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A systematic review and meta-analysis

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Review article

The bidirectional risk of inflammatory bowel disease and anxiety or depression: A systematic review and meta-analysis

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) is associated with anxiety and depression, but the magnitude and directionality of risk remains uncertain. This study quantifies the risk of anxiety or depression following a diagnosis of IBD, and the risk of IBD in individuals with anxiety or depression, using population representative data.

Method: We performed a systematic literature search using MEDLINE and Embase and included unselected cohort studies reporting risk of anxiety or depression in patients with IBD or risk of IBD in patients with anxiety or depression. We undertook Random Effect Model meta-analysis to calculate pooled Hazard Ratios (HR) for the risk of anxiety and depression in IBD and subgroup meta-analysis to calculate risk by IBD subtype and in pediatric-onset IBD.

Results: Nine studies were included; seven of which examined incidence of anxiety or depression among a total of >150,000 IBD patients. Meta-analysis showed an increased risk of both anxiety (HR: 1.48, 95% CI: 1.29–1.70) and depression (HR: 1.55, 95% CI: 1.35–1.78) following IBD diagnosis. Two studies investigating >400,000 individuals with depression showed a 2-fold increased risk of IBD.

Conclusions: The bidirectional association between IBD and anxiety and depression is clinically relevant and could indicate shared or mutually dependent disease mechanisms.

1. Introduction

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic and relapsing intestinal diseases, which are usually diagnosed in early adulthood. Patients suffer life-long symptoms due to chronic inflammation of the gastrointestinal tract, and the disease course and treatment response can be unpredictable [1]. Anxiety and depression frequently affect patients with IBD, one recent meta-analysis found a pooled prevalence of anxiety of 31.1% and pooled prevalence of depression symptoms of 25.2% [2]. The psychiatric comorbidities can have detrimental impact on quality of life [3]. While IBD in itself can be difficult to manage, studies suggest that patients with co-occurring anxiety and depression could be at greater risk of severe disease course [4,5]. While anxiety and depression might result from the strain of coping with chronic illness and are common comorbidities in many chronic diseases such as heart disease [6] and multiple sclerosis [7], bidirectional signaling between the gastrointestinal system and the central nervous system through the gut-brain axis could increase the risk of developing these psychiatric comorbidities in patients with IBD. Mechanisms at play include neurological signaling through the vagal nerve, humoral signaling through pro-inflammatory cytokines [8] and changes in gut microbiome [9]. Despite the reported co-occurrence of IBD and anxiety and depression, it is not well understood how the diseases impact one another, in which order they occur, or what the magnitude of risk is. This, in turn, limits our ability to understand the etiology of these diseases, accurately inform patients of their risk, and

Abbreviations: CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IRR, incidence rate ratio; REM, random effects model; UC, ulcerative colitis.

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hinders optimal clinical management. Several systematic reviews have investigated the prevalence of anxiety and depression and patients with IBD with very broad inclusion criteria resulting in inclusion of many studies with selective patient groups, e.g. representing only patients with severe IBD [10,11]. We aimed to conduct a systematic review with meta-analysis of all available unselected cohort studies examining the risk of anxiety or depression following a diagnosis of IBD and, conversely, the risk of IBD after a diagnosis of anxiety or depression. By only including unselected cohort studies, meaning cohorts that represent all patients with IBD in a given area, we aim to accurately depict the bidirectional risk of anxiety and depression that is generalizable to all patients with IBD.

2. Materials and methods

2.1. Literature search

We used PRISMA reporting guidelines [12] to conduct a systematic literature search for studies assessing the risk of anxiety or depression in IBD patients and, conversely, the risk of IBD in patients with anxiety or depression. Medline and Embase were searched for all relevant English language articles published from 1991 until July 2022. Both the following subject headings and search terms were used: (inflammatory bowel disease OR ulcerative colitis OR crohn$ disease OR IBD) AND (depression OR anxiety), all terms were searched both as exploded subject headings and as key words. We did a manual reference list search of all articles selected for final inclusion and any relevant reviews identified.

