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# CONTROVERSIES REVISITED: A SYSTEMATIC REVIEW OF THE CO-MORBIDITY OF DEPRESSION AND ANXIETY WITH INFLAMMATORY BOWEL DISEASES

Running Head: Depression and Anxiety in IBD

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**ABSTRACT**

**Background**: While mental health concerns are known to occur commonly for those with inflammatory bowel disease (IBD), the nature of this comorbid relationship has not been systematically reviewed to date. A review in 2007 identified five controversies regarding anxiety/depression rates and various comparators between and within IBD (1). We aimed to systematically analyse and critique the current evidence regarding this comorbidity, providing an update to the five controversies.

**Methods**: Ebscohost Medline, CINAHL, Embase, and PsychINFO were searched between 2005 and 2014 using systematic review methodology. Controlled quantitative studies examining either symptoms or diagnoses of anxiety and depression in IBD were included in the review, with study quality assessed using a scale developed a priori to evaluate observational research.

**Results:** (1) IBD versus healthy controls (pooled mean proportions) (n=13 studies): Anxiety 19.1% vs 9.6%, depression 21.2% vs 13.4%; (2) IBD inactive versus IBD active disease (n=26): Anxiety 28.2% vs 66.4%, depression 19.9% vs 34.7%; (3) ulcerative colitis (UC) versus Crohn's disease (CD) (n=28): Anxiety 31% vs 37%, depression 22% vs 24.4%; (4) IBD versus other chronic medical conditions (n=17): Anxiety 41.9% vs 48.2%, depression 14.5% vs 28.4%; (5) Onset of anxiety/depression before or after IBD onset (n=2): adults more likely to develop anxiety/depression prior to IBD onset, but substantial proportion develop depression after onset; an increased risk for children of developing anxiety/depression following IBD onset.

**Conclusions**: The high rates of anxiety and depression for those with IBD, particularly when disease is active, warrant a systemic approach to screening and treatment.

**Keywords**: anxiety; depression; inflammatory bowel disease; systematic review

## INTRODUCTION

Inflammatory bowel diseases (IBD), of which Crohn's disease (CD) and ulcerative colitis (UC) are subtypes, are chronic relapsing inflammatory conditions of the gastrointestinal tract with unclear aetiology and unpredictable course. Currently, 322 per 100,000 people are diagnosed with CD and up to 505 per 100,000 people are affected by ulcerative colitis around the world (2).

Due to the multiple challenges of this disease, including its incurability, unpredictability, severity of symptoms, as well as surgery and medication side effects, patients' quality of life (QoL) can be profoundly impaired, resulting in a significant psychosocial burden (3-8). In particular, a sizeable proportion of individuals with IBD have been identified as experiencing co-morbid anxiety and/or depression (8, 9). When left untreated, these mental disorders have been linked to more severe IBD symptoms and more frequent IBD flares (7), higher hospitalisation rates (10), and lower compliance with treatment (11) than for individuals without these co-morbidities. However, despite their frequency, psychological symptoms in IBD remain largely untreated. A recent Dutch study (n=231) showed that over 60% of adult IBD patients attending a tertiary care centre with co-morbid anxiety and/or depressive symptoms did not receive adequate care (12). According to a recent national audit in the United Kingdom (UK), only 12% of IBD services have access to clinical psychology via a defined referral pathway (13).

A significant contributor to the lack of recognition for the importance of mental health in IBD is the quality of available evidence. Psychological and psychiatric research in IBD has traditionally been plagued by an abundance of small and often poorly controlled studies with diverse methodologies and settings, which present conflicting findings and consequently make it difficult to draw any firm conclusions from the data. No systematic reviews documenting and clarifying this comorbidity have been published to date and thus no high-level evidence has informed the guidelines on IBD management in relation to the mental health of patients with IBD.

In 2007, the first author and her collaborators published a review paper exploring the comorbidity of anxiety and depression with IBD (1). We endeavoured to answer five major questions related to

rates of depression and anxiety, comparing groups both within IBD (i.e. active and inactive disease; CD and UC; onset before or after IBD onset), and between IBD and other groups (i.e., healthy individuals; individuals with other chronic medical conditions). However, since the quality of the available 17 studies at the time was poor, it was difficult to provide an answer to these questions, other than to confirm that anxiety and depression were highly prevalent within IBD. The academic community was invited to address these controversies by designing high quality studies. Indeed, in recent years, studies of anxiety and depression in IBD have proliferated all over the world, with some excellent large-scale population-based research, for example, providing a rich source of data for better understanding of psychiatric and psychological co-morbidity in the IBD context.

In the present review we systematically identify, analyse and critique the current evidence in relation to the comorbidity of anxiety, depression and IBD, revisiting and providing an updated response to the following questions:

Controversy 1: Are rates of anxiety/depression (both symptoms and disorders) in IBD similar or different to that reported for the healthy/general population controls?

Controversy 2: Are rates of anxiety/depression (both symptoms and disorders) similar or different during active versus inactive IBD?

Controversy 3: Are rates of anxiety/depression (both symptoms and disorders) similar or different in UC versus CD?

Controversy 4: Are rates of anxiety/depression (both symptoms and disorders) in IBD similar or different to that reported in other groups of medically ill patients?

Controversy 5: Do anxiety/depression (both symptoms and disorders) precede and/or follow onset of IBD?

In the previous review, databases were searched for papers published between 1980 and 2005; we are now re-assessing the status of these controversies and reporting progress in the understanding of these relationships by reviewing all available studies published from 2005 until 2014.

## MATERIALS AND METHODS

This systematic review was registered in the International Prospective Register of systematic reviews PROSPERO (CRD42014014960).

### Types of studies

Studies meeting the selection criteria listed below were included.

*Inclusion criteria*

- Studies concerning IBD (including Crohn's disease, ulcerative colitis and indeterminate colitis) diagnosed using any well-established criteria (e.g. Montreal classification);
- Studies examining either symptoms (based on validated screening scales e.g. the Hospital Anxiety and Depression Scale (HADS)) or diagnosis (based on a clinical interview such as the Structured Clinical Interview for DSM (SCID)) of anxiety and depression;
- Studies with either adult or paediatric populations;
- Studies published between 2005 and 2014;
- Controlled studies, including randomised controlled trials (baseline data only), with any of prospective, retrospective and cross-sectional designs;
- Peer-reviewed papers.

*Exclusion criteria*

- Studies using mood or quality of life scales where no independent anxiety or depression scale/dimension exists;
- Studies focusing on other psychological variables such as distress, coping, personality or quality of life, without specific measures of depression or anxiety;
- Interventional studies (i.e. natural course of IBD / mental disorders cannot be observed);
- Studies in languages other than English;
- Studies published before 2005 as the study is an update to a previous review (1);
- Conference abstracts or any short papers with incomplete data presented;

- Case reports, case series or qualitative research;
- Reviews, opinion papers;
- Animal studies.

**Search methodology**

*Sources*

A systematic and comprehensive literature search of Ebscohost Medline, CINAHL, Embase, and PsychINFO was conducted in November and December 2014.

*Search strategy*

Two versions of a search strategy, using relevant search terms, were used: 1) FULL: Limited to peer reviewed AND NOT case-studies OR dissertations OR animal studies; 2) LIMITED: Limited to peer reviewed AND NOT case-studies OR dissertations OR animal studies AND only published between 2005 and 2014. Table 1 provides the search strategy and search results. Reference management was done through EndNote (version X6 Thomson Reuters).

*Data collection and analysis*

The systematic review was undertaken based upon the recommended PRISMA statement guidelines (http://www.prisma-statement.org) (Appendix 1). In the first phase, two reviewers independently screened the titles and abstracts identified by the search to determine whether they met the inclusion criteria. Any disagreements were resolved by discussion with a third reviewer. In the second phase, the full papers of those identified in phase one were independently evaluated by two reviewers to determine if they included data to address any one or more of the five controversies. That is, after checking general selection criteria, papers were screened again to verify whether information required to respond to a particular controversy was reported (e.g. in controversy 2, we checked

whether data for depression/anxiety by active and inactive IBD were reported), with disagreements resolved through discussion with a third reviewer (see Figure 1 for exclusion reasons).

Given the general heterogeneity of studies - the range of different recruitment strategies, settings, participant groups, outcome measures, methodologies - there was a limited scope for a meta-analysis. Further, this review focused on anxiety and depression rates at one point in time (controversies 1-4) or before/after IBD onset (controversy 5) rather than on treatment effect. We calculated mean percentages (and 95% confidence intervals (CI) or odds ratios, as appropriate) for rates, and weighted means on a common scale where data were available.

*Data extraction*

Extracted data included: authors, year of publication, and country of origin, design, setting, participant characteristics (IBD subtype, age, gender, disease activity status) and sample size, outcome measures, and results for main outcome measures.

*Data synthesis*

We provided a narrative synthesis of the findings from the included studies, structured around the co-occurrence of anxiety and depression with IBD, calculating mean percentages for the IBD and appropriate comparator group.

*Quality and risk of bias assessment*

Two reviewers independently inspected the full articles identified for inclusion for each controversy, to evaluate study quality. Any disagreement was discussed with a third reviewer. The quality appraisal of the studies was assessed using a scale developed a priori for the specific needs of this study (see Appendix 2), based on recommendations from Sanderson (14) regarding key domains to assess in critical appraisal. The scale included evaluation of 1) appropriate selection of participants; 2) appropriate measurement of variables; and 3) appropriate control of confounding

variables. We also consulted with IBD experts not involved in this review regarding the scale, and piloted it with a sub-sample of studies before undergoing the quality appraisal of the included articles. We interpreted the quality in the following manner: if the mean quality score for the controversy was between 0-30% on the rating scale it was considered low; if it was between 31-60% it was considered moderate; and if it was between 61-100% it was considered high.

## RESULTS

Of the 4,985 studies identified during the database searches, 1,264 were removed as duplicates. Of the 3,721 papers for which we screened titles and abstracts, 3,511 did not meet the inclusion criteria (see Figure 1), leaving 210 included for full review to determine specific applicability for each controversy. In controversy 1, 13 studies were included in the final review; 26 studies were applicable for controversy 2; 28 studies for controversy 3; 17 studies for controversy 4; and 2 studies for controversy 5. This amounts to 66 unique studies, as some studies addressed more than one controversy.

### Study characteristics

Study characteristics are presented in Tables 2-6.

*Controversy 1: IBD versus healthy/general population controls*

Of the 13 studies which had applicable data in relation to this question (9, 15-26), seven came from Europe, five from North America, and one from Australia. Seven were cross-sectional, three were case-control, and three were cohort studies, two of which were prospective and one was retrospective. Samples ranged in size from 47 to 2,144 IBD participants (total n=4,098) and from 20 to 10,720 healthy or general population controls (total n=13,190). Five studies included paediatric /adolescent populations. In terms of anxiety and depression measurement, the majority incorporated self-report measures, with the HADS being the most common measure (n=6) (15-17, 20, 24, 26).

Two studies used diagnostic information (International Statistical Classification of Diseases-9 (ICD-9) codes, n=1; Comprehensive International Diagnostic Interview (CIDI); n=1) (9, 22).

*Controversy 2: IBD active versus IBD inactive*

Overall, 26 studies had applicable data in relation to this controversy (4, 18, 20, 27-49). Of these, 13 came from Europe, 12 from North America, and one from Korea. Fifteen were cross-sectional, seven were prospective cohorts, including one that was population-based, two were retrospective cohorts, there was one case-control study, and one was a randomised controlled trial where just the baseline data was used. Samples ranged in size from 47 to 10,634 (total n=15,931) participants. Of the 26 studies, three (total n=11,062) did not report total numbers of participants or provide percentages of those with active versus inactive IBD. Of the remaining 23 studies (n=4,805), 2,297 (48%) participants were in an inactive disease phase; not included in this proportion were six studies which presented data for participants with inactive IBD only (n=784). Anxiety and depression were most frequently measured using the HADS (n=11) (20, 29, 31-33, 36, 39, 41, 46, 49, 50). For disease activity measurement, in CD, the most commonly used was the Crohn's Disease Activity Index (CDAI) (n=12) (20, 27, 28, 30, 31, 36, 38, 43, 46-49) while in UC, it was the Simple Clinical Colitis Activity Index (n=4) (20, 35, 38, 43).

*Controversy 3: CD versus UC*

Overall, 28 studies met the inclusion criteria in relation to this question (20, 21, 26, 27, 29, 33, 38, 39, 41, 43, 46, 47, 51-66). Of these, 17 came from Europe, 8 came from North America, two from Australia, and one from Korea. Twenty-two were cross-sectional, three were prospective-based studies, two were cohort studies and one was a population-based case control study. Samples ranged in size from 48 to 11,028 IBD participants (total n=42,564), with subsets of CD participants ranging from 26 to 6,689 (n=23,564), and UC participants ranging from 22 to 5,522 (n=19,319). Two studies included paediatric/adolescent populations. The HADS was the most commonly used

anxiety or depression scale (n=16) (20, 26, 29, 33, 39, 41, 46, 54, 56-59, 61-64). Two studies used the ICD-9 criteria (51, 52). In terms of disease activity, for CD, the CDAI was used most commonly (n=10) (27, 38, 43, 46, 47, 55, 60, 62-64) while for UC, the SCCAI was most commonly used (n=5) (20, 26, 38, 43, 53).

*Controversy 4: IBD versus medically ill controls*

Overall, 17 studies met the inclusion criteria in relation to this controversy (15, 17, 21, 24, 27, 67-78). Of these, 12 came from Europe, two from Australia, one from Brazil, Malaysia, and the USA. Fifteen studies were cross-sectional, with one of these reporting gender- and age-matching, one was a cohort-based study and one was a population-based case study. Three of the 17 studies were based on child/adolescent cohorts. Samples ranged in size from 26 to 305 IBD participants (total n=1,874), and from 38-1506 for the medically ill controls (total n=3419). The most common comparator was irritable bowel syndrome, used in six studies, with four studies using a mix of illness groups (e.g. chronic liver disease, celiac, food allergy), two studies utilising colon cancer groups as comparators, and the remaining five studies using participants with gastroesophageal reflux disease (GERD), juvenile idiopathic arthritis, multiple sclerosis (MS), rheumatoid arthritis (RA) or self-limited colitis cohorts (ASLC), respectively as comparators. The most commonly used measure of anxiety or depression was the HADS (n=8) (15, 17, 24, 67-69, 74, 75).

*Controversy 5: Preceding or following IBD onset*

Only two studies (n=2,495) had applicable data in relation to this controversy (9, 22). Both were cohort studies from North America, with one of them being population-based. One examined a paediatric IBD population (n=2,144) and the other studied an adult IBD population (n=351), with 10,720 paediatric and 779 adult age- and gender-matched controls, respectively. Diagnostic criteria for anxiety and depression were used in both studies (ICD9 codes; CIDI). IBD was identified using

the ICD9 coding in the paediatric study, and using a validated administrative data definition which was then verified through a chart review in the adult study.

**Anxiety and Depression Study Outcomes**

*Controversy 1: IBD versus healthy/general population controls*

Eleven of the 13 studies measured anxiety, with seven of these reporting either significantly higher rates (% or levels (mean scores) of anxiety in those with IBD than in healthy control participants (n=3,262 IBD; n=12,024 controls) (9, 15, 20-22, 24, 26).

For adult IBD participants, the rates of anxiety ranged from 15.1% (± 3.75, 95% CI) [all anxiety combined] based on diagnostic criteria in the population-based study by Walker (9), to 40% (±14.1, 95% CI), reported in a small case control study measuring anxiety symptoms for those with CD only (18). The rates for healthy controls were 16.3% (± 2.6, 95% CI) and 7.6% (± 6.4, 95% CI) in these studies, respectively. In children, a small cross-sectional study found low rates of clinically significant anxiety for both the IBD participants (2% ± 3.88, 95% CI) and the healthy non-IBD individuals (5% ± 6.59, 95% CI) (23). A pooled mean rate of anxiety symptoms in all IBD samples reporting proportions (study n=3 (9, 18, 23); total IBD n=448) was 19.1% (± 3.63, 95% CI) compared to 9.6% (± 1.94, 95% CI) in healthy controls (n=887).

