Journal of Psychosomatic Research 177 (2024) 111592

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Inflammation as an aetiological trigger for depressive symptoms in a prospective cohort of patients with inflammatory bowel disease

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ARTICLE INFO

Keywords:
Depression
IBD
Crohn's disease
Ulcerative colitis
Inflammation
CRP

ABSTRACT

Objective: Inflammatory bowel disease (IBD) is often comorbid with mood disorders and depressive symptoms. The aetiology of depressive symptoms in IBD, however, remains largely unknown. Consistent with the inflammatory hypothesis of depression, the aim of this study was to explore the prospective associations between inflammatory biomarkers and depressive symptoms in a cohort of IBD patients with and without a previous clinical diagnosis of mood disorder.

Method: IBD clinical activity was determined using the Harvey-Bradshaw Index for CD and the Partial Mayo score for UC; serum C-reactive protein (CRP) and faecal calprotectin (fCAL) were used as biomarkers of systemic and intestinal inflammation, respectively. Participants were administered the Hospital Anxiety and Depression Scale-depression (HADS-D) at baseline and 1-year follow-up.

Results: Eighty-four participants (50 ± 16 years; 75% UC and 25% CD) were included in the main analyses. Longitudinal moderated regression models showed that baseline CRP significantly predicted follow-up HADS-D scores among individuals with a previous mood disorder diagnosis ($\beta = 0.843$, $p < .001$), but not among individuals without ($\beta = -0.013$, $p = .896$), after controlling for baseline HADS-D scores, body mass index, IBD phenotype, sex, and perceived stress. Likely due to lower power, results on FCAL ($n = 31$) were not statistically significant.

Conclusion: This study suggests that IBD patients with previous diagnosis of mood disorder may be at higher risk of inflammation-related depressive symptoms.

1. Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and life-threatening idiopathic inflammatory disease of the gastrointestinal tract that affect >0.3% of the population in Western countries. IBD is characterised by a relapsing-remitting course and a heterogeneous clinical presentation that includes chronic diarrhoea, rectal bleeding, episodes of abdominal pain, and weight loss, which are often associated with systemic symptoms such as malaise, fatigue, and occasionally fever. The aetiopathogenesis of IBD remains unknown, although current knowledge suggests that it may be the result of a complex interaction between genetic susceptibility, environmental factors, gut microbiota, and abnormal innate and adaptive immune responses, with an increased levels of pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, and acute phase proteins such as C-reactive protein (CRP).

Individuals with IBD have a higher prevalence of hospital admissions for mood disorders [1] especially depression compared to the general population (OR 1.4; 95% CI 1.3–1.6, [2]). In a meta-analysis of epidemiological data, the prevalence of depressive disorders and symptoms in IBD was estimated to be 15.2% and 21.6%, respectively [3]. The aetiology of depressive symptoms in IBD remains unknown, although biopsychosocial model would suggest that stress-related factors and the immunology of the disease may be involved [4,5,6]. In fact, levels of

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https://doi.org/10.1016/j.jpsychores.2024.111592
Received 12 November 2023; Received in revised form 7 January 2024; Accepted 8 January 2024
Available online 10 January 2024

peripheral pro-inflammatory markers such as serum CRP, IL-6, and TNF-α are on average higher in individuals diagnosed with depression than in healthy controls (e.g., [7]). Up to 27% of those with depression have CRP > 3 mg/l [8] which is usually interpreted as a cut-off for low-grade chronic inflammation [9]. Interestingly, longitudinal literature shows that CRP and IL-6 may not only correlate with depression, but rather be a precursor of depression in community samples [10]. Nevertheless, direct evidence of the relationship between inflammation and depression in IBD remains scarce. Findings from cross-sectional studies are highly variable, with some showing small to moderate correlations between both CRP and fCAL and depressive symptoms [11,12], and others reporting null findings (e.g., [13,14]). Longitudinal data in IBD are much more limited and showing non-significant associations between inflammation and depression [15]. Another potential limitation of the available evidence is the lack of exploration of the role of other co-morbid mood disorders. In fact, depression is not the only mood disorder associated with increased inflammation. Case-control studies have shown higher peripheral CRP in individuals with bipolar disorder [16] as well as changes in cytokine and chemokine expression in dysthymic disorder [17].

