Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis

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Summary

Background Inflammatory bowel disease (IBD) is a lifelong condition with no cure. Patients with IBD might experience symptoms of common mental disorders such as anxiety and depression because of bidirectional communication via the gut–brain axis and chronicity of symptoms, and because of impaired quality of life and reduced social functioning. However, uncertainties remain about the magnitude of this problem. We aimed to assess prevalence of symptoms of anxiety or depression in adult patients with IBD.

Methods In this systematic review and meta-analysis, we searched MEDLINE, Embase, Embase Classic, and PsycINFO for papers published from inception to Sept 30, 2020, reporting observational studies that recruited at least 100 adult patients with IBD and that reported prevalence of symptoms of anxiety or depression according to validated screening instruments. We excluded studies that only used a structured interview to assess for these symptoms and studies that did not provide extractable data. We extracted data from published study reports and calculated pooled prevalences of symptoms of anxiety and depression, odds ratios (OR), and 95% CIs.

Findings Of 5544 studies identified, 77 fulfilled the eligibility criteria, including 30 118 patients in total. Overall, pooled prevalence of anxiety symptoms was 32·1% (95% CI 28·3–36·0) in 58 studies (I^2=96·9%) and pooled prevalence of depression symptoms was 25·2% (22·0–28·5) in 75 studies (I^2=97·6%). In studies that reported prevalence of anxiety or depression in patients with Crohn's disease and ulcerative colitis within the same study population, patients with Crohn's disease had higher odds of anxiety symptoms (OR 1·2, 95% CI 1·1–1·4) and depression symptoms (1·2, 1·1–1·4) than patients with ulcerative colitis. Overall, women with IBD were more likely to have symptoms of anxiety than were men with IBD (pooled prevalence 33·8% [95% CI 26·5–41·5] for women *vs* 22·8% [18·7–27·2] for men; OR 1·7 [95% CI 1·2–2·3]). They were also more likely to have symptoms of depression than men were (pooled prevalence 21·2% [95% CI 15·4–27·6] for women *vs* 16·2% [12·6–20·3] for men; OR 1·3 [95% CI 1·0–1·8]). The prevalence of symptoms of anxiety (57·6% [95% CI 38·6–75·4]) or depression (38·9% [26·2–52·3]) was higher in patients with active IBD than in patients with inactive disease (38·1% [30·9–45·7] for anxiety symptoms and 24·2% [14·7–35·3] for depression symptoms; ORs 2·5 [95% CI 1·5–4·1] for anxiety and 3·1 [1·9–4·9] for depression).

Interpretation There is a high prevalence of symptoms of anxiety and depression in patients with IBD, with up to a third of patients affected by anxiety symptoms and a quarter affected by depression symptoms. Prevalence was also increased in patients with active disease: half of these patients met criteria for anxiety symptoms and a third met criteria for depression symptoms. Encouraging gastroenterologists to screen for and treat these disorders might improve outcomes for patients with IBD.

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Introduction

Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, are chronic disorders that cause inflammation of the gastrointestinal tract,[1] and for which incidence and prevalence are increasing worldwide.[2] These diseases are thought to arise from dysregulation of the innate and adaptive immune systems,[3] leading to an abnormal inflammatory response to commensal bacteria in a genetically susceptible individual.[4] Although a better understanding of the disease together with newly developed drugs have improved prognosis and life expectancy in patients with inflammatory bowel disease (IBD),[5,6] an increased life span with a chronic disease is likely to negatively affect the patient's quality of life.[7] For instance, patients with IBD report loss of work productivity, and their disease seems to influence career choice and the decision to retire early.[8]

In addition, because IBD is a lifelong condition with chronic symptoms, reduced quality of life and social functioning, and no cure, with bidirectional communication via the gut–brain axis,[9] patients with IBD might have psychological illness,[10] including symptoms of common mental disorders and somatisation.[11,12] Psychological illness further negatively affects quality of

Research in context

Evidence before this study

As inflammatory bowel disease (IBD) is a lifelong condition with chronic symptoms, reduced quality of life and social functioning, and no cure, patients with IBD might experience symptoms of common mental disorders, including those of anxiety and depression. Uncertainties remain about the magnitude and strength of the association between symptoms of anxiety and depression and the different types of IBD, the influence of disease activity, and sex. A comprehensive search of the medical literature using MEDLINE, Embase, Embase Classic, and PsycINFO identified two systematic reviews that have examined some of these issues, but the literature search used in these reviews only included studies published up to 2014.

Added value of this study

We did a contemporaneous systematic review and meta-analysis to assess prevalence of symptoms of anxiety or depression in adult patients with IBD. We investigated whether type of IBD, disease activity, or sex influence the prevalence, as well as whether prevalence varied on the basis of questionnaire and cutoff used. Pooled prevalence of anxiety symptoms in patients with IBD was 32·1%, and pooled prevalence of depression symptoms was 25·2%, but this pooled prevalence varied according to the questionnaire used. Women with IBD had a higher probability of experiencing anxiety symptoms than did men with IBD, particularly women with Crohn's disease. Patients with active disease also had a higher probability of experiencing both anxiety symptoms and depression symptoms than did patients with inactive disease.

