TITLE PAGE

Title: Longitudinal Impact of IBS-type Symptoms on Disease Activity, Healthcare Utilization, Psychological Health, and Quality of Life in Inflammatory Bowel Disease.

Short Title: Longitudinal Impact of IBS-type Symptoms in IBD.

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Abbreviations:	CD	Crohn's disease
	CI	confidence interval
	FC	fecal calprotectin
	GI	gastrointestinal
	HADS	hospital anxiety and depression scale
	HR	hazard ratio
	IBD	inflammatory bowel disease
	IBS	irritable bowel syndrome
	IL	interleukin
	PHQ-15	patient health questionnaire-15

RCT   randomized controlled trial

SD   standard deviation

TNF   tumor necrosis factor

UC   ulcerative colitis

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ABSTRACT

Objectives: The impact of irritable bowel syndrome (IBS)-type symptoms on the natural history of inflammatory bowel disease (IBD) is uncertain. We aimed to address this in a longitudinal study of secondary care patients.

Methods: Longitudinal disease activity was defined by disease flare, escalation of medical therapy, hospitalization, or intestinal resection. The number of investigations performed and clinics attended determined healthcare utilization. Psychological well-being and quality of life were assessed using validated questionnaires. These outcomes were compared over a minimum period of 2 years between patients reporting IBS-type symptoms and patients with quiescent disease, occult inflammation, and active disease at baseline.

Results: In 360 IBD patients, there were no differences in longitudinal disease activity between patients with IBS-type symptoms and patients with quiescent disease or occult inflammation. Disease flare and escalation of medical therapy was more common in patients with active disease than in patients with IBS-type symptoms (hazard ratio (HR) = 3.16; 95% confidence interval (CI) 1.93-5.19 and HR = 3.24; 95% CI 1.98-5.31, respectively). A greater number of investigations were performed in patients with IBS-type symptoms than quiescent disease (P = 0.008), but not compared with patients with occult inflammation or active disease. Anxiety, depression, and somatization scores at follow-up were higher, and quality of life scores lower, in patients with IBS-type symptoms when compared with patients with quiescent disease, but were similar to patients with active disease.

Conclusions: IBS-type symptoms in IBD were associated with increased healthcare utilization, psychological co-morbidity, reduced quality of life, but not adverse disease activity outcomes during extended follow-up.

What is current knowledge?

- IBS-type symptoms affect one-in-four patients with IBD.

- IBS-type symptoms are associated with psychological co-morbidity and poor quality of life.

- The impact of IBS-type symptoms on disease activity, healthcare utilization, and psychological well-being during extended follow-up is uncertain.

What is new here?

- The association between IBS-type symptoms and psychological co-morbidity and poor quality of life persisted during at least 2 years of longitudinal follow-up.

- Healthcare utilization was greater in patients reporting IBS-type symptoms.

- Reporting IBS-type symptoms was not associated with adverse longitudinal disease activity outcomes.

- The latter suggests that occult mucosal inflammation is unlikely to be responsible for the development of these symptoms.

INTRODUCTION

Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are chronic

disorders of the gastrointestinal (GI) tract without cure. The reporting of GI symptoms, including

abdominal discomfort and alterations in stool frequency and form, is common to both. In IBD,

symptoms are thought to arise as a consequence of active GI inflammation, whereas altered gut

motility, visceral hypersensitivity and activation of the brain-gut axis have been implicated in

IBS.(1, 2) Despite this, many of the etiological factors that contribute to the development of

these conditions, including alterations in the fecal microbiome, dysregulation of enteric

immunity, and impaired intestinal permeability, are shared.(3) Although traditionally considered

distinct disorders, the prevalence of symptoms compatible with IBS in patients with quiescent

IBD is as high as 35%.(4) This figure is reduced to between 18% and 24% when objective

markers of inflammatory disease activity are used to define remission,(5, 6) but remains

substantially higher than the overall background population.(7)

In IBD, the distinction between symptom-reporting secondary to genuine inflammatory

disease activity and IBS-type symptom reporting is important to make for several reasons. There

is no evidence that traditional pharmacological therapies for IBD are effective in patients without

active inflammation, (8) yet they may still be prescribed, with substantial cost implications, and

with the risk of adverse events. In addition, these IBS-type symptoms are associated with

considerable psychological co-morbidity and reduced quality of life. The impact appears at least

equivalent to that from overt inflammatory disease activity.(5, 6, 9, 10) The increasing use of

non-invasive biomarkers of GI inflammation in order to assess disease activity in patients with

IBD, without the need for lower GI endoscopy, has led to the emergence of a hitherto poorly

characterized cohort of patients. These individuals have no biochemical evidence of active

inflammation, but report ongoing GI symptoms, poor psychological health, and reduced quality of life, and there are few available therapeutic options for this subset of patients.