As both CD and UC are associated with a higher risk of mood disorders such as bipolar and unipolar depression and dysthymia [1], it is possible that the presence of mood disorders and higher levels of inflammation in IBD may interact in influencing the severity of depressive symptoms (i.e., exposing those with higher inflammation and comorbid mood disorders are at higher risk of depression). Therefore, this study aimed to 1) test the longitudinal associations between biomarkers of systemic and local inflammation and depressive symptoms in IBD, 2) test whether the associations between baseline inflammation and follow-up depressive symptoms vary according to comorbid diagnosis of mood disorders.

2. Method

2.1. Study design and population

This was an observational, prospective, single-centre cohort study. Consecutive adult patients aged 18 or above with established diagnosis of IBD seen in a referral centre of Sant'Andrea University Hospital, Sapienza University of Rome between September 2021 and March 2022 were prospectively included in the study. Each eligible patient willing to participate provided written informed consent and was evaluated at baseline and at 1-year follow-up. Exclusion criteria were: current cognitive deficits or neuropsychiatric disorders that would interfere with the compilation of the questionnaires (i.e., substance abuse, psychotic disorders, neurocognitive disorders); current medical illness with a known impact on mental status (e.g., cancer, cerebrovascular disease, neurodegenerative disease); inability to write and/or read. The study received ethical approval by local committee.

3. Measures

3.1. Sociodemographic and health information

An ad hoc questionnaire was designed to collect socio-demographic information, including sex, age, marital status, educational background, employment status, smoking status, body mass index (BMI), sports activities, and comorbidities. Participants were also asked to indicate whether they had received a diagnosis of mood disorder by a professional in the past, using a dichotomous (yes/no) item. To limit the possibility of self-diagnosis, the item specified to give a “no” response if participants suspected they had a mood disorder but had not received a formal diagnosis from a mental health professional. Self-reported paper and pencil tests were administered by a Master level health psychology student under the supervision of a gastroenterologist and a clinical psychologist.

3.2. Clinical measures

The diagnosis of IBD was based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations. The clinical history of all eligible patients was reviewed by a team of specialised gastroenterologists in order to confirm the previous diagnosis of IBD. At baseline and at 1-year follow-up, all participants underwent a full clinical evaluation, by the same team of clinicians, and the following data were collected: age at diagnosis and at enrolment; IBD phenotype (UC, CD or unclassified IBD); the presence of perianal disease; the presence of extra-intestinal manifestations; previous intestinal resections; specific IBD therapy and other medications, particularly psychotropic and sedative-hypnotic drugs. In addition, the extent of the disease was categorized using the Montreal classification [18]. IBD clinical activity was determined using the Harvey-Bradshaw Index (HBI) for CD and the Partial Mayo score (PMS) for UC [19]. The HBI was designed in 1980 as a simplified version of the Crohn's Disease Activity Index, to facilitate the systematic collection of clinical data in CD [20]. HBI considers five clinical parameters (i.e., general wellbeing, abdominal pain, number of liquid/soft stools on the previous day, abdominal mass, presence of complications). A score $\geq$ 5 is used to define CD clinical activity. The PMS is widely used in clinical trials and may be applied in clinical practice; it includes the non-invasive components of the full Mayo Score (i.e., stool frequency measurement, rectal bleeding, and a physician global assessment), each of which is assigned a score from 0 to 3. Disease is considered clinically active if the PMS is $\geq$2.

