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**TITLE PAGE**

**Title:** Bi-directional Brain-Gut Axis Effects Influence Mood and Prognosis in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis.

**Short title:** Brain-Gut Interactions in IBD.

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**Abbreviations:**

| | |
|---|---|
| CD | Crohn's disease |
| CI | confidence interval |
| IBD | inflammatory bowel disease |
| HR | hazard ratio |
| RR | relative risk |

UC ulcerative colitis

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**ABSTRACT**

**Objective:** The role of the brain-gut axis is of increasing interest in inflammatory bowel disease (IBD), as the link between common mental disorders and gastrointestinal inflammation may be bi-directional. We performed a systematic review examining these issues.

**Design:** We searched EMBASE Classic and EMBASE, MEDLINE, and APA PsychInfo (to July 11, 2021) for longitudinal follow-up studies examining effect of symptoms of anxiety or depression on subsequent adverse outcomes in IBD, or effect of active IBD on subsequent development of symptoms of anxiety or depression. We pooled relative risks (RRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) for adverse outcomes (flare, escalation of therapy, hospitalisation, emergency department attendance, surgery, or a composite of any of these) according to presence of symptoms of anxiety or depression at baseline, or RRs and HRs with 95% CIs for new onset of symptoms of anxiety or depression according to presence of active IBD at baseline.

**Results:** We included 12 separate studies, recruiting 9192 patients. All 12 studies examined brain-to-gut effects. Anxiety at baseline was associated with significantly higher risks of escalation of therapy (RR=1.68; 95% CI 1.18-2.40), hospitalisation (RR=1.72; 95% CI 1.01-2.95), emergency department attendance (RR=1.30; 95% CI 1.21-1.39), or a composite of any adverse outcome. Depression at baseline was associated with higher risks of flare (RR=1.60; 95% CI 1.21-2.12), escalation of therapy (RR=1.41; 95% CI 1.08-1.84), hospitalisation (RR=1.35; 95% CI 1.17-1.57), emergency department attendance (RR=1.38; 95% CI 1.22-1.56), surgery (RR=1.63; 95% CI 1.19-2.22), or a composite of any of these. Three studies examined gut-to-brain effects. Active disease at baseline was associated with future development of

anxiety or depression (RR=2.24; 95% CI 1.25-4.01 and RR=1.49; 95% CI 1.11-1.98, respectively).

**Conclusion:** Bi-directional effects of the brain-gut axis are present in IBD and may influence both the natural history of the disease and psychological health.

**SUMMARY BOX**

**What is already known about this subject?**

- Symptoms of common mental disorders affect more than one-third of patients with inflammatory bowel disease (IBD) in remission.
- Adverse disease outcomes may be more common in patients with IBD with underlying symptoms of anxiety and depression.
- Therefore, the brain-gut axis may have bi-directional effects in IBD, but previous studies have been underpowered and demonstrate conflicting results.

**What are the new findings?**

- We performed a systematic review and meta-analysis to assess the effect of symptoms of common mental disorders on future adverse outcomes in IBD patients (including flare, escalation of therapy, hospitalisation, emergency department attendance, surgery, or a composite of any of these) and the effect of active disease on future development of common mental disorders.
- Symptoms of anxiety at baseline were significantly associated with future risk of escalation of therapy hospitalisation, emergency department attendance, or a composite of any adverse outcome.
- Symptoms of depression at baseline were significantly associated with future risk of flare, escalation of therapy, hospitalisation, emergency department attendance, surgery, or a composite of any adverse outcome.
- Clinically active disease at baseline was associated with future development of symptoms of anxiety or depression.

**How might it impact on clinical practice for the foreseeable future?**

- The brain-gut axis has a bi-directional influence on the prognosis of IBD and the development of new symptoms of common mental disorders.
- Patients with symptoms of active disease or symptoms of anxiety and depression should be offered psychological support alongside specialist IBD management.
- Further longitudinal research assessing the trajectory of symptoms of anxiety and depression, and their impact on IBD activity, is required to help better select cohorts of patients to be involved in trials of gut-brain neuromodulators or psychological therapies.

## INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal tract that encompasses both Crohn's disease (CD) and ulcerative colitis (UC), with increasing prevalence across Europe and North America.[1] The natural history of IBD fluctuates through periods of relapse and remission, with management strategies focused on immunosuppressive medications and surgery. The pathophysiology is incompletely understood, but felt to be influenced by environmental and genetic factors, combined with immunological dysregulation and alteration of the intestinal microbiome.[2]

Recently, there has been increasing focus on the brain-gut axis and its role in disease progression. This complex interaction encompasses communication of neuroendocrine pathways with the hypothalamic-pituitary-adrenal axis and the central, peripheral, and autonomic nervous systems. Activation of these pathways have been observed in murine models with colitis in remission, whereby induction of depression activates the inflammatory response of the gut, through attenuation of the vagal response and leading to suppression of pro-inflammatory cytokine release.[3] With common immune-inflammatory markers found in both depression and IBD, this interaction may be bi-directional.[4] This would suggest that symptoms of common mental disorders and gastrointestinal inflammation are interlinked and have the potential to drive each other.

