

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

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## Summary

**Background** Patients with inflammatory bowel disease (IBD) often report symptoms compatible with irritable bowel syndrome (IBS), which might have an effect 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 to better quantify the magnitude of this issue.

**Methods** In this systematic review and meta-analysis, Embase, Embase Classic, and MEDLINE were searched (from Jan 1, 2012, to May 11, 2020) to identify prospective case-control or cross-sectional studies reporting prevalence of symptoms meeting diagnostic criteria for IBS in adults with IBD in remission. Studies were required to have recruited an unselected adult population (more than 90% of participants aged  $\geq 16$  years) with histologically or radiologically confirmed IBD and include at least 50 participants. Pooled prevalence and odds ratios (ORs) with 95% CIs were calculated according to the definition of remission, criteria used to define IBS-type symptoms, and type of IBD. The association between IBS-type symptom reporting and psychological comorbidity was examined using weighted mean difference (WMD) or standardised mean difference (SMD) in anxiety and depression scores between those reporting IBS-type symptoms and those not, for cases in which these data were available.

**Findings** Of 3370 studies identified, 27 were eligible, of which 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;  $P=90.1\%$ ). Prevalence was lower when remission was defined by endoscopic assessment (23.5%, 95% CI 17.9–29.6;  $P=59.9\%$ ) or histological assessment (25.8%, 95% CI 20.2–31.7;  $P=\text{not applicable}$ ) than when defined by validated clinical disease activity index (33.6%, 26.3–41.2;  $P=91.8\%$ ) and higher in Crohn's disease than in ulcerative colitis (36.6%, 29.5–44.0;  $P=82.9\%$  vs 28.7%, 22.9–34.8;  $P=87.2\%$ ). Anxiety (WMD 2.5; 95% CI 0.8–4.3) and depression (SMD 0.64; 0.44–0.84) scores were significantly higher among those who reported IBS-type symptoms than in those who did not.

**Interpretation** Prevalence of symptoms compatible with IBS in patients with IBD varied according to how remission was defined. However, even when stringent criteria such as endoscopic or histological remission were used, about a quarter of patients reported these symptoms. Such symptoms were more common in patients with Crohn's disease and were associated with psychological comorbidity. Addressing psychological wellbeing might improve outcomes in this specific group of patients.

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## Introduction

Inflammatory bowel disease (IBD) is a chronic condition of the gastrointestinal tract that encompasses both ulcerative colitis and Crohn's disease. Over the past 30 years, the prevalence of IBD has increased and is now estimated to be between 250 and 440 cases per 100 000 people in high-income countries.<sup>1</sup> 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 9% with the Rome III criteria.<sup>2</sup> The cause of IBS and IBD is uncertain but changes to the intestinal microbiota, low-grade mucosal inflammation, altered intestinal permeability, and immune activation could be common to both conditions.<sup>3</sup> Because of its high prevalence, IBS might coexist in patients with an established diagnosis of IBD. However, IBS is also common after acute inflammatory events, such as diverticulitis or acute gastroenteritis,<sup>4,5</sup> suggesting that IBD is a risk factor for subsequent development of IBS. Differentiating IBS-type symptoms from ongoing IBD activity can be difficult

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See [Comment](#) page 1029

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### Research in context

#### 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, because of 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 whether inflammatory disease activity is the main driver remains unclear. Observational studies have also reported an association between IBS-type symptoms and increased psychological comorbidity, 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. Embase, Embase Classic, and MEDLINE were searched for medical literature with no language restriction from Jan 1, 2012, to May 11, 2020, to identify prospective case-control studies or cross-sectional surveys reporting the prevalence of IBS-type symptoms in patients with Crohn's disease, ulcerative colitis, or IBD-unclassified who were in remission. Inclusion criteria were cross-sectional or case control studies that recruited an unselected adult population (more than 90% of participants aged  $\geq 16$  years) with histologically or radiologically confirmed IBD. Eligible studies had to include at least 50 participants.

#### 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, showing an overall prevalence of 32.5%. A significantly higher prevalence of IBS-type symptoms was observed in patients 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 about a quarter of 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 to find evidence-based treatments for these symptoms.