CRP and fCAL are the two most widely used biomarkers in IBD. Serum CRP is an acute-phase reactant used in clinical practice as a general measure of systemic inflammation. In a meta-analysis of cohort and case-control studies that compared the diagnostic accuracy of CRP with endoscopy as the reference standard in patients with symptomatic IBD, a CRP concentration of $\geq$5 mg/L appeared to have a high specificity for detecting endoscopic disease activity [21]. However, the sensitivity was low, and a negative test does not exclude the presence of a flare. fCAL, a neutrophil-derived protein, appears to be the most sensitive marker of intestinal inflammation in IBD. fCAL levels correlate well with endoscopic indices of disease activity and are thus important in several clinical settings including initial diagnosis, diagnosis of relapse, and response to treatment. The cut-off value of fCAL with greater specificity for identifying an endoscopically active disease would be >250 μg/g (specificity of 82%, sensitivity of 80%) [22]. The assay of inflammatory biomarkers has not been centralised as the laboratory techniques used for this purpose are standardized.

3.3. Psychometric measures

The Depression subscale of the Hospital Anxiety and Depression Scale (HADS-D, [23]) was used to assess the severity of depressive symptoms at baseline and at 1-year follow-up. The HADS-D is a self-report scale specifically developed to assess depressive symptoms in outpatients in general practice. The score for HADS-D ranges from 0 to 21, with higher scores indicating greater symptom severity. For the purposes of this study, the Italian version of the HADS was administered [24].

The Perceived Stress Scale (PSS, [25]) was used to assess the presence and severity of perceived psychological stress. The PSS is a widely used self-report measure consisting of 10 items relating to the previous month. The total score ranges from 0 to 40, with higher scores indicating greater perceived stress. For the purposes of this study, the Italian version of the PSS was administered (e.g., [26]). Psychometric measures were completed autonomously; a licensed clinical psychologist of the Department of Psychology, Sapienza University of Rome, was available for any doubts or clarifications.

3.4. Data analysis

Data were analysed using jamovi (http://jamovi.org/). Descriptive statistics were calculated to characterize the patient population. Results are presented as frequencies (percentages) for categorical variables and mean (standard deviation) for continuous variables. Initially, potential outliers were detected following the procedure described in Tabachnick and Fidell [27]. In addition, skewness and kurtosis values were calculated to evaluate whether continuous variables approximated a univariate normal distribution. Due to a substantial deviation, a log transformation was applied to CRP to normalize the shape of the distribution (see [27]).

Correlation analyses were first performed to examine the relationships between the investigated variables, separately for individuals with and without a diagnosis of mood disorder. Subsequently, we employed longitudinal moderated regression models to examine the potential moderating effect of mood disorder diagnosis on the association between inflammatory markers and depressive symptoms. Before creating the cross-product vector, representing the interaction effect, we centred the predictors according to Aiken and West [28]. Then, two separate hierarchical regression models on follow-up depressive symptoms (HADS-D) were conducted, one for CRP and one for fCAL. The models included the inflammatory marker, baseline depressive symptoms (HADS-D), and mood disorder diagnosis (0 = no; 1 = yes) as predictors in the first step. In addition, the analysis accounted for several covariates (entered in Step 1) that may be associated with depressive symptoms and inflammation levels including BMI, IBD phenotype and therapy, baseline levels of perceived stress (PSS score), and sex (0 = male, 1 = female) (e.g., [29,30,31]). In the second step, the interaction term between the inflammatory marker and mood disorder diagnosis was entered, and changes in R-squared were calculated. To interpret the interaction effect, the simple slopes for the relationship between inflammatory markers and follow-up depressive symptoms (HADS-D) were tested among individuals both with and without a mood disorder diagnosis. Moreover, as a preliminary step, we verify the assumptions of independence of residuals and absence of multicollinearity underlying the linear regression by performing Durbin-Watson tests and calculating variance inflation factor (VIF) values, respectively (see [32,27]).