In a systematic review and meta-analysis, symptoms of common mental disorders were almost twice as prevalent in patients with IBD compared with the general population and affected over half of patients during periods of disease activity,[5] suggesting gut-to-brain effects. In a cohort of patients with IBD with biochemical evidence of remission, but with symptoms of common mental disorders, there was a cumulative effect of psychological co-

morbidity at baseline on risk of future adverse outcomes, including flare of disease activity, the need for escalation of therapy due to uncontrolled IBD activity, hospitalisation for IBD, and IBD-related surgery.[6] Other studies have demonstrated that individuals with gastrointestinal symptoms and co-existent depression are more likely to develop IBD in the future.[7, 8] Taken together, this suggests that common mental disorders may play an independent role in the aetiology of IBD, and also contribute to adverse disease outcomes, via brain-to-gut effects.

However, studies examining these issues in patients with IBD are often relatively small or have reported conflicting results. A prior systematic review identified only four studies describing brain-to-gut effects that were suitable for meta-analysis. In this study, although there was a trend towards depression influencing the course of CD, the results were not significant.[9] In a systematic review examining gut-to-brain effects there was a statistically significant association between aggressive disease and subsequent development of depression in patients with IBD,[10] but only in a single study.[11] However, to date, there has been no definitive systematic assessment of gut-to-brain and brain-to-gut effects in patients with IBD. We, therefore, conducted a contemporaneous systematic review and meta-analysis of observational studies to examine this issue. Our hypothesis was that such effects, including deleterious effects of psychological co-morbidity at baseline on risk of future adverse outcomes related to IBD activity and deleterious effects of IBD activity on future psychological health, would be apparent from synthesis of all available data. This would support potential benefits from addressing both gastrointestinal inflammation and psychological health. This could be achieved via integration of a biopsychosocial care model into the management of patients with IBD.

## METHODS

### Search Strategy and Selection Criteria

We used EMBASE Classic, EMBASE, MEDLINE and APA PsychInfo to search the medical literature from inception up to July 2021 to identify longitudinal follow-up studies examining the effect of anxiety or depression at baseline on adverse outcomes related to IBD activity (brain-to-gut) or, conversely, the influence of IBD activity at baseline upon subsequent symptoms of anxiety or depression (gut-to-brain). We defined our eligibility criteria prospectively (Box 1). For studies examining brain-to-gut effects, we required use of a validated measure of anxiety or depression or registered International Statistical Classification of Diseases and Related Health Problems (ICD) code at baseline, with subsequent assessment of adverse outcomes related to IBD activity during longitudinal follow-up. These included a flare of disease activity (via self-report, physician's global assessment, use of a validated disease activity index, or review of medical records) or glucorticosteroid prescription, escalation of therapy due to uncontrolled IBD activity, hospitalisation due to IBD activity, emergency department attendance due to IBD activity, IBD-related surgery, or a composite outcome of any of these combined. For studies examining gut-to-brain effects, we required assessment of IBD activity at baseline, via a validated disease activity index, with subsequent assessment of symptoms of a common mental disorder, via a validated measure of anxiety or depression or registered ICD code during longitudinal follow-up. We included only studies with ≥50 participants with radiologically, endoscopically, or histologically confirmed IBD, recruited from an unselected adult population of patients (i.e., studies recruiting only patients with a recent flare of disease activity or hospitalisation, or limiting recruitment by disease location, behaviour, or severity were

excluded), with at least 90% aged ≥16 years. Studies had to consist of a minimum of two points of follow-up, separated by ≥6 months.

We used the following search terms to identify studies related to IBD, combined with the set operator OR: *inflammatory bowel disease, ulcerative colitis, Crohn$, regional enteritis, ileitis, IBD*. We used the following terms to identify studies related to common mental disorders, again combined with the set operator OR: *anxiety, depression, mood, mental health, soma$, psych$, gut AND brain*. We combined these two searches using the set operator AND. There were no language restrictions; we translated foreign language articles. Two investigators (KMF and JL) reviewed titles and abstracts independently and retrieved those felt to be relevant for further eligibility assessment. In addition, we performed a recursive search for other potentially eligible studies among the bibliographies of selected articles. We resolved disagreements between investigators (KMF and JL) by discussion.