#### Implications of all the available evidence

Evidence published over the past 30 years shows that IBS-type symptoms are common, affecting 25% of patients with IBD, despite objective evidence of so-called deep remission. This casts doubt on the theory that occult inflammatory disease activity is the primary cause of these symptoms. Pooling data from studies demonstrated that rates of anxiety and depression were significantly higher among patients with IBD who reported IBS-type symptoms. Randomised trials of psychological therapies and antidepressants in this specific subgroup of IBD patients are scarce, which could be a focus for future studies.

and could hamper clinical decision making if judgements are based on symptoms alone.<sup>6</sup> Escalating drug treatment in patients with no evidence of inflammatory activity is ineffective and potentially costly.<sup>7-9</sup>

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

A previous 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 Crohn's disease than in those with ulcerative colitis.<sup>21</sup> However, many of the studies included in that meta-analysis recruited a mixed population of patients, some of whom had active disease. Additionally, more studies examining this issue have been published since that meta-analysis was done. To better quantify the magnitude of reporting of IBS-type symptoms among patients with IBD in remission, and hence emphasise this as an area of unmet therapeutic need, we updated the previous systematic

review. We restricted inclusion to studies that used recognised symptom-based criteria for IBS and to studies that recruited only patients with IBD who were deemed to be in remission. We also aimed to examine the association between IBS-type symptom reporting and psychological comorbidity.

### Methods

#### Search strategy and selection criteria

For this systematic review and meta-analysis, we searched Embase, Embase Classic, and MEDLINE for medical literature from Jan 1, 2012, to May 11, 2020, to identify case-control studies or cross-sectional surveys reporting the prevalence of IBS-type symptoms in patients with Crohn's disease, ulcerative colitis, or IBD-unclassified who were classified as being in remission. We defined our eligibility criteria a priori. These criteria required studies to be prospective cross-sectional or case-control studies that recruited an unselected adult population (more than 90% of participants aged  $\geq 16$  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, validated clinical disease activity indices, faecal calprotectin concentrations, endoscopic assessment, or histological examination of colonic biopsy specimens. The presence of

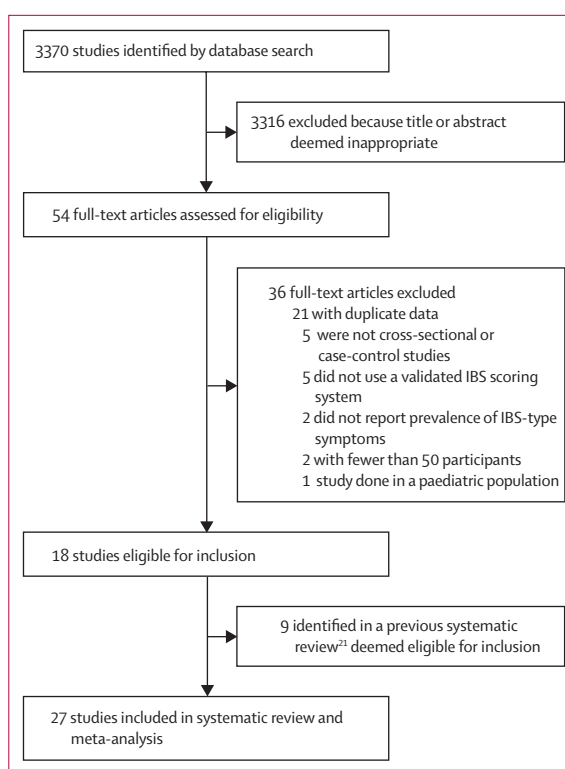
IBS-type symptoms had to be defined using validated diagnostic criteria, including the Kruis scoring system, the Manning criteria, or the Rome I, II, III, or IV criteria.

We combined the following search terms for all databases using the set operator OR to identify studies related to IBS: “irritable bowel syndrome” (both as a medical subject heading 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 medical subject headings and free text terms), and “Crohn\$ disease or “enteritis” (as free text terms). We then combined these two searches using the set operator AND. No language restrictions were applied. All titles and abstracts were reviewed by two investigators independently (KMF and SJC), and we retrieved those studies identified as being potentially relevant for further assessment. We contacted original authors of studies to clarify any queries we had, and we performed a recursive search of the reference lists of eligible studies.

### Data analysis

Data extraction was undertaken independently by two investigators (KMF and SJC), onto a Microsoft Excel spreadsheet (XP professional edition). Studies in abstract form were deemed eligible if sufficient data was extractable. 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 patients providing complete data, and the number of patients with ulcerative colitis, Crohn’s disease, and IBD-unclassified. The prevalence of symptoms meeting criteria for IBS in all patients with IBD in remission, as well as in those with ulcerative colitis, Crohn’s disease, and IBD-unclassified was extracted, as well as the prevalence according to each definition of remission used in individual studies. Any duplicate studies were excluded.

