohn's disease present (%)	9 (7.4)	7 (10.1)	0.61	N/A†	N/A†	N/A†
Ulcerative colitis extent (%)						
Proctitis	N/A†	N/A†		31 (31.3)	14 (21.2)	
Left sided	N/A†	N/A†		42 (42.4)	32 (48.5)	
Extensive	N/A†	N/A†	N/A†	26 (26.3)	20 (30.3)	0.36
5-ASA use (%)	36 (29.5)	17 (24.6)	0.47	79 (79.8)	52 (78.8)	0.88
Immunomodulator use (%)	54 (44.3)	34 (49.3)	0.50	18 (18.2)	16 (24.2)	0.35
Anti TNF-α use (%)	35 (28.7)	17 (24.6)	0.55	1 (1.0)	3 (4.5)	0.15
Glucocorticosteroid use (%)	12 (9.8)	9 (13.0)	0.50	7 (7.1)	10 (15.2)	0.09
Previous intestinal resection (%)	29 (23.8)	33 (47.8)	0.001	N/A†	N/A†	N/A†
Rome III IBS criteria fulfilled (%)	38 (31.1)	48 (69.6)	<0.001	22 (22.2)	27 (40.9)	0.01
Self-reported flare (%)	18 (14.8)	24 (34.8)	0.001	16 (16.2)	35 (53.0)	<0.001
Mean FC (SD)	508 (885)	397 (535)	0.28	333 (556)	857 (1235)	0.002
FC ≥250µg/g (%)	45 (36.9)	28 (40.6)	0.61	31 (31.3)	34 (51.5)	0.009
Mean HADS anxiety score (SD)	6.5 (4.4)	9.2 (4.5)	<0.001	5.8 (4.2)	9.2 (5.2)	<0.001

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

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

†N/A; not applicable

Table 3. Relationship Between Elevated Patient-reported Disease Activity Indices (HBI or SCCAI ≥5) and Personal and Disease Characteristics in Crohn's Disease and Ulcerative Colitis After Logistic Regression.

	Crohn's disease and HBI ≥5 OR (95% CI)	**Ulcerative colitis and SCCAI ≥5 OR (95% CI)**
Female gender	1.06 (0.45 – 2.53)	0.63 (0.23 – 1.72)
Age (per year)	1.00 (0.97 – 1.03)	0.98 (0.96 – 1.01)
Married or co-habiting	1.93 (0.84 – 4.45)	0.35 (0.13 – 0.94)
University/postgraduate	1.33 (0.48 – 3.68)	0.66 (0.24 – 1.84)
BMI (per unit)	1.05 (0.98 – 1.12)	1.04 (0.97 – 1.13)
Tobacco use	1.34 (0.47 – 3.79)	3.95 (0.41 – 38.2)
Alcohol use	1.23 (0.52 – 2.89)	1.70 (0.60 – 4.77)
5-ASA use	0.79 (0.29 – 2.20)	1.13 (0.38 – 3.41)
Immunomodulator use	1.35 (0.61 – 2.97)	1.74 (0.57 – 5.25)
Anti-TNFα use	0.92 (0.37 – 2.28)	1.55 (0.09 – 26.9)
Glucocorticosteroid use	1.13 (0.33 – 3.83)	0.80 (0.20 – 3.22)
Previous intestinal resection	**2.63 (1.12 – 6.16)**	N/A*
Rome III IBS criteria fulfilled	**2.46 (1.11 – 5.47)**	1.25 (0.44 – 3.50)
Self-reported flare	1.21 (0.48 – 3.02)	**4.83 (1.85 – 12.6)**
FC ≥250µg/g	1.77 (0.76 – 4.13)	**3.11 (1.26 – 7.72)**
Anxiety (per 1-point change on HADS anxiety score)	0.95 (0.84 – 1.07)	0.94 (0.81 – 1.08)
Depression (per 1-point change on HADS depression score)	1.04 (0.90 – 1.19)	**1.21 (1.02 – 1.44)**
Somatization (per 1-point change on PHQ-15 score)	**1.31 (1.13 – 1.52)**	**1.17 (1.03 – 1.33)**

*N/A; not applicable

Table 4. Relationship Between Elevated Fecal Calprotectin (≥250 µg/g) and Personal and Disease Characteristics in Crohn's Disease and Ulcerative Colitis.

