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TITLE PAGE

Title: Persistence of Symptoms of Anxiety and Depression in Inflammatory Bowel Disease:
A Longitudinal Follow-Up Study.

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Abbreviations:	5-ASA	5-aminosalicylate
	ANOVA	analysis of variance
	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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ABSTRACT

Introduction: Poor psychological health affects many patients with inflammatory bowel disease (IBD), but persistence of these symptoms is unclear.

Methods: We performed a longitudinal follow-up study of patients whose anxiety and depression trajectories were established by symptom data collected at 3-monthly intervals over the course of 1 year. We collected further anxiety and depression symptom data at yearly intervals over 2-years to determine persistence of these symptoms in patients with IBD. Disease outcomes (flare/need for glucocorticosteroids, escalation of medical therapy, hospitalisation, or intestinal resection) were recorded to determine effect of mood trajectories on the natural history of IBD.

Results: Of 770 patients with established anxiety trajectories, 486 (63.1%) provided further anxiety symptom data at 12 months, and 358 (45.5%) at 24 months. Of the 777 patients with established depression trajectories, 491 (63.2%) provided further depression symptom data at 12 months, and 362 (45.6%) at 24 months. Participants with symptoms of anxiety at 24 months were more likely to have a fluctuating, or persistently abnormal or worsening, anxiety trajectory during the first year ($p < 0.001$ for trend). Participants with symptoms of depression at 24 months were more likely to have a fluctuating, or persistently abnormal or worsening, depression trajectory during the first year ($p < 0.001$ for trend). Adverse disease outcomes were no more likely according to anxiety or depression trajectories.

Discussion: Poor psychological health persists for a substantial number of patients with IBD. Further work is needed to establish the long-term effect of mood-trajectories on disease outcomes.

Key words: Inflammatory bowel disease, psychological health, mood trajectories.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) with debilitating gastrointestinal symptoms. These diseases impact work productivity, personal relationships, and quality of life negatively,¹⁻⁴ and can result in complications, including stricture and fistula formation, intestinal obstruction, and perforation.¹ Equipped with an expanding arsenal of efficacious medical therapies,^{5, 6} and a drive to reduce these adverse outcomes, the standard of IBD care now demands the prompt recognition and treatment of persistent mucosal inflammation.^{7, 8} This approach has been associated with a reduction in both the number of IBD-related surgeries and mortality over the last two decades.⁹ Healthcare utilisation trends, however, remained unchanged, suggesting that factors other than inflammatory activity contribute to the natural history of IBD.^{10, 11}

Poor psychological health is a substantial issue for patients with IBD. Common mental disorders, including anxiety and depression, are twice as prevalent as in the general population.¹²⁻¹⁵ Moreover, these symptoms may be associated with future adverse disease outcomes and increased healthcare utilisation.¹⁶⁻¹⁸ Symptoms of anxiety or depression peak during a flare, affecting almost half of patients,¹⁵ which may be attributable to the release of pro-inflammatory cytokines crossing the blood-brain barrier and upregulating the hypothalamic-pituitary-adrenal axis, inducing a stress response.¹⁹ However, this fails to explain why almost one-third of patients experience poor psychological health during periods of disease quiescence,¹⁵ which may imply gut-brain axis communication is involved.^{12, 14, 20} In health, these complex bi-directional signals serve to enable central regulation of peripheral gut functions.¹⁹ Dysregulation in these communications could explain both the high prevalence of symptoms of anxiety and depression in IBD and their apparent negative impact on the subsequent disease course.²¹

