The prevalence and incidence of Irritable Bowel Syndrome and Inflammatory Bowel Disease in depression and bipolar disorder: a systematic review and meta-analysis

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The prevalence and incidence of irritable bowel syndrome and inflammatory bowel disease in depression and bipolar disorder: a systematic review and meta-analysis

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Abstract

Objective: The increased prevalence and incidence of affective disorders among patients with gastrointestinal disease has been well established. However, few studies have investigated the inverse relationship. We aimed to identify all evidence of the prevalence and incidence of irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) in people with depression and bipolar disorder. Methods: We conducted a systematic review of studies reporting the association between affective disorders (exposure) and IBS or IBD (outcome) in adults. Evidence was evaluated for quality using Joanna Briggs Institute Critical Appraisal tools. Where suitable data were available, meta-analyses were performed. Results: We identified eighteen studies that met selection criteria, of which eleven provided data on IBS, five on IBD, and two on both. Overall, people with depression were significantly more likely to have comorbid IBS (RR = 2.42, 95% CI 1.98-2.96) as well as to develop new-onset IBS (RR=1.90, 95%CI 1.41-2.56) compared to people without depression. They were also more likely to have and develop IBD and, among patients with IBD, significantly increased rates of depression were observed as early as 5 years pre-diagnosis. Bipolar disorder was not consistently associated with risk of either condition.

Conclusions: People with depression are at an increased risk of both having and developing lower gastrointestinal disorders. These findings have important implications for how we understand, manage and prevent this comorbidity in clinical practice. Further studies are needed to improve our understanding of the relationship between bipolar disorder and bowel disease as well as the role of psychotropic medication, particularly SSRIs.

Keywords: depression, bipolar disorder, irritable bowel syndrome, inflammatory bowel disease, prevalence, risk

Introduction

Over 300 million people are affected by depression and bipolar disorder worldwide (1). Individuals suffering from these conditions experience a significantly diminished quality of life and excess mortality (2–4). Partly, this is attributable to the increased multimorbidity between affective disorders and a wide range of chronic physical illnesses (5,6). It is well documented that the comorbidity of depression and chronic disease worsens health outcomes significantly more than depression alone or the chronic condition alone (6). Compounding this further, there are indications of suboptimal screening, under-recognition and under-treatment of common medical disorders among individuals with mental illness (7–9).

Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are two debilitating gastrointestinal conditions (10). With a prevalence of approximately 7-16% in the Western world (11), IBS describes a persistent change in bowel habit associated with abdominal pain. Although described as a ‘functional gastrointestinal disorder’ in which psychological stress has an important aetiological role, IBS is likewise associated with morphologic changes in the gut involving lymphocytes, enterochromaffin cells and enteric nerves (12), as well as structural changes in the brain (13). In addition to diet and lifestyle interventions, treatments for IBS include psychological therapy, antispasmodic medications, antimotility medications and low-dose antidepressants (14).

Meanwhile, IBD is comprised of two main diseases, Crohn’s disease (CD) and ulcerative colitis (UC), both characterised by macroscopic bowel inflammation, diarrhoea, weight loss and gastrointestinal bleeding. The most recent estimates of IBD prevalence in the UK are 9–144/100,000 for CD and 66–389/100,000 for UC (15,16). Treatments for IBD are primarily immunosuppressive, including corticosteroids, immunomodulators and biologic therapies, as well as surgical bowel resection in some patients (17). Notably, people with IBD exhibit structural brain changes in areas implicated in depression (18).

A significant body of research has established that patients with IBS and IBD experience higher rates of depression, with recent reviews suggesting a three-fold increase in odds among those diagnosed with IBS compared to healthy counterparts (19) and a two to four times increase among those with IBD compared to general population estimates (20). The prevalence of bipolar disorder is also increased among people with immune-mediated inflammatory diseases, such as IBD (21,22), as well as IBS (23,24). However, despite the recognised bidirectional relationship between physical and psychiatric disorders and the known bidirectional nature of the gut-brain communication via the microbiota-gut-brain axis, far less research has distinguished
between affective disorders that develop as a consequence of IBS/IBD and those that are present prior to illness onset and may represent a risk factor. In keeping with this, some recent reviews have identified depression in the context of various conditions such as gastroenteritis, gastroesophageal reflux disease, chronic liver disease, fibromyalgia and migraine to be among the risk factors for development of new onset IBS (25,26). Further, gastrointestinal and affective disorders exhibit shared aetiology such as heightened immune system activation presenting with chronic inflammation as well as a heightened stress response (21). Clinically, an elevated prevalence of IBS or IBD in people with affective disorders would have important implications for treatment and management. For example, persistent gastrointestinal symptoms may require tailoring of antidepressant therapies according to their differential effects on bowel habit (27). Moreover, there is increasing evidence that dietary interventions and probiotic therapies can impact positively on affective disorders (28,29); it is therefore possible, though as yet untested, that these therapies could have greatest benefit in people with affective disorders and comorbid lower gastrointestinal disorders. To date, however, the prevalence of IBS and IBD in people with affective disorders has not been systematically evaluated.

The aim of this review was to: 1) identify the prevalence of IBS and IBD among people with depression and bipolar disorder; and 2) summarise all available evidence of depression and bipolar disorder as risk factors for the development of new onset IBS and IBD.

Materials and Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (30) and the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) (31) guidelines.

Search details

The search was conducted on EMBASE and MEDLINE and supplemented with manual searching through reference lists of relevant articles and Google Scholar. The final search was performed on 23/Jan/2020 with no limits set on publication date. Four sets of terms were searched, as follows: (1) terms defining the exposure conditions of interest: depress* or depressive disorder or bipolar disorder; (2) terms defining the outcome conditions of interest: irritable bowel syndrome or IBS or inflammatory bowel disease or IBD or Crohn* or colitis or diarrhea or diarrhoea or constipation; (3) terms defining the outcome measure of interest: epidemiolog* or prevalence or incidence or frequenc* or co-occurrence or occurrence or comorbid* or risk factor; and (4) terms
defining relevant study methodology: cross-sectional or cohort or observational or longitudinal or retrospective or prospective or case-control or ‘population study’. The search was limited to human studies and English language.

