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TITLE PAGE

Title: Prevalence of Symptoms of Anxiety and Depression in Inflammatory Bowel Disease: Systematic Review and Meta-analysis

Short running head: Symptoms of Anxiety and Depression in Inflammatory Bowel Disease: A Meta-analysis

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Abbreviations:

CD	Crohn's disease
CI	confidence interval
IBD	inflammatory bowel disease

OR	odds ratio
UC	ulcerative colitis

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ABSTRACT

Background: Inflammatory bowel disease (IBD) is a lifelong condition without a cure. Due to bidirectional communication, via the gut-brain axis, as well as the chronicity of symptoms, impaired quality of life, and reduced social functioning, patients with IBD may experience symptoms of common mental disorders, including anxiety and depression. 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: We conducted a systematic review and meta-analysis examining this issue. MEDLINE (from inception to 30th September 2020), EMBASE, EMBASE Classic (from inception to 30th September 2020), and PSYCINFO (from inception to 30th September 2020) were searched to identify observational studies that reported prevalence of symptoms of anxiety or depression according to validated screening instruments recruiting ≥100 adult ((≥90% aged ≥18 years old) patients with IBD. We excluded studies that only used a structured interview to assess for presence of symptoms of anxiety or depression, and those that did not provide extractable data. Data were extracted from published study reports, and pooled prevalence, odds ratios (OR), and 95% confidence intervals (CIs) were calculated.

Findings: Of 5544 citations evaluated, 77 studies fulfilled eligibility criteria, containing 30,118 patients. Overall, pooled prevalence of symptoms of anxiety was 32.1% (95% CI 28.3%-36.0%) in 58 studies (I^2=96.9%) and pooled prevalence of symptoms of depression was 25.2% (95% CI 22.0%-28.5%) in 75 studies (I^2=97.6%). The OR for symptoms of either anxiety or depression were 1.2-times higher in patients with CD compared with UC (I^2=7.1% for anxiety and I^2=23.5% for depression). Overall, women were more prone to symptoms of common mental disorders, in particular the OR for symptoms of anxiety in women with CD versus men was 2.4 (95% CI 1.5-3.9) (I^2=51.4%). The prevalence of symptoms of anxiety or depression was increased in patients with active IBD (57.6% and 38.9%, respectively),

compared with those with inactive disease (38.1% and 24.2%, respectively). The OR for symptoms of depression in patients with active CD versus patients with inactive disease was 5.6 (95% CI 1.2-26.0) (I^2=86.5%).

Interpretation: We demonstrated a high prevalence of symptoms of common mental disorders in patients with IBD, with up to one-in-three patients affected by symptoms of anxiety and one-in-four depression. Prevalence increased in active disease; one-in-two and one-in-three patients with active disease met criteria for symptoms of anxiety or depression. Encouraging gastroenterologists to screen for, and treat, these disorders might improve outcomes for patients with IBD.

Funding: None

Evidence before this study

As inflammatory bowel disease (IBD) is a lifelong condition without a cure, and due to the chronicity of symptoms, and their impact on quality of life and social functioning, patients with IBD may experience symptoms of common mental disorders, including anxiety and depression. Uncertainties remain about the magnitude of this problem, as well as the strength of the association between symptoms of common mental disorders and the different types of IBD, influence of IBD activity, and impact of sex. A comprehensive search of the medical literature using MEDLINE, EMBASE, EMBASE Classic, and PSYCINFO identified two previous systematic reviews that have examined some of these issues, but the literature search used to inform them only included studies published up to 2014.

Added value of this study

We have conducted a contemporaneous systematic review and meta-analysis to assess prevalence of symptoms of anxiety or depression in adult patients with IBD. We also aimed to investigate whether type of IBD, disease activity, or sex influenced prevalence rates, as well as whether prevalence varied based on the questionnaire, and cut-off, used. Pooled prevalence of symptoms of anxiety in patients with IBD was 32.1%, and pooled prevalence of symptoms of depression was 25.2%, but this varied according to the questionnaire used. Odds of either symptoms of anxiety or depression were 1.2-times higher in patients with CD than UC. The odds of symptoms of anxiety were almost two-times higher in women with IBD compared with men, and more than two-times higher in female patients with CD. Patients with active disease had a more than two-times higher odds of symptoms of anxiety and a more than three-times higher odds of symptoms of depression. The prevalence of symptoms of depression was particularly increased in patients with active CD, compared with those with inactive disease, with a greater than five-times higher odds.

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.

INTRODUCTION

The inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic disorders causing inflammation of the gastrointestinal tract,[1] whose incidence and prevalence are increasing worldwide.[2] They are proposed 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 of patients with IBD,[5,6] a longer life span with a chronic disease is likely to impact on quality of life.[7] For instance, patients with IBD report loss of work productivity and their disease seems to influence career choice and also the decision to retire early.[8]

In addition, as IBD is a lifelong condition without a cure, and due to the chronicity of symptoms, and their impact on quality of life and social functioning, as well as bidirectional communication via the gut-brain axis,[9] patients with IBD may experience psychological illness,[10] including symptoms of common mental disorders and somatization.[11,12] This can further impact adversely on quality of life, and also disease outcomes.[13-17] An analysis of administrative claims data demonstrated that both direct and indirect costs of care were significantly higher in patients with IBD and a co-existent common mental disorder, compared with IBD patients without.[18]

However, although numerous studies have reported on symptoms of anxiety and depression in patients with IBD, these demonstrate greatly varying prevalence rates, up to 80% in some studies.[19,20] Some of this variation may 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 the strength of the association between symptoms of common mental disorders and type of IBD,[13,24,25] the influence of IBD

activity,[26-28] and the impact of sex.[29] Two previous systematic reviews have examined some of these issues,[30,31] but the literature search used to inform them only included studies published up to 2014. Although one of these systematic reviews examined these issues in detail,[30] a meta-analysis was not performed, so pooled estimates of prevalence were not calculated, while the second study performed only a limited number of analyses.[31]

We have conducted a contemporaneous systematic review and meta-analysis to assess prevalence of symptoms of anxiety or depression in adult patients with IBD. We also aimed to investigate whether type of IBD, disease activity, or sex influenced prevalence rates, as well as whether prevalence varied based on the questionnaire, and cut-off, used. Synthesising the existing evidence to provide an estimate of the magnitude of this problem, will hopefully increase awareness among clinicians, facilitating screening of patients in the clinic for evidence of symptoms of anxiety or depression and, if necessary, referring for treatment. Such treatment may 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 (from inception to 30th September 2020), EMBASE CLASSIC and EMBASE (from inception to 30th September 2020), and PSYCINFO (from inception to 30th September 2020) to identify cross-sectional surveys or case-control studies reporting prevalence of symptoms of anxiety or depression in unselected adult patients (≥90% aged ≥18 years) with histologically or radiologically confirmed IBD. To be eligible, studies had to recruit ≥ 100 participants, to minimise the likelihood of overestimating the magnitude of this issue due to 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. These eligibility criteria, which were defined prospectively, are provided in Box 1.

We searched the medical literature using the following terms: *ulcerative colitis or colitis, Crohn's disease, inflammatory bowel diseases* (both as a medical subject headings and free text terms). We combined these using the set operator AND with studies identified with the following free text terms: *anxiety, depression, mood disorders*. There were no language restrictions. We screened titles and abstracts of all citations identified by our search for potential suitability and retrieved those that appeared relevant to examine them in more detail. 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) between 2010 and 2020 were also hand-searched. A recursive search of the literature was performed using bibliographies of all relevant studies. Where there appeared to be multiple study reports from the same group of patients, we contacted study authors to clarify this 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, therefore, maximise available studies. If studies did not report data for extraction, and authors were not contactable, we did not consider them eligible for inclusion. Eligibility assessment was performed independently by two investigators (BB and MZ), 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 kappa statistic. Ethical approval was not required.

