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TITLE PAGE

Title: Prevalence of irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease in remission: A systematic review and meta-analysis.

Short running head: IBS-type symptoms and psychological co-morbidity in IBD: A systematic review and meta-analysis.

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Abbreviations:

CD	Crohn's disease
CI	confidence interval
DAI	disease activity index
FC	faecal calprotectin
HADS	hospital anxiety and depression scale

IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
MeSH	medical subject heading
PHQ-12	patient health questionnaire-12
PGA	physician's global assessment
RCT	randomised controlled trial
SMD	standardised mean difference
UC	ulcerative colitis
WMD	weighted mean difference

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SUMMARY

Background: Patients with inflammatory bowel disease (IBD) often report symptoms compatible with irritable bowel syndrome (IBS), and these may impact on psychological health. However, previous estimates of the magnitude of this issue have not accounted for ongoing inflammation as the potential cause. We updated a previous systematic review and meta-analysis to determine prevalence of IBS-type symptoms in patients with IBD in remission in an attempt to better quantify the magnitude of this issue, and hence highlight this as an area of unmet therapeutic need.

Methods: A search of EMBASE, EMBASE Classic and MEDLINE was conducted (from January 2012 until May 2020) to identify prospective studies reporting prevalence of symptoms meeting diagnostic criteria for IBS in adults with IBD in remission. Pooled prevalence and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated according to definition of remission, criteria used to define IBS-type symptoms, and type of IBD. The association between IBS-type symptom reporting and psychological co-morbidity was examined using weighted (WMD) or standardised mean differences (SMD) in anxiety and depression scores between those reporting IBS-type symptoms and those not, where available.

Findings: Of 3370 studies identified, 27 were eligible; 18 were newly identified. Among 3169 patients with IBD in remission, pooled prevalence of IBS-type symptoms was 32.5% (95% CI 27.4%-37.9 %). Prevalence was lower when remission was defined by endoscopic compared with clinical assessment (23.5% vs. 33.6%) and was higher in Crohn's disease than in ulcerative colitis (34.9% vs. 29.1%; OR 1.58; 95% CI 1.27-1.98). Anxiety (WMD 2.5; 95% CI 0.8-4.3) and depression (SMD 0.64; 95% CI 0.44-0.84) scores were significantly higher among those who reported IBS-type symptoms compared with those who did not.

Interpretation: Prevalence of symptoms compatible with IBS in patients with IBD varied according to how remission was defined. Nevertheless, even when stringent criteria, such as endoscopic or histological remission were used, one-in-four patients reported these symptoms. Such symptoms were more common in patients with CD and were associated with psychological co-morbidity. Addressing psychological wellbeing may improve outcomes in this specific group of patients.

Funding: None.

Evidence before this study

Irritable bowel syndrome (IBS)-type symptom reporting in inflammatory bowel disease (IBD) is common. The pathophysiology behind IBS-type symptoms in IBD is likely to be multifactorial, due to a combination of changes to the intestinal microbiota, altered intestinal permeability, low-grade mucosal inflammation, and immune activation. A previous meta-analysis estimated this issue affects up to 40% of patients. However, studies examining this issue do not always restrict IBD cohorts to those in remission, so it is unclear whether inflammatory disease activity is the main driver. Observational studies have also reported an association between IBS-type symptoms and increased psychological co-morbidity, which is in turn linked to poor quality of life, but evidence-based treatments for the management of IBS-type symptoms in patients with IBD in remission are lacking.

Added value of this study

This systematic review and meta-analysis of studies of IBS-type symptom reporting has specifically focused on patients with IBD in remission, demonstrating an overall prevalence of 35%. There was a significantly higher prevalence of IBS-type symptoms in those with inactive Crohn's disease compared with ulcerative colitis. Subgroup analysis demonstrated that, even when objective markers of disease activity, such as endoscopic or histological remission were used, IBS-type symptoms still affected at least one-in-four patients. Those with IBS-type symptoms had significantly higher rates of anxiety, depression, and somatisation. The results of this study provide a better estimate of the magnitude of this issue and should serve as a mandate for the design of randomised controlled trials (RCTs) to find evidence-based treatments for these symptoms.