2.2. Inclusion and exclusion criteria

We defined the inclusion and exclusion criteria before performing the literature search. We included published, unselected cohort studies defined as being either population-based (i.e., including all patients with the disease under study in a geographical area over a given calendar period) or covering >50,000 individuals (hence assumed to be representative for the average patient with the disease). We chose to include only unselected cohorts to be able to calculate the pooled risk across all types of patients with IBD and not only selected groups, e.g. those ill enough to be included from a tertiary referral center. Studies had to report risk estimates of anxiety or depression in IBD patients or risk estimates of IBD in patients with anxiety or depression. Studies were excluded if the outcome was not clearly reported, if there was no non-IBD or non-anxiety or -depression reference group or if the cohort was selected by treatment or disease severity. When several studies were found to use the same cohort, only the most recent study was included to avoid duplication of data.

2.3. Data collection

Two authors (TB and RE) independently performed initial title and abstract screening and any discrepancies were discussed before consensus was reached. From all included studies, we collected data on outcomes as well as other data. The primary outcome was a risk estimate of anxiety or depression in patients with IBD or IBD in patients with anxiety or depression. In studies where risk estimates of anxiety or depression were not reported for IBD overall, we assumed that CD and UC patients together represented the IBD population and used the risk estimates presented for anxiety and depression in CD and UC, along with their respective standard errors to calculate a pooled IBD risk estimate. The secondary outcome was risk estimate of anxiety or depression by disease subtype (CD and UC) and risk estimate of CD or UC in patients with anxiety or depression. Other extracted data included publication year, start and end date of cohort follow-up, average age at inclusion, country, sex, tool for IBD diagnosis, screening tool for anxiety or depression diagnosis, follow-up time in either person-years or mean/median number of years, number of IBD, anxiety or depression patients and reference population, and number of patients with a given outcome (either IBD or anxiety or depression). Overall incidence rates of IBD and non-IBD populations, as reported by each study included, were also extracted and compared.

2.4. Risk of bias assessment

Included studies were assessed using the Newcastle-Ottawa Scale, which is a tool for assessing the quality of non-randomized studies in meta-analyses [13], which is a widely used and valid tool that has been previously evaluated [14]. Each study was awarded 0–9 points, where up to four points could be allocated for selection (exposed and non-exposed cohorts, ascertainment of exposure, and demonstration that outcome of interest was not present at start of study), two points could be allocated for comparability, and three points could be allocated for outcome (how it was assessed, sufficiency of follow-up time, and adequacy of follow-up), see Supplementary Box 1 for criteria behind the score. Scores were allocated by authors TB and reviewed by RE.

2.5. Statistical analysis

We extracted reported adjusted overall hazard ratios (HR) or analogous risk estimates and accompanying 95% CI to calculate standard errors and undertake random effects model (REM) meta-analyses using the inverse-variance method with Sidik-Jonkman estimator for τ^2, a measure of study variance. We chose REM due to a priori assumption of the presence of both intra- and inter- study heterogeneity. Subgroup meta-analyses were undertaken for risk of anxiety or depression by disease subtype separately and sex, where this data was available. Separate meta-analysis was undertaken to assess the risk of anxiety and depression in pediatric-onset IBD. Publication bias was evaluated using Egger's regression test [15] to assess asymmetry of funnel plot of included studies. Analyses were performed in R, using the “metagen” and “metabin” functions in “meta” [16] and “metaphor” [17] packages.

3. Results

3.1. Search results and study selection

Out of 6853 articles identified in the literature search, nine articles were included (Supplementary fig. 1). Of the nine included articles, seven investigated the risk of anxiety or depression following IBD diagnosis. Of those seven articles, five examined adult populations or populations of all ages [18–22] and two articles examined pediatric populations [23,24]. The seven studies were based on cohorts from Canada, USA, Sweden, UK, and South Korea; published between 2011 and 2022, and comprised a total 151,908 IBD patients and 4,869,239 reference individuals (Table 1). Six of the studies were eligible for meta-analysis, five of which included both CD and UC patients [18–20,23] and one included only CD patients [24]. Vigod et al. [21] was not included in the meta-analyses as depression and anxiety diagnoses were grouped as one outcome. Two articles investigated the risk of developing IBD following depression [25,26]. These two studies were based on cohorts from the USA and the UK, were published in 2013 and 2019, and comprised a total of 420,651 depression patients and 5,356,934 reference individuals (Table 2). As we only identified two studies investigating patients with depression and none with anxiety, we did not undertake meta-analysis of those studies.