Data Analysis

Data were extracted independently by two investigators (BB and MZ) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA), again with any discrepancies resolved by the opinion of a third investigator (ACF). The following data were collected for each study: country, setting (community, primary, secondary, or tertiary care, or national registry), questionnaire, and cut-off, 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 (UC, CD, or IBD-unclassified (IBD-U)), 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 with 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, convenience samples of controls who were outpatients attending a Gastroenterology clinic were excluded). We assessed study quality for 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 assessed heterogeneity between studies using the I^2 statistic. The I^2 measure ranges between 0% and 100%. Values of 25% to 49%, 50% to 74%, and ≥75% are typically considered low, moderate, and high levels of heterogeneity, respectively.[33] We conducted subgroup analyses according to the different types of IBD (UC, CD, or IBD-U), questionnaire used and, where multiple studies used the same questionnaire, cut-off used to define the presence of symptoms of anxiety or depression, sex, and disease activity. Finally, we compared prevalence of symptoms of anxiety or depression according to type of IBD (UC, CD, or IBD-U), sex, and disease activity using an odds ratio (OR), with a 95% confidence interval (CI). We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England) 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] where ≥10 studies were available.[35]

Role of the Funding Source

No funding was received. All authors had full access to all of the data and accept responsibility to submit for publication.

RESULTS

The search strategy generated 5544 citations. From these we identified 260 separate articles that appeared to be relevant to the study question. In total, 77 of these articles fulfilled the eligibility criteria (Figure 1), containing 30,118 patients with IBD recruited from 23 different countries.[11,13,17,19,20,22,24,28,36-104] Almost all studies were conducted in a single country, with the exception of a multi-national survey including 33 countries.[79] Eleven studies recruited unselected 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 for patients with UC or CD separately, five studies recruited only patients with UC,[40,41,49,65,79] and four studies only patients with CD.[46,53,61,101] No study recruited only patients with IBD-U, and none of the included studies reported prevalence of symptoms of anxiety or depression for patients with IBD-U separately. Only two studies reported the prevalence of symptoms of anxiety in healthy controls,[85,89] and five studies reported the prevalence of symptoms of depression in these subjects.[40,42,63,85,89] Two of these studies scored five on the Newcastle-Ottawa scale,[63,89] two scored four,[42,85] and one scored three.[40] Agreement between investigators for assessment of study eligibility was excellent (kappa statistic = 0.85). Detailed characteristics of all included studies are provided in the web extra material (appendix pages 1 to 5)**.**

Pooled prevalence of Symptoms of Anxiety and Depression

The pooled prevalence of symptoms of anxiety in patients with IBD, based on 58 studies, [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] which contained 18,915 patients was 32.1% (95% CI 28.3% to 36.0%; I^2=96.9%, p<0.001). The lowest pooled prevalence of symptoms of anxiety reported in patients with IBD was 10.5% in two Spanish studies (716 and 793 patients respectively),[57,59] while 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 (2000-2005, 2006-2010, 2011-2105, 2016-2020) (appendix page 6). When we considered UC or CD separately, the pooled prevalence of symptoms of anxiety was 34.2% (95% CI 27.1% to 41.8%; I^2=95.6%, p<0.001) in 22 studies containing 3,915 patients with UC,[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% (95% CI 30.7% to 42.9%; I^2=93.8%, p<0.001) in 21 studies recruiting 4,318 patients with CD. [11,13,19,24,28,39,45-47,50,59,61,64,70,72,76,80,84,85,92,95] The OR for symptoms of anxiety in patients with CD versus patients with UC, in 19 studies that reported prevalence in both CD and UC 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 to 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 symptoms of depression among 29,438 patients with IBD, recruited by 75 studies,[11,13,17,19,20,22,24,28,36-65,68-104,]was 25.2% (95% CI 22.0% to 28.5%; I^2=97.6%, p<0.001). The lowest prevalence of symptoms of depression reported in patients with IBD was 10.5% in one Greek study (153 patients),[85] and the highest 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 page 6). The pooled prevalence of symptoms of depression in 8,219 patients with UC, reported in 31 studies,[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% to 29.9%; I^2=97%, p<0.001), compared with 24.8% (95% CI 20.7% to 29.3% I^2=94.7%, p<0.001) in 8692 patients with CD, in 30 studies (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 symptoms of depression in patients with CD versus patients with UC, in 26 studies that reported prevalence in both CD and UC 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 to 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 symptoms of anxiety in healthy controls, based on two studies including only 142 subjects,[85]·[89] was 10.4% (95% CI 5.5% to 16.6%, I^2=14.9%, p=0.28). The OR for symptoms of anxiety in patients with IBD versus healthy controls in these two studies was 2.6 (95% CI 1.4 to 4.9) with no heterogeneity between studies (I^2=0%, p=0.65).[85,89] The pooled prevalence of symptoms of depression in healthy controls, based on five studies including 694 subjects, was 17.9% (95% CI 8.4% to 30.2%, I^2=92.6%, p<0.001).[40,42,63,85,89] The OR for symptoms of depression in patients with IBD versus healthy controls in these five studies was 1.9 (95% CI 1.4 to 2.7) with no significant heterogeneity between studies (I^2=34.3%, p=0.19).[40,42,63,85,89]

Prevalence of Symptoms of Common Mental Disorders According to the Questionnaire Used

Of the 58 studies reporting the prevalence of symptoms of anxiety 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% to 37.2%; I^2=96.5%, p<0.001). Among studies that used other questionnaires, the lowest prevalence was reported in one study using the Beck anxiety and depression scale (6.6%; 95% CI 4.3% to 9.5%),[36] and the highest pooled prevalence in two studies using the state-trait anxiety inventory questionnaire (57.8%; 95% CI 12.3% to 96.0%).[19,67]

Of the 75 studies reporting the prevalence of symptoms of depression in patients with IBD, 44 administered 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 symptoms of depression in these studies was 21.6% (95% CI 18.4% to 24.9%; I^2=96%, p<0.001). Among the remaining

articles that used different questionnaires, the lowest pooled prevalence was reported in three studies using the Zung self-rating depression scale (21.0%; 95% CI 6.9% to 40.1%),[19,85,89] and the highest in one study using the Hamilton depression rating scale questionnaire (88.9%; 95% CI 83.4% to 93.1%).[20] Further subgroup analyses are reported in Table 1. Heterogeneity persisted even when studies that used the same cut-off on the HADS to define the presence of symptoms of anxiety or depression were pooled separately (appendix pages 7 to 8). Prevalence of symptoms of anxiety or depression using a HADS score of ≥11, the cut-off recommended by the original investigators,[105] was 21.3% (95% CI 17.2% to 25.6%) and 10.6% (95% CI 8.6% to 12.8%), respectively.

Prevalence of Symptoms of Common Mental Disorders According to Sex

There were seven studies that reported the prevalence of symptoms of anxiety in patients with IBD according to sex.[17,39,46,50,61,80,85] The pooled prevalence of symptoms of anxiety was higher in women with IBD (33.8%; 95% CI 26.5% to 41.5%) compared with men (22.8%; 95% CI 18.7% to 27.2%) (Table 2A). The OR for symptoms of anxiety in women with IBD, versus men, in these seven studies was 1.7 (95% CI 1.2 to 2.3), with moderate heterogeneity between studies (I^2 =64.3%, p=0.01) (Table 3A). When the same analyses were conducted on four studies reporting prevalence of symptoms of anxiety in patients with CD,[39,46,61,80] and two studies in patients with UC,[39,80] separately the pooled prevalence of symptoms of anxiety was higher in women with CD (37.8%; 95% CI 25.1% to 51.5%) compared with men (19.8%; 95% CI 16.0% to 24.0%). Conversely, prevalence of symptoms of anxiety was slightly higher in men with UC (18.0%; 95% CI 13.1% to 23.5%) compared with women (14.6%; 95% CI 2.8% to 33.3%) (Table 2A). The OR for symptoms of anxiety in women with CD versus men was 2.4 (95% CI 1.5 to 3.9, I^2=51.4%, p=0.10),

while in women with UC versus men it was 0.69 (95% CI 0.13 to 3.71; I^2=82.0%, p=0.02) (Table 3A).