Study selection criteria

Studies were included if they: (1) employed an observational design (prospective cohort, retrospective cohort, cross-sectional or case-control); (2) reported the association between depression or bipolar disorder (exposure) and IBS or IBD (outcome) in terms of prevalence or incidence; (3) had a control group free of the exposure or outcome of interest (as applicable); (4) included men and/or women aged 18 and above; (5) used diagnostic instruments (e.g. Rome criteria for IBS) or medical record diagnosis (e.g. International Classification of Diseases (ICD) codes) to ascertain the presence of IBS and IBD; and (6) defined depression or bipolar disorder on the basis of a structured clinical interview, medical record diagnosis, or, for depression specifically, National Institute for Health and Care Excellence (NICE)-endorsed rating scale for assessment of depression in adults (i.e. the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI) or the Patient Health Questionnaire (PHQ)). We only included studies in general adult groups due to an appreciation of the specialist nature of child-adolescent and elderly populations (65+). Reviews, case-reports, case-series, editorials or articles not available in English were not considered.

Data extraction

From each study we extracted prevalence or incidence data (crude event data or effect measures, depending on availability) and corresponding confidence intervals (CIs). We did not extract sex-specific rates, as the majority of included studies did not report these. Study characteristics including sample size, age, sex, country of origin, case ascertainment method for both the affective and bowel disorders were also extracted. We were also interested in any consideration of affective disorder severity, IBS subtypes (diarrhoea-predominant, constipation-predominant, mixed or unspecified), IBD sub-types (Crohn’s disease, ulcerative colitis or both) and psychotropic medication use.

Quality assessment
Data were also extracted to assess the quality of each included study. We used the Critical Appraisal Checklist for Prevalence Studies (9 criteria) (32) and the Critical Appraisal Checklist for Cohort Studies (11 criteria) (33) developed by the Joanna Briggs Institute, to evaluate prevalence and incidence studies, respectively. The criteria were applied independently by two authors and discrepancies were resolved by discussion.

Quantitative synthesis

Where a sufficient number of studies reported comparable data (i.e. at least two studies reporting incidence or prevalence using comparable methodology and outcome measures), we performed random-effects meta-analyses on risk ratios (RR) as the effect measure applying the Mantel-Haenszel method. Cross-sectional data were used to calculate relative risks from prevalences and cohort study data for the calculation of relative risks from incidences (34). Inter-study heterogeneity was quantified using the DerSimonian-Laird estimator and was reported with the $I^2$ statistic, which represents the fraction of variation between studies attributable to heterogeneity. The $I^2$ value should not be regarded as precise but values of 30-60% may represent moderate heterogeneity; 50-90% substantial heterogeneity; and 75-100% considerable heterogeneity (35). Analyses were performed using the `meta` package in R (version 4.0.0). Subgroups planned to explore clinical and methodological sources of heterogeneity were type of affective disorder, method used to define depression and sample characteristics. However, in accordance with recommendations (36), we did not perform additional sensitivity analyses or assessment of publication bias due to the low number of studies in each analysis.

Results

Figure 1 presents a breakdown of the review process. Our search identified 2693 records, of which 2207 were unique publications. 2170 were excluded as irrelevant upon review of title/abstract. The full text of 37 was reviewed for eligibility. Eighteen met our selection criteria and were included in the qualitative synthesis; eleven looked at IBS only, five at IBD only and two at both. For the quantitative synthesis, there was a sufficient number of comparable studies for the prevalence and incidence of IBS in affective disorders only (n=12); the results of IBD studies have been summarised as a table due to substantial methodological heterogeneity.
Quality assessment

Study quality ranged between average to high and no exclusions were made based on quality score. Among prevalence studies, convenience sampling was noted in some, either with a sample recruited from a particular clinical service (2/10 studies) or from already available study samples (3/10). Of the latter studies, two may have been underpowered due to the relatively small size of the available sample (37,38) and the third had
an age-restricted sample (40-69 years) (39). Among incidence studies, the most frequent concern (3/9) was the absent or incomplete consideration of confounding factors. See Supplementary Materials for the complete evaluation.

Affective disorders and IBS

Key characteristics of the fifteen studies that met selection criteria are reported in Table 1. These studies came from ten countries spanning four geographic regions (Europe, Asia, Africa and Oceania). Eleven cross-sectional studies provided prevalence data of comorbid IBS (9,17,37–45) and four prospective cohort studies provided incidence data of newly developed IBS (46–49) in people with affective disorders and controls. Of these, three studies included people with bipolar disorder, but none investigated associations according to disorder subtype. All studies included both female and male participants and the sex distribution ranged between 46-92% female. Age also varied between studies, ranging from a birth cohort sampled at age 26 (48) to a smaller study of people with recurrent depression with an average age was 61.5 (37). The presence of IBS was established using medical record diagnosis/codes or with the use of diagnostic instruments in all studies. Affective disorders were identified at the diagnostic level in n=7 studies (with diagnostic instruments/medical records) and at the symptom level in the remaining n=8 studies using a NICE-endorsed rating scale.
Table 1. Characteristics of included studies for Irritable Bowel Syndrome (IBS), by year of publication.