We used the  $\kappa$  statistic to measure the degree of agreement between the two investigators when judging study eligibility, with a cutoff of greater than 0.6 defined as substantial agreement. For cases in which questions with regards to inclusion arose, the papers were reviewed by a third investigator (ACF). 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 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 cutoff of more than 50%, and the  $\chi^2$  test with a p value of less than 0.10<sup>22</sup>



**Figure 1: Study selection**  
IBS=irritable bowel syndrome.

to define a significant degree of heterogeneity. We also compared the proportion of patients with ulcerative colitis, Crohn’s disease, or IBD-unclassified who noted symptoms compatible with IBS, for studies in which this was reported, using an odds ratio (OR) with a 95% 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 planned to assess for evidence of publication bias by applying Egger’s test (for which  $p < 0.05$  is significant to suggest publication bias) to funnel plots of ORs<sup>23</sup> for ten studies or more.<sup>24</sup>

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

Forest plots of pooled prevalence and pooled ORs with 95% CIs were generated with StatsDirect (version 3.2.10).

### Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the

	Country	Study type	Criteria used to define IBS-type symptoms	Number of patients with quiescent IBD	Criteria used to define remission of IBD	Number of patients with IBS-type symptoms
Isgar et al, 1983 <sup>41</sup>	UK	Case-control	Manning	Total, 98; all ulcerative colitis	In endoscopic remission and only using maintenance sulfasalazine	33/98 (34%)
Zaman et al, 2002 <sup>43</sup>	USA	Cross-sectional	Rome II	Total, 55; ulcerative colitis, 25; Crohn's disease, 30	Stable symptoms and no changes in medications for 3 months	35/55 (64%)
Minderhoud et al, 2004 <sup>42</sup>	Netherlands	Case-control	Rome II	Total, 107; ulcerative colitis, 73; Crohn's disease, 34	Ulcerative colitis: ulcerative colitis activity index score <10 for 2 consecutive days; Crohn's disease: Crohn's disease activity index <150	37/107 (35%)
Farrokhyar et al, 2006 <sup>40</sup>	Canada	Cross-sectional	Rome II	Total, 149; ulcerative colitis, 44; Crohn's disease, 105	No change in medications for >1 year	31/149 (21%)
Ansari et al, 2008 <sup>38</sup>	Iran	Case-control	Rome II	Total, 50; all ulcerative colitis	Mayo score ≤2, with bleeding score 0 and endoscopy score 0–1	23/50 (46%)
Keohane et al, 2010 <sup>15</sup>	Eire	Cross-sectional	Rome II	Total, 106; ulcerative colitis, 44; Crohn's disease, 62	Ulcerative colitis: physician's global assessment, C-reactive protein <10 mg/L, no use of glucocorticosteroids or biological agents in >6 months, ulcerative colitis activity index score ≤3; Crohn's disease: physician's global assessment, C-reactive protein <10 mg/L, no use of glucocorticosteroids or biological agents in >6 months, Crohn's disease activity index ≤150	54/106 (51%)
Piche et al, 2010 <sup>16</sup>	France	Cross-sectional	Rome III	Total, 92; all Crohn's disease	Crohn's disease activity index ≤150 for >6 months, normal inflammatory markers, and endoscopic remission with Crohn's disease endoscopic index of severity <6 in past 12 months	42/92 (46%)
Barratt et al, 2011 <sup>39</sup>	UK	Case-control	Rome II	Total, 276; ulcerative colitis, 166; Crohn's disease, 110	Ulcerative colitis: simple clinical colitis activity index <5; Crohn's disease: Harvey Bradshaw Index <5	31/276 (11%)
Bryant et al, 2011 <sup>14</sup>	Australia	Cross-sectional	Rome III	Total, 93 (data not reported separately)	Physician's global assessment using inflammatory markers, clinical data with endoscopic activity, and histological data (if available)	12/93 (13%)
James et al, 2012 <sup>29</sup>	Australia	Cross-sectional	Rome III	Total, 78 (data not reported separately)	Ulcerative colitis: simple clinical colitis activity index <4; Crohn's disease: Harvey Bradshaw Index <3	34/78 (44%)
Jelsness-Jørgensen et al, 2012 <sup>30</sup>	Norway	Cross-sectional	Rome II	Total, 89; ulcerative colitis 61; Crohn's disease, 28	Ulcerative colitis: simple clinical colitis activity index <3; Crohn's disease: simple Crohn's disease activity index <4, with no use of glucocorticosteroids in either group	21/89 (24%)
Hui et al, 2013 <sup>36</sup>	China	Cross-sectional	Rome III	Total, 185; all ulcerative colitis	Physician's global assessment, C-reactive protein <10 mg/L, ulcerative colitis activity index <3	107/185 (58%)
Berrill et al, 2013 <sup>13</sup>	UK	Cross-sectional	Rome III	Total, 97; ulcerative colitis, 57; Crohn's disease, 40	Ulcerative colitis: simple clinical colitis activity index <3, C-reactive protein <10 mg/L, a secondary marker of faecal calprotectin <90 µg/g was used to define biochemical remission; Crohn's disease: Harvey Bradshaw Index <5, C-reactive protein <10 mg/L, a secondary marker of faecal calprotectin <90 µg/g was used to define biochemical remission	31/97 (32%)
Kim et al, 2013 <sup>32</sup>	Korea	Cross-sectional	Rome III	Total, 226; ulcerative colitis 119; Crohn's disease, 107	Ulcerative colitis: no change in medication for >12 months, normal inflammatory markers, no blood or mucus in stool; Crohn's disease: no change in medication for >12 months and normal inflammatory markers	82/226 (36%)
Jonefjäll et al, 2013 <sup>31</sup>	Sweden	Cross-sectional	Rome II	Total, 56; all ulcerative colitis	Mayo score ≤2 (includes physician's global assessment) and endoscopic subscore 0, with no relapse at 3 months	7/56 (13%)
Fukuba et al, 2014 <sup>26</sup>	Japan	Case-control	Rome III	Total, 172; all ulcerative colitis	Clinical activity index ≤4 for 6 months, Matts endoscopic grade ≤2	46/172 (27%)
Pojoga and Dumitrascu, 2015 <sup>34</sup>	Romania	Case-control	Rome III	Total, 67; ulcerative colitis, 56; Crohn's disease, 11	Clinical assessment of remission, no details reported	30/67 (45%)
Boztepe et al, 2015 <sup>25</sup>	Turkey	Cross-sectional	Rome III	Total, 81; ulcerative colitis 43; Crohn's disease, 38	Clinical remission for 6 months and all underwent colonoscopy and biopsy	20/81 (25%)
Jonefjäll et al, 2016 <sup>33</sup>	Sweden	Cross-sectional	Rome III	Total, 132; all ulcerative colitis	Mayo score ≤2 (includes Physician's global assessment) and endoscopic subscore ≤1	24/132 (18%)
Sanges et al, 2016 <sup>25</sup>	Italy	Cross-sectional	Rome III	Total, 70; ulcerative colitis, 40; Crohn's disease, 30	Clinical assessment and stable on treatment for 6 months	29/70 (41%)
Tomita et al, 2016 <sup>20</sup>	Japan	Case-control	Rome III	Total, 147; ulcerative colitis, 40; Crohn's disease, 107	Ulcerative colitis: ulcerative colitis activity index score ≤4, C-reactive protein <0.3 mg/dL; Crohn's disease: Crohn's disease activity index ≤150, C-reactive protein <0.3 mg/dL	36/147 (24%)