**Data Extraction**

Two investigators (KF and JL) undertook data extraction onto a Microsoft Excel Spreadsheet (XP professional edition; Microsoft, Redmond, WA) independently, with all disagreements resolved by discussion. For each eligible study we collected the following data: country, duration of longitudinal follow-up, number of participants with complete data, number of included participants with CD or UC, criteria used to define presence of a common mental disorder at baseline, criteria used to measure IBD activity at baseline, and whether the study examined brain-to-gut effects, gut-to-brain effects, or both. We extracted the adjusted hazard ratio (HR) or adjusted relative risk (RR), with 95% confidence intervals (CI), for each of the events of interest, where possible. If unavailable, we extracted raw data according to presence or

absence of symptoms of anxiety or depression at baseline and subsequent adverse outcomes related to IBD activity for brain-to-gut studies, or according to presence or absence of active IBD at baseline and subsequent symptoms of anxiety or depression for gut-to-brain studies. For studies where the adjusted HR, adjusted RR, or raw data were not reported, we used the unadjusted HR or unadjusted RR, depending on study reporting, with 95% CI. For studies that reported odds ratios, authors were contacted for raw data to calculate unadjusted RRs and 95% CIs for pooled analyses, because if the prevalence of events of interest is greater than 10% the OR will no longer approximate the RR.[12] The quality of included studies was judged according to the Newcastle-Ottawa scale, with a total possible score of 9.[13] Higher scores indicate higher quality studies.

**Data Synthesis and Statistical Analysis**

We measured the degree of agreement between the two investigators for judging of study eligibility of study using a kappa statistic. We assessed heterogeneity between studies using the $I^2$ statistic with values of 0% to 24%, 25% to 49%, 50% to 74%, and ≥75% typically considered no, low, moderate, and high levels of heterogeneity, respectively, and the $\chi^2$ test with a P value <0.10, as the threshold used to define statistically significant heterogeneity.[14] We planned to apply Egger's test to funnel plots to assess for evidence of publication bias,[15] or other small study effects, where ≥10 studies were present, in line with published recommendations.[16] We pooled data using the inverse variance method and a random effects model to provide a conservative estimate of the effect of symptoms of anxiety or depression at baseline on subsequent adverse outcomes related to IBD activity or the effect of IBD activity at baseline on subsequent symptoms of anxiety or depression.[17] We assumed the HR to be equivalent to the

RR, so these were pooled together across studies to produce an overall RR with a 95% CI. This is an assumption that has been used by other groups previously in prior meta-analyses,[18, 19] but we tested this by pooling HRs and RRs separately for the outcome with the largest number of contributing studies, and the pooled ratios were indeed similar. We used Stats Direct version 3.2.10 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled RRs with 95% CIs.

## RESULTS

The literature search identified 17,928 citations, of which 124 were obtained for further review. Following retrieval and review, seven articles fulfilled eligibility criteria and had data suitable for extraction (Figure 1).[11, 20-25] We contacted the authors of a further eight articles for raw data.[26-33] For two of these,[31, 32] the data were either unavailable or we received no response, so they were excluded. There was substantial agreement between reviewers for study eligibility (Kappa statistic = 0.86). The 13 eligible articles reported on 12 separate study populations,[11, 20-30, 33] containing 9192 patients. Ten articles examined brain-to-gut effects only,[20-25, 27, 28, 30, 33] one gut-to-brain effects only,[11] and two articles both.[26, 29] Therefore, in total there were 12 articles examining brain-to-gut effects (Table 1), and three articles examining gut-to-brain effects (Table 2). One of the brain-to-gut articles was a duplicate publication of an earlier study.[21] However, the initial study only reported a composite endpoint of flare of disease activity, escalation of therapy due to uncontrolled IBD activity, or IBD-related surgery,[28] whereas the subsequent study reported these endpoints separately.[21] Study quality is provided in Supplementary Tables 1 and 2; five studies scored 7 or more on the Newcastle-Ottawa scale.[11, 20, 23, 24, 26]

### Adverse Outcomes Related to IBD Activity During Longitudinal Follow-up Among Patients with Symptoms of Anxiety at Baseline

Eight brain-to-gut studies reported adverse outcomes related to IBD activity in those with symptoms of anxiety at baseline (Table 3).[20, 25-30, 33] The minimum duration of follow-up was 1 year, and the maximum 3.9 years. Only two studies restricted recruitment to patients in