Implications of all the available evidence

Evidence published over the last 30 years demonstrates that IBS-type symptoms are common, affecting 25% of patients with IBD, despite objective evidence of "deep" remission. This casts doubt on the theory that occult inflammatory disease activity is the primary aetiological factor. Pooling data from studies demonstrated that rates of anxiety and depression were significantly higher among patients with IBD with IBS-type symptoms. There is currently a lack of RCTs of psychological therapies and antidepressants in this specific subgroup of IBD patients, which could be a focus for future studies.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic condition of the gastrointestinal tract that encompasses both ulcerative colitis (UC) and Crohn's disease (CD). Over the last 30 years, the prevalence of IBD has increased, and is now estimated to be between 250 and 440 per 100,000 people in Western populations.[1] The clinical course fluctuates from periods of disease activity, during which time symptoms such as disordered bowel habit, abdominal pain, and bleeding per rectum are common, through to periods of clinical remission.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, which is also characterised by features of abdominal pain and disordered bowel habit. IBS is common, with a global prevalence of approximately 11%.[2] The aetiology of IBS and IBD is uncertain but changes to the intestinal microbiota, low-grade mucosal inflammation, altered intestinal permeability, and immune activation may be common to both.[3] Due to its high prevalence, it is possible that IBS may co-exist in patients with an established diagnosis of IBD. However, IBS is also common after acute inflammatory events, such as diverticulitis or acute gastroenteritis,[4, 5] so it is conceivable that IBD itself is a risk factor for subsequent IBS. Differentiating IBS-type symptoms from ongoing IBD activity can be difficult and may hamper clinical decision-making, if judgements are based on symptoms alone.[6] Escalating drug treatment in patients with limited evidence of inflammatory activity is ineffective and potentially costly.[7-9]

The cause of IBS-type symptoms in IBD is unclear and is likely to be multifactorial. Mood disorders are more prevalent in both patients with IBS and IBD, compared with healthy individuals,[10-12] and observational studies have reported an association between the reporting of IBS-type symptoms and psychological co-morbidity.[13-20] These findings suggest that clinical trials of antidepressants and psychological therapies in this specific subgroup of patients with IBD may be worthwhile.

A prior systematic review and meta-analysis of observational studies estimated the prevalence of IBS-type symptoms in IBD to be almost 40%, and prevalence was higher in patients with CD than UC.[21] However, many of the studies included in this meta-analysis recruited a mixed population of patients, some of whom had active disease. In addition, more studies examining this issue have been published since this meta-analysis was conducted. In an attempt to better quantify the magnitude of reporting of IBS-type symptoms among patients with IBD in remission, and hence highlight this as an area of unmet therapeutic need, we updated this systematic review. We restricted inclusion to only studies using recognised symptom-based criteria for IBS and recruiting only patients with IBD deemed to be in remission. We also aimed to examine the association between IBS-type symptom reporting and psychological co-morbidity.

METHODS

Search strategy and selection criteria

We searched the medical literature using EMBASE, EMBASE Classic, and MEDLINE from January 2012 to May 2020 in order to identify case-control studies or cross-sectional surveys reporting the prevalence of IBS-type symptoms in patients with CD, UC, or IBD-unclassified (IBD-U) who were judged as being in remission. We defined our eligibility criteria *a priori* (Box 1). These required studies to be prospective and to recruit an unselected adult population (≥90% of participants aged ≥16 years) with histologically or radiologically confirmed IBD. Eligible studies had to include at least 50 participants. Definitions of remission considered included a physician's global assessment, according to validated clinical disease activity indices (DAI), according to faecal calprotectin (FC), at endoscopic assessment, or on histological examination of colonic biopsy specimens. The presence of IBS-type symptoms had to be defined using validated diagnostic criteria, including the Kruis scoring system, the Manning criteria, or the Rome I, II, III, or IV criteria.