(Table 1 continues on next page)

	Country	Study type	Criteria used to define IBS-type symptoms	Number of patients with quiescent IBD	Criteria used to define remission of IBD	Number of patients with IBS-type symptoms
(Continued from previous page)						
Gracie et al, 2017 <sup>27</sup>	UK	Cross-sectional	Rome III	Total, 231; ulcerative colitis, 103; Crohn's disease, 128	Ulcerative colitis: simple clinical colitis activity index, faecal calprotectin <100 µg/g; Crohn's disease: Harvey Bradshaw Index <5, faecal calprotectin <100 µg/g	63/231 (27%)
Hoekman et al, 2017 <sup>28</sup>	Netherlands	Cross-sectional	Rome III	Total, 53 (data not reported separately)	Faecal calprotectin <100 µg/g	24/53 (45%)
Henriksen et al, 2018 <sup>27</sup>	Norway	Cross-sectional	Rome III	Total, 209; all ulcerative colitis	Mayo endoscopic score <2 for endoscopic and histological remission, or faecal calprotectin <100 µg/g	53/209 (25%)
Nigam et al, 2019 <sup>37</sup>	UK	Cross-sectional	Rome IV	Total, 61; all ulcerative colitis	IBD-control-8 score ≥13 and IBD-control-VAS ≥85, or faecal calprotectin ≤250 µg/g, or both	14/61 (23%)
Perera et al, 2019 <sup>19</sup>	USA	Cross-sectional	Rome III	Total, 96; ulcerative colitis, 19; Crohn's disease, 77	C-reactive protein <0.5 mg/dL and erythrocyte sedimentation rate <30 mm/h, colonoscopy and histology showing quiescent disease and no active disease on recent imaging	35/96 (36%)
Ozer et al, 2020 <sup>33</sup>	Turkey	Case-control	Rome IV	Total, 137; ulcerative colitis, 56; Crohn's disease, 81	Ulcerative colitis: modified Mayo score with a disease activity index ≤2; Crohn's disease: Harvey Bradshaw Index ≤4	47/137 (34%)
IBS=irritable bowel syndrome. IBD=inflammatory bowel disease.						
<b>Table 1: Studies included in the meta-analysis</b>						