All 13 studies examined depression. Nine found significantly higher rates and/or levels of depression in IBD participants than in healthy controls (n=3,517 IBD; n=12,212 controls) (9, 15, 16, 19-22, 24, 26). Two studies with adolescents (one cross-sectional and one prospective; total n=734) (23, 25), reported the opposite relationship, namely that healthy non-IBD individuals had higher rates/levels of depression than those with IBD, although only one of these studies found that the group differences were significant (n=78 IBD; n=564 controls) (25).

Depression rates for adults with IBD ranged from 7% (± 7.3, 95% CI) reported in a small case control study (18), to 59% (± 6.2, 95% CI) in a population-based case control study with nearly 500 participants (21). The latter study however used the BDI, which can overestimate depression in

medically ill populations including IBD, due to its emphasis on somatic symptoms. A population-based IBD study which used the gold standard of a structured clinical diagnostic interview reported that 27.2% (± 4.7, 95% CI) of cases met criteria for lifetime depression illness (9). Rates of depression for the healthy control individuals were 1.5% (± 2.9, 95% CI), 38% (± 5.9, 95% CI), and 12.3% (± 2.3, 95% CI) in these studies, respectively. In children, the rates of depression ranged from 0% (versus 2% [± 4.2, 95% CI] in controls) in a small cross-sectional study (23) to 13% (± 7.5, 95% CI) in another cross-sectional study (rates unreported for controls) (25). A pooled mean rate of depressive symptoms in all IBD samples reporting percentages (study n=5; total n=767) was 21.2% (± 2.9, 95% CI) compared to 13.4% (± 1.9, 95% CI) for healthy controls (n=1,142).

*Controversy 2: IBD active versus IBD inactive*

Of the 26 studies, 21 measured anxiety, with six of these providing data for inactive IBD only (28, 32, 36, 37, 39, 49). Of the remaining 15, 11 reported significantly higher rates or levels of anxiety in participants with active IBD compared to those with inactive IBD (n=13,585) (4, 18, 20, 27, 29, 31, 38, 41, 42, 44, 45). A study by Goodhand et al. (20), which reported disease activity results stratified by IBD disease type, found that those with active UC or active CD had higher rates of anxiety than those with inactive disease, although the findings were only significant for the UC group. Only one cross-sectional study reported slightly lower levels of anxiety in individuals with active IBD compared to participants with inactive IBD, although the group differences were not statistically significant (n=147) (46).

In adults, the rates of anxiety in inactive IBD ranged from 9.1% (± 9.8, 95% CI) in a small case-control study (18) to 70.6% (± 11.8, 95% CI) in another small study (32). The pooled mean rate for all the studies reporting percentages (study n=8; total n=1,069) was 28.2% (± 2.7, 95% CI) (18, 27-29, 32, 33, 36, 39). In the four largest studies (n=839) which provided data on rates, 22% (± 2.8, 95% CI) of IBD patients with inactive IBD had clinically elevated anxiety (28, 29, 33, 39). During active disease, the rates of anxiety were typically much higher, ranging from 56.3% (± 17.2,

95% CI) to 71.4% (± 9.1, 95% CI), with a pooled mean rate of 66.4% (± 7.8, 95% CI) (study n=3; total n=140) (18, 27, 29). In the largest sample reporting rates for active IBD, 71.4% (± 9.1, 95% CI) of IBD patients with active IBD had elevated anxiety (27). No data for children were available.

Of the 26 studies, 23 measured depression, with six providing data for inactive IBD only. Of the remaining 17 studies, 12 reported significantly higher rates or levels of depression for those with active IBD (n=13,553) (18, 20, 27, 29, 31, 34, 35, 38, 41, 43, 45, 48). In adults, the rates of depression in inactive IBD ranged from 0 in one small study (n=33) (18) to 49.6% (±14.3, 95% CI) in another small study (n=47) (40). The pooled mean rate of depressive symptoms for those with inactive IBD was 19.9% (± 2.05, 95% CI) (study n=10; total n=1,132) (18, 27-29, 32, 33, 36, 39, 40, 48). During active disease, the rates of depression ranged from 14% (± 18.2, 95% CI) in a small case-control study (18) to 50% (± 18.5, 95% CI) in a small prospective study (n=28) (40). The pooled mean rate of depressive symptoms during active IBD was 34.7% (study n=5; total n=319) (18, 27, 29, 40, 48). For children, one study (n=156) reported a 30% rate of depression (± 7.2, 95% CI) in inactive IBD (48), and a depression rate of 49% (±7.97, 95% CI; n=151) for those with active disease (48).

*Controversy 3: CD versus UC*

Twenty-one of the 28 studies measured anxiety, with only three of them concluding there were statistically significant differences between IBD subtypes, all of which indicated higher anxiety for those with CD (21, 29, 41). Based on 14 studies reporting anxiety rates, the pooled average was 37% (± 9.9, 95% CI) for CD (n=1144) and 31% (± 14.2, 95% CI) for UC (n=628). Nine of 24 studies reported mean HADS scores; the mean HADS-A score for CD (n=1818) was 7.0 (± .85, 95% CI) and the mean HADS-A score for UC (n=1423) was 6.4 (± .5, 95% CI). No data for children were available.

Twenty-seven of 28 studies assessed depression, however, only two studies noted significant differences, demonstrating higher depression rates in CD (39, 41). The pooled average depression

rate, acquired from 15 of the 27 studies, was 24.4% (± 7.3, 95% CI) for CD (n=9496) and 22% (± 6.9, 95% CI) for UC (n=7136). Pooled means for HADS-D scores (n=8/27 studies) were 6.09 (± .89, 95% CI) for CD (n=1299) and 5.5 (± 1.08, 95% CI) for UC (N = 1694). Two studies with adolescent (55, 60) and one with elderly populations (43) were available, all three showing no difference between CD and UC participants in rates or levels of depression.

*Controversy 4: IBD versus medically ill controls*

Fourteen of the 17 studies assessed anxiety. Of these only six studies (n=915 IBD and 815 controls) showed the differences between IBD and other medically ill participants to be statistically significant (17, 21, 71, 74, 77, 78). Three studies (n=276 IBD and 213 controls) (21, 77, 78) reported significantly lower rates of anxiety in IBD than in controls with IBS or self-limited colitis, while another three studies (n=639 IBD and 602 controls) showed IBD participants as having higher rates of anxiety than controls with rheumatoid arthritis, colorectal cancer and several other disorders (coeliac disease, food allergy, congenital disorders) (17, 71, 74). The pooled average anxiety rate was 41.9% (± 9.2, 95% CI) for IBD and 48.2% (± 31.1, 95% CI) for controls. HADS-A scores (n=6 studies), for IBD had a mean of 7 (± 1.2, 95% CI) versus 8.4 (± 1.4, 95% CI) among controls. One study showed that adolescents with IBD had significantly higher rates of anxiety than controls with congenital disorders, food allergy, coeliac disease but not those with chronic liver disease (17).

Of the 17 studies assessing depression, 10 showed statistically significant differences between IBD and other medically ill cohorts (17, 21, 67, 68, 70, 71, 73-75, 77). Five (n=551 IBD and 372 controls) (67, 73-75, 77) reported lower rates or levels of depression in IBD than in controls with IBS, hepatitis C, rheumatoid arthritis, and multiple sclerosis, and five (n=648 IBD and 601 controls) (17, 21, 68, 70, 71) indicated higher rates or levels in IBD than in participants with self-limited colitis, colorectal cancer, juvenile idiopathic arthritis, and several other conditions (coeliac disease, food allergy, GERD, congenital disorders). A pooled mean depression rate was

14.5% (± 10.5, 95% CI) in IBD (n=550) versus 28.4% (± 17.7, 95% CI) in controls (n=1567). When data from the studies reporting HADS scores (5 of 17 studies) were pooled, IBD participants (n=686) had mean HADS-D scores of 3.9 (± .6, 95% CI) compared to 4.6 (± .6, 95% CI) in controls (n=694). Three studies provided data for paediatric populations (17, 70, 72) but only two conducted significance testing, both showing higher rates of depression in IBD than controls with juvenile idiopathic arthritis, congenital disorders, food allergy, coeliac disease but not chronic liver disease (n=339 IBD and 382 controls) (17, 70).

*Controversy 5: Preceding or following IBD onset*

No prospective studies examining rates of anxiety and depression prior to IBD diagnosis were identified from the past decade. However, two studies were relevant to this controversy, examining incidence of anxiety and depression post-diagnosis in children, and retrospective evaluation of timing of onset in relation to IBD in adults (9, 22).

For adults, 70% of those with IBD and a lifetime history of an anxiety or mood disorder, had a first episode of an anxiety disorder 10 years or more before the IBD diagnosis, while just 8% developed anxiety two or more years after IBD onset, suggesting anxiety is much more likely to predate the IBD. Overall, the lifetime prevalence of anxiety was 15.1% (± 3.7, 95% CI) versus 16.3% (± 2.6, 95% CI) for age and gender-matched controls (9). In children with IBD, the incidence rates of anxiety disorders (1.81 per 100 patient-years of observation) were significantly higher than in the healthy controls (0.57 cases, $p < 0.0001$). After adjustment for IBD patient characteristics, having CD was associated with more than a twofold increase in the risk of developing anxiety disorders in the paediatric population (HR = 2.28; 95% CI = 1.65–3.17; $p < 0.0001$ for both comparisons) (n=2,144 CD patients and n=10,720 controls) (22).

With regard to depression in adults, 54% of those with IBD and a lifetime history of an anxiety or mood disorder had an onset of depression two years or more before the IBD onset while 23% developed depression two or more years after IBD onset, suggesting risk both before and after

disease onset. The lifetime prevalence of depression was 27.2% (± 4.7, 95% CI) versus 12.3% (± 2.3, 95% CI) for age and gender matched controls (13). In children with IBD, the incidence rate of depressive disorders (2.69 cases per 100 patient-years of observation) was significantly higher than in the healthy controls (1.22 cases, p< 0.0001). After adjustment for patient characteristics, having CD was associated with a 74% increase in the risk of developing depression (HR = 1.74; 95% CI = 1.35– 2.25, p < 0.0001) (n=2,144 CD patients and n=10,720 controls) (22).

In adults, mean age of IBD onset with lifetime anxiety or mood disorder was 29.1 years as compared to 33.1 years in those with IBD and without an anxiety or mood disorder (p=0.012) (9). No such data were available for children.

**Quality appraisal**

Quality scores for each study are presented in Tables 2-6.

*Controversy 1: IBD versus healthy/general population controls*

Quality ranged from 5 to 12 of a maximum 14 points, with a mean of 7.5 (53.6%), indicating a moderate quality. Overall, seven studies scored at least 50% on the quality scale.

*Controversy 2: IBD active versus IBD inactive*

Quality ranged from 3 to 11 of a maximum 15 points, with a mean of 7.3 (48.6%), indicating a moderate quality. Overall, 12 studies scored over 50% (a score of at least 8) on the quality scale.

*Controversy 3: CD versus UC*

Quality ranged from 3 to 11 of a maximum 12 points, with a mean of 5.7 (47.5%), indicating a moderate quality. Overall, 12 studies scored at least 50% on the quality scale.

*Controversy 4: IBD versus medically ill controls*

Quality ranged from 4 to 11 of a maximum 14 points, with a mean of 6.4 (45.7%), indicating a moderate quality. Overall, nine studies scored at least 50% on the quality scale.

*Controversy 5: Preceding or following IBD onset*

Quality ranged from 11 to 12 of a maximum 14 points in the two included studies, and was considered high, with a mean of 11.5 (82%).

## DISCUSSION

This systematic review examined five primary questions regarding the comorbidity of anxiety and depression with IBD. The original review (1), of which the present paper is an update, identified these five areas of controversy, but was unable to provide definitive answers to these questions due to the paucity of data available at that time. The current review was able to address four of the five questions more definitively, as summarized in Table 7. Specifically, in this review we observed that there were higher rates of both anxiety and depression symptoms in those with IBD compared to healthy individuals without IBD (controversy 1). The bulk of the studies support that the rates of both anxiety and depression are higher during active compared to inactive disease phase (controversy 2), and that overall rates and mean levels of anxiety and depression are significantly but only modestly higher for those with CD compared to UC (controversy 3). Rates of anxiety and depression in IBD were observed to be lower when compared to those with other chronic health conditions, noting that most of the available comparators were gastrointestinal GI conditions of varying clinical severity (controversy 4). Given the variety of comparators and major differences between them and IBD in their presentation, aetiology and burden, the biopsychosocial mechanisms behind this finding prove difficult to decipher.

Almost all of the studies measured symptoms of anxiety or depression, and not clinically diagnosed disorders, so the mean rates presented may be higher than rates of anxiety and mood disorders. While there is some relationship between elevated symptom scores and clinical diagnoses

of mood and anxiety disorders, they are not fully concordant (79, 80). Nevertheless, the Walker study (9), which was population-based, had age and gender-matched controls, and used a structured diagnostic interview, the gold-standard for clinical diagnosis, clearly indicated elevated rates of depression for individuals with IBD.

The quality of evidence for these first four research questions, in terms of study design, was moderate, so there can be some confidence in the observations. However, further method improvements are needed. Study participants were commonly recruited as convenience samples from clinics, increasing the potential for bias and threats to external validity. Only 10% of the studies which met the inclusion criteria and had applicable data to address these research questions were population-based. The reliance on symptom measures, the wide variability of screening measures used, the use of differing cut-offs even with the same measures (e.g., HADS cut-off of >7, >8, $\geq$ 8, $\geq$11), and the range of ways that mental health data was reported (e.g., different measures of central tendency and variability), make cross comparison difficult, adding confusion and unnecessary heterogeneity in this area. As well, the majority of studies did not provide sample size calculations, despite the need for such calculations in every scientific study to ensure that there is sufficient power so that if a difference of clinical interest is found, it is likely to be statistically significant (81).

The most challenging aspect to address regarding the comorbidity of anxiety and depression with IBD is whether these mental disorders precede or develop after IBD onset (controversy 5). The vast majority of studies used a cross-sectional design and were unable to shed light on this question, with only 2 of the 210 studies which met general inclusion criteria having applicable data (9, 22). The study which evaluated adults found that the large majority of individuals had first onset of anxiety well before the IBD (more than 10 years) (9). Since anxiety onset is very common in adolescence and young adulthood, the high rates of anxiety onset around this time point may well be reflecting the natural course of an anxiety disorder. With regard to depression, just over half of those experiencing depression had first onset of depression prior to IBD onset, with one-quarter

developing the depression a few years or more after IBD onset (9). These findings are intriguing, and raise the question of bidirectional risk. They are in line with experimental work with animals, which has demonstrated that depression may precede and can increase vulnerability to inflammation (82, 83). However, the timelines were established retrospectively through structured clinical interviews to determine lifetime prevalence of mental disorders, so there is potential for recall bias. The epidemiological study of children, which evaluated incident cases of depression and anxiety, concluded that having IBD increased the risk of developing anxiety or depression (22). Its use of diagnostic criteria, large sample size, and age and gender-matched controls provide some confidence in the conclusions.

**Recommendations**

The high rate of anxiety and depression in individuals with IBD and the impact of mental comorbidities on the disease-related outcomes warrant a systemic approach to screening and treatment. While studies on mental health in primary care do not always support the value of routine screening (84), its benefit has been established in populations with chronic conditions or mental disorders (85). However, as was evident in our review, there are a myriad of mental health screening measures used, and it is notable that few have been validated in an IBD population (38, 86). Thus, the approach to and effectiveness of screening for mental disorders as part of IBD care has yet to be empirically validated. Nonetheless, new approaches to healthcare delivery such as stepped care or integrated care may facilitate better detection and management of anxiety and depression coexistent with IBD (87-89).

This review has demonstrated a significant level of psychological co-morbidities in IBD. Yet, treatment of anxiety and depression is often not considered as part of standard IBD care (90). While financial strain of the public healthcare systems around the world and medical training of IBD physicians to treat the somatic symptoms may contribute to lack of integration of mental health care with general IBD care, another contributing factor may be the controversy on the efficacy of

mental health treatments in IBD. To date, there have been no published trials on the use of antidepressants in IBD (91, 92). Psychotherapy has been more carefully examined, with conflicting results. A 2011 Cochrane review, which broadly defined psychotherapy and pooled all modalities together, concluded that psychotherapy had no effect on distress, disease activity, or quality of life in the unselected IBD patients (93). However, recent reviews which used more appropriate categorization of psychological interventions, analysing different types of treatments separately, demonstrated that one type of psychotherapy, cognitive-behavioural therapy (CBT), improves psychological distress, with modest changes in gastrointestinal symptoms (94, 95). These differing conclusions largely stem from methodological differences in the approach to the reviews, but also from the paucity of well-designed large-scale clinical trials on psychotherapy in IBD. Clinical trials need to ensure sufficient power, selection of participants with elevated distress and active disease, validated and objective measures of outcome (e.g., changes in depression, measurement of inflammatory processes), and appropriate control conditions (96). Until there is clearer direction regarding the IBD-specific treatment of anxiety and depression, use of evidenced-based therapies such as cognitive behavioural therapy for anxiety and depression in general, as specified in the National Institute for Health and Care Excellence (NICE) guidelines, appears prudent (97).