Until now, the majority of studies that have drawn attention to the prevalence and impact of IBS-type symptoms in patients with IBD have been cross-sectional in nature. Thus, the impact of these symptoms on the longer term natural history and prognosis of patients remains uncertain. We aimed to address this issue in a longitudinal follow-up study of patients with IBD recruited into a cross-sectional survey examining the prevalence and impact of IBS-type symptom reporting on psychological well-being and quality of life.(5) Specifically, our aims were to assess the impact of reporting symptoms compatible with IBS at study entry on subsequent disease activity, healthcare utilization, psychological well-being and quality of life during a minimum follow-up period of 2 years. Our *a priori* hypothesis was that presence of IBS-type symptoms at baseline would not impact adversely on the natural history of IBD.

METHODS

Participants and Setting

Individuals recruited into a previous cross-sectional survey(5, 11) were included in this longitudinal follow-up study. All patients had an established radiological, histological, or endoscopic diagnosis of CD or UC, and were aged ≥16 years at the time of baseline recruitment. Exclusion criteria were an inability to understand written English, a diagnosis of IBD-unclassified, and anyone with an end ileostomy or colostomy, due to the difficulties in assessing disease activity indices in these patients. Participants were sent a follow-up postal invitation to participate after a minimum period of 2 years had elapsed from recruitment, including a written information sheet explaining the nature of the study, a consent form, and a questionnaire similar to that completed at baseline. To maximize response rates, a second postal invitation was sent if the first questionnaire was not returned. Non-responders were also contacted at their scheduled outpatient clinic appointments during the study period. The longitudinal follow-up study was approved by the local research ethics committee in September 2014 (REC ref: 12/YH/0443), and data collection continued until June 2017. Study findings were reported in accordance with the STROBE guidelines for observational studies.(12)

Data Collection and Synthesis

Date of recruitment into the original cross-sectional survey, demographic data, type of IBD, medication use for IBD, Rome III IBS symptom data, anxiety and depression data, somatization data, quality of life data, and fecal calprotectin (FC) (Immundiagnostik, Bensheim, Germany) were recorded at baseline, as described in the original cross-sectional survey.(5, 11)

Definition of Disease Activity and Presence of IBS-type Symptoms

Using a combination of disease activity indices (Harvey-Bradshaw index for CD,(13) and simple clinical colitis activity index for UC,(14) with a score ≥5 used to define clinical disease activity for both (15, 16)), presence or absence of symptoms compatible with Rome III-defined IBS,(17) and an FC level of ≥250µg/g to define active inflammation,(18-20) we were able to categorize patients into four groups, as we have described previously.(5) Briefly, those who reported IBS-type symptoms with an FC <250µg/g were defined as having IBD with IBS-type symptoms, regardless of disease activity indices. Those who did not report IBS-type symptoms with an FC <250µg/g were defined as having quiescent disease, regardless of disease activity indices. Those with normal disease activity indices and FC ≥250µg/g were defined as having occult inflammation, regardless of IBS symptom status. Finally, those with abnormal disease activity indices with an FC ≥250µg/g were defined as having active disease, regardless of whether or not they reported IBS-type symptoms.

Definition of Anxiety or Depression

Anxiety and depression data were collected using the hospital anxiety and depression scale (HADS). (21) 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 HADS score 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). (21)

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. (22, 23) The PHQ-15 enquires about the presence of 15 somatic symptoms (or

symptom clusters) over the last 4 weeks, which contribute to >90% of physical complaints

reported in the outpatient environment. (24) Individuals were 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). Therefore 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.

Assessment of Quality of Life

We used the medical outcomes study 36-item short-form (SF-36) health survey, a

validated questionnaire used to assess physical and mental health status,(25) to make an

assessment of health-related quality of life. This comprises 36 questions, which are grouped into

eight health domains (physical functioning, role limitations due to physical health, role

limitations due to emotional health, energy or fatigue, emotional well-being, social functioning,

pain, and general health). Patients were asked to complete the questionnaire, giving responses to

each question from zero to one hundred, from which a mean score for each health domain was

calculated, with higher scores indicating more favorable health-related quality of life.

Longitudinal Objective Assessment of IBD Activity

Objective assessment of disease activity during longitudinal follow-up was made by

detailed case note review by a sole investigator (DJG), blinded to the baseline questionnaire data.

The case notes of each of the 378 patients included at baseline were assessed for the following clinical endpoints, with the date of each endpoint recorded, where applicable: glucocorticosteroid prescription or flare of disease activity identified by physician's global assessment, escalation of medical therapy due to uncontrolled disease activity, hospitalization secondary to objectively confirmed IBD activity, and intestinal resection. Escalation of medical therapy in response to therapeutic drug monitoring, but in the absence of inflammatory activity, was not included as an endpoint, nor was surgical intervention for isolated perianal Crohn's disease.

