Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases

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Background: Although mental health concerns are known to occur commonly for those with inflammatory bowel diseases (IBD), the nature of this comorbid relationship has not been systematically reviewed to date. A review in 2007 identified 5 controversies regarding anxiety/depression rates and various comparators between and within IBD. We aimed to systematically analyze and critique the current evidence regarding this comorbidity, providing an update to the 5 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% versus 9.6%, depression 21.2% versus 13.4%; (2) IBD inactive versus IBD active disease (n = 26): anxiety 28.2% versus 66.4%, depression 19.9% versus 34.7%; (3) ulcerative colitis versus Crohn's disease (n = 28): anxiety 31% versus 37%, depression 22% versus 24.4%; (4) IBD versus other chronic medical conditions (n = 17): anxiety 41.9% versus 48.2%, depression 14.5% versus 28.4%; (5) onset of anxiety/depression before or after IBD onset (n = 2): adults more likely to develop anxiety/depression before IBD onset, but a substantial proportion develops depression after onset; an increased risk for children of developing anxiety/depression after 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.

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Key Words: anxiety, depression, inflammatory bowel disease, systematic review

Inflammatory bowel diseases (IBDs), of which Crohn's disease (CD) and ulcerative colitis (UC) are subtypes, are chronic relapsing inflammatory conditions of the gastrointestinal tract with unclear etiology and unpredictable course. Currently, 322 per 100,000 people are diagnosed with CD and up to 505 per 100,000 people are affected by UC around the world.[1]

Because of 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.[2–7] In particular, a sizeable proportion of individuals with IBD have been identified as experiencing comorbid anxiety and/or depression.[7–9] When left untreated, these mental disorders have been linked to more severe IBD symptoms and more frequent IBD flares,[6] higher hospitalization rates,[10] and lower compliance with treatment[11] than for individuals without these comorbidities. 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 center with comorbid anxiety and/or depressive symptoms did not receive adequate care.[12] According to a recent national audit in the United Kingdom, only 12% of IBD services have access to clinical psychology through 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

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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 article exploring the comorbidity of anxiety and depression with IBD.[9] We endeavored to answer 5 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 comorbidity in the IBD context.

In the present review, we systematically identify, analyze, 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: Does anxiety/depression (both symptoms and disorders) precede and/or follow onset of IBD?

In the previous review, databases were searched for articles published between 1980 and 2005; we are now reassessing 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

1. Studies concerning IBD (including CD, UC, and indeterminate colitis) diagnosed using any well-established criteria (e.g., Montreal classification);
2. 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) of anxiety and depression;
3. Studies with either adult or pediatric populations;
4. Studies published between 2005 and 2014;
5. Controlled studies, including randomized controlled trials (baseline data only), with any of prospective, retrospective, and cross-sectional designs;
6. Peer-reviewed papers.

Exclusion Criteria

1. Studies using mood or QoL scales where no independent anxiety or depression scale/dimension exists;
2. Studies focusing on other psychological variables, such as distress, coping, personality, or QoL, without specific measures of depression or anxiety;
3. Interventional studies (i.e., natural course of IBD/mental disorders cannot be observed);
4. Studies in languages other than English;
5. Studies published before 2005 as the study is an update to a previous review[9];
6. Conference abstracts or any short articles with incomplete data presented;
7. Case reports, case series, or qualitative research;
8. Reviews, opinion articles;
9. 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, Supplemental Digital Content 1, http://links.lww.com/IBD/B142 provides the search strategy and search results. Reference management was done through EndNote (version X6; Thomson Reuters, Philadelphia, PA).

Data Collection and Analysis

The systematic review was undertaken based on the recommended PRISMA statement guidelines (http://www.prisma-statement.org). In the first phase, 2 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 articles of those identified in phase one were independently evaluated by 2 reviewers to determine if they included data to address any one or more of the 5 controversies. That is, after checking general selection criteria, articles 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 (Fig. 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. Furthermore, this review focused on anxiety and depression rates at 1 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 [CIs] or odds ratios, as appropriate) for rates, and weighted mean values on a common scale where data were available.

Data Extraction

Extracted data included authors, year of publication, 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, Supplemental Digital Content 2, http://links.lww.com/IBD/B144), 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 subsample 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% and 30% on the rating scale, it was considered low; if it was between 31% and 60%, it was considered moderate; and if it was between 61% and 100%, it was considered high.

RESULTS

Of the 4985 studies identified during the database searches, 1264 were removed as duplicates. Of the 3721 articles for which we screened titles and abstracts, 3511 did not meet the inclusion criteria (Fig. 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 1 controversy.