4. Results

4.1. Sample description

Ninety-five participants provided biological samples for baseline assessment of inflammatory markers and measures of depressive symptoms at baseline and follow-up. Of these, 11 participants were not included in the analysis due to data missing on confounding variables. Moreover, one participant showed missing data on confounders and was identified as a univariate outlier in depression scores [27]. Therefore, analyses on CRP were based on a total sample of 84 patients, of which 14 with and 70 without a previous diagnosis of mood disorder. Instead, analyses on fCAL were conducted on a total sample of 31 patients, of which 6 with and 25 without a previous diagnosis of mood disorder.

4.2. Preliminary analyses

Table 1 summarises the descriptive statistics of clinical, biochemical, and psychometric variables investigated at baseline and at 1 year follow up. All variables were approximately normally distributed, falling within the criterion range of ±2 for skewness and kurtosis values [33]. The only exception was CRP, which was log-transformed falling within the proposed range [27]. Bivariate correlations showed that CRP was largely and significantly correlated with follow-up HADS-D scores among individuals with a previous mood disorder diagnosis ($r = 0.606$, $p = .022$), while the correlation was small and non-significant for those without a previous mood disorder diagnosis ($r = -0.109$, $p = .369$). The correlation between fCAL and follow-up HADS scores was moderate in size but did not reach the statistical significance threshold in those with a previous mood disorder diagnosis ($r = 0.453$, $p = .367$), while it was negligible and not significant in those without ($r = 0.025$, $p = .906$).

Table 1
Descriptive statistics of the main variables. Note: CRP was log-transformed following Tabachnick and Fidell [27]. Abbreviations: BMI, body mass index; CD; Crohn's disease; CRP, C-reactive protein; fCAL, faecal calprotectin; HADS-D, Depression subscale of the Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale; UC, Ulcerative colitis. Notes: [a]active disease was defined by a partial Mayo score ≥ 2 or Harvey-Bradshaw Index ≥5.

	Mean (SD) / n (%)	Skewness	Kurtosis
Age (y)	50.54 (16.37)	−0.17	−1.05
Female sex	37 (44%)		
IBD phenotype			
CD	21 (25%)		
UC	63 (75%)		
Active disease [a]			
Baseline	16 (19%)		
1y follow up	14 (16.5%)		
BMI (baseline)	25.10 (3.62)	0.36	0.90
Inflammatory markers (baseline)			
CRP (mg/l)	3.58 (3.25)	2.26	6.22
CRP_Log	0.54 (0.28)	0.10	−0.14
fCAL (μg/g)	452.19 (615.92)	1.33	0.59
Depressive symptoms			
HADS-D (baseline)	6.57 (3.71)	−0.01	−0.82
HADS-D (1y follow up)	3.96 (3.22)	1.12	1.14
PSS (1y follow up)	15.89 (6.55)	−0.07	−0.11
Mood disorder diagnosis (1y follow up)	14 (16.7%)		

4.3. Moderated regression models

4.3.1. C-reactive protein (CRP)

In the first moderated regression analysis on follow-up HADS-D scores, CRP, previous mood disorder diagnosis, baseline HADS-D scores, and covariates were included as predictors in the first step, while the interaction term between CRP and mood disorder diagnosis was entered in the second step. The VIF indicators did not reveal multicollinearity issues (VIF ranged between 1.10 and 2.18; [34]). The Durbin-Watson statistic was 1.86, supporting the absence of autocorrelation among the residuals [32]. The results are summarised in Table 2.

In the first step, a previous mood disorder diagnosis (B = 3.242, $p < .001$) and perceived stress ($\beta = 0.232$, $p = .033$) emerged as significant predictors of follow-up HADS-D scores. The unique effects of the other predictors were not significant, and the accounted variance was

Table 2
Longitudinal moderated regression model testing the association between baseline CRP and follow-up HADS-D scores. Notes: Regression coefficients are reported in both unstandardized and standardized forms, except for categorical predictors and the cross-product term, which are reported solely in unstandardized form. *$p < .05$; **$p < .01$; ***$p < .001$. Abbreviations: BMI, Body mass index; CRP, C-reactive protein; HADS-D, Depression subscale of the Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale.