**Future directions**

The research on mental health comorbidity in IBD is quite extensive, as evidenced by the thousands of citations identified in the search for the past decade alone. The strengths of this review include the comprehensive and systematic approach to evaluating this extensive body of literature, the inclusion of controlled studies, and the focus on a broad range of comparators both within and between those with IBD and others. The review also has some limitations. The available studies were largely from Western Europe and North America, with few to none from areas such as Eastern Europe, South America, Asia and Africa. As there are differing rates of IBD in various regions of the world (2), there may also be differing rates of comorbid depression and anxiety than what was

identified in the current review. In addition, we were unable to examine gender differences in anxiety and depression comorbidity as virtually no studies provided a male/female breakdown of their results. Gender differences in the clinical course of IBD such as earlier disease relapse post-surgery for women have been reported (98), so a careful evaluation of mental health comorbidity for men and women may provide direction for contributory mechanisms. Further, primary depression is much more common for women than for men (99). Many of the studies in our review had a modestly larger proportion of female participants, raising the possibility that rates are somewhat elevated due to overrepresentation of females in these samples. Finally, most of the studies involved adult IBD participants, with relatively few providing data for paediatric samples, and only one study using a geriatric IBD sample (43). Where data was available, we provided anxiety and depression rates that were specific to these age groups, but it is difficult to draw conclusions about comparative rates of anxiety and depression for children and the elderly in the IBD context at this time.

We have briefly highlighted some of the ongoing methodological problems and study heterogeneity in the clinical literature. In order to improve the quality of research in this area, and facilitate the use of meta-analytic approaches in the future, researchers are encouraged to consider the following design and reporting elements: a) cohort, case-control designs rather than cross-sectional; b) population-based or at a minimum consecutively recruited participants; c) comparison groups, including both healthy and chronically ill controls; d) justification for the sample size and attrition; e) control for confounders (e.g., psychiatric history); f) present data separately for IBD subtypes, disease activity, and male/female and provide means (SD) and proportions with confidence intervals where appropriate; g) measure IBD outcomes such as time to relapse, as well as inclusion of objective measures such as faecal calprotectin, or optimally endoscopy; and h) use of validated screening measures as well as validated clinical diagnostic measures (e.g., ICD codes, structured clinical interviews), with effort to be more homogeneous. With regard to this latter point, there was tremendous variability in measurement of anxiety and depression; 16 scales (5 for both

anxiety and depression; 6 for depression alone; and 5 for anxiety alone) were used across the 66 unique studies examined in this systematic review and only two appear to have been validated in individuals with IBD (38, 86). We observed that the HADS was the most commonly used measure, among the studies with applicable data for the controversies addressed in this review, and that it aims to evaluate anxiety and depression symptoms using a common metric. Despite the extensive use of the HADS in medical patients generally (based on PubMed, since its development in the 1980s it has been used in over 3,700 studies) and with IBD patients to date, it has yet to be validated in IBD. It also must be noted that more recently the HADS has been shown to differentiate poorly between anxiety and depression (100, 101). Given this, further research is required to both validate, and develop clear cut-offs and meaning in the IBD context.

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**ABBREVIATIONS**

BAS = Bates Anxiety Scale

BDI = Beck Depression Inventory

CAI = Clinical Activity Index

CD = Crohn's disease

CDAI = Crohn's Disease Activity Index

CDI = Children's Depression Inventory

CIDI = Comprehensive International Diagnostic Interview

CRP = C-reactive protein

DAI = Modified/Simplified Disease Activity Index

ESR = erythrocyte sedimentation rate

GDS = Geriatric Depression Scale

HADS = Hospital Anxiety and Depression Scale

HAM = Hamilton Anxiety and Depression (HAM-A = anxiety scale; HAM-D = depression scale)

Hb = haemoglobin

HBI = Harvey Bradshaw Index

HC = healthy controls

IBD = inflammatory bowel disease

IBS = irritable bowel syndrome

IQR = inter-quartile range

LCAI = Lichtiger Colitis Activity Index

MIBDI = Manitoba IBD index

MSDAI = Mayo Score Disease Activity Index

N/A = not available

ns = not significant

PCDAI = Paediatric Crohn's Disease Activity Index

PGWBI = Psychological General Wellbeing Index

PHQ = Patient Health Questionnaire

PROMIS = Patient Reported Outcomes Measurement Information System

RMAS = Revised Manifest Anxiety Scale

SAI = Seo's Activity Index

SCARED = Screen for Child Anxiety Related Disorders

SCCAI = Simple Clinical Colitis Activity Index

SCL90R = Symptom Checklist questionnaire- revised

SD = standard deviation

STAI = State-trait Anxiety Inventory

TWI = Truelove-Witts Index

UC = ulcerative colitis

Zung SDS = Zung Self-Rating Depression Scale

**LIST OF SUPPLEMENTAL DIGITAL CONTENT**

Supplemental Appendix 1 (Prisma Checklist) word document

Supplemental Appendix 2 (Quality appraisal scale) word document

Supplemental Table 1 (Search strategy and search results) word document

**Table 1: the search strategy and search results**

| | Ebscohost Medline | | CINAHL | | Embase | | PsychINFO | |
|---|---|---|---|---|---|---|---|---|
| IBD KEY WORDS | FULL (N) | Limited (N) | FULL (N) | Limited (N) | FULL (N) | Limited (N) | FULL (N) | Limited (N) |
| "Inflammatory bowel" | 31,361 | 19,001 | 2,626 | 2,055 | 47,740 | 33,491 | 407 | 272 |
| colitis | 53,511 | 20,895 | 2,669 | 1,904 | 97,954 | 50,637 | 637 | 194 |
| "Crohn disease" | 28,507 | 10,082 | 2,176 | 1,518 | 62,914 | 35,603 | 19 | 12 |
| enterocolitis | 12,883 | 5,327 | 1,610 | 1,245 | 15,440 | 7,925 | 67 | 52 |
| pancolitis | 505 | 283 | 25 | 18 | 1,187 | 913 | 0 | 0 |
| proctitis | 2,916 | 849 | 80 | 60 | 5,526 | 2,579 | 9 | 5 |
| proctocolitis | 644 | 124 | 6 | 3 | 1,194 | 310 | 1 | 1 |
| "toxic megacolon" | 626 | 180 | 30 | 18 | 1,447 | 593 | 1 | 1 |
| ulcerative | 40,798 | 14,364 | 2,090 | 1,412 | 67,880 | 31,699 | 467 | 104 |
| Ileitis | 3,285 | 637 | 37 | 31 | 6,056 | 2,639 | 14 | 1 |
| Enteritis | 12,973 | 2,820 | 215 | 151 | 59,054 | 32,555 | 39 | 16 |
| "Inflammatory bowel" OR Colitis OR "Crohn disease" OR enterocolitis OR pancolitis OR proctitis OR proctocolitis OR "toxic megacolon" OR ulcerative OR Ileitis OR Enteritis ***PUT ALL THE LIMITED ABSTRACTS FOUND FOR THIS SEARCH INTO 1 DOCUMENT ENTITLED "IBD"*** | 113,846 | 45,888 | 7,774 | 5,765 | 196,500 | 100,359 | 1,091 | 484 |

| | Ebscohost Medline | | CINAHL | | Embase | | PsychINFO | |
|---|---|---|---|---|---|---|---|---|
| IBD KEY WORDS | FULL (N) | Limited (N) | FULL (N) | Limited (N) | FULL (N) | Limited (N) | FULL (N) | Limited (N) |
| PSYCH KEY WORDS | | | | | | | | |
| "depress* disorder*" | 78,299 | 35,515 | 2,570 | 1,976 | 31,646 | 21,116 | 18,457 | 11,111 |
| "depressive disorder, major" | 17,628 | 12,975 | 5 | 3 | 59 | 45 | 25 | 14 |
| "major depressive disorder" | 13,134 | 9,620 | 1,535 | 627 | 17,803 | 13,863 | 10,930 | 7,371 |
| depression | 277,941 | 122,160 | 63,520 | 44,490 | 468,859 | 246,765 | 159,620 | 76,946 |
| "depress* symptoms" | 29,165 | 21,626 | 8,743 | 6,841 | 37,108 | 28,174 | 25,219 | 17,331 |
| "adjustment disorder" | 728 | 353 | 128 | 82 | 3,581 | 1,758 | 715 | 300 |
| "anxiety disorder*" | 33,588 | 18,717 | 4,843 | 3,743 | 59,467 | 43,435 | 41,613 | 22,692 |
| "anxiety symptoms" | 4,309 | 3,218 | 879 | 728 | 5,743 | 4,340 | 4,260 | 2,920 |
| anxious | 11,540 | 6,072 | 1,982 | 1,228 | 16,360 | 8,712 | 12,979 | 5,631 |
| anxiety | 154,128 | 77,237 | 32,762 | 22,496 | 236,096 | 137,136 | 133,489 | 61,941 |
| "panic disorder" | 8,786 | 3,592 | 1,217 | 749 | 9,797 | 4,174 | 7,871 | 2,716 |
| OCD | 6,268 | 3,988 | 649 | 442 | 8,885 | 5,993 | 5,980 | 3,640 |
| "obsessive-compulsive disorder" | 13,086 | 5,909 | 2,050 | 1,428 | 20,685 | 12,845 | 10,236 | 5,206 |
| "phobic disorder" | 90 | 17 | 10 | 2 | 123 | 34 | 103 | 14 |
| "mood disorder*" | 19,879 | 11,284 | 1,425 | 1,052 | 38,786 | 28,861 | 8,306 | 6,660 |
| "social anxiety" | 3,459 | 2,558 | 560 | 448 | 4,555 | 3,328 | 4,980 | 3,141 |
| hypochondriasis | 2,583 | 454 | 221 | 115 | 4,500 | 1,314 | 1,631 | 370 |
| PTSD | 13,573 | 9,824 | 3,045 | 2,409 | 18,070 | 13,307 | 15,774 | 9,724 |
| "post traumatic stress" | 6,846 | 4,739 | 1,998 | 1,385 | 9,624 | 6,686 | 5,483 | 3,707 |
| "posttraumatic stress" | 12,185 | 8,579 | 2,763 | 2,173 | 37,680 | 25,638 | 19,577 | 12,009 |
| distress | 85,743 | 40,387 | 20,439 | 13,559 | 139,805 | 77,110 | 34,666 | 19,067 |
| "depress* disorder*" OR "depressive disorder, major" OR "major depressive disorder" OR depression OR "depress* symptoms" OR "adjustment disorder" OR "anxiety disorder*" OR "anxiety symptoms" OR anxious OR anxiety OR "panic disorder" OR OCD OR "obsessive-compulsive disorder" OR "phobic disorder" OR "mood disorder*" OR "social anxiety" OR hypochondriasis OR PTSD OR "post traumatic stress" OR "posttraumatic stress" OR distress<br>***PUT ALL THE LIMITED ABSTRACTS FOUND FOR THIS SEARCH INTO 1 DOCUMENT ENTITLED "PSYCH"*** | 502,723 | 221,825 | 105,400 | 72,118 | 767,079 | 400,915 | 295,610 | 139,258 |

| | Ebscohost Medline | | CINAHL | | Embase | | PsychINFO | |
|---|---|---|---|---|---|---|---|---|
| IBD KEY WORDS | FULL (N) | Limited (N) | FULL (N) | Limited (N) | FULL (N) | Limited (N) | FULL (N) | Limited (N) |
| COMBINED KEY WORDS | | | | | | | | |
| ("Inflammatory bowel" OR Colitis OR "Crohn disease" OR enterocolitis OR pancolitis OR proctitis OR proctocolitis OR "toxic megacolon" OR ulcerative OR Ileitis OR Enteritis) AND ("depress* disorder*" OR "depressive disorder, major" OR "major depressive disorder" OR depression OR "depress* symptoms" OR "adjustment disorder" OR "anxiety disorder*" OR "anxiety symptoms" OR anxious OR anxiety OR "panic disorder" OR OCD OR "obsessive-compulsive disorder" OR "phobic disorder" OR "mood disorder*" OR "social anxiety" OR hypochondriasis OR PTSD OR "post traumatic stress" OR "posttraumatic stress" OR distress)<br><br>***PUT ALL THE LIMITED ABSTRACTS FOUND FOR THIS SEARCH INTO 1 DOCUMENT ENTITLED "IBD AND PSYCH"***<br><br>***ALSO PUT ALL REFERENCES FOUND INTO AN ENOTE FILE*** | 1,840 | **891** | 266 | **197** | 5,498 | **3,812** | 230 | **85** |

**Table 2. Summary characteristics of the studies addressing controversy 1:** Are rates of anxiety/depression in IBD similar or different to that reported for the healthy/general population controls? *(special populations indicated in grey)*

| **Authors, year, country and quality score** | **Study information Design; setting; recruitment** | **Participant characteristics (sample size, IBD type, median/mean age and age range, sex)** | **Measures of anxiety, depression, disease activity** | **Results** |
|---|---|---|---|---|
| Berrill et al. 2013 (15)<br><br>UK<br><br>Quality: 8/14 | **cross sectional;** IBD adult outpatients attending gastroenterology hospital-based clinics; healthy controls from local advertising | **IBD**: 150 participants (36% CD) mean age 45.7 (11.3), 63% female<br><br>**Controls:** 41 healthy individuals, mean age 43.8 (13.4), 61% female | Anxiety: Hospital Anxiety and Depression Scale – Anxiety (HADS-A)<br><br>Depression: HADS-D<br><br>Disease activity: faecal calprotectin | Anxiety: IBD median=9, range 1-20<br>Healthy Controls median=5, range 0-14<br>HC< IBD, p<0.001<br><br>Depression: IBD median= 5, range 0-16<br>Healthy Controls median=2, range 0-8<br>HC< IBD, p<0.001 |
| Bessissow et al 2013 (16)<br><br>Belgium<br><br>Quality: 6/14 | **case-control;** IBD recruited from tertiary care centre database if **having colonoscopy**; age and sex matched non-IBD controls from electronic record database having colonoscopy; measured before and during colonoscopy | **IBD**: 100 participants (63% CD); median age 40 (IQR 31-49), range 19-66, 52% female<br><br>**Controls**: 100 non-IBD participants, median age 41 (IQR 31-51), 52% female | Anxiety: State-trait Anxiety Inventory – State (STAI-S), HADS-A<br><br>Depression: HADS-D<br><br>Disease activity: endoscopy | Anxiety (STAI-S) before colonoscopy:<br>IBD median=41.5, IQR 34-49.5;<br>Controls median 39.0, IQR 30.5-49.5, p=ns<br><br>Anxiety (HADS-A):<br>IBD median=6, IQR 3-9<br>Controls median=5 IQR=2-8, p=.09<br><br>Depression (HADS-D):<br>IBD median =5, IQR 4-7,<br>Controls median=4, IQR 3-5.5 p=.01 |
| Calsbeek et al 2006 (17)<br><br>The Netherlands<br><br>Quality: 5/14 | **cross sectional; adolescents and young adults;** IBD recruited via medical specialists in academic and specialized hospitals; diagnosis at least 6 months; controls recruited from patient files of 173 general practitioners who were | **IBD:** 305 participants, mean age 20 (3.7); 54.8% females<br><br>**Controls**: 306 non-IBD participants from same GP practices; mean age 18.5 (3.9); 54.9% females | Anxiety: HADS-A<br><br>Depression: HADS-D<br><br>Disease activity – not measured | Anxiety: IBD mean =5.0 (3.8);<br>Controls mean=4.3 (3.0); p=ns<br><br>Depression: IBD mean=2.8 (2.9)<br>Controls mean=2.6 (2.5) p=ns |