Study Characteristics

Study characteristics are presented in the supplementary tables (Supplemental Digital Content 3, http://links.lww.com/IBD/B208).

Controversy 1: IBD Versus Healthy/General Population Controls

Of the 13 studies that had applicable data in relation to this question,[8,15–26] 7 came from Europe, 5 from North America, and 1 from Australia. Seven were cross-sectional, 3 were case–control, and 3 were cohort studies, 2 of which were prospective and one was retrospective. Samples ranged in size from 47 to 2144 IBD participants (total n = 4098) and from 20 to 10,720 healthy or general population controls (total n = 13,190). Five studies included pediatric/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; n = 1).[9,22]

Controversy 2: IBD Active Versus IBD Inactive

Overall, 26 studies had applicable data in relation to this controversy.[3,18,20,27–49] Of these, 13 came from Europe, 12 from North America, and 1 from Korea. Fifteen were cross-sectional, 7 were prospective cohorts, including one that was population-based, 2 were retrospective cohorts, there was 1 case–control study, and one was a randomized controlled trial where just the baseline data were used. Samples ranged in size from 47 to 10,634 (total n = 15,931) participants. Of the 26 studies, 3 (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

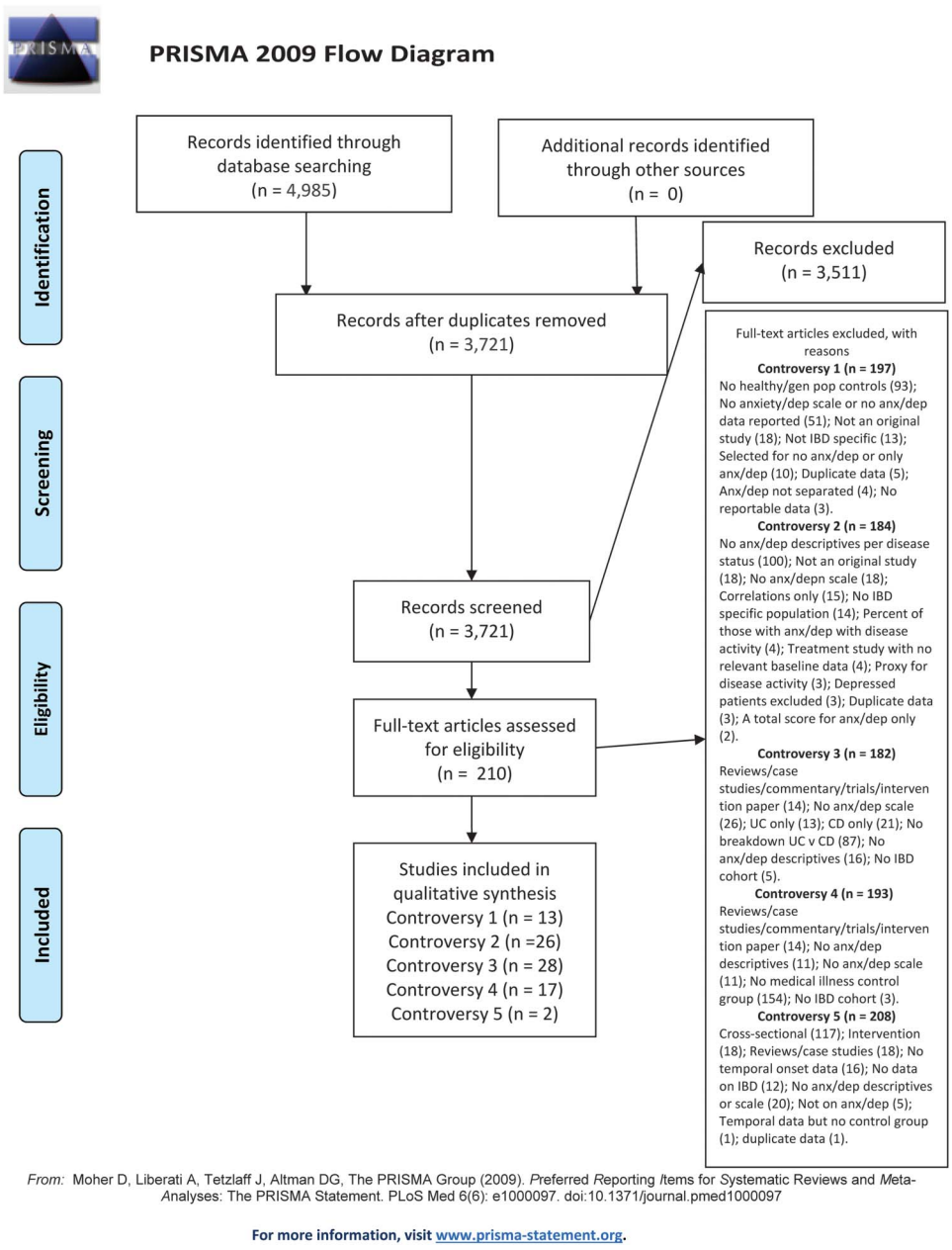

FIGURE 1. A study selection flow diagram for the five areas of controversy.

