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The relationships between depression, inflammation and self-reported disease activity in IBD and their impact on healthcare usage

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Abstract

Background Depression is common in people living with Inflammatory Bowel Disease (IBD). Depression rates increase with active disease and are linked to poorer clinical outcomes. Previous studies investigating the relationship between contemporaneous IBD disease activity and depression are often poorly controlled, use small samples and/or rely on self-reported measures of disease activity. Depression and self-reported disease activity (SRDA) are linked to increased healthcare usage, however, objective inflammation is rarely statistically controlled. The primary aim was to understand how self-reported disease activity and inflammation are related to depression. Secondary aims included assessing the relative influence of self-reported disease activity, inflammation and depression on healthcare usage.

Methods This was a cross-sectional analysis of baseline data collected as part of a randomised controlled trial (trial registration no: ISRCTN71618461) of a digital treatment for symptom self-management in IBD ($n = 599$). Bivariate associations of demographic and clinical variables with depression were conducted to identify relevant covariates. Multiple linear regressions assessed (i) the relationships between depression (Patient Health Questionnaire-9 (PHQ-9)), SRDA (IBD-Control) and intestinal inflammation (faecal calprotectin (FCP)) and (ii) whether these variables explained variance in healthcare usage and economic indicators.

Results Depression was significantly predicted by SRDA ($\beta = -0.82$, $p < 0.001$) but not FCP, with the model explaining 37% of the variance in depression ($F(2,596) = 175.1$, $p < 0.001$). FCP was only weakly associated with SRDA ($r = -0.16$, $p < 0.001$). Depression was independently associated with visits to primary care ($\beta = 0.19$, $p < 0.001$), IBD secondary care ($\beta = 0.13$, $p < 0.001$), IBD-related A&E attendance ($\beta = 0.10$ $p < 0.05$) and the impact of IBD on productivity ($\beta = 0.24$ $p < 0.001$) in the last 3 months.

Conclusions Depression was related to SRDA but not FCP. Depression was also associated with healthcare usage even when SRDA and inflammation were statistically controlled. Routinely assessing and treating depression in IBD alongside managing inflammation may improve symptoms for patients and reduce healthcare costs.

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Keywords Inflammatory bowel disease, Crohn's disease, Ulcerative Colitis, Depression, Self-reported disease activity, Faecal calprotectin, Healthcare usage

Introduction

Inflammatory Bowel Disease (IBD) refers to a group of autoimmune diseases, including Crohn's Disease and Ulcerative Colitis, where maladaptive immune responses result in gastrointestinal inflammation [1, 2]. IBD manifests as a relapsing and remitting condition, with periods of activity (called 'flares') associated with increased symptom report [3]. Symptoms include gastrointestinal symptoms, such as abdominal pain, urgency, diarrhoea and rectal bleeding, but also include systemic issues including depression and fatigue [4]. Depression is prevalent, affecting 25.2% of IBD patients, rising to 38.9% when disease is active [5]. Symptom burden and psychological stress surrounding the unpredictable and uncontrollable nature of IBD are said to explain high depression rates [6], but it has also been argued that depression is an extraintestinal manifestation of IBD, caused by inflammatory activity [7].

Depression and inflammation may be causally linked in IBD through the gut-brain axis, a bidirectional communication system connecting the gastrointestinal system and central nervous system. Gut-brain mechanisms of action have been reviewed extensively elsewhere [8–10]. In brief, intestinal inflammation in IBD leads to release of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) [11, 12]. Cytokines can lead to neuroinflammation by permeating the blood-brain barrier, activating microglia to initiate an immune response and contributing to inflammatory depression symptoms [7, 10, 11]. Gut microbiota dysbiosis can also occur, impairing the production of short-chain fatty acids and neurotransmitters, which may impact mood [7–9]. Moreover, inflammation in the gut can stimulate vagal afferent nerves and the hypothalamic-pituitary-adrenal (HPA) axis which are also implicated in mood regulation and depression aetiology [7, 10].

Moreover, depression may exacerbate IBD pathophysiology, including permeability, motility, sensitivity and secretion of the intestine, as well as altering microbiota composition and increasing intestinal inflammation [8]. Clinical studies indicate that depression independently predicts poorer IBD outcomes when controlling for baseline disease activity [13]. Treatments for depression have shown reductions in inflammatory markers like faecal calprotectin (FCP) [14], a non-invasive, highly sensitive marker of inflammation frequently used in IBD management [15].

Despite this, there is limited evidence for contemporaneous relationships between depression and disease activity [16]. In a meta-analysis, disease activity and depression were significantly associated; however, included studies are typically poorly controlled, underpowered, and rely on self-reported disease activity (SRDA) measures [17, 18], such as the Harvey Bradshaw Index [19] or the Crohn's Disease Activity Index [20] for Crohn's Disease and the Simple Clinical Colitis Activity Index [21] for Ulcerative Colitis; or the IBD-Control [22, 23] for any IBD subtype. These patient-reported outcome measures (PROMs) are increasingly being used clinically to assess disease activity, support patient-centred care, and inform treatment decisions [24, 25].