There were 12 studies reporting prevalence of symptoms of depression 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% to 27.6%) compared with men (16.2%; 95% CI 12.6% to 20.3%) (Table 2A). The OR for symptoms of depression in women with IBD versus men in these 12 studies was 1.3 (95% CI 1.0 to 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 3A). Subgroup analyses according to type of IBD confirmed a higher pooled prevalence of symptoms of depression in women with CD (22.6%; 95% CI 10.5% to 37.6%) compared with men (14.7%; 95% CI 9.8% to 20.3%) (OR for women with CD versus men = 1.6; 95% CI 0.8 to 3.1; I^2=66.5%, p=0.02). However, prevalence of symptoms of depression was higher in men with UC (12.3%; 95% CI 5.0 to 22.2) compared with women (10.7%; 95% CI 6.5 to 15.9) (OR for women with UC versus men = 0.8; 95% CI 0.2 to 3.5; I^2=74.1%, p=0.05) (Tables 2A and 3A).

Prevalence of Symptoms of Common Mental Disorders According to Disease Activity

Criteria used to define disease activity in the 19 studies that reported prevalence of symptoms of anxiety or depression in those with active or inactive disease are reported in the web extra material (appendix page 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 symptoms of anxiety in patients with IBD with active disease was 57.6% (95% CI 30.9% to 45.7%) in eight studies,[17,19,43,49,65,70,84,95] and the pooled prevalence in patients with IBD with inactive disease was 38.1% (95% CI 30.9% to 45.7%) in 15 studies (Table 2B).[11,17,19,20,28,43,49,61,65,70,72,84,92,95,104] The OR for symptoms of

anxiety in active versus inactive disease, in 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 to 4.1), with high levels of heterogeneity between studies (I^2 = 77.2%, p<0.001) (Table 3B). Subgroup analyses in patients with CD or UC separately demonstrated that the pooled prevalence of symptoms of anxiety in active CD was 74.7% (95% CI 53.2% to 91.2%) in three studies,[19,70,84] and 38.7% (95% CI 33.3% to 44.2%) in inactive CD in eight studies (Table 2B).[11,19,28,61,70,72,84,92] In active UC the pooled prevalence of symptoms of anxiety was 70.8% (95% CI 49.2% to 88.4%) in five studies,[19,49,65,70,84] and in inactive UC it was 38.7% (95% CI 27.8% to 50.3%) in nine studies (Table 2B).[11,19,28,49,65,70,72,84,92] Odds ratios for prevalence of symptoms of anxiety in active versus inactive CD and UC are provided in Table 3B.

Regarding symptoms of depression, the pooled prevalence in patients with IBD with active disease was 38.9% (95% CI 26.2% to 52.3%) in 11 studies,[17,19,49,53,63,65,70,84,88,95,101] and in those with inactive disease it was 24.2% (95% CI 14.7% to 35.3%) in 18 studies (Table2B).[11,17,19,20,28,49,53,61,63,65,70,72,84,88,92,95,101,104] The OR for symptoms of depression in active versus inactive IBD was 3.1 (95% CI 1.9 to 4.9) in eleven studies that reported prevalence in both active and 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<0.001), but no evidence of funnel plot asymmetry (Egger test, p=0.84) (Table 3B). Subgroup analyses in patients with CD demonstrated a pooled prevalence of symptoms of depression in active disease of 51.0% (95% CI 31.0% to 70.8%) in five studies,[19,53,70,84,101] and 20.2% (95% CI 12.0% to 30.0%) in inactive CD in ten studies.[11,19,28,53,61,70,72,84,92,101] In active UC prevalence of symptoms of depression was 41.3% (95% CI 26.6% to 56.8%) in five studies,[19,49,65,70,84] and 21.8% (95% CI 13.7% to 31.1%) in

inactive UC in nine studies (Table 2B).[11,19,28,49,65,70,72,84,92] Odds ratios for prevalence of symptoms of depression in active versus inactive CD and UC are provided in Table 3B.

DISCUSSION

This systematic review and meta-analysis has assembled 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 symptoms of anxiety in patients with IBD of 32.1%, based on 58 studies, while pooled prevalence of symptoms of depression was 25.2% in 75 studies. The prevalence of both symptoms of anxiety and depression was significantly higher than among healthy controls without IBD. Using the more stringent cut-off of a HADS score of ≥11 on either scale led to a lower prevalence for symptoms of anxiety or depression, 21.3% and 10.6%, respectively. Although pooled prevalence rates of symptoms of anxiety or depression were similar among patients with either CD or UC, the odds of either symptoms of anxiety or symptoms of depression were 1.2-times higher in patients with CD. Prevalence of symptoms of common mental disorders varied according to the questionnaire used. For example, prevalence of symptoms of anxiety in patients with IBD ranged from 6.6%, when the Beck anxiety scale was used in one study, to 55.2% when the patient-reported outcomes measurement information system questionnaire was used in two studies. However, 44 of 58 studies reporting prevalence of symptoms of anxiety used the HADS questionnaire, with a pooled prevalence of 33.2%. Similarly, prevalence of symptoms of depression ranged from 14.9%, when the short-form 36 questionnaire was administered in one study, to 88.9% when the Hamilton depression rating scale questionnaire was applied in another study, although 44 out of 75 studies used the HADS questionnaire with a pooled prevalence of 21.6%. The pooled prevalence of symptoms of anxiety and depression were almost two-times higher in women with IBD compared with men, and more than two-times higher in female patients with CD. Moreover, patients with active disease had a significantly higher prevalence of symptoms of anxiety and depression, compared with patients with inactive disease, with a more than two-times higher odds of symptoms of anxiety and a more

than three-times higher odds of symptoms of depression. The prevalence of symptoms of depression was particularly increased in patients with active CD, compared with those with inactive disease, with a greater than five-times higher odds.

We used a contemporaneous search strategy to maximise likelihood of identifying pertinent literature. Judging of study eligibility and data extraction were carried out by two investigators independently, with discrepancies resolved by consensus. We included data from eligible foreign language articles, after translation, to be as inclusive as possible. 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 influence of heterogeneity on our results, we performed 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 include the fact that there was significant heterogeneity between studies in all analyses, which was not explained by the subgroup analyses we conducted. There was variability in questionnaires used. It may be that these different approaches to collecting data led to different estimates of the prevalence of symptoms of common mental disorders. In addition, even where identical questionnaires were used, cut-off values to define presence of symptoms of anxiety or depression were not consistent between all studies, which may have contributed to the variation observed. However, when we conducted subgroup analyses based on identical cut-offs on the HADS questionnaire, heterogeneity persisted. Another source of variation might be that data were from 23 different countries, and perhaps both symptoms of anxiety and depression prevalence varied based on the country where they were collected. Further, disease activity was associated with prevalence of symptoms of both anxiety and depression, but most studies did not report prevalence data separately based on disease

activity. However, given that the heterogeneity persisted even when the analysis was limited to studies that recruited the same type of IBD, studies that applied the same questionnaire, reported prevalence of symptoms of anxiety and depression in patients with active and inactive disease separately, or were published in the same 5-year period, this suggests the variation that we observed between studies is genuine, and relates to other factors that were not examined by individual studies. This has led some investigators to avoid performing a meta-analysis in this area,[30] although others have done so.[31] A possible and plausible explanation for variations in our findings may be the lack 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, there were only five studies reporting these data.[40,42,63,85,89] Finally, we included cross-sectional and case-control studies, thus, causality cannot be implied from our results.