(n = 4805), 2297 (48%) participants were in an inactive disease phase; not included in this proportion were 6 studies which presented data for participants with inactive IBD only (n = 784). Anxiety and depression were most frequently measured using the HADS (n = 11).[20,29,30,32–34,37,40–42,47] For disease activity measurement, in CD, the most commonly used was the Crohn's Disease Activity Index (n = 12)[20,27–29,31,32,37,39,44,47–49] while, in UC, it was the Simple Clinical Colitis Activity Index (n = 4).[20,36,39,44]

Controversy 3: CD Versus UC

Overall, 28 studies met the inclusion criteria in relation to this question.[4,20,21,26,27,30,34,39,40,42,44,47,48,50–64] Of these, 17 came from Europe, 8 came from North America, 2 from Australia, and 1 from Korea. Twenty-two were cross-sectional, 3 were prospective-based studies, 2 were cohort studies, and 1 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 6689 (n = 23,564) and UC participants ranging from 22 to 5522 (n = 19,319). Two studies included pediatric/adolescent populations. The HADS was the most commonly used anxiety or depression scale (n = 16).[4,20,26,30,34,40,42,47,54–56,58,60–63] Two studies used the ICD-9 criteria.[50,51] In terms of disease activity, for CD, the Crohn's Disease Activity Index was used most commonly

TABLE 1. Summary of Evidence for Controversies in Relation to Co-occurrence of Anxiety and Depression with IBD

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

[a]Based on the quality appraisal process.

(n = 10)[27,39,44,47,48,53,59,61–63] while, for UC, the SCCAI was most commonly used (n = 5).[20,26,39,44,52]

Controversy 4: IBD Versus Medically Ill Controls

Overall, 17 studies met the inclusion criteria in relation to this controversy.[15,17,21,24,27,65–76] Of these, 12 came from Europe, 2 from Australia, and 1 each 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 = 1874) and from 38 to 1506 for the medically ill controls (total n = 3419). The most common comparator was irritable bowel syndrome, used in 6 studies, with 4 studies using a mix of illness groups (e.g., chronic liver disease, celiac, food allergy), 2 studies using colon cancer groups as comparators, and the remaining 5 studies using participants with gastroesophageal reflux disease, juvenile idiopathic arthritis, multiple sclerosis, rheumatoid arthritis, or self-limited colitis cohorts, respectively as comparators. The most commonly used measure of anxiety or depression was the HADS (n = 8).[15,17,24,65–67,72,73]

Controversy 5: Preceding or After IBD Onset

Only 2 studies (n = 2495) 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 pediatric IBD population (n = 2144), and the other examined an adult IBD population (n = 351), with 10,720 pediatric and 779 adult age- and gender-matched controls, respectively. Diagnostic criteria for anxiety and depression were used in both studies (ICD-9 codes; Comprehensive International Diagnostic Interview). IBD was identified using the ICD-9 coding in the pediatric 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 7 of these reporting either significantly higher rates (% or levels [mean scores]) of anxiety in those with IBD than in healthy control participants (n = 3262 IBD; n = 12,024 controls).[8,15,20–22,24,26]

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 et al,[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[8,18,23]; total IBD n = 448) was 19.1% (±3.63, 95% CI) compared with 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 = 3517 IBD; n = 12,212 controls).[8,15,16,19–22,24,26] Two studies with adolescents (1 cross-sectional and 1 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), reported 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, because of its emphasis on somatic symptoms. A population-based IBD study that 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 with 13.4% (±1.9, 95% CI) for healthy controls (n = 1142).