Measurement of anxiety and depression was in most included studies done as diagnoses using ICD-codes [18–21,23,24], while two studies used READ codes [22,26] and one study used the 5-question Mental Health Index [25] (Table 1 and Table 2).

Table 1
Characteristics of included cohort studies on risk of depression and anxiety in inflammatory bowel disease.

Study	Country	Source population	Follow up time	IBD cohort size	Reference cohort size	Crude incidence rate / 1000 person years		Adjusted risk estimate depression (95% CI)		Adjusted risk estimate anxiety (95% CI)		Adjustment variables	Method for measuring anxiety or depression
						IBD	References	CD	UC	CD	UC		
Bernstein et al., 2019 [20]	Canada	Regional adult population-based cohort, 55% female	Mean follow up time 10.4 years	IBD: 5346 CD: 2389 UC: 2957	26,716	Depression: 18.6 Anxiety: 25.0	Depression: 10.8 Anxiety: 16.3	IRR 1.76 (1.51–2.05)	IRR 1.43 (1.24–1.64)	IRR 1.56 (1.35–1.79)	IRR 1.27 (1.11–1.44)	Age, sex, socioeconomic status, region (urban/rural), fiscal year	ICD-9 and ICD-10 diagnostic codes
Butwicka et al., 2019 [23]	Sweden	Swedish National Patient register, pediatric population, 44% female	Median follow up time 9 years	IBD: 6464 CD: 2536 UC: 3228	323,200	Depression: 6.1 Anxiety: 9.8	Depression: 4.0 Anxiety: 5.3	HR 1.6 (1.4–1.9)	HR 1.4 (1.4–1.7)	HR 2.2 (1.9–2.4)	HR 1.6 (1.4–1.8)	Year of birth, sex	ICD-8, ICD-9 and ICD-10 diagnostic codes
Choi et al., 2019 [19]	South Korea	The National Healthcare Insurance Service, 27% female	Mean follow up time 6 years	IBD: 15,569 CD: 6396 UC: 9173	46,707	Depression: CD: 14.99 UC: 19.63 Anxiety: CD:20.88, UC: 31.19	Depression: CD-references: 7.75 UC-references: 11.18 Anxiety: CD-references: 14.31, UC-references: 21.55	HR 2.06 (1.74–2.44)	HR 1.93 (1.7–2.18)	HR 1.58 (1.38–1.82)	HR 1.58 (1.43–1.74)	Age, sex, residence, income, comorbidities	ICD-10 diagnostic codes
Loftus et al., 2011 [24]	USA	Health service database cohort (Market Scan), 46% female	Not available	CD: 2144	10,720	Depression: 26.9 Anxiety: 18.1	Depression: 12.2 Anxiety: 5.7	1.74 (1.35–2.25)	Not assessed	2.28 (1.65–3.17)	Not assessed	Age, sex, Charlson comorbidity index score, region, type of health care plan	ICD-9 diagnostic codes
Ludvigsson et al., 2021 [18]	Sweden	Swedish National Patient Register, adult population, 48% female	Median follow up time 11 years	IBD: 69,865 CD: 21,245 UC: 43,557	3,472,913	Depression: 3.6 Anxiety: 4.0	Depression: 2.5 Anxiety: 3.0	HR 1.5 (1.4–1.6)	HR 1.4 (1.3–1.4)	HR 1.4 (1.3–1.5)	HR 1.2 (1.2–1.3)	Age, sex, year, and place of birth	ICD-8, ICD-9 and ICD-10 diagnostic codes
Umar et al., 2022 [22]	UK	National representative cohort from electronic medical database (IMRD), 48.3% female	Not available	IBD: 48,799 CD: 20,447 UC: 28,352	190,075	Depression: 10.75 Anxiety: 5.48	Depression: 7.9 Anxiety: 4.67	HR 1.36 (1.26–1.47)	HR 1.24 (1.16–1.33)	HR 1.38 (1.16–1.65)	HR 1.26 (1.07–1.47)	Age, sex, Townsend deprivation score, ethnicity, smoking status, Charlson comorbidity score	READ codes (coding system with information on symptoms, examinations, and diagnoses)
Vigod et al., 2019 [21]	Canada	Regional cohort (Manitoba), all pregnant and post-partum women	Follow up from conception to 1 year post-partum (~1 year and 9 months)	IBD: 3721	798,908	150.17 (number only available for overall mental illness)	132.76 (number only available for overall mental illness)	HR for any new onset mood or anxiety disorder 1.13 (1.05–1.22)				Maternal age, neighborhood income quintile, rural/urban residence, medical comorbidity, prenatal care type, maternal and neonatal health conditions	ICD-9 and ICD-10 diagnostic codes

Table 2
Characteristics of included studies on risk of inflammatory bowel disease in patients with depression.