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting, Country</th>
<th>Affective disorder</th>
<th>Sample N</th>
<th>Age (Avg)</th>
<th>% F (Avg)</th>
<th>Affective disorder definition</th>
<th>IBS definition</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karling (2007)</td>
<td>available study samples, Sweden</td>
<td>Depression</td>
<td>Depression: 73</td>
<td>61.5</td>
<td>57.8</td>
<td>DSM-IV</td>
<td>Medical record diagnosis or Rome II</td>
<td>6/9</td>
</tr>
<tr>
<td>Ladep (2007)</td>
<td>3 general outpatient clinics, Nigeria</td>
<td>Depression</td>
<td>Depression: 129</td>
<td>32.0</td>
<td>54.7</td>
<td>DSM-IV</td>
<td>Rome II</td>
<td>6/9</td>
</tr>
<tr>
<td>Hillila (2008)</td>
<td>Population-based postal survey, Finland</td>
<td>Depression</td>
<td>Depression: 602</td>
<td>42.9</td>
<td>55.9</td>
<td>BDI-SF</td>
<td>Rome II</td>
<td>8/9</td>
</tr>
<tr>
<td>Smith (2013)</td>
<td>primary care medical records, Scotland, UK</td>
<td>Bipolar disorder</td>
<td>Bipolar: 2,582</td>
<td>51.2</td>
<td>56.2</td>
<td>Medical record diagnosis</td>
<td>Medical record diagnosis</td>
<td>8/9</td>
</tr>
<tr>
<td>Study</td>
<td>Setting, Country</td>
<td>Affective disorder</td>
<td>Sample N</td>
<td>Age (Avg)</td>
<td>% F (Avg)</td>
<td>Affective disorder definition</td>
<td>IBS definition</td>
<td>Quality score</td>
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<tr>
<td>Smith (2014)</td>
<td>primary care medical records, Scotland, UK</td>
<td>Depression</td>
<td>143,943</td>
<td>50.1</td>
<td>59.1</td>
<td>Medical record diagnosis</td>
<td>Medical record diagnosis</td>
<td>8/9</td>
</tr>
<tr>
<td>(40)</td>
<td></td>
<td></td>
<td>Controls: 1,280,435</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lee (2015)</td>
<td>Endoscopy clinic medical records, South Korea</td>
<td>Depression</td>
<td>1,257</td>
<td>45.7</td>
<td>46.3</td>
<td>BDI</td>
<td>Rome III</td>
<td>7/9</td>
</tr>
<tr>
<td>(42)</td>
<td></td>
<td></td>
<td>Control: 22,018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karling (2016)</td>
<td>Outpatient affective unit &amp; available study sample (control), Sweden</td>
<td>Bipolar</td>
<td>136</td>
<td>50.5</td>
<td>60.5</td>
<td>DSM-IV</td>
<td>Medical record diagnosis or Rome III</td>
<td>7/9</td>
</tr>
<tr>
<td>(38)</td>
<td></td>
<td></td>
<td>Control: 136</td>
<td></td>
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<tr>
<td>Lee (2017)</td>
<td>available community-based cohort, South Korea</td>
<td>Depression</td>
<td>1,085</td>
<td>52.2</td>
<td>48.7</td>
<td>BDI</td>
<td>Rome II</td>
<td>6/9</td>
</tr>
<tr>
<td>(39)</td>
<td></td>
<td></td>
<td>Controls: 2,344</td>
<td></td>
<td></td>
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<tr>
<td>Schauer (2019)</td>
<td>population-based cohort, Germany</td>
<td>Depression</td>
<td>767</td>
<td>49.0</td>
<td>55.8</td>
<td>PHQ9-BDI linking approach</td>
<td>Rome III</td>
<td>7/9</td>
</tr>
<tr>
<td>(43)</td>
<td></td>
<td></td>
<td>Controls: 3427</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Ibrahim</td>
<td>Medical students,</td>
<td>Depression</td>
<td>86</td>
<td>21.7</td>
<td>49.7</td>
<td>HADS</td>
<td>Rome III</td>
<td>8/9</td>
</tr>
<tr>
<td>Study</td>
<td>Setting, Country</td>
<td>Affective disorder</td>
<td>Sample N</td>
<td>Age (Avg)</td>
<td>% F (Avg)</td>
<td>Affective disorder definition</td>
<td>IBS definition</td>
<td>Quality score</td>
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<tr>
<td>(2013) (44)</td>
<td>Saudi Arabia</td>
<td>Affective disorder</td>
<td>Controls: 472</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibrahim</td>
<td>Nurses, Saudi Arabia</td>
<td>Depression</td>
<td>Depression: 16</td>
<td>36.5</td>
<td>92.1</td>
<td>HADS</td>
<td>Rome III</td>
<td>8/9</td>
</tr>
<tr>
<td>(2016)(45)</td>
<td>Saudi Arabia</td>
<td>Depression</td>
<td>Controls: 210</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Incidence studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting, Country</th>
<th>Affective disorder</th>
<th>Sample N</th>
<th>Age (Avg)</th>
<th>% F (Avg)</th>
<th>Affective disorder definition</th>
<th>IBS definition</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talley (2001)</td>
<td>Dunedin birth cohort, New Zealand; Follow-up at 8 years</td>
<td>Depression</td>
<td>Depression: 222</td>
<td>26.0</td>
<td>49.2</td>
<td>DSM-III-R</td>
<td>Rome II, Manning*</td>
<td>8/11</td>
</tr>
<tr>
<td>(48)</td>
<td>UK; Follow-up at 15 months</td>
<td>Controls: 555</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nicholl</td>
<td>population-based postal survey, UK; Follow-up at 15 months</td>
<td>Depression</td>
<td>Depression: 540</td>
<td>45.9</td>
<td>55.5</td>
<td>HADS</td>
<td>Rome II</td>
<td>10/11</td>
</tr>
<tr>
<td>Koloski **</td>
<td>Population-based postal survey, Australia; Follow-up at 1 year</td>
<td>Depression</td>
<td>Total: 1,900</td>
<td>57.0</td>
<td>53.0</td>
<td>HADS</td>
<td>Rome III</td>
<td>7/11</td>
</tr>
<tr>
<td>(2016) (46)</td>
<td></td>
<td>Depression: nr</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Lin (2017)</td>
<td>Health Insurance Database, Taiwan; Mean follow up 5.7 years</td>
<td>Depression, Bipolar disorder</td>
<td>Total: 98,265</td>
<td>25%≥ 60</td>
<td>58.5</td>
<td>Medical record diagnosis</td>
<td>ICD-9</td>
<td>7/11</td>
</tr>
<tr>
<td>(49)</td>
<td></td>
<td>Depression: 5044</td>
<td>34% 40-59 33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Setting, Country</td>
<td>Affective disorder</td>
<td>Sample N</td>
<td>Age (Avg)</td>
<td>% F (Avg)</td>
<td>Affective disorder definition</td>
<td>IBS definition</td>
<td>Quality score</td>
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<td></td>
<td>20-40</td>
<td>7%≤20</td>
<td></td>
<td></td>
<td>20-40</td>
</tr>
</tbody>
</table>