study and had final responsibility for the decision to submit for publication.

## Results

The literature search identified 3370 citations, of which 3316 were excluded because the titles and abstracts were not relevant. 54 studies seemed relevant and were retrieved for further review. 36 studies were then excluded for a variety of reasons, including duplicate data, not being cross-sectional or case-control studies, or not having used a validated IBS scoring system. 18 studies in total fulfilled the eligibility criteria for inclusion,<sup>13,17–20,25–37</sup> in addition to nine studies identified in a previous systematic review<sup>21</sup> that remained eligible according to our updated eligibility criteria (figure 1).<sup>14–16,38–43</sup> There was substantial agreement between both reviewers for judging eligibility of the newly identified studies ( $\kappa$  statistic 0.77). Detailed characteristics of these 27 studies are provided in table 1. Of the 27 studies, eight included only patients with ulcerative colitis,<sup>18,26,27,31,36–38,41</sup> one recruited only patients with Crohn's disease,<sup>16</sup> and four recruited patients with IBD, but did not report the prevalence of IBS-type symptoms separately for patients with ulcerative colitis or Crohn's disease.<sup>14,28,29,35</sup> Although Sanges and colleagues<sup>35</sup> reported the total number of patients with ulcerative colitis and Crohn's disease in remission separately, they did not report the prevalence of IBS-type symptoms for each IBD type. The remaining 14 studies included a combination of patients with ulcerative colitis and those with Crohn's disease, with prevalence of IBS-type symptoms reported separately for each. No studies reported prevalence of IBS-type symptoms in patients with IBD-unclassified.

Several studies reported prevalence of IBS-type symptoms according to more than one definition of remission. Specifically, 15 used a validated clinical disease activity index,<sup>13,15–17,19,20,26,29,30,33,36–39,42</sup> and eight used a

physician's global assessment of remission.<sup>14,19,25,32,34,35,40,43</sup> Six studies provided data on endoscopic remission,<sup>18,25–27,31,41</sup> four reported biochemical remission, using a faecal calprotectin concentration of higher than 100 µg/g,<sup>13,17,28,30</sup> and two by use of histologically confirmed remission.<sup>25,27</sup> Eight studies used the Rome II criteria to define the presence of IBS-type symptoms,<sup>15,30,31,38–40,42,43</sup> 16 used the Rome III criteria,<sup>13,14,16–20,25–29,32,34–36</sup> two used the Rome IV criteria,<sup>33,37</sup> and one used the Manning criteria.<sup>41</sup> Four studies compared mean anxiety scores between patients with and without IBS-type symptoms using the Hospital Anxiety and Depression Scale.<sup>13,16,17,19</sup> Three studies also used this scale to compare mean depression scores between these two groups,<sup>13,17,19</sup> and one used the Beck Depression Inventory.<sup>16</sup> Mean somatic symptom scores were compared between patients with and without IBS-type symptoms in two studies,<sup>17,18</sup> using the Patient Health Questionnaire-12 (PHQ-12).