Longitudinal Assessment of Healthcare Utilization

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

Longitudinal Assessment of Psychological Health and Quality of Life

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

Statistical Analysis

Baseline demographic, disease-related, and psychological data for all IBD patients included at baseline were compared between patients with CD and UC. After classification of disease activity and IBS-type symptom status, baseline demographic characteristics, HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatization were compared between IBD patients reporting IBS-type symptoms and the other three groups of patients individually (quiescent disease, occult inflammation, or active disease), using a χ^2 test for categorical variables, and an independent samples *t*-test for continuous data. Comparisons across all four groups were performed using a χ^2 test for categorical variables and a one-way analysis of variance (ANOVA) for continuous data. The same comparisons were made between these groups for each of the four objective disease activity outcomes and the three measures of healthcare utilization during longitudinal follow-up. Similarly, follow-up HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatization at follow-up were compared between the four groups to determine the effect of IBS-type symptoms on psychological health and quality of life over time. Independent predictors of the occurrence of any of the objective disease activity outcomes of interest were determined by performing multivariate Cox regression analysis to control for all baseline demographic characteristics, baseline IBD activity category, medications, and the presence or absence of

baseline abnormal anxiety or depression scores, or high somatization scores. The results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). We performed sensitivity analyses using a FC <100μg/g to define those who reported IBS-type symptoms as having IBD with IBS-type symptoms.

As our *a priori* hypothesis was that presence of IBS-type symptom reporting at baseline would not impact adversely on objective markers of disease activity, we considered a 2-tailed P-value of <0.01 to be statistically significant, in order not to underestimate the impact of IBS-type symptom reporting on the natural history of IBD. For all other comparisons examining impact of IBS-type symptoms on healthcare utilization, psychological health, and quality of life a 2-tailed P value of <0.001 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 360 (95.2%) of 378 patients included in the initial cross-sectional survey had

available follow-up disease activity data after case note review. Of these, 200 (55.6%) had CD

and 160 (44.4%) UC. At baseline, patients with CD were more likely to smoke, to use

immunomodulator therapy and anti-tumor necrosis factor-α (TNFα) drugs, but less likely to use

5-aminosalicylates (ASAs) when compared with those with UC (P <0.001 for all)

(Supplementary Table 1). There was no difference in the proportion of patients who were

defined as having IBS-type symptoms, quiescent disease, occult inflammation, or active disease,

and no difference in levels of anxiety, depression, or somatization at baseline. Patients with CD

had lower mean SF-36 quality of life scores at baseline for energy/fatigue (P = 0.003), pain (P =

0.003), and general health (P <0.001) than patients with UC.

Characteristics of IBD patients with and without IBS-type Symptoms

Based on FC results, Rome III IBS status, and clinical disease activity indices at baseline,

the 360 IBD patients included in longitudinal follow-up were divided into four groups as

follows: 85 (23.6%) had IBS-type symptoms, 133 (36.9%) had quiescent disease, 78 (21.7%) had

occult inflammation, and 64 (17.8%) had active disease. Baseline demographic and disease

characteristics, psychological data, and quality of life data across the four groups was as

previously reported,(5) and as illustrated in Supplementary Table 2. In brief, patients reporting

IBS-type symptoms were more likely to be female and to smoke than patients with quiescent

disease (P = 0.002 for both), but there were no other differences in baseline demographic or

disease characteristics across the four groups. Mean baseline anxiety, depression, and

somatization scores were significantly higher, and quality of life scores significantly lower, in

patients with IBS-type symptoms when compared with patients with quiescent disease or occult inflammation, but were equivalent to those observed in patients with active disease.

Impact of IBS-type Symptoms on Disease Activity During Longitudinal Follow-up

During longitudinal follow-up, patients reporting IBS-type symptoms at baseline were no more likely to receive a glucocorticosteroid prescription or experience a flare of disease activity, require escalation of medical therapy in response to uncontrolled IBD activity, be hospitalized, or undergo intestinal resection than patients with quiescent disease or occult inflammation at baseline (Table 1). However, patients with active disease at baseline were more likely to receive a glucocorticosteroid prescription or experience a flare of disease activity, or require escalation of medical therapy in response to uncontrolled IBD activity, than patients reporting IBS-type symptoms at baseline, and compared with all three of the other patient groups. There was also a non-significant trend towards patients with active disease being more likely to require hospitalization or intestinal resection, compared with the other three groups (P = 0.01 and P = 0.02, respectively). Sensitivity analyses using a FC <100µg/g to define those who reported IBS-type symptoms as having IBD with IBS-type symptoms are provided in Supplementary Table 3. The lack of any association between presence of IBS-type symptoms at baseline and subsequent disease activity remained consistent.

Following multivariate Cox regression analysis, during a mean length of follow-up of 754 days (standard deviation (SD) ± 517), patients reporting IBS-type symptoms had a similar likelihood of requiring a glucocorticosteroid prescription or experiencing a flare of disease activity to those with quiescent disease (HR = 0.66; 95% CI 0.41-1.06) or occult inflammation (HR = 0.82; 95% CI 0.47-1.44) at baseline (Table 2 and Figure 1). However, this endpoint was

significantly more likely in patients with active disease at baseline (HR = 3.16; 95% CI 1.93-5.19). Similarly, over a mean length of follow-up of 773 days (SD ± 505), when compared with patients reporting IBS-type symptoms at baseline, need for escalation of medical therapy in response to uncontrolled IBD activity was significantly higher in patients with active disease at baseline (HR = 3.24; 95% CI 1.98-5.31). However, the likelihood of this event was similar in patients with IBS-type symptoms and those with quiescent disease (HR = 0.80; 95% CI 0.48-1.32) or occult inflammation (HR = 0.87; 95% CI 0.47-1.58) (Figure 2). There were no differences in need for hospitalization, over a mean length of follow-up of 1019 days (SD ± 430) (Figure 3), or intestinal resection, over a mean length of follow-up of 1073 days (SD ± 1117) (Figure 4), when patients with IBS-type symptoms were compared with those with quiescent disease, occult inflammation, or active disease at baseline. Sensitivity analyses using a FC <100µg/g revealed similar findings (Supplementary Table 4).