Predictor	B	SE	*p*-value	Beta
CRP	1.335	1.139	0.245	0.117
Baseline HADS-D	0.148	0.089	0.101	0.171
Mood disorder diagnosis	3.242	0.874	<0.001	//
PSS	0.114	0.052	0.033	0.232
BMI	−0.045	0.091	0.622	−0.051
IBD phenotype	0.049	0.728	0.947	//
IBD therapy	2.279	2.075	0.276	//
Sex	−0.140	0.648	0.829	//
$\mathbf{R^2} = 0.339$***				
CRP * Mood disorder diagnosis	9.733	2.947	0.001	//
$\mathbf{\Delta R^2} = 0.085$**				

approximately 34% ($p < .001$). In the second step, the interaction between CRP and previous mood disorder diagnosis explained a significant incremental amount of variance (R^2 change = 0.085, $p = .001$). Specifically, simple slope analyses (see Fig. 1) revealed that CRP significantly predicted follow-up HADS-D scores among individuals with a previous mood disorder diagnosis ($\beta = 0.843$, $p < .001$), but not among individuals without a previous mood disorder diagnosis ($\beta = -0.013$, $p = .896$).

4.3.2. Exploratory analysis on faecal calprotectin (fCAL)

For exploratory purposes, despite the limited number of patients having fCAL measures ($n = 31$), we conducted a moderated regression analysis on follow-up HADS-D scores. In the first step, we included fCAL, previous mood disorder diagnosis and baseline HADS-D scores as predictors. In the second step, we added the interaction term between fCAL and previous mood disorder diagnosis. The VIF indicators did not reveal multicollinearity issues (VIF ranged between 1.00 and 1.25; e.g., [34]). The Durbin-Watson statistic was 1.54, supporting the absence of autocorrelation between the residuals [32]. Results are summarised in Table 3.

In the first step, only a previous diagnosis of mood disorder was marginally associated with HADS-D scores (B = 3.076, $p = .060$). The unique effects of the other predictors were not significant (ps >0.05), as well as the accounted variance ($R^2 = 0.169$, $p = .165$). In the second step, the interaction between fCAL and previous mood disorder diagnosis did not explain a significant incremental amount of variance (R^2 change = 0.020, $p = .433$). Nevertheless, from a purely exploratory perspective, we conducted simple slope analysis (see Fig. 2), which graphically suggested differences in the relationships between fCAL and follow-up HADS-D scores for individuals with a previous mood disorder diagnosis ($\beta = 0.389$, $p = .247$) compared to individuals without a previous mood disorder diagnosis ($\beta = 0.077$, $p = .725$).

Table 3
Longitudinal moderated regression model testing the association between baseline fCAL and follow-up HADS-D scores. Notes: Regression coefficients are reported in both unstandardized and standardized forms, except for categorical predictors and the cross-product term, which are reported solely in unstandardized form. Abbreviations: fCAL, faecal calprotectin; HADS-D, Depression subscale of the Hospital Anxiety and Depression Scale.

Predictor	B	SE	p-value	Beta
fCAL	0.001	0.001	0.351	0.171
Baseline HADS-D	0.185	0.169	0.284	0.197
Mood disorder diagnosis $\mathbf{R^2} = 0.169$	3.076	1.569	0.060	//
fCAL * Mood disorder diagnosis $\mathbf{\Delta R^2} = 0.020$	0.002	0.002	0.433	//

