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TITLE PAGE

Title: Characteristics and Impact of Anxiety and Depression Trajectories in Inflammatory Bowel Disease.

Short Title: Anxiety and Depression Trajectories in IBD.

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Abbreviations:

5-ASA	5-aminosalicylate
ANOVA	analysis of variance
CBT	cognitive behavioral therapy
CD	Crohn's disease
HADS	hospital anxiety and depression scale
HBI	Harvey-Bradshaw index
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified

PHQ	patient health questionnaire
SCCAI	simple clinical colitis activity index
UC	ulcerative colitis

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STUDY HIGHLIGHTS

What is known?

- Common mental disorders, such as anxiety or depression, are more than twice as common in patients with inflammatory bowel disease (IBD) compared with the general population.
- Symptoms of anxiety and depression may be associated with adverse disease outcomes in IBD.
- Persistent or worsening anxiety or depression are associated with increased risk of morbidity and mortality in other chronic diseases, but this has not been examined in IBD.

What is new here?

- Predictors of fluctuating, or persistently abnormal or worsening, anxiety or depression scores included a diagnosis of IBD within the preceding 12 months, clinically active disease, and lower IBD-related quality of life.
- Between 40% and 50% of individuals with abnormal anxiety or depression scores at baseline had persistently abnormal scores throughout the study.
- Almost 12% of IBD patients reported persistently abnormal or worsening anxiety scores during 1 year of follow-up, and 6% persistently abnormal or worsening depression scores.
- As seen in other chronic disease states, those with persistently abnormal or worsening anxiety or depression scores were significantly more likely to require clinical contact and undergo a greater number of investigations.

ABSTRACT

Introduction: Symptoms of common mental disorders, like anxiety or depression, are associated with adverse clinical outcomes in inflammatory bowel disease (IBD). We report trajectories of these symptoms in IBD, patient characteristics associated with different trajectories, and effects on healthcare utilization and prognosis.

Methods: We collected demographic, symptom, psychological, and quality of life data, with questionnaires at 3-month intervals, over 12 months of follow-up. We collected healthcare utilization and IBD outcomes via notes review. We compared characteristics of those with persistently normal or improving anxiety or depression scores with those with persistently abnormal or worsening scores, as well as the number of flares, glucocorticosteroid prescriptions, escalations of therapy, hospitalizations, or intestinal resections due to IBD activity.

Results: Among 771 and 777 patients, respectively, worsening or persistently abnormal anxiety or depression scores were associated with increased antidepressant (28.6% vs. 12.3% anxiety, 35.8% vs. 10.1% depression, p <0.001) and opiate use (19.0% vs. 7.8% anxiety, p = 0.001 and 34.0% vs. 7.4% depression, p <0.001), compared with those with persistently normal or improving scores. These individuals were also more likely to have been diagnosed with IBD in the last 12 months (16.3% vs. 5.0% anxiety, p = 0.001 and 15.1% vs. 5.5% depression, p = 0.006), to have clinically active disease at baseline (57.1% vs. 26.6% anxiety and 71.7% vs. 29.1% depression, p <0.001) and lower quality of life scores (p <0.001). Individuals with worsening or persistently abnormal trajectories of anxiety or depression required significantly more outpatient appointments, radiological investigations, and endoscopic procedures for IBD-related symptoms.

Discussion: In this 12-month follow-up study, patients with IBD with worsening or persistently high anxiety or depression scores were higher utilizers of healthcare but were not at increased risk of future adverse disease outcomes.

Key words: inflammatory bowel disease; trajectories; common mental disorder; prognosis

INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), cycles through periods of remission and flare. The underlying pathogenesis is incompletely understood, but is a combination of genetics, environment, and immunology, alongside microbial alternations. Gut-brain axis communication occurs via complex interactions between the hypothalamic-pituitary-adrenal axis and neural and inflammatory pathways. Environmental and emotional stimuli may activate the hypothalamic-pituitary-adrenal axis, leading to release of cortisol and pro-inflammatory cytokines.[1] In addition, afferent signals from the gut can be transmitted to the brain, which can send signals via efferent pathways back to the intestine. Thus, there is bidirectional gut-brain communication.[2, 3]

Patients with IBD may report symptoms compatible with common mental disorders, with up to 50% reporting anxiety or depression during a flare.[4] A case-control study of almost 12,500 patients demonstrated significantly higher levels of both anxiety and depression, compared with the general population, particularly in the 12 months after diagnosis.[5] Depression is a pro-inflammatory condition associated with elevations in plasma cytokine levels, including tumor necrosis factor-alpha and interleukin-6,[6, 7] supporting a role of mood in immune dysregulation and inflammation. This highlights the influence common mental disorders may have on natural history of IBD, not only via inflammatory pathways but also due to altered neural input. In turn, common mental disorders are influenced by physical aspects of disease severity, activity, and chronicity,[8, 9] as well as sex,[10] age,[9] socioeconomic status,[9] adherence to treatment,[11] and past history of mental stress or mental ill health.[12]