We combined the following search terms using the set operator OR to identify studies related to IBS: *irritable bowel syndrome* (both as a medical subject heading (MeSH) and a free text term), and *spastic colon*, *functional adj5 bowel*, *Manning*, *Rome 1*, *Rome I*, *Rome 2*, *Rome II*, *Rome 3*, *Rome III*, *Rome 4*, or *Rome IV* (all as free text terms). We combined the following terms to identify articles related to IBD, again using the set operator OR: *ulcerative colitis*, *inflammatory bowel disease*, *Crohn disease*, *ileitis*, or *colitis* (both as MeSH and free text terms), and *Crohn$ disease* or *enteritis* (as free text terms). We then combined these two searches using the set operator AND. There were no language restrictions. All titles and abstracts were reviewed by two investigators independently, and we

retrieved those studies identified as being potentially relevant for further assessment. We performed a recursive search of the reference lists of eligible studies.

Data Extraction

Data extraction was undertaken independently by two investigators onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA). For each eligible study we extracted the following data: country, study design (cross-sectional survey or case-control study), criteria used to define IBS-type symptoms, criteria used to define remission of IBD activity, number of subjects providing complete data, and the number of patients with UC, CD, and IBD-U. The prevalence of symptoms meeting criteria for IBS in all subjects with IBD in remission, as well as in those with UC, CD, or IBD-U was extracted, as well as the prevalence according to each definition of remission used in individual studies.

Data Synthesis and Statistical Analysis

We used the kappa statistic to measure the degree of agreement between the two investigators when judging study eligibility. We combined the proportion of patients with IBD with IBS-type symptoms from all eligible studies, according to the primary definition of remission used in the study, in order to give a pooled prevalence of IBS-type symptoms, in all studies. We also pooled data according to each individual definition of remission used. We assessed for heterogeneity between studies using the I^2 statistic with a cut off of 50%, and the χ^2 test with a *P* value <0·10,[22] used to define a statistically significant degree of heterogeneity. We also compared the proportion of patients with UC, CD, or IBD-U reporting symptoms compatible with IBS, where reported, using an odds ratio (OR) with a 95% confidence intervals (CI).

We pooled data using a random effects model to give a more conservative estimate of the prevalence of symptoms meeting criteria for IBS and the odds of IBS-type symptoms in these various groups. We used StatsDirect version 3.2.10 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled prevalence and pooled ORs with 95% CIs. We planned to assess for evidence of publication bias, by applying Egger's test to funnel plots of ORs,[23] where sufficient studies existed.[24]

In studies that compared mood or somatic symptom scores in patients with IBD with IBS-type symptoms and those without, mean scores and standard deviations (SD) were extracted. These continuous data were pooled using a weighted mean difference (WMD) with 95% CIs, where identical scoring systems were used, and a standardised mean difference (SMD), where different scoring systems were utilised.

Role of the funding source

No funding was received. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

The literature search identified 3370 citations, of which 54 appeared relevant and were retrieved for further review. Of these, 18 new studies fulfilled the eligibility criteria for inclusion.[13, 17-20, 25-37] There was substantial agreement between both reviewers for judging eligibility of the newly identified studies (kappa statistic = 0·77). Detailed characteristics of these 18 studies, together with the nine studies from the original meta-analysis that remained eligible according to our updated eligibility criteria,[14-16, 38-43] are provided in Table 1. Of the 27 studies, eight included only patients with UC,[18, 26, 27, 31, 36-38, 41] one recruited only patients with CD,[16] and four recruited patients with IBD, but did not report the prevalence of IBS-type symptoms separately for patients with UC or CD.[14, 28, 29, 35] The remaining 14 studies included a combination of UC and CD patients, with prevalence of IBS-type symptoms reported separately for each. There were no studies reporting prevalence of IBS-type symptoms in patients with IBD-U.

Several studies reported prevalence of IBS-type symptoms according to more than one definition of remission. Specifically, 15 used a validated clinical DAI,[13, 15-17, 19, 20, 26, 29, 30, 33, 36-39, 42] and eight used a physician's global assessment of remission.[14, 19, 25, 32, 34, 35, 40, 43] Six studies provided data on endoscopic remission,[18, 25-27, 31, 41] four reported biochemical remission, using a faecal calprotectin <100mcg/g,[13, 17, 28, 30] and two histological remission.[25, 27] In terms of criteria used to define the presence of IBS-type symptoms, 16 studies used the Rome III criteria,[13, 14, 16-20, 25-29, 32, 34-36] eight the Rome II criteria,[15, 30, 31, 38-40, 42, 43] two the Rome IV criteria,[33, 37] and one the Manning criteria.[41] Four studies compared mean anxiety scores between patients with and without IBS-type symptoms using the Hospital Anxiety and Depression Scale (HADS).[13, 16, 17, 19] Three studies also used the HADS to compare mean depression scores between these two groups,[13, 17, 19] and one used the Beck Depression Inventory.[16] Mean somatic symptom scores were compared between

patients with and without IBS-type symptoms in two studies,[17, 18] using the Patient Health Questionnaire-12 (PHQ-12).