Despite these advantages, PROMs often correlate poorly with objective disease indicators of inflammation, such as endoscopic activity, FCP and C-Reactive protein (CRP) [26–29]. Instead, a systematic review has demonstrated that depression, anxiety, perceived stress and pain catastrophising are strongly and significantly associated with self-reported symptoms [6], even when objective disease activity is controlled [30–32]. This may be due to psychological factors altering sensory processing, attention, or pain perception [30, 31]. Depression may increase symptom perception and the reporting of symptoms through psychological, physiological, and neurobiological mechanisms [33]. Depression is related to somatosensory amplification, whereby heightened sensitivity to bodily sensations lowers detection and pain thresholds for sensations [34]. Depression may also cause activation of the HPA axis which elicits physiological sensations as well as heightening symptom awareness [35]. Moreover, negative cognitive interpretations common in depression, such as catastrophizing and selective attention to distressing stimuli, can lead to the magnification of physical sensations [36]. Additionally, neurobiological overlap between brain regions involved in pain perception and mood regulation, such as the anterior cingulate cortex, may exacerbate physical symptom perception [33, 37, 38]. As such, if clinicians rely heavily on PROMs, treatment decision making may be problematic if patients receive biomedical treatments when their self-reported symptoms are driven in part by emotional and psychological factors. Behavioural interventions, either targeting distress, self-management and/or symptoms in remission may be more appropriate [14, 39–43].

Depression is also routinely associated with negative health outcomes, healthcare costs, healthcare usage and absenteeism at work [44–47]. One prospective study found that IBD patients with a psychiatric diagnosis had twice the odds of high IBD-related expenditure, even when disease severity and complexity were controlled

[45]. A meta-analysis of prospective studies pooled data from 9192 IBD patients and showed that depression increased the risk of hospitalisation, emergency department attendance and medical escalation [46]. However, studies rarely collect objective inflammation, so it is unclear whether the relationship between depression and negative physical health outcomes is explained by greater levels of objective inflammation or SRDA, or if depression is an independent risk factor for negative health outcomes. Understanding these relationships will enable clinicians to use appropriate, evidence-based gut-brain axis treatments.

Rationale for the study

The gut-brain axis is highly relevant in the understanding of IBD prognosis and symptomatology. Depression is common in people living with IBD, yet existing research, focussed on the contemporaneous relationships between objective inflammation, depression and SRDA, are limited by inadequately controlled analyses [48]. The primary marker in this study was FCP, chosen for its specificity with IBD disease activity (compared with CRP) as well as its convenience, low cost and non-invasiveness (compared with endoscopy) [49] and strong correlation with endoscopic disease activity [50]. Moreover, it is a good potential candidate to explore associations with depression as IBD inflammation is related to systemic immune activation, which has been shown to influence neurological and psychological processes, contributing to depressive symptoms. Thus, FCP serves as an objective measure of mucosal inflammation while enabling investigation into relationships between inflammation and depression. Despite associations with endoscopy, FCP is limited in detecting small bowel inflammation, common in Crohn's Disease [51–53]. Therefore, to address previous issues with inadequately controlled analyses, this study included disease subtype as an effect modifier of FCP, as well as other relevant confounders. When assessing contributors to healthcare usage, inflammation is rarely collected. This prevents the assessment of the relative salience of SRDA and objective inflammation in treatment and healthcare usage.

Research aims

1. Explore the relationships between depression, objective inflammation and SRDA in people living with IBD.
    a. Assess how much variance in depression is explained by SRDA and objective inflammation, when controlling for relevant disease and demographic factors.
2. Explore whether depression, SRDA and objective inflammation predict health service use and their relative influence.

Methods

This study is a cross-sectional analysis of baseline data collected within a UK National Institute of Health Research (NIHR; RP-PG-0216-20001) two-arm randomised controlled trial (RCT) trialling a supported online self-management intervention for symptoms of fatigue, pain and urgency/incontinence in people with inflammatory bowel disease: the IBD-BOOST trial. The full methodology of the RCT can be found in the study protocol [43] (Clinical trial number: ISRCTN71618461, https://www.isrctn.com/; Registration date: 09/09/2019). This study received ethical approval from the NRES Research Ethics Committee & Health Research Authority (London - Surrey Research Ethics Committee/ 19/LO/0750). It was conducted in accordance with the principles of the Declaration of Helsinki. Online informed consent was obtained from all participants.

Participants and procedure

In brief, participants were initially recruited for the RCT from the IBD-BOOST survey, a UK national survey [54]. These participants were recruited from IBD clinic hospital sites, the UK National IBD BioResource, the charity Crohn's & Colitis UK or via social media. Participants were sent the survey in the post or by an email containing a link. If participants consented to be contacted for follow-up research, they were screened for eligibility prior to entering the BOOST trial. They received information sheets, and completed online consent and trial baseline questionnaires before they were randomised.

Eligibility criteria

Eligibility criteria for participants were: being 18 years or older; living in England, Scotland, or Wales, having a diagnosis of IBD; having access to a computer or mobile device; and having self-scored one or more symptoms of fatigue, pain, or urgency/incontinence as having an impact on their quality of life of 5 or more on a 0–10 scale when completing the IBD-BOOST survey.

Participants were excluded if they were unable to give informed consent, had insufficient command of the English language for study procedures or demonstrated any 'red flags' (potentially serious issues, for example, new bleeding, rapid weight loss or vomiting that had not been previously reported to a healthcare practitioner). Additionally, for the purpose of this cross-sectional analysis, participants were excluded if they did not provide an FCP sample as part of the baseline assessment.

Data

This study used data collected at baseline for an RCT, in accordance with GDPR guidelines and handled as per the Data Protection Act (2018). The data collection process for this baseline assessment included a questionnaire assessment (online or paper), as well as a postal stool sample sent to a central laboratory for measurement of FCP.