Implications of all the available evidence

These data provide a useful primer for clinicians, as to which patients should be screened routinely for symptoms of common mental disorders, and suggest that there is a need to assess for symptoms of anxiety and depression using validated disease-specific screening tools. Encouraging gastroenterologists to screen for and treat these disorders might improve outcomes for patients.

life and disease outcomes.[13–17] An analysis of data on administrative claims showed that both direct and indirect costs of care were significantly higher for patients with IBD and a co-existent common mental disorder than for patients with IBD only.[18]

Although numerous studies have reported symptoms of anxiety and depression in patients with IBD, they show that prevalence rates vary greatly, by up to 80% in some studies.[19,20] Some of this variation might reflect differences in the psychometric tools used to define the presence or absence of these disorders,[19,21,22] but uncertainties remain about the magnitude of this problem,[23] as well as about the strength of association between symptoms of common mental disorders and type of IBD,[13,24,25] disease activity,[26–28] and sex.[29] Two systematic reviews have examined some of these issues,[30,31] but the literature search used only included studies published up to 2014. Although one of these systematic reviews examined these issues in detail,[30] a meta-analysis was not done and pooled prevalence estimates were not calculated; the other systematic review did only a few analyses.[31]

We did a contemporaneous systematic review and meta-analysis to assess the prevalence of symptoms of anxiety or depression in adult patients with IBD. We aimed to investigate whether type of IBD, disease activity, or sex influenced the prevalence of these symptoms, as well as whether prevalence varied on the basis of questionnaire and cutoff used. Synthesising the existing evidence to provide an estimate of the prevalence of symptoms of anxiety and depression will hopefully increase awareness among clinicians, facilitating screening of patients for evidence of these disorders and, if necessary, referral for treatment. Such treatment might also serve to reduce the total burden of disease in these patients, given that there is increasing evidence that mood influences IBD activity.[13–17]

Methods

Search strategy and selection criteria

We searched MEDLINE, Embase, Embase Classic, and PsycINFO, from inception of these databases to Sept 30, 2020, to identify cross-sectional surveys or case-control studies reporting prevalence of symptoms of anxiety or depression in adult patients (for which at least 90% of patients were aged 18 years or older) with histologically or radiologically confirmed IBD. To be eligible, studies had to recruit at least 100 participants (to minimise the likelihood of overestimating the magnitude of the issue due to a small sample size) and define the presence of symptoms of anxiety or depression according to a validated questionnaire; we did not consider studies that used a structured interview. The eligibility criteria, which were defined prospectively, are provided in the panel.

We searched the medical literature using the following terms: "ulcerative colitis" or "colitis", "Crohn's disease", and "inflammatory bowel diseases" (both as medical subject headings [MeSH] and free-text terms). We combined these terms, using the set operator AND, with the following free-text terms: "anxiety", "depression", and "mood disorders". There were no language restrictions. We screened titles and abstracts of all citations identified by our search for potential suitability and retrieved citations that appeared relevant for detailed examination. Foreign language papers were translated. To identify potentially eligible studies published only in abstract form, conference proceedings (Digestive Disease Week, American College of Gastroenterology, and United European Gastroenterology Week) from 2010–20 were also hand-searched. We did a recursive search of the literature using bibliographies of all relevant studies. Where there appeared to be multiple

***Panel*: Study eligibility criteria**

- Cross-sectional surveys or case-control studies
- Adults (more than 90% of participants must be aged 18 years or older) with histologically or radiologically confirmed inflammatory bowel disease (ie, Crohn's disease, ulcerative colitis, or unclassified inflammatory bowel disease)
- Reported number of patients with inflammatory bowel disease with symptoms of anxiety or depression according to a validated questionnaire (eg, Hospital Anxiety and Depression Scale)
- Sample size of at least 100 participants

study reports from the same group of patients, we contacted study authors to clarify the issue. We also planned to contact authors if a study appeared potentially eligible but did not report the data required, to obtain supplementary information and maximise available studies. If studies did not report data for extraction and authors were not contactable, we did not consider them eligible for inclusion. BB and MZ independently assessed study eligibility using pre-designed eligibility forms. Any disagreements were resolved by the opinion of a third reviewer (ACF), and the degree of agreement was measured with a κ-statistic. Ethics approval was not required.

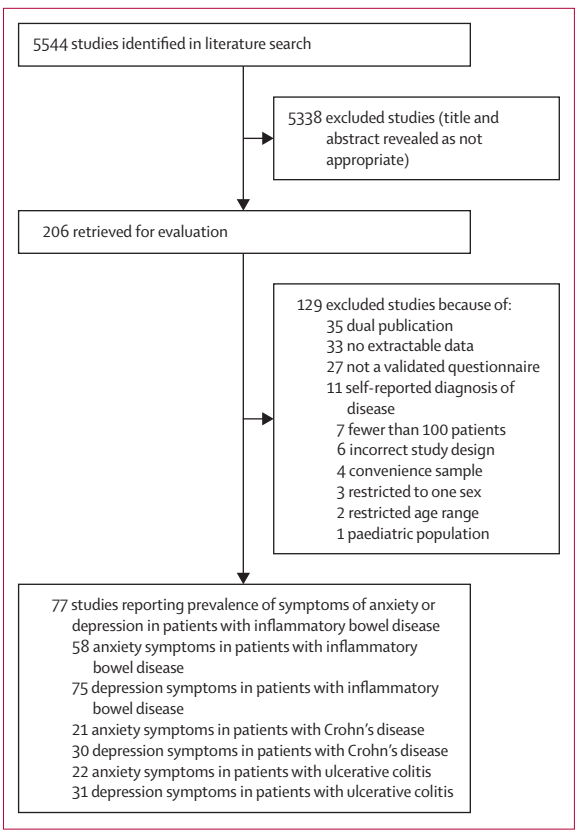

***Figure*: Flow chart of study eligibility assessment**

Data analysis

BB and MZ independently extracted data on to a Microsoft Excel spreadsheet (XP professional edition), with any discrepancies resolved by the opinion of a third investigator (ACF). For each study, we collected data on: country; setting (ie, community, primary, secondary, or tertiary care, or national registry); questionnaire and cutoff used to define presence of symptoms of anxiety or depression; number of patients providing complete data; number of male or female patients; type of IBD (ie, ulcerative colitis, Crohn's disease, or unclassified IBD); number of patients with active or inactive IBD; number of patients with symptoms of anxiety or depression; number of male or female patients with symptoms of anxiety or depression; number of patients with active or inactive IBD and symptoms of anxiety or depression; number of healthy controls (if recruited); and number of healthy controls with symptoms of anxiety or depression. Data were only extracted for healthy controls if there was an exhaustive explanation of their provenance (for example, we excluded convenience samples of controls who were outpatients attending a gastroenterology clinic). We assessed the quality of case-control studies using the Newcastle-Ottawa scale, with a total possible score of 9 (higher scores indicating higher quality studies).[32] For studies that measured symptoms of anxiety or depression at various time points, only the first time point was used.