Overall, our meta-analysis is in keeping with the previous literature on this subject, with conflicting data and divergent opinions on the psychological impact of IBD. One point of controversy touches on the question of whether symptoms of common mental disorders are more likely with CD than UC. Some studies have observed an association between symptoms of common mental disorders and CD, but not UC.[13,25,38] Nordin and colleagues, in their cross-sectional study on 492 patients with IBD, found a high rate of symptoms of anxiety or depression in CD, but not UC, and hypothesised that this may result from more severe somatic symptoms in CD.[38] Conversely, other studies showed that patients with both CD and UC were equally prone to symptoms of common mental disorders.[24,106,107] Our results, pooling data from all available studies, demonstrated that although prevalence of symptoms of anxiety and depression were similar between patients with CD and UC, there was a slightly increased risk in patients with CD compared with those with UC. Previous studies have also questioned whether an association between sex and symptoms of common mental

disorders is present, with some studies demonstrating women to be more prone to these symptoms.[29,80] In our meta-analysis, we confirmed that the odds of both symptoms of anxiety and depression was higher in women with IBD compared with men, and, especially, that women with CD were more likely to meet criteria for symptoms of anxiety compared with men.

A further area of uncertainty is whether there is an association between symptoms of common mental disorders and disease activity. Tabatabaien *et al.* reported that the severity of psychological comorbidity was strongly associated with disease activity.[26] However, it has been demonstrated that both symptoms of anxiety and depression are not only common in patients with active disease, but also reported by between 25% and 40% of patients in remission.[27,28] Moreover, a recent meta-analysis, aiming to investigate the impact of depressive state on disease course in IBD demonstrated that in CD this may be associated with a subsequent deterioration in disease course, but not in UC, and that there were 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 a higher odds of both symptoms of anxiety and depression in patients with active disease, suggesting these patients are more likely to demonstrate symptoms of common mental disorders than patients with inactive disease. However, it is worth underlining 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 may be an overestimate, and could relate to higher levels of symptom-reporting *per se* in those who also met clinical criteria for active disease.

Another critical issue is that symptoms of common mental disorders such as anxiety or depression are difficult to assess in patients with IBD as, to date, no disease-specific

instruments to measure these disorders have been validated. This may 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] the HADS was the most commonly 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 presence of common mental disorders, as they measure symptoms rather than actual disorders. One study demonstrated a 60% agreement between these and a physician diagnosis of a common mental disorder in patients with IBD.[110] The latter are only able to be established via a psychiatric or psychological interview. However, these proxies are practical, often used and widely accepted in studies like this. Until we have more precise, standardised tools to quantify both the psychological and inflammatory aspects of IBD together, it is likely that controversies regarding the link between common mental disorders and IBD will remain. Symptoms of common mental disorders are clearly a substantial issue in patients with IBD, who had a significantly higher prevalence of symptoms of anxiety and depression than healthy controls in our meta-analysis, and in a previous systematic review by Mikocka-Walus *et al.*[30] However, in the latter study although the authors reported that the rates of symptoms of anxiety for healthy controls ranged from 7.6% to 16.3%, which were lower than those reported among patients with IBD, findings for depression were more heterogeneous with nine studies reporting higher rates in patients with IBD than in controls, and two studies reporting the opposite.[30]

The high prevalence of symptoms of common mental disorders in patients with IBD, confirmed by our meta-analysis, has been used to support the premise that a patient's

psychology might play a role in both the development and clinical course of IBD.[16,111,112] In fact, a recent nested case-control study, including 19,555 patients, found that individuals with UC and CD had a higher prevalence of depression than matched controls without IBD in the years prior to their diagnosis.[111] Likewise, a previous cohort study observed that patients with a history of depression were more likely to be diagnosed subsequently with IBD, and that antidepressants significantly protected against this.[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 may be important in improving treatment adherence, and therefore enhancing long-term patient outcomes. 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 demonstrated a high prevalence of symptoms of common mental disorders in IBD, with up to one-in-three patients affected by symptoms of anxiety and one-in-four by symptoms of depression. Prevalence increased with disease activity; one-in-two and one-in-three patients with active disease met criteria for symptoms of anxiety or depression. Our results provide estimates of the magnitude of these issues in patients with IBD, which may provide clearer evidence 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 screening tools. Encouraging gastroenterologists to detect and treat these disorders might improve outcomes, leading to improved symptom control, higher levels of patient satisfaction, better quality of life, and reduced health service and societal costs of managing IBD.

Box 1: Eligibility Criteria

Cross-sectional surveys or case-control studies.

Participants not specially selected.

Adults (>90% of participants aged ≥18 years) with histologically or radiologically confirmed inflammatory bowel disease (Crohn's disease, ulcerative colitis, inflammatory bowel disease-unclassified).

Reported the number of patients with IBD with symptoms of anxiety or depression according to a validated questionnaire (e.g. hospital anxiety and depression scale).

Sample size of ≥100 participants.

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AUTHOR CONTRIBUTIONS

BB, MZ, CJB, EVS, and ACF conceived and drafted the study. BB, MZ, and ACF collected, analysed, and interpreted all data. ACF and BB drafted the manuscript. BB, MZ, CJB, EVS, and ACF commented on drafts of the paper. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS

Brigida Barberio: none. Mohammad Zamani: none. Christopher J. Black: none. Edoardo V. Savarino: none. Alexander C. Ford: none.

ETHICS COMMITTEE APPROVAL

Not required.

DATA SHARING STATEMENT

No additional data available.

REFERENCES

[1] Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet 2007;369:1627–40.

[2] Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;390:2769–78.

[3] Choy MC, Visvanathan K, De Cruz P. An overview of the innate and adaptive immune system in inflammatory bowel disease. Inflamm Bowel Dis 2017;23:2–13.

[4] Walker AW, Sanderson JD, Churcher C, et al. High-throughput clone library analysis of the mucosa-associated microbiota reveals dysbiosis and differences between inflamed and non-inflamed regions of the intestine in inflammatory bowel disease. BMC Microbiol 2011;11.

[5] Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. J Crohn's Colitis 2017;11:769–84.

[6] Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: Medical treatment. J Crohn's Colitis 2020;14:4–22.

[7] Marinelli C, Savarino E, Inferrera M, Lorenzon G, Rigo A, Ghisa M, et al. Factors Influencing Disability and Quality of Life during Treatment: A Cross-Sectional Study on IBD Patients. Gastroenterol Res Pract 2019. https://doi.org/10.1155/2019/5354320.

[8] Topal F, Camyar H, Yuksel ES, Gunay S, Topal F, Gür EÖ. Work Productivity Loss in Inflammatory Bowel Disease Patients in Turkey. Gastroenterol Res Pract 2020. https://doi.org/10.1155/2020/6979720.

[9] Gracie DJ, Hamlin PJ, Ford AC. The influence of the brain–gut axis in inflammatory bowel disease and possible implications for treatment. Lancet Gastroenterol Hepatol

2019;4:632–42.

[10] Drossman DA, Leserman J, Madeline Mitchell C, Li Z, Zagami EA, Patrick DL. Health status and health care use in persons with inflammatory bowel disease - A national sample. Dig Dis Sci 1991;36:1746–55.

[11] Farrokhyar F, Marshall JK, Easterbrook B, Irvine JE. Functional gastrointestinal disorders and mood disorders in patients with inactive inflammatory bowel disease: Prevalence and impact on health. Inflamm Bowel Dis 2006;12:38–46.

[12] Hyphantis TN, Tomenson B, Bai M, Tsianos E, Mavreas V, Creed F. Psychological distress, somatization, and defense mechanisms associated with quality of life in inflammatory bowel disease patients. Dig Dis Sci 2010;55:724–32.

[13] Mikocka-Walus A, Pittet V, Rossel JB, von Känel R. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. Clin Gastroenterol Hepatol 2016;14:829-835.e1.