Measures

A full list of the measures collected as part of the BOOST trial are reported elsewhere [43]. Listed below are measures that were used in this analysis collected as part of the trial baseline assessment:

- Self-reported disease activity (SRDA) of IBD disease was measured with the IBD-Control, an 8-item questionnaire [22] designed to measure disease control from the patient's perspective over the last two weeks. Higher scores indicate better control and lower disease activity [22] (Cronbach $\alpha = 0.78$).
- Objective disease activity was assessed with faecal calprotectin (FCP) [15] from stool samples. Calprotectin is a protein that can bind to calcium and zinc, typically presented in neutrophil cells [55]. FCP calprotectin is highly sensitive marker of inflammation in the gastrointestinal tract and a key indicator for an IBD diagnosis. Furthermore, it is used to monitor disease activity, guide treatment decisions, and predict relapse in IBD [15]. FCP was the primary clinical biomarker of disease severity used in the current study. It was analysed using the Diasorin Liaison XL Calprotectin assay, an in vitro diagnostic chemiluminescent immunoassay (CLIA), at King's College Hospital, London.
- Depressive symptoms was assessed using the nine-item Patient Health Questionnaire– 9 (PHQ-9) [56]. Each item asks about the frequency of a depression symptom over the last two weeks and is responded to on a 4-point Likert Scale (0–3). The PHQ-9 has a scale range of 0–27, with higher scores indicating increased depressive symptoms [56]. Scores of 0–4, 5–9, 10–14, 15–29, and ≥ 20 on the PHQ-9 indicate levels of no, mild, moderate, moderately severe, and severe depressive symptoms respectively [56] (Cronbach $\alpha = 0.87$).
- Data on health service use and employment were measured using a study-specific IBD Resource Use questionnaire. This instrument was developed within the BOOST programme, and covers primary and secondary care, investigations, medications, hospitalisations, employment and out-of-pocket expenses over the last 3 months. The questionnaire was found to be reliable and its online functionality was tested in a pilot study [57]. For the purposes of this analysis, primary care data (GP, and GP nurse visits) secondary care data (gastroenterologist, colorectal surgeon, pharmacist, IBD nurse and IBD advice visits), Accident and Emergency (A&E) visits, and hospitalisations were extracted. Composite scores for primary care, secondary care and total visits were calculated by summing the relevant visits to specific services. The economic indicators asked participants over the last 3 months (1) the number of sick leave days due to IBD and (2) the impact of IBD on productivity (0 = no effect on work, 10 = completely prevented me from working).

Sociodemographic variables (age, gender, ethnicity, education level, relationship status, employment) and additional clinical information (IBD subtype, body mass index (BMI)) were linked across from the IBD-BOOST Survey.

Statistical analysis

Data were analysed with Stata (version 18, Windows), with questionnaires scored in accordance with original authors' guidelines. Cronbach's alpha was used to assess internal consistency and reliability. Descriptive statistics were computed for all variables using means and standard deviations and/or medians and ranges/interquartile ranges for continuous data, and frequencies and percentages for categorical data. Firstly, bivariate associations assessed relationships between depression and demographics, clinical covariates, visits to specific health services, composite health service visits (primary care, secondary care, total visits) and economic indicators (number of sick leave days, impact of IBD on productivity), as well as association between inflammation (FCP) and SRDA (IBD-Control). These associations were examined using independent samples t-tests for binary variables, Pearson's for normally distributed continuous data, and Spearman's rank for non-normal continuous data. Categorical variables were dummy coded and analysed using multiple linear regression models. For the associations between FCP and depression, sub-group analyses were run, splitting the sample firstly, by disease subtype (UC/other and CD) and secondly, by biochemical activity status (remission, FCP < 200 μg/g and flare, FCP ≥ 200 μg/g).

Next, a series of regression models were run. Firstly (for Aim 1), both objective (FCP) and subjective (IBD-Control) measures of IBD activity were inputted as linear predictors in a multiple linear regression model with depression as the outcome variable, whilst controlling for relevant sociodemographic and clinical factors. FCP has limited ability to detect small bowel inflammation, which is more common in Crohn's Disease, therefore an interaction term of FCP and disease subtype (Crohn's

Disease coded as 1, Ulcerative Colitis coded as 0) was included. Variables were inputted in two steps: firstly, objective and subjective measures of IBD activity; next, key variables with significant associations with depression identified from the bivariate analyses and the FCP-subtype interaction term were entered. Secondly (for Aim 1), a multiple linear regression to explain variance in SRDA (IBD-Control) was conducted including FCP, disease subtype and the subtype-FCP interaction term as explanatory variables. Next for the analysis of health service and economic indicators (Aim 2), depression, FCP and SRDA were all inputted into multiple linear regressions to determine the variance explained for each outcome (primary care visits, secondary care visits, A&E visits, days taken off work due to IBD and impact of IBD on productivity at work). Outcomes were operationalised to be linear, instead of categorical, to increase statistical power [58], and to emulate previous research [47]. Composite scores were calculated for primary care visits (summing GP and GP nurse visits), secondary care visits (summing gastroenterologist, colorectal surgeon, pharmacist, IBD nurse and IBD advice visits) and total visits (summing primary and secondary care visits). A sensitivity analysis was conducted, additionally including the FCP-subtype interaction term. Standardised beta values, 95% confidence intervals and *p* values were reported in linear regressions. Significance level for all analyses was set to $p < 0.05$. In our sample, the minimum detectable effect (80% power, 5% significance level) was a $r = 0.12$.

