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TITLE PAGE

Title: Bi-directionality of Brain–Gut Interactions in Patients With Inflammatory Bowel Disease.

Short Title: Brain-gut Axis Activity in IBD.

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Abbreviations:

CBT	cognitive behavioral therapy
CD	Crohn's disease
CI	confidence interval
FC	fecal calprotectin
GI	gastrointestinal
HADS	hospital anxiety and depression scale

HBI	Harvey-Bradshaw index
HR	hazard ratio
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
PHQ-15	patient health questionnaire-15
RCT	randomized controlled trial
SCCAI	simple clinical colitis activity index
SD	standard deviation
UC	ulcerative colitis

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ABSTRACT

Background & Aims: Inflammatory bowel diseases (IBD) are associated with mood disorders, such as anxiety or depression, but it is not clear whether one contributes to development of the other, or if the interaction is bi-directional (anxiety or depression contributes to the progression of IBD, and IBD affects psychologic health). We performed a 2-year longitudinal prospective study of patients in secondary care to investigate the bi-directionality of IBD and mood disorders.

Methods: We collected data from 405 adult patients with a diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) from November 2012 through June 2017. Demographic features, subtypes of IBD, treatments, symptoms, somatization, and fecal level of calprotectin were recorded at baseline. IBD activity was determined at baseline and after the follow-up period (2 years or more) using the Harvey-Bradshaw index for CD and the simple clinical colitis activity index for UC (scores ≥5 used to define disease activity). Anxiety and depression data were collected using the hospital anxiety and depression scale (HADS), at baseline and after the follow-up period. Objective markers of disease activity, including glucocorticosteroid prescription or flare of disease activity, escalation of therapy, hospitalization secondary to IBD activity, and intestinal resection during follow-up were assessed via case note review. A brain–gut direction of disease activity was defined as development of new IBD activity in patients with quiescent IBD and abnormal HADS scores at baseline. A gut–brain direction of disease activity was defined by subsequent development of abnormal HADS scores in patients with active IBD and normal HADS scores at baseline. We performed multivariate Cox regression controlling for patient characteristics and follow-up duration.

Results: Baseline CD or UC disease activity were associated with an almost 6-fold increase in risk for a later abnormal anxiety score (hazard ratio [HR], 5.77; 95% CI, 1.89–17.7). In patients with quiescent IBD at baseline, baseline abnormal anxiety scores were associated with later need for

glucocorticosteroid prescription or flare of IBD activity (HR, 2.08; 95% CI, 1.31–3.30) and escalation of therapy (HR, 1.82; 95% CI, 1.19–2.80). These associations persisted when normal IBD activity index scores and fecal level of calprotectin below 250μg/g were used to define quiescent disease at baseline.

Conclusions: In a 2-year study of patients with CD or UC, we found evidence for bi-directional effects of IBD activity and psychological disorders. Patients with IBD should be monitored for psychologic well-being.

KEY WORDS: pathogenesis, disease progression, gut–brain axis, enteric nervous system

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBD), with a prevalence of between 249 and 319 per 100,000 people in North America.[1] The etiology of IBD is unknown, but is thought to arise from dysregulation of the innate and adaptive immune systems, leading to an abnormal inflammatory response to commensal bacteria in a genetically susceptible individual. Both CD and UC are chronic disabling conditions that cause symptoms referable to the gastrointestinal (GI) tract, including abdominal pain, rectal bleeding, and diarrhea.

There appears to be an association between IBD and mood disorders, such as anxiety or depression, with a higher prevalence in patients with IBD compared with healthy individuals.[2-6] However, the direction of the relationship between the gut and brain in IBD is unclear. In people with functional GI disorders, such as irritable bowel syndrome (IBS) and functional dyspepsia, longitudinal studies suggest that there is a higher risk of developing anxiety or depression in people without mood disorders who report GI symptoms at baseline, but also an increased likelihood of asymptomatic people who demonstrate anxiety or depression at baseline developing GI symptoms de novo.[7, 8] This raises the possibility that the relationship between brain and gut may also be bi-directional in IBD. Hence, co-existent anxiety or depression, if unrecognized or untreated, may have deleterious effects on the natural history and prognosis of IBD, while ongoing disease activity may have implications for psychological health.