5. Discussion

This study investigated the longitudinal associations between inflammatory biomarkers and depressive symptoms in a cohort of IBD patients with and without a previous clinical diagnosis of mood disorder. Main result showed that in those with a previous mood disorder diagnosis, higher levels of serum CRP were predictive of greater depressive symptoms at 1-year follow-up, even after controlling for baseline depressive symptoms and relevant confounders such as perceived stress and BMI. This result is consistent with and corroborates previous cross-sectional evidence in IBD [11,12] and echoes more robust evidence in non-IBD samples [8,7]. CRP is a protein which is produced by the liver mainly in response to IL-6, TNF-α, and IL-1-β signalling during the acute phase of inflammatory response. The prognostic value of CRP has been highly studied in chronic physical illness (e.g., [35,36]), and more recently, CRP emerged as a biomarker of specific symptoms profiles in mental disorders, and specifically depression (e.g., [37]).

Possible links between inflammation and depressive symptoms may involve complex immune-to-brain pathways. According to the inflammatory hypothesis of depression, the effects of peripheral inflammation on mood are thought to be mediated by central inflammation [38]. Specifically, peripheral inflammation may subsequently lead to microglial activation through humoral (i.e., cytokines diffusion across intact or leaky regions of the blood-brain-barrier, i.e., circumventricular organs), or neuronal (e.g., binding of cytokines to afferent vagus nerve fibres), or cellular pathways [39], determining changes in neurotransmitters, neurotrophic activity, and oxidative stress processes with the

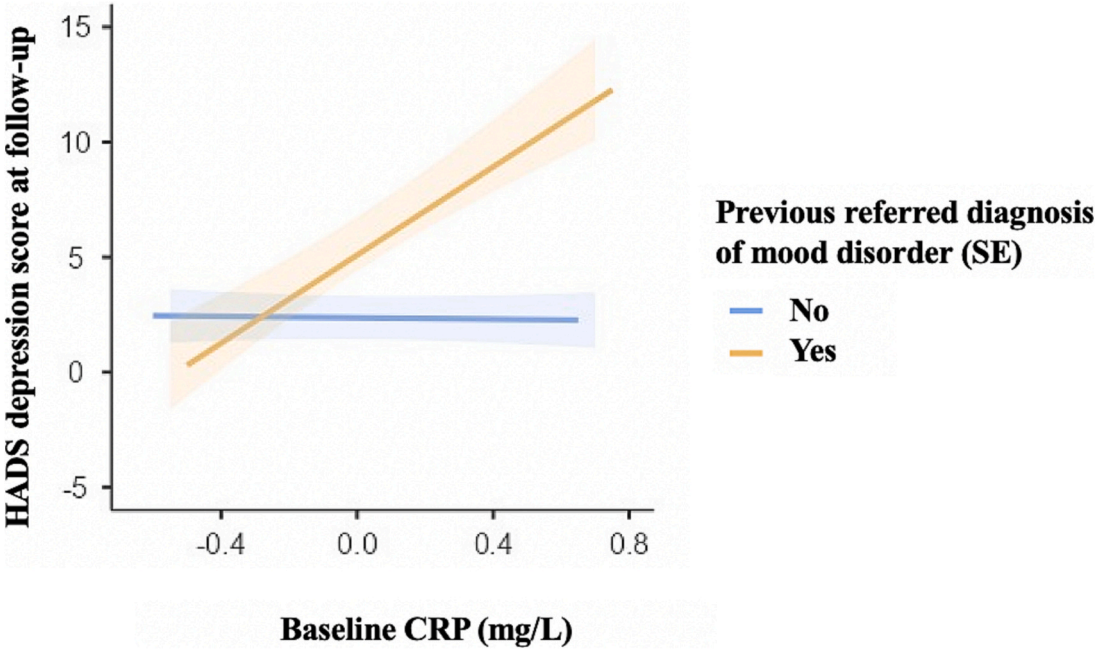

Fig. 1. Simple slope analysis of the relationship between CRP and follow-up HADS-D scores for individuals with and without a previous mood disorder diagnosis. Note: log-CRP was mean-centred [28]. Shaded lines indicate standard errors (SE). Abbreviations: CRP, C-reactive protein; HADS-D, Depression subscale of the Hospital Anxiety and Depression Scale.