Study	Country	Source population	Follow up time	Depression cohort size	Reference cohort size	Crude incidence		Adjusted risk estimate (95% CI)	Adjustment variables	Method for measuring anxiety or depression
						Depression	References			
Ananthakrishnan, 2013 [25]	USA	Cohort from Nurses' Health Study, 100% female	Not available	16,986	32,948	CD: 0.15 /1000 person years UC: 0.13 /1000 person years	CD: 0.07 /1000 person years UC: 0.10 /1000 person years	HR for CD: 1.62 (0.95–2.77) HR for UC: 1.07 (0.63–1.83)	Race, ethnicity, cigarette smoking, menopause status, BMI, use of oral contraceptives, postmenopausal hormones, aspirin and NSAID	5-question Mental Health Index (MHI-5)
Frolkis, 2019 [26]	UK	National representative cohort from electronic medical database (THIN), 65% female	Median follow up time 6.7 years	403,665	5,323,986	CD: 203 (0.05%) UC: 539 (1.13%) *	CD: 1589 (0.03%) UC: 4675 (0.09%) *	HR for CD: 2.11 (1.65–2.7) HR for UC: 2.23 (1.92–2.6)	Age, sex, socioeconomic status, comorbid conditions, smoking status, anxiety, antidepressant use	READ codes (coding system with information on symptoms, examinations, and diagnoses)

* crude incidence numbers per person years not available.

3.2. Incidence and risk of anxiety and depression following IBD

Seven studies addressing the risk of anxiety and depression in IBD patients (Table 1) reported the crude incidence of depression as 3.6–26.9/1000 person-years among patients with IBD compared with 2.5–12.2/1000 person-years in the reference populations. The crude incidence of anxiety was 4.0–25.0/1000 person-years among patients with IBD compared with 3.0–16.3/1000 person-years in the reference populations (Table 1).

Five studies reported data on the primary end point: risk of anxiety or depression in patients with IBD compared with the reference population [18–20,22,23], while Loftus et al. reported this only for CD [24]. Risk estimates were similar for depression in the four adult (HR 1.4, 95% CI 1.4–1.5 [18]; HR 1.98, 95% CI 1.78–2.19 [19]; incidence rate ratio (IRR) 1.58, 95% CI 1.41–1.76 [20]; HR 1.3, 95% CI 1.23–1.36 [22]) and one pediatric (HR 1.6, 95% CI 1.4–1.7) [23] population. There was a numerically lower risk of anxiety in adult populations (HR 1.3, 95% CI 1.3–1.4 [18]; 1.58, 95% CI 1.52–1.64 [19]; IRR 1.39, 95% CI 1.26–1.53 [20]; HR 1.31, 95% CI 1.16–1.47 [22]) than in the pediatric population (HR 1.9, 1.7–2.0) [23]. In one study, the sub-analysis of patients with pediatric-onset IBD (age 10–18 years) showed no increased risk of anxiety, IRR 0.96, 95% CI 0.72–1.15 [22].

Meta-analysis of the five studies reporting on the risk of anxiety or depression following an IBD diagnosis showed that patients with IBD were at increased risk of both anxiety (HR 1.48, 95% CI 1.29–1.70) and depression (HR 1.55, 95% CI 1.35–1.78) (Fig. 1).

Only two studies reported risk estimates by sex [19,20]. Subgroup meta-analysis showed no significant difference in risk of anxiety (female: HR 1.56, 95% CI 1.14–2.13, male: HR 1.56, 95% CI 1.04–2.32) or depression (female: HR 1.51, 95% CI 1.39–1.64, male: HR 1.73, 95% CI 1.59–1.88).

