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Inflammatory bowel diseases (IBDs): a cross-sectional analysis of the psychological and biological mechanisms underlying intestinal and extra-intestinal symptoms—GastroPsy study protocol

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ABSTRACT

Introduction Inflammatory bowel diseases (IBDs) are chronic conditions characterised by intestinal and systemic inflammation, often associated with significant psychological distress. Emerging evidence highlights a bidirectional relationship between inflammation and psychological factors, mediated by the gut-brain axis. Psychological distress may not only result from chronic inflammation but also contribute to symptom persistence and disease exacerbation. Despite this, clinical management of IBD primarily focuses on controlling inflammation, often overlooking psychological factors that may influence disease activity and treatment response.

Method and analysis GastroPsy protocol will last for 24 months and will follow a cross-sectional design. At least 150 participants will undergo a clinical evaluation based on the detection of biological, medical and psychological indicators and variables. The evaluation battery will comprise seven validated questionnaires. Through a k-means cluster analysis, the study aims to derive and describe data-driven clusters of IBD patients, finally exploring associations between identified clusters and external clinical variables (e.g. clinical activity).

Ethics and dissemination Ethical Committee Approval was obtained from the CEtRA Abruzzo Region (IT) (Protocol ID 228/2025). The results of the present project will be published in peer-reviewed journals, disseminated electronically and in print, and presented as abstracts and/or personal communications during national and international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Medical/psychological measurement will be analysed into patient profile.
⇒ Multidimensional model by integrating medical and psychological clinical variables.
⇒ Cross-sectional design.
⇒ Self-report questionnaires.
⇒ Sample representativeness.

INTRODUCTION

Inflammatory bowel diseases (IBDs), encompassing Crohn's disease (CD) and Ulcerative colitis (UC), are immune-mediated disorders characterised by chronic inflammation of the gastrointestinal tract.[1 2] CD can affect any part of the digestive tract, from mouth to anus, whereas UC is limited exclusively to colon and rectum.[3 4] Another difference lies in the pattern of inflammation. In UC, it appears as a single continuous spot, while in CD, it manifests through distinct and discontinuous spots, known as skip lesions, which make it more challenging to treat both pharmacologically and surgically.[3 5] Prevalence of IBD has been rapidly increasing in the last decades, with an estimated global prevalence of 0.2% and approximately 2.2 million affected individuals in Europe alone.[6 7] IBD follows a chronic course, characterised by alternating periods of remission and relapse.[8] It can lead to a wide range of intestinal symptoms, including abdominal pain, diarrhoea, rectal bleeding, faecal incontinence and weight loss that significantly impacts patients' perceived quality of life.[4 8 9] In addition, extraintestinal manifestations (EIMs), affecting various organs and body systems, occur in 6% to 47% of IBD patients, mainly during adulthood.[10–12] This broad spectrum of intestinal and extraintestinal symptoms, often associated with psychological distress,[13] represents the primary concern of IBD patients, even more than the risk of developing colorectal cancer.[14] Currently, IBD management primarily aims at reducing inflammation,[15] but, despite significant advances in

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this direction, particularly due to the introduction and increasing use of biologic therapies,[16] psychological intestinal and extraintestinal symptoms often persist even in the remission phase.[14 15 17 18]

IBD and fatigue

Chronic fatigue, which affects approximately 40% of IBD patients, is one of the most common and debilitating EIMs.[19–22] It can be defined as a persistent sense of tiredness and weakness that does not resolve with rest and significantly impacts psychological well-being.[20 23] The potential causes of fatigue in IBD involve a complex interplay of factors, including anaemia, inflammation and mood disorders.[24] However, fatigue remains highly prevalent even when inflammation is under control and with regular haemoglobin levels.[25–29] More recently, research has begun to investigate the link between fatigue and psychological factors in IBD patients, with growing evidence of a strong association with depression, both in those with active disease and in remission.[26 28 30 31]

IBD, stress and trauma

The aetiology of IBD is multifactorial, involving the interaction between genetic and environmental factors that trigger an uncontrolled immune response.[32 33] Recent research has increasingly focused on the role of stress and stressful events, not only in relapses but also in the onset of IBD. Stress is frequently linked to intestinal inflammation and increased levels of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β.[34 35] A recent paper further clarified how glucocorticoids, released in response to stress, impact IBD by impairing the development of enteric nervous system neurons, leading to reduced intestinal motility and activation of glial cells, which, in turn, stimulate the immune system and inflammation.[36] Several studies have found an association between perceived stress and worse IBD outcomes, such as an increased risk of symptomatic flare-ups, hospitalisations and surgeries.[37 38] A prospective study found that baseline stress levels correlated with a higher risk of relapse in the next months.[39] Early-life stress exposure appears to increase the risk of IBD onset. Additionally, low stress resilience during adolescence has been associated with an increased risk of developing IBD in adulthood.[40] Few studies have examined different trauma types in relation to IBD specifically. A 2023 study comparing IBD patients and healthy controls found a higher prevalence of childhood traumatic events in IBD patients, particularly sexual trauma. Authors also showed how complex trauma exposure was linked to a worse IBD prognosis.[41]

Clinical monitoring of IBD

The gold standard for IBD activity monitoring includes ileocolonoscopy, gastroscopy and MRI.[42] However, due to their invasiveness and high cost, clinical practice tends to favour inflammatory biomarkers in disease monitoring, particularly faecal calprotectin (FC) and C-reactive protein (CRP). Another emerging biomarker for IBD activity is the CRP-to-Albumin ratio (CAR), which serves as a systemic inflammation marker and a predictor of poor prognosis (eg, treatment failure or increased complication).[43 44] Despite this evidence, some clinicians may still rely on clinical indices, such as the Harvey-Bradshaw Index (HBI) for CD,[45] and the Simple Clinical Colitis Activity Index (SCCAI) for UC.[46] However, these symptom-based indices correlate poorly with actual inflammation levels, making them inadequate for guiding treatment decisions.[15 47]