| | | | | |
|---|---|---|---|---|
| | also GPs of chronic disease participants | | | |
| Calvet et al. 2006 (18)<br><br>Spain<br><br>Quality: 9/14 | **case-control;** consecutive IBD patients **treated with azathioprine or 6-mercaptopurine**; healthy controls age and sex-matched 2:1, recruited from families of patients at ambulatory surgery facilities for minimally invasive procedures. | **IBD**: 33 **CD** participants with **inactive** IBD mean age =35.1 (SD 9.8), 9% female<br><br>14 CD participants with **active** disease mean age= 34.2 (SD 11.1), 93% female<br><br>**Controls**: 66 healthy individuals mean age= 34.7 (SD 9.4), 54% female | Anxiety: Hamilton Anxiety and Depression –Anxiety (HAM-A)<br><br>Depression: HAM-D<br><br>Cut-off score for severe anxiety=15; for major depression =18<br><br>Disease activity: Harvey Bradshaw Index (HBI) | Anxiety: Inactive CD mean=6.45 (SD 5.4)<br>Active CD mean=16.2 (SD 6.8)<br>Controls mean=5.48 (SD 4.9)<br>Active CD>inactive CD/controls p<0.01;<br>Depression: inactive CD mean=3.73 (SD 3)<br>Active CD mean=10.86 (SD 5.9)<br>Controls mean=3.26 (SD 3.6),<br>Active CD>inactive CD/controls p<0.01;<br>Anxiety: proportion above cut-off<br>Inactive CD 9.1%<br>Active CD 71.4%<br>Controls 7.6%<br>Depression: proportion above cut-off<br>Inactive CD 0%<br>Active CD 14%<br>Controls 1.5% |
| Cotton et al. 2009 (19)<br><br>USA<br><br>Quality: 5/14 | **cross-sectional** ; **adolescents;** IBD patients recruited from hospital IBD clinic and university hospital; controls recruited from hospital teen health clinic | **IBD**: 67 participants; CD=52, UC=13, indeterminate=2; mean age=15.5 (1.98; range 11-19), 55% female<br><br>**Controls**: 88 healthy individuals; mean age=14.8 (1.9; range 11-18 ), 43% female | Anxiety: not measured<br><br>Depression: Children's Depression Inventory-short form (CDI, 10 item)<br><br>Disease activity: Lloyd-Still and Green score | Depression: IBD mean=2.46 (SD 2.82)<br>Controls mean=1.68 (SD 2.22) p=0.04 |
| Goodhand et al. 2012 (20)<br><br>UK<br><br>**Quality: 6/14** | **cross-sectional;** IBD patients recruited from tertiary referral centre; controls recruited from healthy volunteers attending the hospital for an unrelated research study | **IBD**: 204 IBD participants, 103 UC mean age 42.1 years (SD 14.2), 59% female, 72% Caucasian, 38% active disease; 101 CD mean age 42.8 years (SD 14.3), 57% female, 88% Caucasian, 27% active disease | Anxiety: HADS-A<br><br>Depression: HADS-D<br><br>Cut-off score > 7<br><br>Disease activity: Simple Clinical Colitis Activity Index (SCCAI), sigmoidoscopy, | Anxiety: inactive UC mean=7.8 (SD 3.5)<br>inactive CD mean=8.1 (SD 3.7)<br>active UC mean=9.7 (SD 4.7)<br>active CD mean=9.7 (SD 3.7)<br>Controls mean=3.2 (SD 1.8)<br>Inactive UC/CD=Active CD/UC > controls p<0.0001<br><br>Depression: inactive UC mean =3.3 (SD 2.4)<br>inactive CD mean=4.2 (SD 3.6)<br>active UC mean= 6.1 (SD 3.6)<br>active CD mean=5.6 (SD 2.3) |

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|---|---|---|---|---|
| | | **Controls:** 124 healthy individuals, mean age 28.7 years (SD 8.3), 43% female, 74% Caucasian | Crohn's Disease Activity Index (CDAI), faecal calprotectin | controls mean= 1.7 (SD 1.4)<br>Inactive UC/CD=Active CD/UC > controls p<0.0001 |
| Lerebours et al 2007 (21)<br><br>France<br><br>Quality: 11/14 | **population-based case-control**; recruited newly diagnosed IBD patients (< 6 months) from IBD registry of 1009 incident IBD cases; healthy controls recruited from blood donor clinics in the same area and time period, with no GI disease history | **IBD:** 241 IBD participants; 167 CD, mean age 32.3 (SD 13.1), 62% female; 74 UC , mean age 36.1 (SD 15.1), 50% female<br><br>**Controls**: 255 blood donor individuals, mean age 37.1 (SD 11.9), 51% female | Anxiety: Bates Anxiety Scale<br><br>Depression: Beck Depression Inventory-short (BDI, 13 items) cut-off score $\geq$ 4<br><br>Disease activity: unspecified | Anxiety: CD mean=52.22 (25.19)<br>UC mean=40.31 (21.65)<br>Controls: mean=37.09 (21.28)<br>CD>UC=controls p<0.0083<br><br>Depression: CD mean=7.41 (5.87)<br>UC mean =6.13 (4.93)<br>Controls mean=4.40 (4.18)<br>CD & UC > controls p<0.0083<br><br>Depression: proportion above cut-off<br>CD=61%<br>UC=57%<br>Controls=38% |
| Loftus et al. 2011 (22)<br><br>USA<br><br>Quality: 12/14 | **retrospective cohort; youth**; IBD and nonIBD age and sex-matched cases taken from national database of health service claims data for approximately 100 third-party payers, including employers and health plans; observations from minimum of 6 months to a 6.5 years | **IBD**: 2,144 CD cases<br><br>**Controls**: 10,720 non-IBD cases<br><br>Both groups: mean age at index date 11.8 years, (SD N/A) ,46.1% female | Anxiety: ICD 9 CM codes 293.84, 300.0x, 313.0x (includes anxiety states and disorder)<br><br>Depression: ICD 9 CM codes 296.2x, 296.3x, 298.0x, 300.4x, 309.1x, 311.xx (includes major depressive disorder, depressive type psychosis, dysthymia)<br><br>Disease activity: based on treatment history | Anxiety:<br>CD incident rate=1.81 cases per 100 patients years<br>Controls incident rate= 0.57 cases; p<0.0001<br><br>Depression:<br>CD incident rate=2.69 cases per 100 patient years<br>Controls incident rate=1.22 cases; p<0.0001 |
| Mackner & Crandall 2005 (23) | **cross sectional; adolescents**;<br>IBD patients identified from a clinic schedule | **IBD**: 50 IBD participants, mean age=14.69 (SD 1.92), 38% female, 80% | Anxiety: Revised Manifest Anxiety Scale (RMAS) | Anxiety: IBD mean= 45.26 (SD 11.51)<br>Control mean=44.12 (SD 10.65); p=n.s.<br><br>Depression: IBD mean=42.86 (SD 7.36) |

| | | | | |
|---|---|---|---|---|
| USA<br><br>Quality: 7/14 | review and chart review. Controls recruited from ambulatory clinics and hospital employee families. | Caucasian<br><br>**Controls**: 42 healthy individuals, mean age 14.08 (SD 2.05), 48% female, 79% Caucasian<br><br>Age range 11-17 for both groups | Depression: CDI<br><br>Cut-off score for each >66<br><br>Disease activity: Paediatric Crohn's Disease Activity Index (PCDAI) | Control mean=44.24 (SD 8.80); p=n.s.<br><br>Anxiety: proportion above cut-off<br>IBD =2%<br>Controls=5%<br><br>Depression: proportion above cut-off<br>IBD=0%<br>Controls=2 |
| Piche et al 2010 (24)<br><br>France<br><br>Quality: 7/14 | **cross sectional; CD in remission;**<br>IBD patients recruited from 5 university hospitals; healthy controls recruited from patients having screening colonoscopy (i.e., family history, and no GI symptoms) | **IBD**: 92 participants, mean age 35.9 (SD 12.3), 59% female<br><br>**Controls**: 20 individuals, mean age 38.1 (SD 7.3), 65% female | Anxiety: HADS-A<br><br>Depression: BDI-S<br><br>Disease activity: CDAI plus haemoglobin, CRP, ESR, platelet count, albumin | Results stratified by CD with and without IBS-type symptoms<br><br>Anxiety:<br>CD with IBS-type symptoms mean = 8.7 (SD 3.9),<br>CD without IBS-type symptoms mean =8.5 (SD 3.4)<br>Controls mean=4.5 (SD 3.0)<br>CD with IBS-type > controls p=0.004<br><br>Depression:<br>CD with IBS-type symptoms mean=6.4 (SD 5.6)<br>CD without IBS-type symptoms mean=4.2 (SD 3.9)<br>Controls mean=1.7 (SD 2.4)<br>CD with IBS-type>controls p=0.001<br>CD with IBS-type>CD without IBS-type p=0.02 |
| Reed-Knight et al. 2014 (25)<br><br>USA<br><br>Quality: 5/14 | **prospective cohort study; adolescents;** IBD patients recruited from IBD research registry at 1 (US) of 24 US and Canadian sites; controls from community sample data from a different study with similar age, ethnicity and geographic region | **IBD**: 78 participants, 79% CD, 21% UC (mostly inactive/mild disease activity); mean age=13.79 (SD 2.79), 49% female<br><br>**Controls:** 564 non-IBD individuals, mean age 12.43 (SD 0.87), 51% female<br>Age range 8-17.5 years | Anxiety: not measured<br><br>Depression: CDI (27 items)<br><br>Cut-off score (conservative)=12<br>Disease activity: abbreviated PCDAI | Depression: IBD mean=4.83 (SD 4.90)<br>Controls mean=6.08 (SD 5.79); p=0.03<br><br>Depression: proportion above cut-off 12<br>IBD=13%;<br>Controls=proportion not available |
| Van Langenberg & Gibson 2014 | **cross-sectional;** consecutive patients who | **IBD**: 181 CD participants, median age | Anxiety: HADS-A | Anxiety: CD median= 8<br>UC median=7 |

| | | | | |
|---|---|---|---|---|
| (26)<br><br>Australia<br><br>Quality: 6/14 | attended a hospital IBD clinic, invited in person at a clinic visit or through phone;<br>age- and sex-matched cohort of healthy subjects consecutively recruited through local advertisement | 41 years (range 18–68), 54% female, 113 UC patients mean age 50 years, 55% female<br><br>**Controls:** 85 healthy volunteers mean age 38 years, 69% female | Depression: HADS-D<br><br>Disease activity: HBI, SCCAI | Controls median=4<br>($p<0.01$)<br><br>Depression: CD median=8<br>UC median=7<br>Controls median=2<br>($p<0.01$) |
| Walker et al. 2008 (9)<br><br>Canada<br><br>Quality: 11/14 | **population-based cohort;** recruited from province-wide university IBD research registry, 24 months into cohort data collection; control cases obtained from national health survey and age, gender and region-matched | **IBD**: 351 participants, mean age=43 years (SD 14.06), 60% female, 95% Caucasian, 48% CD, 46% UC/ulcerative proctitis, 6% indeterminate colitis.<br><br>**Controls**: 779 cases, mean age=40 years (SD 14.51), 59.1% female | Anxiety: 12 month and lifetime prevalence of anxiety disorders assessed by Comprehensive International Diagnostic Interview (CIDI);<br><br>Depression: 12 month and lifetime prevalence of mood disorders assessed by CIDI<br><br>Disease activity: Manitoba IBD index (MIBDI) | Anxiety: lifetime prevalence<br>Social anxiety<br>IBD 6%<br>Controls 11%; OR 0.52, 95% CI 0.32–0.85<br>Panic Disorder<br>IBD 8.0%<br>Controls 4.7%; OR 1.59, 95% CI 0.96–2.63<br>Agoraphobia without panic<br>IBD 1.1%<br>Controls 0.6%; OR 1.44, 95% CI 0.37–5.55<br><br>Depression: lifetime prevalence<br>Major depression<br>IBD 27.2%<br>Controls 12.3%; OR 2.20, 95% CI 1.64–2.95 |

**Table 3. Summary characteristics of the studies addressing controversy 2:** Are rates of anxiety/depression similar or different during inactive versus active disease? *(special populations indicated in grey)*

| **Authors, year and country** | **Study information: Design; setting; recruitment** | **Participant characteristics (sample size, IBD type, age, sex)** | **Measures anxiety, depression, disease activity** | **Results** |
|---|---|---|---|---|
| Addolorato et al. 2008 (27)<br><br>Italy<br><br>Quality: 7/15 | **cross-sectional;** consecutively recruited IBD outpatients from internal medicine outpatient setting | 135 IBD participants, 948 (57.8%) female<br><br>**Active:** 53 UC mean age=34 years (SD 12.7); 41 CD mean age=36.6 years (SD 14.5) % female N/A<br><br>**Inactive**: 21 UC mean age=37.5 years (SD 11.1); 20 CD mean age=40.6 (SD 12.9) % female N/A | Anxiety: STAI<br>Cut-off score =40<br><br>Depression: Zung Self-Rating Depression Scale (Zung SDS)<br>Cutoff score >49<br><br>Disease activity: CDAI, Truelove-Witts Index (TWI), cut-off N/A | Anxiety: proportion above cut-off<br>State- UC active 92.4%<br>UC inactive 66%<br>CD active 87.8%<br>CD inactive 55%<br><br>Trait- UC active 47.1%<br>UC inactive 47.6%<br>CD active 58.5%<br>CD inactive 35%<br><br>Depression: proportion above cut-off<br>UC active 15%<br>UC inactive 0%<br>CD active 21.9%<br>CD inactive 15% |
| Agostini et al. 2010 (28)<br><br>Italy<br><br>Quality: 7/15 | **case-control;** members of a regional IBD association recruited by mail; controls randomly selected from the general population | 307 IBD participants<br><br>**Active:** none<br><br>**Inactive:** 174 CD, 133 UC, mean age=43.14 years, 51% female | Anxiety: Symptom Checklist questionnaire (SCL-90–R)<br><br>Depression: SCL90-R<br>Cut-off score >/= 63<br><br>Disease activity – CDAI (cut-off >/=150), Clinical Activity Index (CAI) (cut-off >/= 2) | Anxiety: proportion above cut-off<br>IBD active – n/a<br>IBD inactive 10.9%<br><br>Depression: proportion above cut-off<br>IBD active-n/a<br>IBD inactive 12.7% |
| Banovic et al. 2010 (49)<br><br>France<br><br>Quality: 6/15 | **prospective** 12-month observation; recruited outpatients from a Parisian hospital experiencing | 52 CD participants<br><br>**Active**: none<br><br>**Inactive:** 52, mean age =41.21 (SD 12.54 | Anxiety: HADS-A<br><br>Depression: HADS-D<br><br>Disease activity: CDAI (cut-off >/=150) | Anxiety: (baseline)<br>IBD active n/a<br>IBD inactive mean=7.42 (SD 4.77)<br>(12 months)<br>IBD active n/a<br>IBD inactive mean=7.07 (SD 4.55) |