There is increasing interest in brain-gut axis effects in IBD.[2, 13-15] Symptoms of common mental disorders increase subsequent risk of adverse outcomes, including flare or need for glucorticosteroids,[15-17] escalation of therapy,[15, 16] hospitalization,[16, 18] and intestinal

resection.[16, 17] Among individuals with no history of a common mental disorder, active disease is significantly associated with *de novo* development of symptoms of anxiety or depression.[10, 14, 15] There may also be a cumulative negative impact of psychological co-morbidity on IBD; in one study individuals in biochemical remission, but with symptoms of more than one common mental disorder, were at significantly increased risk of glucocorticosteroid prescription, flare of disease activity, escalation of therapy, or a composite of these that also included hospitalization and intestinal resection, during longitudinal follow-up.[19] Finally, a recent study suggests that symptoms of common mental disorders may influence IBD prognosis independent of disease activity.[13]

However, most studies only examine prevalence or impact of symptoms of a common mental disorder at a single time point, which may be overly simplistic. Persistent or worsening anxiety and depression are associated with poor outcomes in other chronic diseases, such as ischemic heart disease, chronic obstructive pulmonary disease, and type 1 diabetes mellitus,[20-22] but this has not been well-studied in IBD. All-cause and cardiovascular mortality was two-fold higher among depressed individuals post-myocardial infarction,[23] with persistent or worsening depression associated with significantly greater healthcare costs.[20] In patients with chronic obstructive pulmonary disease, persistent depression was associated with increased mortality, more frequent and severe disease exacerbations, more frequent hospitalizations, shorter walking distance, and reduced quality of life.[21]

We conducted a 12-month longitudinal follow-up study to examine natural history of symptoms of common mental disorders in patients with IBD, to better understand the characteristics of patients with different symptom courses, and how such symptom trajectories influence disease outcomes and healthcare utilization. We hypothesized those with persistent, or worsening, symptoms were more likely to experience adverse outcomes of disease activity, resulting in more frequent healthcare contacts and investigations.

METHODS

Participants and Setting

We sent postal invitations to all patients aged ≥18 years with an established histological, endoscopic, or radiological diagnosis of CD, UC, or IBD-unclassified (IBD-U) who had attended outpatient clinics between 2017 and 2020 at Leeds Teaching Hospitals NHS Trust. Each invitation included a web-link with a personalized uniform resource locator to an online patient information sheet, consent form, and online questionnaire. If preferred, we offered a paper version of these documents. We sent four follow-up questionnaires, at 3-month intervals, over a 12-month period. To limit losses to follow-up, we sent a second reminder to all those who initially consented to participate but did not respond to each of the 3-monthly questionnaires. We excluded individuals with end ileostomy, colostomy, or ileo-anal pouch from follow up due to potential inaccuracies in assessing clinical disease activity. The Wales research ethics committee approved this longitudinal study in February 2020 (REC ref: 20/WA/0044).

Data Collection and Synthesis

We recorded demographic data, including sex, age, marital status, ethnicity, educational level, and lifestyle factors, including tobacco and alcohol use. Clinical disease activity was assessed using a modified Harvey-Bradshaw index (HBI) for CD, excluding examination for abdominal mass,[24, 25] and the simple clinical colitis activity index (SCCAI) for UC,[26] with a score of <5 used to define remission for both, as recommended.[27, 28] The hospital anxiety and depression scale (HADS) was used to assess for symptoms of anxiety or depression.[29] The total HADS scores range from 0 to 21. We defined HADS-anxiety or depression scores as normal (score 0-7), borderline (8-10), or abnormal (≥11), as previously

recommended.[29] We used these data to create anxiety or depression trajectories, based on data provided at baseline and at least two points of follow-up. We classified patients with normal HADS-anxiety or HADS-depression scores throughout, or those with a score of ≥11 at baseline that improved to <8 at the last point of follow-up, as having normal or improving HADS-anxiety or HADS-depression scores. We classified those with scores of ≥11 throughout, or those with a score of <8 at baseline that worsened to ≥11 at the last point of follow-up, as having persistently abnormal or worsening HADS-anxiety or HADS-depression scores. We classified all other individuals as having fluctuating HADS-anxiety or HADS-depression scores. We created identical trajectories for those providing data at baseline and all four points of follow-up. We collected somatoform symptom data using the patient health questionnaire-12 (PHQ-12),[30] which is derived from the PHQ-15,[31] with scores ranging from 0 to 24. We characterized severity as high (total score ≥13), medium (8-12), low (4-7), or minimal (≤3). We assessed quality of life using the short IBD questionnaire (SIBDQ) health survey.[32]

One investigator (KMF), blinded to questionnaire responses, reviewed electronic medical records for all participants. We verified IBD type (CD, UC, or IBD-U), extent and location of disease, and prior IBD-related intestinal resection. We documented current IBD-related medication use, including 5-aminosalicylates (5-ASAs), immunosuppressants, biologic therapies, or glucocorticosteroids, as well as current use of antidepressant drugs or opioids. We also collected healthcare utilization data during the 12 months of follow-up, including number of physician-led or nurse-led IBD outpatient clinic visits, contact with the IBD helpline through either telephone calls or e-mails, and clinic visits related to extra-intestinal manifestations of IBD, as well as the number of endoscopic and radiological investigations requested to assess IBD activity. We excluded investigations arranged for surveillance, therapeutic indications, or routine follow-up. Finally, we extracted the following

clinical outcomes, along with the date of their occurrence: flare of disease activity based on a physician's global assessment; glucocorticosteroid prescription; escalation of medical therapy due to uncontrolled IBD activity; hospitalization due to uncontrolled IBD activity; intestinal resection due to uncontrolled IBD activity; or death. We also recorded the number of each of these events of interest, other than death. We did not include changes to medication without evidence of uncontrolled IBD activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, as endpoints.