Prevalence of IBS-type symptoms in those with IBD in remission.

The 27 studies identified included 3169 patients with IBD in remission, according to the various criteria used. When all studies were pooled, according to the primary definition of remission used in each study, the pooled prevalence of IBS-type symptoms among patients with IBD in remission was 32·5% (95% CI 27·4% to 37·9%), ranging from 11·2% to 63·6% in individual studies. Subgroup analyses demonstrated higher levels of heterogeneity when subjective measures, such as a PGA or a DAI, were used to define remission, compared with more objective measures, such as biochemical or endoscopic confirmation of remission (Table 2). Prevalence of IBS-type symptoms was highest when a faecal calprotectin <100mcg/g was used to define remission (35·1%), although prevalence according to both PGA and a validated DAI were similar (34·1% and 33·6% respectively). Prevalence was lowest when either endoscopic or histological assessment was used to define remission (23·5% and 25·8% respectively).

Prevalence of IBS-type symptoms in those with IBD in remission based on IBS criteria.

The pooled prevalence of IBS-type symptoms when the Rome III criteria were used, in 16 studies, was 33·5% (95% CI 27·6% to 39·6%) with significant heterogeneity (Table 2). In the eight studies using the Rome II criteria the pooled prevalence of IBS-type symptoms was 31·5% (95% CI 19·2% to 45·4%), again with significant heterogeneity between studies. In the two studies that used the Rome IV criteria, the pooled prevalence was 29·6% (95% CI 19·4% to 40·9%).

Prevalence of IBS-type symptoms in those with CD in remission compared with UC in remission.

Data on IBS-type symptoms in patients with CD in remission were available in 15 studies, with a pooled prevalence of 36·6% (95% CI 29·5% to 44·0%), again with significant heterogeneity between studies (Table 2). There were 22 studies reporting prevalence of IBS-type symptoms in patients with UC in remission, with a pooled prevalence of 28·7% (95% CI 22·9% to 34·8%), again with significant heterogeneity. Of the included studies, 14 reported the prevalence of IBS-type symptoms in 1864 patients with either CD or UC separately. IBS-type symptoms were more common in those with CD (366 of 1050 patients (34·9%)), compared with UC patients (483 of 1660 patients (29·1%)). The OR for IBS-type symptoms was significantly higher among patients with CD (1·58; 95% CI 1·27 to 1·98) (Figure 2), with no heterogeneity between studies. There was no evidence of funnel plot asymmetry to suggest publication bias or other small study effects (Egger test P = 0·32).

Mood scores according to presence or absence of IBS-type symptoms in those with IBD in remission.

Data concerning anxiety and depression scores among those with and without IBS-type symptoms were provided by four studies.[13, 16, 17, 19] Anxiety scores were significantly higher among patients who reported IBS-type symptoms (WMD = 2·5; 95% CI 0·8 to 4·3 (P = 0·004)), with significant heterogeneity between studies (I^2 = 76%). Depression scores were also significantly higher in patients with IBD with IBS-type symptoms (SMD = 0·64; 95% CI 0·44 to 0·84 (P <0·0001)) with no heterogeneity between studies (I^2 = 0%). Finally, two studies provided PHQ-12 scores.[17, 18] Somatic symptoms scores were significantly higher in patients who reported IBS-type symptoms (WMD = 2·7; 95% CI 1·8 to 3·7 (P <0·0001))