We combined the proportion of individuals with symptoms of anxiety or depression in each study to give a pooled prevalence for all studies. We used a random effects model to pool data to provide a conservative estimate of prevalence of symptoms of anxiety or depression and assessed heterogeneity between studies using the I^2 statistic, which ranges between 0% and 100%. Values of 25–49% typically denote low levels of heterogeneity, 50–74% moderate levels, and more than 75% high levels.[33] We did subgroup analyses according to the different types of IBD (ie, ulcerative colitis, Crohn's disease, or unclassified IBD), year of study publication (ie, 2000–05, 2006–10, 2011–15, 2016–20), the questionnaire used (and the cutoff used to define the presence of anxiety or depression symptoms for studies that used the same questionnaire), sex, and disease activity. Finally, we compared prevalence of symptoms of anxiety or depression according to type of IBD, sex, and disease activity using an odds ratio (OR) with 95% CIs. We used StatsDirect version 3.2.7 to generate forest plots of pooled prevalences 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,[34] for which at least ten studies were available.[35]

Role of the funding source

There was no funding source for this study.

Results

The search strategy identified 5544 articles. From these articles, we identified 206 articles that appeared relevant to the study question. 77 of these articles fulfilled the eligibility criteria (figure), comprising 30 118 patients with IBD recruited from 23 different countries.[11,13,17,19,20,22,24,28,36–104] Almost all studies were done in a single country, with the exception of a multinational survey that included 33 countries.[79] 11 studies recruited patients with IBD[45,48,55,57,62,77,83,90,97,102,103] (of which one study reported prevalence of symptoms of anxiety or depression in patients with ulcerative colitis or Crohn's disease separately), five studies recruited only patients with ulcerative colitis,[40,41,49,65,79] and four studies recruited only patients with Crohn's disease.[46,53,61,101] No study recruited only patients with unclassified IBD, and none of the included studies reported prevalence of symptoms of anxiety or depression in patients with unclassified IBD separately. Only two studies reported the prevalence of anxiety symptoms in healthy controls,[85,89] whereas five studies reported the prevalence of depression symptoms in healthy controls.[40,42,63,85,89] Two of these five studies scored 5 on the Newcastle-Ottawa scale,[63,89] two scored 4,[42,85] and one scored 3.[40] Agreement between investigators on study eligibility was excellent (κ-statistic=0·85). Detailed characteristics of all included studies are provided in the appendix (pp 1–5).

See Online for appendix

	Number of studies	Number of patients	Pooled prevalence (%, 95% CI)	I^2	p value for χ^2
IBD					
Anxiety					
Any	58	18 915	32·1% (28·3–36·0)	96·9%	<0·0001
HADS	44	15 893	33·2% (29·3–37·2)	96·5%	<0·0001
GAD-7	5	1139	14·4% (9·2–20·5)	86·2%	<0·0001
HAM-A 14	2	333	38·1% (28·1–48·7)	74·7%	0·047
PROMIS	2	417	55·1% (27·0–81·4)	96·5%	<0·0001
STAI	2	492	57·8% (12·3–96·0)	99·0%	<0·0001
BAI	1	381	6·6% (4·3–9·5)	NA	NA
HRQoL	1	156	28·8% (21·9–36·6)	NA	NA
Zung SAS	1	104	16·3% (9·8–24·9)	NA	NA
Depression					
Any	75	29 438	25·2% (22·0–28·5)	97·6%	<0·0001
HADS	44	16 123	21·6% (18·4–24·9)	96·0%	<0·0001
PHQ-9	13	9106	24·5% (17·5–32·3)	98·2%	<0·0001
BDI	7	1508	33·3% (24·6–42·7)	92·8%	<0·0001
PROMIS	2	417	36·3% (31·7–40·9)	0·0%	0·41
Zung SDS	3	392	21·0% (6·9–40·1)	94·4%	<0·0001
CES-D	1	108	43·5% (34·0–53·4)	NA	NA
HAM-D	1	180	88·9% (83·4–93·1)	NA	NA
HRQoL	1	156	21·1% (15·0–28·4	NA	NA
QIDS	1	102	40·2% (30·6–50·4)	NA	NA
SF36	1	1030	14·9% (12·8–17·3)	NA	NA
SIBDQ	1	316	63·9% (58·4–69·2)	NA	NA
Crohn's disease					
Anxiety					
Any	21	4318	36·7% (30·7–42·9)	93·8%	<0·0001
HADS	19	4156	34·7% (28·8–40·8)	93·5%	<0·0001
HAM-A	1	101	36·6% (27·3–46·8)	NA	NA
STAI	1	61	77·0% (64·5–86·8)	NA	NA
Depression					
Any	30	8692	24·8% (20·7–29·3)	94·7%	<0·0001
HADS	19	4179	23·0% (18·8–27·6)	90·3%	<0·0001
BDI	4	608	36·9% (21·4–53·9)	94·0%	<0·0001
PHQ-9	4	3232	29·0% (18·8–40·3)	93·5%	<0·0001
Zung SDS	2	162	13·9% (5·2–26·0)	73·0%	0·054
SF-36	1	511	18·6% (15·3–22·2)	NA	NA

(Table 1 continues on next page)