In the general population symptoms of anxiety and depression fluctuate over time,²² but most existing studies in IBD usually assess mood at a single time point,^{14, 15} which falls short of the official recommendation of the diagnostic and statistical manual of mental disorders, that symptoms of depression must be present consistently over a minimum period of two weeks, and anxiety over 6 months.²³ Unless these symptoms remain stable over time in IBD, the results of studies examining their impact on prognosis of IBD may be inaccurate.²² To address this issue, our group has previously examined mood trajectories at 3-month intervals over the course of 1 year in a large cohort of patients with IBD. We demonstrated that improvement in anxiety and depression scores occurred in only 10% of patients reporting these symptoms at baseline,²⁴ suggesting symptoms persist for most patients with IBD. However, poor psychological health is not unique to IBD, and mood trajectories in multiple sclerosis, another chronic immune mediated relapsing-remitting inflammatory disease, do not remain stable beyond 1 year.²⁵ Similarly, researchers examining mood trajectories in chronic obstructive pulmonary disease demonstrated that mood remained stable in only 25% of patients over 3 years.²⁶ Mood may, therefore, also be more fluctuant over a prolonged period in IBD. This is of particular relevance, given the positive impact of initiating biological therapy on mood in IBD,²⁷⁻²⁹ and the negative impact of anxiety or depression symptoms on longitudinal disease activity outcomes.^{12, 14}

Whether symptoms of anxiety and depression demonstrate long-term stability in IBD remains unclear. Furthermore, although we have established that persistently abnormal or worsening mood trajectories in IBD are associated with increased healthcare utilisation, less is known regarding the effects of these trajectories on adverse disease outcomes.²⁴ We, therefore, performed a longitudinal follow-up study, examining these issues.

METHODS

Participants and Setting

All adult patients aged ≥ 18 years with an established diagnosis of CD, UC, or IBD-unclassified (IBD-U) based on histological, endoscopic, or radiological findings, under active follow-up within the Leeds Teaching Hospitals NHS Trust IBD service were sent a postal invitation to participate in this study between June and September of 2020. The invitation contained both a web-link and a personalised uniform resource locator to access a participant information sheet, consent form, and an online questionnaire. Patients preferring written documentation were provided with paper versions. Follow-up questionnaires were distributed, in the preferred format for each participant, at 3-month intervals throughout an initial 12-month period. All participants were invited to participate in the longitudinal follow-up extension study in September 2022. Mood symptom data was then collected annually over the subsequent 2 years. To mitigate losses to follow-up, a single reminder letter was issued to each consenting participant who did not respond to one or more of the follow-up questionnaires. Due to a lack of validated disease activity indices to determine clinical disease activity, participants with an ileo-anal pouch or end stoma were excluded. There were no other exclusion criteria. The study and longitudinal follow-up extension were both approved by the Wales research ethics committee (REC ref: 20/WA/0044 and 20/WA/0044/01).

Data Collection and Synthesis

Demographic data, including age, sex, ethnicity, marital status, educational level, and lifestyle factors, including tobacco and alcohol consumption were recorded at baseline. We used the Harvey-Bradshaw index (HBI) to determine clinical disease activity for patients with

CD, excluding the detection of an abdominal mass,^{30, 31} and the simple clinical colitis activity index (SCCAI) for patients with UC.³² A score of <5 was considered as clinical remission for both, as previously recommended.^{33, 34} We collected somatoform symptom data using the patient health questionnaire-12 (PHQ-12).³⁵ The score ranges from 0 to 24 and is derived from the PHQ-15 by omission of gastrointestinal symptom-related questions and symptom severity classified as high (total score ≥ 13), medium (8-12), low (4-7), or minimal (≤ 3). Quality of life was assessed using the short IBD questionnaire (SIBDQ) health survey.³⁶ Finally, to determine the presence of symptoms of anxiety or depression, we used the hospital anxiety and depression scale (HADS).³⁷ This 14-item validated questionnaire gives a total score for anxiety or depression of 0 to 21, with scores considered normal (score 0-7), borderline (8-10), or abnormal (≥ 11) in either domain.³⁷ We utilised these to create initial anxiety and depression trajectories for participants who provided data at baseline and a minimum of two further points of follow up in the first 12 months of the study. Normal or improving trajectories were classified as a normal HADS-anxiety or HADS-depression scores throughout, or a baseline score of ≥ 11 improving to <8 at the last point of follow-up. Similarly, abnormal or worsening trajectories were classified as HADS-anxiety or HADS-depression scores of ≥ 11 throughout or having a score of <8 at baseline which worsened to ≥ 11 at the last point of follow-up. The remaining individuals were classified as fluctuating trajectories. To determine the stability of anxiety or depression symptoms over time, we then compared the initial symptom trajectories with the presence or absence of anxiety or depression symptoms at subsequent annual intervals, again using HADS-anxiety and HADS-depression scores, with identical cut-off values applied to determine normal, borderline abnormal, or abnormal scores.