Six studies reported data on the secondary outcome: risk of anxiety or depression by IBD subtype. Five of these studies included both CD and UC patients [18–20,22,23], the last study included only CD patients

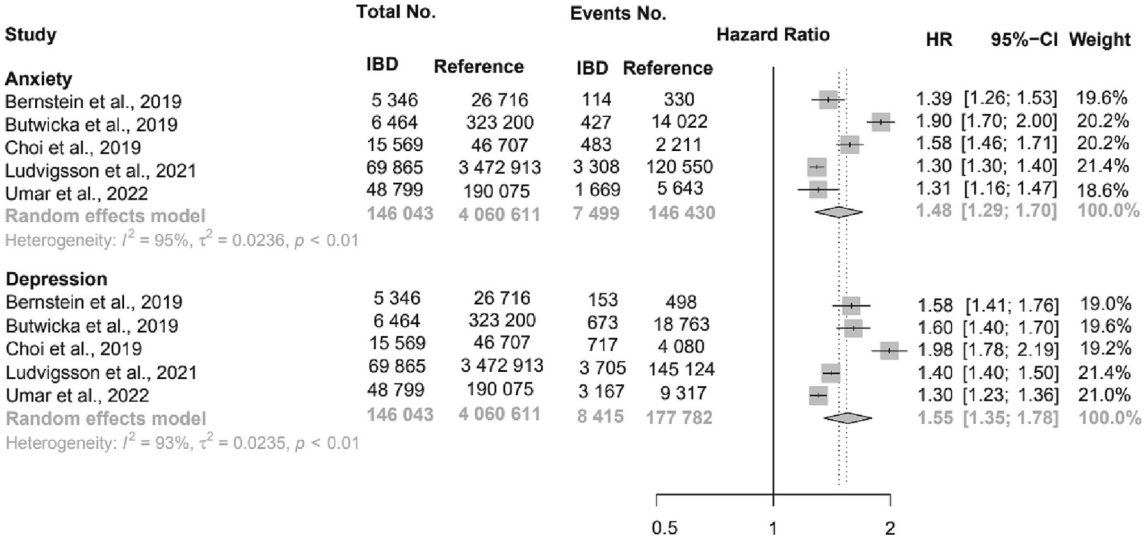

Fig. 1. Risk of anxiety and depression in patients with inflammatory bowel disease (IBD). Squares represent the hazard ratios (HR) from each study, and the horizontal lines represent 95% confidence intervals. The vertical lines represent the pooled HR of anxiety and depression, respectively, and the diamonds represent the confidence intervals of the pooled HRs of anxiety and depression, respectively.

[24]. The reported HRs for depression ranged from 1.36 (95% CI 1.26–1.47) to 2.06 (95% CI 1.74–2.44) for patients with CD and from 1.24 (95% CI 1.16–1.33) to 1.93 (95% CI 1.7–2.18) in patients with UC. The HRs for anxiety ranged from 1.38 (95% CI 1.16–1.65) to 2.28 (95% CI 1.65–3.17) for CD patients and from 1.2 (95% CI 1.2–1.3) to 1.6 (95% CI 1.4–1.8) for UC patients (Table 1).

Meta-analyses showed an increased risk of depression both among patients with CD (HR 1.63, 95% CI 1.45–1.83) and UC (HR 1.46, 95% CI 1.26–1.68) compared with non-IBD individuals (Fig. 2). Following exclusion of studies only including pediatric patients, the risk of depression remained increased both in patients with CD (HR 1.63, 95% CI 1.37–1.94) and UC (HR 1.47, 95% CI 1.23–1.76) (Supplementary fig. 2).

Likewise, meta-analyses showed an increased risk of anxiety both in patients with CD (HR 1.67, 95% CI 1.41–1.98) and UC (HR 1.37, 95% CI 1.21–1.55) compared with non-IBD individuals (Fig. 2). Removing the two pediatric cohorts resulted in a slightly lower, although still significantly increased estimate for the risk of anxiety among patients with CD (HR 1.47, 95% CI 1.36–1.58) but did not change the estimate for patients with UC (HR 1.32, 95% CI 1.17–1.49). Meta-analysis of two studies on pediatric-onset CD patients showed a particularly elevated risk of anxiety (HR 2.21, 95% CI 1.98–2.47), but meta-analysis of two studies with estimates for anxiety in pediatric IBD overall did not show an elevated risk of anxiety (HR 1.47, 95% CI 0.66–3.27) (Supplementary fig. 3).