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

Crohn's disease behavior (%)						
Non-stricturing, non-penetrating	103 (87.3)	60 (82.2)		N/A†	N/A†	
Stricturing	8 (6.8)	12 (16.4)		N/A†	N/A†	
Penetrating	6 (5.1)	1 (1.4)	0.05	N/A†	N/A†	N/A†
Perianal Crohn's disease present (%)	10 (8.5)	6 (8.2)	0.73	N/A†	N/A†	N/A†
Ulcerative colitis extent (%)						
Proctitis	N/A†	N/A†		27 (27.0)	18 (27.7)	
Left sided	N/A†	N/A†		48 (48.0)	26 (40.0)	
Extensive	N/A†	N/A†	N/A†	25 (25.0)	21 (32.3)	0.52
5-ASA use (%)	37 (31.4)	16 (21.9)	0.16	81 (81.0)	50 (76.9)	0.53
Immunomodulator use (%)	59 (50.0)	29 (39.7)	0.17	21 (21.0)	13 (20.0)	0.88
Anti TNF-α use (%)	39 (33.1)	13 (17.8)	0.02	3 (3.0)	1 (1.5)	0.55
Glucocorticosteroid use (%)	10 (8.5)	11 (15.1)	0.16	9 (9.0)	8 (12.3)	0.50
Previous intestinal resection (%)	40 (33.9)	22 (30.1)	0.59	N/A†	N/A†	N/A†
Rome III IBS criteria fulfilled (%)	54 (45.8)	32 (43.8)	0.80	33 (33.0)	16 (24.6)	0.25
Mean HBI/SCCAI (SD)	4.1 (3.5)	4.5 (3.6)	0.54	3.3 (2.7)	4.9 (3.6)	0.003
HBI/SCCAI ≥5 (%)	41 (34.7)	28 (38.4)	0.61	32 (32.0)	34 (52.3)	0.009
Self-reported flare (%)	24 (20.3)	18 (24.7)	0.48	25 (25.0)	26 (40.0)	0.04
Mean HADS anxiety score (SD)	7.5 (4.8)	7.5 (4.4)	0.91	7.5 (5.2)	6.6 (4.5)	0.24

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

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

†N/A; not applicable

Table 5. Relationship Between Elevated Fecal Calprotectin (≥250 µg/g) and Personal and Disease Characteristics in Crohn's Disease and Ulcerative Colitis After Logistic Regression.

	Crohn's disease and FC ≥250µg/g OR (95%CI)	**Ulcerative colitis and FC ≥250µg/g OR (95%CI)**
Female gender	1.81 (0.86 – 3.82)	0.62 (0.27 – 1.42)
Age (per year)	1.01 (0.99 – 1.04)	0.99 (0.96 – 1.01)
Married or co-habiting	0.89 (0.44 – 1.81)	1.34 (0.58 – 3.11)
University/postgraduate	0.85 (0.37 – 1.97)	1.13 (0.46 – 2.78)
BMI (per unit)	1.04 (0.98 – 1.10)	1.05 (0.98 – 1.12)
Tobacco use	1.01 (0.40 – 2.56)	1.63 (0.22 – 12.0)
Alcohol use	0.98 (0.47 – 2.04)	0.43 (0.19 – 1.00)
5-ASA use	**0.38 (0.16 – 0.90)**	0.67 (0.27 – 1.67)
Immunomodulator use	0.49 (0.24 – 1.01)	0.90 (0.36 – 2.24)
Anti-TNFα use	0.56 (0.24 – 1.29)	0.32 (0.02 – 5.20)
Glucocorticosteroid use	2.75 (0.86 – 8.76)	0.78 (0.23 – 2.73)
Previous intestinal resection	0.70 (0.32 – 1.50)	N/A*
Rome III IBS criteria fulfilled	1.11 (0.53 – 2.33)	0.69 (0.27 – 1.77)
Self-reported flare	1.87 (0.78 – 4.46)	1.86 (0.76 – 4.57)
HBI/SCCAI ≥5	1.69 (0.74 – 3.83)	**3.36 (1.34 – 8.47)**
Anxiety (per 1-point change on HADS anxiety score)	1.00 (0.90 – 1.12)	0.95 (0.84 – 1.07)
Depression (per 1-point change on HADS depression score)	1.10 (0.97 – 1.24)	0.97 (0.84 – 1.13)
Somatization (per 1-point change on PHQ-15 score)	**0.85 (0.75 – 0.96)**	0.97 (0.87 – 1.09)

*N/A; not applicable