Statistical Analysis

We converted data from SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA) to tables in R for Windows version 4.0.2 and RStudio for Windows version 2022.02.0.443 (2009-2022 RStudio Inc., Boston, MA). We created alluvial diagrams to display anxiety or depression trajectories visually for those providing data at baseline and all four points of follow-up using packages 'gg_plot' and 'gg_alluvial'. Among those providing data at baseline and at least two points of follow-up, we compared characteristics of those with persistently normal or improving, fluctuating, or persistently abnormal or worsening HADS-anxiety or HADS-depression scores. We compared healthcare utilization across these three trajectories. To assess the impact of the three anxiety or depression trajectories on each of the disease activity outcomes of interest (flare of disease activity, glucocorticosteroid prescription, escalation of therapy, hospitalization, intestinal resection, or death) during longitudinal follow-up we compared their rates in each trajectory. We used a Pearson's χ^2 test for categorical data where at least 75% of groups had counts ≥ 5. In cases where counts <5 were expected in $\leq 75\%$ of groups we applied the Fisher's exact Test. For continuous data, we used Kruskal-Wallis one-way analysis of variance (ANOVA) for comparisons between >2 groups, while we used Mann-Whitney U for comparison of continuous data between 2

groups. Due to multiple comparisons, we considered a 2-tailed P value of <0.01 as statistically significant. We performed these analyses using SPSS for Windows version 26.0.

RESULTS

We contacted 4823 patients with IBD seen in the outpatient clinic between January 2017 and June 2020 and 1119 (23.2%) responded to the baseline questionnaire. Of these, 88 (7.9%) were ineligible due to either a stoma or ileo-anal pouch, meaning 103126 (92.1%) responders (mean age 52.6 years (SD 16.9 years), 565 (54.8%) female, 460 (44.6%) CD) were eligible for the study. In total, 771 (74.8%) of these 1031 patients provided HADS-anxiety data at baseline and two or more follow-up points and 777 (75.4%) provided HADS-depression scores at baseline and at least two points of follow-up. There were no significant differences in characteristics between responders and non-responders, including baseline HADS-anxiety or depression scores, other than those who provided data at baseline and two or more follow-up points were older (Supplementary Table 1).

Characteristics of Patients According to HADS-anxiety Trajectories.

Among the 771 patients providing HADS-anxiety data at baseline and two or more follow-up points, those with either fluctuating (266 (34.5%) patients) or persistently abnormal or worsening (105 (13.6%) patients) HADS-anxiety scores were significantly younger (p <0.001) and more likely to be female (p <0.001) compared with those with persistently normal or improving (400 (51.9%) patients) scores (Table 1). Although there were no significant differences between groups with respect to IBD-related therapy, those with either fluctuating or persistently abnormal or worsening HADS-anxiety scores were significantly more likely to be prescribed opiates (p = 0.001) and antidepressants (p <0.001). In addition, those with either fluctuating or persistently abnormal or worsening HADS-anxiety scores were more likely to have been diagnosed with IBD in the last 12 months (p = 0.001), to self-report a flare of disease activity at baseline, and to have active disease according to either the HBI or SCCAI at baseline (p <0.001 for both). These individuals were

also more likely to have higher somatoform symptom scores on the PHQ-12 and reported lower quality of life according to the SIBDQ (p <0.001 for both), compared with those with persistently normal or improving HADS-anxiety scores.

There were 449 (45.8%) individuals (mean age 56.6 years (SD 15.7 years), 235 (52.3%) female, 197 (43.9%) CD) who provided HADS-anxiety data at baseline and all four follow-up points, with 204 (45.4%) having persistently normal or improving scores, 192 (42.8%) fluctuating, and 53 (11.8%) persistently abnormal or worsening scores. Of 282 patients with normal HADS-anxiety scores at baseline, 195 (69.1%) had persistently normal scores throughout 12 months of follow-up, 77 (27.3%) fluctuating, and 10 (3.5%) worsening (Figure 1). Of 81 patients with abnormal HADS-anxiety scores at baseline, 43 (53.1%) had persistently abnormal scores throughout, 29 (35.8%) fluctuating, and nine (11.1%) improving (p <0.001 for comparison).

Healthcare Utilization and Clinical Outcomes of Patients According to HADS-anxiety Trajectories.

Individuals with persistently abnormal or worsening HADS-anxiety scores were significantly more likely see a gastroenterologist in the outpatient clinic (p <0.001) and more likely to access the IBD helpline (p <0.001) (Table 2 and Figure 2). Those with persistently abnormal or worsening HADS-anxiety trajectories were also more likely to undergo more radiological investigations (p = 0.002) and endoscopic procedures (p = 0.002) for suspected IBD activity, compared with those with persistently normal or improving HADS-anxiety scores, and this trend persisted across all three groups (p = 0.007 and p = 0.008 respectively). Finally, individuals with persistently abnormal or worsening HADS-anxiety trajectories were significantly more likely to be seen in other clinics for extra-intestinal manifestations of IBD (p <0.001, overall trend p = 0.002). In terms of disease activity outcomes over the 12-month

period, those with persistently abnormal or worsening trajectories were more likely to experience a flare of disease activity compared with those with persistently normal or improved HADS-anxiety trajectories ($p = 0.004$), and the number of flares was also significantly higher ($p = 0.009$), but no other significant differences were detected. Results for all these analyses were similar when patients diagnosed with IBD within the last 12 months were excluded from the analysis (Supplementary Table 2).