**Table 1. Characteristics of Studies Examining Brain-to-Gut Effects in Inflammatory Bowel Disease.**

| Study and year | Country and setting | Number of patients (CD, UC) | Number of subjects in remission at baseline (%) | Duration of follow-up (years) | Criteria used to define presence of symptoms of anxiety at baseline | Criteria used to define presence of symptoms of depression at baseline | Adverse outcomes related to IBD activity studied during longitudinal follow-up |
|---|---|---|---|---|---|---|---|
| Levenstein 2000 [24] | Italy, tertiary care | 62 (0, 62) | 62 (100) | 1.45 | N/A | CES-D | Composite outcome of flare of disease activity defined by PGA, escalation of therapy due to uncontrolled IBD activity, or evidence of endoscopic disease activity. |
| Bitton 2008 [20] | Canada, secondary and tertiary care | 101 (101, 0) | 101 (100) | 1 | SCL-90 | SCL-90 | Flare of disease activity defined by CDAI >150 and an increase of ≥70 points from baseline. |
| Mikocka-Walus 2008 [29] | Australia, tertiary care | 59 (32, 27) | 40 (67.8) | 1 | HADS-A | HADS-D | Flare of disease activity defined by CDAI >150 for CD or SCCAI >2 for UC. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Langhorst 2013 [23] | Germany, secondary care | 75 (0, 75) | 75 (100) | 1 | N/A | HADS-D | Flare of disease activity defined by CAI >4 and an increase of >3 from baseline, with endoscopic evidence of disease activity at the time of the flare. |
| Barreiro-De Acosta 2014 [33] | Spain, tertiary care | 716 (299, 417) | Not reported | 1.5 | HADS-A | HADS-D | Hospitalisation due to IBD.<br>Emergency department attendance due to IBD. |
| Sirin 2014 [25] | Turkey, tertiary care | 381 (126, 255) | Not reported | 2 | BDAI | BDAI | Emergency department attendance due to IBD. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mikocka-Walus 2016 [28] | Switzerland, secondary and tertiary care | 2007 (1122, 885) | Not reported | 1 | HADS-A | HADS-D | Composite outcome of PGA of flare of disease activity, escalation of therapy due to uncontrolled IBD activity, or IBD-related surgery. |
| Jordi 2021 [21]† | | 1973 (1137, 836ǂ) | 154 (9.2) | 11.6 | N/A | HADS-D | Flare of disease activity defined by CDAI ≥150 for CD or MTWAI ≥10 for UC/IC. Escalation of therapy due to uncontrolled IBD activity. IBD-related surgery. |
| Gracie 2018 [26] | UK, tertiary care | 423 (250, 173) | 423 (100) | 2.5 | HADS-A | HADS-D | Flare of disease activity defined by glucocorticosteroid prescription or PGA. Escalation of therapy due to uncontrolled IBD activity. Hospitalisation due to IBD IBD-related surgery. Composite of any of the above. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Kochar 2018 [22] | USA, tertiary care | 4314 (2798, 1516) | 2473 (57.3) | 1.9 | N/A | PHQ-8 | Flare of disease activity defined by HBI ≥5 or SCCAI >2. Escalation of therapy due to uncontrolled IBD activity. Hospitalisation due to IBD. IBD-related surgery. |
| Narula 2019 [30] | Canada, tertiary care | 414 (227, 188) | 65 (15.7) | 3.9 | HADS-A | HADS-D | Flare of disease activity defined by glucocorticosteroid prescription. Hospitalisation due to IBD. Emergency department attendance due to IBD. Composite of any of the above. |
| Marrie 2021 [27] | Canada, secondary and tertiary care | 247 (153, 94) | 146 (59.1) | 3 | HADS-A | HADS-D | Flare of disease activity defined by defined by HBI ≥5 for CD or Powell-Tuck index ≥5 for UC. Escalation of therapy due to uncontrolled IBD activity. |

†Dual of Mikocka-Walus 2016,[28] but reported data for flare of disease activity, escalation of therapy due to uncontrolled IBD activity, and IBD-related surgery separately, so eligible for these analyses, as Mikocka-Walus 2016 only reported a composite endpoint.

ǂCombined ulcerative colitis and inflammatory bowel disease unclassified

BDAI, Beck's depression and anxiety index; CAI, colitis activity index; CES-D, Center for Epidemiological Studies - depression; HADS-A, hospital anxiety and depression scale, anxiety subscale; HADS-D, hospital anxiety and depression scale, depression subscale; HBI, Harvey-Bradshaw index; N/A, not applicable as no data collected; PGA, physician's global assessment; PHQ, patient health questionnaire; SCCAI, simple clinical colitis activity index; SCL-90, symptom checklist-90**.**

**Table 2. Characteristics of Studies Examining Gut-to-Brain Effects in Inflammatory Bowel Disease.**

| Study and year | Country and setting | Number of patients (CD, UC) | Number of subjects in remission at baseline (%) | Duration of follow-up (years) | Criteria used to define presence of clinically active disease at baseline | Criteria used to define presence of symptoms of anxiety at follow-up | Criteria used to presence of symptoms of depression at follow-up |
|---|---|---|---|---|---|---|---|
| Mikocka-Walus 2008 [29] | Australia, tertiary care | 57 (23, 29†) | 35 (61.4) | 1 | CDAI >150 for CD or SCCAI >2 for UC. | HADS-A | HADS-D |
| Panara 2014 [11] | USA, secondary and tertiary care | 393 (272, 121) | Not reported | 8 | PGA assessment of medical records including endoscopy and radiology reports | N/A | ICD-9-CM |
| Gracie 2018 [26] | UK, tertiary care | 192 (112, 80) | 124 (64.6) | 2.6 | HBI ≥5 for CD or SCCAI ≥5 for UC. | HADS-A | HADS-D |

†Missing data n=5

CDAI, Crohn's disease activity index; HADS-A, hospital anxiety and depression scale, anxiety subscale; HADS-D, hospital anxiety and depression scale, depression subscale; HBI, Harvey-Bradshaw index; ICD-9-CM, International Classification of Diseases, clinical modification codes; PGA, physician's global assessment; SCCAI, simple clinical colitis activity index.