[14] Gaines LS, Slaughter JC, Horst SN, et al. Association between affective-cognitive symptoms of depression and exacerbation of Crohn's disease. Am J Gastroenterol 2016;111:864–70.

[15] Mardini HE, Kip KE, Wilson JW. Crohn's disease: A two-year prospective study of the association between psychological distress and disease activity. Dig Dis Sci 2004;49:492–7.

[16] Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain–Gut Interactions in Patients With Inflammatory Bowel Disease. Gastroenterology 2018;154:1635-1646.e3.

[17] Narula N, Pinto-Sanchez MI, Calo NC, et al. Anxiety but not depression predicts poor outcomes in inflammatory bowel disease. Inflamm Bowel Dis 2019;25:1255–61.

[18] Szigethy E, Murphy SM, Ehrlich OG, et al. Mental Health Costs of Inflammatory

Bowel Diseases. Inflamm Bowel Dis 2021;27:40–8.

[19] Addolorato G, Mirijello A, D'Angelo C, et al. State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. Int J Clin Pract 2008;62:1063–9.

[20] Trikos L, Jovanovic A, Bojic D, Gligorijevic V, Jojic N. Depression and anxiety in inflammatory bowel disease in remission. Eur Psychiatry 2012;27:1.

[21] Yamamoto-Furusho JK, Sarmiento-Aguilar A, García-Alanis M, et al. Hospital Anxiety and Depression Scale (HADS): Validation in Mexican Patients with Inflammatory Bowel Disease. Gastroenterol Hepatol 2018;41:477–82.

[22] Clark NR, Horst SN, Armstrong S, et al. Depression and Inflammatory Bowel Disease Patients: A Tertiary Care Center Experience. Gastroenterology 2011;140:S-784.

[23] Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ. Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: A literature review. Inflamm Bowel Dis 2007;13:225–34.

[24] Goodhand JR, Wahed M, Mawdsley JE, Farmer AD, Aziz Q, Rampton DS. Mood disorders in inflammatory bowel disease: Relation to diagnosis, disease activity, perceived stress, and other factors. Inflamm Bowel Dis 2012;18:2301–9.

[25] Andrews H, Barczak P, Allan RN. Psychiatric illness in patients with inflammatory bowel disease. Gut 1987;28:1600–4.

[26] Tabatabaeian M, Afshar H, Roohafza HR, et al. Psychological status in Iranian patients with ulcerative colitis and its relation to disease activity and quality of life. J Res Med Sci 2015;20:577–84.

[27] Iglesias-Rey M, Barreiro-de Acosta M, Vazquez I, Figueiras A, Nieto L, Lorenzo A. Psychological impact of Crohn's disease on patients in remission: anxiety and

depression risks - PubMed. Rev Esp Enferm Dig 2009;101–4:249–57.

[28] Kim ES, Cho KB, Park KS, et al. Predictive factors of impaired quality of life in korean patients with inactive inflammatory bowel disease: Association with functional gastrointestinal disorders and mood disorders. J Clin Gastroenterol 2013;47:e38–44.

[29] Maconi G, Gridavilla D, Viganò C, et al. Perianal disease is associated with psychiatric co-morbidity in Crohn's disease in remission. Int J Colorectal Dis 2014;29:1285–90.

[30] Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. Inflamm Bowel Dis 2016;22:752–62.

[31] Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review. J Psychosom Res 2016;87:70–80.

[32] Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses n.d. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[33] Higgins J, Thompson S, Deeks J, Douglas G. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60.

[34] Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997;315:629-34.

[35] Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:1–8.

[36] Sirin G, Celebi A, Senturk O, Hülagu S. Is depression associated with more emergency visits in inflammatory bowel disease? J Crohn's Colitis 2014;8:S146.

[37] Visser M, Geelen A, Pot G, et al. Stress, Anxiety and Depression in Patients with Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS). J Crohn's Colitis Suppl 2008;2:15–6.

[38] Nordin K, Påhlman L, Larsson K, Sundberg-Hjelm M, Lööf L. Health-related quality of life and psychological distress in a population-based sample of Swedish patients with inflammatory bowel disease. Scand J Gastroenterol 2002;37:450–7.

[39] Janke KH, Klump B, Gregor M, Meisner C, Haeuser W. Determinants of life satisfaction in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:272–86.

[40] Costa A, Chaves EC. Processos de enfrentamento do estresse e sintomas depressivos em pacientes portadores de retocolite ulcerativa idiopática. Rev Esc Enferm USP 2006;40.4:507–14.

[41] Rutter MD, Saunders BP, Wilkinson KH, Schofield G, Forbes A. Intangible costs and benefits of ulcerative colitis surveillance: A patient survey. Dis Colon Rectum 2006;49:1177–83.

[42] Lerebours E, Gower-Rousseau C, Merle V, et al. Stressful life events as a risk factor for inflammatory bowel disease onset: A population-based case-control study. Am J Gastroenterol 2007;102:122–31.

[43] Larsson K, Lööf L, Rönnblom A, Nordin K. Quality of life for patients with exacerbation in inflammatory bowel disease and how they cope with disease activity. J Psychosom Res 2008;64:139–48.

[44] Miehsler W, Weichselberger M, Öfferlbauer-Ernst A, et al. Which patients with IBD need psychological interventions? A controlled study. Inflamm Bowel Dis 2008;14:1273–80.

[45] Alshumrany M, Van Langenberg D, Holtmann G, Hetzel D, Andrews J. Comparative Complexity of Crohn's Disease (CD) Compared to Ulcerative Colitis (UC) in a

Metropolitan Hospital Setting. Effects of Gender and Disease Activity. Gastroenterology 2009;1365(Suppl:A-656).

[46] Brandi MT, Ribeiro MS, Chebli LA, et al. Psychological distress in Brazilian Crohn's disease patients: Screening, prevalence, and risk factors. Med Sci Monit 2009;15.

[47] Hardt J, Muche-Borowski C, Conrad S, Balzer K, Bokemeyer B, Raspe H. Chronisch entzündliche darmerkrankungen als multifokale erkrankungen: Körperliche und psychosoziale probleme von patienten mit CED. Ergebnisse eines fragebogen-surveys. Z Gastroenterol 2010;48:381–91.

[48] Schlesinger N, Hassett AL, Savage SV, Das KM. Fibromyalgia-Like Symptoms in Inflammatory Bowel Disease. Gastroenterology 2010;138:S-533.

[49] Fakheri H, Zarghami M, Shahsavari M, Bari Z, Yazdani J. Evaluation of the correlation between anxiety, depression and personality traits with immunologic markers (ANCAs) in ulcerative colitis. Iran Assoc Gastroenterol Hepatol Shiraz Univ Med Sci 2011;16:91–7.

[50] Häuser W, Janke K-H, Klump B, Hinz A. Anxiety and depression in patients with inflammatory bowel disease. Inflamm Bowel Dis 2011;17:621–32.

[51] Vogelaar L, Van 't Spijker A, Kuipers EJ, van der Woude CJ. Determinants Contributing to Fatigue in IBD Patients. Gastroenterology 2011;140:S-783-S-784.

[52] Bennebroek Evertsz' F, Thijssens NAM, Stokkers PCF, et al. Do Inflammatory Bowel Disease patients with anxiety and depressive symptoms receive the care they need? J Crohn's Colitis 2012;6:68–76.

[53] Cho OH, Yoo YS, Yang SK. Depression and risk factors in patients with Crohn's disease. J Korean Acad Nurs 2012;42:207–16.

[54] Bokemeyer B, Hardt J, Hüppe D, et al. Clinical status, psychosocial impairments, medical treatment and health care costs for patients with inflammatory bowel disease

(IBD) in Germany: An online IBD registry. J Crohn's Colitis 2013;7:355–68.