Controversy 2: IBD Active Versus IBD Inactive

Of the 26 studies, 21 measured anxiety with 6 of these providing data for inactive IBD only.[28,29,33,37,38,40] Of the remaining 15, 11 reported significantly higher rates or levels of anxiety in participants with active IBD compared with those with inactive IBD (n = 13,585).[3,18,20,27,30,32,39,42,43,45,46] 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 1 cross-sectional study reported slightly lower levels of anxiety in individuals with active IBD compared with participants with inactive IBD, although the group differences were not statistically significant (n = 147).[47]

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.[33] The pooled mean rate for all the studies reporting percentages (study n = 8; total n = 1069) was 28.2% (±2.7, 95% CI).[18,27,28,30,33,34,37,40] In the 4 largest studies (n = 839) that provided data on rates, 22% (±2.8, 95% CI) of IBD patients with inactive IBD had clinically elevated anxiety.[28,30,34,40] 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).[18,27,30] 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 6 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).[18,20,27,30,32,35,36,39,42,44,46,49] In adults, the rates of depression in inactive IBD ranged from 0% in 1 small study (n = 33)[18] to 49.6% (±14.3, 95% CI) in another small study (n = 47).[41] The pooled mean rate of depressive symptoms for those with inactive IBD was 19.9% (±2.05, 95% CI) (study n = 10; total n = 1132).[18,27,28,30,33,34,37,40,41,49] 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).[41] The pooled mean rate of depressive symptoms during active IBD was 34.7% (study n = 5; total n = 319).[18,27,30,41,49] For children, 1 study (n = 156) reported a depression rate of 30% (±7.2, 95% CI) in inactive IBD[49] and a depression rate of 49% (±7.97, 95% CI; n = 151) for those with active disease.[49]

Controversy 3: CD Versus UC

Twenty-one of the 28 studies measured anxiety, with only 3 of them concluding there were statistically significant differences between IBD subtypes, all of which indicated higher anxiety for those with CD.[21,30,42] 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 (±0.85, 95% CI) and the mean HADS-A score for UC (n = 1423) was 6.4 (±0.5, 95% CI). No data for children were available.

Twenty-seven of 28 studies assessed depression, however, only 2 studies noted significant differences, demonstrating higher depression rates in CD.[40,42] 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 mean values for HADS-D scores (n = 8/27 studies) were 6.09 (±0.89, 95% CI) for CD (n = 1299) and 5.5 (±1.08, 95% CI) for UC (n = 1694). Two studies with adolescent[53,59] and one with elderly populations[44] were available, all 3 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 6 studies (n = 915 IBD and 815 controls) showed the differences between IBD and other medically ill participants to be statistically significant.[17,21,69,72,75,76] Three studies (n = 276 IBD and 213 controls)[21,75,76] reported significantly lower rates of anxiety in IBD than in controls with irritable bowel syndrome or self-limited colitis, whereas another 3 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 (celiac disease, food allergy, and congenital disorders).[17,69,72] 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, and celiac 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.[17,21,65,66,68,69,71–73,75] Five (n = 551 IBD and 372 controls)[65,71–73,75] reported lower rates or levels of depression in IBD than in controls with irritable bowel syndrome, hepatitis C, rheumatoid arthritis, and multiple sclerosis, and 5 (n = 648 IBD and 601 controls)[17,21,66,68,69] indicated higher rates or levels in IBD than in participants with self-limited colitis, colorectal cancer, juvenile idiopathic arthritis, and several other conditions (celiac disease, food allergy, gastroesophageal reflux disease, and 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 (±0.6, 95% CI) compared with 4.6 (±0.6, 95% CI) in controls (n = 694). Three studies provided data for pediatric populations[17,68,70] but only 2 conducted significance testing, both showing higher rates of depression in IBD than controls with juvenile idiopathic arthritis, congenital disorders, food allergy, and celiac disease but not chronic liver disease (n = 339 IBD and 382 controls).[17,68]

Controversy 5: Preceding or After IBD Onset

No prospective studies examining rates of anxiety and depression before IBD diagnosis were identified from the past decade. However, 2 studies were relevant to this controversy, examining incidence of anxiety and depression postdiagnosis in children, and retrospective evaluation of timing of onset in relation to IBD in adults.[8,22]

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, whereas just 8% developed anxiety 2 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 2-fold increase in the risk of developing anxiety disorders in the pediatric population (hazard ratio = 2.28; 95% CI = 1.65–3.17; $P < 0.0001$ for both comparisons) (n = 2144 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 2 years or more before the IBD onset while 23% developed depression 2 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 (hazard ratio = 1.74; 95% CI = 1.35–2.25, $P < 0.0001$) (n = 2144 CD patients and n = 10,720 controls).[22]

In adults, the mean age of IBD onset with lifetime anxiety or mood disorder was 29.1 years as compared with 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 the supplementary tables (Supplemental Digital Content 4, http://links.lww.com/IBD/B208).