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 27.4–37.9;  $I^2=90.1\%$ ), ranging from 11.2% to 63.6% in individual studies. Subgroup analyses showed higher levels of heterogeneity when subjective measures, such as a physician's global assessment or a disease activity index, were used to define remission, than when more objective measures were used, such as biochemical or endoscopic confirmation of remission (table 2). Prevalence of IBS-type symptoms was highest when a faecal calprotectin concentration of less than 100 µg/g was used to define remission (35.1%, 95% CI 28.1–42.6;  $I^2=38.7\%$ ), although prevalence according to physician's global assessment (34.1%, 24.6–44.3;  $I^2=89.0\%$ ) and a validated disease



	Number of studies	Total number of patients	Number of patients meeting criteria for IBS-type symptoms	Pooled prevalence of IBS-type symptoms (95% CI)	I <sup>2</sup>	p value*
<b>Criteria used to define remission</b>						
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 clinical 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%	<0.0001
Endoscopic healing	6	704	174	23.5% (17.9–29.6)	59.9%	0.029
Faecal calprotectin <100 µg/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
<b>Criteria used to define presence of IBS-type symptoms</b>						
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
<b>Type of IBD</b>						
Ulcerative colitis	22	1825	527	28.7% (22.9–34.8)	87.2%	<0.0001
Crohn's disease	15	1050	366	36.6% (29.5–44.0)	82.9%	<0.0001

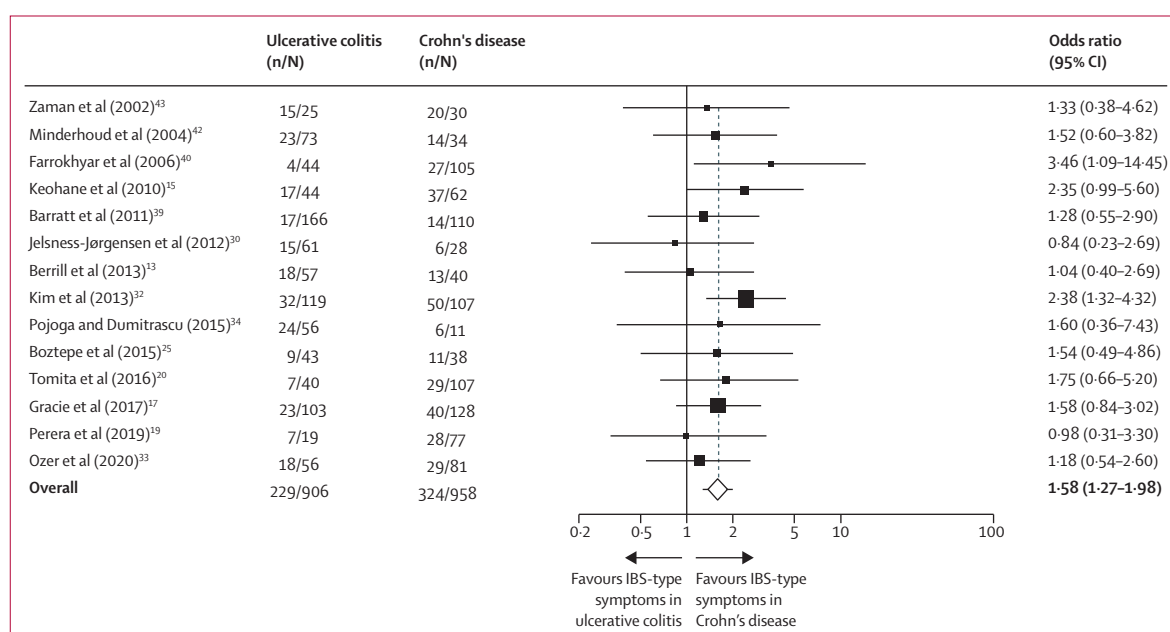
IBS=irritable bowel syndrome. IBD=inflammatory bowel disease. NA=not applicable; too few studies. \*p value derived from for  $\chi^2$  test.

**Table 2: Subgroup analyses of prevalence of IBS-type symptoms in IBD**

activity index (33.6%, 26.3–41.2;  $I^2=91.8\%$ ) were similar. Prevalence was lowest when either endoscopic (23.5%, 95% CI 17.9–29.6;  $I^2=59.9\%$ ) or histological assessment (25.8%, 20.2–31.7;  $I^2$ = not applicable) was used to define remission.

The pooled prevalence of IBS-type symptoms in the eight studies that used the Rome II criteria was 31.5% (95% CI 19.2–45.4), with significant heterogeneity ( $I^2=94.3\%$ ,  $p<0.0001$ ; table 2). In the 16 studies for which the Rome III criteria were used, prevalence was 33.5% (95% CI 27.6–39.6), again with significant heterogeneity between studies ( $I^2=87.7\%$ ;  $p<0.0001$ ). In the two studies that used the Rome IV criteria, the pooled prevalence was 29.6% (95% CI 19.4–40.9;  $I^2$ =not applicable).