[55] Selinger CP, Lal S, Eaden J, et al. Better disease specific patient knowledge is associated with greater anxiety in inflammatory bowel disease. J Crohn's Colitis 2013;7.

[56] Zhang CK, Hewett J, Hemming J, et al. The influence of depression on quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis 2013;19:1732–9.

[57] Barreiro de Acosta M, Iglesias M, Ferreiro R, Lorenzo A, Dominguez-Muñoz JE. Influence of anxiety and depression in the clinical course of inflammatory bowel disease patients. J Crohn's Colitis 2014;8:S149.

[58] Cohen BL, Zoëga H, Shah SA, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. Aliment Pharmacol Ther 2014;39:811–22.

[59] Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, et al. Psychological Factors Are Associated with Changes in the Health-related Quality of Life in Inflammatory Bowel Disease. Inflamm Bowel Dis 2013;20:1.

[60] Loomes DE, Dittrich AE, Madsen K, et al. Effect of Anti-TNFα Therapy on Prevalence of Depression in Patients With Inflammatory Bowel Disease. Gastroenterology 2014;146:S-779.

[61] Maconi G, Gridavilla D, Viganò C, et al. Perianal disease is associated with psychiatric co-morbidity in Crohn's disease in remission. Int J Colorectal Dis 2014;29:1285–90.

[62] Victor C, Jana H, Gregory T, et al. Clinical Predictors of Moderate Depression and Suicidality in Adults With IBD. Inflamm Bowel Dis 2014;20:S5.

[63] Bel LGJ, Vollebregt AM, Van der Meulen-de Jong AE, et al. Sexual Dysfunctions in

Men and Women with Inflammatory Bowel Disease: The Influence of IBD-Related Clinical Factors and Depression on Sexual Function. J Sex Med 2015;12:1557–67.

[64] Freitas TH, Andreoulakis E, Alves GS, et al. Associations of sense of coherence with psychological distress and quality of life in inflammatory bowel disease. World J Gastroenterol 2015;21:6713–27.

[65] Tabatabaeian M, Afshar H, Roohafza HR, et al. Psychological status in Iranian patients with ulcerative colitis and its relation to disease activity and quality of life. J Res Med Sci 2015;20:577–84.

[66] Barnes EL, Nadkarni A, Levine JS, Alonso Y, Korzenik JR. Unrecognized Psychiatric Disease in Patients with Inflammatory Bowel Disease (IBD): Patients With Worse IBD Specific Patient Reported Outcome Measures Demonstrate Increased Anxiety and Depression Scores Even Without a Psychiatric History. Gastroenterology 2016;150:S166–7.

[67] Bertomoro P, Vettorato MG, Simonetti F, et al. Inflammatory Bowel Disease And Psychological Status: Determinants And Social Consequences. Gastroenterology 2016;150:S1004.

[68] DeBoer A, Evertsz FB, Stokkers PC, et al. Employment status, difficulties at work and quality of life in inflammatory bowel disease patients. Eur J Gastroenterol Hepatol 2016;28:1130–6.

[69] Gauss A, Geib T, Hinz U, et al. Quality of life is related to fecal calprotectin concentrations in colonic Crohn disease and ulcerative colitis, but not in ileal Crohn disease. Med (United States) 2016;95.

[70] Gracie DJ, Williams CJM, Sood R, et al. Poor correlation between clinical disease activity and mucosal inflammation, and the role of psychological comorbidity, in inflammatory bowel disease. Am J Gastroenterol 2016;111:541–51.

[71] Keogh A. Faecal Incontinence in inflammatory bowel disease and its association with anxiety and depression in an Irish tertiary centre. J Crohn's Colitis 2016;10:S496.2-S496.

[72] Kim MC, Jung YS, Song YS, et al. Factors associated with anxiety and depression in Korean patients with inactive inflammatory bowel disease. Gut Liver 2016;10:399–405.

[73] Vachon A, Altman L, Hashash J, et al. Risk Factors for Suicidality Amongst Depressed IBD Patients. Inflamm Bowel Dis 2016;22:S15.

[74] Byrne G, Rosenfeld G, Leung Y, et al. Prevalence of anxiety and depression in patients with inflammatory bowel disease. Can J Gastroenterol Hepatol 2017;2017.

[75] Calloway A, Dalal R, Beaulieu DB, et al. Depressive Symptoms Predict Anti-tumor Necrosis Factor Therapy Noncompliance in Patients with Inflammatory Bowel Disease. Dig Dis Sci 2017;62:3563–7.

[76] Chan W, Shim HH, Lim MS, et al. Symptoms of anxiety and depression are independently associated with inflammatory bowel disease-related disability. Dig Liver Dis 2017;49:1314–9.

[77] Cohen I, Benyamini Y, Tulchinsky H, Dotan I. Illness perceptions and coping with health-related quality of life in patients with inflammatory bowel disease. J Crohn's Colitis 2017;11:S229–30.

[78] Frigstad SO, Høivik M, Jahnsen J, et al. Vitamin D deficiency is not associated with depression in IBD patients. J Crohn's Colitis 2017;11:S444–5.

[79] Ghosh S, Peyrin-Biroulet L, Sensky T, Casellas F, O'Shea C, Pappalardo B. Correlation between physician and patient disease assessments in ulcerative colitis: baseline data from the ICONIC study of 1816 patients in 33 countries. J Crohn's Colitis 2017;11:S259–60.

[80] Huppertz-Hauss G, Høivik ML, Jelsness-Jørgensen LP, Opheim R, Henriksen M, Høie O, et al. Fatigue in a population-based cohort of patients with inflammatory bowel disease 20 years after diagnosis: The IBSEN study. Scand J Gastroenterol 2017;52:351–8.

[81] Luo XP, Mao R, Chen BL, et al. Over-reaching beyond disease activity: The influence of anxiety and medical economic burden on health-related quality of life in patients with inflammatory bowel disease. Patient Prefer Adherence 2017;11:23–31.

[82] Sehgal P, Abrahams E, Ungaro RC, Dubinsky M, Keefer L. Resilience is Associated with Lower Rates of Depression and Anxiety, and Higher Quality of Life in Inflammatory Bowel Disease Patients. Gastroenterology 2017;152:S797–8.

[83] Williet N, Sarter H, Gower-Rousseau C, et al. Patient-reported Outcomes in a French Nationwide Survey of Inflammatory Bowel Disease Patients. J Crohns Colitis 2017;11:165–74.

[84] Calixto RP, Flores C, Francesconi CF. Inflammatory bowel disease: Impact on scores of quality of life, depression and anxiety in patients attending a tertiary care center in brazil. Arq Gastroenterol 2018;55:202–7.

[85] Dimitriadis N, Xanthis D, Paschos P, et al. Psychosexual dysfunction in Greek patients with inflammatory bowel disease in remission. J Crohn s Colitis 2018;12:S374–5.

[86] Henriques D, Baima J, DeBarros J, Jeslei V, Oliveira R. Complementary and Alternative Medicine in Brazilian Patients With Inflammatory Bowel Diseases. Am J Gastroenterol 2018;113:S23.

[87] Kochar B, Barnes EL, Long MD, et al. Depression is associated with more aggressive inflammatory bowel disease. Am J Gastroenterol 2018;113:80–5.

[88] Litster B, Bernstein CN, Graff LA, et al. Validation of the PHQ-9 for Suicidal Ideation in Persons with Inflammatory Bowel Disease. Inflamm Bowel Dis 2018;24:1641–8.

[89] Liu R, Tang A, Wang X, Shen S. Assessment of Quality of Life in Chinese Patients with Inflammatory Bowel Disease and their Caregivers. Inflamm Bowel Dis 2018;24:2039–47.

[90] Navabi S, Gorrepati VS, Yadav S, et al. Influences and impact of Anxiety and Depression in the setting of inflammatory bowel disease. Inflamm Bowel Dis 2018;24:2303–8.