Evidence to support a bi-directional relationship between the brain and gut in IBD comes mainly from animal models. Mice with chronic GI inflammation develop behavioral changes akin to mood disorders in humans.[9] Studies have also demonstrated that, in murine models of quiescent colitis, the induction of depression can reactivate inflammation of the colonic mucosa.[10] This can be attenuated by the administration of antidepressant drugs, which may have some of their effects via the vagus nerve.[11] Some antidepressants, like amitriptyline, also appear to have direct effects on pro-

inflammatory cytokines that may arise via actions on the nuclear factor-κB and nitric oxide pathways, which are implicated in the pathogenesis of IBD.[12] In humans, meanwhile, there is evidence to suggest that vagal nerve stimulation can induce clinical and endoscopic remission in some patients with CD.[13] Additionally, acute psychological stress induces the production of pro-inflammatory cytokines in both the serum and mucosa of patients with IBD.[14] Small retrospective studies of the effect of psychological counselling or antidepressants in IBD have demonstrated fewer relapses of disease activity, and reduced use of glucocorticosteriods.[15, 16] Although a recent meta-analysis showed no clear benefit of psychological therapies on disease activity in IBD,[17] individual trials of hypnotherapy, cognitive behavioral therapy (CBT), and meditation have all shown some promise.[18-20]

These are important issues because patients with quiescent IBD may be at a lower risk of relapse if co-existing mood disorders are identified and treated. This in turn may lead to a more benign disease course, with a reduced need for subsequent escalation of therapy to drugs with more serious side effects, hospitalization, or surgery. Conversely, patients with active IBD may be at risk of developing potentially treatable mood disorders, which are known to negatively affect quality of life.[21] We aimed to investigate the possibility that brain-gut interactions in IBD may be bi-directional in a longitudinal follow-up study conducted over a minimum of 2 years. On the basis of previous research,[7, 8] where bi-directional relationships between the brain and gut have been identified in functional GI disorders, our hypothesis was that the same relationships would exist between anxiety and depression, and disease activity in IBD. Confirmation of a bi-directional relationship between mood and disease activity would reinforce the need for the integration of therapies targeting inflammatory disease activity with novel interventions aiming to improve psychological wellbeing in patients with IBD.

METHODS

Participants and Setting

Individuals recruited into a previous cross-sectional study from November 2012 through June 2015[21, 22] were sent a postal invitation to participate in a longitudinal follow-up study, after a minimum interval of 2 years had elapsed. All patients had an established radiological, histological, or endoscopic diagnosis of CD or UC, and were aged ≥16 years at the time of baseline recruitment. Exclusion criteria were an inability to understand written English, a diagnosis of IBD-unclassified, and anyone with an end ileostomy or colostomy, due to the difficulties in assessing disease activity indices in these patients. The follow-up postal invitation included a written information sheet explaining the nature of the study, a consent form, and a questionnaire similar to that completed at baseline. If no response to the initial invitation to participate was received, a second questionnaire was sent. In order to maximize response rates, we also recruited non-responders to the postal invitation into the study at their scheduled outpatient clinic appointments during the study period. The longitudinal follow-up study was approved by the local research ethics committee in September 2014 (REC ref: 12/YH/0443), and data collection continued until June 2017. Study findings were reported in accordance with the STROBE guidelines for reporting observational studies.[23]

Data Collection and Synthesis

Date of recruitment into the original cross-sectional survey, demographic data, type of IBD, medications, Rome III IBS symptom data,[24] somatization data, captured using the patient health questionnaire-15 (PHQ-15),[25] and fecal calprotectin (FC) (Immundiagnostik, Bensheim, Germany) were recorded at baseline, as described in the original cross-sectional survey.[21, 22] In total, 401 (50.2%) of 799 patients provided a stool sample for FC analysis at baseline.

Longitudinal Assessment of IBD Activity

This was done both at baseline and follow-up using the Harvey-Bradshaw index (HBI) for CD,[26] and the simple clinical colitis activity index (SCCAI) for UC,[27] with a score ≥5 used to define clinical disease activity for both, as previously recommended.[28, 29] Objective assessment of disease activity during longitudinal follow-up was made by detailed case note review by a sole investigator (DJG), blinded to the baseline questionnaire data. The case notes of each patient included at baseline were assessed for the following clinical endpoints, with the date of each endpoint recorded, where applicable: glucocorticosteroid prescription or flare of disease activity identified by physician's global assessment, escalation of medical therapy due to uncontrolled disease activity, hospitalization secondary to objectively confirmed IBD activity, and intestinal resection. Escalation of medical therapy in response to therapeutic drug monitoring, but in the absence of inflammatory activity, was not included as an endpoint, nor was surgical intervention for isolated perianal Crohn's disease. We selected a minimum follow-up period of 2 years for our study, in order to maximize the occurrence of these clinical endpoints of interest.

Definition of Normal and Abnormal Anxiety and Depression Scores

Anxiety and depression data were collected using the hospital anxiety and depression scale (HADS),[30] and scored as detailed in the original cross-sectional survey. Briefly, a normal HADS score at either baseline or follow-up was classified as both a total HADS anxiety and depression score ≤7, and an abnormal HADS score at either baseline or follow-up as either a HADS anxiety or depression score ≥11, as previously recommended.[30]

Statistical Analysis

We compared all baseline data between those who responded to the follow-up questionnaire and those who did not, using a χ^2 test for categorical variables, and an independent samples t-test for continuous data.