*only Rome II data were extracted for this meta-analysis for comparability purposes; ** not included in the meta-analysis; BDI (SF)=Beck depression inventory (Short form), HADS= Hospital anxiety and depression scale, PHQ9= patient health questionnaire, ICD= international classification of disease, DSM= diagnostic and statistical manual of mental disorders, nr= not reported
Prevalence

The eleven studies included in this meta-analysis captured 150,676 people with affective disorders (147,958 with depression and 2,718 with bipolar disorder) and 2,734,200 controls. Overall, people with an affective disorder were 2.2 times as likely to have co-morbid IBS compared to controls (RR = 2.24, 95% CI 1.81-2.76), with high heterogeneity between studies (I² = 90%, p<0.01) (see Figure 2 for the forest plot). People with depression had 2.4 times the risk of having IBS compared to people without depression (RR = 2.42, 95% CI 1.98-2.96). Visual inspection of subgroups based on method used to define depression indicated no differences between diagnosis and the BDI self-report scale (the only scale used in these studies, see Table 1). Regarding people with bipolar disorder, the risk was increased compared to the control group, but not statistically significant (RR = 1.55, 95% CI 0.75-3.19). In additional analyses, Karling et al. reported that among people with bipolar disorder (38) and recurrent depression (37), only those currently reporting depressive symptoms (HADS ≥8) reported significantly higher IBS-like symptoms.

![Figure 2. Forest plot of prevalence of IBS in affective disorders. RR=Risk Ratio, CI= confidence interval.](image-url)
Incidence

Of the four cohort studies reporting incidence data, three were suitable for meta-analysis; two reported incidence in depression and one in both depression and bipolar disorder. The fourth study (46) was excluded as it was the only one to report depression as a continuous variable. This meta-analysis captured 6,209 people with affective disorders (5,806 with depression and 403 with bipolar disorder) and 193,554 healthy controls. The overall risk of developing IBS was almost double for those with depression compared to those without (RR = 1.90, 95% CI 1.41-2.56) (see Figure 3 for the forest plot). The $I^2$ statistic showed low heterogeneity between studies ($I^2 = 0\%$, $p>0.05$), although this should be cautioned by the low number of studies. Notably, participants in the study by Talley et al. (48) were considerably younger (26y), which may be a source of heterogeneity. Further, this study did not report whether individuals with IBS at baseline were excluded. Only one study provided data of newly developed IBS among patients with bipolar disorder (49) for which the CI was large and crossed the line-of-no-effect (RR = 1.71, 95%CI 0.71-4.10). It should be noted that the primary aim of this study was to investigate the relationship between SSRI use and IBS, so the selected patient sample may not have captured a representative sample of cases with bipolar disorder from the Taiwanese Health Insurance Database comprising 1 million individuals. We found no studies which directly investigated the link between bipolar disorder and new onset IBS.

![Figure 3. Forest plot of incidence of IBS in affective disorders. RR=Risk Ratio, CI= confidence interval.](image-url)
The findings from the study that reported depression as a continuous variable are in line with the results of this meta-analysis: Koloski and colleagues (46) reported higher levels of depression at baseline to be a significant predictor of new onset IBS at follow-up (OR 1.54, 95% CI 1.29-1.83).

**Psychotropic medication and IBS**

In the Taiwanese Health Insurance Database study, Lin et al. reported that the risk of IBS was significantly increased among SSRI users (HR 1.74, 95% CI 1.44-2.10) compared to people who do not use SSRIs, regardless of indication (49). There was no significant increase among those on other antidepressants or on a combination of SSRI and other antidepressants. In their two studies, Karling and colleagues noted a higher rate of IBS-like symptoms among recurrent depression patients treated with SSRIs (37) and no difference in IBS-like symptoms among bipolar disorder patients on the basis of treatment type (38). No studies included psychotropic medication as a moderator in their analyses of the affective disorder-IBS relationship.