The pooled prevalence of anxiety symptoms in patients with IBD, based on 58 studies including 18 915 patients,[11,13,17,19,20,24,28,36–39,41,43–47,49–52,55,57,59,61,64–68,70–72,74,76,77,80–86,88–96,98–100,102–104] was 32·1% (95% CI 28·3–36·0; I^2=96·9%, p<0·0001; table 1). The lowest pooled prevalence of anxiety symptoms in patients with IBD was 10·5% in two Spanish studies (716 and 793 patients, respectively),[57,59] whereas the highest pooled prevalence was 56·2% in two Iranian studies (108 and 120 patients, respectively).[49,65] Heterogeneity persisted even when studies were pooled separately according to year of conduct (appendix p 6). When we considered patients with ulcerative colitis or Crohn's disease separately, the pooled prevalence of anxiety symptoms was 34·2% (95% CI 27·1–41·8; I^2=95·6%, p<0·0001) in 22 studies including 3915 patients with ulcerative colitis,[11,13,19,24,28,39,41,45,47,49,50,57,64,65,70,72,76,80,84,85,92,95] and 36·7% (30·7–42·9; I^2=93·8%, p<0·0001) in 21 studies including 4318 patients with Crohn's disease.[11,13,19,24,28,39,45–47,50,59,61,64,70,72,76,80,84,85,92,95] The OR for anxiety symptoms in patients with Crohn's disease versus patients with ulcerative colitis, from 19 studies that reported prevalence in both patients with Crohn's disease and patients with ulcerative colitis within the same study population,[11,13,19,24,28,39,45,47,50,59,64,70,72,76,80,84,85,92,95] was 1·2 (95% CI 1·1–1·4), with no heterogeneity between studies (I^2=7·1%, p=0·37) and no evidence of funnel plot asymmetry (Egger test, p=0·63).

The pooled prevalence of depression symptoms among 29 438 patients with IBD recruited by 75 studies was 25·2% (95% CI 22·0–28·5; I^2=97·6%, p<0·0001).[11,13,17,19,20,22,24,28,36–65,68–104] The lowest prevalence of depression symptoms reported in patients with IBD was 10·5% in one Greek study (153 patients),[85] and the highest prevalence was 88·9%, reported in one Serbian study (180 patients).[20] Again, heterogeneity persisted even when studies were pooled separately according to year of conduct (appendix p 6). The pooled prevalence of depression symptoms in patients with ulcerative colitis in 31 studies including 8219 patients,[11,13,19,22,24,28,39–42,45,47,49,50,54,56,58,59,64,65,69,70,72,76,79,80,84,85,87,92,95] was 24·0% (95% CI 18·6–29·9; I^2=97·0%, p<0·0001), compared with 24·8% (95% CI 20·7–29·3; I^2=94·7%, p<0·0001) in patients with Crohn's disease in 30 studies including 8692 patients (table 1).[11,13,19,22,24,28,39,42,45–47,50,53,54,56,58,59,61,64,69,70,72,76,80,84,85,87,92,95,101] The OR for depression

symptoms in patients with Crohn's disease versus patients with ulcerative colitis, from 26 studies that reported prevalence in both patients with Crohn's disease and patients with ulcerative colitis within the same study population,[11,13,19,22,24,28,39,42,45,47,50,54,56,58,59,64,69,70,72,76,80,84,85,87,92,95] was 1·2 (95% CI 1·1–1·4), with no heterogeneity between studies (I^2=23·5%, p=0·14) and no evidence of funnel plot asymmetry (Egger test, p=0·28).

The pooled prevalence of anxiety symptoms in healthy controls, based on two studies that included 142 patients,[85,89] was 10·4% (95% CI 5·5–16·6; I^2=14·9%, p=0·28). The OR for anxiety symptoms in patients with IBD versus healthy controls in these two studies was 2·6 (95% CI 1·4–4·9), with no heterogeneity between studies (I^2=0%, p=0·65).[85,89] The pooled prevalence of depression symptoms in healthy controls, based on five studies that included 694 patients, was 17·9% (95% CI 8·4–30·2; I^2=92·6%, p<0·0001).[40,42,63,85,89] The OR for depression symptoms in patients with IBD versus healthy controls in these five studies was 1·9 (95% CI 1·4–2·7), with no significant heterogeneity between studies (I^2=34·3%, p=0·19).[40,42,63,85,89]

Of the 58 studies reporting the prevalence of anxiety symptoms in patients with IBD, 44 used the Hospital Anxiety and Depression Scale (HADS),[11,13,17,24,28,37–39,41,43–47,49–52,55,57,59,61,64,65,68,70–72,76,80,81,83,84,86,88,90,92,93,95,96,98–100,103] with a pooled prevalence of 33·2% (95% CI 29·3–37·2; I^2=96·5%, p<0·0001; table 1). Among studies that used other questionnaires, the lowest prevalence was reported in one study that used Beck's Anxiety Inventory and Beck's Depression Inventory (6·6%, 95% CI 4·3–9·5),[36] and the highest pooled prevalence was in two studies using the State-Trait Anxiety Inventory (57·8%, 95% CI 12·3–96·0).[19,67]

Of the 75 studies reporting the prevalence of depression symptoms in patients with IBD, 44 used the HADS.[11,13,17,24,28,37–39,41,43,44,45,47,50–52,55,57,59,61,63–65,68,70–72,76,78,80,81,83,84,86,90,92,93,95,96,98,99–101,103] The pooled prevalence of depression symptoms in these studies was 21·6% (95% CI 18·4–24·9; I^2=96·0%, p<0·0001). Among the remaining articles that used different questionnaires, the lowest pooled prevalence was in three studies that used the Zung Self-rating Depression Scale (21·0%, 95% CI 6·9–40·1),[19,85,89] and the highest prevalence was in one study that used the Hamilton Depression Rating Scale (88·9%, 95% CI 83·4–93·1).[20] Further subgroup analyses are reported in table 1. Heterogeneity persisted when studies that used the same cutoff on the HADS for defining the presence of symptoms of anxiety or depression were pooled separately (appendix pp 7–8). Prevalence of symptoms of anxiety or depression using a HADS score of at least 11 (the cutoff recommended by the original investigators)[105] was 21·3% (95% CI 17·2–25·6) for anxiety symptoms and 10·6% (95% CI 8·6–12·8) for depression symptoms.