To assess for the presence of a gut-to-brain interaction during longitudinal follow-up, we compared the proportion of patients with new onset of abnormal anxiety or depression scores (i.e. normal HADS scores at baseline, but above threshold HADS anxiety or depression scores at follow-up) according to baseline IBD activity. We used HBI or SCCAI scores ≥5 to define active disease at baseline, but also performed a sensitivity analysis in patients with biochemical evidence of IBD activity at baseline (FC ≥250μg/g). To assess for the presence of a brain-to-gut interaction during longitudinal follow-up, we compared the proportion of patients with clinically quiescent disease at baseline (defined by HBI or SCCAI scores <5) who subsequently developed one of the objective measures of disease activity detailed above, according to the presence of either abnormal HADS anxiety or depression scores at baseline. Furthermore, the relationship between the presence of clinical disease activity at follow-up (defined by HBI or SCCAI scores ≥5) and the presence of baseline psychological co-morbidity was also assessed in patients with HBI or SCCAI scores <5 at baseline, dichotomized into those with and without abnormal HADS anxiety or depression scores at baseline. Again sensitivity analysis, where only those in clinical remission and with no biochemical evidence of IBD activity at baseline (FC <250μg/g) were considered as having quiescent disease, were conducted for all these analyses. We compared proportions using a χ^2 test. As we had defined our hypothesis that there would be a bi-directional effect of the brain-gut axis in IBD a priori, we considered a 2-tailed P value of 0.05 to be statistically significant for all these analyses.

Independent predictors of the development of abnormal anxiety or depression scores during longitudinal follow-up in those with normal scores at baseline, or any of the clinical endpoints of interest during longitudinal follow-up in those with quiescent disease at baseline, were determined by performing multivariate Cox regression analysis to control for baseline demographic characteristics, type of IBD, medications, presence or absence of Rome III IBS-type symptoms, and somatization severity. Due to multiple comparisons in these analyses, a 2-tailed P value of <0.01 was considered to be statistically significant, and the results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 405 (50.7%) of 799 patients included in the initial cross-sectional survey consented to participate and returned a follow-up questionnaire (Supplementary Figure 1). Of these, 239 (59.0%) had CD and 166 (41.0%) UC. Participants who returned the follow-up questionnaire were older, more likely to be married or co-habiting, and were more likely to report IBS-type symptoms. There were no other differences in baseline characteristics, including disease activity, defined by either FC or clinical disease activity indices, or psychological co-morbidity, between responders and non-responders (Supplementary Table 1).

Effect of Baseline Disease Activity on Development of Abnormal Anxiety Scores During Longitudinal Follow-up

There were 192 patients with normal HADS anxiety and depression scores at baseline, and 22 (11.5%) of these developed abnormal anxiety scores over a mean length of follow-up of 929 days (SD ± 180). Of these 22, 11 (50.0%) had evidence of clinical disease activity at baseline, compared with 46 (27.1%) of the 170 patients who did not develop abnormal anxiety scores (P = 0.03; Table 1). Following multivariate Cox regression analysis, clinical disease activity remained significantly associated with the development of abnormal anxiety scores (HR = 5.77; 95% CI 1.89-17.7; Figure 1). In sensitivity analysis, when FC ≥250μg/g was used to define baseline disease activity, there was no association between this and abnormal anxiety scores (P = 0.80; Table 1), and this was confirmed following Cox regression analysis (HR = 4.48; 95% CI 0.07-271).

Effect of Baseline Disease Activity on Development of Abnormal Depression Scores During Longitudinal Follow-up

Of the 192 patients with normal HADS anxiety and depression scores at baseline, only three (1.6%) developed abnormal depression scores during follow-up. There was no significant association between baseline disease activity and the development of abnormal depression scores (Table 1), and too few patients developing abnormal depression scores to perform Cox regression analysis. Sensitivity analysis for abnormal depression scores could not be performed, because none of the three patients provided FC at baseline.