Impact of IBS-type Symptoms on Healthcare Utilization During Longitudinal Follow-up

When compared with patients reporting IBS-type symptoms at baseline during a mean length of follow-up of 1073 days (SD ± 1117), there was a trend towards the mean number of investigations performed being lower in patients with quiescent disease (1.2 (SD ± 1.3) vs. 0.8 (SD ± 0.9), P = 0.008), but not those with occult inflammation or active disease at baseline (Table 3). There was no significant difference in the number of clinic attendances, or IBD telephone helpline consultations held, between patients reporting IBS-type symptoms, and those with quiescent disease, occult inflammation, or active disease at baseline. Again, sensitivity analyses using a FC <100µg/g revealed similar findings (Supplementary Table 5).

Impact of IBS-type Symptoms on Psychological Health and Quality of Life During

Longitudinal Follow-up

228 (63.3%) of 360 patients returned a follow-up questionnaire and therefore provided

anxiety, depression, somatization, and quality of life data after a minimum follow-up period of 2

years. There were no significant differences in baseline characteristics between IBD patients who

did, and did not, return a follow-up questionnaire (Supplementary Table 6). During longitudinal

follow-up (mean duration 928 days (SD ± 198)), patients reporting IBS-type symptoms at

baseline had higher mean anxiety, depression, and somatization scores when compared with

patients with quiescent disease at baseline (Table 4). These were also generally higher than

among patients with occult inflammation at baseline, although not statistically significant, but

were similar to those in patients with active disease at baseline. Follow-up quality of life scores

across all eight domains of the SF-36 were impaired among those reporting IBS-type symptoms

at baseline, compared with those with either quiescent disease or occult inflammation, and in

several instances these differences were statistically significant. The degree of impairment of

quality of life during longitudinal follow-up was similar among patients reporting IBS-type

symptoms and those with active disease at baseline. Again, sensitivity analyses using a FC

<100µg/g revealed similar findings (Supplementary Table 7).

DISCUSSION

This longitudinal follow-up study has demonstrated that the reporting of IBS-type symptoms in patients with objectively confirmed quiescent IBD is not associated with adverse disease activity outcomes, but is associated with increased investigation requesting. The previously reported association between IBS-type symptom reporting and poor psychological heath and quality of life persisted during longitudinal follow-up, and may endure independent of inflammatory disease activity. Although the reporting of these symptoms does not appear to affect longitudinal disease activity, suggesting that they are not related to ongoing occult inflammation, their impact on psychological well-being and the possible association with increased healthcare utilization highlights the importance of our findings. Although the association between the reporting of IBS-type symptoms and psychological co-morbidity and reduced quality of life has been demonstrated in prior cross-sectional studies,(5, 6, 9, 10) none has attempted to address the impact of these symptoms on longitudinal outcomes in IBD. Specifically, this is the first study to examine the effect of IBS-type symptom reporting on subsequent IBD activity, using objective endpoints, and to provide data on the impact of these symptoms on healthcare utilization, as well as the durability of the association between the reporting of these symptoms and psychological co-morbidity and poor quality of life over time.

We followed-up a cohort of 360 patients with complete baseline clinical characteristics successfully, and obtained longitudinal disease activity outcome data. The observational nature of this study, and the recruitment of patients from a secondary care population, means that our findings are likely to be generalizable to the IBD population at large. Our use of four distinct, and objectively defined, disease activity outcomes has allowed us to provide in-depth analysis of the impact of IBS-type symptom reporting on longitudinal disease activity. Furthermore,

performing Cox regression analysis for each of these variables permitted the identification of independent predictors of longitudinal disease activity over time. Our stratification of patients into those with IBS-type symptoms, quiescent disease, occult inflammation, and active disease is a further strength as it permitted independent assessment of the longitudinal impact of baseline inflammatory disease activity, and GI symptom reporting on objective measures of disease activity, healthcare use, psychological well-being, and quality of life over time. Our use of validated questionnaires to assess for the presence of anxiety,(21) depression,(21) somatization,(26) and quality of life,(25) both at baseline and at longitudinal follow-up, is a further strength. Finally, objective longitudinal disease activity assessment data were collected blinded to baseline disease activity and psychological data, therefore eliminating researcher confirmation bias.