**Affective disorders and IBD**

Seven studies investigated the relative risk of IBD in affective disorders using two broad strategies: 1) by comparing the prevalence or incidence of IBD in people with and without affective disorders (3 studies); or 2) by comparing cohorts with and without IBD for rates of prior exposure to affective disorders (4 studies). Figure 4 provides an illustration of these two methodologies. Given the relatively low prevalence of IBD, prospective cohort studies measuring new-onset IBD in individuals with an established affective diagnosis at baseline would be large and costly; therefore, the latter approach has been utilised as a cost-effective alternative. Table 2 summarises the key characteristics of the seven studies: these have been separated according to the strategy employed (see Figure 4) as this guided the definition of the sample, the criterion according to which controls were selected, the analytical strategy and the primary outcome measure. The wide range of designs and methodologies meant that a meta-analysis could not be conducted. Overall, all studies included both female and male participants, with a similar sex distribution (55-60% female). The average age ranged from 37 to 51 years. The most common data source was population-based medical records (6/7 studies). IBD diagnosis was established through medical records or diagnostic codes. Only two studies presented data separately for UC and CD (see Table 2). Affective disorders were diagnostically defined in all studies through medical records/codes or diagnostic instruments.
Figure 4. Designs used to study the relative risk of IBD in affective disorders. A. Studies assessing the prevalence or incidence of IBD in people with and without affective disorders. These studies begin in a group with a known rate of exposure (e.g. to depression) and select a non-exposed (control) group with characteristics matching the exposed group (or in population-based studies, the entire non-exposed population is included); the primary outcome measure is the incidence or prevalence of the outcome (IBD) and is evaluated either cross-sectionally or prospectively (relative to the selected starting point). B. Studies assessing the prevalence or incidence of pre-existing affective disorders in people with and without IBD. These studies begin in a group with a known rate of outcome (IBD) and select a control group (without the outcome) with characteristics matching the IBD group (unless population-based, as above); the primary outcome measure is the prevalence or incidence of the exposure (depression/bipolar disorder) and is evaluated either cross-sectionally or retrospectively. Incidence refers to the probability of occurrence of a given outcome or exposure in a population within a period of time. Incidence conveys information about the risk of getting the outcome or being exposed to a risk factor. Prevalence refers to the proportion of the population to have the outcome or exposure of interest at a specific time. Prevalence can be lifetime (at any point up to data collection), period (for a pre-defined timeframe, e.g., at least 5 years before the outcome of interest) or point (measured at a specific time point, e.g., at 5 years before the outcome or at the point of data collection). HR=hazard ratio, IRR=incident rate ratio, OE=observed/expected ratio, OR=odds ratio, RR=risk ratio, PR=prevalence ratio.
Table 2. Characteristics of included studies for Inflammatory Bowel Disease (IBD), by year of publication.

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting, Country</th>
<th>Design</th>
<th>Affective disorder</th>
<th>Sample N</th>
<th>Age</th>
<th>%F</th>
<th>Affective disorder definition</th>
<th>IBD definition</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence or incidence of IBD in individuals with an affective disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith (2013)</td>
<td>Primary care medical records, Scotland, UK</td>
<td>Cross-sectional</td>
<td>Bipolar disorder</td>
<td>Bipolar: 2,582 Controls: 1,421,796</td>
<td>51.2</td>
<td>56.2</td>
<td>Medical record diagnosis</td>
<td>Medical record diagnosis</td>
<td>9/9</td>
</tr>
<tr>
<td>Frolkis</td>
<td>Medical records database, UK</td>
<td>Prospective cohort*</td>
<td>Depression</td>
<td>Depression: 403,665 Controls: 5,323,986</td>
<td>50.1</td>
<td>59.1</td>
<td>Medical record diagnosis</td>
<td>Medical record diagnosis</td>
<td>11/11</td>
</tr>
</tbody>
</table>

Prevalence or incidence of pre-existing affective disorders in individuals with IBD
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting, Country</th>
<th>Design</th>
<th>Affective disorder</th>
<th>Sample N</th>
<th>Age</th>
<th>%F</th>
<th>Affective disorder definition</th>
<th>IBD definition</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurina (2001)</td>
<td>Hospital admissions &amp; psychiatric care database, England, UK</td>
<td>Retrospective cohort</td>
<td>Depression</td>
<td>IBD: 12,499</td>
<td>-</td>
<td>55.0</td>
<td>ICD 7-10 codes</td>
<td>ICD 7-10 codes</td>
<td>6/11</td>
</tr>
<tr>
<td>Walker (2008)</td>
<td>IBD cohort study &amp; National cohort study (controls), Canada</td>
<td>Cross-sectional</td>
<td>Depression</td>
<td>IBD: 351</td>
<td>43.0</td>
<td>60.0</td>
<td>DSM-IV</td>
<td>Medical record diagnosis</td>
<td>6/9</td>
</tr>
<tr>
<td>Bernstein (2019)</td>
<td>administrative health records, Canada</td>
<td>Retrospective cohort</td>
<td>Depression</td>
<td>IBD: 6,619</td>
<td>-</td>
<td>-</td>
<td>Medical record</td>
<td>Medical record diagnosis</td>
<td>10/11</td>
</tr>
<tr>
<td>Marrie (2019)</td>
<td>medical record databases, Canada</td>
<td>Retrospective cohort</td>
<td>Depression</td>
<td>IBD: 3,766</td>
<td>41.3</td>
<td>55.0</td>
<td>ICD-9-10</td>
<td>Medical record diagnosis</td>
<td>11/11</td>
</tr>
</tbody>
</table>

*The study by Frolkis et al. (2019) is generally classed as a retrospective study as it draws data from a pre-existing database; however, they evaluate the prospective development of IBD in a sub-group of people with depression and a referent control group by following them up until development of IBD, death or drop-out from the database (see panel A, Figure 4). In contrast, Bernstein et al (2019) and Marrie et al (2019) evaluate the retrospective exposure to depression in individuals with known IBD and a referent control group (panel B, Figure 4). ICD= international classification of disease, DSM= diagnostic and statistical manual of Mental Disorders.*
Depression and IBD

Six studies investigated the relative risk of IBD in depression; their results are summarised in Table 3. We identified only one study reporting on the prevalence of IBD in depression. This study included 143,943 individuals with depression and 1,280,435 controls and found those with depression to have a 39% increase in odds of having IBD (40). There was also only one study investigating the risk of new onset IBD in a large cohort of people with (N = 403,665) and without (N = 5,323,986) a diagnosis of depression (50). To ensure the separation of prevalent from incident cases and that depression was not the consequence of an already present but undiagnosed IBD, the minimum washout period was set as three years in this study. Results showed that people with depression had over double the risk of developing either type of IBD (Crohn’s disease HR 2.11, ulcerative colitis HR 2.23). This was also the only study to consider the effects of antidepressant medication. The use of SSRIs and TCAs was found to be protective against Crohn’s disease (HR 0.63 and 0.77, respectively), while the use of mirtazapine (HR 0.34), SNRIs (HR 0.46), SSRIs (HR 0.48), serotonin modulators (HR 0.46) and TCAs (HR 0.59) was found to be protective against ulcerative colitis.