Effect of Baseline Abnormal Anxiety Scores on Development of Disease Activity During Longitudinal Follow-up

Glucocorticosteroid Prescription or Flare of Disease Activity

Of 388 patients with clinically quiescent disease at baseline, 128 (33.0%) required a prescription of glucocorticosteroids or developed a flare of disease activity over a mean length of follow-up of 838 days (SD ± 436 days). Of these 128, 35 (27.3%) had abnormal anxiety scores at baseline, compared with 38 (14.6%) of the 260 patients who did not (P = 0.003; Table 2). When only need for glucocorticosteroids was considered, there were 22 (30.6%) of 72 patients requiring a glucocorticosteroid prescription with abnormal anxiety scores at baseline, compared with 51 (16.1%) of 316 not requiring a glucocorticosteroid prescription (P = 0.005). Following multivariate Cox regression analysis, baseline abnormal anxiety scores were associated with glucocorticosteroid prescription or a flare of disease activity (HR = 2.08; 95% CI 1.31-3.30; Table 3 and Figure 2). In sensitivity analysis,

abnormal baseline anxiety scores remained associated with need for glucocorticosteroid prescription or flare of disease activity (P = 0.02; Supplementary Table 2), and this was also the case following Cox regression analysis (HR = 2.29; 95% CI 1.03-5.07).

Escalation of Medical Therapy due to Uncontrolled Disease Activity

Of 403 patients with clinically quiescent disease at baseline, 148 (36.7%) underwent escalation of medical therapy in response to uncontrolled IBD activity over a mean length of follow-up of 807 days (SD ± 454 days). Of these 148, 38 (25.7%) had abnormal anxiety scores at baseline compared with 37 (14.5%) of 255 patients who did not undergo escalation of medical therapy (P = 0.005; Table 2). Following multivariate Cox regression analysis, baseline abnormal anxiety scores were associated with escalation of medical therapy (HR = 1.82; 95% CI 1.19-2.80; Table 3 and Figure 3). In sensitivity analysis, abnormal baseline anxiety scores remained associated with escalation of medical therapy (P = 0.02; Supplementary Table 2), and this persisted following Cox regression analysis (HR = 2.43; 95% CI 1.13-5.20).

Hospitalization due to IBD Activity

Of 423 patients with clinically quiescent disease at baseline, 58 (13.7%) were hospitalized as a result of objectively quantified IBD activity over a mean length of follow-up of 979 days (SD ± 414 days). Of these 58, 17 (29.3%) patients had an abnormal baseline anxiety score, compared with 59 (16.2%) of 365 patients who were not hospitalized (P = 0.02; Table 2). Following multivariate Cox regression analysis, baseline abnormal anxiety score was no longer associated with hospitalization (HR

= 1.59; 95% CI 0.77-3.31; Table 3). In sensitivity analysis, there was no association between baseline abnormal anxiety scores and hospitalization (Supplementary Table 2).

Intestinal Resection

Of 423 patients with clinically quiescent disease at baseline, 22 (5.2%) underwent intestinal resection over a mean length of follow-up of 1032 days (SD ± 384 days). Of these, seven (31.8%) had abnormal baseline anxiety scores compared with 69 (17.2%) of 401 patients who did not undergo intestinal resection (P = 0.08; Table 2). Following multivariate Cox regression analysis, baseline abnormal anxiety scores were not associated with intestinal resection (HR = 1.62; 95% CI 0.50-5.26; Table 3). In sensitivity analysis, there remained no association between baseline abnormal anxiety scores and intestinal resection (Supplementary Table 2).

Clinical Disease Activity

Of 226 patients with clinically quiescent disease at baseline (defined as baseline HBI or SCCAI score <5), 47 (20.8%) reported symptoms consistent with clinical disease activity (defined as HBI or SCCAI score ≥5) over a mean length of follow-up of 935 days (SD ± 187 days). Of these, 11 (23.4%) had abnormal baseline anxiety scores, compared with 32 (17.9%) of 179 who did not report symptoms consistent with clinical disease activity (P = 0.39; Table 2). Following Cox regression analysis, there remained no association between abnormal anxiety scores at baseline and the development of clinically active IBD (HR = 0.88; 95% CI 0.35-2.16, Table 3). In sensitivity analysis, when only patients in clinical remission with FC <250µg/g at baseline were included, abnormal baseline anxiety scores were

associated with the development of clinically active IBD (P = 0.005; Supplementary Table 2). There were too few patients to perform Cox regression analysis.

Effect of Baseline Abnormal Depression Scores on Development of Disease Activity During Longitudinal Follow-up

Glucocorticosteroid Prescription or Flare of Disease Activity

Of the 128 patients requiring a prescription for glucocorticosteroids or developing a flare of disease activity, four (3.1%) had abnormal depression scores at baseline, compared with 13 (5.0%) of the 259 patients who did not (P = 0.39; Table 2). There remained no association following multivariate Cox regression analysis (HR = 0.72; 95% CI 0.24-2.10; Table 3), or in sensitivity analysis.