The seventh study by Vigod et al., based on a cohort of perinatal women [21], did not report separate risk estimates for depression and anxiety, so was therefore not eligible for meta-analysis. This study did however show that perinatal women with a pre-pregnancy IBD diagnosis were at increased risk for mood and anxiety disorders (HR 1.13, 95% CI

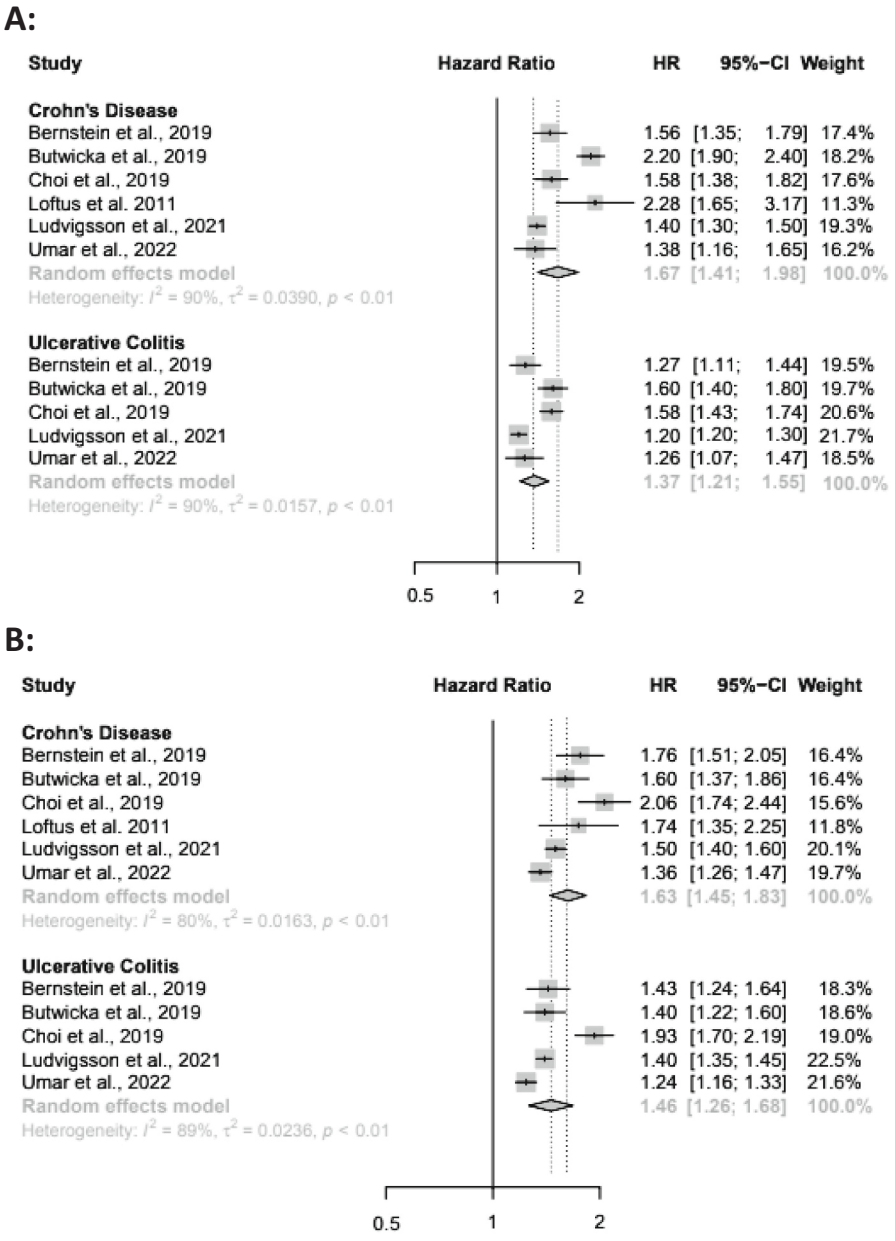

Fig. 2. Risk of anxiety (A) and depression (B) among patients with Crohn's disease and ulcerative colitis. Squares represent the hazard ratios (HR) from each study, and the horizontal lines represent 95% confidence intervals. The vertical lines represent the pooled HR of anxiety (A) and depression (B) in Crohn's disease and ulcerative colitis, respectively, and the diamonds represent the confidence intervals of the pooled HRs of anxiety and depression, respectively.