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| | **fatigue** and no comorbid rheumatoid or peripheral arthritis. | years), 27% female | | Depression: (baseline)<br>IBD active n/a<br>IBD inactive mean= 4.61 (SD 3.51)<br><br>(12 months)<br>IBD active n/a<br>IBD inactive mean= 3.5 (SD 3.26) |
| Bennebroek Evertsz et al. 2012 (29)<br><br>The Netherlands<br><br>Quality: 6/15 | **cross-sectional**; consecutive outpatients attending a tertiary care centre. | 231 IBD participants, 59.7% CD, mean age=43.4 (SD 13.8, range 18-78), 56.3% female<br><br>**Active:** 32<br>**Inactive:** 157 | Anxiety: HADS-A<br><br>Depression: HADS-D<br>Cut-off score >/=8 for both<br><br>Disease activity: HBI (cut-off >6) and TWI (cut-off >6) | Anxiety: proportion above cut-off<br>IBD active 56.3%<br>IBD inactive 31.8% (OR=2.72 \| 95% CI: 1.14–6.52 \| p=0.024)<br><br>Depression: proportion above cut-off<br>IBD active 41.9%<br>IBD inactive 21.1% (OR=3.36 \| 95% CI: 1.38–8.21 \| p=0.008). |
| Bitton et al. 2008 (30)<br><br>Canada<br><br>Quality: 9/15 | **prospective cohort;** 12 month observation; consecutively recruited from university health centre and general hospital | 101 CD patients (60 females, aged 33.6 (SD=12.9) years)<br><br>**Active**: 37<br>**Inactive:** 64 | Anxiety: SCL90R<br><br>Depression: SCL90R<br><br>Disease activity: CDAI (cut-off >/=150) , CRP, ESR, cytokines | Anxiety: IBD active mean=0.58 (SD 0.62)<br>IBD inactive mean=0.43 (SD 0.56); p=0.25.<br><br>Depression:<br>IBD active mean= 0.86 (SD 0.76)<br>IBD inactive mean= 0.57 (SD 0.50); p=0.10 |
| Calvet et al. 2006 (18)<br><br>Spain<br><br>Quality: 9/15 | **case-control;** consecutive IBD patients **treated with azathioprine or 6-mercaptopurine**; healthy controls age and sex-matched 2:1, recruited from families of patients at ambulatory surgery facilities for minimally invasive procedures. | 47 CD participants<br><br>**Active**: 14, mean age= 34.2 (SD 11.1), 93% female<br>**Inactive:** 33, mean age =35.1 (SD 9.8), 55% female | Anxiety: Hamilton Anxiety and Depression –Anxiety (HAM-A)<br><br>Depression: HAM-D<br><br>Cut-off score for severe anxiety=15; for major depression =18<br><br>Disease activity: Harvey Bradshaw Index (HBI) (cut-off > 2) | Anxiety: CD active mean=16.2 (SD 6.8)<br>CD inactive mean=6.45 (SD 5.4)<br>Active >inactive p<0.01;<br><br>Depression: CD active mean=10.86 (SD 5.9)<br>CD inactive mean=3.73 (SD 3)<br>Active >inactive p<0.01;<br><br>Anxiety: proportion above cut-off<br>CD active 71.4%<br>CD inactive 9.1%<br>Depression: proportion above cut-off<br>CD active 14%<br>CD inactive 0% |

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| Camara et al. 2011 (31)<br><br>Switzerland<br><br>Quality: 9/15 | **prospective cohort;** 18 months observation, recruited from regional hospitals, and private practices | 468 **CD** participants, mean age= 41.83 (SD 14.42), 50.6% female<br><br>**Active:** 106<br>**Inactive:** 362 | Anxiety: HADS-A<br><br>Depression: HADS-D<br><br>Disease activity: CDAI (>/=100 points increase from baseline), need for aggressive treatment, complications | Anxiety: CD active mean=8.82 (SD 4.45)<br>CD inactive mean=6.12 (SD 4.01); p<0.001<br><br>Depression: CD active mean=5.97 (SD 4.28)<br>CD inactive mean=3.81 (SD 3.68); p<0.001 |
| Diaz Sibaja et al. 2007 (32)<br><br>Spain<br><br>Quality: 5/15 | **randomised controlled trial;** baseline data reported | 57 IBD participants, 34 CD, 23 UC<br><br>**Active:** none<br>**Inactive**: 57 | Anxiety: HADS-A, SCL90R<br><br>Depression: BDI (cut-off >9), HADS-D (>/= 8), SCL-90-R (no cut-off)<br><br>Disease activity: unreported | Anxiety:<br>Treatment, inactive IBD<br>HADS-A mean=9.62 (SD N/A)<br>SCL90-A mean=1.07 (SD N/A)<br>Control, inactive IBD<br>HADS-A mean= 6.36 (SD N/A)<br>SCL90-A mean= 0.75 (SD N/A)<br><br>Depression:<br>Treatment, inactive IBD<br>BDI mean=13.9 (SD N/A)<br>HADS-D mean= 6.30 (SD N/A)<br>SCL90-A mean=1.51(SD N/A)<br>Control, inactive IBD<br>BDI mean=7.71 (SD N/A)<br>HADS-D mean= 4.36 (SD N/A)<br>SCL90-D mean= 0.81(SD N/A)<br><br>Anxiety, proportion above cut-off<br>Treatment, inactive IBD HADS-A 35.3%<br>SCL90R-A 50%<br>Depression, proportion above cut-off<br>Treatment, inactive IBD<br>BDI moderate 20.6%, severe 5.9%<br>HADS-D 17.6%<br>SCL90-D 55.9% |

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| Farrokhyar et al. 2006 (33)<br><br>Canada<br><br>Quality: 8/15 | **cross-sectional;** consecutively recruited from university ambulatory gastroenterology clinic | 361 IBD participants<br>239 CD, 122 UC<br><br>**Active:** 212; other data N/A<br>**Inactive**: 149; 77 aged <40 years, 54% female | Anxiety: HADS-A<br><br>Depression: HADS-D<br><br>Cut-off score >7 for both<br><br>Disease activity: Modified/Simplified Disease Activity Index (DAI) (cut-off N/A) | Anxiety: proportion above cut-off<br>IBD inactive 20.9%<br>CD inactive 29.8%<br>UC inactive 20.5%<br><br>Depression: proportion above cut-off<br>IBD inactive 3.4%<br>CD inactive 7.7%<br>UC inactive 13.6%<br><br>Anxiety & Depression:<br>IBD inactive 6.1%<br>CD inactive N/A<br>UC inactive N/A<br><br>Data for active IBD N/A |
| Gandhi et al. 2014 (34)<br><br>USA<br><br>Quality: 5/15 | **cross-sectional;** recruited from the GI/IBD and infusion university clinics during a regularly scheduled visit | 70 IBD participants, 69% CD, mean age 43.26 years (SD 16.50), 59% female, 73% Caucasian<br><br>**Active:** 18<br>**Inactive:** 43<br>(does not add up to 70, some data missing) | Anxiety: not measured<br><br>Depression: BDI<br><br>Disease activity: HBI, modified HBI (cut-off >/= 5) | Depression:<br>IBD active mean=16.4 (SD 9.9)<br>IBD inactive mean= 6.4 (SD 6.0); p<.0.001 |
| Goodhand et al. 2012 (20)<br><br>UK<br><br>Quality: 8/15 | **cross-sectional;** IBD patients recruited from tertiary referral centre; controls recruited from healthy volunteers attending the hospital for an unrelated research study | 204 IBD participants<br><br>103 UC mean age 42.1= years (SD 14.2), 59% female, 72% Caucasian, 38% active UC; 101 CD mean age 42.8=years (SD 14.3), 57% female, 88% Caucasian, 27% active CD<br><br>**Active:** 62 | Anxiety: HADS-A<br><br>Depression: HADS-D<br>Cut-off score > 7 for both<br><br>Disease activity: SCCAI (cut-off >2 with a Baron's sigmoidoscopic score >1), CDAI (cut-off >150), faecal calprotectin (cut-off >50 mg/kg) and/or CRP(cut-off >10 mg/L) | Anxiety: UC active mean=9.7 (SD 4.7)<br>CD active mean=9.7 (SD 3.7)<br>UC inactive mean=7.8 (SD 3.5)<br>CD inactive mean=8.1 (SD 3.7)<br>Controls mean=3.2 (SD 1.8)<br>Inactive UC/CD=Active CD/UC > controls p<0.0001<br><br>Depression: UC active mean= 6.1 (SD 3.6)<br>CD active mean=5.6 (SD 2.3)<br>UC inactive mean =3.3 (SD 2.4)<br>CD inactive mean=4.2 (SD 3.6)<br>Controls mean= 1.7 (SD 1.4)<br>Inactive UC/CD=Active CD/UC > controls p<0.0001 |

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| | | **Inactive:** 142 | | |
| Graff et al. 2006 (4)<br><br>Canada<br><br>Quality: 11/ 15 | **population-based cohort;** recruited from province-wide university IBD research registry | 356 IBD patients<br><br>169 UC mean age= 43.0 years (SD 14.7), 58% female, 88% Caucasian; 187 CD mean age= 38.5 years (SD 14.6), 61% female, 93% Caucasian<br><br>**Active:** 109 UC; 135 CD<br>**Inactive**: 56 UC; 48 CD | Anxiety: Health Anxiety Questionnaire<br><br>Depression: not measured<br><br>Disease activity: MIBDI Active disease=symptoms daily-few days/month | Anxiety: UC active mean=15.07 (SD 9.16)<br>UC inactive mean=9.29 (SD 5.59); p=0.01<br><br>CD active mean=17.98 (SD 10.6)<br>CD inactive mean=11.85 (SD=7.70); p=0.01 |
| Horst et al. 2015 (35)<br><br>USA<br><br>Quality: 10/15 | **retrospective cohort;** consecutively recruited from single tertiary care IBD | 69 IBD participants, 16 UC, 53 CD, median age 33 years, 58% female<br><br>**Active:** 69 active initially<br>**Inactive:** some (n=N/A) became inactive during study | Anxiety: not measured<br><br>Depression: Patient Health Questionnaire-9 (PHQ-9)<br><br>Cut-off score >/=10<br><br>Disease activity: HBI, SCCAI (cut-off N/A) | Depression: IBD active mean=12 (IQR 5,14<br>IBD inactive mean=6 (IQR: 3, 14)<br>p<0.05 |
| Iglesias et al. 2009 (36)<br><br>Spain<br><br>Quality: 8/15 | **cross-sectional**; consecutively recruited from inflammatory bowel disease unit | 92 **CD** participants mean age=37 years (SD=11.4), 47.8% female<br><br>**Active:** none<br>**Inactive:** 92 | Anxiety: HADS-A<br><br>Depression: HADS-D<br>Cut-off score >/=8 for both<br><br>Disease activity – CDAI (cut-off >/=150), HBI (cut-off >3), CRP (cut-off >5 mg/L) | Anxiety: proportion above cut-off<br>CD inactive 39%<br><br>Depression: proportion above cut-off<br>CD inactive 24% |
| Jedel et al. 2013 | **cross-sectional;** | 50 **UC** participants | Anxiety: STAI | Anxiety: UC mild active mean=35.37 (SD 8.72) |

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| (37)<br><br>USA<br><br>Quality: 6/15 | recruited from university medical centre | mean age 42.2 years (SD 12.3), 62% female, 78% Caucasian<br><br>**Active:** none<br>**Inactive:** 50 | Depression: BDI<br><br>Disease activity: Mayo Score Disease Activity Index (MSDAI), 0=inactive, 1-2=mild symptoms | UC inactive mean=40.74 (SD 14.17)<br>(p=n.s.)<br><br>Depression: UC mild active mean=8.27 (SD 8.5)<br>UC inactive mean=8.13 (SD 8.18)<br>(p=n.s.) |
| Kappelman et al. 2014 (38)<br><br>USA<br><br>Quality: 6/15 | **Cross-sectional and longitudinal;** internet-based cohort recruited from IBD patient organisation | 10,634 IBD participants (6689 CD, 3945 UC or IC), mean = 44 years (SD 14.8), 71% female<br><br>**Active:** N/A<br>**Inactive:** N/A | Anxiety: PROMIS anxiety items<br><br>Depression: PROMIS depression items<br><br>Disease activity: CDAI-short, SCCAI; active disease corresponds to a SCDAI of </=150 points or a score >2 or an increase in SCCAI of >5 points. | Anxiety: IBD mild active mean=52 (SD 9)<br>IBD moderate active mean=55 (SD 9)<br>IBD severe active mean=59 (SD 9)<br>IBD inactive mean=49 (SD 8)<br>Depression: IBD mild active mean=50 (8)<br>IBD moderate active mean= 53 (SD 9)<br>IBD severe active mean=58 (SD 10)<br>IBD inactive mean=47 (SD 7)<br><br>all p <0.0001 |
| Kim et al. 2013 (39)<br><br>Korea<br><br>Quality: 7/15 | **cross-sectional;** recruited from 5 tertiary hospitals; age and sex-matched healthy controls recruited from university health centre of those attending for routine medical check-up | 226 IBD participants 107 CD , 119 UC, mean age =39.01 years (SD 15.63) years, 38% female<br><br>**Active:** none<br>**Inactive**: 226 | Anxiety: HADS-A<br><br>Depression: HADS –D Cut-off score >7 for both<br><br>Disease activity: CRP, ESR, haemoglobin, no new medications required or no change of dose required | Anxiety: proportion above cut-off<br>IBD inactive 27.4%<br><br>Depression: proportion above cut-off<br>IBD inactive 33.6% |
| Langhorst et al. 2013 (40)<br><br>Germany<br><br>Quality: 8/15 | **prospective;** 12 month observation, recruited through advertisements in local, regional newspapers and journal of IBD patient organisation | 75 IBD patients<br><br>**Active**: 28, mean age=45.1 years (SD 13.4), 32% female<br><br>**Inactive:** 47, mean age=48.7 years (SD 12.8) 57% female | Anxiety: HADS-A<br><br>Depression: HADS –D Cut-off score >7 for both<br><br>Disease activity: CAI (cut-off > 4 or an increase of >3 from baseline), patient diary, & sigmoidoscopy | Anxiety:<br>IBD active N/A<br>IBD inactive N/A<br><br>Depression:<br>IBD active mean=7.9 (SD=4.4)<br>IBD inactive mean =7.2 (SD 4) |

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| | | | | Depression: proportion above cut-off >7; >10<br>IBD active 50%; 32.1%<br>IBD inactive 49.6%; 23.4%<br>(all p=n.s.) |
| Larsson et al. 2008 (41)<br><br>Sweden<br><br>Quality: 4/15 | **cross-sectional;** recruited from university hospital | 742 IBD participants mean age 45 years (range 19–65) 51% female<br><br>**Active:** 166<br>**Inactive**: 554 (does not add up to 742, some missing) | Anxiety: HADS-A<br><br>Depression: HADS-D<br>Cut-off score >7 for both<br><br>Disease activity: yes/no questions | Anxiety:<br>IBD active median=7.0 (IQR 5.0-10.0)<br>IBD inactive median=5.0 (IQR 1.0-8.0)<br>(p<0.001)<br><br>Depression:<br>IBD active median=4.0 (IQR 2.0–7.0)<br>IBD inactive median=3.0 (IQR 1.0-5.0)<br>(p<0.001) |
| Lix et al. 2008 (42)<br><br>Canada<br><br>Quality: 11/15 | **population-based cohort;** 24 month disease activity monitoring; recruited from province-wide university IBD research registry | 356 IBD participants<br>187 CD, mean age= 38.5 years (SD 14.6) 61% female; 169 UC mean age= 43 years (SD 14.7), 59% female<br><br>**Active** (consistently): 109<br>**Inactive** (consistently): 60<br>**Fluctuating** activity: 174 | Anxiety: HAQ<br><br>Depression: not measured<br><br>Disease activity: MIBDI<br>Active disease=symptoms daily-few days/month | Anxiety: baseline; 24 months<br>CD consistently active mean=17.7 (SD 9.5); mean=14.6 (SD 9.6)<br>CD fluctuating mean=16.7 (SD 10.9); mean=10.5 (SD 7.3)<br>CD consistently inactive mean=12.2 (SD 9.1); mean=8.1 (SD 8.5)<br><br>UC consistently active mean=14.1 (SD 7.7); mean=12.9 (SD 8.7)<br>UC fluctuating mean=14.1 (SD 9.4); mean=10.6 (SD 8.2)<br>UC consistently inactive mean=9.0 (SD 5.4); mean=6.2 (SD 5.2)<br><br>consistently active> consistently inactive p<0.0001 |
| Long et al. 2014 (43)<br><br>USA<br><br>Quality: 6/15 | **cohort, internet based; elderly** (>/= 65 years); recruited from IBD patient organisation | 359 IBD participants mean age=70.2 years (SD 4.7) 62% female<br><br>**Active:** N/A<br>**Inactive:** N/A | Anxiety: not measured<br><br>Depression: Geriatric Depression Scale (GDS)<br>Cut-off score ≥5<br><br>Disease activity: CDAI , SCCAI, MIBDI (cut-offs N/A) | Depression: proportion above cut-off<br>IBD active 28.9%<br>IBD inactive 15.1%; p=0.002 |