Escalation of Medical Therapy due to Uncontrolled Disease Activity

Of 148 patients undergoing escalation of medical therapy, five (3.4%) had abnormal depression scores at baseline compared with 13 (5.1%) of 254 patients who did not undergo escalation (P = 0.42; Table 2). Following multivariate Cox regression analysis, there was no association between escalation of medical therapy and abnormal depression scores at baseline (HR = 0.86; 95% CI 0.33-2.27; Table 3), and in sensitivity analysis.

Hospitalization due to IBD Activity

Among the 58 patients hospitalized, five (8.6%) had abnormal baseline depression scores, compared with 16 (4.4%) of 364 patients who were not hospitalized (P = 0.17; Table 2). There was no association between abnormal depression scores at baseline and hospitalization following multivariate Cox regression analysis (HR = 0.79; 95% CI 0.22-2.84; Table 3), or in sensitivity analysis (Supplementary Table 2).

Intestinal Resection

Of 22 patients undergoing intestinal resection, three (13.6%) had abnormal baseline depression scores compared with 18 (4.5%) of 400 patients who did not undergo resection (P = 0.06; Table 2). Following Cox regression analysis, there was no association between baseline abnormal depression scores and intestinal resection (HR = 0.68; 95% CI 0.07-7.06; Table 3), and this remained the case in sensitivity analysis (Supplementary Table 2).

Clinical Disease Activity

Six (12.8%) of 47 patients reporting symptoms consistent with clinically active disease had abnormal baseline depression scores, compared with six (3.4%) of 178 who did not report symptoms (P = 0.01; Table 2). However, this association was lost following Cox regression analysis (HR = 0.82; 95% CI 0.22-3.13; Table 3). In sensitivity analysis, abnormal depression scores were associated with development of clinically active IBD (P <0.001; Supplementary Table 2). There were too few patients to perform Cox regression analysis.

DISCUSSION

This longitudinal follow-up study has demonstrated that bi-directional brain-gut axis interactions appear to exist in patients with IBD. Evidence for a significant gut-to-brain interaction is provided by the development of new-onset abnormal anxiety scores in patients with clinically active IBD, but no psychological co-morbidity at baseline. A brain-to-gut interaction is highlighted by the relationship between antecedent psychological co-morbidity and the subsequent development of objective markers of disease activity both in patients in clinical remission and, in sensitivity analysis, asymptomatic patients without evidence of biochemical IBD activity at baseline. The identification of bi-directional brain-gut axis interactions is a novel finding in IBD, and defining the impact of this has potential implications for the future management of patients. Our findings suggest that augmenting traditional IBD management strategies, based on pharmacological therapies, with novel interventions designed to impart beneficial effects on disordered brain-gut axis interactions in IBD may lead to improved disease outcomes. This lends further weight to the need to develop an evidence-based, integrated, biopsychosocial model of care for patients with IBD.[31, 32]

Our data set comprising almost 800 patients with complete clinical data at baseline, over 400 of whom provided longitudinal follow-up questionnaire data, is larger than the only other study that has sought to describe these relationships in IBD.[33] Recruitment took place as part of routine clinical practice, in a secondary care setting, meaning our findings are likely to be generalizable to the wider IBD population. Performing Cox regression analysis allowed us to determine independent baseline predictors of subsequent new-onset psychological co-morbidity, and new-onset disease activity, after adjusting for other variables, including total duration of follow-up in all patients. Our definition of normal and abnormal anxiety and depression scores at baseline and follow-up is a further strength. Here, only the effect of definitely abnormal HADS anxiety and depression scores at baseline on

longitudinal disease activity was assessed, rather than including those with borderline scores at baseline. Similarly, only patients with definitely normal HADS scores at baseline who subsequently developed definitely abnormal scores de novo in longitudinal follow-up were classified as developing the endpoint of interest, with those with borderline scores at follow-up excluded. Excluding patients with borderline abnormal HADS scores from these definitions ensured that we provided the most conservative estimate of the bi-directional relationship between disease activity and psychological co-morbidity over time. Additionally, our sensitivity analysis, assessing the effect of mood on longitudinal disease outcomes only in patients in clinical remission at baseline, and with no biochemical evidence of IBD activity, allowed us to control for any potential confounding effect of occult inflammation. This differentiates our findings from those of authors investigating bi-directional relationships between the brain and gut in functional GI disorders, which have relied on symptom reporting alone.[7, 8]

Limitations of this study include our inability to collect FC data on all patients included in the initial cross-sectional survey. This meant that, although we performed a sensitivity analysis incorporating baseline inflammatory disease activity in these analyses, our principle gut-to-brain findings were based on clinical indices, rather than objectively quantified inflammatory disease activity at baseline. As a result, these analyses were performed in smaller numbers of patients. This meant that for longitudinal outcomes, including abnormal depression scores, hospitalization, and intestinal resection, there were too few cases with the outcome of interest to perform Cox regression, despite some of these outcomes trending towards significance in univariate analysis. We were also unable to collect repeat FC data at the end of study follow-up, but compensated for this by using objective clinical markers of the natural history of IBD in our brain-to-gut analyses, rather than clinical indices of disease activity alone. Although our use of FC as an objective marker of intestinal inflammation in assessing for biochemical evidence of disease activity at baseline is a strength, the cut-off value of