**Table 3. Adverse Outcomes Related to Inflammatory Bowel Disease Activity During Longitudinal Follow-up Among Patients with Symptoms of Anxiety or Depression at Baseline.**

| | Number of studies | Total number of patients | Pooled RR (95% CI) | $I^2$ (%) | P value for $\chi^2$ |
|---|---|---|---|---|---|
| **Adverse outcomes related to IBD activity among patients with symptoms of anxiety at baseline** | | | | | |
| Flare of IBD activity | 5 | 1244 | 1.20 (0.93-1.55) | 53.7 | 0.071 |
| Escalation of therapy due to uncontrolled IBD activity | 2 | 670 | 1.68 (1.18-2.40) | 0.0 | 0.513 |
| Hospitalisation due to IBD | 3 | 1553 | 1.72 (1.01-2.95) | 73.4 | 0.023 |
| Emergency department attendance due to IBD | 3 | 1511 | 1.30 (1.21-1.39) | 1.0 | 0.364 |
| IBD-related surgery | 1 | 423 | 1.62 (0.50-5.25) | N/A | N/A |
| Composite endpoint combining any of the above | 3 | 2844 | 1.21 (1.08-1.36) | 19.8 | 0.291 |
| **Adverse outcomes related to IBD activity among patients with symptoms of depression at baseline** | | | | | |
| Flare of IBD activity | 8 | 7606 | 1.60 (1.21-2.12) | 73.5 | <0.001 |
| Escalation of therapy due to uncontrolled IBD activity | 4 | 6957 | 1.41 (1.08-1.84) | 43.1 | 0.135 |
| Hospitalisation due to IBD | 3 | 5151 | 1.35 (1.17-1.57) | 40.7 | 0.168 |
| Emergency department attendance due to IBD | 3 | 1511 | 1.38 (1.22-1.56) | 0.0 | 0.985 |
| IBD-related surgery | 3 | 6710 | 1.63 (1.19-2.22) | 57.4 | 0.070 |
| Composite endpoint combining any of the above | 4 | 2906 | 1.26 (1.07-1.48) | 19.8 | 0.289 |

CI, confidence interval; RR, relative risk; N/A, not applicable – too few studies

clinical remission, defined in one study by a Crohn's disease activity index <150 for at least 1 month prior to study inclusion,[20] or a simple clinical colitis activity index for UC and a Harvey-Bradshaw index for CD of <5.[26] When data were pooled from five studies,[20, 26, 27, 29, 30] containing 1244 patients, the risk of developing a flare of disease activity was no higher among those with symptoms of anxiety at baseline (RR = 1.20; 95% CI 0.93-1.55), with moderate heterogeneity between studies ($I^2$=53.7%). When we restricted the analysis to include only the two studies that recruited patients in clinical remission,[20, 26] the risk of flare among those with symptoms of anxiety at baseline was significantly higher (RR = 1.80; 95% CI 1.24-2.61). Escalation of IBD therapy was more likely among those with symptoms of anxiety at baseline (RR = 1.68; 95% CI 1.18-2.40) in two studies,[26, 27] containing 670 patients. Three studies,[26, 30, 33] recruiting 1553 patients, reported risk of hospitalisation according to presence or absence of symptoms of anxiety at baseline, which again was significantly higher in those with symptoms of anxiety (RR = 1.72; 95% CI 1.01-2.95), but with high heterogeneity between studies ($I^2$=73.4%) (Figure 2a). Emergency department attendance was also significantly more likely in those with symptoms of anxiety at baseline (RR = 1.30; 95% CI 1.21-1.39) in three studies,[25, 30, 33] recruiting 1511 patients, with no heterogeneity ($I^2$=1.0%) (Figure 2b). Only one study reported that IBD-related surgery was no more likely in those with symptoms of anxiety at baseline (RR = 1.62; 95% CI 0.50-5.25).[26] Finally, among three studies that recruited 2844 patients,[26, 28, 30] and which reported a composite endpoint of one or more of these adverse outcomes, risk was significantly higher among those with symptoms of anxiety at baseline (RR = 1.21; 95% CI 1.08-1.36), with low heterogeneity ($I^2$=19.8%) (Figure 2c).

**Adverse Outcomes Related to IBD Activity During Longitudinal Follow-up Among Patients with Symptoms of Depression at Baseline**