All studies examining pre-exposure provided some evidence that depression was increased prior to onset of IBD (Table 3). Bernstein et al. (53) examined point prevalence at 5 years before diagnosis and reported a 47% increase in depression among those with IBD compared to matched controls. Regarding lifetime prevalence, Walker et al (52) reported 120% increase in the odds of depression among those with a diagnosis of IBD. Notably, within the IBD group 54% had their first depressive episode at least two years prior to IBD diagnosis. Kurina et al. (51) assessed depression prevalence over two periods with sufficient washout: 1-4 years and 5+ years before diagnosis of either ulcerative colitis or Crohn’s disease. They found a significant elevation in depression prevalence 5+ years before diagnosis of ulcerative colitis only. Finally, in a larger study of psychiatric disorders in immune-mediated inflammatory diseases, Marrie et al. (21) found that the incidence of depression was significantly increased beginning five years before diagnosis of IBD and peaked in the year of diagnosis.
### Table 3. Results of studies investigating the relative risk of IBD in affective disorders.

<table>
<thead>
<tr>
<th>Study</th>
<th>Affective disorder</th>
<th>Outcome of interest</th>
<th>Time period between affective disorder and IBD</th>
<th>Effect measure</th>
<th>Findings</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence or incidence of IBD in affective disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith (2013)</td>
<td>Bipolar disorder</td>
<td>Prevalence of IBD in bipolar disorder</td>
<td>n/a (point prevalence)</td>
<td>OR</td>
<td>IBD: 1.99 (1.42-2.78)</td>
<td>↑</td>
</tr>
<tr>
<td>(7)</td>
<td></td>
<td></td>
<td></td>
<td>(95%CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith (2014)</td>
<td>Depression</td>
<td>Prevalence of IBD in depression</td>
<td>n/a (point prevalence)</td>
<td>OR</td>
<td>IBD: 1.39 (1.31-1.39)</td>
<td>↑</td>
</tr>
<tr>
<td>(39)</td>
<td></td>
<td></td>
<td></td>
<td>(95%CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frolkis (2019)</td>
<td>Depression</td>
<td>Incidence of new onset IBD in depression</td>
<td>depression &gt;3 years before IBD</td>
<td>HR</td>
<td>CD: 2.11 (1.65-2.70)</td>
<td>↑</td>
</tr>
<tr>
<td>(50)</td>
<td></td>
<td></td>
<td></td>
<td>(95%CI)</td>
<td>UC: 2.23 (1.92-2.60)</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Prevalence or incidence of pre-existing affective disorders prior to IBD diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td>O/E</td>
<td>Depression in CD: 1.66 (0.75-3.16)</td>
<td>⇔</td>
</tr>
<tr>
<td>Kurina (2001)</td>
<td>Depression</td>
<td>Prevalence of depression</td>
<td>&lt; 1 year before IBD</td>
<td></td>
<td>Depression in UC: 2.14 (1.22-3.49)</td>
<td>↑</td>
</tr>
<tr>
<td>(51)</td>
<td></td>
<td></td>
<td></td>
<td>(95%CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nikolova et al.  
Risk of Lower GI Disease in Mood Disorders

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Disorder</th>
<th>Time Before IBD</th>
<th>Effect Measure</th>
<th>Effect Size (95%CI)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker (2008)</td>
<td>Depression</td>
<td>1-4 years</td>
<td>O/E</td>
<td>Depression in CD: 0.94 (0.51-1.58)</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95%CI)</td>
<td>Depression in UC: 1.01 (0.62-1.55)</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>≥ 5 years</td>
<td>O/E</td>
<td>Depression in CD: 1.15 (0.76-1.67)</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95%CI)</td>
<td>Depression in UC: 1.49 (1.12-1.93)</td>
<td>↑</td>
</tr>
<tr>
<td>Bernstein (2019)</td>
<td>Depression</td>
<td>lifetime prevalence</td>
<td>OR</td>
<td>Depression: 2.20 (1.64-2.95)</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder</td>
<td>lifetime prevalence</td>
<td>(95%CI)</td>
<td>Bipolar disorder: 0.56 (0.22–1.40)</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time of depression onset</td>
<td>-</td>
<td>Depression onset for 54% preceded IBD by at least 2 years</td>
<td></td>
</tr>
<tr>
<td>Marrie (2019)</td>
<td>Depression</td>
<td>at 5 years</td>
<td>PR</td>
<td>Depression: 1.47 (1.32-163)</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>before IBD</td>
<td>(95%CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder</td>
<td>&lt; 1 year</td>
<td>IRR</td>
<td>Depression: 2.76 (2.10-3.62)</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>before IBD</td>
<td>(95%CI)</td>
<td>Bipolar disorder: 1.73 (0.93-3.23)</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>Incidence of depression</td>
<td>up to 5 years</td>
<td></td>
<td>Depression: Incidence significantly elevated compared to controls beginning 5 years pre-diagnosis of IBD*</td>
<td>↑</td>
</tr>
</tbody>
</table>
Incidence of bipolar disorder up to 5 years before IBD Bipolar disorder: incidence elevated compared to controls beginning 2–3 years pre-diagnosis of IBD, but not significantly*

* as this was a large study of multiple psychiatric and immune-mediated inflammatory diseases, individual numerical results were not presented; HR=hazard ratio, IRR= incident rate ratio, O/E= observed over expected ratio, OR= odds ratio, RR= risk ratio, SES = socioeconomic status, CI= confidence interval, CD = Crohn’s Disease, UC = Ulcerative Colitis
Bipolar disorder and IBD

Only three studies investigated the relative risk of IBD in bipolar disorder and yielded inconclusive results (see Table 3). None of these studies considered bipolar disorder subtype. In a cross-sectional investigation of medical records of nearly 1.5 million people, Smith et al. (7) demonstrated that people with bipolar disorder had almost double the odds of having IBD compared to those without a bipolar disorder diagnosis. Conversely, a smaller cross-sectional study of patients with IBD (n=351) and matched controls (n=779) found a lower rate of lifetime prevalence of bipolar disorder in the IBD group, even though this was not statistically significant (52). It should be noted that the former study included a broader range of diagnostic codes related to bipolar disorder, whereas the latter only included bipolar type I and II diagnosed with a structured clinical interview. Finally, in a retrospective population-based study, Marrie et al. found that those with IBD had an increased rate of bipolar disorder compared to those without IBD in the year preceding diagnosis and the incidence of bipolar disorder was elevated as early as 2–3 years pre-diagnosis, but this rise did not reach statistical significance (21).