There were seven studies that reported the prevalence of anxiety symptoms in patients with IBD according to sex.[17,39,46,50,61,80,85] The pooled prevalence of anxiety symptoms was higher in women with IBD (33·8%, 95% CI 26·5–41·5) than in men with IBD (22·8%, 95% CI 18·7–27·2; table 2). The OR for anxiety symptoms in women with IBD versus men with IBD in these seven studies was 1·7 (95% CI 1·2–2·3), with moderate heterogeneity between studies (I^2=64·3%, p=0·01; table 2). When the same analyses were done separately on four studies that reported prevalence of anxiety symptoms in patients with Crohn's disease[39,46,61,80] and two studies that reported the same prevalence in patients with ulcerative colitis,[39,80] the pooled prevalence of anxiety symptoms was higher in women with Crohn's disease (37·8%, 95% CI 25·1–51·5) than in men with Crohn's disease (19·8%, 16·0–24·0). Conversely, prevalence of anxiety symptoms was slightly higher in men with ulcerative colitis (18·0%, 13·1–23·5) than in women with ulcerative colitis (14·6%, 2·8–33·3; table 2). The OR for anxiety symptoms in women with Crohn's disease versus men with Crohn's disease was 2·4 (95% CI 1·5–3·9; I^2=51·4%, p=0·10), whereas in women with ulcerative colitis versus men with ulcerative colitis it was 0·7 (95% CI 0·1–3·7; I^2=82·0%, p=0·02; table 2).

There were 12 studies that reported prevalence of depression symptoms in patients with IBD according to sex.[17,39,46,50,60–63,80,85,101,102] Again, the pooled prevalence was higher in women with IBD (21·2%, 95% CI 15·4–27·6) than in men with the disease (16·2%, 12·6–20·3; table 2). The OR for depression symptoms in women with IBD versus men with the same disease in these 12 studies

	Number of studies	Number of patients	Pooled prevalence (%, 95% CI)	I^2	p value for χ^2
(Continued from previous page)					
Ulcerative colitis					
Anxiety					
Any	22	3915	34·2% (27·1–41·8)	95·6%	<0·0001
HADS	20	3789	32·2% (25·4–39·3)	95·0%	<0·0001
HAM-A	1	52	25·0% (14·0–38·9)	NA	NA
STAI	1	74	85·1% (75·0–92·3)	NA	NA
Depression					
Any	31	8219	24·0% (18·6–29·9)	97·0%	<0·0001
HADS	19	3681	22·6% (18·5–27·1)	88·9%	<0·0001
PHQ-9	5	3561	27·9% (14·8–43·4)	98·5%	<0·0001
BDI	3	224	31·6% (11·2–56·7)	93·2%	<0·0001
Zung SDS	2	126	12·4% (7·3–18·7)	0·0%	0·64
CES-D	1	108	43·5% (34·0–53·4)	NA	NA
SF-36	1	519	11·4% (8·8–14·4)	NA	NA

For entries classed as not applicable, there were too few studies to assess heterogeneity. BAI=Beck's Anxiety Inventory. BDI=Beck's Depression Inventory. CES-D=Center for Epidemiologic Studies Depression scale. GAD-7=General Anxiety Disorder-7. HADS=Hospital Anxiety and Depression Scale. HAM-A=Hamilton Anxiety Rating Scale. HAM-D=Hamilton Depression Rating Scale. HRQoL=Health-Related Quality of Life questionnaire. IBD=inflammatory bowel disease. NA=not applicable. PHQ-9=Patient Health Questionnaire-9. PROMIS=Patient-Reported Outcomes Measurement Information System. SF-36=36-Item Short-Form Survey. SIBDQ=Short Inflammatory Bowel Disease Questionnaire (depression sub-score). STAI=State-Trait Anxiety Inventory. QIDS=Quick Inventory of Depressive Symptomatology. Zung SAS=Zung Self-rating Anxiety Scale. Zung SDS=Zung Self-rating Depression Scale.

Table 1: **Pooled prevalence of symptoms of anxiety or depression in patients with IBD according to questionnaire used and disease type**

	Number of studies	Number of patients	Pooled prevalence (%, 95% CI)	I^2	p value for χ^2	OR for women *vs* men (95% CI)	p value for χ^2
IBD							
Anxiety	..	..	..	..	..	1·7 (1·2–2·3)	0·0030
Women	7	1101	33·8% (26·5–41·5)	85·4%	<0·0001	..	..
Men	7	1062	22·8% (18·7–27·2)	62·5%	0·014	..	..
Depression	..	..	..	..	..	1·3 (1·0–1·8)	0·057
Women	12	1794	21·2% (15·4–27·6)	89·9%	<0·0001	..	..
Men	12	1653	16·2% (12·6–20·3)	77·3%	<0·0001	..	..
Crohn's disease							
Anxiety	..	..	..	..	..	2·4 (1·5–3·9)	0·00050
Women	4	386	37·8% (25·1–51·5)	85·9%	<0·0001	..	..
Men	4	382	19·8% (16·0–24·0)	0·0%	0·59	..	..
Depression	..	..	..	..	..	1·6 (0·8–3·1)	0·15
Women	5	425	22·6% (10·5–37·6)	91·1%	<0·0001	..	..
Men	5	476	14·7% (9·8–20·3)	62·7%	0·029	..	..
Ulcerative colitis							
Anxiety		..	..	..	..	0·7 (0·1–3·7)	0·66
Women	2	198	14·6% (2·8–33·3)	86·9%	0·005	..	..
Men	2	208	18·0% (13·1–23·5)	0·0%	0·51	..	..
Depression	..	..	..	..	..	0·8 (0·2–3·5)	0·73
Women	2	198	10·7% (6·5–15·9)	11·3%	0·29	..	..
Men	2	208	12·3% (5·0–22·2)	69·7%	0·069	..	..