Data for IBS-type symptoms in patients with Crohn's disease in remission were available in 15 studies, with a pooled prevalence of 36.6% (95% CI 29.5–44.0), again with significant heterogeneity between studies ( $I^2=82.9\%$ ,  $p<0.0001$ ). There were 22 studies reporting prevalence of IBS-type symptoms in patients with ulcerative colitis in remission, with a pooled prevalence of 28.7% (95% CI 22.9–34.8), again with significant heterogeneity ( $I^2=87.2\%$ ,  $p<0.0001$ ; table 2). Of the included studies, 14 reported the prevalence of IBS-type symptoms in 1864 patients with either Crohn's disease or ulcerative colitis separately. IBS-type symptoms were more common in those with Crohn's disease (366 [34.9%] of 1050 patients) than they were in patients with ulcerative colitis (527 [28.9%] of 1825 patients). The OR for IBS-type symptoms was significantly higher among patients with Crohn's disease (OR 1.58, 95% CI 1.27–1.98; figure 2),



**Figure 2: Forest plot**

Odds ratios for IBS-type symptoms in patients with Crohn's disease in remission versus patients with ulcerative colitis in remission. IBS=irritable bowel syndrome.

with no heterogeneity between studies. There was no evidence of funnel plot asymmetry to suggest publication bias or other small study effects (Egger test  $p=0.32$ ).

Data concerning anxiety and depression scores among those with and without IBS-type symptoms were provided by four studies.<sup>13,16,17,19</sup> Anxiety scores were significantly higher among patients who reported IBS-type symptoms (WMD 2.5, 95% CI 0.8–4.3;  $p=0.0042$ ), with significant heterogeneity between studies ( $I^2=76.3\%$ ;  $p=0.0054$ ). Depression scores were also significantly higher in patients with IBD with IBS-type symptoms (SMD 0.64, 95% CI 0.44–0.84;  $p<0.0001$ ) with no heterogeneity between studies ( $I^2=0\%$ ). Finally, two studies provided PHQ-12 scores.<sup>17,18</sup> Somatic symptom scores were significantly higher in patients who reported IBS-type symptoms (WMD 2.7, 95% CI 1.8–3.7;  $p<0.0001$ ).

## 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. The results show that about a third of patients with IBD report symptoms compatible with IBS. The study restricted eligibility to 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 were used, including endoscopic or histological remission, the prevalence of IBS-type symptom reporting was still as high as 25.8%. The criteria used to define the presence of IBS-type symptoms did not seem to affect their prevalence. When we pooled data from 14 studies, there was a significantly higher proportion of patients with Crohn's disease than with ulcerative colitis meeting criteria for IBS. 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 might explain the increased access to the health-care system observed previously in these patients.<sup>44</sup>

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. A random effects model was used to pool data for the analysis 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.<sup>21</sup> 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. Notably, this was most apparent when subjective measures of remission were used, such as a patient-reported disease activity indices or physician's global assessment, 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 could further account for variability between study results. Population groups across a wide geographical region might 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 because of the difficulties of incorporating endoscopic procedures into the study design, or the acceptability of faecal sampling for research purposes.<sup>45</sup> Finally, the criteria for the definition of IBS-type symptoms varied, with only two recently published studies using the Rome IV criteria.<sup>33,37</sup> 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 emphasises that even when endoscopic or histological measures are used to define disease remission, about a quarter of patients report IBS-type symptoms. Therefore, there is a cohort of patients with IBD who report a symptom complex that is inadequately addressed by conventional IBD treatments, emphasising an unmet need in management and 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 casts doubt on the previous supposition that occult inflammatory activity is the primary aetiological factor responsible for these symptoms.<sup>15,46</sup> This is further supported by data from an observational study describing the effect of IBS-type symptom-reporting on longitudinal disease activity outcomes in IBD.<sup>44</sup> In that study, Gracie and colleagues<sup>44</sup> showed that 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, admission to hospital, 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,<sup>7-9</sup> reinforce the need for alternative management strategies for these patients.