≥250μg/g of stool that we used is contentious, although it is advocated by expert opinion,[34] and has been used in other studies in this field.[21, 33, 35-37] We were only able to measure two points over time, using data analyzed at a group level. We acknowledge that the relationship between disease activity and psychological distress is likely to be more complex and individualistic. A recent within-subject study, using vector autoregressive modeling, with multiple time points for individual patients post myocardial infarction has shown a range of different complex interactions between psyche and soma.[38] This kind of personalized response has yet to be delineated in IBD, but may underlie the aggregated data outcomes we have reported. Although we collected disease activity endpoints based on objectively defined criteria, there is the possibility that some of these endpoints, such as escalation of therapy, were reached based on symptoms, rather than true inflammatory activity. However, we feel this is unlikely as, in the UK, decisions to escalate to biologic therapy are based solely on definite evidence of inflammatory activity, in line with National Institute for Health and Care Excellence guidelines.[39, 40] Finally, our use of HADS scores as a marker of anxiety or depression could be criticized as, although these are widely used, their psychometric properties have been challenged by some experts.[41] In addition, the HADS does not collect data concerning somatic depressive symptoms, such as anhedonia, change in appetite, and irritability, which have been shown to be associated with biomarkers of inflammation,[42] and this could also explain the relatively low prevalence of abnormal depression scores observed in our study.

We based our longitudinal outcomes on blinded and objective assessments of inflammatory activity. Given the poor association between clinical and inflammatory disease activity, particularly in CD,[22, 35] studies using clinical indices as their assessment of choice only provide evidence of a relationship between psychological co-morbidity and subjective symptom reporting,[5, 43-48] which has been well described in patients with functional GI disorders.[7, 8] Within our study population, a baseline

abnormal anxiety score was significantly associated with the development of flare or glucocorticosteroid prescription, escalation of medical therapy, and hospitalization. However, there was no consistent association between baseline anxiety scores and subsequent development of clinical disease activity, suggesting that our longitudinal objective disease activity endpoints are likely to reflect the presence of genuine inflammatory activity, rather than subjective symptom reporting alone. This is further supported by the fact that there was no significant association between high levels of somatoform-type behavior and our clinical endpoints. Importantly, in the majority of our analyses studying the effect of abnormal baseline anxiety and depression scores on longitudinal disease activity, the absolute proportions of patients with abnormal scores who subsequently developed one of the objective markers of disease activity was greater but, in the case of abnormal depression scores, failed to achieve statistical significance. The proportion of patients with baseline depression scores above threshold on the HADS was lower in our sample than might be expected in an IBD population. A recent systematic review, which included 23 studies, reported pooled mean rates of depression between 19.9% for patients with non-active disease and 34.7% for active disease,[49] but this reflects the more stringent threshold we used to define abnormal depression scores.

The majority of previous observational studies in this field have reported either brain-to gut,[5, 43-46, 50-52] or gut-to brain interactions separately.[2, 47, 48] To the best of our knowledge, only one longitudinal study has reported a bi-directional relationship between psychological co-morbidity and disease activity during follow-up.[33] This focused on the relationship between clinical disease activity and perceived stress, rather than anxiety and depression, and failed to demonstrate any relationship between this and objective markers of inflammatory disease activity in longitudinal follow-up. We are also aware of two large multi-center database registry studies examining these issues, but these either used clinical disease activity indices as their sole measure of disease activity, or failed to restrict their

analyses to only those with quiescent disease at baseline, meaning that they may have overestimated any relationship between mood and longitudinal disease activity.[44, 45] With the exception of these two database registry studies, our length of follow-up of almost 3 years is longer than any other observational study that has investigated this issue, thus allowing us to maximize the likelihood of detecting significant associations between the brain and the gut, and vice versa, in IBD.

Our identification of possible bi-directional effects of the brain-gut axis in IBD demonstrates the importance of addressing factors other than disease activity in its management, and highlights the need for considering an overhaul of traditional management strategies. A systematic review assessing the effect of antidepressants on psychological and disease activity outcomes in IBD has suggested that these therapies may be of benefit,[53] but the available studies included only one RCT, containing just 26 patients.[54] Another systematic review and meta-analysis of RCTs of the effect of psychological therapy on mood, quality of life, and IBD activity highlighted that, although CBT appeared to impart short-term benefits on quality of life, the overall effect of these treatments on other disease outcomes was questionable.[17] However, a trial of hypnotherapy included in this meta-analysis demonstrated a significant reduction in likelihood of relapse in UC,[18] a recent RCT of CBT demonstrated a benefit in terms of effects on health-related quality of life, anxiety, and depression,[19] and meditation also appeared to improve physical and psychological symptoms in one small study.[20] Nevertheless, there remains a need for further RCTs of psychological therapies and antidepressants, perhaps in a more selected group of patients with IBD, after appropriate screening for baseline mood disorders and objective quantification of inflammatory burden.