Limitations of this study include the sample size and length of follow-up. Following Cox regression analysis, there was no statistically significant difference in the need for hospitalization secondary to objectively quantified inflammatory disease activity or intestinal resection, when patients reporting IBS-type symptoms were compared with those with active disease at baseline. Despite this, in univariate analysis, the absolute proportion of patients fulfilling these endpoints was higher in those defined as having active disease at baseline. This is likely to be secondary to the relatively low event rate for these variables. If our sample size had been larger, or follow-up continued for a longer period of time, these comparisons may have become statistically significant. Although our use of FC to objectively quantify inflammatory disease activity is a strength, the FC cut off of ≥250μg/g used to define the presence of active mucosal inflammation is contentious, despite it being advocated by expert consensus and having been used by previous researchers.(5, 18-20, 27, 28) For this reason, we conducted sensitivity analyses using a FC cut

off of ≥100µg/g to define active disease, and our observations remained relatively consistent. Our assessment of quality of life and psychological well-being in longitudinal follow-up was based on questionnaire responses at a single point in time after a minimum of 2 years. Because of this, we are unable to comment on the consistency of the association between baseline IBS-type symptom reporting and psychological well-being and poor quality of life over multiple points of follow-up. However, in sensitivity analysis, patients reporting IBS-type symptoms who had abnormal anxiety scores at baseline were more likely to continue to report abnormal anxiety scores at longitudinal follow-up than those who did not (16 (64.0%) of 25 vs. 13 (33.3%) of 39; P = 0.02). Similar findings were also true for those with IBS-type symptoms and abnormal baseline depression scores (9 (69.2%) of 13 vs. 3 (5.9%) of 51; P <0.001) and high baseline somatization scores (12 (54.5%) of 22 vs. 5 (13.5%) of 37; P = 0.001). This suggests that, in susceptible individuals, the association between IBS-type symptoms and psychological co-morbidity is likely to be durable. Finally, due to the low event rate for some of the longitudinal disease activity outcomes, and the attrition rate associated with administering postal follow-up questionnaires for longitudinal psychological and quality of life, we chose not to present data on IBD patients dichotomized into those with UC and CD.

To the best of our knowledge, only one other study has attempted to address the longitudinal impact of IBS-type symptom reporting in IBD.(29) Jonefjäll *et al.* reported data from an inception cohort of 94 UC patients followed up annually over a 3-year period. In keeping with our findings, the authors describe an association between IBS-type symptom reporting in patients with objectively confirmed quiescent disease, and poor psychological well-being and quality of life over time. However, the impact of IBS-type symptom reporting on overall longitudinal disease activity, or healthcare utilization, was not addressed. In addition, the

study population was relatively small, and excluded patients with CD. A relationship between

IBS-type symptom reporting and healthcare utilization has been described in another study,(30)

but this was cross-sectional in design, relied on patient recall of healthcare interactions over the

preceding year, rather than accurate prospective data collection, and did not examine effects on

investigation requesting.

The etiology of IBS-type symptom reporting in patients with IBD remains uncertain. The

role of subclinical mucosal inflammation is debated, with some authors suggesting it is likely to

be central to the development of these symptoms,(10, 31) although others disagree.(5, 9, 29)

Increased colonic mucosal pro-inflammatory cell infiltrates, and increased mucosal TNFα

mRNA protein expression have been described in patients reporting IBS-type symptoms.(31) In

keeping with this, raised serum levels of pro-inflammatory cytokines, including interleukin (IL)-

1β, IL-6, IL-13, IL-10 and IL-8 have also been observed in patients reporting IBS-type

symptoms.(6) Despite this, in the same study, there was no difference in median FC levels

between patients who did, and who did not, report IBS-type symptoms, although again an

association between IBS-type symptom reporting and psychological co-morbidity was

observed.(6)

Studies identifying antecedent gastroenteritis as a risk factor for the subsequent

development of IBS in non-IBD populations have led to the suggestion that post-inflammatory

dysmotility and visceral hypersensitivity may contribute to the development of chronic GI

symptoms.(32) Whether this concept is transferrable to the IBD population is unclear,

particularly as the extent and severity of inflammation at the time of first presentation does not

appear to be associated with the subsequent development of IBS-type symptoms following

mucosal healing in IBD.(33) These findings, in conjunction with the lack of association between

objective longitudinal disease activity and IBS-type symptom reporting described here, cast further doubt on the role of subclinical inflammation in the etiology of these symptoms. Our description of a distinct group of patients with occult GI inflammation who have objective evidence of inflammatory disease activity, but who do not report GI symptoms further supports this. When compared with patients with occult inflammatory activity, the greater consistency with which psychological co-morbidity was associated with IBS-type symptom reporting in our patients with IBD suggests that brain-gut axis activation, rather than the presence of subclinical mucosal inflammation, could be central to the development of these symptoms. However, this hypothesis remains speculative.