All 12 brain-to-gut studies provided data for adverse outcomes related to IBD activity in patients with symptoms of depression at baseline (Table 3).[20-30, 33] Of these, four recruited only patients with evidence of remission at baseline, according to a Crohn's disease activity index <150,[20] a clinical colitis activity index ≤4,[23] stable disease with no use of glucocorticosteroids for 2 months prior to recruitment and in clinical remission according to a non-validated questionnaire,[24] or a simple clinical colitis activity index for UC and a Harvey-Bradshaw index for CD of <5.[26] The minimum duration of follow-up was 1 year, and the maximum 11.6 years. When data were pooled from eight studies,[20-23, 26, 27, 29, 30] which included 7606 patients, symptoms of depression at baseline were associated with a significantly increased risk of flare of disease activity during longitudinal follow-up (RR = 1.60; 95% CI 1.21-2.12), with high heterogeneity between studies ($I^2$=73.5%) (Figure 3a). However, when the analysis was restricted to include only three studies that recruited only patients in clinical remission,[20, 23, 26] there was no longer a significant increase in risk (RR = 1.36; 95% CI 0.88-2.09). Pooling data from four studies,[21, 22, 26, 27] containing 6957 patients, there was an increased risk of escalation of therapy due to uncontrolled IBD activity in those reporting symptoms of depression at baseline (RR = 1.41; 95% CI 1.08-1.84) (Figure 3b), with low heterogeneity ($I^2$=43.1%). Patients with symptoms of depression at baseline were also more likely to require hospitalisation due to IBD when data were pooled from three studies,[22, 26, 30] recruiting 5151 patients (RR = 1.35; 95% CI 1.17-1.57) (Figure 3c), with moderate heterogeneity between studies ($I^2$=40.7%). Similarly, emergency department attendance was significantly more likely in those with symptoms of depression at baseline in three studies,[25,

30, 33] recruiting 1511 patients (RR = 1.38; 95% CI 1.22-1.56) (Figure 3d), with no heterogeneity ($I^2$=0%). When data were pooled from three studies,[21, 22, 26] containing 6710 patients, IBD-related surgery was also significantly more likely among those with symptoms of depression at baseline (RR = 1.63; 95% CI 1.19-2.22) (Figure 3e), with moderate heterogeneity between studies ($I^2$=57.4%). Finally, four studies reported a composite endpoint of one or more of the above,[24, 26, 28, 30] recruiting 2906 patients. In those with symptoms of depression at baseline there was a significantly increased risk of one or more adverse outcomes, compared with those without (RR = 1.26; 95% CI 1.07-1.48; $I^2$=19.8%) (Figure 3f).

**Development of Symptoms of Anxiety or Depression During Longitudinal Follow-up Among Patients with IBD with Clinically Active Disease at Baseline**

Only two gut-to-brain studies, with a minimum duration of follow-up of 1 year and a maximum of 2.6 years, examined effect of active IBD at study entry on subsequent symptoms of anxiety in a total of 249 patients (Table 4).[26, 29] Three gut-to-brain studies, with a minimum duration of follow-up of 1 year and a maximum of 8 years, examined effect of active IBD at baseline on subsequent development of depression in 642 patients.[11, 26, 29] All studies in these analyses only included patients with normal anxiety or normal depression scores at baseline, or no history of psychiatric symptoms or common mental disorder, for each analysis. There was a significant impact of clinically active disease at baseline on the future development of symptoms of anxiety (RR = 2.24; 95% CI 1.25-4.01), with no heterogeneity between studies ($I^2$=0%).[26, 29] Similarly, the effect of clinically active disease at baseline on future symptoms of depression was also significant (RR = 1.49; 95% CI 1.11-1.98), with no heterogeneity ($I^2$=0%).[11, 26, 29]

**Table 4. Development of Symptoms of Anxiety or Depression During Longitudinal Follow-up Among Patients with Inflammatory Bowel Disease with Clinically Active Disease at Baseline.**

| | Number of studies | Total number of patients | Pooled RR (95% CI) | $I^2$ (%) | P value for $\chi^2$ |
|---|---|---|---|---|---|
| Development of symptoms of anxiety among patients with IBD with clinically active disease at baseline | 2 | 249 | 2.24 (1.25-4.01) | 0.0 | 0.828 |
| Development of symptoms of depression among patients with IBD with clinically active disease at baseline | 3 | 642 | 1.49 (1.11-1.98) | 0.0 | 0.964 |

CI, confidence interval; RR, relative risk.

## DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to examine bi-directional effects of the brain-gut axis in IBD, including 13 longitudinal follow-up studies and over 9000 patients. Patients with symptoms of anxiety at baseline were at significantly increased risk of escalation of therapy due to uncontrolled IBD activity, hospitalisation due to IBD activity, emergency department attendance due to IBD activity, or a composite outcome of any of the adverse outcomes of interest we examined. When we restricted the analysis to studies recruiting patients in clinical remission at baseline, there was also a significant increase in risk of flare of disease activity in patients with symptoms of anxiety at baseline. Patients with symptoms of depression at baseline were at increased risk of all the adverse outcomes of interest, including flare of disease activity and IBD-related surgery. Finally, patient with clinically active disease at baseline, but no evidence of symptoms of anxiety or depression at study entry, were at increased risk of developing new symptoms of anxiety or symptoms of depression during longitudinal follow-up. These findings support the existence of bi-directional brain-gut axis effects in IBD.