A single investigator (KMF), blinded to questionnaire responses, reviewed the electronic medical records for each participant to verify the type (CD, UC, or IBD-U), extent

and location of IBD, and determine any prior IBD-related intestinal resections. Baseline IBD-related medication use, including 5-aminosalicylates (5-ASAs), immunosuppressants, biologic therapies, or glucocorticosteroids, as well as current use of antidepressant drugs or opioids was recorded. Two assessors (KMF or CR) extracted clinical outcome data during longitudinal follow-up, including flare of disease activity based on a physician's global assessment; glucocorticosteroid prescription; escalation of medical therapy due to uncontrolled IBD activity; hospitalisation due to uncontrolled IBD activity; intestinal resection due to uncontrolled IBD activity; or death. In addition, we recorded the date of occurrence of each outcome. Escalation of medical therapy without evidence of uncontrolled IBD activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, were excluded as endpoints.

Statistical Analysis

As described, the initial anxiety or depression trajectories were established among patients providing baseline data and a minimum of two further points of follow-up during the first year of the study.²⁴ To understand the influence of these initial symptom trajectories on the persistence of symptoms of anxiety or depression subsequently, we then calculated the prevalence of symptoms of subsequent anxiety or depression, defined by the presence of abnormal HADS-anxiety or HADS-depression scores, at both 12 and 24 months in patients providing further longitudinal follow-up data at these time points, in each of the three initial anxiety or depression symptom trajectories. To determine if the three initial anxiety and depression symptom trajectories influenced the natural history of IBD, we compared rates of adverse disease outcomes, including flare of disease activity, glucocorticosteroid prescription, escalation of therapy, hospitalisation, intestinal resection, or death during longitudinal follow-up between them. When examining categorical data we applied a Pearson's χ^2 test for all

analyses. For continuous data we applied a one-way analysis of variance (ANOVA) for comparisons between more than two groups, or a two-sided t-test to compare continuous data between two groups. Due to multiple comparisons, a 2-tailed P value of <0.01 was considered statistically significant. If the univariate analyses were significant for persistence of symptoms of anxiety or depression, we performed logistic regression controlling for all baseline characteristics, including sex, age, marital status, tobacco and alcohol consumption, educational level, type of IBD, baseline clinical disease activity, IBD-related medications, level of somatoform symptom-reporting according to the PHQ-12, and initial anxiety and depression trajectories, to identify independent predictors of persistence of these symptoms, with the outcomes expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Similarly, if the results on univariate analysis were statistically significant for adverse disease outcomes, we performed multivariate Cox regression analyses controlling for all baseline characteristics, with the outcomes expressed as hazard ratios (HRs) with 95% CIs. All analyses were performed using SPSS for Windows version 29.0.

RESULTS

Of the 4823 patients with IBD under the care of the IBD service in Leeds Teaching Hospitals NHS trust who were contacted between June and September of 2020, 1027 (21.3%) responded to the baseline questionnaire and did not have either an ileo-anal pouch or end stoma. The mean age of these 1027 participants was 52.6 years (SD 16.9 year), 564 (54.9%) were female, and 457 (44.5%) had CD. Of these, 770 (75.0%) provided at least two further follow-up questionnaires to enable establishment of anxiety trajectories and 777 (75.7%) depression trajectories. The baseline characteristics of the 770 participants providing data for anxiety trajectories and for the 777 providing data for depression trajectories have been described previously,²⁴ and are provided in Supplementary Table 1.