Controversy 1: IBD Versus Healthy/General Population Controls

Quality ranged from 5 to 12 of a maximum of 14 points, with a mean of 7.5 (53.6%), indicating a moderate quality. Overall, 7 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 of 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 of 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 of 14 points, with a mean of 6.4 (45.7%), indicating a moderate quality. Overall, 9 studies scored at least 50% on the quality scale.

Controversy 5: Preceding or After IBD Onset

Quality ranged from 11 to 12 of a maximum of 14 points in the 2 included studies and was considered high, with a mean of 11.5 (82%).

DISCUSSION

This systematic review examined 5 primary questions regarding the comorbidity of anxiety and depression with IBD. The original review,[9] of which this article is an update, identified these 5 areas of controversy but was unable to provide definitive answers to these questions because of the paucity of data available at that time. The current review was able to address 4 of the 5 questions more definitively, as summarized in Table 1. Specifically, in this review, we observed that there were higher rates of

both anxiety and depression symptoms in those with IBD compared with healthy individuals without IBD (controversy 1). The bulk of the studies supports that the rates of both anxiety and depression are higher during active compared with 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 with UC (controversy 3). Rates of anxiety and depression in IBD were observed to be lower when compared with those with other chronic health conditions, noting that most of the available comparators were gastrointestinal conditions of varying clinical severity (controversy 4). Given the variety of comparators and major differences between them and IBD in their presentation, etiology, 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; therefore, the mean rates presented may be higher than rates of anxiety and mood disorders. Although there is some relationship between elevated symptom scores and clinical diagnoses of mood and anxiety disorders, they are not fully concordant.[77,78] Nevertheless, the Walker et al study,[8] 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 4 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 that 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 cutoffs even with the same measures (e.g., HADS cutoff of >7, >8, ≥ 8, ≥ 11), and the range of ways that mental health data were reported (e.g., different measures of central tendency and variability) all 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.[79]

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 majority of studies used a cross-sectional design and were unable to shed light on this question, with only 2 of the 210 studies that met general inclusion criteria having applicable data.[8,22] The study that evaluated adults found that the large majority of individuals had first onset of anxiety well before the IBD (more than 10 years).[8] Because 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 before 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.[80,81] However, the timelines were established retrospectively through structured clinical interviews to determine lifetime prevalence of mental disorders; therefore, 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. Although studies on mental health in primary care do not always support the value of routine screening,[82] its benefit has been established in populations with chronic conditions or mental disorders.[83] 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.[39,84] 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 health care delivery such as stepped care or integrated care may facilitate better detection and management of anxiety and depression coexistent with IBD.[85–87]

This review has demonstrated a significant level of psychological comorbidity in IBD. Yet, treatment of anxiety and depression is often not considered as part of standard IBD care.[88] Although financial strain of the public health care 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.[89,90] 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 QoL in the unselected IBD patients.[91] However, recent reviews that used more appropriate categorization of psychological interventions, analyzing different types of treatments separately, demonstrated that one type of psychotherapy, cognitive behavioral therapy, improves psychological distress, with modest changes in gastrointestinal symptoms.[92,93] These differing conclusions largely stem not only 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.[94] Until there is clearer direction regarding the IBD-specific treatment of anxiety and depression, use of evidence-based therapies such as cognitive behavioral therapy for anxiety and depression in general, as specified in the National Institute for Health and Care Excellence guidelines, seems prudent.[95]

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,[1] 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 postsurgery for women have been reported[96]; therefore, a careful evaluation of mental health comorbidity for men and women may provide direction for contributory mechanisms. Furthermore, primary depression is much more common for women than for men.[97] Many of the studies in our review had a modestly larger proportion of female participants, raising the possibility that rates are somewhat elevated because of overrepresentation of females in these samples. Finally, most of the studies involved adult IBD participants, with relatively few providing data for pediatric samples and only 1 study using a geriatric IBD sample.[44] Where data were 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. 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: (1) cohort, case–control designs rather than cross-sectional; (2) population-based or at a minimum consecutively recruited participants; (3) comparison groups, including both healthy and chronically ill controls; (4) justification for the sample size and attrition; (5) control for confounders (e.g., psychiatric history); (6) present data separately for IBD subtypes, disease activity, and male/female and provide mean (SD) values and proportions with CIs where appropriate; (7) measure IBD outcomes such as time to relapse, as well as inclusion of objective measures such as fecal calprotectin, or, optimally, endoscopy and (8) use of validated screening measures and 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 2 seem to have been validated in individuals with IBD.[39,84] 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 3700 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.[98,99] Given this, further research is required to both validate and develop clear cutoffs and meaning in the IBD context.

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