[91] Regueiro M, Click B, Anderson A, et al. Reduced Unplanned Care and Disease Activity and Increased Quality of Life After Patient Enrollment in an Inflammatory Bowel Disease Medical Home. Clin Gastroenterol Hepatol 2018;16:1777–85.

[92] Viganò CA, Beltrami MM, Bosi MF, Zanello R, Valtorta M, Maconi G. Alexithymia and Psychopathology in Patients Suffering From Inflammatory Bowel Disease: Arising Differences and Correlations to Tailoring Therapeutic Strategies. Front Psychiatry 2018;9:324.

[93] Yongwen Ng J, Chauhan U, Armstrong D, et al. A comparison of the prevalence of anxiety and depression between uncomplicated and complex IBD patient groups. Gastroenterol Nurs 2018;41:427–35.

[94] Borren NZ, Tan W, Colizzo FP, et al. Longitudinal Trajectory of Fatigue with Initiation of Biologic Therapy in Inflammatory Bowel Diseases: A Prospective Cohort Study. J Crohn's Colitis 2020;14:309–15.

[95] Bulut EA, Toruner M. The influence of disease type and activity to sexual life and health quality in inflammatory bowel disease. Turkish J Gastroenterol 2019;30:33–9.

[96] Chao CY, Lemieux C, Restellini S, et al. Maladaptive coping, low self-efficacy and disease activity are associated with poorer patient-reported outcomes in inflammatory bowel disease. Saudi J Gastroenterol 2019;25:159–66.

[97] Coates M, Stuart A, Tinsley A, Clarke K, Williams ED, Stine JG. Psychiatric

Outcomes are Significantly Impacted with Inflammatory Bowel Disease and Comorbid Nonalcoholic Fatty Liver Disease. Gastroenterology 2019;156:S-441.

[98] Cronin O, Yang L, Spizzo P, Fehily S, Hair C, Bell S. Anxiety, depression, and disability in patients with inflammatory bowel disease. J Gastroenterol Hepatol 2019;34 (Suppl2:120).

[99] Ferreiro-Iglesias R, Calviño C, Baston I, Dominguez-Munoz JE, Barreiro-de Acosta M. Female gender increases the risk of anxiety and depression in patients with inflammatory bowel disease under anti-TNFα therapy. J Crohn's Colitis 2019;13:S216–S216.

[100] Lores T, Goess C, Mikocka-Walus A, et al. Integrated Psychological Care is Needed, Welcomed and Effective in Ambulatory Inflammatory Bowel Disease Management: Evaluation of a New Initiative. J Crohn's Colitis 2019;13:819–27.

[101] Tang Y, Zhao L, Lei N, Chen P, Zhang Y. Crohn's Disease Patients with Depression Exhibit Alterations in Monocyte/Macrophage Phenotype and Increased Proinflammatory Cytokine Production. Dig Dis 2020;38:211–21.

[102] Wilkinson B, Trick L, Knight A, et al. Factors associated with depression in people with inflammatory bowel disease: The relationship between active disease and biases in neurocognitive processing. Neurogastroenterol Motil 2019;31:1–11.

[103] Eindor-Abarbanel A, Naftali T, Ruhimovich N, et al. Important relation between self-efficacy, sense of coherence, illness perceptions, depression and anxiety in patients with inflammatory bowel disease. Gastroenterology 2020;0:1–7. https://doi.org/10.1136/flgastro-2020-101412.

[104] Mancina RM, Pagnotta R, Pagliuso C, et al. Gastrointestinal symptoms of and psychosocial changes in inflammatory bowel disease: A nursing-led cross-sectional study of patients in clinical remission. Med 2020;56.

https://doi.org/10.3390/medicina56010045.

[105] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–70.

[106] Kurina LM, Goldacre MJ, Yeates D, Gill LE. Depression and anxiety in people with inflammatory bowel disease. J Epidemiol Community Health 2001;55:716–20.

[107] Guthrie E, Jackson J, Shaffer J, Thompson D, Tomenson B, Creed F. Psychological disorder and severity of inflammatory bowel disease predict health-related quality of life in ulcerative colitis and Crohn's disease. Am J Gastroenterol 2002;97:1994–9.

[108] Alexakis C, Kumar S, Saxena S, Pollok R. Systematic review with meta-analysis: the impact of a depressive state on disease course in adult inflammatory bowel disease. Aliment Pharmacol Ther 2017;46:225–35.

[109] Bernstein CN, Zhang L, Lix LM, et al. The Validity and Reliability of Screening Measures for Depression and Anxiety Disorders in Inflammatory Bowel Disease. Inflamm Bowel Dis 2018;24:1867–75.

[110] Lewis K, Marrie RA, Bernstein CN, Graff LA, Patten SB, Sareen J, et al. The Prevalence and Risk Factors of Undiagnosed Depression and Anxiety Disorders among Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2019;25:1674–80.

[111] Blackwell J, Saxena S, Petersen I, Hotopf M, Creese H, Bottle A, et al. Depression in individuals who subsequently develop inflammatory bowel disease: a population-based nested case-control study. Gut 2020;doi:10.1136/gutjnl-2020-322308.

[112] Frolkis A, Vallerand A, Shaheen A, et al. Depression increases the risk of inflammatory bowel disease, which may be mitigated by the use of antidepressants in the treatment of depression. Gut 2018;68.9:1606–12.

[113] Sewitch MJ, Abrahamowicz M, Bitton A, et al. Psychological distress, social support,

and disease activity in patients with inflammatory bowel disease. Am J Gastroenterol 2001;96:1470–9.

[114] López-Sanromán A, Bermejo F. How to control and improve adherence to therapy in inflammatory bowel disease. Aliment Pharmacol Ther 2006;24:45–9.

[115] Lores T, Goess C, Mikocka-Walus A, et al. Integrated Psychological Care Reduces Health Care Costs at a Hospital-Based Inflammatory Bowel Disease Service. Clin Gastroenterol Hepatol 2020. https://doi.org/10.1016/j.cgh.2020.01.030.

Figure 1. Flow Diagram of Assessment of Studies Identified in the Meta-analysis.