Again, we provide data on an emerging cohort of IBD patients with distinct needs. The lack of association between IBS-type symptom reporting and objective longitudinal disease activity outcomes may explain the limited efficacy of traditional pharmacological therapies in these patients.(8) Evidence-based management strategies for the treatment of IBS exist,(34-37) but are of unproven benefit in IBD. Trials of alternative therapies including psychological therapy,(38) probiotics,(39) and antidepressants (40, 41) have been conducted in patients with IBD but the results, to date, have been disappointing, perhaps because none of these studies has sought to address the needs of this specific patient group. In the UK, there has been a recent call from the Health Technology Assessment for a trial of therapies for ongoing diarrhea and abdominal pain in patients with stable UC, which may help to address this deficit in current knowledge.(42)

In summary, our previous work has highlighted the existence of a distinct group of IBD patients who report IBS-type symptoms in the absence of inflammatory disease activity. Patients reporting these symptoms are more likely to experience psychological co-morbidity and poor

quality of life when compared with asymptomatic patients with quiescent disease. The current

study confirms that the deleterious impact of IBS-type symptom reporting on psychological well-

being and quality of life persists over extended longitudinal follow-up, and is associated with an

increase in healthcare utilization, but not adverse outcomes related to inflammatory activity. The

consistent association between psychological co-morbidity and IBS-type symptom reporting

over time, and the lack of any equivalent relationship with mucosal inflammation, suggests that

activation of the brain-gut axis, rather than subclinical inflammatory disease activity, could be

contributory to the development of these symptoms. Future trials of therapies targeting

disordered brain-gut axis activity in this specific group of IBD patients may therefore be helpful.

CONFLICTS OF INTEREST/STUDY SUPPORT

REFERENCES

1.   Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. N Engl J Med 2017;376:2566-2578.

2.   Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol 2016;1:133-146.

3.   Spiller R, Major G. IBS and IBD - separate entities or on a spectrum? Nat Rev Gastroenterol Hepatol 2016;13:613-21.

4.   Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: Systematic review and meta-analysis. Am J Gastroenterol 2012;107:1474-1482.

5.   Gracie DJ, Williams CJ, Sood R, et al. Negative Effects on Psychological Health and Quality of Life of Genuine Irritable Bowel Syndrome-type Symptoms in Patients With Inflammatory Bowel Disease. Clin Gastroenterol Hepatol 2017;15:376-384 e5.

6.   Jonefjall B, Ohman L, Simren M, et al. IBS-like Symptoms in Patients with Ulcerative Colitis in Deep Remission Are Associated with Increased Levels of Serum Cytokines and Poor Psychological Well-being. Inflamm Bowel Dis 2016;22:2630-2640.

7.   Lovell RM, Ford AC. Global prevalence of, and risk factors for, irritable bowel syndrome: A meta-analysis. Clin Gastroenterol Hepatol 2012;10:712-721.

8.   Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383-95.

9.   Berrill JW, Green JT, Hood K, et al. Symptoms of irritable bowel syndrome in patients with inflammatory bowel disease: examining the role of sub-clinical inflammation and the impact on clinical assessment of disease activity. Aliment Pharmacol Ther 2013;38:44-51.

10.   Keohane J, O'Mahony C, O'Mahony L, et al. Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: A real association or reflection of occult inflammation? Am J Gastroenterol 2010;105:1789-1794.

11.   Gracie DJ, Williams CJ, Sood R, et al. Poor Correlation Between Clinical Disease Activity and Mucosal Inflammation, and the Role of Psychological Comorbidity, in Inflammatory Bowel Disease. Am J Gastroenterol 2016;111:541-51.

12.   von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344-9.

13.   Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.

14.   Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. Gut 1998;43:29-32.

15.   Vermeire S, Schreiber S, Sandborn WJ, et al. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. Clin Gastroenterol Hepatol 2010;8:357-63.

16.   Jowett SL, Seal CJ, Phillips E, et al. Defining relapse of ulcerative colitis using a symptom-based activity index. Scand J Gastroenterol 2003;38:164-71.

17.   Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006;130:1480-1491.

18.   Targownik LE, Sexton KA, Bernstein MT, et al. The Relationship Among Perceived Stress, Symptoms, and Inflammation in Persons With Inflammatory Bowel Disease. Am J Gastroenterol 2015;110:1001-12.

19.   Rogler G, Aldeguer X, Kruis W, et al. Concept for a rapid point-of-care calprotectin diagnostic test for diagnosis and disease activity monitoring in patients with inflammatory bowel disease: expert clinical opinion. J Crohns Colitis 2013;7:670-7.

20.   D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis 2012;18:2218-24.

21.   Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-370.

22.   Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999;282:1737-44.

23.   Spitzer RL, Williams JB, Kroenke K, et al. Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. Am J Obstet Gynecol 2000;183:759-69.

24.   Kroenke K, Arrington ME, Mangelsdorff AD. The prevalence of symptoms in medical outpatients and the adequacy of therapy. Arch Intern Med 1990;150:1685-9.

25.   McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-63.

26.   Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;64:258-266.

27.   Sexton KA, Walker JR, Graff LA, et al. Evidence of Bidirectional Associations Between Perceived Stress and Symptom Activity: A Prospective Longitudinal Investigation in Inflammatory Bowel Disease. Inflamm Bowel Dis 2017;23:473-483.