Presence of Subsequent Symptoms of Anxiety According to Baseline Disease

Characteristics and Initial Anxiety or Depression Trajectories

Of the patients providing sufficient anxiety symptom data to establish their initial anxiety trajectory, 486 (63.1%) patients provided subsequent anxiety symptom data at 12 months, and 358 (45.5%) at 24 months. For patients who provided sufficient depression symptom data to establish initial depression trajectories, 491 (63.2%) patients provided subsequent anxiety symptom data at 12 months, and 362 (46.6%) at 24 months. Of the patients reporting symptoms of anxiety at 12 months, 8 (3.0%) belonged to a persistently normal or improving, 50 (30.5%) to a fluctuating, and 41 (71.9%) to a persistently abnormal or worsening anxiety trajectory (Table 1). Of the patients reporting symptoms of anxiety at 24 months, 4 (2.1%) belonged to a persistently normal or improving, 37 (29.8%) to a fluctuating, and 32 (76.2%) to a persistently abnormal or worsening anxiety trajectory (Table 1). Baseline factors associated with the reporting of symptoms of anxiety at 12 months

included having received a diagnosis of IBD within the 12 months prior to recruitment ($p=0.001$), active disease according to HBI or SCCAI scores ($p < 0.001$), higher levels of somatoform symptom-reporting on the PHQ-12 ($p < 0.001$) and use of antidepressants ($p < 0.001$). In addition, both persistently abnormal or worsening anxiety trajectories ($p < 0.001$) and persistently abnormal or worsening depression trajectories ($p < 0.001$) were significantly associated with the reporting of symptoms of anxiety at 12 months. Of these factors, only the use of antidepressants ($p < 0.001$), higher levels of somatoform symptom-reporting ($p < 0.001$), and persistently abnormal or worsening anxiety or depression trajectories ($p < 0.001$ for both) remained significantly associated with the reporting of symptoms of anxiety at 24 months. The reporting of symptoms of anxiety at 24 months was also significantly associated with female sex ($p < 0.001$) and a self-reported disease flare at baseline ($p=0.002$).

Following multivariate logistic regression, controlling for all baseline data, factors significantly associated with the reporting of anxiety at 12 months were antidepressant use (OR 2.86; 95% CI 1.23-6.66, $p=0.015$), being married (OR 2.93; 95% CI 1.31-6.54, $p=0.009$), and a fluctuating anxiety trajectory (OR 18.1; 95% CI 6.54-50.3, $p < 0.001$) as well as a persistently abnormal or worsening anxiety trajectory (OR 58.8 95% CI 17.2-202 $p < 0.001$) ($p < 0.001$ for trend) (Table 1). The use of antidepressants (OR 4.42; 95% CI 1.60-12.2, $p=0.004$) and a fluctuating anxiety trajectory (OR 23.8; 95% CI 5.94-95.0, $p < 0.001$), as well as a persistently abnormal or worsening anxiety trajectory (OR 199 95% CI 34.1-1160 $p < 0.001$) ($p < 0.001$ for trend) (Table 1) remained significantly associated with the reporting of symptoms of anxiety at 24 months. No other baseline characteristics were significantly associated with the subsequent reporting of symptoms of anxiety at either time point.

Clinical Outcomes According to Initial Anxiety Trajectories

During a mean duration of follow-up of 3.9 years, patients with a persistently abnormal or worsening anxiety trajectory were significantly more likely than those with a persistently normal or improving trajectory to experience a flare of disease activity or require glucocorticosteroids ($p=0.003$), but there was no significant difference between any of the trajectories for escalation of medical therapy, hospitalisation, or intestinal resection due to uncontrolled disease activity (Table 2). Furthermore, mortality was not significantly different between trajectory groups. Following multivariate Cox regression, experiencing a flare or requiring glucocorticosteroids was no longer significantly associated with a persistently abnormal or worsening anxiety trajectory.

Presence of Subsequent Symptoms of Depression According to Baseline Disease Characteristics and Initial Anxiety or Depression Trajectories

Of the patients providing sufficient depression symptom data to establish their initial depression trajectory, 491 (63.2%) patients provided subsequent depression symptom data at 12 months, and 362 (45.6%) at 24 months. For patients who provided sufficient anxiety symptom data to establish initial anxiety trajectories, 486 (63.1%) patients provided subsequent depression symptom data at 12 months, and 358 (46.5%) at 24 months. Of the patients reporting symptoms of depression at 12 months, 3 (0.9%) belonged to a persistently normal or improving, 24 (17.6%) to a fluctuating, and 14 (56.0%) to a persistently abnormal or worsening depression trajectory (Table 1). Of the patients reporting symptoms of depression at 24 months, 2 (0.8%) belonged to a persistently normal or improving, 23 (24.0%) to a fluctuating, and 11 (68.8%) to a persistently abnormal or worsening depression trajectory (Table 1). Baseline factors associated with the reporting of symptoms of depression