Table 2: **Pooled prevalence of symptoms of anxiety or depression in patients with inflammatory bowel disease according to sex and disease type**

was 1·3 (95% CI 1·0–1·8), with moderate heterogeneity (I^2=57·5%, p=0·007) and no evidence of funnel plot asymmetry (Egger test, p=0·20; table 3). Subgroup analyses according to type of IBD confirmed a higher pooled prevalence of depression symptoms in women with Crohn's disease (22·6%, 95% CI 10·5–37·6) than in men with Crohn's disease (14·7%, 9·8–20·3). The OR for women versus men with Crohn's disease was 1·6 (95% CI 0·8–3·1; I^2=66·5%, p=0·02). However, prevalence of depression symptoms was higher in men with ulcerative colitis (12·3%, 95% CI 5·0–22·2) than in women with ulcerative colitis (10·7%, 6·5–15·9). The OR for women versus men with ulcerative colitis was 0·8 (95% CI 0·2–3·5; I^2=74·1%, p=0·05; table 2).

The criteria used to define disease activity in the 19 studies that reported the prevalence of symptoms of anxiety or depression in patients with active or inactive disease are shown in the appendix (p 9). Most studies used clinical disease activity indices, with only three studies incorporating objective biochemical or endoscopic markers of inflammation.[17,28,70] The pooled prevalence of anxiety symptoms in patients with active IBD was 57·6% (95% CI 38·6–75·4) in eight studies,[17,19,43,49,65,70,84,95] and the pooled prevalence in patients with inactive IBD was 38·1% (95% CI 30·9–45·7) in 15 studies (table 3).[11,17,19,20,28,43,49,61,65,70,72,84,92,95,104] The OR for anxiety symptoms in active versus inactive disease, in the eight studies that reported prevalence in both active and inactive disease within the same study population,[17,19,43,49,65,70,84,95] was 2·5 (95% CI 1·5–4·1), with high levels of heterogeneity between studies (I^2=77·2%, p=0·0006; table 3). Subgroup analyses in patients with Crohn's disease or ulcerative colitis separately showed that the pooled prevalence of anxiety symptoms in patients with active Crohn's disease was 74·7% (95% CI 53·2–91·2) in three studies,[19,70,84] whereas prevalence was 38·7% (33·3–44·2) in patients with inactive Crohn's disease in eight studies (table 3).[11,19,28,61,70,72,84,92] For patients with active ulcerative colitis, the pooled prevalence of anxiety symptoms was 70·8% (95% CI 49·2–88·4) in five studies,[19,49,65,70,84] and for patients with inactive ulcerative colitis it was 38·7% (27·8–50·3) in nine studies (table 3).[11,19,28,49,65,70,72,84,92] ORs for the prevalence of anxiety symptoms in patients with active versus inactive Crohn's disease and active versus inactive ulcerative colitis are provided in table 3.

Regarding depression symptoms, the pooled prevalence in patients with active IBD was 38·9% (95% CI 26·2–52·3) in 11 studies,[17,19,49,53,63,65,70,84,88,95,101] whereas it was 24·2% (14·7–35·3) in patients with inactive IBD in 18 studies (table 3).[11,17,19,20,28,49,53,61,63,65,70,72,84,88,92,95,101,104] The OR for depression symptoms in patients with active versus inactive IBD was 3·1 (95% CI 1·9–4·9) in 11 studies that reported prevalence in both patients with active disease and patients with inactive disease within the same study population,[17,19,49,53,63,65,70,84,88,95,101] with high levels of heterogeneity between studies (I^2=70·8%, p<0·0001), but no evidence of funnel plot asymmetry (Egger test, p=0·84; table 3). Subgroup analyses in patients with Crohn's disease revealed a pooled prevalence of depression symptoms in patients with active disease of 51·0%

	Number of studies	Number of patients	Pooled prevalence (%, 95% CI)	I^2	p value for χ^2	OR for active disease *vs* inactive disease (95% CI)	p value for χ^2
Inflammatory bowel disease							
Anxiety	..	..	..	..	..	2·5 (1·5–4·1)	0·0006
Inactive	15	2247	38·1% (30·9–45·7)	92·0%	<0·0001	..	..
Active	8	1004	57·6% (38·6–75·4)	97·1%	<0·0001	..	..
Depression	..	..	..	..	..	3·1 (1·9–4·9)	<0·0001
Inactive	18	2249	24·2% (14·7–35·3)	96·9%	<0·0001	..	..
Active	11	1125	38·9% (26·2–52·3)	95·5%	<0·0001	..	..
Crohn's disease							
Anxiety	..	..	..	..	..	2·9 (1·7–4·9)	<0·0001
Inactive	8	736	38·7% (33·3–44·2)	54·0%	0·033	..	..
Active	3	119	74·7% (53·2–91·2)	79·8%	0·0070	..	..
Depression	..	..	..	..	..	5·6 (1·2–26·0)	0·023
Inactive	10	961	20·2% (12·0–30·0)	91·0%	<0·0001	..	..
Active	5	303	51·0% (31·0–70·8)	91·2%	<0·0001	..	..
Ulcerative colitis							
Anxiety	..	..	..	..	..	2·9 (1·9–4·5)	<0·0001
Inactive	9	570	38·7% (27·8–50·3)	86·7%	<0·0001	..	..
Active	5	281	70·8% (49·2–88·4)	92·8%	<0·0001	..	..
Depression	..	..	..	..	..	2·9 (1·7–5·0)	<0·0001
Inactive	9	570	21·8% (13·7–31·1)	83·9%	<0·0001	..	..
Active	5	281	41·3% (26·6–56·8)	85·1%	<0·0001	..	..