DISCUSSION

This updated systematic review and meta-analysis has assembled evidence spanning more than 30 years, to examine prevalence of IBS-type symptoms in patients with IBD. It has demonstrated that as many as one-in-three patients with IBD report symptoms compatible with IBS. This is despite deliberately restricting eligibility to only studies that recruited patients considered to be in remission, to minimise the potential confounding effect of occult inflammatory disease activity as a driver of symptom-reporting in these patients. Although the pooled prevalence was lower when more objective definitions of remission, including endoscopic or histological remission, were used, the prevalence of IBS-type symptom reporting was still as high as 25%. The criteria used to define the presence of IBS-type symptoms did not appear to affect their prevalence. When we pooled data from 14 studies, there was a significantly higher proportion of patients with CD meeting criteria for IBS, compared with patients with UC. Mirroring studies in non-IBD populations, anxiety and depression scores were significantly higher in those reporting IBS-type symptoms. These patients were also more likely to have high somatisation scores, which may explain the excess healthcare use observed previously in these patients.[44]

We used an extensive search strategy, along with strict inclusion criteria to ensure that we extracted prevalence of IBS-type symptom data only in patients with IBD deemed to be in remission, according to various definitions. This meta-analysis included a further 18 studies published since 2012 with a total of 3169 patients with IBD. Agreement between reviewers for judging eligibility of the newly identified studies was substantial. We contacted authors of two studies to ensure there was no duplication of data, and a further research group for additional information. For the analysis, a random effects model was used to pool data, to ensure we did not overestimate the prevalence of IBS-type symptoms. We also only included studies that used validated criteria for IBS, rather than approximating the presence of IBS-

type symptoms using non-validated measures, such as an adapted gastrointestinal symptom rating scale, which was used in some previously included studies.[21] The prevalence of IBS-type symptom reporting, according to the various definitions of remission used in each study was extracted and pooled separately. Finally, we assessed for evidence of publication bias.

The study was limited by significant heterogeneity in several of our analyses. Of note, this was most apparent when subjective measures of remission, such as a patient-reported DAI or PGA were applied, compared with more objective markers, such as faecal calprotectin and endoscopic healing. We also noted differences in methods of data collection, from invasive investigations and face-to-face consultations to self-administered postal questionnaires, which may further account for variability between study results. Population groups across a wide geographical region may account for some of the heterogeneity we observed, although this also suggests our results are likely to be generalisable to the global IBD population. Some analyses were limited by a small number of studies, with few using objective measures of remission, presumably due to the difficulties of incorporating endoscopic procedures into the study design, or the acceptability of faecal sampling for research purposes.[45] Finally, the criteria for the definition of IBS-type symptoms varied, with only two recently published studies using the Rome IV criteria.[33, 37] Although the Rome and Manning criteria are validated for the diagnosis of IBS, we acknowledge that they have not been validated in an IBD specific population.

This meta-analysis highlights that, even when endoscopic or histological measures are used to define disease remission, one-in-four patients reports IBS-type symptoms. There is, therefore, a cohort of patients with IBD who report a symptom complex that is inadequately addressed by conventional IBD treatments, highlighting an unmet need in management. This is a neglected area of study. Although definitions of endoscopic remission were not identical in all studies, and only two studies reported histological remission, the high prevalence of

IBS-type symptom-reporting in patients with objectively confirmed quiescent disease that we report casts doubt on the prior supposition that occult inflammatory activity is the primary aetiological factor responsible for these symptoms.[15, 46] This is further supported by data from an observational study describing the impact of IBS-type symptom-reporting on longitudinal disease activity outcomes in IBD.[44] In this study, the presence of IBS-type symptoms at baseline was not associated with any significant increase in the future incidence of disease flare or glucocorticosteroid use, escalation of medical therapy, hospitalisation, or surgery, which would be expected if these symptoms were indicative of active disease. These findings, combined with the understanding that conventional IBD therapy targeting active bowel inflammation using biologic drugs is ineffective in symptomatic patients with a limited inflammatory burden,[7-9] reinforce the need for alternative management strategies for these patients.