Characteristics of Patients According to HADS-depression Trajectories.

Among the 777 patients providing HADS-depression scores at baseline and at least two points of follow-up, those with either fluctuating (209 (26.9%) patients) or persistently abnormal or worsening (53 (6.8%) patients) scores were less likely to have reached a university or postgraduate level of education ($p = 0.004$) but there were no other significant differences in demographic or disease characteristics (Table 3). Again, those with persistently abnormal or worsening scores were more likely to be prescribed opiates ($p <0.001$) and antidepressants ($p <0.001$), but there were no significant differences according to IBD-related therapy. Significantly more individuals with either fluctuating or persistently abnormal or worsening HADS-depression scores had been diagnosed with IBD in the last 12 months ($p = 0.006$), and significantly more reported a flare at baseline and had active disease according to either the HBI or SCCAI ($p <0.001$ for both). Those with either fluctuating or worsening or persistently abnormal HADS-depression scores had higher somatoform symptom scores and reported lower quality of life according to the SIBDQ ($p <0.001$ for both).

There were 458 (44.6%) individuals (mean age 56.6 years (SD 15.7 years), 241 (52.6%) female, 200 (43.7%) CD) providing HADS-depression scores at all five time points. Of these, 284 (62.0%) had persistently normal or improving scores, 147 (32.2%) fluctuating, and 27 (5.9%) persistently abnormal or worsening scores. Of 355 patients with normal

HADS-depression scores at baseline, 279 (78.6%) had persistently normal scores throughout 12 months of follow-up, 69 (19.4%) fluctuating, and seven (2.0%) worsening (Figure 3). Of 47 patients with abnormal HADS-depression scores at baseline, 20 (42.6%) had persistently abnormal scores throughout, 22 (46.8%) fluctuating, and five (10.6%) improving (p <0.001 for comparison).

Healthcare Utilization and Clinical Outcomes of Patients According to HADS-depression Trajectories.

Individuals with persistently abnormal or worsening HADS-depressions scores were more likely to see a gastroenterologist or an IBD nurse specialist in the outpatient clinic (p <0.001 for both) (Table 4 and Figure 4). The number of endoscopic investigations performed for suspected IBD activity was higher in those with fluctuating HADS-depression scores (p = 0.002) compared with those with persistently normal or improving scores. Similarly, fluctuating scores were associated with a greater number of appointments in other clinics for extra-intestinal manifestations of IBD (p = 0.003). There were no significant differences between groups with regards to any disease activity outcomes. Again, results were similar when patients diagnosed with IBD within the last 12 months were excluded from the analysis (Supplementary Table 3).

DISCUSSION

This study has examined the natural history of symptoms of common mental disorders in patients with IBD and to assess the impact of trajectories of these symptoms on healthcare utilization and prognosis. Of note, high HADS-anxiety or depression scores at study entry were a strong predictor of future anxiety or depression trajectory, with most individuals reporting abnormal HADS scores at baseline continuing a trajectory of persistently abnormal or fluctuating scores, and only one in 10 individuals with abnormal scores at baseline improving subsequently. Characteristics associated with persistently abnormal or worsening scores, included female sex and younger age for anxiety, lower educational level for depression, and higher levels of somatoform symptom-reporting, and opiate and antidepressant use for both anxiety and depression. Those with persistently abnormal or worsening anxiety or depression scores were more likely to have received a diagnosis of IBD within the preceding 12 months, more likely to self-report a flare of disease activity at study entry, and significantly more likely to have elevated clinical disease activity scores and lower IBD-related quality of life scores at baseline. Finally, although rates of escalation of therapy, hospitalization, or intestinal resection were not significantly higher in these individuals, those with persistently abnormal or worsening HADS scores were significantly more likely to require clinical contact, via appointments and helpline support, and underwent a greater number of investigations.

We recruited a large, unselected cohort of patients with IBD, which means our results are likely to be generalizable to many secondary and tertiary centers managing such patients. Initial enrollment, and subsequent follow-up, was predominantly via personalized links to online questionnaires, minimizing missing data from participants. Although a structured interview may have provided greater sensitivity or specificity than the HADS for the detection of common mental disorders,[33] we also used the PHQ-12 questionnaire, which

collects other somatic symptoms of depression, such as sleep and fatigue, which are not captured by the HADS. In addition, our use of validated online questionnaires enabled distribution at regular intervals to a large cohort of over 1000 patients enrolled at baseline. This regular contact with participants, at 3-monthly intervals, allows us to better understand the fluctuation of symptoms of a common mental disorder, and assessment of the impact of these trajectories on disease outcomes was enabled by a thorough blinded review of medical records, including clinic appointments and investigations, undertaken by a single investigator, thereby limiting variation in their assessment between different observers.