Other contributing factors to the relationship we observed could be central effects of some of the drugs used to treat IBD, or differences in the microbiome between individuals who went on to develop abnormal anxiety and/or depression scores compared with those who did not.

Glucocorticosteroids may have central effects, including depletion of L-tryptophan,[55] which is required for serotonin synthesis, and can induce mood disorders.[56] However, only 10% of patients recruited into this study were using these at baseline, and we controlled for all medication use in our multivariate Cox regression analysis. The role of the microbiota in mood is also an expanding area, with some studies in humans demonstrating alterations in the fecal microbiota in patients with depression, with increased levels of Bacteroidetes, Proteobacteria, and Actinobacteria, and reductions in Firmicutes.[57] In addition, animal studies suggest that abnormalities of mood can be induced by fecal microbial transfer between depressed humans and non-depressed rats.[58] Despite this, in a cross-sectional study of secondary care IBD patients, distinct differences in fecal microbial composition between 31 individuals with abnormal, and 206 individuals with normal, depression scores were not observed, possibly due to the confounding effect of inflammatory disease activity.[59]

In summary, our findings highlight the existence of bi-directional brain-gut axis interactions in patients with IBD. Patients with normal anxiety scores at baseline and active disease were almost six times more likely to develop abnormal anxiety scores during follow-up. Similarly, patients with quiescent disease activity at baseline, but abnormal anxiety scores, had two-fold higher rates of flare of disease activity or need for glucocorticosteroids, and escalation of therapy. An acceptance of the existence of brain-gut axis activity in IBD, and its influence on disease course, has important implications for future management strategies. Our findings underline the need for the development of novel approaches towards IBD management, away from one that focuses solely on the management of inflammatory activity, to one that integrates this with the need for proactive management of psychological wellbeing.

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Table 1: Relationship Between the Presence of IBD Activity at Baseline and Subsequent Development of Abnormal Anxiety or Depression Scores, Among Patients with Normal Anxiety and Depression Scores at Baseline.

	Normal follow-up HADS anxiety score	**Abnormal follow-up HADS anxiety score**	**P value**	**Normal follow-up HADS depression score**	**Abnormal follow-up HADS depression score**	**P value**
HBI/SCCAI ≥5 (%)	46/170 (27.1)	11/22 (50.0)	0.03	56/189 (29.6)	1/3 (33.3)	0.89
FC ≥250µg/g (%)	45/112 (40.2)	4/9 (44.4)	0.80	49/121 (40.5)	0/0 (0)	N/A

Table 2: Relationship Between the Presence of Abnormal Anxiety or Depression Scores at Baseline, and Subsequent Development of IBD Activity, Among Patients with IBD in Clinical Remission at Baseline.

	Glucocorticosteroid prescription or flare of disease activity			**Escalation of Medical Therapy in Response to Uncontrolled Disease Activity**			**Hospitalization due to Disease Activity**			**Intestinal resection**			**Clinical disease activity**		
	No	**Yes**	**P value**	**No**	**Yes**	**P value**	**No**	**Yes**	**P value**	**No**	**Yes**	**P value**	**No**	**Yes**	**P value**
Abnormal baseline anxiety score (%)	38/260 (14.6)	35/128 (27.3)	0.003	37/255 (14.5)	38/148 (25.7)	0.005	59/365 (16.2)	17/58 (29.3)	0.02	69/401 (17.2)	7/22 (31.8)	0.08	32/179 (17.9)	11/47 (23.4)	0.39
Abnormal baseline depression score (%)	13/259 (5.0)	4/128 (3.1)	0.39	13/254 (5.1)	5/148 (3.4)	0.42	16/364 (4.4)	5/58 (8.6)	0.17	18/400 (4.5)	3/22 (13.6)	0.06	6/178 (3.4)	6/47 (12.8)	0.01

Table 3: Independent Predictors of Subsequent IBD Activity Following Multivariate Cox Regression Analysis, Among Patients with IBD in Clinical Remission at Baseline.