Our results showed that the prevalence of IBS-type symptoms was significantly higher in those with Crohn's disease than in those with ulcerative colitis. The distribution of disease location in those with Crohn's disease could partly explain the variable symptom profile. No study assessed for the presence of small bowel inflammatory activity using gold-standard investigations, such as magnetic resonance enterography or wireless capsule endoscopy. This might have resulted in a misclassification bias in studies for which the proportion of patients with Crohn's disease with small bowel disease was high,<sup>28</sup> with symptoms being secondary to occult small bowel inflammation, and therefore incorrectly labelled as IBS. This potential misclassification might explain the high prevalence of IBS-type symptoms observed when prevalence data from studies using faecal calprotectin to define disease remission were pooled, particularly as the utility of faecal calprotectin as a measure of small bowel inflammation in Crohn's disease is uncertain.<sup>47,48</sup> Additionally, small bowel disease increases the risk of bacterial overgrowth, and terminal ileal Crohn's disease might be associated with bile acid diarrhoea, particularly in patients who have undergone previous ileal resection.<sup>49-51</sup> Delays in the diagnosis of small bowel Crohn's disease might also lead to a prolonged inflammatory insult, potentially increasing the risk of fibrosis, stricturing, and mechanical dysfunction of the gastrointestinal tract.<sup>16,39</sup> These associated conditions can mimic IBS-type symptoms and could explain the increased prevalence observed in Crohn's disease. For studies that reported phenotypic characteristics in Crohn's disease, the numbers were small and underpowered, with no significant difference in IBS-type symptoms between groups defined by either disease location or behaviour.<sup>17</sup> Additionally, because of 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 ulcerative colitis, we were unable to assess whether the various definitions of remission affected prevalence in patients with Crohn's disease versus ulcerative colitis. Therefore, the potential confounding effect of these factors on our results remains uncertain.

There was an association between the reporting of IBS-type symptoms and psychological comorbidity, 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 comorbidity is well established in the general population. Notably, disordered gut-brain axis activity might contribute to the development of IBS in a subset of patients.<sup>32</sup> To our

knowledge, we provide the first pooled assessment of the association between psychological comorbidity and the reporting of IBS-type symptoms in patients with IBD, demonstrating a clear association between the presence of these symptoms and anxiety, depression, and somatisation. Mood disorders and somatic symptoms in IBD are linked to increased use of health-care systems and an increased number of gastrointestinal investigations.<sup>44</sup> Furthermore, somatoform behaviour is likely to extend beyond gastrointestinal services and affect the need for multi-specialty review.

Evidence-based interventions for the management of IBS in the general population include neuromodulators,<sup>53</sup> psychological therapies,<sup>54</sup> and treatments targeting the gastrointestinal microbiome such as antibiotics,<sup>55</sup> probiotics,<sup>56</sup> faecal microbial transfer,<sup>57</sup> or a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP).<sup>58</sup> However, randomised controlled trials assessing the effect of these interventions in patients with IBD reporting IBS-type symptoms are scarce. Psychological therapies are associated with a short-term improvement in depression scores and quality of life in patients with IBD,<sup>59</sup> but efficacy in patients reporting IBS-type symptoms is unknown. In one database study, patients with IBD using antidepressants were significantly less likely to have a relapse of disease activity, or require escalation of therapy compared with non-users,<sup>60</sup> but only one study has been done in patients with IBD reporting persistent symptoms in the absence of inflammation, which was limited by its retrospective design.<sup>61</sup> In that study, 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 randomised controlled trials of antibiotics,<sup>62</sup> probiotics,<sup>63</sup> faecal microbial transfer,<sup>64</sup> and the low FODMAP diet<sup>65-67</sup> have been done, but with the exception of the low FODMAP diet, these have largely focused on disease activity outcomes rather than IBS-type symptom reporting. In one of these trials,<sup>66</sup> a significantly higher proportion of patients reporting IBS-type symptoms who were randomly assigned to receive a low FODMAP diet achieved adequate relief of IBS-type symptoms than did patients randomly assigned to a control diet. The number needed to treat with low FODMAP diet versus control diet for one patient to achieve adequate relief of symptoms was three.

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, about a quarter of patients reported these symptoms. IBS-type symptoms were more common in Crohn's disease, and were associated with psychological comorbidity 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



coexistent mood disorders, might be of benefit in this area of unmet therapeutic need, but clinical trials of these interventions in this specific subgroup of patients with IBD are scarce. The outcomes of ongoing studies such as MODULATE (ISRCTN16086699), a large multi-arm, randomised controlled trial investigating various treatments, including antidepressants, ondansetron, loperamide, or a low FODMAP diet in patients with stable ulcerative colitis with ongoing diarrhoea, will be of particular interest in the future.

# Contributors

KMF, SJC, and ACF collected all the 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

We declare no competing interests.

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