Results

Descriptives

In total, 780 participants consented to participate in the trial and completed baseline surveys. A total of 181 participants did not have a value for FCP either because they had a stoma ($n = 48$) or because they did not return their sample ($n = 133$). This resulted in a sample of 599 participants who were mostly (66.44%) female, the majority had Crohn's Disease (56.43%), and the majority were White (95.49%) with a mean age of 50.17 (SD = 14.17). FCP tests were performed a median of 30 days (IQR: 21, 44) after completion of the questionnaire. FCP was positively skewed, with a median value of 48 (IQR: 16–141.5). Using the standard cut-off of 200 µg/g, 19.03% of the sample were in biochemical flare. The majority (75.63%) of participants had clinically significant levels of depression (mild, moderate or severe), with a mean score of 9.01 (SD = 5.72). Based on IBD-Control cut-offs (≤ 13 indicate flare [22]), 76.29% self-reported that they were in flare. Full sample characteristics are reported in Table 1.

Depression and relationships with objective inflammation and SRDA

Table 1 shows the associations between depression and key sociodemographic variables, and other variables identified to be influential with depression and inflammation. Depression was significantly associated with employment status ($F(5,593) = 9.40$, $p < 0.001$), with retirees demonstrating the lowest level of depression and those unemployed demonstrating the highest level of depression. Additionally, depression was associated with BMI ($F(2,580) = 9.41$, $p < 0.001$), with overweight BMI positively associated with depression. Depression was negatively associated with age (r=-0.194, $p < 0.001$). Depression was associated with SRDA, with higher depression related to more severe SRDA (r=-0.605, $p < 0.001$, see Supplementary Material 1 for scatter plot). There was a non-significant relationship with FCP ($r = 0.038$, $p = 0.252$, See Supplementary Material 2 for scatter plot). Two sub-group analyses were performed. Depression and FCP associations remained nonsignificant when the sample was split by disease subtype (UC: $r = 0.091$, $p = 0.144$; CD: r=-0.028, $p = 0.603$), and by biochemical remission/flare status (remission, FCP < 200: r=-0.002, $p = 0.974$; flare, FCP ≥ 200: $r = 0.032$, $p = 0.738$).

Table 2 shows the results of the multivariate analyses. The model including SRDA (IBD-Control) and objective inflammation (FCP) (Step 1) explained 36.6% of the variance in depression ($F(2,596) = 175.1$, $p < 0.001$). SRDA was a significant predictor (β=-0.611, $p < 0.001$, 95%CI: −0.676, −0.546), but FCP was non-significant (β=-0.040, $p = 0.227$, 95%CI: −0.105, 0.025). When relevant demographic variables (age, gender, employment status), BMI, disease subtype and the subtype-FCP interaction term were added into the model (Step 2), the model explained 40.68% of the variance ($F(12,570) = 34.26$, $p < 0.001$). SRDA remained a significant predictor of depression (β=-0.573, $p < 0.001$, 95%CI: −0.639, −0.507) and FCP remained nonsignificant (β=-0.076, $p = 0.102$, 95%CI: −0.166, 0.015). Age additionally negatively predicted depression (β=-0.151, $p = 0.001$, 95%CI: −0.238, −0.063). Being unemployed significantly predicted depression (β = 0.125, $p < 0.001$, 95%CI: 0.060, 0.189), as did being overweight (β = 0.213, $p = 0.002$, 95%CI: 0.079, 0.346). Neither disease subtype nor the subtype-FCP interaction term were significant.

The relationship between objective inflammation and SRDA

SRDA, measured by the IBD-Control, showed a significant, weak, negative correlation with intestinal inflammation as measured by FCP (r=-0.165, $p < 0.001$, 95%CI: −0.240, −0.089; see Supplementary Material 3 for scatterplot). A multivariate regression model of FCP, disease subtype and the subtype-FCP interaction term

Table 1 Demographic and clinical characteristics of the sample and their associations with depression ($n = 599$)