Although the sample size was large and rates of most adverse disease outcomes of interest were numerically higher among those with persistently abnormal or worsening anxiety or depression scores, the 12-month study duration resulted in relatively low event rates for some endpoints. This is a limitation, and studies with longer follow-up will be important.[13, 15] We were unable to assess the characteristics of non-responders to our baseline questionnaire and, therefore, cannot exclude a volunteer bias, with those with abnormal anxiety or depression scores being more likely to participate. This may have led to an overestimation of the impact of anxiety or depression trajectories on disease course and healthcare utilization. However, the converse could also be true, which may have reduced the likelihood of detecting a significant impact of the trajectories on either of these endpoints. In addition, approximately 25% of participants did not provide follow-up anxiety or depression scores at a sufficient number of time points to assess their trajectories. However, there were few differences between those who did and those who did not respond meaning those successfully followed-up were broadly representative of the original participants. Finally, we relied on patient-reported clinical disease activity scores, rather than an objective measure of inflammation, such as fecal calprotectin, to assess IBD activity at baseline. Given the COVID-19 pandemic, persuading patients with IBD to attend an appointment in-person to

provide a stool sample would have been impractical. Previous studies have shown that the SCCAI is correlated with both fecal calprotectin and the endoscopic Mayo sub-score in UC. However, in small bowel CD even objective markers such as fecal calprotectin may overlook active disease and invasive measures such as regular endoscopy would not have been feasible for such a large cohort.[34, 35]

Our recruitment began in 2020, at the height of the COVID-19 pandemic, and at the end of the first lockdown period in the UK. Thus, IBD management over the subsequent 12 months is likely to have differed substantially from usual practice pre-COVID-19, with fewer routine clinic appointments available, and surgery restricted only to emergency or urgent cases. In addition, escalation of therapy for persistently active disease may have been more commonplace, to avoid requirement for hospitalization. Furthermore, concerns from patients regarding continuation of immunosuppressant drugs or presentation to an inpatient or outpatient setting during this period could have influenced our findings. We also cannot exclude an impact of repeated lockdowns and concerns over shielding, among a group of patients who are clinically vulnerable to COVID-19, which may have affected mental health among those who took part in our study. Somatoform symptom-reporting and "functional" gastrointestinal symptoms are also associated with increased healthcare use and symptoms of common mental disorders in IBD.[36]

Changes in physical illness and symptoms of common mental disorders track closely together in chronic disease, including IBD,[37, 38] with both mental and physical aspects influencing the course of disease.[13, 39] Our results support existing literature describing the prevalence and negative impact of persistent symptoms of anxiety or depression in other chronic diseases. In a 3-year study involving over 1500 patients with chronic obstructive pulmonary disease, 24% had persistent depression.[21] These individuals were more likely to undergo treatment for disease exacerbations and experience a loss in exercise tolerance

during the study. A 5-year longitudinal study of patients with newly diagnosed type 1 diabetes demonstrated almost one-in seven individuals followed a trajectory of worsening depressive symptoms, and these patients were significantly more likely to have higher HbA_{1c} values and worse disease control.[22] In these studies, those with persistently abnormal mood scores shared similar baseline characteristics to our participants, being younger, more likely to be female,[20, 21] and having attained a lower level of education.[37] In addition, in our study persistently abnormal or worsening anxiety or depression scores were more prevalent in those with IBD diagnosed within the prior 12 months. These latter findings are supported by observations from two large case-control studies, which demonstrated a significant association between new initiation of antidepressant therapy or new presentation of a psychiatric disorder in the first year after a diagnosis of IBD.[40, 41] There have been few other studies examining the impact of fluctuations in mood on natural history of IBD. One small study, recruiting 32 patients with IBD who answered monthly depression questionnaires, reported that there was no evidence that depressed mood led to worse disease outcomes.[42]

Common mental disorders may be underdiagnosed in chronic diseases, as symptoms of physical illness such as changes in appetite, sleeping patterns, pain, fatigue, and side effects from medications, can overlap those of anxiety and depression. Recognition of, and screening for, common mental disorders in clinical practice in patients with IBD remains poor,[43] and although there is increasing acceptance that anxiety and depression have a detrimental impact on disease outcomes, there is a lack of consensus on management.[44] Based on our findings, higher risk patients with IBD, such as younger or newly diagnosed individuals, may benefit from regular routine screening for common mental disorders,[45] with appropriate intervention. However, despite UK national recommendations for IBD services to have a defined referral pathway to a clinical psychologist or counselor with an interest in IBD, in a 2014 survey by the Royal College of Physicians only 12% of centers provided this

service.[46] Whether treatment of anxiety or depression in IBD has a beneficial effect on disease activity and outcomes is unclear, with most randomized controlled trials assessing antidepressant drugs or psychological therapies in unselected groups of patients.[47, 48] There is some support for an effect of antidepressants on mood, but relatively few studies.[49] In unselected patient groups, evidence suggests that psychological therapies with the potential for benefit in IBD, such as cognitive behavioral therapy (CBT), tend to lose efficacy over time.[47] A systematic review of 31 studies, containing almost 2400 patients, demonstrated those with active IBD had a significant improvement in quality of life scores following psychological therapy, including CBT, stress management, mindfulness, or hypnotherapy, with CBT demonstrating the most consistent positive impact.[50] Recently, there has been increasing focus on resilience training, incorporating a personalized approach to psychotherapy including CBT and mindfulness-based training. In patients with IBD with low resilience this approach has been shown to have a beneficial effect, reducing hospitalizations by over 90% in 12 months, opiate use by almost 50%, and primary care prescriptions for glucocorticosteroids by more than 70%.[51] High resilience among individuals with IBD is associated with lower anxiety scores, improved quality of life, lower disease activity scores, and reduced need for IBD-related surgery.[52, 53] These findings require replication using rigorous methodology but underline the need to identify patients at high risk of adverse outcomes, to select those most likely to respond to psychological interventions.