We also demonstrate that the prevalence of IBS-type symptoms is significantly higher in those with CD. The distribution of disease location in those with CD may, in part, explain the variable symptom profile. Assessing for the presence of small bowel inflammatory activity using gold-standard investigations, such as magnetic resonance enterography or wireless capsule endoscopy, was not performed in any of the studies. This may have resulted in a misclassification bias in studies where the proportion of CD patients with small bowel disease was high,[28] with symptoms being secondary to occult small bowel inflammation, and therefore incorrectly labelled as IBS. This may explain the high prevalence of IBS-type symptoms observed when prevalence data from studies using FC to define disease remission were pooled, particularly as the utility of FC as a measure of small bowel inflammation in CD is uncertain.[47, 48] In addition, small bowel disease increases the risk of bacterial overgrowth, and terminal ileal CD may be associated with bile acid diarrhoea, particularly in those who have undergone prior ileal resection.[49-51] Delays in diagnosis of small bowel CD

may also lead to a prolonged inflammatory insult, potentially increasing the risk of fibrosis, stricturing, and mechanical dysfunction of the gastrointestinal tract.[16, 39] These associated conditions can mimic IBS-type symptoms and could explain the increased prevalence observed in CD. Where studies reported phenotypic characteristics in CD, the numbers were small and underpowered, with no significant difference in IBS-type symptoms between groups defined by either disease location or behaviour.[17] In addition, due to how data were reported in the eligible studies, as well as the fact that five of the six studies examining prevalence of IBS-type symptoms in patients with endoscopic remission only recruited patients with UC, we were unable to assess whether the various definitions of remission affected prevalence in patients with CD versus UC. The potential confounding effect of these factors on our results, therefore, remains uncertain.

There was an association between the reporting of IBS-type symptoms and psychological co-morbidity, including higher depression, anxiety, and somatisation scores in patients with IBD reporting IBS-type symptoms, when compared with those who did not. The relationship between IBS-type symptom reporting and psychological co-morbidity is well-established in the general population. Indeed, disordered gut-brain axis activity may contribute to the development of IBS in a subset of patients.[52] To our knowledge, we provide the first pooled assessment of the association between psychological co-morbidity and the reporting of IBS-type symptoms in patients with IBD, demonstrating a clear relationship between the presence of these symptoms and anxiety, depression, and somatisation. Mood disorders and somatic symptoms in IBD are linked to increased healthcare use and an increased number of gastrointestinal investigations.[44] Furthermore, somatoform behaviour is likely to extend beyond gastrointestinal services and impact the need for multi-specialty review.

Evidence-based interventions for the management of IBS in the general population include neuromodulators,[53] psychological therapies,[54] and treatments targeting the gastrointestinal microbiome such as antibiotics,[55] probiotics,[56] faecal microbial transfer (FMT),[57] or a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP).[58] However, randomised controlled trials (RCTs) assessing the impact of these interventions in patients with IBD reporting IBS-type symptoms are lacking. Psychological therapies are associated with a short-term improvement in depression scores and quality of life in patients with IBD,[59] but efficacy in patients reporting IBS-type symptoms is unknown. Antidepressants appear to have a positive impact on the natural history of IBD,[60] but only one study has been conducted in patients with IBD reporting persistent symptoms in the absence of inflammation, which was limited by its retrospective design.[61] Here, the use of tricyclic antidepressants was associated with a reduction in symptom burden in these patients. The intestinal microbiome is an attractive target for therapeutic intervention in IBD, and RCTs of antibiotics,[62] probiotics,[63] FMT,[64] and the low FODMAP diet,[65-67] have been conducted but, with the exception of the low FODMAP diet, these have largely focused on disease activity outcomes rather than IBS-type symptom reporting specifically. In one of these RCTs,[66] a significantly higher proportion of patients reporting IBS-type symptoms who were randomised to receive a low FODMAP diet achieved adequate relief of IBS-type symptoms than was observed in patients randomised to a control diet, with a number needed to treat of 3.

In conclusion, the prevalence of IBS-type symptom reporting in patients with IBD in remission in this meta-analysis was as high as 35%. Even when more objective measures of remission were used, one-in-four patients reported these symptoms. IBS-type symptoms were more common in CD, and were associated with psychological co-morbidity including anxiety, depression, and somatisation. These data suggest that occult inflammatory disease

activity does not drive IBS-type symptom reporting in these patients. Alternative treatments, particularly those targeting co-existent mood disorders, may be of benefit, but clinical trials of these interventions in this specific subgroup of patients with IBD are lacking.

AUTHOR CONTRIBUTIONS:

KMF, SJC, and ACF collected all data. KMF, DJG, and ACF analysed and interpreted the data. KMF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS:

The authors declared no conflicts of interest.

ETHICS COMMITTEE APPROVAL:

Not required.