Variable	*N* (%) / M(SD)	Depression M(SD)	Statistical test	β	95%CI	*P* value
Demographic variables						
Gender			F(2,596) = 0.44			0.641
Female	398 (66.44%)	9.08 (5.67)	*t* = 0.88	0.296	−0.363, 0.954	0.378
Male	199 (33.22%)	8.90 (5.85)	*t* = 0.84	0.280	−0.379, 0.939	0.404
Other / Prefer not to say	2 (0.33%)	5.50 (4.95)	-	-		
Ethnicity			F(5,593) = 1.96			0.083
Arab	2 (0.33%)	19.00 (5.66)	*t* = 2.09	0.103	0.306, 0.201	0.038
Asian or Asian British	14 (2.34%)	6.86 (5.50)	*t*=-0.59	-0.050	−0.218, 0.118	0.556
Black or Black British	1 (0.17%)	6.00	*t*=-0.43	-0.020	−0.109, 0.070	0.666
Mixed/multiple ethnic groups	6 (1.00%)	6.33 (3.72)	*t*=-0.66	-0.042	−0.168, 0.084	0.512
White	572 (95.49%)	9.06 (5.73)	*t* = 0.11	0.011	−0.379, 0.215	0.913
Other/unknown	4 (0.67%)	8.75 (4.03)	-			
Age	35.55 (12.67)		*r* =-0.194		−0.270, −0.116	< 0.001
Employment			F(5,593) = 9.40			< 0.001
Employed	336 (56.09%)	8.84 (5.28)	*t*=-2.42	-0.169	−0.306, −0.032	0.016
Retired	147 (24.54%)	7.50 (5.41)	*t*=-3.75	-0.247	−0.377, −0.118	< 0.001
Student	13 (2.17%)	10.54 (5.78)	*t*=-0.14	-0.006	−0.092, 0.080	0.886
Unemployed due to illness disability	47 (7.85%)	12.43 (6.59)	*t* = 1.49	0.077	−0.025, 0.179	0.138
Other (e.g., homemaker)	56 (9.35%)	10.79 (6.70)	-			
Education			F(2,594) = 1.87			0.156
Further or higher	457 (76.88%)		*t*=-1.77	-0.284	−0.600, 0.031	0.078
School	131 (21.94%)		*t*=-1.51	-0.242	−0.558, 0.073	0.131
No formal education	7 (1.17%)		-	-		
Relationship status			F(5,590) = 1.16			0.329
Married or civil partnership	338 (56.71%)		*t*=-1.79	-0.172	−0.360, 0.017	0.074
Cohabiting	94 (15.77%)		*t*=-1.14	-0.088	−0.240, 0.064	0.257
Divorced or separated	40 (6.71%)		*t*=-1.62	-0.099	−0.219, 0.021	0.105
Widowed	15 (2.52%)		*t*=-1.48	-0.074	−0.172, 0.024	0.140
Single	80 (13.42%)		*t*=-0.79	-0.058	−0.204, 0.087	0.431
Not living with partner	29 (4.87%)		-			
Clinical variables						
Diagnosis			*t* = 1.928			0.054
Crohn's Disease	338 (56.43%)	9.41 (5.83)				
Ulcerative Colitis and other diagnoses	261 (43.57%)	8.50 (5.55)				
Body Mass Index (BMI)			F(2,580) = 9.41			< 0.001
Underweight	22 (3.77%)	10.14 (6.49)	*t* = 1.92	0.080	−0.002, 0.163	0.055
Overweight	342 (58.56%)	9.78 (5.85)	*t* = 4.23	0.178	0.095, 0.260	< 0.001
Healthy weight	219 (37.56%)	7.72 (5.15)	-			
Faecal calprotectin (median, IQR)	48, 16–141.5		*r* = 0.024		−0.055, 0.103	0.561
Faecal calprotectin categories			*t* = -1.107			0.269
Biochemical remission (< 200 µg/g)	485 (80.97%)	8.88 (6.00)				
Biochemical flare (≥ 200 µg/g)	114 (19.03%)	9.54 (6.22)				
Self-report disease activity (IBD-Control)	9.00 (4.31)		*r* = -0.605		−0.654, −0.552	< 0.001
Self-report disease activity categories			*t* = -11.57			< 0.001
Inactive/Good control (IBD-Control > 13)	142 (23.71%)	4.62 (3.70)				
Active/Poor control (IBD-Control ≤ 13)	457 (76.29%)	10.37 (5.55)				
Economic indicators						
Number of sick leave days (median, IQR)	0 (0–1)		*r* = 0.378		0.286, 0.471	< 0.001
IBD impact on productivity	3.26 (2.34)		*r* = 0.460		0.373, 0.549	< 0.001
Health service use						
Gastroenterologist			*t* = -2.617			0.009
Yes	239 (39.90%)	9.76 (0.39)				

Table 1 (continued)

Variable	*N* (%) / M(SD)	Depression M(SD)	Statistical test	β	95%CI	*P* value
No	360 (60.10%)	8.51 (0.29)				
Colorectal Surgeon			*t* = -2.991			0.003
Yes	48 (8.04%)	11.38 (0.91)				
No	549 (91.96%)	8.81 (0.24)				
IBD nurse			*t* = -1.940			0.053
Yes	278 (46.41%)	9.50 (0.37)				
No	321 (53.59%)	8.59 (0.30)				
IBD advice helpline			*t* = -2.694			0.007
Yes	141 (23.58%)	10.15 (0.54)				
No	457 (76.42%)	8.67 (0.26)				
A&E attendance			*t* = -2.680			0.008
Yes	27 (4.52%)	11.89 (0.24)				
No	571 (95.48%)	8.88 (1.33)				
GP			*t* = -4.707			< 0.001
Yes	175 (29.26%)	10.70 (0.47)				
No	423 (70.74%)	8.32 (0.26)				
GP Nurse			*t* = -2.643			0.008
Yes	103 (17.22%)	10.37 (0.58)				
No	495 (82.78%)	8.74 (0.25)				
Pharmacist			*t* = -3.540			< 0.001
Yes	108 (18.09%)	10.76 (0.54)				
No	489 (81.91%)	8.63 (0.26)				
Hospitalised			*t* = -1.672			0.095
Yes	17 (2.84%)	11.29 (2.06)				
No	582 (97.16%)	8.94 (0.23)				
Sick leave due to IBD*			*t* = -6.623			< 0.001
Yes	107 (32.62%)	11.38 (0.49)				
No	221 (67.38%)	7.54 (0.33)				
Total visits (median, IQR)	2 (0–5)		*r* = 0.260		0.181, 0.331	< 0.001
Primary care visits (median, IQR)	0 (0–1)		*r* = 0.205		0.126, 0.283	< 0.001
Secondary care visits (median, IQR)	2 (0–4)		*r* = 0.207		0.131, 284	< 0.001
Times hospitalised (median, range)	0 (0–3)		*r* = 0.034		− 0.057, 0.124	0.416
Days in hospital (median, range)	0 (0–38)		*r* = 0.036		− 0.058, 0.126	0.414
Depression (PHQ-9)	9.01 (5.72)		-			-
Depression categories			-			-
None (PHQ-9 < 5)	146 (24.37%)	-				
Mild (5 ≤ PHQ-9 ≤ 9)	206 (34.39%)	-				
Moderate-Severe (PHQ-9 > 9)	247 (41.24%)	-				