We have reported the trajectories of symptoms of common mental disorders in patients with IBD over a 12-month period and their associated characteristics. In doing so, we have identified those with worsening or persistently high anxiety or depression scores are significantly higher utilizers of healthcare, requiring more appointments and undergoing more investigations. This highlights a potentially vulnerable group of patients, particularly those early on in their diagnosis or with active IBD, who may be at higher risk of future

adverse disease outcomes, although further longitudinal follow-up studies are needed to confirm or refute this. In addition, 90% of patients with abnormal anxiety or depression scores at baseline continued a trajectory of persistently abnormal or fluctuating scores, and only 10% improved, suggesting that if any clinical assessment of mood detects an abnormality, then this is likely to persist, and may affect future healthcare utilization. Based on our findings, there is a clear need to offer formal psychological support to a subgroup of patients with IBD, via a defined referral pathway, to reduce healthcare utilization and, potentially, improve disease prognosis. We, therefore, advocate for screening for common mental disorders in all patients with IBD, with appropriate intervention, particularly within the first year of diagnosis, and again routinely during periods of flare of disease activity, so that the treatment of both physical and mental health problems can be addressed simultaneously.

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Table 1. Baseline Characteristics of Patients According to HADS-anxiety Trajectories.

	Persistently normal or improving (n = 400)	**Fluctuating (n = 266)**	**Persistently abnormal or worsening (n = 105)**	***p* value***
Mean age in years at baseline (SD)	56.2 (16.6)	52.0 (15.9)	48.6 (15.9)	<0.001
Female sex (%)	181 (45.4)	170 (64.4)	65 (62.5)	<0.001
Married or co-habiting (%)	292 (73.6)	183 (69.3)	66 (63.5)	0.11
University graduate/professional (%)	150 (38.1)	103 (39.0)	43 (41.3)	0.83
Tobacco user (%)	24 (6.1)	18 (6.8)	10 (9.5)	0.46
Alcohol user (%)	285 (72.0)	190 (72.0)	71 (67.6)	0.66
IBD type (%)				
CD	174 (43.9)	118 (44.7)	46 (44.7)	
UC	196 (49.5)	130 (49.2)	49 (47.6)	
IBD-U	26 (6.6)	16 (6.1)	8 (7.8)	0.98

CD location (%)[†]				
Ileal	60/174 (34.5)	43/118 (36.4)	18/45 (40.0)	
Colonic	67/174 (33.3)	26/118 (22.0)	12/45 (24.4)	
Ileocolonic	56/174 (32.2)	49/118 (41.5)	16/45 (35.6)	0.24
Stricturing CD (%)	53/174 (30.5)	30/118 (25.4)	13/46 (28.3)	0.65
Penetrating CD (%)	18/174 (10.3)	27/118 (22.9)	5/46 (10.9)	0.01
Perianal CD (%)	19/174 (10.9)	16/118 (13.6)	10/46 (21.7)	0.16
Previous intestinal resection (%)	77 (19.4)	52 (19.7)	20 (19.2)	0.99
UC extent (%)[‡]				
Proctitis	56/190 (29.5)	37/128 (28.9)	14/46 (30.4)	
Left-sided	70/190 (36.8)	53/128 (41.4)	20/46 (43.5)	
Extensive	64/190 (33.7)	38/128 (29.7)	12/46 (26.1)	0.82
Current 5-ASA use (%)	214 (54.0)	143 (54.2)	51 (49.5)	0.69
Current immunomodulator use (%)	106 (26.8)	77 (29.2)	32 (31.1)	0.62
Current biologic use (%)	81 (20.5)	55 (20.8)	27 (26.2)	0.43
Current glucocorticosteroid use (%)	9 (2.3)	6 (2.3)	4 (3.9)	0.62
Current antidepressant use (%)	49 (12.3)	52 (19.7)	30 (28.6)	<0.001
Current opiate use (%)	31 (7.8)	38 (14.3)	20 (19.0)	0.001
Diagnosed with IBD in the last 12 months (%)	20 (5.0)	21 (8.0)	17 (16.3)	0.001

Self-reported a flare at baseline (%)	43 (10.8)	62 (23.5)	30 (28.8)	<0.001
Active disease on HBI or SCCAI at baseline (%)	105 (26.6)	124 (47.0)	60 (57.1)	<0.001
PHQ-12 somatoform symptom categories at baseline (%)				
Minimal	159 (42.7)	42 (16.7)	9 (9.6)	
Low	136 (36.6)	108 (42.9)	21 (22.3)	
Medium	65 (17.5)	79 (31.3)	38 (40.4)	
High	12 (3.2)	23 (9.1)	26 (27.7)	<0.001
Mean SIBDQ score at baseline (SD)	57.2 (9.3)	47.1 (12.1)	37.3 (12.9)	<0.001

*One-way ANOVA for comparison of normally distributed continuous data, χ^2 for comparison of categorical data across all three groups.

†Data on CD location missing for one patient with persistently abnormal or worsening HADS-anxiety scores.

‡Data on UC extent missing for 11 patients; six with persistently normal or improving HADS-anxiety scores, two with fluctuating HADS-anxiety scores, and three with persistently abnormal or worsening HADS-anxiety scores.

Table 2. Healthcare Utilization and Clinical Outcomes of Patients According to HADS-anxiety Trajectories Over 12-month Longitudinal Follow-up.