We used an exhaustive search strategy and rigorous inclusion criteria to ensure that we were able to assess the temporal association between symptoms of anxiety or depression at baseline and future disease activity, and active disease at baseline and future symptoms of anxiety or depression. To that end, we included several longitudinal follow-up studies recruiting large numbers of patients with follow-up beyond 3 years in some instances. This meant that we were able to pool data for rarer events such as hospitalisation for active IBD and IBD-related surgery, which have been examined in previous studies, but which were likely underpowered for these endpoints. We used a random effects model to pool data in all our analyses so as not to

overestimate the impact of either brain-to-gut or gut-to-brain effects. We also contacted original investigators and obtained additional data from six studies,[26-30, 33] to maximise the number of eligible studies for analysis. We performed subgroup analyses for brain-to-gut studies, where we included only studies recruiting patients in remission at baseline, given that a potential confounding factor on adverse disease outcomes in those with symptoms of anxiety or depression at baseline could be ongoing disease activity. Notably, all three studies that examined gut-to-brain effects only recruited individuals with no symptoms of anxiety or depression at baseline, or no history of psychiatric illness, increasing the likelihood that IBD activity is an independent risk factor for the new development of symptoms of anxiety or depression.

Despite an extensive search, and contact with original investigators, this meta-analysis is limited by a relatively small number of eligible studies, of variable quality, for some of the outcomes of interest. This was particularly the case for studies examining gut-to-brain effects, and for studies reporting on escalation of therapy and IBD-related surgery in patients with symptoms of anxiety at baseline. Although longitudinal follow-up was up to 11 years in one study, four studies had a follow-up duration of 12 months or less, which is likely too short for some of the endpoints of interest to have occurred. We extracted adjusted HRs or RRs, wherever possible, but also relied on raw data from the studies or unadjusted HRs or RRs in some instances, which do not consider potential confounding. There was significant heterogeneity in some of our analyses, and too few studies to examine reasons for this. This heterogeneity is likely to have affected the accuracy of some of the estimates. We were also unable to examine for publication bias in any of our analyses, again due to the number of studies eligible for each analysis, although this is probable given the small number of studies for some of our outcomes of interest. The eligible studies we identified came from several different countries, in almost all

instances these were conducted in North America, Europe, or Australia, and all were conducted in hospital settings. However, our findings cannot be generalised to patients with IBD in other geographical regions or in community settings. In addition, data were not reported for patients with CD or UC separately in sufficient studies for us to examine whether these bi-directional effects are more pronounced according to IBD subtype. Finally, although we excluded cross-sectional studies from this meta-analysis, to be able to examine temporal associations, there were only four brain-to-gut studies that restricted their recruitment to patients who were in clinical remission at baseline. It is, therefore, possible that those with symptoms of anxiety or depression at baseline were also more likely to be suffering from active, or more aggressive, disease at study entry and, as a result, were at higher risk of experiencing one or more of the adverse disease outcomes we examined.

We identified more studies, with follow-up over an extended period, and were able to pool data from more patients than the prior meta-analysis studying brain-to-gut effects in IBD.[9] As a result, we have been able to demonstrate, for the first time, a significant association between symptoms of anxiety or depression and subsequent adverse outcomes related to disease activity in IBD, including hospitalisation or IBD-related surgery, rather than trends as described previously. Some of this may relate to patients with IBD with symptoms of a common mental disorder being more likely to report gastrointestinal symptoms, and therefore meet criteria for a flare of IBD.[34] Gastrointestinal symptoms, despite evidence of endoscopic or histological remission, affect more than one-in-four patients with IBD and are also associated with a higher risk of symptoms of anxiety or depression.[35] However, most of our endpoints were objective markers of IBD activity, such as escalation of therapy, hospitalisation, or IBD-related surgery. Studies examining gut-to-brain effects remain limited and our results are similar to those already

observed.[10] However, all of the brain-to-gut studies we identified only included individuals without pre-existing common mental disorders at baseline, which strengthens our findings as it means there is unlikely to be confounding.

This meta-analysis has demonstrated significant bi-directional effects of brain-gut interactions in patients with IBD. The time scales involved in these events is difficult to ascertain, due to the variable duration of follow-up. It is, therefore, hard to determine the point at which a deterioration in disease activity or the new onset of symptoms of common mental disorders occurs in brain-to-gut and gut-to-brain studies, respectively. Given the association between symptoms of a common mental disorder at baseline and subsequent adverse disease outcomes there is the potential to improve the natural history of IBD by screening for these symptoms and instituting appropriate therapy. However, symptoms of common mental disorders are likely to fluctuate over time and the brain-to-gut studies included in this meta-analysis only report the presence of symptoms compatible with a common mental disorder at a single point in time, rather than the trajectory of symptoms observed over time among those individuals. Studies of these trajectories conducted in other chronic conditions, including ischemic heart disease, diabetes, and chronic obstructive pulmonary disease, have demonstrated that persistent symptoms of a common mental disorder during follow-up are more likely to lead to adverse outcomes of these diseases, increased healthcare consumption, and higher costs.[36-38] In patients with IBD, depression has been linked to poor adherence to therapy,[39] higher healthcare utilisation and costs,[40] as well as a higher risk of failure to achieve remission despite escalation of therapy.[41] Unfortunately, the evidence to date for any benefit of gut-brain neuromodulators[42] or psychological therapies[43], including cognitive behavioural therapy, gut-directed hypnotherapy, and mindfulness as an adjunct to conventional treatment in IBD is

inconclusive, largely due to the fact that these have been tested in unselected patients. High levels of resilience appear to be associated with fewer adverse disease outcomes, and resilience may be modifiable.[44] There is preliminary evidence to suggest that resilience training may be a useful alternative biopsychosocial approach.[45] In addition, there have been no studies of symptom trajectories of common mental disorders in patients with IBD. Such studies might better characterise groups of patients with persistent symptoms of a common mental disorder who are more likely to respond to such interventions, and this may improve the natural history of the disease and reduce healthcare costs.