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Box 1: Inclusion Criteria

- Prospective cross-sectional or case-control studies.
- Unselected adult patients (>90% aged over 16 years) with confirmed Crohn's disease, ulcerative colitis, or IBD-unclassified.
- Sample size ≥50 patients.
- Reported definition of remission using physician's global assessment, disease activity indices, faecal calprotectin, endoscopic, or histological assessment.
- Reported prevalence of IBS-type symptoms using a validated IBS scoring system including Rome I, Rome II, Rome III, Rome IV, Manning criteria, or Kruis scoring system.

TABLES

Table 1. Characteristics of Included Studies.

Study	Country	Study Type	Criteria used to define IBS-type symptoms	Number of subjects with quiescent IBD (UC, CD)	Criteria used to define remission of IBD	Number with IBS-type symptoms (%)
Isgar, 1983**(41)**	UK	Case-control	Manning	98 (98,0)	In endoscopic remission and only using maintenance sulfasalazine	33 (33·7)
Zaman 2002**(43)**	USA	Cross-sectional	Rome II	55 (25,30)	Stable symptoms and no changes in medications for 3 months	35 (63·6)
Minderhoud 2004**(42)**	Holland	Case control	Rome II	107 (73,34)	UC: CAI UC score <10 for 2 consecutive days CD: CDAI <150	37 (34·6)
Farrokhyar 2006**(40)**	Canada	Cross-sectional	Rome II	149 (44,105)	No change in medications for >1 year	31 (20·8)
Ansari 2008**(38)**	Iran	Case control	Rome II	50 (50,0)	Mayo score ≤2, with bleeding score 0 and endoscopy score 0-1	23 (46)
Keohane 2010**(15)**	Eire	Cross-sectional	Rome II	106 (44,62)	UC: PGA, C-reactive protein <10mg/l, no use of glucocorticosteroids or biological agents in >6 months, UCAI ≤3 CD: As above but with CDAI ≤150	54 (50·9)
Piche 2010**(16)**	France	Cross-sectional	Rome III	92 (0,92)	CDAI ≤150 for >6 months, normal inflammatory markers and endoscopic remission with CDEIS <6 in last 12 months	42 (45·7)
Barratt 2011**(39)**	UK	Case control	Rome II	276 (166,110)	UC: SCCAI <5 CD: HBI <5	31 (11·2)
Bryant 2011**(14)**	Australia	Cross-sectional	Rome III	93 (data not reported separately)	PGA using inflammatory markers, clinical data with endoscopic activity and histological data if available	12 (12·9)
James 2012**(29)**	Australia	Cross-sectional	Rome III	78 (data not reported separately)	UC: SCCAI <4 CD: HBI <3	34 (43·6)
Jelness-Jorgensen 2012**(30)**	Norway	Cross-sectional	Rome II	89 (61,28)	UC: SCCAI <3 CD: SCDAI <4, with no use of glucocorticosteroids in either group	21 (23·6)
Hui 2013**(36)**	China	Cross-sectional	Rome III	185 (185,0)	PGA, C-reactive protein <10mg/l, UCAI <3	107 (57·8)
Berrill 2013**(13)**	UK	Cross-sectional	Rome III	97 (57,40)	UC: SCCAI <3, C-reactive protein <10mg/l CD: As above but with HBI <5 A secondary marker of FC <90µg/g was used to define biochemical remission	31 (32·0)