at 12 months included having received a diagnosis of IBD within the previous 12 months ($p=0.008$), self-reporting of a flare ($p=0.004$), active disease according to HBI or SCCAI scores ($p < 0.001$), higher levels of somatoform symptom-reporting on the PHQ-12 ($p < 0.001$), and use of either antidepressants ($p < 0.001$) or opioids ($p < 0.001$). In addition, both persistently abnormal or worsening anxiety trajectories ($p < 0.001$) and persistently abnormal or worsening depression trajectories ($p < 0.001$) were significantly associated with the reporting of symptoms of depression at 12 months. Of these factors, self-reporting of a flare ($p < 0.001$), having active disease according to HBI or SCCAI scores ($p=0.002$), higher levels of somatoform symptom-reporting ($p < 0.001$), the use of antidepressants ($p < 0.001$) or opioids ($p < 0.001$), and both persistently abnormal or worsening anxiety or depression trajectories ($p < 0.001$ for both) continued to be significantly associated with the reporting of symptoms of depression at 24 months. In addition, consumption of any alcohol ($p=0.008$) was significantly associated with the reporting of symptoms of depression at 24 months.

Following multivariate logistic regression, factors significantly associated with the reporting of depression at 12 months included clinical disease activity according to the HBI or SCCAI (OR 4.29; 95% CI 1.44-12.8, $p=0.009$), a fluctuating depression trajectory (OR 11.9; 95% CI 2.80-50.8, $p < 0.001$), and a persistently abnormal or worsening depression trajectory (OR 51.2; 95% CI 7.77-337, $p < 0.001$) ($p < 0.001$ for trend) (Table 1). This association persisted at 24 months, for both a fluctuating depression trajectory (OR 26.1; 95% CI 4.34-157, $p < 0.001$) and a persistently abnormal or worsening depression trajectory (HR 202; 95% CI 16.2-2520, $p < 0.001$). Antidepressant use (OR 3.17; 95% CI 1.05-9.64, $p=0.042$) was the only other factor associated with the reporting of symptoms of depression at 24 months.

Clinical Outcomes According to Initial Depression Trajectories

During a mean duration of follow-up of 3.9 years, patients with a persistently abnormal or worsening depression trajectory were not significantly more likely to experience a flare of disease activity or require glucocorticosteroids, an escalation of medical therapy, hospitalisation, or intestinal resection due to uncontrolled disease activity (Table 2). Mortality was significantly higher in those with a persistently abnormal or worsening depression trajectory than those with a persistently normal or improving trajectory. Following multivariate Cox regression, mortality was no longer significantly associated with a persistently abnormal or worsening depression trajectory.

DISCUSSION

We have previously established mood trajectories using anxiety and depression symptom data taken at 3-monthly intervals over the course of 1 year in this cohort of patients with IBD. In that study, we demonstrated that almost 90% of patients with abnormal anxiety or depression scores at baseline continued to have abnormal scores, and that persistently abnormal or worsening mood trajectories were associated with increased healthcare utilisation.²⁴ In the current study we examined the persistence of symptoms of a common mental disorder in IBD, by examining the effect of these baseline anxiety and depression trajectories on subsequent symptoms of anxiety or depression at yearly intervals. Both anxiety and depression trajectories established during the initial 1 year of the study were significantly associated with the reporting of symptoms of anxiety and depression in the subsequent 12 and 24 months of longitudinal follow-up. This suggests that these symptoms persist for the majority of patients with IBD during extended follow-up. When considering all baseline characteristics, the only factors that remained significantly associated with symptoms of anxiety at both 12 and 24 months were fluctuating anxiety trajectories, persistently abnormal or worsening anxiety trajectories, and the use of antidepressants. Similarly for symptoms of depression, fluctuating depression trajectories or persistently abnormal or worsening depression trajectories remained the only factor significantly associated with symptoms of depression at both subsequent time points. We also examined the impact of anxiety and depression trajectories on adverse disease outcomes during almost 4 years of follow-up but found no significant association between these and any of the adverse disease outcomes of interest.