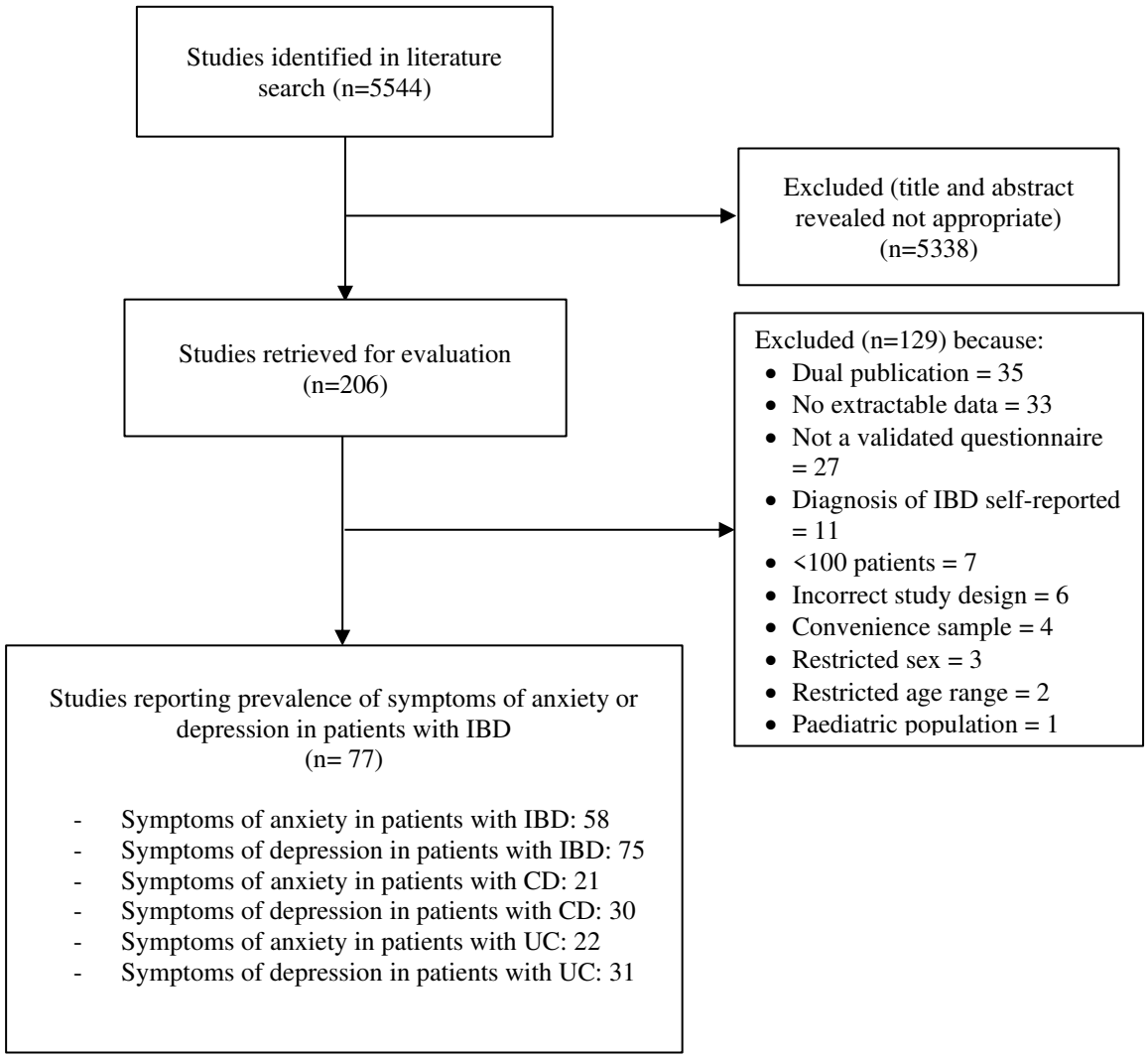

Table 1. Pooled Prevalence of Symptoms of Anxiety or Depression in Patients with IBD According to Questionnaire Used.

	Symptoms of Common Mental Disorder Studied	Questionnaire	Number of Studies	Number of Patients	Pooled Prevalence (%)	95% Confidence Interval (%)	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
		HAMA-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	N/A*	N/A*
		HRQoL	1	156	28.8	21.9 – 36.6	N/A*	N/A*
		Zung SAS	1	104	16.3	9.8 – 24.9	N/A*	N/A*
IBD	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%	<0.0001

		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%	0.41
		Zung SDS	3	392	21.0	6.9 – 40.1	94.4%	<0.0001
		CES-D	1	108	43.5	34.0 – 53.4	N/A*	N/A*
		HAM-D	1	180	88.9	83.4 – 93.1	N/A*	N/A*
		HRQoL	1	156	21.1	15.0 – 28.4	N/A*	N/A*
		QIDS	1	102	40.2	30.6 – 50.4	N/A*	N/A*
		SF36	1	1030	14.9	12.8 – 17.3	N/A*	N/A*
		SIBDQ	1	316	63.9	58.4 – 69.2	N/A*	N/A*
CD	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	N/A*	N/A*
		STAI	1	61	77.0	64.5 – 86.8	N/A*	N/A*
CD	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	N/A*	N/A*
UC	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	N/A*	N/A*
		STAI	1	74	85.1	75.0 – 92.3	N/A*	N/A*
UC	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%	0.64
		CES-D	1	108	43.5	34.0 – 53.4	N/A*	N/A*
		SF-36	1	519	11.4	8.8 – 14.4	N/A*	N/A*

*N/A; not applicable, too few studies to assess heterogeneity

BAI=Beck's Anxiety Scale; BDI = Beck's depression inventory; CES-D = Center for Epidemiologic Studies depression scale; CD = Crohn's disease; 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; I^2 = Inconsistency; IBD = inflammatory bowel disease; PHQ-9 = patient health questionnaire-9; PROMIS = patient-reported outcomes measurement information system; SF-36 = short-form 36 health survey; SIBDQ = short inflammatory bowel disease questionnaire (depression sub-score); STAI = state-trait anxiety inventory; QIDS = quick

inventory of depressive symptomatology; UC = ulcerative colitis; Zung SAS = Zung self-rating anxiety scale; Zung SDS = Zung self-rating depression scale.

Table 2. Pooled prevalence of Symptoms of Anxiety or Depression in Patients with IBD According to Sex (A) and Disease Activity (B).

A.

	Symptoms of Common Mental Disorder Studied	Sex	Number of Studies	Number of Patients	Pooled Prevalence (%)	95% Confidence Interval	I^2	P Value for χ^2
IBD	Anxiety	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
IBD	Depression	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
CD	Anxiety	Women	4	386	37.8	25.1 – 51.5	85.9%	<0.0001
		Men	4	382	19.8	16.0 – 24.0	0	0.59
CD	Depression	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
UC	Anxiety	Women	2	198	14.6	2.8 – 33.3	86.9%	0.0050
		Men	2	208	18.0	13.1 – 23.5	0	0.51
UC	Depression	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

B.

	Symptoms of Common Mental Disorder Studied	Disease Activity*	Number of Studies	Number of Patients	Pooled Prevalence (%)	95% Confidence Interval	I^2	P Value for χ^2
IBD	Anxiety	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
IBD	Depression	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
CD	Anxiety	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
CD	Depression	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
UC	Anxiety	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
UC	Depression	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

CD=Crohn's disease; IBD = inflammatory bowel disease; UC = ulcerative colitis

*Criteria used to define disease activity in individual studies are provided in Supplementary Table 4.

Table 3. Pooled Prevalence and Odds Ratios of Symptoms of Anxiety or Depression in Patients with IBD According to Sex (A) and Disease Activity (B).

A.

	Symptoms of Common Mental Disorder Studied	Number of Studies	Proportion of Men with Symptoms of a Common Mental Disorder (%)	Proportion of Women with Symptoms of a Common Mental Disorder (%)	Odds Ratio for Women Versus Men	95% Confidence Interval	P Value for χ^2
IBD	Anxiety	7	22.8	30.8	1.7	1.2 – 2.3	0.0030
	Depression	12	16.2	19.1	1.3	1.0 – 1.8	0.057
CD	Anxiety	4	19.6	34.5	2.4	1.5 – 3.9	0.00050
	Depression	5	14.1	17.9	1.6	0.8 – 3.1	0.15
UC	Anxiety	2	17.8	18.7	0.7	0.1 – 3.7	0.66
	Depression	2	11.1	10.6	0.8	0.2 – 3.5	0.73

B.

	Symptoms of Common Mental Disorder Studied	Number of Studies	Proportion of Patients with Inactive Disease with Symptoms of a Common Mental Disorder (%)	Proportion of Patients with Active Disease with Symptoms of a Common Mental Disorder (%)	Odds Ratio for Active Disease Versus Inactive Disease	95% Confidence Interval	P Value for χ^2
IBD	Anxiety	8	32.3	46.7	2.5	1.5 – 4.1	0.00060
	Depression	11	17.5	30.4	3.1	1.9 – 4.9	<0.0001
CD	Anxiety	3	43.8	71.4	2.9	1.7 – 4.9	<0.0001
	Depression	5	13.8	40.9	5.6	1.2 – 26.0	0.023
UC	Anxiety	5	40.0	68.0	2.9	1.9 – 4.5	<0.0001
	Depression	5	20.9	40.2	2.9	1.68 – 5.0	<0.0001

CD=Crohn's disease; IBD = inflammatory bowel disease; UC = ulcerative colitis