Discussion

Despite the recognised bidirectional relationship between gut disorders and mental illness, little effort has been made to evaluate systematically the relative risk of lower GI disease such as IBS and IBD in people with affective disorders compared to the wide literature devoted to estimating the development of mental illness as a consequence to IBS/IBD. To our knowledge, this is the first study to summarise all evidence for the prevalence and incidence of IBS and IBD in people with affective disorders.

Affective disorders and IBS

The results from our meta-analysis of prevalence studies indicate that the risk of having IBS was more than double among people with affective disorders. Those suffering from depression had 2.4 times the risk of having IBS compared to non-depressed individuals. We also performed a meta-analysis of incidence studies, which showed that the risk of developing new-onset IBS was also almost double among people with depression (RR 1.90), suggesting depression may be a risk factor for developing IBS in some cases.

Bipolar disorder was not consistently associated with risk of either having or developing the condition, but the available evidence is limited at present. Furthermore, the variability in results could be at least partially
due to differences in bipolar disorder definition – one of the studies included only types I and II, one included the full range of associated diagnostic codes, including unipolar mania and psychotic depression, and one provided no further detail. Interestingly, two studies indicated that among people with bipolar disorder or recurrent depression only those currently presenting with depressive symptoms had a significant increase in IBS-like symptoms, which suggests that an active depressive phase may be the driver of risk for poor gut health in affective disorders. This also points to the complexities of evaluating risk of episodic physical illness in episodic mental illness. None of the included studies took into consideration current phase or severity of illness at the point of collection of IBS incidence or prevalence.

As a diagnosis of IBS requires the presence of persistent abdominal pain (11), our findings are unlikely to be explained by the potential side-effects of antidepressant therapy on bowel habit alone. Nevertheless, it is conceivable that a proportion of IBS cases in people with affective disorders may be resultant of the use of psychiatric medication. According to the limited evidence summarised here, SSRI use seems to be related to an increase in IBS diagnoses as well as IBS-like symptoms. It is possible that some of these cases represent misdiagnosed medication-induced side-effects, however, in the study by Lin et al (49), the mean time from SSRI exposure to IBS diagnosis was 2 years, while SSRI-related side effects typically resolve within a few weeks of stopping medication. This finding may be at odds with some reviews indicating a therapeutic benefit of antidepressants for IBS, SSRIs and TCAs in particular (54,55), although others have concluded that the evidence for SSRIs is conflicting (56,57). An alternative explanation may be that due to their known low-side effect profile compared to other antidepressants, SSRIs may be disproportionately prescribed to patients presenting with sub-clinical or yet undiagnosed gastrointestinal symptoms. Therefore, the relationship between psychotropic medication and IBS needs to be investigated further within the context of psychiatric illness in cohort studies where patients are reliably assessed for the presence of IBS at baseline. Further, understanding which type of IBS (i.e. constipation-predominant, diarrhoea-predominant, or mixed type) is most prominent may be another component necessary to fully understand this relationship. None of the studies we found reported rates of IBS according to subtype.

One explanation for the increased risk of incident IBS in depression is that patients with depression have a heightened sensitivity to physical symptoms. IBS is often associated with other somatic comorbidities, such as fibromyalgia and other pain syndromes, migraine and visceral sensitivity (11). As in IBS, there is an
increased prevalence of depression in ‘functional’ disorders such as fibromyalgia and non-ulcer dyspepsia (58). Notably, research in other functional disorders has tended to study depression as a correlate or consequence of physical symptoms, rather than as a precursor, and indeed somatoform symptom episodes may be poorly predictive of incident depression (59). This suggests that there is a subgroup of patients who, partly through visceral sensitivity and hypersensitivity to pain, show vulnerability to the development of depression and multiple functional disorders. In future studies, it is important to test whether other functional comorbidities, such as fibromyalgia, may explain the increased incidence of depression in IBS and likewise for the reverse association. The finding that the risk of developing IBS is increased among people with depression compared to general population samples also lends further support to the notion that the gut and the brain interact bidirectionally in IBS. This is supported by studies investigating the order of diagnosis among patients presenting with both a gastrointestinal and an affective disorder and has also been noted for other gut disorders, such as functional dyspepsia (46,60,61). The gut-brain axis, encompassing the neuroendocrine system, neuroimmune systems and the gut microbiota, has been identified as a key component in the pathophysiology of both IBS and depression (62). In keeping with this, a recent review of gut microbiota characterisation studies demonstrated that the comorbidity of IBS and depression/anxiety was associated with lower alpha diversity compared to IBS-alone (63). Therefore, a move away from symptomatic treatment towards treatments targeting shared aetiology may be necessary to improve outcomes in patients presenting with both depression and IBS.