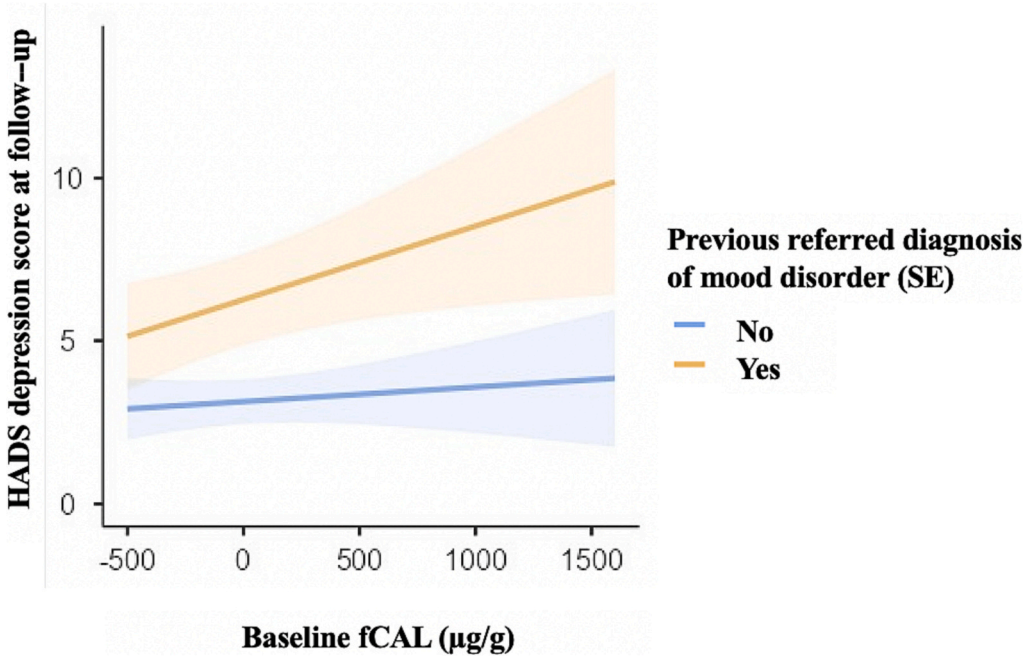

Fig. 2. Simple slope analysis of the relationship between fCAL and follow-up HADS-D scores for individuals with and without a mood disorder diagnosis. Note: fCAL was mean-centred [28]. Shaded lines indicate standard errors (SE). Abbreviations: fCAL, faecal calprotectin; HADS-D, Depression subscale of the Hospital Anxiety and Depression Scale.

following onset of depressive symptoms (e.g., [40,38,41,42,43,44]). This hypothesis is consistent with the sickness behaviour model according to which, individuals facing an immune challenge such as exposure to a virus through vaccination can develop a "cytokine-released syndrome" consisting of increased slow-wave sleep and social withdrawal, as well as reduced activity and appetite, all symptoms which resemble depressive states (e.g., [44]). Consistently, intravenous endotoxin injection in healthy humans induces a well-known inflammatory cascade, with increased serum and cerebrospinal fluid concentrations of pro-inflammatory cytokines and acute phase proteins and depressive symptoms (e.g., [45]), suggesting that inflammation may be causally involved in the development of depression. Furthermore, a recent meta-analysis showed higher levels of IL-6 and TNF-α in the cerebrospinal fluid of individuals with depression compared to controls [46], highlighting the presence of central nervous system inflammation in depression, i.e., neuroinflammation (e.g., [43]). Our findings also suggest that the "depressogenic" effect of peripheral inflammation in individuals with IBD may be particularly relevant for individuals with a previous mood vulnerability. Analysis on fCAL, a specific maker of intestinal inflammation, although conducted in a small sample and therefore not statistically significant, seem to suggest a similar path. It is worth noting that depression may occur on a range from subthreshold depressive states to clinically relevant mood disorders [47]. Research conducted in non-IBD samples showed that the association between CRP and depression is stronger when studied in clinically relevant depression vs. subclinical samples [48,49]. Furthermore, it is currently recognised that inflammation may be an aetiopathogenic factor for depression only in a subsample of individuals (e.g., [50]). Several factors may contribute to increase levels of inflammation in these individuals, including health behaviour [51], sleep disturbances [29], and chronic infection and inflammatory diseases [52] such as IBD. Therefore, if replicated in larger samples, results of this study suggest the possibility that screening for relevant mental comorbidity in IBD may inform clinicals about possible detrimental effects of inflammation on depression.