Our study has several strengths. Firstly, by using validated questionnaires in an online format, we were able to distribute initial invitations to the entirety of the IBD population that we serve. Furthermore, the option for participants to receive a postal questionnaire, if

preferred, reduced the risk of age- and wealth-related bias in our recruitment selection, allowing those without access to modern technology an equal chance to participate. Attrition is a significant issue in observational research. Therefore, offering a single reminder at each longitudinal follow-up point contributed to our large cohort size, and the successful establishment of anxiety and depression trajectories during the first year in three-quarters of participants, and with data for subsequent mood in just over 50% of the original cohort at 24 months. We, therefore, present data from a large, unselected IBD cohort with a range of disease characteristics, who are likely to be generalisable to many patients in secondary care. Finally, the combination of electronic health records and two assessors, blinded to symptom response data, assessing adverse disease outcomes against pre-defined criteria ensured that these endpoints were captured accurately during longitudinal follow-up.

There are, of course limitations which must be acknowledged. Validated questionnaires have a lower sensitivity and specificity in detecting common mental disorders than structured interviews,³⁸ and our study could be criticised for using HADS scores as a surrogate for the presence of a common mental disorder. However, in this large observational study, which was conducted in parallel with routine clinical care, it was not feasible to conduct structured interviews, without impacting participant retention negatively, and the cut-offs we have used demonstrate good specificity in IBD, suggesting this is an accurate assessment of the prevalence of such symptoms.³⁸ By inviting all patients with IBD in our centre to participate, we avoided selection bias, but volunteer bias is an inherent flaw of observational research,³⁹ and we cannot rule out that patients with symptoms of anxiety or depression were more likely to participate in the study, creating the potential to overestimate the prevalence of these symptoms in our cohort. That said, the prevalence of symptoms of a common mental disorder we report is similar to that in other studies.¹⁵ Patient-reported disease activity measures demonstrate inferiority to non-invasive biomarkers and endoscopic

assessments in determining the degree of inflammatory activity in IBD, with the former likely to overestimate disease activity.^{40, 41} As the study commenced during the COVID-19 pandemic, collection of faecal calprotectin samples would have required patients to return a specimen in-person to an NHS location for research purposes, which was not feasible at the time. In addition, a recent study examining symptoms of anxiety and depression in IBD determined that both endoscopic and biochemical activity did not predict symptoms of a common mental disorder, with only perceived disease activity, as determined by disease activity scores, being independently associated with such symptoms. This suggests that perceived symptoms of a flare correlate with mood rather than genuine underlying disease activity.⁴² Persistent depression is associated with several key risk factors, including a history of childhood adversity and maltreatment, a family history of depression, earlier onset of depressive symptoms, comorbidity with anxiety and other psychiatric disorders, poor social support and a higher frequency of depressotypic cognitions.⁴³ It was not possible to measure these factors other than anxiety in the present study, or establish whether those participants with persistent depression or anxiety had symptoms which pre-dated the onset of IBD. Finally, we did not record whether patients had accessed psychological therapies during the study, which may explain some of the fluctuation in symptoms of anxiety and depression, although previous surveys have shown that access for patients with IBD to these is limited in the UK.⁴⁴

Mood trajectories have been studied in the context of chronic disease, with a recent meta-analysis of over 60,000 patients with cancer, diabetes, and cardiovascular and liver disease demonstrating persistently abnormal anxiety and depression scores over a period of almost 4 years among one-in-eight patients following diagnosis.⁴⁵ Our study is, to our knowledge, the first to examine the stability of future mood according to such mood trajectories in IBD, and suggests that abnormal mood is even more stable over time in this