* denotes *p* value ≤ 0.05; ** denotes *p* value ≤ 0.01; *** denotes *p* value ≤ 0.001

A&E = accident and emergency, IBD = inflammatory bowel disease, IQR = interquartile range, PHQ-9 = Patient Health Questionnaire-9

significantly predicted SRDA (F(3,595) = 6.85) explaining 2.85% of the variance. Only FCP was a significant predictor of SRDA (β=-0.204, $p = 0.001$, 95%CI: − 0.319, − 0.088). The subtype-FCP interaction term was not a significant predictor, indicating the relationship between FCP and SRDA did not significantly differ between Crohn's Disease and Ulcerative Colitis (β=-0.112, $p = 0.355$, 95%CI: − 0.125, 0.348).

Health service and economic indicators and relationships with depression, objective inflammation and SRDA

Test statistics of bivariate analyses (Pearson's r, Spearman's rho, t values) are summarised in Table 1. Depression was significantly associated with primary care visits (composite variable as well as visits to GP, GP nurse and pharmacist), secondary care visits (composite variable as well as visits to gastroenterologist, colorectal surgeon, IBD nurse, IBD advice), A&E attendance, sick leave days and impact of IBD on productivity, but not with times hospitalised or with days in hospital.

Table 2 Multivariate regression analysis of predictors for depression

	Step 1			Step 2		
	β	***p***	**95%CI**	**β**	***p***	**95%CI**
SRDA (IBD-Control)	-0.611	< 0.001	−0.676, −0.546	-0.573	< 0.001	−0.639, −0.507
FCP	-0.040	0.227	−0.105, 0.025	-0.076	0.102	−0.166, 0.015
Age				-0.150	0.001	−0.238, −0.063
Gender (reference = female)				0.063	0.056	−0.002, 0.127
Employment (reference = employed)						
Retired				0.012	0.794	−0.075, 0.098
Student				0.037	0.262	−0.028, 0.101
Unemployed				0.125	< 0.001	0.060, 0.190
Other				0.064	0.057	−0.002, 0.131
BMI (reference = healthy weight)						
Underweight				0.001	0.970	−0.064, 0.067
Overweight				0.105	0.002	0.039, 0.171
Disease subtype (reference = UC)				-0.001	0.967	−0.068, 0.071
Disease subtype interaction term				0.053	0.276	−0.042, 0.146

Note. BMI = body mass index, FCP = faecal calprotectin, IBD = inflammatory bowel disease, SRDA = self-reported disease activity, UC = Ulcerative Colitis

Table 3 Results of regression models for health service ($n = 599$), sick leave days ($n = 327$) and impact of IBD on productivity at work ($n = 336$) with depression, inflammation and self-reported disease activity entered as predictor variables

	Adjusted *r* Square	**Model significance**	**Depression (PHQ-9) β (95%CI)**	**Faecal calprotectin β (95%CI)**	**SRDA (IBD-Control) β (95%CI)**
Primary care visits	0.064***	F(3,595) = 14.61	0.192 (0.094, 0.290)***	0.022 (-0.057,0.101)	−0.093 (-0.192, 0.006)
Secondary care visits	0.123***	F(3,595) = 29.07	0.130 (0.035, 0.224)**	0.169 (0.092, 0.246)***	−0.197 (-0.293, −0.101)***
A&E visits	0.019**	F(3,595) = 4.92	0.101 (0.001,0.201)*	0.056 (-0.025, 0.137)	−0.053 (-0.155, 0.048)
Total visits	0.140***	F(3,595) = 33.42	0.180 (0.086, 0.274)***	0.144 (0.069, 0.220)***	−0.193 (-0.289, −0.098)***
Sick leave days [Ψ]	0.026**	F(3,323) = 3.95	0.058 (-0.086, 0.203)	0.023 (-0.083, 0.129)	−0.149 (-0.286, −0.012)*
Impact on productivity [Ψ]	0.317***	F(3,332) = 52.77	0.236 (0.118, 0.354)***	0.038 (-0.049, 0.126)	−0.413 (-0.526, −0.300)***

Note. *** indicates $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

[Ψ] analysis only conducted in proportion of sample in employment (i.e., not retired or not working for reasons unrelated to IBD)

A&E = accident and emergency, IBD = inflammatory bowel disease, PHQ-9 = Patient Health Questionnaire-9, SRDA = self-reported disease activity

In the multivariate analyses, multiple linear regressions including depression, FCP and SRDA, significantly predicted all health service use outcomes (See Table 3). Depression was the only significant predictor in the models for primary care visits and accident and emergency visits, with models explaining 6.4% and 1.9%, respectively. The model explained 12.3% of the variance for secondary care visits and 14.0% for total visits, with depression, FCP and SRDA all emerging as significant predictors. Although depression was significantly associated with days taken off work in the bivariate analysis ($r = 0.378$, $p < 0.001$), when other factors were controlled, depression was rendered non-significant and SRDA was the only significant predictor of sick leave days (β=-0.149, 95%CI: −0.286, −0.012, $p = 0.033$), with the model explaining 2.6% of the variance. The model for impact of IBD on work productivity explained 31.7% of the variance, with depression and SRDA emerging as significant predictors. Sensitivity analyses for each health service/economic outcome were conducted additionally including disease subtype and the subtype-FCP interaction term. The size and significance of the betas did not change substantially from the original analysis. Crohn's Disease was predictive of primary care visits and total visits. The subtype-FCP interaction term was significant for primary care visits, secondary care visits and total visits, indicating a more pronounced effect of FCP on usage in Ulcerative Colitis patients rather than Crohn's Disease patients (See Supplementary Material 4).