Our study is subject to several limitations. First, the sample size of the two IBD phenotypes (UC and CD) were imbalanced, and this may have influenced the results, as the power of CRP to detect and follow up disease activity may be different between UC and CD [35,36]. However, including IBD phenotype as control variable in the regression model did not substantially change the results. Second, data on fCAL were only available for a small subsample of participants, possibly limiting model testing on intestinal inflammation. For instance, an exploratory power analysis indicated that a minimum of 84 participants was necessary to detect a medium effect size in correlation analyses ($\rho = 0.3$, power = 0.80, alpha = 0.05), underscoring the underpowered nature of the analyses on fCAL. Third, assessment of depressive symptoms and previous mood disorder diagnosis was based on a self-reported screening question. Indeed, despite being one of the most frequently used measures to assess depression in IBD samples [3], the latent structure of the HADS has been debated due to the potential overlapping of depression and anxiety dimensions [53]. Nevertheless, previous studies on IBD provided evidence of the convergent validity of the two HADS dimensions [54], as well as their unique contribution in predicting IBD-related outcomes [55]. Additionally, a moderate correlation between anxiety and depression diagnoses derived from HADS scores was observed in an IBD sample [56], falling well below suggested cutoffs indicating discriminant validity issues (0.80/0.85, e.g., [57]). Therefore, future studies may benefit from including a larger and balanced sample of UC and CD, a depression measure with more robust psychometric properties [53], and a clinician-based interview for establish the presence of mood disorders. With respect to the assessment of previous mood disorder, several additional information should be carefully collected in future research, including chronicity of the condition, possible treatment, and remission phases.

In conclusion, the findings of the present study suggest that individuals with IBD and concomitant mood disorder diagnosis may be at increased risk to develop inflammation-related depressive symptoms beyond the role of relevant predictors of depression such as perceived stress and sex. If replicated in larger samples, these results could highlight a potential role of neuro-immune factors linking IBD and depressive symptoms. Several aspects, however, remain to be investigated. For instance, whether IBD-specific depressive symptoms can be reversible following anti-inflammatory therapy has not yet been clearly established. Indeed, to the best of our knowledge, while some anti-

inflammatory drugs have been shown to improve depressive symptoms (e.g., [58]), their efficacy in IBD remains untested. Similarly, while several psychological treatments such as mindfulness-based interventions have been shown to improve depression and reduce inflammation [41] in non-IBD samples, their effectiveness in IBD is less studied [59,60].

CRediT authorship contribution statement

Andrea Ballesio: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Federica Micheli:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation. **Flavia Baccini:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation. **Andrea Zagaria:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis. **Alessandro Del Forno:** Methodology, Investigation, Data curation. **Valeria Fiori:** Methodology, Investigation, Data curation. **Gloria Palombelli:** Methodology, Investigation, Data curation. **Silvia Scalamonti:** Methodology, Investigation, Data curation. **Andrea Ruffa:** Investigation, Data curation. **Ambra Magiotta:** Investigation, Data curation. **Giovanni Di Nardo:** Writing – review & editing, Writing – original draft, Supervision, Resources. **Caterina Lombardo:** Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors have no competing interests to report.

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