particular patient group, with over three-quarters of patients with persistently abnormal or worsening anxiety trajectories continuing to report symptoms of anxiety and over two-thirds with persistently abnormal or worsening depression trajectories reporting ongoing symptoms of depression in the subsequent 2 years. These findings suggest that, for patients with an established diagnosis of IBD reporting symptoms of anxiety or depression, unlike other chronic inflammatory conditions,^{25, 26} these symptoms remain stable in the majority over time. Our findings support the notion that a single assessment of mood may be sufficient to diagnose common mental disorders in this context. An exception to this observation is patients with a new diagnosis, in whom abnormal anxiety trajectories predicted abnormal anxiety scores at 12 months, but not at 24 months, suggesting that in this group of patients, mood may be more fluctuant and reflect psychological adjustment to the disease state. Indeed, psychological adaptation has been reported in the context of chronic disease,⁴⁶ and similar improvements in anxiety scores have also been observed in patients with other chronic inflammatory disorders, including multiple sclerosis, in the 6 months following diagnosis.⁴⁷ The limited research conducted amongst IBD inception cohorts suggests a high prevalence of symptoms of a common mental disorder in this particular group of patients,^{48, 49} and studies examining the risk factors for persistently abnormal mood in newly diagnosed patients may be key to implementing preventative strategies to mitigate subsequent high volume healthcare use.⁴⁶

We have shown previously that persistently abnormal or worsening anxiety or depression trajectories were associated with increased healthcare utilisation in IBD.²⁴ However, data from the current study did not identify a relationship between these mood trajectories and subsequent adverse disease outcomes. These findings mirror those of a much smaller study of 32 patients with IBD,⁵⁰ which demonstrated that future adverse disease outcomes were not linked with mood fluctuations, and contradicts the findings of the wealth

of observational data suggesting the existence of brain-gut effects in IBD.^{13, 14, 20, 21} As inflammatory and psychological burden have been proven to influence disease outcomes cumulatively in IBD,¹³ it may be that studies adopting a more rigorous assessment of IBD activity are required to determine the role of mood trajectories on these outcomes. However, despite the large sample size, the number of patients with a persistently abnormal or worsening mood trajectory was relatively small and the study may be underpowered to detect such associations, particularly given the relatively short duration of follow-up in comparison with other studies.¹³ Regardless, avoidance of adverse disease outcomes should not be the only consideration, and the consistent association between poor psychological health and reduced quality of life and increased healthcare utilisation is important to consider.^{16, 24, 51, 52} Other factors that may be involved in fluctuations of mood include the emotional concerns of patients related to specific issues such as fatigue, urgency, fear of incontinence, or pain.⁵³⁻

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Despite an abundance of observational data highlighting the high prevalence of symptoms of a common mental disorder in patients with IBD,¹⁵ there remains a lack of consensus as to how we can address these symptoms appropriately within the constraints of routine care.⁵⁶ Policy makers with finite resources are faced with difficulty in this regard. Firstly, little is known regarding the longevity of these symptoms, or indeed if there is substantial fluctuation over time in a relapsing-remitting disease, particularly given the highest prevalence of symptoms of a common mental disorder appears to be during periods of disease activity.¹⁵ Second, randomised controlled trials examining the efficacy of psychological therapies and gut-brain neuromodulators in IBD continue to recruit unselected patients without evidence of psychological co-morbidity, and show no clear benefit of such interventions, which means there is little evidence to support widespread uptake.⁵⁷ Our study adds value in this regard, by demonstrating that over two-thirds of patients with persistently

abnormal or worsening mood trajectories, continued to experience symptoms of anxiety or depression over a 2-year period. Validated questionnaires are simple cost-effective tools with a low time-resource burden, which could be utilised in everyday practice to identify symptoms of a common mental disorder in patients with IBD. This could then enable clinicians to allocate scarce psychological health resources to those most likely to benefit.⁵⁷ A similar strategy has been trialled across a range of chronic illnesses in secondary care for healthcare-related anxiety, with those identified with this condition being randomised to receive cognitive behavioural therapy (CBT) or treatment as usual; there were significant and sustained improvements in psychological health with CBT, although no difference in healthcare-related costs between groups.⁵⁸

In conclusion poor psychological health, as determined by persistently abnormal or worsening anxiety and depression trajectories, remains unchanged amongst many patients with established IBD over a prolonged period. Although this study did not demonstrate an association between these trajectories and future adverse disease outcomes, we have previously demonstrated that they predict higher healthcare utilisation in this cohort of patients, and a wealth of data suggests poor psychological health negatively impacts quality of life, suggesting that poor psychological health exerts a negative influence on IBD. Further studies examining this issue in patients with IBD in other geographical regions would be informative. A clear consensus on screening and addressing psychological health in routine care is essential to address the unmet needs of a substantial proportion of patients with IBD.