Discussion

This analysis included 599 IBD patients, finding that 76% had at least mild depression. Notably, 81% were in biochemical remission (FCP < 200 µg/g), but 76% indicated poor self-reported control of IBD (IBD-Control ≤ 13). Higher self-reported depression was associated with greater SRDA (lower IBD-Control). Sociodemographic and clinical characteristics associated with depression included older age, being unemployed and being overweight based on BMI. Depression was not significantly associated with inflammation levels, as measured by FCP. A regression model including both objective inflammation and IBD disease control explained 36.8% of the variance in depression, however only SRDA was a significant

predictor, which remained significant after relevant variables were controlled. Although SRDA was significantly negatively associated with inflammation, the correlation was weak. Depression was an independent predictor of visits to primary care, secondary care, and A&E, as well as impact of IBD on productivity.

Contrary to our prediction, FCP was not related to depression. However, our findings corroborated previous research linking anxiety and depression with gastrointestinal symptoms, but not with inflammation [6]. This contradicts the conceptual framework of the gut-brain axis, which proposes depression as having pro-inflammatory consequences and inflammatory disease activity impacting psychological processes [7, 8, 11, 14, 46]. Methodological issues may explain our null findings. For instance, most of the sample were in biochemical remission, with a median lag of 30 days between sample collection and questionnaire completion. However, our sub-group analysis of those in biochemical flare was also yielded nonsignificant results. This accords with other studies [26, 59–62], including those reporting a broader range of inflammation (e.g., FCP median = 132.7, IQR: 47, 507 [6]) that also found no contemporaneous associations between depression and FCP. Studies that do find significant associations between FCP are often limited by small sample sizes, inadequate inclusion of control variables (for instance, subtype, demographics or self-reported disease activity) and/or failure to adjust for multiple statistical comparisons [63–66]. One study found a positive weak association ($r = 0.142$, $p = 0.04$) between FCP and depression in 193 CD patients but not in UC [66]. However, this study did not control for clinical disease activity, and it is unclear why there was no relationship with depression in the UC sub-group [66], where FCP should have greater salience as a biomarker [51–53]. The null findings, and some of the inconsistencies observed in previous research, may represent the complexity and individual variability within the gut-brain axis, and the mechanisms through which peripheral inflammation drives central inflammation and depression [67]. Peripheral inflammation does not cause depression in all individuals [68], and factors such as the blood brain barrier [68] or microbiome composition and function [69–71] have been shown to moderate the relationship between psychological factors and inflammation. Conversely, associations have been found with depression and other measures of inflammation in IBD, such as mucosal inflammation as measured by endoscopy, proinflammatory cytokines, monocyte and macrophage concentrations [72–76]. Future studies would also benefit from using multiple inflammatory markers to clarify these relationships within the gut-brain axis, as well as longitudinal study designs so causality can be inferred.

Moreover, given the heterogeneity of IBD, it may be that depression has different gut-brain implications between individuals, based on environmental, genetic, pharmacological or behavioural differences [77]. Therefore, the eligibility criterion of those with symptom burden with a greater impact on quality of life may have led to overrepresentation of people whose depression and related psychological factors have a larger influence on symptom perception. This may preclude the inclusion of individuals with greater vulnerability to bidirectional neuroinflammatory pathways where depression and gut inflammation have stronger associations, irrespective of symptoms. Future research should attempt to use representative samples and stratify people living with IBD into different 'gut-brain' profiles [78] to assess individual differences in gut-brain mechanisms.

Furthermore, the recruitment strategy selecting patients where symptoms have high impact on quality of life may have influenced our findings that SRDA weakly correlated with objective inflammatory disease activity, even when differential relationships of inflammation and SRDA between disease subtypes were investigated. However, this finding is strongly corroborated by other studies, where self-reported measures of symptoms are more strongly associated with psychological factors, including depression [6], than objective inflammatory disease markers [26–29]. Many neurobiological and cognitive processes may underly the relationship between depression and symptoms [79]. Psychological factors may perpetuate or exacerbate symptom perception and reporting, potentially contributing to the high symptom burden [80], despite low levels of inflammation. For instance, in IBD, illness perceptions, stress, anxiety and depression are routinely associated with IBD symptom reports, disability and health-related quality of life [30, 81–85]. Specific cognitive biases that may contribute to symptoms in the absence of inflammation include (i) somatic hypervigilance [86, 87], whereby excessive focus on bodily sensations predisposes patients to misinterpret sensations as meaningful symptoms [86, 87]; (ii) confirmation bias [88], where prior experiences prime patients to attribute mild symptoms to be more severe, overlooking alternative explanations; and (iii) catastrophising, a cognitive distortion where patients anticipate the worst outcome from their symptoms which can increase symptom perception [30, 89].