Although the effect sizes seen in this meta-analysis are relatively modest, they are likely to be driven by patients who are high utilisers of medical care, much of which is unplanned,[46] and in whom intervention is likely to lead to substantial reductions in the costs of managing IBD.[47] Despite this, access to mental health services is limited for many patients. A recent survey suggested that only 15% of patients were currently seeing a mental health practitioner, only 16% reported having been asked about their mental health by their gastroenterologist, and only 12% stated that they had access to a mental health practitioner as part of their outpatient service.[48] In a Crohn's and Colitis Australia survey less than 5% of hospitals surveyed reported that their IBD service included a mental health clinician.[49] Finally, in the Royal College of Physician's national audit of IBD service provision in the UK, only 12% of centres surveyed stated that they had access to clinical psychology via a defined referral pathway.[50]

In conclusion, we have shown a significant association between symptoms of a common mental disorder and future adverse disease outcomes, as well as clinical activity and future development of symptoms of a common mental disorder, in patients with IBD. These findings support bi-directional effects of the brain-gut axis in IBD. Future studies should focus on

identifying patients at highest risk of these deleterious effects, perhaps by examining symptom trajectories during longitudinal follow-up, to institute appropriate treatments to minimise the impact of poor psychological health on IBD activity, as well as active disease on psychological health. This has the potential to inform the design of future clinical trials to improve long-term outcomes in patients with IBD.

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**CONTRIBUTOR AND GUARANTOR INFORMATION**

**Guarantor:** ACF is guarantor. He accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Specific author contributions:** Study concept and design: ACF, DJG, and KMF conceived and drafted the study. KMF and ACF analysed and interpreted the data. KMF, DJG, and ACF drafted the manuscript. All authors have approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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## COMPETING INTERESTS DECLARATION

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## TRANSPARENCY STATEMENT

The lead author (ACF, the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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None.

## PATIENT AND PUBLIC INVOLVEMENT STATEMENT

We did not involve patients or the public in this work. We will disseminate our findings in lay terms via the national charity for people living with digestive diseases, “Guts UK”.

## DATA SHARING

No additional data available.

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**Box 1. Eligibility Criteria.**

Longitudinal follow-up studies with at least two established time points separated by ≥6 months.

Unselected adult population, with >90% aged ≥16 years.

≥50 participants.

Patients with radiologically, histologically, or endoscopically confirmed inflammatory bowel disease.

Assessment for presence or absence of symptoms of depression or anxiety* at baseline with recording of the development of adverse disease outcomes† during longitudinal follow-up in brain-to-gut studies.

Assessment for presence or absence of disease activity± at baseline with recording of the development of symptoms of anxiety or depression* during longitudinal follow-up in gut-to-brain studies.

*Via a validated measure of anxiety or depression or registered International Statistical Classification of Diseases and Related Health Problems code.

†Flare of disease activity (via self-report, physician's global assessment, use of a validated disease activity index, or review of medical records) or glucorticosteroid prescription, escalation of therapy due to uncontrolled IBD activity, hospitalisation due to IBD activity, emergency department attendance due to IBD activity, IBD-related surgery, or a composite outcome of any of these combined.

±Via a validated disease activity index.

**FIGURE LEGENDS**

**Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.**

**Figure 2a. Forest Plot for Risk of Hospitalisation Due to IBD Among Patients with Symptoms of Anxiety at Baseline.**

**Figure 2b. Forest Plot for Risk of Emergency Department Attendance Due to IBD Among Patients with Symptoms of Anxiety at Baseline.**

**Figure 2c. Forest Plot for Risk of Any of the Endpoints of Interest Among Patients with Symptoms of Anxiety at Baseline.**

**Figure 3a. Forest Plot for Risk of Flare of IBD Activity Among Patients with Symptoms of Depression at Baseline.**

**Figure 3b. Forest Plot for Risk of Escalation of Therapy Due to Uncontrolled IBD Activity Among Patients with Symptoms of Depression at Baseline.**

**Figure 3c. Forest Plot for Risk of Hospitalisation Due to IBD Among Patients with Symptoms of Depression at Baseline.**

**Figure 3d. Forest Plot for Risk of Emergency Department Attendance Due to IBD Among Patients with Symptoms of Depression at Baseline.**

**Figure 3e. Forest Plot for Risk of IBD-related Surgery Among Patients with Symptoms of Depression at Baseline.**

**Figure 3f. Forest Plot for Risk of Any of the Endpoints of Interest Among Patients with Symptoms of Depression at Baseline.**