Criteria used to define disease activity in individual studies are provided in the appendix (p 9).

Table 3: **Pooled prevalence of symptoms of anxiety or depression in patients with inflammatory bowel disease according to disease activity and disease type**

(95% CI 31·0–70·8) in five studies,[19,53,70,84,101] and 20·2% (12·0–30·0) in patients with inactive disease in ten studies.[11,19,28,53,61,70,72,84,92,101] In patients with active ulcerative colitis, prevalence of depression symptoms was 41·3% (95% CI 26·6–56·8) in patients with active ulcerative colitis in five studies,[19,49,65,70,84] and 21·8% (13·7–31·1) in patients with inactive ulcerative colitis in nine studies (table 3).[11,19,28,49,65,70,72,84,92] ORs for the prevalence of depression symptoms in patients with active versus inactive Crohn's disease and patients with active versus inactive ulcerative colitis are provided in table 3.

Discussion

This systematic review and meta-analysis includes data from 77 studies that reported prevalence of symptoms of anxiety or depression in patients with IBD using validated questionnaires. We found a pooled prevalence of anxiety symptoms in patients with IBD of 32·1%, on the basis of 58 studies, and a pooled prevalence of depression symptoms of 25·2%, on the basis of 75 studies. The prevalence of both symptoms of anxiety and symptoms of depression in patients with IBD was significantly higher than in healthy controls. Using the more stringent cutoff of a HADS score of at least 11 on either scale led to a lower prevalence of anxiety symptoms (21·3%) and depression symptoms (10·6%). Although pooled prevalence rates of symptoms of anxiety or depression were similar among patients with either Crohn's disease or ulcerative colitis, the odds of either anxiety symptoms or depression symptoms were 1·2 times higher in patients with Crohn's disease than in patients with ulcerative colitis. Prevalence of symptoms of common mental disorders varied according to the questionnaire used. For example, prevalence of anxiety symptoms in patients with IBD ranged from 6·6% with Beck's Anxiety Inventory in one study, to 57·8% with the State-Trait Anxiety Inventory in two studies. However, 44 of 58 studies reporting prevalence of anxiety symptoms used the HADS questionnaire, with a pooled prevalence of 33·2%. Similarly, prevalence of depression symptoms ranged from 14·9% with the 36-item Short-Form Survey in one study, to 88·9% with the Hamilton Depression Rating Scale in another study. 44 of 75 studies used the HADS questionnaire, with a pooled prevalence of depression symptoms of 21·6%. The pooled prevalences of symptoms of anxiety and depression were almost twice as high in women with IBD than in men with IBD, and more than twice as high in women with Crohn's disease than in men with Crohn's disease. Moreover, patients with active disease had a significantly higher pooled prevalence of symptoms of anxiety and depression than patients with inactive disease did, with more than double the odds of anxiety symptoms and more than three times the odds of depression symptoms. The prevalence of depression symptoms was particularly increased in patients with active Crohn's disease, compared with patients with

inactive disease, with more than five times higher odds of developing symptoms.

Strengths of this study include that we used a contemporaneous search strategy to maximise the likelihood of identifying pertinent literature, including foreign language articles. We used a random effects model to pool data to provide a more conservative estimate of prevalence of symptoms of anxiety or depression, and assessed for publication bias where sufficient studies existed. In addition, to minimise the influence of heterogeneity on our results, we did subgroup analyses based on type of IBD, disease activity, sex, questionnaire used, and year of publication. Finally, we only included studies that used a validated instrument to assess for presence of symptoms of anxiety or depression.

Weaknesses in our systematic review and meta-analysis include the considerable heterogeneity between studies in all analyses, which was not explained by the subgroup analyses we did, and the variation in questionnaires used. It might be that these different approaches to data collection led to different estimates of the prevalence of symptoms of common mental disorders. In addition, even when identical questionnaires were used, cutoff values to define the presence of symptoms of anxiety or depression were not consistent between all studies, which might have contributed to the variation observed. However, when we did subgroup analyses based on identical cutoffs on the HADS questionnaire, heterogeneity persisted. Another reason for the variation might be that the data used were from 23 different countries, and perhaps the prevalence of both anxiety symptoms and depression symptoms varied on the basis of the country where the data were collected. Furthermore, disease activity was associated with prevalence of symptoms of both anxiety and depression, but most studies did not separately report prevalence data on the basis of disease activity. However, given that the heterogeneity persisted even when the analysis was limited to studies that recruited patients with the same type of IBD, studies that applied the same questionnaire, studies that reported prevalence of symptoms of anxiety and depression in patients with active and inactive disease separately, or studies that were published in the same 5-year period, we conclude that the variation we observed between studies is genuine and relates to other factors that were not examined by individual studies. This variation has led some investigators to avoid doing a meta-analysis in this area,[30] although others have done so.[31] A possible and plausible explanation for the variation in our findings might be the absence of a disease-specific tool to measure and assess symptoms of anxiety or depression in patients with IBD. Although we examined the prevalence of symptoms of common mental disorders in healthy controls, only five studies reported these data.[40,42,63,85,89] Finally, we included cross-sectional and case-control studies, so causality cannot be implied from our results.