Relatedly, both depression and SRDA independently predicted most healthcare usage and economic indicators, even when objective inflammation was controlled. PROMs are increasingly used in IBD clinical management and as efficacy measures in IBD clinical trials [90]. This has implications for clinical practice as although severe symptoms warrant medical attention, biomedical treatments may not be wholly appropriate if symptoms

are weakly related to inflammation. This is supported by qualitative research findings that gastroenterologists prefer to focus on objective disease activity and struggle to address functional symptoms in the absence of inflammation and clear underlying pathology [91]. Moreover, depression as an independent predictor, may directly and indirectly affect healthcare usage; indirectly by influencing symptoms such as pain or fatigue [79, 92] and exacerbating severity [30] and directly through increase help-seeking behaviour due to feeling unable to cope with disease or treatment [93]. Given that the gut-brain axis is bidirectional, inflammation may increase both symptoms and depression, which would be related to both disease severity and healthcare usage [13]. However, in this study inflammation, as measured by FCP, was not associated with depression, and only showed a small effect [94] with secondary care visits, but was nonsignificant with other indicators of healthcare usage. Such relationships may emerge if inflammation, disease activity and depression in longitudinal investigations or if other inflammatory markers were measured [72], particularly due to the limitation of FCP in detecting small bowel inflammation. Regardless, our findings emphasise the need for a holistic approach to healthcare that considers both mental and physical health factors to optimise resource allocation within IBD treatment [95]. Given that substantial variance in healthcare usage was explained by psychological factors, treating depression may help to reduce costs for health services [96].

Strengths and limitations

This study used a large sample size and objective measures of inflammation to assess the relationships between depression and disease activity in people living with IBD. Analyses were adequately controlled, and the relationships with health service use and economic indicators were additionally explored.

This study was limited in several ways. (1) It used cross-sectional data, so causality cannot be determined. Previous evidence suggests bidirectionality between depression and negative health outcomes (e.g., hospitalisations) [46], so the associations in the current study may additionally reflect these relationships. The PHQ-9 and IBD-Control ask about symptoms over the last two weeks, whereas, the Resource Use questionnaire collects data from previous 3 months. However, given that our findings do not contradict existing literature [44–47], these approximations appear to have been adequate. (2) Study participants had high rates of clinically relevant depression (75.6%), poor IBD control (76.3%) and biochemical remission (80.1%). Therefore, relationships between inflammation, depression and disease activity may be different when participants with higher levels of inflammation and/or better IBD control are investigated. (3) Relatedly, although the study originally recruited from NHS hospitals, due to the COVID-19 pandemic, recruitment shifted online to access community samples. As such, participants self-selected, possibly leading to unrepresentative samples, thus limiting the generalisability of the findings. (4) Despite the IBD resource use questionnaire demonstrating good test re-test reliability [57], it has yet to be fully validated and healthcare usage data may be susceptible to recall bias that would impact findings. (5) Although medications may impact pain perception independent of inflammation (for instance, antidepressants can reduce pain [97, 98]; steroids can contribute to mood alterations, fatigue and gastrointestinal discomfort [99]), it was beyond the scope of the study to investigate medications as confounding variables.

Conclusions

This study demonstrated that higher depression was associated with greater SRDA, but not with intestinal inflammation. Moreover, SRDA only weakly correlated with FCP. Depression and SRDA appear to independently explain variance in healthcare usage, emphasising the need for holistic approaches to IBD treatment that address both mental and physical health. Future research should utilise longitudinal data to understand causal relationships between these variables and their impact on healthcare usage and investigate relationships between depression and other inflammatory biomarkers.

Abbreviations

A&E	Accident and emergency
BMI	Body mass index
CD	Crohn's disease
CI	Confidence interval
CLIA	ChemiLuminescent immunoassay
CRP	C-Reactive protein
FCP	Faecal calprotectin
GP	General practitioner
HPA	Hypothalamic-pituitary-adrenal
IBD	Inflammatory bowel disease
NHS	National health service
NIHR	National institute of health research
PHQ-9	Patient health questionnaire-9
PROMs	Patient-reported outcome measures
RCT	Randomised controlled trial
SRDA	Self-reported disease activity
UC	Ulcerative Colitis

Supplementary Information

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Supplementary Material 1

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Author contributions
NS: conceptualisation, data analysis, writing (drafting, review, editing). VW: data management, writing (review, editing). CN: project principal investigator, writing (review, editing). JH: data analysis, writing (review, editing). VM: conceptualisation, writing (review, editing). RMM: project principal investigator, conceptualisation, writing (review, editing).

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Data availability
The data that support the findings of this study are available from the corresponding author on reasonable request subject to appropriate data sharing permissions.

Declarations

Ethics approval and consent to participate
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Favourable ethical opinion was granted for the trial and the risk assessment protocol by a Research Ethics Committee (London - Surrey Research Ethics Committee/ 19/LO/0750).

Consent for publication
All participants provided written informed consent for participation and publication before their commencement in the study.

Competing interests
CN has received speaker fees from Janssen, WebMD, Medscape, Merck Pharmaceutical; Tillotts Pharms UK. Pfizer advisory board. RMM is a beneficiary of a licence agreement signed between King's College London and Mahana Therapeutics for a digital cognitive behavioural therapy for an irritable bowel syndrome product. RMM receives personal fees from Mahana Therapeutics for scientific advisory work and from other universities and hospital trusts for cognitive behavioural therapy training in irritable bowel syndrome. Co-authors declare no further competing interests.

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