28.   Lin JF, Chen JM, Zuo JH, et al. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. Inflamm Bowel Dis 2014;20:1407-15.

29.   Jonefjall B, Strid H, Ohman L, et al. Characterization of IBS-like symptoms in patients with ulcerative colitis in clinical remission. Neurogastroenterol Motil 2013;25:756-e578.

30.   Abdalla MI, Sandler RS, Kappelman MD, et al. Prevalence and Impact of Inflammatory Bowel Disease-Irritable Bowel Syndrome on Patient-reported Outcomes in CCFA Partners. Inflamm Bowel Dis 2017;23:325-331.

31.   Vivinus-Nebot M, Frin-Mathy G, Bzioueche H, et al. Functional bowel symptoms in quiescent inflammatory bowel diseases: role of epithelial barrier disruption and low-grade inflammation. Gut 2014;63:744-52.

32.   Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. Aliment Pharmacol Ther 2007;26:535-44.

33.   Jonefjall B, Simren M, Ohman L, et al. The severity of inflammation at onset of ulcerative colitis is not associated with IBS-like symptoms during clinical remission. J Crohns Colitis 2015;9:776-83.

34.   Ford AC, Quigley EM, Lacy BE, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol 2014;109:1547-61; quiz 1546, 1562.

35.   Ford AC, Quigley EM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol 2014;109:1350-65; quiz 1366.

36.   Ford AC, Talley NJ, Schoenfeld PS, et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut 2009;58:367-78.

37.   Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ 2008;337:a2313.

38.   Gracie DJ, Irvine AJ, Sood R, et al. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;2:189-199.

39.   Derwa Y, Gracie DJ, Hamlin PJ, et al. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. Aliment Pharmacol Ther 2017;46:389-400.

40.   Mikocka-Walus A, Hughes PA, Bampton P, et al. Fluoxetine for Maintenance of Remission and to Improve Quality of Life in Patients with Crohn's Disease: a Pilot Randomized Placebo-Controlled Trial. J Crohns Colitis 2017;11:509-514.

41.   Macer BJ, Prady SL, Mikocka-Walus A. Antidepressants in Inflammatory Bowel Disease: A Systematic Review. Inflamm Bowel Dis 2017;23:534-550.

42.   http://www.nihr.ac.uk/funding-and-support/funding-opportunities/1733-management-of-diarrhoea-in-patients-with-stable-ulcerative-colitis/5984. (accessed online 10/10/2017).

Table 1: Impact of IBS-type Symptoms on Objective Markers of Disease Activity During Longitudinal Follow-up.

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

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

†χ^2 for comparison across all four groups.

Table 2: Baseline Independent Predictors of Objective Markers of Disease Activity During Longitudinal Follow-up.

	Glucorticosteroid Prescription or Flare of Disease Activity		Escalation of Medical Therapy in Response to Uncontrolled IBD Activity		Hospitalization due to Disease Activity		Intestinal resection	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Female sex	1.05 (0.73-1.53)	0.79	0.91 (0.61-1.36)	0.66	0.85 (0.43-1.68)	0.64	1.89 (0.54-6.61)	0.32
Age (per year)	0.97 (0.96-0.99)	<0.001	0.98 (0.96-0.99)	<0.001	0.98 (0.96-1.00)	0.07	0.99 (0.95-1.03)	0.66
Married or co-habiting	0.92 (0.64-1.32)	0.64	1.52 (1.00-2.31)	0.05	1.32 (0.64-2.71)	0.46	0.70 (0.24-2.03)	0.52
Tobacco use	0.37 (0.18-0.75)	0.006	0.69 (0.39-1.24)	0.22	0.71 (0.25-2.05)	0.53	1.61 (0.47-5.58)	0.45
Alcohol use	1.04 (0.71-1.52)	0.83	0.95 (0.64-1.41)	0.80	0.64 (0.32-1.27)	0.20	0.30 (0.10-0.92)	0.04
University/postgraduate education	0.96 (0.65-1.41)	0.82	0.89 (0.59-1.35)	0.59	0.81 (0.36-1.82)	0.62	1.36 (0.37-5.01)	0.64
Body mass index (per unit)	1.01 (0.98-1.05)	0.35	1.03 (1.00-1.06)	0.07	1.05 (0.99-1.10)	0.10	1.02 (0.94-1.11)	0.64
CD	0.66 (0.43-1.02)	0.06	0.69 (0.44-1.09)	0.11	1.12 (0.48-2.62)	0.79	1.09 (0.27-4.52)	0.90
5-ASA use	1.29 (0.83-2.01)	0.26	1.10 (0.70-1.73)	0.69	0.67 (0.29-1.55)	0.35	0.44 (0.11-1.69)	0.23
Immunosuppressant use	0.85 (0.58-1.25)	0.40	0.56 (0.37-0.86)	0.007	1.30 (0.65-2.60)	0.46	1.04 (0.35-3.15)	0.94
Anti-TNFα use	0.81 (0.45-1.47)	0.49	1.05 (0.59-1.87)	0.86	1.49 (0.61-3.64)	0.39	7.41 (2.10-26.2)	0.002
Glucorticosteroid use	2.40 (1.51-3.82)	<0.001	1.86 (1.14-3.06)	0.01	2.47 (1.14-5.38)	0.02	2.76 (0.61-12.6)	0.19