1.05–1.22).

3.3. Risk of IBD following depression or anxiety

Only two studies on IBD following anxiety or depression [25,26] fulfilled the inclusion criteria (Table 2). Both studies examined depression, not anxiety, as exposure. In a study of 152,371 female nurses [25] with recent depressive symptoms, risk of CD was significantly increased (HR 2.36, 95% CI 1.40–3.99), whereas risk of UC was not (HR 1.14, 95% CI 0.68–1.92) compared with female nurses without depressive symptoms. In a second study of 403,665 individuals with a physician-diagnosed clinical depression and 5,323,986 individuals without depression [26], risk of both CD (HR 2.11, 95% CI 1.65–2.70) and UC (HR 2.23, 95% CI 1.92–2.6) was increased following depression. A meta-analysis was not performed.

3.4. Study quality assessment and risk of bias assessment

Quality assessment using the Newcastle-Ottawa scale showed a high quality of included studies with all but one scoring 8 or 9 (Supplemental table 1). One study had a score of 5 [25] due to inclusion of only nurses in the cohort, self-reporting of exposure and outcome, and unclear follow-up time. Two studies received 8 points due to short or unclear follow up time for the outcome (less than two years or not stated) [21,24].

The systematic review was performed in accordance with PRISMA guidelines, see the PRISMA checklist in Supplementary table 2.

Studies appeared symmetrically distributed in the funnel plot of included studies on visual inspection (Supplementary fig. 4). However, potential asymmetry was identified when assessed with Egger's regression test (intercept 2.14, $p = 0.55$;), indicating potential publication bias.

The heterogeneity ranged between 80% and 95% in the main analyses and 0% to 97% in the supplementary analyses indicating that study populations differed substantially (Figs. 1-2 and Supplementary Figs. 2–3).

4. Discussion

In this systematic review for bidirectional risk of anxiety and depression in IBD, we identified nine studies for inclusion. Seven population-based studies all reported an increased risk of anxiety and depression following IBD diagnosis. Only two population-based cohort studies investigated risk of IBD in patients with depression and none in patients with anxiety. The two studies showed an approximately 2-fold increased risk of IBD following depression.

Meta-analysis of six of these unselected cohort studies included 151,908 IBD patients and 4,869,239 reference individuals and revealed a 1.5-fold increased risk of anxiety and depression among patients with IBD. The increased risk was present in both pediatric and adult populations and both in patients with CD and UC, with no difference in risk between men and women.

Our findings support the existence of a bidirectional relationship between IBD and depression. While previous reviews have focused on the prevalence of depression and anxiety in patients with IBD [2,10], to our knowledge, this is the first systematic review and meta-analysis that focuses on the temporal occurrence of incident anxiety, depression, and IBD. In a 2016 review on anxiety and depression in IBD of both selected and unselected study populations [11], only two studies were included for assessment of the temporal relationship, and only one of these was population-based. The interplay between IBD and anxiety and depression has also been examined in the context of IBD disease course. Two recent systematic reviews found aggressive IBD [27] and active IBD [28] to be associated with increased risk of depression and anxiety. When looking at brain-to-gut effects, a 2017 systematic review did not see a significant association between depressive state and worsening in IBD disease course [29]. However, two more recent systematic reviews both found associations between anxiety and depression and several indicators of worsening outcomes in IBD patients such as flares, escalation of therapy, and hospitalization [28,30]. This is further supported by the two studies presented in this meta-analysis examining the risk of IBD in individuals with depression or depressive symptoms, which both point to an increased risk of IBD following depression. It is also in line with a recent large case-control study from the UK showing depression to be more prevalent among IBD patients five years prior to diagnosis compared with matched controls [31]. Whether the increased risk of IBD attributed to depression could be an indication of a delayed diagnosis of IBD or if depression could be an independent causative risk factor for IBD merits further investigation.

The risk of anxiety among patients with CD decreased when removing pediatric patients from the meta-analysis. This could be because anxiety often debuts in childhood or early adulthood [32], and so this may be a product of timing of diagnosis of the two conditions. However, we did not see the same pattern in UC patients, where the risk of anxiety was comparable in both adult and pediatric populations. This underscores the notion that IBD might interplay with anxiety and depression and that the diseases might mutually exacerbate each other, either by directly affecting each other or through shared disease processes.