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| Reigada et al. 2014 (44)<br><br>USA<br><br>Quality: 7/15 | **retrospective medical chart review; youth;** recruited from paediatric gastroenterology practice (completed survey as part of a different study) | 93 CD participants mean age= 14.7 years (SD 2.1) age range 9-18, 45% female<br><br>**Active:** 4<br>**Inactive:** 76 | Anxiety: Screen for Child Anxiety Related Disorders (SCARED); *higher scores indicate higher anxiety*<br>Cut-off score >/=20<br><br>Depression: not measured<br><br>Disease activity: HBI (cut-off >/=5) | Anxiety:<br>CD active mean rank=67.6<br>CD inactive mean rank=39.0; p=0.01 |
| Simren et al. 2006 (45)<br><br>Sweden<br><br>Quality: 8/15 | **cross-sectional;** recruited consecutive IBD and other GI patients attending a GI outpatient clinic | 223 IBD participants , 90 CD, 133 UC mean age=46 years (SD 0.9) years N/A % female<br><br>**Active:** 82<br>**Inactive:** 138 (does not add up to 223, some missing) | Anxiety: Psychological General Wellbeing Index-A, anxiety and depression subscales<br><br>Depression: Psychological General Wellbeing Index-D (PGWBI: *higher scores indicate better psychological well-being*)<br><br>Disease activity: CRP, ESR, platelets, endoscopy, steroid use | Anxiety: IBD active mean=21 (SD 4.8)<br>IBD inactive mean=23 (SD 4.7); p=0.004<br><br>Depression: IBD active mean=14 (SD 3.3)<br>IBD inactive mean=15 (SD 2.6); p=0.007 |
| Vidal et al. 2008 (46)<br><br>Spain<br><br>Quality: 7/15 | **cross-sectional;** recruited consecutive patients attending IBD outpatient hospital-based clinic | 147 IBD participants 76 CD, 71 UC mean age 37.2 years (range 18-75), 51.7% female<br><br>**Active:** 36<br>**Inactive:** 111 | Anxiety: HADS-A<br><br>Depression: HADS-D<br>Cut-off score >8 for both<br><br>Disease activity: CDAI (cut-off >/=150), TWI (cut-off >/=7) | Anxiety: IBD active mean=7.1 (range 1-13)<br>IBD inactive mean=7.2 (range 0-21); p=n.s.<br><br>Depression: IBD active mean=3.8 (range 1-13)<br>IBD inactive mean=3.7 (range 0-15);<br>p=n.s. |
| Zhang et al. 2013 (47)<br><br>USA<br><br>Quality: 6/15 | **cross-sectional;** recruited from university IBD program during regularly scheduled outpatient clinic appointments | 105 IBD participants 55 CD, 50 UC, mean age=33 ( SD 12.9) 45.5% female,<br><br>**Active:** 45<br>**Inactive**: 60 | Anxiety: not measured<br><br>Depression: BDI II cut-off >/=14<br>BDI for Primary Care (BDI-PC) cut-off score >/=4 | Depression: BDI-PC<br>CD active median = 12 (SD 8.89);<br>median = 4 (SD 2.93)<br>CD inactive median = 8 (SD 6.60);<br>Median =2 (SD 2.51)<br>UC active median = 10 (SD 8.66); |

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| | | | Disease activity: CDAI cut-off >/=150), Seo's Activity Index (SAI) (cut-off >/=120) | median=2 (SD=2.86)<br>UC inactive median = 6 (SD 10.3);<br>median = 1 (SD 3.69) |
| Zimmerman et al. 2013 (48)<br><br>USA<br><br>Quality: 8/15 | c**ross-sectional; youth;** recruited from 2 hospitals for sub-study of a cognitive behavioural therapy trial | 307 **CD** participants, 139 with **abdominal pain;** mean age=14 years (range 9-17), 50.1% female<br><br>**Active:** 151<br>**Inactive:** 156 | Anxiety: not measured<br><br>Depression: CDI<br>Cut-off score >9<br><br>Disease activity: P-CDAI (cut-off >10) | Depression: proportion above cut-off<br>CD active & abdominal pain 59 (49%)<br>CD inactive & no abdominal pain 47 (30%)<br>(p= N/A) |

**Table 4. Summary characteristics of the studies addressing controversy 3: Are rates of anxiety/depression similar or different in CD versus UC?** *(special populations indicated in grey)*

| **Authors, year and country** | **Study information Design; setting; recruitment** | **Participant characteristics (sample size, IBD type, age, sex)** | **Measures anxiety, depression , disease activity** | **Results** |
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| Addolorato et al. 2008 (27)<br><br>Italy<br><br>Quality: 6/12 | **cross-sectional;** consecutively recruited IBD outpatients from internal medicine outpatient setting | 135 IBD participants, mean age=43.9 years (SD 15.9), 57.8% female<br><br>**UC:** 74<br>**CD:** 61 | Anxiety: STAI<br>Cut-off score =40<br><br>Depression: Zung Self-Rating Depression Scale (Zung SDS)<br>Cut-off score >49<br><br>Disease activity: CDAI, Truelove-Witts Index (TWI) | Anxiety: proportion above cut-off<br>State- UC inactive 66%<br>UC active 92.4%<br>CD inactive55%<br>CD active 87.8%<br>Trait-UC inactive 47.6%<br>UC active 47.1%<br>CD inactive 35%<br>CD active 58.5%<br><br>Depression: proportion above cut-off<br>UC inactive 0%<br>UC active 15%<br>CD inactive 15%<br>CD active 21.9% |
| Ananthakrishnan et al. 2013 (51)<br><br>USA<br><br>Quality: 11/12 | **prospective registry-based cohort; bowel resection surgery** | 1237 IBD participants -no depression prior to surgery, mean age=48 years (SD N/A) , 47% female<br><br>**UC:** 530<br>**CD:** 707 | Anxiety: ICD9 codes for generalized anxiety (293.84, 300.0, 313.0)<br><br>Depression: ICD-9 codes for depressive disorders (296.2, 296.3, 298.0, 311)<br><br>Disease activity: complications, medications from medical chart | Anxiety (risk following IBD-related surgery):<br>CD year 1: 7%<br>CD year 2: 9%<br>CD year 5: 14%<br>UC year 1: 7%<br>UC year 2: 10%<br>UC year 5: 12%<br><br>Risk of anxiety post-surgery (compared to those without surgery)<br>CD (OR 1.20, 95% CI 0.93 – 1.55)<br>UC (OR 1.26, 95% CI 0.96 – 1.65).<br><br>Depression (risk following IBD-related surgery): |

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| | | | | CD year 1: 6%<br>CD year 2: 8%<br>CD year 5: 16%<br>UC year 1: 5%<br>UC year 2: 7%<br>UC year 5: 11%<br><br>UC=CD for risk of depression post-surgery (adjusted OR 1.11, 95% CI 0.84 – 1.47)<br>Risk of depression post-surgery (compared to those without surgery)<br>CD (adjusted OR 1.34, 95% CI 1.01 – 1.77)<br>UC (OR 1.21, 95% CI 0.93 – 1.58). |
| Ananthakrishnan, et al. 2013 (52)<br><br>USA<br><br>Quality: 10/12 | **cross-sectional;** cases from large multi-institution study using electronic medical record (EMR) | 10834 IBD cases<br><br>**UC**: 5429, mean age=50.3 years (SD 18.4), 58% female<br><br>**CD**: 540, mean age=47.1 years (SD 18.4), 57% female | Anxiety: ICD9 codes for generalized anxiety (293.84, 300.0, 313.0)<br><br>Depression: ICD-9 codes for depressive disorders (296.2, 296.3, 298.0, 311)<br><br>Disease activity: complications, medications from medical chart | Anxiety/Depression (reported combined)<br>UC: 19% prior to first surgery<br>CD: 18% prior to first surgery |
| Bennebroek Evertsz et al. 2012 (29)<br><br>the Netherlands<br><br>Quality: 5/12 | **cross-sectional**; consecutive outpatients attending a tertiary care centre. | 231 IBD participants, mean age=43.4 (SD 13.8 range 18-78), 56.3% female<br><br>**UC:** 93<br>**CD:** 138 | Anxiety: HADS-A<br><br>Depression: HADS-D<br>Cut-off score >/=8 for both<br><br>Disease activity: HBI and TWI | Anxiety: proportion above cut-off<br>UC 25.0%<br>CD 44.9%<br>(p=0.004)<br>Depression: proportion above cut-off<br>UC 21.1%<br>CD 27.8%<br>(p=0.329) |

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| Cohen at al. 2014 (53)<br><br>USA<br><br>Quality: 8/12 | **Population-based cohort;** newly diagnosed IBD patients recruited from state-wide IBD registry | 220 IBD participants<br><br>**UC:** 95, 44% between 18-34 years, 57% female, 40% married<br><br>**CD:** 125, 53% between 18-34 years, 64% female, 38% married | Anxiety: not measured<br><br>Depression: PHQ-8 Cut-off >/=10<br><br>Disease activity: HBI, SCCAI | Results stratified by IBD type and fatigue<br><br>Depression: proportion above cut-off<br>UC & fatigue 41.7%<br>CD & fatigue 42.3%<br>UC & nonfatigue 4.3%<br>CD & nonfatigue 6.4%<br><br>Fatigued vs. Non-fatigues CD p<.001<br>Fatigued vs. Non-fatigues UC p=.006 |
| Farrokhyar et al. 2006 (33)<br><br>Canada<br><br>Quality: 7/12 | **cross-sectional;** recruited consecutively from university ambulatory gastroenterology clinic | 149 participants with **inactive disease** 52% aged <40 years, 54% female and the analysis is provided for them<br>**UC**: 144, 47.7% female<br>**CD:** 105 , 57.1% female | Anxiety: HADS-A<br><br>Depression: HADS-D Cut-off score >/=7 for both<br><br>Disease activity: simplified Disease Activity Index (DAI) | Anxiety: proportion above cut-off<br>UC 20.5%<br>CD 29.8%<br>(p=0.24)<br>Depression: proportion above cut-off<br>UC 13.6%<br>CD 7.7%<br>(p=0.26) |
| Goodhand et al. 2012 (20)<br><br>UK<br><br>Quality: 5/12 | A **cross-sectional study**, IBD patients recruited at a tertiary referral centre, controls were healthy volunteers attending the hospital for an unrelated research study | 204 IBD participants<br>**UC**: 103, mean age= 42.1 years (SD14.2), 59% female, 72% Caucasian, 38% active disease<br><br>**CD:** 101 mean age= 42.8 years (SD 14.3), 57% female, 88% Caucasian, 27% active disease | Anxiety: HADS – cut-off > 7<br><br>Depression: HADS – cut-off > 7<br><br>Disease activity: CDAI and SCCAI, sigmoidoscopy, CRP | Anxiety:<br>Active CD M=9.7, SD=3.7<br>Active UC M=9.7, SD=4.7 (p= n.s.)<br>Inactive CD M=8.1, SD=3.7<br>Inactive UC M=7.8, SD=3.5 (p= n.s.)<br>Depression :<br>Active CD M=5.6, SD=2.3<br>Active UC M=6.1, SD=3.6 (p= n.s.)<br>Inactive CD M=4.2, SD=3.6<br>Inactive UC M=3.3, SD=2.4 (p= n.s.) |
| Hauser et al. 2011 (54)<br><br>Germany<br><br>Quality: 5/12 | A **cross-sectional study**, consecutive adult IBD patients attending three tertiary care centers for evaluation and/or therapy and members of the patient | 422 IBD participants<br><br>**UC**: 108 (44.5 (SD=13.7), 41.7% female)<br><br>**CD**: 314 (aged 43.2 (SD=11.0) years, 52.9% female) | Anxiety: HADS – cut-off >/=11<br><br>Depression: HADS – cut-off >/=11<br><br>Disease activity: the German Inflammatory Bowel Disease Activity | Anxiety:<br>CD M=7.4, SD=4.2<br>UC M=6.9, SD=3.6 (p=0.3)<br>Depression:<br>CD M=5.1, SD=4.0<br>UC M=5.7, SD=3.8 (p=0.2) |

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| | organisation, chronic liver disease patients attending one tertiary referral center, a random representative sample of German population | | Index | |
| Herzog at al. 2013 (55)<br><br>Switzerland<br><br>Quality: 5/12 | **cross-sectional; adolescents;** recruited as part of a prospective cohort study from regional hospitals, and private practices | 126 IBD participants<br><br>**CD**: 71, mean age 13.4 (SD=3.2), 38% female;<br><br>**UC/IC** 55, mean age 12.8 (2.7), 54% female | Anxiety: not measured<br><br>Depression: Child Depression Inventory (CDI) – cut-off N/A<br><br>Disease activity: PCDAI, PCAI | Depression:<br>CD M=6.57, SD=6.5<br>UC/IC=6.67, SD=4.1 |
| Iglesias-Rey at al. 2012 (57)<br><br>Spain<br><br>Quality: 5/12 | **cross-sectional**; consecutive patient recruitment from the hospital IBD unit | 484 IBD participants<br><br>**CD**: 192, mean age 38.3, 58.3% female, 46.9% single<br><br>**UC**: 292 mean age 47.0, 49.3% female, 25.0% single | Anxiety: HADS – cut-off >11<br><br>Depression: HADS – cut-off >11<br><br>Disease activity: HBI, Mayo Index | Anxiety:<br>CD M=4.73 (95% CI 4.14-5.34)<br>UC M=4.71 (95% CI 4.21-5.21) (p= N/A)<br><br>Depression:<br>CD M=7.18 (95% CI 6.58-7.78)<br>UC M=7.34 (95% CI 6.79-7.88) |
| Iglesias-Rey at al. 2014 (56)<br><br>Spain<br><br>Quality:5/12 | **cross-sectional**; consecutive patient recruitment from the hospital IBD unit | 793 IBD participants<br><br>**CD**: 323, mean age 39.9, 57.6% female, 45.2% single;<br><br>**UC**: 470 mean age 47.8, 49.8% female, 26.4% single | Anxiety: HADS – cut-off >/=11<br><br>Depression: HADS – cut-off >/=11<br><br>Disease activity: HBI, Mayo Index | Anxiety:<br>CD M=4.84 (95% CI 4.39–5.92)<br>UC M=4.92 (95% CI 4.53–5.31) (p=N/A)<br><br>Depression:<br>CD M=7.27 (95% CI 6.82–7.72)<br>UC=7.43 (95% CI 7.02–7.85) (p=N/A) |

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| Janke at al. 2006 (58)<br><br>Germany<br><br>Quality: 6/12 | **cross-sectional**; consecutive patients recruited from tertiary care centres and members of patient organisation | 429 IBD participants<br><br>**CD**: 317, mean age=43.2 (SD=11.0), 52.7% female<br><br>**UC**: 112, mean age=44.4 (SD=13.6), 42.8% female | Anxiety: HADS – cut-off >/= 11<br><br>Depression: HADS – cut-off >/= 11<br><br>Disease activity: German Inflammatory Bowel Disease Activity Index | Anxiety: proportion above cut-off<br>CD 20.5%<br>UC 14.8% (p= N/A)<br><br>Depression: proportion above cut-off<br>CD 9.3%<br>UC 13.0% (p= N/A) |
| Kappelman et al. 2014 (38)<br><br>USA<br><br>Quality: 4/12 | **nested cross-sectional;** part of longitudinal internet-based cohort of patients with IBD recruited via a patient organisation | 10,634 IBD patients 44 years, 71% female<br><br>CD: 6689<br><br>UC/IC: 3945 | Anxiety: The PROMIS, a minimally important difference between 2 and 6<br><br>Depression: The PROMIS, a minimally important difference between 2 and 6<br><br>Disease activity: CDAI (short), SCCAI | Anxiety:<br>CD M=52, SD=10<br>UC/IC M=52, SD=9 (p= N/A)<br><br>Depression:<br>CD M=54, SD=10<br>UC/IC M=54, SD=10 (p= N/A) |
| Kim et al. 2013 (39)<br><br>Korea<br><br>Quality: 5/12 | **cross-sectional;** IBD patients recruited from 5 tertiary hospitals and healthy controls (matched for age and sex) from people who visited a university health promotion center for a routine medical check-up | 226 IBD participants **with inactive IBD**, mean age 39.01 (SD=15.63) years, 37% female<br><br>CD: 107<br>UC: 119, | Anxiety: HADS – cut-off >7<br><br>Depression: HADS – cut-off >7<br><br>Disease activity: CRP, ESR, Hb, no new medications required or no change of dose required | Anxiety: proportion above cut-off and means (SD)<br>CD 30.8%, M=6.12 ± 3.89<br>UC 24.4%, M=4.97 ± 3.89 (p= n.s.)<br><br>Depression: proportion above cut-off and means (SD)<br>CD 40.2%, M= 6.12 ± 3.58<br>UC 27.7% M=4.97 ± 3.53 (p = 0.05) |
| Larsson et al. 2008 (41)<br><br>Sweden<br><br>Quality: 4/12 | **cross-sectional**; patients attending a university hospital | 742 IBD participants, aged 45 years, 51% female<br><br>**UC**: 496<br>**CD**: 246 | Anxiety: HADS – cut-off >7<br><br>Depression: HADS – cut-off >7<br><br>Disease activity: yes/no questions | Anxiety:<br>CD Median=8.0, IQR= 5.7-13<br>UC Median=6.0, IQR= 3.0-9.5 (p<.01)<br><br>Depression:<br>CD Median=6.0, IQR= 2.0-9.0<br>UC Median =4.0, IQR= 1.0-6.0 (p<.05) |