	Persistently normal or improving (n = 400)	**Fluctuating (n = 266)**	***p* value***	**Persistently abnormal or worsening (n = 105)**	***p* value***	***p* value****
Healthcare utilization						
Median number of clinic appointments with a gastroenterologist (IQR)	1 (0-2)	1 (0-2)	0.024	1 (0-2)	<0.001	<0.001
Median number of clinic appointments with an IBD specialist nurse (IQR)	1 (0-1)	0 (0-1)	0.34	0 (0-1)	0.22	0.40
Median number of IBD helpline calls (IQR)	0 (0-2)	0 (0-2)	0.31	1 (0-4)	<0.001	<0.001
Median number of radiological investigations related to IBD activity (IQR)	0 (0-0)	0 (0-0)	0.07	0 (0-0)	0.002	0.007
Median number of endoscopic investigations related to IBD activity (IQR)	0 (0-0)	0 (0-0)	0.38	0 (0-0)	0.002	0.008
Median number of other specialty clinics related to extra-intestinal manifestations of IBD (IQR)‡	0 (0-0)	0 (0-0)	0.10	0 (0-1)	<0.001	0.002

Clinical outcomes						
Flare of disease activity (%)	47 (11.8)	38 (14.3)	0.34	24 (22.9)	0.004	0.015
Median number of flares of disease activity (IQR)	0 (0-0)	0 (0-0)	0.33	0 (0-0)	0.009	0.032
Glucocorticosteroid prescription due to uncontrolled disease activity (%)	29 (7.2)	17 (6.4)	0.67	11 (10.5)	0.28	0.40
Median number of glucocorticosteroid prescriptions due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.68	0 (0-0)	0.27	0.40
Escalation of IBD therapy due to uncontrolled disease activity (%)	40 (10.0)	36 (13.5)	0.16	18 (17.1)	0.04	0.10
Median number of escalations of IBD therapy due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.17	0 (0-0)	0.04	0.10
Hospitalization due to uncontrolled disease activity (%)	11 (2.8)	15 (5.6)	0.06	2 (1.9)	0.63	0.089
Median number of hospitalizations due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.06	0 (0-0)	0.62	0.09
Intestinal resection due to uncontrolled disease activity (%)	3 (0.8)	6 (2.3)	0.10	0 (0)	0.50	0.10

Median number of intestinal resections due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.10	n/a	0.37	0.10
Death (%)†	4 (1.0)	1 (0.4)	0.34	3 (2.9)	0.16	0.10
Median number of deaths (IQR)	0 (0-0)	0 (0-0)	0.36	0 (0-0)	0.15	0.10

*Mann-Whitney U for continuous data, χ^2 for categorical data with counts ≥5 and Fisher's Exact Test for categorical data with <5 counts, for comparison to those with persistently normal or improving HADS-anxiety trajectories.

**Kruskal-Wallis One-way ANOVA for comparison of continuous data, and χ^2 for comparison of categorical data across all three groups.

‡Clinics included rheumatology, dermatology, hepatology, oral medicine, or colorectal surgery.

†No deaths were related directly to complications of IBD.

Table 3. Baseline Characteristics of Patients According to HADS-depression Trajectories.

	Persistently normal or improving (n = 515)	**Fluctuating (n = 209)**	**Persistently abnormal or worsening (n = 53)**	***p* value***
Mean age in years at baseline (SD)	54.3 (16.7)	53.0 (16.1)	50.5 (15.4)	0.15
Female sex (%)	267 (52.0)	121 (58.5)	33 (62.3)	0.15
Married or co-habiting (%)	376 (73.7)	138 (66.0)	29 (55.8)	0.01
University graduate/professional (%)	213 (42.0)	72 (34.6)	11 (20.8)	0.004
Tobacco user (%)	27 (5.3)	19 (9.1)	6 (11.3)	0.07
Alcohol user (%)	376 (73.9)	143 (68.8)	30 (56.6)	0.019
IBD type (%)				
CD	219 (42.8)	94 (45.9)	27 (51.9)	
UC	261 (51.0)	97 (47.3)	21 (40.4)	
IBD-U	32 (6.3)	14 (6.8)	4 (7.7)	0.64
CD location (%)†				
Ileal	74/219 (33.8)	39/93 (41.9)	7/27 (25.9)	
Colonic	68/219 (31.1)	19/93 (20.4)	8/27 (29.6)	
Ileocolonic	77/219 (35.2)	35/93 (37.6)	12/27 (44.4)	0.27

Stricturing CD (%)	64/219 (29.2)	29/94 (30.9)	3/27 (11.1)	0.12
Penetrating CD (%)	27/219 (12.3)	21/94 (22.3)	3/27 (11.1)	0.06
Perianal CD (%)	25/219 (11.4)	15/94 (16.0)	6/27 (22.2)	0.22
Previous intestinal resection (%)	95 (18.6)	46 (22.3)	11 (21.2)	0.50
UC extent (%)‡				
Proctitis	73/254 (28.7)	29/95 (30.5)	7/19 (36.8)	
Left-sided	101/254 (39.8)	36/95 (37.9)	7/19 (36.8)	
Extensive	80/254 (31.5)	30/95 (31.6)	5/19 (26.3)	0.96
Current 5-ASA use (%)	282 (55.1)	106 (51.7)	22 (42.3)	0.18
Current immunomodulator use (%)	139 (27.1)	59 (28.8)	21 (40.4)	0.13
Current biologic use (%)	104 (20.3)	45 (22.0)	14 (26.9)	0.51
Current glucocorticosteroid use (%)	13 (2.5)	4 (2.0)	2 (3.8)	0.72
Current antidepressant use (%)	52 (10.1)	62 (29.7)	19 (35.8)	<0.001
Current opiate use (%)	38 (7.4)	34 (16.3)	18 (34.0)	<0.001
Diagnosed with IBD in the last 12 months (%)	28 (5.5)	22 (10.6)	8 (15.1)	0.006
Self-reported a flare at baseline (%)	61 (12.0)	56 (26.8)	17 (32.7)	<0.001
Active disease on HBI or SCCAI at baseline (%)	148 (29.1)	106 (51.0)	38 (71.7)	<0.001