The study by Umar et al. [22] found no increased risk of anxiety in pediatric patients with IBD overall, while the two studies with data on anxiety by IBD subtype did find and increased risk, particularly in pediatric patients with CD [23,24]· The estimate found by Umar et al. thus contrasts that of the other estimates from pediatric populations. Although data from Umar et al. use a population representative English cohort, derived from a country-wide primary healthcare database, the Townsend score of the populations included, indicate an underrepresentation of lower socioeconomic groups, which might contribute to the lack of association between pediatric-onset IBD and anxiety identified in this study. These conflicting results underscore the particular need for further research into these outcomes in pediatric populations.

It is well-known that both anxiety and depression are almost twice as common in females [33,34], but we found no differences in risk between males and females. This reflects that the incidence rates for anxiety and depression were higher in both women with and without IBD compared with their male counterparts, resulting in similar relative risks. Thus, the increased risk of anxiety and depression associated with IBD does not appear to be sex dependent.

Living with a chronic and debilitating disease can lead to the development of anxiety and depression, but in addition to this strain, several biological mechanisms pertaining to the gut-brain axis might contribute further. Via the bidirectional communication through the gut-brain axis diseases of the gastrointestinal tract and the brain can interact and possibly exacerbate each other. Among suggested mechanisms, which are summarized in a recent review [3] are increases in pro-inflammatory cytokines in the brain and in the periphery, changes in brain morphology, impaired vagal nerve signaling, changes to the gut microbiome, and shared genetics.

The primary strength of the present study is the comprehensive literature search covering >30 years of research. The review is designed to include only unselected cohort studies to ensure generalizability of results. The broad search for literature yielded >6000 results which indicates that search terms were sufficiently broad. In terms of study quality, all but one included study – and all studies included in the meta-analysis – received 8 or 9 out of 9 points possible on the Newcastle-Ottawa Scale, where a score <5 indicates high risk of bias [14]. Despite criticism regarding validity of this scale [35], the Newcastle-Ottawa Scale remains a useful tool for evaluating study quality. It is well-known, each index is adaptable based on the research topic, it is validated for longitudinal studies [14], and it can be easily interpreted by clinicians and researchers.

There are possible limitations to the present study. Patients with IBD

could be more likely to receive a diagnosis of anxiety or depression, as they are more often seen by a doctor, potentially leading to detection bias. However, studies using survey-based design for symptoms of anxiety and depression also find an increased occurrence of anxiety and depression in patients with IBD [36–38], which speaks against such bias. The included studies differed somewhat with regards to exposure and outcome definitions. As the definitions were the same for the at risk and reference group in each study, however, this likely did not result in any systematic error in estimation of relative risk. Since all included studies are from high income countries (USA, UK, South Korea, Sweden, Canada), results are primarily representative for such populations and cannot be directly extrapolated to populations from other countries. As the Egger's regression test did not significantly show a symmetrical distribution of included studies on the funnel plot, we cannot rule out publication bias. We identified only two eligible studies on risk of IBD in patients with depression and no studies on patients with anxiety, which prevents us from drawing definite conclusions about the risk of IBD in these patient groups. This was partly due to our strict inclusion criteria, and it highlight the lack of high-quality population-based studies. Lastly, we assumed separate censoring for anxiety and depression in all included studies, although it was only explicitly stated in three of six studies included [18,23,24]. However, in all studies, there is a potential challenge in separating anxiety and depression, as symptoms can overlap, and the two diseases often co-exist.

This systematic review and meta-analysis shows that patients with IBD are at increased risk of developing anxiety and depression compared with non-IBD individuals, and that individuals with depression may also be at increased risk of developing IBD following their depression. These findings point towards a mutual relationship between IBD and depression, which has several potential biological explanations involving the gut-brain-axis. Future research should focus on the etiology of this bidirectional relationship, the temporal relationship between anxiety, depression and IBD *within* the same population, and on the burden of psychiatric diseases throughout the lifespan of IBD patients.

Author contributions

Conceptualization: all authors; literature search and review: TB, RE; statistical analyses: RE; drafting of manuscript: TB, interpretation of data and revision of manuscript: all authors. All authors have approved the final manuscript for publication.

Conference presentation

This work was presented at United European Gastroenterology (UEG) Week in Vienna October 8th–11th 2022.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2023.05.002.

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