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| Lerebours et al. 2007 (21)<br><br>France<br><br>Quality: 9/12 | **population-based case-control**; recruited newly diagnosed IBD patients (< 6 months) identified from an IBD registry; healthy controls recruited from blood donor clinics in the same area and in the same time period– no GI disease history | 241 IBD cases<br><br>**UC**: 74, mean age 36.1 (SD=15.1), 50% female<br><br>**CD**: 167, mean age 32.3 (SD=13.1), 62% female | Anxiety: Bates Anxiety Scale – cut-off N/A<br><br>Depression: BDI – cut-off ≥ 4<br><br>Disease activity: unspecified | Anxiety: proportion above cut-off and means (SD<br>CD M=52.2±25.2,<br>UC M=40.31 ± 21.65 (p<.03)<br><br>Depression: proportion above cut-off and means (SD)<br>CD 61%, M=7.41 ± 5.87<br>UC 57%, M=6.13 ± 4.93 (p<.14) |
| Long et al. 2014 (43)<br><br>USA<br><br>Quality: 5/12 | **cohort;**<br>elderly patients recruited from a patient organisation | 359 IBD participants<br>mean age=70.2 years (SD 4.7) 62% female<br><br>**UC**: 134<br>**CD**: 224 | Anxiety: not measured<br><br>Depression: Geriatric Depression Scale (GDS) – cut-off ≥5<br><br>Disease activity: CDAI, SCCAI, Manitoba IBD Index | Depression: proportion above cut-off<br>CD 24.1%<br>UC 20.2% (p=n.s.) |
| Pellissier et al. 2010 (66)<br><br>France<br><br>Quality: 5/12 | **cross-sectional**;<br>IBD patients recruited from hospital tertiary GI clinic; age and sex matched healthy controls from clinical investigation centre | 48 IBD participants;<br><br>**UC**: 22, mean age=42 (SD=16), 59% female<br><br>**CD**: 26, mean age 43 (SD=14), 69% female | Anxiety: STAI – cut-off N/A<br><br>Depression: CES-D – cut-off N/A<br><br>Disease activity: HBI, UCAI | Anxiety :<br>State Anxiety<br>CD M=30.50 +/- 1 1.39<br>UC M=31.30 +/- 1.71 (p= N/A)<br>Trait Anxiety<br>CD M=35.85 +/- 1.60<br>UC 38.92 +/-2.03 (p= N/A)<br>Depression:<br>CD M=7.71 +/- 1.22<br>UC 12.30 +/- 2.17(p= N/A) |

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| Rochelle and Fidler 2013 (59)<br><br>UK<br><br>Quality: 3/12 | **cross-sectional;** outpatients prospectively enrolled out of a gastroenterology department at a teaching hospital. | 102 IBD participants, mean age 41.9 years (SD = 16.57), 65.7% female<br><br>**UC**: 46<br>**CD**: 56 | Anxiety: HADS – cut-off >/=8<br><br>Depression: HADS – cut-off >/=8<br><br>Disease activity: blood tests | Anxiety:<br>UC M=9, SD= N/A<br>CD M=8.68, SD = N/A (p= N/A)<br>Depression:<br>UC M=6.93, SD= N/A<br>CD M=6.8, SD= N/A (p= N/A) |
| Schuman at al. 2013 (60)<br><br>USA<br><br>Quality: 4/12 | **cross-sectional**; **youth**; part of a larger longitudinal multisite assessment project, recruited at hospital-based paediatric gastrointestinal clinics. | 122 IBD adolescents mean age 15.7 (SD = 1.3) years, 48.4% female<br><br>**UC**: 26<br>**CD**: 96 | Anxiety: not measured<br><br>Depression: CDI – cut-off N/A<br><br>Disease activity: The Lichtiger Colitis Activity Index (LCAI), PCDAI, blood tests | Depression: proportion above cut-off<br>CD 21.2 %<br>UC 16.7% (p=n.s.) |
| Selinger et al. 2013 (61)<br><br>Australia<br><br>Quality: 4/12 | **cross-sectional**; recruited from tertiary care hospital outpatient clinics and local office based gastroenterologists | 192 IBD patients, age N/A, 53% female<br><br>**CD**: 106<br>**UC**: 124 | Anxiety: HADS – cut-off >7<br><br>Depression: not measured<br><br>Disease activity: unspecified | Anxiety:<br>CD M=7.2<br>UC M=6.6 (p=0.3) |
| Sulz et al. 2013 (62)<br><br>Switzerland<br><br>Quality: 6/12 | nationwide multicentre **prospective observational population-based;** must have been diagnosed at least 4 months before inclusion or had at least one recurrence | 1187 participants, median age 42.6±13.9, 53% females<br><br>**CD**: 699<br>**UC**: 488 | Anxiety: not measured<br><br>Depression: HADS – cut off >/= 8<br><br>Disease activity: CDAI and TWI, blood | Depression: proportion above cut-off<br>CD 17%<br>UC 18% (p=n.s.) |

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| Timmer et al. 2007 (63)<br><br>Germany<br><br>Quality: 5/12 | Cross-sectional; consecutive **males** with IBD presenting to the departments of internal medicine and surgery, and randomly selected from the members' list of the national patient organization | 280 IBD males (4 groups A clinical population, B patient organisation) median age 38 years<br><br>**CD**: 170 (61 in group A, 109 in group B)<br>**UC**: 110 (33 in group A, 77 in group B) | Anxiety: HADS > 10<br><br>Depression: HADS > 10<br><br>Disease activity: CDAI, CAI | Anxiety: proportion above cut-off<br>CDA 33%<br>UCA 36%<br>CDB 17%<br>UCB 20% (p= N/A)<br><br>Depression: proportion above cut-off<br>CDA 25%<br>UCA 18%<br>CDB 9%<br>UCB 9% (p= N/A) |
| Timmer at al. 2008 (64)<br><br>Germany<br><br>Quality: 4/12 | **cross-sectional;** females with IBD presenting to the university departments of internal medicine and surgery, and a random sample from the national patients organization | 336 IBD participants (4 groups A clinical population, B patient organisation), median age 38 years<br><br>**UC**: 117<br><br>**CD**: 219 | Anxiety: HADS > 10<br><br>Depression: HADS > 10<br><br>Disease activity: CDAI, CAI | Anxiety: proportion above cut-off<br>CDA 37%<br>UCA 30%<br>CDB 30%<br>UCB 22% (p= N/A)<br><br>Depression: proportion above cut-off<br>CDA 21%<br>UCA 35%<br>CDB 10%<br>UCB 10% (p= N/A) |
| Van der Valk et al. 2014 (65)<br><br>the Netherlands<br><br>Quality: 8/12 | **prospective cohort;** web-based survey circulated to IBD outpatients at university hospitals and general hospitals | 2282 IBD participants<br><br>**UC:** 909, mean age=46.1 (SD 11.4), 55% female, 83% in remission<br><br>**CD**: 1,373, mean age=44.1 (SD 11.8), 66% female, 85% in remission | Anxiety: not measured<br><br>Depression: No scale name provided.<br><br>Disease activity: patient self-reported | Depression: proportion above cut-off<br>UC 9.9%<br>CD 10.3%; p= N/A |

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| Van Langenberg & Gibson 2014 (26)<br><br>Australia<br><br>Quality: 5/12 | **cross-sectional** and **longitudinal;** recruited consecutively from hospital IBD clinic, invited in person at a clinic visit or through phone; age- and sex-matched cohort of healthy subjects was consecutively recruited through local advertisement | 294 IBD participants<br><br>**UC**:113, mean age=50 years (range 18–72), 55% female<br><br>**CD**:181, mean age= 41 years (range 18-68), 54% female | Anxiety: HADS cut-off >7<br><br>Depression: HADS cut-off >7<br><br>Disease activity: HBI and SCCAI | Anxiety:<br>UC median=7<br>CD median=8; p= N/A<br><br>Depression:<br>UC median=7<br>CD median=8; p= N/A |
| Vidal et al. 2008 (46)<br><br>Spain<br><br>Quality: 6/12 | **cross-sectional;** recruited consecutively from those attending IBD outpatient hospital clinic | 147 IBD participants, mean age=37.2 years ( range: 18-75), 51.7% female, 111 in remission<br><br>**UC**:71<br>**CD**:76 | Anxiety: HADS – Cut-off score >8<br><br>Depression: HADS – Cut-off score >8<br><br>Disease activity: CDAI, TWI | Anxiety:<br>UC M=6.6 (SD 3.3)<br>CD M=7.6 (SD 3.7); p=n.s.<br><br>Depression:<br>UC M=3.3 (SD 3.6)<br>CD M=4.2 (SD 3.4); p=n.s. |
| Zhang et al. 2013 (47)<br><br>USA<br><br>Quality: 6/12 | **cross-sectional;** recruited from university IBD program during regularly scheduled outpatient clinic appointments | 105 IBD participants, mean age=33 years (SD 12.9), 45.5% female, 60 in remission<br>**UC**: 50<br>**CD**: 55 | Anxiety: not measured<br><br>Depression: BDI II cut-off >/=14, BDI for Primary Care (BDI-PC) cut-off score >/=4<br><br>Disease activity: CDAI, Seo's Activity Index (SAI) | Depression: BDI II; BDI-PC<br>UC median=8.5 (SD 9.13); median=1.5 (SD 3.11)<br>CD median=8 (SD 7.38); median=2 (SD 2.67); p=n.s.<br><br>Depression: proportion above cut-off<br>UC 20%<br>CD 29% |

**Table 5. Summary characteristics of the studies addressing controversy 4:** Are rates of anxiety/depression in IBD similar or different to that reported in other groups of medically ill patients? *(special populations indicated in grey)*

| **Authors, year and country** | **Study information Design; setting; recruitment** | **Participant characteristics (sample size, IBD type, age, sex)** | **Measures anxiety, depression, disease activity** | **Results** |
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| Addolorato et al. 2008 (27)<br><br>Italy<br><br>Quality: 7/14 | **cross-sectional;** consecutively recruited IBD outpatients from internal medicine outpatient setting | 1641 participants with GI disorders: mean age 43.9 (SD=15.9), 57.8% female<br><br>**IBD:** 135; 53 active UC, 41 active CD, 21 inactive UC, 20 inactive CD<br><br>**GI nonIBD**: helicobacter pylori (Hp) (n=559), small intestinal bacterial overgrowth (SIBO) (n=554), sugar malabsorption (n=394), rrritable bowel syndrome (IBS) (n=309), coeliac disease (n=168), chronic hepatitis (n=122), gastro-esophageal reflux disease (GERD) (n = 107), chronic gastritis without Hp infection (n=60), food allergy (n=25) | Anxiety: STAI<br>Cut-off score =40<br><br>Depression: Zung Self-Rating Depression Scale (Zung SDS)<br>Cut-off score >49<br><br>Disease activity: CDAI, Truelove-Witts Index (TWI) | Anxiety: proportion above cut-off<br>CD inactive (state) 55%<br>CD inactive (trait) 35%<br>CD inactive had lowest proportions compared to other 13 conditions (p=N/A)<br>UC active (state) 92.4%<br>Food allergies (state) 93%<br>UC active had second highest proportion compared to other 13 conditions<br><br>Depression: proportion above cut-off<br>UC inactive 0%<br>CD active 21.9%<br>IBS 51.7%<br>UC inactive had lowest proportion of depression compared to other 13 conditions (p=N/A) |
| Berrill et al. 2013 (15)<br><br>UK<br><br>Quality: 8/14 | **cross sectional;** IBD and IBS adult outpatients attending gastroenterology hospital-based clinics; healthy controls from local advertising | **IBD**: 150 (36% CD) mean age 45.7 (11.3), 63% female<br><br>**IBS:** 40, mean age 37.9 (11.7) 67% female<br><br>**Healthy:** 41, mean age 43.8 (13.4), 61% female<br>Age range for whole sample 18 to 65 | Anxiety: HADS-A<br><br>Depression: HADS-D<br><br>Disease activity: fecal calprotectin | Anxiety: IBD median=9, range 1-20<br>IBS controls median =11, range 0-20; (p=N/A)<br><br>Depression: IBD median= 5, range 0-16<br>IBS median=5, range 0-16; (p=N/A) |

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| Bol et al. 2010 (67)<br><br>the Netherlands<br><br>Quality: 8/14 | **cross-sectional;** IBD patients recruited from database at GI clinic in medical center, age and sex-matched; multiple sclerosis (MS) patients consecutive recruited from those referred to MS clinic in medical centre; IBD patients age and sex-matched to MS patients | **IBD:** 76 UC, mean age=45.3 years (SD 8.8) 68% female<br><br>**MS**: 88, mean age=43.6 years (SD 9.0), 70% female | Anxiety: not measured<br><br>Depression: HADS-D<br><br>Disease activity: CAI | Depression: UC mean=4.0 (SD 3.6)<br>MS mean=5.6 (SD 4.0); p<0.01 |
| Brandi et al. 2009 (68)<br><br>Brazil<br><br>Quality: 7/14 | **cross-sectional**; consecutive adult outpatients recruited from IBD centre at university hospital; consecutive adult GERD patients recruited from GI clinic at university hospital | **IBD**: 110 CD, mean age=38.2 years (SD 10.8), 50% female<br><br>**GERD:** 110, mean age=39.9 years (SD 13.9) 53% female | Anxiety: HADS-A<br><br>Depression: HADS-D; BDI<br>Cut-off score HADS≥ 8<br>Cut-off score BDI ≥21<br><br>Disease activity: CDAI | Anxiety: proportion above cut-off<br>CD 33.6%<br>GERD 22.7%; p=n.s.<br><br>Depression: BDI<br>CD mean=14, range 8-45<br>GERD mean = 13, range 4-49, p=n.s.<br><br>Depression: proportion above cut-off<br>CD 25.4%<br>GERD 8.2%; p=0.003 |
| Bullen et al. 2012 (69)<br><br>Australia<br><br>Quality: 5/14 | **cohort study;** recruited consecutive colorectal surgical patients with IBD or colon cancer prior to surgery | **IBD:** 29, mean age=60.62 years (SD 15.38), 59% female)<br><br>**Colon Cancer:** 38, mean age=59.32 years (SD 14.75), 50% female | Anxiety: HADS-A<br><br>Depression: HADS-D<br><br>Disease activity: not specified | Anxiety: IBD mean=5.93 (SD 3.38)<br>CC mean=7.22 (SD 4.74)<br>(p=0.222)<br>Depression: IBD mean=3.52 (SD 3.66)<br>CC mean=4.43 (SD 4.65)<br>(p=0.402) |