PHQ-12 somatoform symptom categories (%)				
Minimal	188 (38.9)	20 (10.4)	3 (6.5)	
Low	197 (40.8)	65 (33.9)	6 (13.0)	
Medium	84 (17.4)	79 (41.1)	18 (39.1)	
High	14 (2.9)	28 (14.6)	19 (41.3)	<0.001
Mean SIBDQ score (SD)	56.1 (9.9)	43.0 (11.6)	33.0 (12.8)	<0.001

*One-way ANOVA for comparison of normally distributed continuous data, χ^2 for comparison of categorical data across all three groups.

†Data on CD location missing for one patient with fluctuating HADS-depression scores.

‡Data on UC extent missing for 11 patients; seven with persistently normal or improving HADS-depression scores, two with fluctuating HADS-depression scores, and two with persistently abnormal or worsening HADS-depression scores.

Table 4. Healthcare Utilization and Clinical Outcomes of Patients According to HADS-depression Trajectories Over 12-month Longitudinal Follow-up.

	Persistently normal or improving (n = 515)	**Fluctuating (n = 209)**	***p* value***	**Persistently abnormal or worsening (n = 53)**	***p* value***	***p* value****
Healthcare utilization						
Median number of clinic appointments with a gastroenterologist (IQR)	1 (0-2)	1 (0-2)	0.01	1 (1-2)	<0.001	<0.001
Median number of clinic appointments with an IBD specialist nurse (IQR)	1 (0-1)	1 (0-1)	0.22	0 (0-1)	<0.001	<0.001
Median number of IBD helpline calls (IQR)	0 (0-2)	1 (0-3)	0.051	1 (0-3.5)	0.84	0.065
Median number of radiological investigations related to IBD activity (IQR)	0 (0-0)	0 (0-0)	0.013	0 (0-0)	0.10	0.03
Median number of endoscopic investigations related to IBD activity (IQR)	0 (0-0)	0 (0-0)	0.002	0 (0-0)	0.10	0.005
Median number of other specialty clinics related to extra-intestinal manifestations of IBD (IQR)‡	0 (0-0)	0 (0-1)	0.003	0 (0-1)	0.02	0.003
Clinical outcomes						

Flare of disease activity (%)	68 (13.2)	33 (15.8)	0.36	10 (18.9)	0.25	0.41
Median number of flares of disease activity (IQR)	0 (0-0)	0 (0-0)	0.55	0 (0-0)	0.13	0.04
Glucocorticosteroid prescription due to uncontrolled disease activity (%)	39 (7.6)	15 (7.2)	0.85	5 (9.4)	0.63	0.86
Median number of glucocorticosteroid prescriptions due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.90	0 (0-0)	0.62	0.40
Escalation of IBD therapy due to uncontrolled disease activity (%)	58 (11.3)	27 (12.9)	0.43	9 (17.0)	0.22	0.44
Median number of escalations of IBD therapy due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.50	0 (0-0)	0.21	0.11
Hospitalization due to uncontrolled disease activity (%)	19 (3.7)	9 (4.3)	0.70	0 (0)	0.16	0.32
Median number of hospitalizations due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.70	n/a	0.16	0.09
Intestinal resection due to uncontrolled disease activity (%)	5 (1.0)	4 (1.9)	0.24	0 (0)	0.61	0.40

Median number of intestinal resections due to uncontrolled disease activity (IQR)	0 (0-0)	0 (0-0)	0.30	n/a	0.47	0.10
Death (%)†	3 (0.6)	3 (1.4)	0.23	2 (3.8)	0.071	0.072
Median number of deaths (IQR)	0 (0-0)	0 (0-0)	0.25	0 (0-0)	0.02	0.11

*Mann-Whitney U for continuous data, χ^2 for categorical data with counts ≥5 and Fisher's Exact Test for categorical data with <5 counts, for comparison to those with persistently normal or improving HADS-depression trajectories.

**Kruskal-Wallis One-way ANOVA for comparison of continuous data, and χ^2 for comparison of categorical data across all three groups.

‡Clinics included rheumatology, dermatology, hepatology, oral medicine, or colorectal surgery.

†No deaths were related directly to complications of IBD.

Figure 1. Trajectory of HADS-Anxiety Scores Over 12-month Longitudinal Follow-up.

Figure 2. Future Adverse Disease Outcomes According to HADS-Anxiety Trajectories Over 12-month Longitudinal Follow-up.

Figure 3. Trajectory of HADS-Depression Scores Over 12-month Longitudinal Follow-up.

Figure 4. Future Adverse Disease Outcomes According to HADS-Depression Trajectories Over 12-month Longitudinal Follow-up.