	Glucocorticosteroid prescription or flare of disease activity		**Escalation of Medical Therapy in Response to Uncontrolled Disease Activity**		**Hospitalization due to Disease Activity**		**Intestinal resection**		**Clinical disease activity**	
	Hazard ratio (95% CI)	**P value**	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**	**Hazard ratio (95% CI)**	**P value**
Female sex	0.82 (0.56-1.22)	0.33	0.89 (0.62-1.29)	0.53	1.12 (0.63-1.98)	0.70	1.13 (0.43-2.98)	0.81	2.55 (1.15-5.65)	0.02
Age (per year)	0.96 (0.95-0.98)	<0.001	0.97 (0.96-0.98)	<0.001	0.97 (0.94-0.99)	0.002	0.96 (0.91-1.00)	0.06	0.99 (0.97-1.02)	0.55
Married or co-habiting	1.10 (0.73-1.66)	0.64	1.49 (1.01-2.21)	0.05	1.22 (0.67-2.24)	0.52	0.58 (0.20-1.65)	0.31	1.00 (0.49-2.06)	1.00
Tobacco use	1.28 (0.72-2.27)	0.40	0.97 (0.56-1.66)	0.90	1.66 (0.79-3.50)	0.19	1.52 (0.44-5.18)	0.51	1.90 (0.81-4.47)	0.14

Alcohol use	0.60 (0.40-0.91)	0.02	0.74 (0.51-1.08)	0.12	0.45 (0.25-0.81)	0.008	1.14 (0.38-3.46)	0.82	0.74 (0.36-1.52)	0.41
University/postgraduate education	1.12 (0.73-1.71)	0.61	1.10 (0.74-1.63)	0.65	0.76 (0.38-1.51)	0.43	0.90 (0.30-2.71)	0.85	0.75 (0.30-1.84)	0.53
Body mass index (per unit)	1.04 (1.00-1.07)	0.03	1.02 (0.99-1.06)	0.24	1.03 (0.98-1.08)	0.28	1.06 (0.97-1.17)	0.20	0.99 (0.93-1.06)	0.77
Crohn's disease	0.54 (0.32-0.90)	0.02	0.79 (0.49-1.28)	0.35	0.68 (0.29-1.57)	0.36	0.41 (0.04-4.15)	0.45	1.39 (0.58-3.30)	0.46
5-aminosalicylate use at baseline	1.06 (0.65-1.72)	0.82	0.97 (0.61-1.54)	0.90	0.60 (0.28-1.31)	0.20	0.15 (0.02-1.39)	0.10	1.20 (0.54-2.66)	0.65
Immunosuppressant use at baseline	1.15 (0.77-1.73)	0.49	0.73 (0.50-1.08)	0.12	1.60 (0.87-2.94)	0.13	1.25 (0.47-3.29)	0.66	0.56 (0.28-1.14)	0.11
Biologic use at baseline	0.90 (0.52-1.54)	0.70	1.33 (0.83-2.14)	0.24	1.36 (0.66-2.80)	0.40	1.31 (0.48-3.55)	0.60	0.79 (0.32-1.90)	0.59
Glucocorticosteroid use at baseline	1.81 (0.96-3.42)	0.07	2.56 (1.51-4.32)	<0.001	2.91 (1.46-5.78)	0.002	1.09 (0.26-4.60)	0.91	1.48 (0.46-4.83)	0.51
Presence of Rome III IBS-type symptoms at baseline	1.17 (0.77-1.78)	0.45	1.30 (0.88-1.91)	0.18	1.36 (0.74-2.50)	0.32	1.09 (0.38-3.11)	0.88	1.52 (0.74-3.10)	0.25
Abnormal anxiety scores at baseline	2.08 (1.31-3.30)	0.002	1.82 (1.19-2.80)	0.006	1.59 (0.77-3.31)	0.21	1.62 (0.50-5.26)	0.42	0.88 (0.35-2.16)	0.77

Abnormal depression scores at baseline	0.72 (0.24-2.10)	0.54	0.86 (0.33-2.27)	0.77	0.79 (0.22-2.84)	0.72	0.68 (0.07-7.06)	0.75	0.82 (0.22-3.13)	0.78
High level of somatisation at baseline	0.63 (0.30-1.30)	0.21	0.72 (0.36-1.44)	0.36	1.07 (0.44-2.59)	0.88	2.04 (0.49-8.42)	0.33	1.01 (0.34-3.03)	0.98

Figure 1: Survival Analysis For New-onset Abnormal Anxiety Scores Between Patients with Quiescent and Active Disease at Baseline

Figure 2: Survival Analysis For Glucocorticosteroid Prescription or Flare of Disease Activity Between Patients With and Without Abnormal Anxiety Scores at Baseline

Figure 3: Survival Analysis For Escalation of Medical Therapy in Response to Uncontrolled IBD Between Patients With and Without Abnormal Anxiety Scores at Baseline