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| Calsbeek et al. 2006 (17)<br><br>the Netherlands<br><br>Quality: 5/14 | c**ross-sectional study; adolescents and young adults;** recruited via medical specialists in academic and specialized hospitals; diagnosis at least 6 months. Controls with chronic liver diseases, congenital disorders, food allergy and coeliac disease. | **IBD:** 305, mean age=20 years (SD 3.7), 54.8% females<br><br>**CLD**: 94 with chronic liver diseases, mean age=19.4 years (SD 4), 56.4% female<br><br>**ConD**: 137 with congenital disorders, mean age= 18.1 years (SD 3.8), 46.7% female<br><br>**FA**: 98 with food allergy, mean age =18.5 years (SD 3.8), 69.4% female<br><br>**CelD:** 124 with celiac disease, mean age=17.5 years (SD 3.7), 64.5% female | Anxiety: HADS-A<br><br>Depression: HADS-D<br><br>Disease activity: not measured | Anxiety: IBD mean=5.0 (SD 3.8)<br>CLD mean=6.2 (SD 4.4)<br>ConD mean=4.5 (SD 3.9)<br>FA mean=5.1 (SD 3.9)<br>CelD mean=3.7 (SD 3.2) (<0.001)<br><br>Depression: IBD mean=2.8 (SD 2.9)<br>CLD mean=3.6 (SD 3.5)<br>ConD mean=2.4 (SD 2.7)<br>FA mean= 2.6 (SD 2.5)<br>CelD mean=2 (SD 2.2) (p=0.026)<br><br>IBD participants had second highest anxiety and depression scores after chronic liver diseases. |
| Castaneda et al. 2013 (70)<br><br>Finland<br><br>Quality: 5/14 | **cross-sectional**; recruited consecutive **adolescents** with BD or juvenile idiopathic arthritis (JIA) from a children's hospital | **IBD**: 34; 17 CD, 16 UC, IC 1, mean age =16.3 years (SD 1.7), 44% female<br><br>**JIA:** 23, mean age=15.5 years (SD 1.2), 61% female | Anxiety: not measured<br><br>Depression: BDI<br><br>Disease activity: Physician Global Assessment, inflammatory markers (ESR, CRP, calprotectin) | Depression: IBD mean=7.9 (SD 7.6)<br>JIA mean=4.0 (SD 4.0); p=0.029 |
| Filipović et al. 2007 (71)<br><br>Serbia<br><br>Quality: 7/14 | **cross-sectional;** first episode IBD and newly diagnosed colon cancer (ColCa) recruited from hospital | **IBD**: 32, 11 CD, 21 UC, mean age=49.2 (SD 16.58) 59% female<br><br>**ColCa**: 40, mean age=63.5 (SD 9.14) 25% female | Anxiety: Hamilton's Anxiety Rating Inventory (HARI)<br><br>Depression: Hamilton's Depression Rating Inventory | Anxiety: IBD mean=16.22 (SD 7.42)<br>ColCa mean=9.73 (SD 6.03); p<0.01<br><br>Depression: IBD: mean=18.56 (SD 8.77)<br>ColCa mean=10.83 (SD 5.26); p<0.001 |

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| | | | (HDRI)<br><br>Disease activity: CDAI, Ulcerative Disease Scoring System (UDSS) | |
| Jayanath et al. 2014 (72)<br><br>Malaysia.<br><br>Quality: 5/14 | **cross-sectional**; **children** with a variety of GI issues recruited consecutively from a medical centre | 100 children, 49% aged 7–12 years, 51% aged 13-17 years old, 56% female<br><br>**IBD**: 26<br>**FAP**: 22 (functional abdominal pain)<br>**Biliary atresia**: 17<br>**Other GI illnesses:** 35 | Anxiety: not measured<br><br>Depression: CDI cut-off >55 (high score), 45-55 (moderate)<br><br>Disease activity: not specified | Depression: proportion scoring moderate; high<br>IBD: 46.2%; 23.1%<br>FAP: 27.3%, 50.0%<br>Biliary atresia: 41.2%, 23.5%<br>Other GI: 51.4%, 17.1% |
| Kovács & Kovács 2007 (73)<br><br>Hungary<br><br>Quality: 7/14 | **cross-sectional**; recruited IBS patients presenting to GI unit; recruited age and sex-matched IBD patient | **IBD:** 43, mean age=38.4 years (SD 12.9), 63% female<br><br>**IBS:** 46, mean age=39.8 years (SD 13.9), 70% female | Anxiety: STAI<br><br>Depression: BDI<br><br>Disease activity: not reported | Anxiety: IBD (state) mean =46.88 (SD 11.31)<br>IBS (state) mean=48.58 (SD 10.83); p=n.s.<br>IBD (trait) mean=46.80 (SD 11.75)<br>IBS (trait) mean=50.19 (SD 8.27); p=n.s.<br><br>Depression: IBD mean=11.62 (SD 9.72)<br>IBS mean=15.84 (SD 7.88); $p<0.05$ |

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| Lerebours et al. 2007 (21)<br><br>France<br><br>Quality: 11/14 | **population-based case-control**; recruited newly diagnosed IBD patients (< 6 months) and self-limited colitis (ASLC) patients identified from a registry of patients presenting with new GI symptoms | **IBD**: 167 CD mean age= 32.3 years (SD 13.1), 62% female; 74 UC mean age=36.1 years (SD 15.1), 50% female<br><br>**ASLC:** 69 mean age=40.6 years (SD 17.2), 36 female | Anxiety: Bates Anxiety Scale<br><br>Depression: BDI-short Cut-off score≥4<br><br>Disease activity: unreported | Anxiety: UC mean=40.31 (SD 21.65)<br>CD mean=52.2 (SD 25.2),<br>ASLC mean=46.99 (SD 22.93)<br>UC<ASLC p<0.002; CD=ASLC p=n.s.<br><br>Depression: UC mean=6.13 (SD 4.93)<br>CD mean=7.41 (SD 5.87)<br>ASLC mean=5.01 (SD 3.96)<br>UC>ASLC p<0.002; CD >ASLC p<0.03<br><br>Depression: proportion above cut-off<br>UC 57%<br>CD 61%<br>ASLC 45% |
| Miehsler et al. 2008 (74)<br><br>Austria<br><br>Quality: 7/14 | **cross-sectional;** consecutive outpatients with IBD and rheumatoid arthritis (RA) recruited from clinic at a university hospital | **IBD:** 302 mean age=37.3 years (SD 11.8), 56% female<br><br>**RA:** 109 mean age=53.3 years (SD 12.6), 78% female | Anxiety: HADS-A<br><br>Depression: HADS-D Cut-off score >/=8; >/==11<br><br>Disease activity: CDAI, CAI | Anxiety: proportion above cut-off 8; above cut-off 11<br>IBD 37%; IBD 18%<br>RA 25%; p=0.02 RA 14%;p=n.s.<br><br>Depression: IBD 18%; IBD 7%<br>RA 29%; p=0.01 RA15%; p=0.02 |

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| Mikocka-Walus et al. 2008 (75)<br><br>Australia<br><br>Quality: 5/14 | **cross-sectional** ; recruited consecutive outpatients with IBD, hepatitis C (HepC), and IBS from a gastroenterology outpatient clinic | **IBD**: 64, mean age=51 years (SD 15), 61% female<br><br>**HepC**: 41, mean age=45 years (SD 10), 49% female<br><br>**IBS:** 34 mean age=54 years (SD 13), 77% female | Anxiety: HADS-A cut-off >/=8; SCL90-A<br><br>Depression: HADS-D cut-off >/=8; SCL90-R-D<br><br>Disease activity : CDAI, SCCAI | Anxiety: HADS-A<br>IBD: mean=6.57 (SD 3.44)<br>HepC mean=6.97 (SD 4.83)<br>IBS mean=7.97 (SD 2.92); p=n.s.<br>SL90-A<br>IBD mean=51.79 (SD 9.74)<br>HepC mean=57.63 (SD 13.61)<br>IBS mean=56.82 (SD 8.77)<br>HepC > IBD, p=0.013<br><br>Anxiety: proportion above cut-off<br>IBD N/A%<br>HepC N/A%<br>IBS N/A%; p=n.s.<br><br>Depression: HADS-D<br>IBD mean=4.07 (SD 2.86)<br>HepC mean=5.36 (SD 4.96)<br>IBS mean=4.29 (SD 3.70); p=n.s.<br>SCL90-D<br>IBD mean=58.04 (SD 9.94),<br>HepC mean=62.26 (SD 12.50)<br>IBS mean=59.99 (SD 10.16); p=n.s.<br><br>Depression: proportion above cut-off<br>IBD 11%<br>HepC 34%<br>IBS 15%<br>HepC>IBD/IBS p=0.009 |
| Naliboff et al. 2012 (76)<br><br>USA<br><br>Quality: 4/14 | **cross-sectional**; recruited IBD and IBS patients seen in a university medical centre | **IBD**: 126, mean age=40.5 years (SD 13.3), 53% female<br><br>**IBS:** 564, mean age=46.7 years (SD 13.7), 69% female | Anxiety: SCL90R-A<br><br>Depression: SCL90-D<br><br>Disease activity: unreported | Anxiety: IBD mean=53.08 (SD 12.61)<br>IBS mean=54.10 (SD 11.58); p=n.s.<br><br>Depression: IBD mean=58.78 (SD 11.28)<br>IBS mean=58.30 (SD 10.36); p=n.s. |

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| Piche et al. 2010 (24)<br><br>France<br><br>Quality: 7/14 | **cross-sectional;** CD and IBS participants recruited from 5 university hospitals | **IBD:** 92 CD in remission, mean age=35.9 years (SD 12.3), 59% female<br><br>**IBS:** 40, mean age=40.9 years (SD 9.5); 70% female | Anxiety: HADS-A<br><br>Depression: BDI-S<br><br>Disease activity: CDAI, Haemoglobin, CRP, ESR, platelet count, albumin | Anxiety:<br>CD with IBS-type symptoms mean=8.7 (SD 3.9)<br>CD without IBS-type symptoms mean=8.5 (SD 3.4)<br>IBS mean=9.7 (SD 4.5)<br>p=n.s.<br><br>Depression:<br>CD with IBS-type symptoms mean=6.4 (SD 5.6)<br>CD without IBS-type symptoms mean=4.2 (SD 3.9)<br>IBS mean=5.9 (SD 5.4)<br>p=n.s. |
| Seres et al. 2008 (77)<br><br>Hungary<br><br>Quality: 5/14 | **cross-sectional;** recruited IBD and IBS patients presenting at three ambulatory tertiary care gastroenterology departments | **IBD**: 66 UC, mean age =38.89 years (SD 13.30), 70% female<br><br>**IBS**: 88, mean age =41.59 years (SD 13.71) , 81% female | Anxiety: SCL90R-A<br><br>Depression: SCL90R-D<br><br>Disease activity: unreported | Anxiety: UC mean (raw score)= 0.88 (SD 0.75)<br>IBS mean (raw score)=1.26 (SD 0.90);p<0.01<br><br>Depression:<br>UC mean (raw score)= 1.13 (SD 0.87)<br>IBS mean (raw score)=1.45 (SD 0.98); p<0.05 |
| Tkalčić, et al. 2010 (78)<br><br>Croatia<br><br>Quality: 6/14 | **cross-sectional;** recruited consecutive IBD and IBS patients from university gastroenterology clinic | **IBD:** 43, mean age=42.90 years (SD 15.44), 49% female<br><br>**IBS**: 56, mean age=48.64 years (SD 13.04), 64% female | Anxiety: STAI<br><br>Depression: BDI cut-off >/=13<br><br>Disease activity: CDAI, CAI | Anxiety: IBD mean=34.51 (SD 12.10)<br>IBS mean=40.98 (SD 11.68); p<0.01<br><br>Depression: IBD mean=12.44 (SD 7.48)<br>IBS mean=13.0 (SD 7.37); p=n.s. |

**Table 6. Summary characteristics of the studies addressing controversy 5: Do anxiety and depression precede and/or follow onset of IBD?** *(special populations indicated in grey)*

| Authors, year and country | Study information: Design; setting; recruitment | Participant characteristics (sample size, IBD type, age, sex) | Measures Anxiety, depression, disease activity | Results |
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| Loftus et al. 2011 (22)<br><br>USA<br><br>Quality: 12/14 | **retrospective cohort;** observations from minimum of 6 months to a 6.5 years; **youth**; IBD and nonIBD age and sex-matched cases taken from national database of health service claims data for approximately 100 third-party payers, including employers and health plans; | **IBD**: 2,144 CD cases<br><br>**Controls**: 10,720 nonIBD cases<br>Both groups: mean age at index date 11.8 years, (SD 0.4) ,46.1% female | Anxiety: ICD 9 CM codes 293.84, 300.0x, 313.0x (includes anxiety states and disorder)<br>Depression: ICD 9 CM codes 296.2x, 296.3x, 298.0x, 300.4x, 309.1x, 311.xx (includes major depressive disorder, depressive type psychosis, dysthymia)<br><br>Disease activity: based on treatment history | Anxiety:<br>CD incident rate=1.81 cases per 100 patient years<br>Controls incident rate= 0.57 cases; p<0.0001<br><br>• Having **CD** increased the risk of developing an anxiety disorder (adjusted HR=2.28, 95% CI=1.65-3.17) p<0.0001<br>• **teenaged girls with CD** had an increased risk of developing an anxiety disorder (HR = 2.45; 95% CI = 1.41–4.25)<br>• **teenaged boys with CD aged 13-17** had an increased risk of developing an anxiety disorders (HR = 3.01; 95% CI = 1.73– 5.24).<br><br>CD persistent anxiety rate=0.53/ 100 patient years<br>Controls persistent anxiety rate=0.09/100 patient years; p<0.0001<br><br>• Having CD increased the risk of developing a persistent anxiety disorder (adjusted HR = 4.35; 95 % CI = 2.22 – 8.50).<br><br>Depression:<br>CD incident rate=2.69 cases per 100 patient years<br>Controls incident rate=1.22 cases; p<0.0001<br><br>• Having CD increased the risk of developing depression (adjusted HR=1.74, 95% CI=1.35-2.25) p<0.0001<br>• **CD boys aged 12 years or younger** had an increased risk of developing depression (HR = 2.55; 95% CI = 1.15–5.67)<br>• **teenaged boys with CD aged 13-17 years** had an increased risk of developing depression |

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| | | | | (HR = 1.99; 95% CI = 1.32– 3.02)<br><br>CD persistent depression rate=0.87/ 100 patient years<br>Controls persistent depression rate=0.26/100 patient years; p<0.0001<br><br>• Having CD increased the risk of developing persistent depression (adjusted HR=2.75, 95% CI=1.73-4.38) |
| Walker et al. 2008 (9)<br><br>Canada<br><br>Quality: 11/14 | **population-based cohort;** 24 months observation; recruited from province-wide university IBD research registry; control cases obtained from national health survey and age, gender and region-matched | **IBD**: 351 participants, mean age=43 years (SD 14.06), 60% female, 95% Caucasian, 48% CD, 46% UC/ulcerative proctitis, 6% indeterminate colitis.<br><br>**Controls**: 779 cases, mean age=40 years (SD 14.51), 59.1% female | Anxiety: 12 month and lifetime prevalence of anxiety disorders assessed by Comprehensive International Diagnostic Interview (CIDI);<br><br>Depression: 12 month and lifetime prevalence of mood disorders assessed by CIDI<br><br>Disease activity: MIBDI | Anxiety disorder:<br>1st onset 10 years or more before IBD onset: 70%<br>1st onset 2-9 years before IBD onset: 9%<br>1st onset and IBD onset < 2 years apart: 13%<br>1st onset 2 or more years after IBD onset: 8%<br><br>Mood disorder:<br>1st onset 10 years or more before IBD onset: 31%<br>1st onset 2-9 years before IBD onset: 23%<br>1st onset and IBD onset < 2 years apart: 23%<br>1st onset 2 or more years after IBD onset: 23%<br><br>Mean age of IBD symptom onset with lifetime anxiety or mood disorder: 29.1 years<br>Mean age of IBD symptom onset without anxiety or mood disorder: 33.1 years.; p=0.012<br><br>Direct comparisons with matched controls (with data available for three anxiety disorders) found lifetime prevalence (IBD vs controls) as follows: **social anxiety disorder lower in IBD** (6% vs 11%, OR 0.52, 95% CI 0.32–0.85), **panic disorder not significantly different** (8.0% vs 4.7%, OR 1.59, 95% CI 0.96–2.63), **agoraphobia without panic not significantly different** (1.1% vs 0.6%, OR 1.44, 95% CI 0.37–5.55), and **major depression higher** (27.2% vs 12.3%, OR 2.20, 95% CI 1.64–2.95). |

Table 7: Summary of evidence for controversies in relation to co-occurrence of anxiety and depression with IBD

| | Controversy | Answer to controversy | Confidence level* |
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| 1 | IBD versus healthy/general population controls | Rates of anxiety and depression higher in IBD participants compared to healthy controls | MODERATE |
| 2 | IBD active versus IBD inactive | Rates of anxiety and depression higher in those with active compared to inactive IBD | MODERATE |
| 3 | CD versus UC | Rates of anxiety and depression modestly higher in those with CD compared to UC | MODERATE |
| 4 | IBD versus medically ill controls | Rates of anxiety and depression lower in IBD participants compared to those with other, primarily gastrointestinal, chronic illnesses | MODERATE |
| 5 | Preceding or following IBD onset | No prospective studies on anxiety or depression preceding IBD.<br><br>Adults with IBD more likely to develop anxiety prior to IBD onset; more likely to develop depression prior to IBD onset, but substantial proportion develop depression after onset. In children, higher risk of developing either anxiety or depression after IBD onset compared to controls. | HIGH |

* based on the quality appraisal process