Kim 2013**(32)**	Korea	Cross-sectional	Rome III	226 (119,107)	No change in medication for >12 months and normal inflammatory markers UC: As above, plus no blood or mucous in stool	82 (36·3)
Jonefjall 2013**(31)**	Sweden	Cross-sectional	Rome II	56 (56,0)	Mayo score ≤2 (includes PGA) and endoscopic sub-score 0, with no relapse at 3 months	7 (12·5)
Fukuba 2014**(26)**	Japan	Case-control	Rome III	172 (172,0)	CAI ≤ 4 for 6 months Matts endoscopic grade ≤ 2	46 (26·7)
Pojoga 2015**(34)**	Romania	Case-control	Rome III	67 (56,11)	Clinical assessment of remission, no details reported	30 (44·8)
Boztepe 2015**(25)**	Turkey	Cross-sectional	Rome III	81 (43,38)	Clinical remission for 6 months and all underwent colonoscopy and biopsy	20 (24·7)
Jonefjall 2016**(18)**	Sweden	Cross-sectional	Rome III	132 (132,0)	Mayo score ≤2 (includes PGA) and endoscopic sub-score ≤1	24 (18·2)
Sanges 2016**(35)**	Italy	Cross-sectional	Rome III	70 (40,30)	Clinical assessment and stable on treatment for 6 months	29 (41·4)
Tomita 2016**(20)**	Japan	Case-control	Rome III	147 (40,107)	UC: UCAI ≤4, C-reactive protein <0.3mg/dL CD: CDAI ≤150, C-reactive protein <0.3mg/dL	36 (24·5)
Gracie 2017**(17)**	UK	Cross-sectional	Rome III	231 (103,128)	UC: SCCAI <5, FC <100µg/g CD: HBI <5, FC <100µg/g	63 (27·3)
Hoekman 2017**(28)**	Netherlands	Cross-sectional	Rome III	53 (data not reported separately)	FC <100µg/g	24 (45·3)
Henriksen 2018**(27)**	Norway	Cross-sectional	Rome III	209 (209, 0)	Mayo endoscopic score <2 for endoscopic and histological remission, or FC <100µg/g	53 (25·4)
Nigam 2019**(37)**	UK	Cross-sectional	Rome IV	61 (61,0)	UC: IBD-control-8 score ≥ 13 and IBD-control-VAS ≥ 85 and / or FC ≤250µg/g	14 (23·0)
Perera 2019**(19)**	USA	Cross-sectional	Rome III	96 (19,77)	C-reactive protein <0.5mg/dL and erythrocyte sedimentation rate <30mm/hr, colonoscopy and histology showing quiescent disease and no active disease on recent imaging.	35 (36·5)
Ozer 2020**(33)**	Turkey	Case-control	Rome IV	137 (56,81)	UC: Modified Mayo Score with a disease activity index ≤ 2 CD: HBI ≤ 4	47 (34·3)

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; FC, faecal calprotectin; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NA, not applicable; PGA, physicians global assessment; SCCAI, simple clinical colitis activity index; UC, ulcerative colitis; UCAI, UC activity index.

Table 2: Subgroup Analyses of Prevalence of IBS-type Symptoms in IBD Based on Criteria Used to Define Remission, Criteria Used to Define Presence of IBS-type Symptoms, and Type of IBD.

		Number of studies	Total number of subjects	Number meeting criteria for IBS-type symptoms	Pooled prevalence of IBS-type symptoms	95% confidence interval	I^2	P value for χ^2
Criteria used to define remission	All IBD patients according to primary definition of remission used in the study	27	3169	992	32·5%	27.4% – 37.9%	90.1%	<0.0001
	Validated disease activity index	15	1924	621	33·6%	26·3% – 41·2%	91·8%	<0·0001
	Physician's global assessment	8	837	274	34·1%	24·6% – 44·3%	89%	<0·0001
	Endoscopic healing	6	704	174	23·5%	17·9% – 29·6%	59·9%	0·03
	Faecal calprotectin <100 mcg/g	4	470	139	35·1%	28·1% – 42·6%	38·7%	0·18
	Histological remission	2	246	64	25·8%	20·2% – 31·7%	NA	NA
Criteria used to define presence of IBS-type symptoms	Rome III	16	1985	659	33·5%	27·6% – 39·6%	87·7%	<0·0001
	Rome II	8	888	239	31·5%	19·2% – 45·4%	94·3%	<0·0001
	Rome IV	2	198	61	29·6%	19·4% – 40·9%	NA	NA
	Manning	1	98	33	33·7%	24·4% – 43·9%	NA	NA
Type of IBD	UC	22	1825	527	28·7%	22·9% – 34.8%	87·2%	<0·0001
	CD	15	1050	366	36·6%	29·5% – 44·0%	82·9%	<0·0001

IBD, inflammatory bowel disease; IBS, irritable bowel syndrome

NA: not applicable; too few studies.

FIGURES

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.

Figure 2. Odds ratio for IBS-type Symptoms in Patients with Crohn's Disease in Remission Versus Ulcerative Colitis in Remission.