Disease category								
IBS-type symptoms	Reference	N/A	Reference	N/A	Reference	N/A	Reference	N/A
Quiescent disease	0.66 (0.41-1.06)	0.09	0.80 (0.48-1.32)	0.38	0.57 (0.22-1.46)	0.24	0.63 (0.13-2.99)	0.56
Occult inflammation	0.82 (0.47-1.44)	0.49	0.87 (0.47-1.58)	0.64	0.75 (0.26-2.18)	0.60	0.58 (0.09-3.74)	0.56
Active disease	3.16 (1.93-5.19)	<0.001	3.24 (1.98-5.31)	<0.001	2.03 (0.86-4.77)	0.11	2.82 (0.77-10.3)	0.12
Abnormal anxiety score	1.12 (0.73-1.71)	0.61	1.30 (0.84-2.01)	0.24	1.73 (0.83-3.62)	0.15	2.13 (0.65-6.97)	0.21
Abnormal depression score	1.46 (0.83-2.55)	0.19	1.60 (0.90-2.82)	0.11	1.73 (0.70-4.27)	0.24	1.19 (0.28-5.04)	0.82
High somatization score	0.73 (0.44-1.21)	0.22	0.94 (0.57-1.57)	0.82	0.73 (0.30-1.79)	0.49	1.21 (0.32-4.58)	0.78

Table 3: Impact of IBS-type Symptoms on Healthcare Utilization During Longitudinal Follow-up.

	IBD with IBS-type Symptoms (n = 85)	Quiescent IBD (n = 133)	P Value*	IBD with Occult Inflammation (n = 78)	P Value*	Active IBD (n = 64)	P Value*	P Value†
Mean number of investigations (SD)	1.2 (1.3)	0.8 (0.9)	0.008	0.9 (1.0)	0.09	1.3 (1.0)	0.74	0.005
Mean number of clinic appointments (SD)	7.2 (4.9)	6.1 (4.4)	0.07	5.9 (3.2)	0.045	8.3 (4.7)	0.18	0.002
Mean number of helpline calls (SD)	1.4 (2.8)	0.9 (2.1)	0.21	1.1 (2.0)	0.43	1.8 (2.1)	0.25	0.06

*Independent samples *t*-test for comparisons vs. IBD with IBS-type symptoms.

†One way ANOVA for comparison across all four groups.

Table 4: Impact of IBS-type Symptoms on Psychological Health and Quality of Life During Longitudinal Follow-up.

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

PHQ-15 somatization categories (%)								
Mild	4 (6.5)	21 (28.4)		10 (20.0)		2 (6.3)		
Low	14 (22.6)	28 (37.8)		14 (28.0)		11 (34.4)		
Medium	26 (41.9)	16 (21.6)		17 (34.0)		11 (34.4)		
High	18 (29.0)	9 (12.2)	<0.001	9 (18.0)	0.10	8 (25.0)	0.67	0.003
Mean SF-36 score (SD)								
Physical functioning	66.9 (27.2)	79.7 (26.7)	0.006	71.4 (29.7)	0.41	70.6 (31.0)	0.55	0.06
Role limitations physical health	42.7 (42.1)	75.0 (38.6)	<0.001	51.6 (43.6)	0.29	57.3 (45.3)	0.13	<0.001
Role limitations emotional problems	63.3 (43.3)	77.3 (37.2)	0.05	66.7 (42.4)	0.69	70.7 (38.0)	0.41	0.22
Energy/fatigue	35.8 (20.8)	52.4 (26.0)	<0.001	43.9 (24.4)	0.08	36.8 (26.2)	0.85	0.001
Emotional well-being	58.0 (22.2)	72.7 (21.4)	<0.001	67.9 (23.6)	0.03	66.8 (21.4)	0.07	0.002
Social functioning	60.1 (27.4)	76.6 (25.8)	<0.001	72.0 (28.4)	0.03	65.5 (29.3)	0.37	0.004
Pain	55.6 (24.5)	69.1 (25.4)	0.002	66.6 (26.2)	0.03	59.6 (26.9)	0.46	0.01
General health	35.9 (22.6)	53.3 (24.8)	<0.001	47.5 (24.4)	0.01	38.5 (22.9)	0.61	<0.001

*Independent samples *t*-test for continuous data, and χ^2 for comparison of categorical data vs. IBD with IBS-type symptoms.

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

Figure 1: Survival Plot of the Impact of IBS-type Symptoms on Flare of Disease Activity or Glucocorticosteroid Prescription.

Figure 2: Survival Plot of the Impact of IBS-type Symptoms on Escalation of Medical Therapy in Response to Uncontrolled IBD.

Figure 3: Survival Plot of the Impact of IBS-type Symptoms on Hospitalization.

Figure 4: Survival Plot of the Impact of IBS-type Symptoms on Intestinal Resection.