Affective disorders and IBD

Our review shows that people with depression are at an increased risk of having and developing IBD compared to people without. Similarly, when cohorts with IBD and matched controls were assessed retrospectively, those with IBD had significantly higher rates of prevalent or incident depression as early as five years pre-diagnosis. Only one study considered a potential moderating role of antidepressants. Frolkis et al. found that treatment with SSRIs and TCAs seemed to have a protective effect against both Crohn’s disease and ulcerative colitis and a wider range of treatments, including SNRIs, serotonin modulators and mirtazapine, reduced the risk of ulcerative colitis alone. This suggests that while the risk of developing IBD is increased in depression, there may be potential for mitigation with the use of antidepressants (50). This may occur due to the anticholinergic effects of these medications and their beneficial impacts on visceral pain (11). As previously discussed elsewhere however, this study was limited by medical records coding. Regarding individual IBD
diagnoses, which were assessed in only two studies, a risk association between depression and ulcerative colitis was confirmed in both, whereas an increased risk of Crohn's disease in only reported in one. Conversely, a study among nurses (not included in this review due to the use of a non-accepted method to define depression) suggested a significant increase in incidence of Crohn's disease, but not ulcerative colitis in this group (64). Therefore, further studies are merited to understand if the risk differs according to disorder subtype.

The increased incidence of IBD in depression and of depression in the pre-diagnosis period for IBD may be explained in several ways. For example, depression may be a risk factor for IBD or the two illnesses may share common aetiology. Regarding shared aetiology, immune dysfunction with a chronic inflammatory state, a defining feature of IMID, is also a well-established feature of depression (65) and a shared pathological process across multiple psychiatric disorders (66). Depression itself is known to induce changes in immune function, inflammation and hyperactivation of the hypothalamic-pituitary-adrenal axis which may increase the risk of IBD, particularly in predisposed individuals (21). Finally, gut dysbiosis is seen in people with IBD who have comorbid depression (67), and we have previously suggested that such changes to the gut microbiome could drive the parallel development of depression and IBD through downstream effects on metabolomic and inflammatory pathways (68). Prospective longitudinal population-based cohort studies collecting a range of biomarker data are necessary to evaluate these potential explanations for the association between depression and IBD.

There is limited evidence to support conclusively or reject a link between bipolar disorder and risk of subsequent IBD. Similarly to IBS studies, there were differences in bipolar disorder case definition between studies and none investigated associations according to disorder subtype. However, in the study by Marrie et al. (21), bipolar disorder followed a similar trajectory relative to IBD onset to that of depression. Further, much like depression, there is evidence for shared aetiology between bipolar disorder and IMID via immune system dysfunction, which leaves the possibility for a bidirectional interaction (69).

**Clinical implications**

The finding that people with affective disorders are at an increased risk of gastrointestinal illness has implications for clinical practice. Improved screening for bowel complaints and identification of people at risk of gastrointestinal disease prior to deciding on a treatment strategy, as well as continued monitoring of symptom progression and tailoring treatments to account for gut symptoms, are all important steps for improving clinical
outcomes and reducing the burden of this comorbidity. For example, psychological therapy has an important role in the treatment of IBS (14), such that current psychological therapies for depression could be broadened to account for comorbid gastrointestinal symptoms. In terms of pharmacotherapy for depression, SSRIs are more likely to cause diarrhoea than constipation and indeed are used as a treatment for constipation-predominant IBS, whereas tricyclic antidepressants are more likely to cause constipation than diarrhoea and so are used in the treatment of diarrhoea-predominant IBS. This suggests that pharmacological therapy for depression should be tailored according to the presence of comorbid gastrointestinal symptoms.

On a structural level, many healthcare systems have single disease-focused interventions and there is a separation between mental health and physical health services, which may partially account for the poorer outcomes observed in patients with comorbid psychiatric and physical illness (40). While in recent years there has been a recognition of the importance of treating depression among those with chronic illness (e.g. the NICE-issued guideline on recognition and management of depression in adults with a chronic physical health problems (70)), less attention has been paid to the health risks of those presenting with a psychiatric diagnosis first. In conjunction with a holistic approach to care provision, an increased awareness among clinicians of the bidirectional relationship between these disorders and their shared aetiology are instrumental for reducing incident bowel disease in psychiatric patients and improving outcomes in prevalent cases.

Dietary intake has profound effects on the gut microbiome and has an important role in the pathogenesis of both IBS and IBD (62,71). Likewise, dietary interventions have been found to impact positively on affective disorders, and there is accumulating evidence from randomised controlled trials that depression, anxiety and bipolar disorder can be improved by probiotic therapies (28,29,72) and even by faecal microbial transplantation (73). This highlights a need for future prospective observational studies and interventional studies to test whether dietary interventions have a role in the treatment – and even prevention – of comorbid gut disease in people with affective disorders.

Limitations

There were several limitations to this review and the included studies. First, we chose to include only studies establishing the presence of affective disorders via confirmation of diagnosis or with the use of scales endorsed by NICE. While this reduced inter-study heterogeneity and provided more reliable evidence for the presence of
depression, it may have resulted in the elimination of true cases. Second, because of the low number of studies addressing the subject of this review, we could not perform subgroup analyses or a meta-regression to investigate further sources of heterogeneity. Therefore, heterogeneity remained substantial and results should be interpreted with caution. Third, our review did not aim to assess the effect of antidepressants on IBS risk independently of psychiatric illness, therefore, the included evidence may not provide a comprehensive account of this relationship. Similarly, as the majority of the included studies measured incidence of IBS at a specific time-point, the exact time of IBS onset after the affective disorder cannot be determined, thus precluding us from assessing further the potential role of medication or overlapping pathophysiology. Nevertheless, it points to the importance of considering psychotropic medication when assessing the impact of psychiatric illness on gut health.

Conclusion

This systematic review with meta-analysis demonstrates that people with depression are at an increased risk of IBS and IBD compared to people without depression. It is recommended that psychiatrists and other clinicians treating patients with affective disorders monitor gastrointestinal symptoms and tailor treatments accordingly. Likewise, clinicians treating patients with bowel disease should also enquire about psychiatric history. At a structural level, integrated or collaborative care would provide greater opportunities for managing comorbid affective- and gastrointestinal disorders. Further studies are needed to understand the relationship between bipolar disorder, its subtypes and phases, and gastrointestinal disorders as well as the role of psychiatric medication in mediating the risk of gastrointestinal illness in affective disorders.

Supplementary materials: The complete quality assessment is available as Supplementary material 1 online.

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