Overall, our meta-analysis is in keeping with previous literature on this subject, with conflicting data and divergent opinions about the psychological impact of IBD. One point of controversy touches on the question of whether symptoms of common mental disorders are more probable in patients with Crohn's disease than in patients with ulcerative colitis. Some studies have observed an association between anxiety and depression symptoms and Crohn's disease but not ulcerative colitis.[13,25,38] Nordin and colleagues, in their cross-sectional study in 492 patients with IBD, found a high prevalence of symptoms of anxiety or depression in patients with Crohn's disease but not in those with ulcerative colitis, and hypothesised that this difference might result from more severe somatic symptoms in patients with Crohn's disease.[38] Conversely, other studies showed that both patients with Crohn's disease and patients with ulcerative colitis were equally prone to symptoms of common mental disorders.[24,106,107] Our results showed that, although prevalence of symptoms of anxiety and depression were similar between patients with Crohn's disease and patients with ulcerative colitis, there was a slightly increased risk in patients with Crohn's disease. Previous studies have also questioned whether an association between sex and symptoms of anxiety and depression is present, with some studies showing women to be more prone to these symptoms than men.[29,80] In our meta-analysis, we confirmed that the odds of having both anxiety symptoms and depression symptoms are higher in women with IBD than in men with IBD, and that women with Crohn's disease in particular are more likely to meet criteria for anxiety symptoms than men are.

A further area of uncertainty is whether there is an association between anxiety and depression symptoms and IBD disease activity. Tabatabaien and colleagues reported that severity of anxiety and depression symptoms was strongly associated with disease activity.[26] However, it has been shown that both anxiety symptoms and depression symptoms are not only common in patients with active disease but also reported by 25–40% of patients in remission.[27,28] Moreover, a 2017 meta-analysis aiming to investigate the effect of depressive state on disease course in patients with IBD showed that, in patients with Crohn's disease, depressive state might be associated with a subsequent deterioration in disease course (although this association was not observed in patients with ulcerative colitis), and also provided evidence for bidirectional effects between psychological status and course of IBD.[108] Our results confirmed an association between symptoms of common mental disorders and disease activity, with higher odds of both anxiety symptoms and depression symptoms in patients with active disease, suggesting these patients are more likely to develop symptoms of common mental disorders than patients with inactive disease. However, it is worth noting that, among the

19 studies that reported prevalence of symptoms of anxiety or depression according to IBD activity, only three incorporated biochemical or endoscopic markers of activity.[17,28,70] As a result, the high prevalence of symptoms of anxiety and depression we observed might be an overestimate due to higher levels of symptom reporting in patients who also met the clinical criteria for active disease.

Another crucial issue is that symptoms of common mental disorders, such as anxiety or depression, are difficult to assess in patients with IBD, as no disease-specific instruments to measure these disorders have been validated to date. This situation might have contributed to the wide variation in prevalence of symptoms of anxiety and depression observed in our meta-analysis. As Mikocka-Walus and colleagues also reported in their systematic review,[30] HADS was the most used questionnaire. However, although it is used extensively in patients with IBD, there has been only one study comparing its performance—and that of other instruments—with a structured clinical interview.[109] The HADS depression score performed similarly to other screening tools for depression and was the most specific, but the HADS anxiety score had the lowest specificity. Questionnaires such as these are proxy measures for the presence of common mental disorders, as they measure symptoms rather than the actual disorders. A clinician's diagnosis can only be established via a structured psychiatric or psychological interview.[110] However, these proxies are practical, often used, and widely accepted in studies such as this one. Until we have more precise and standardised tools to quantify both the psychological and inflammatory aspects of IBD together, it is probable that controversies regarding the link between common mental disorders and IBD will remain. Symptoms of anxiety and depression are clearly a substantial issue in patients with IBD; in our meta-analysis, these patients had a significantly higher prevalence of symptoms of anxiety and depression than healthy controls did, similar to a previous systematic review by Mikocka-Walus and colleagues.[30] However, although Mikocka-Walus and colleagues reported that the rates of anxiety symptoms for healthy controls ranged from 7·6% to 16·3%, which was lower than that among patients with IBD, their findings for depression were more heterogeneous, with nine studies reporting higher rates in patients with IBD than in healthy controls and two studies reporting the opposite.[30]

The high prevalence of symptoms of anxiety and depression, both common mental disorders, in patients with IBD has been used to support the premise that a patient's mental health might play a role in both the development and clinical course of IBD.[16,111,112] In fact, a nested case-control study from 2020 that included 15 360 patients with IBD found that individuals with ulcerative colitis and Crohn's disease had a higher prevalence of depression than matched controls without IBD did in the years before their diagnosis.[111] Likewise, a 2019 cohort study observed that individuals with a history of depression were more likely to be diagnosed subsequently with IBD than individuals without such a history, and that antidepressants significantly protected against developing the disease.[112] Moreover, given that some studies highlight reduced adherence to therapy in patients with IBD and concomitant depression,[113,114] identification and treatment of symptoms of common mental disorders might be important in improving treatment adherence and long-term patient outcomes as a result. Perhaps not surprisingly in the light of these findings, the benefit of an integrated model of care, encompassing the management of both inflammatory activity and psychological comorbidity, has been shown to be effective in reducing health-care use and associated costs.[115]

In conclusion, this systematic review and meta-analysis has shown a high prevalence of symptoms of common mental disorders in patients with IBD, with up to a third of patients affected by symptoms of anxiety and a quarter by symptoms of depression. Our results provide estimates of the magnitude of these issues in patients with IBD, which in turn might provide clearer evidence for clinicians as to which patients should be screened routinely for symptoms of anxiety and depression, and suggest that there is a need to assess for symptoms of anxiety and depression using validated screening tools. Encouraging gastroenterologists to detect and treat these disorders might improve outcomes, which could lead to improved symptom control, higher levels of patient satisfaction, and better quality of life, alongside reduced health-care and societal costs of managing IBD.

Contributions

All authors conceived of and designed the study. BB, MZ, and ACF collected, analysed, and interpreted all data. ACF and BB drafted the manuscript. All authors commented on drafts of the paper, had full access to all of the data, and approved the final manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

No additional data are available.

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