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Table 1. Presence of Subsequent Symptoms of Anxiety or Depression at 12 and 24 Months According to Anxiety or Depression Trajectories

	Anxiety Trajectories				Depression Trajectories			
	Normal or improving	Fluctuating	Abnormal or worsening	<i>p</i> value*	Normal or improving	Fluctuating	Abnormal or worsening	<i>p</i> value*
Symptoms of anxiety at 12 months (%)	8/265 (3.0)	50/164 (30.5)	41/57 (71.9)	<0.001	30/330 (9.1)	50/136 (36.8)	19/25 (76.0)	<0.001
OR for symptoms of anxiety at 12 months	1.00 (reference)	18.1 (6.54-50.3)	58.8 (17.2-202)	<0.001	1.00 (reference)	1.80 (0.84-3.86)	5.71 (1.30-25.1)	0.056
Symptoms of anxiety at 24 months (%)	4/192 (2.1)	37/124 (29.8)	32/42 (76.2)	<0.001	27/250 (10.8)	35/96 (36.5)	12/16 (75.0)	<0.001
OR for symptoms of anxiety at 24 months	1.00 (reference)	23.8 (5.94-95.0)	199 (34.1-1160)	<0.001	1.00 (reference)	0.70 (0.27-1.83)	1.47 (0.24-8.96)	0.55
Symptoms of depression at 12 months (%)	5/265 (1.9)	19/164 (11.6)	17/57 (29.8)	<0.001	3/330 (0.9)	24/136 (17.6)	14/25 (56.0)	<0.001
OR for symptoms of depression at 12 months	1.00 (reference)	1.21 (0.32-4.68)	1.89 (0.39-9.27)	0.69	1.00 (reference)	11.9 (2.80-50.8)	51.2 (7.77-337)	<0.001

Symptoms of depression at 24 months (%)	4/192 (2.1)	16/124 (12.9)	16/42 (38.1)	<0.001	2/250 (0.8)	23/96 (24.0)	11/16 (68.8)	<0.001
OR for symptoms of depression at 24 months	1.00 (reference)	1.57 (0.35-7.11)	2.84 (0.49-16.6)	0.49	1.00 (reference)	26.1 (4.34-157)	202 (16.2-2521)	<0.001

**P* value for trend.

Table 2. Occurrence of Subsequent Adverse Disease Outcomes According to Initial Anxiety or Depression Trajectories.

	Anxiety Trajectories						Depression Trajectories					
	Normal or improving (n=399)	Fluctuating (n=268)	<i>p</i> value*	Abnormal or worsening (n=103)	<i>p</i> value†	<i>p</i> value‡	Normal or improving (n=515)	Fluctuating (n=212)	<i>p</i> value*	Abnormal or worsening (n=50)	<i>p</i> value†	<i>p</i> value‡
Flare or glucocorticosteroid prescription (%)	96 (24.1)	74 (27.6)	0.30	40 (38.8)	0.003	0.011	123 (23.9)	71 (33.5)	0.008	17 (34.0)	0.11	0.016
Escalation (%)	90 (22.6)	68 (25.4)	0.40	29 (28.2)	0.23	0.44	120 (23.3)	56 (26.4)	0.37	11 (22.0)	0.84	0.63
Hospitalisation (%)	24 (6.0)	28 (10.4)	0.036	9 (8.7)	0.32	0.11	35 (6.8)	19 (9.0)	0.31	7 (14.0)	0.064	0.15
Intestinal resection (%)	14 (3.5)	14 (5.2)	0.28	4 (3.9)	0.86	0.55	18 (3.5)	10 (4.7)	0.44	4 (8.0)	0.12	0.27
Death (%)	15 (3.8)	9 (3.4)	0.80	7 (6.9)	0.18	0.30	15 (3.0)	11 (5.2)	0.14	5 (10.4)	0.008	0.026

**P* value for comparison between normal or improving and fluctuating trajectories.

†*P* value for comparison between normal or improving and abnormal or worsening trajectories.

‡*P* value for trend.