Factors associated with symptoms in IBD with resolved inflammation

Persistent symptoms in IBD despite resolved inflammation are particularly relevant in patients with psychological comorbidities.[48] Several studies have reported a significant association between active symptomatology and anxiety/depression.[49 50] One explanation for these residual symptoms is a coexisting irritable bowel syndrome (IBS), which shares overlapping symptoms with IBD.[15 51] The prevalence of IBS in IBD remission is around 50%, and it is strongly linked to mood disorders and traumatic experiences.[17 52–57] A 2020 meta-analysis found that even when using strict remission criteria (endoscopy and histology), 25% of IBD patients still experience IBS-like symptoms.[58] Another factor contributing to persistent symptoms is visceral hypersensitivity (VH), which is highly correlated with IBS.[59 60] VH results from the interaction between psychological distress, low-grade inflammation and gut-brain axis alterations.[61 62] Stress-driven epigenetic mechanisms modulate VH, which has been found to coexist with IBS-like symptoms, anxiety and central sensitisation (CS) in patients in remission.[62 63] Finally, CS, which is characterised by heightened excitability of central nervous system neurons, leading to increased and prolonged pain perception. It is strongly linked to IBD, as well as greater IBS severity, anxiety and depression.[64] Failing to consider these mechanisms when evaluating IBD patients with resolved inflammation but reporting persistent symptomatology may lead to unnecessary invasive investigations (eg, endoscopy) or intensified pharmacological treatments.

IBD and psychological distress

The burden of IBD extends beyond physical symptoms, significantly impacting psychosocial well-being.[65] IBD's chronic nature, symptom unpredictability and disease flares contribute to high rates of anxiety and depression.[48 66] Anxiety and depression are highly prevalent in IBD, with a mean rate of 40% for anxiety and 35% for depression.[14 18 67–71] Despite its clinical significance, psychological distress is under-recognised and undertreated in IBD care. A 2020 survey found that 50% of IBD patients reported anxiety or depression, but only 15.2% received psychological support, and 16.1% had their emotional well-being addressed during specialist visits.[72] Psychological distress complicates clinical management, increasing intestinal and extra-intestinal symptoms

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despite controlled inflammation.[48 73] Moreover, anxiety and depression negatively affect treatment adherence and health behaviours.[13] Psychological distress is also linked to higher rates of hospitalisations, surgeries, imaging procedures, endoscopies, steroid use and biologic therapies, leading to avoidable healthcare costs.[13 69 72–75]

Objectives

The aim of the present study is to enhance the multidimensional model of clinical treatment for patients with IBD by achieving an objective understanding of the interactions between biological and psychological factors and both intestinal and extra-intestinal symptomatology, with the goal of identifying distinct patient profiles that can better guide clinical and therapeutic decision-making. The primary outcome of the current study will be the identification of distinct patient clusters derived from k-means cluster analysis characterised by prespecified clinical and psychological variables. Secondary outcomes will include exploratory post hoc analyses to evaluate associations between the identified clusters and external clinical factors (eg, disease type, clinical activity, etc). The study hypothesises the existence of three distinct clusters of IBD patients: (1) A group with overall adequate control of inflammatory, symptomatic and psychological factors, with fewer adverse childhood experiences (ACEs), (2) A group with high intestinal and systemic inflammation, but low/mild psychological distress and a low number of adverse childhood events and (3) A group characterised by low inflammatory markers, but elevated levels of depression, anxiety, fatigue, central sensitivity, as well as a higher number of adverse childhood events.

METHODS

Study setting

The study will be conducted at the Regional Referral Centre for IBD, ASL 1 Abruzzo, San Salvatore Hospital, L'Aquila (Director: Professor Giovanni Latella), from August 2025 to the end of August 2027.

Study sample

A total of 150 consecutive patients with chronic IBD will participate in the study. All eligible patients for the GastroPsy Project must sign the informed consent form to be enrolled.

Inclusion criteria

1. Confirmed diagnosis of IBD based on clinical, endoscopic and histological criteria.
2. Age range: 18–75 years.
3. Fluency in Italian.
4. Availability of recent laboratory data in medical records (maximum 30 days prior to recruitment).
5. Signed informed consent.

Exclusion criteria

1. IBD-undefined.
2. Patients who have undergone total colectomy.
3. Presence of active malignancy.
4. Cognitive impairment.
5. Current corticosteroid treatment.
6. Current presence of abscesses, fistulas, fissures or infections.
7. Use of non-steroidal anti-inflammatory drugs in the week preceding laboratory tests.

The exclusion of patients undergoing a corticosteroid treatment is justified by the documented association of these therapies with drug-induced, dose-dependent neuropsychiatric disorders, such as mania, hypomania and depression, that typically arise within the first 3 weeks of treatment and resolve after discontinuation, potentially confounding the assessment of psychological symptoms in this study.[76] Similarly, patients with complications, such as fistulas and fissures, will be excluded because those complications can independently elevate FC levels, for example reflecting local fistula activity rather than overall intestinal mucosal inflammation.[77 78] Moreover, patients with acute infections will be excluded because serum concentrations of CRP can significantly increase within 24–72 hours of bacterial acute infections.[79 80] Based on our clinical experience in this specific setting, we estimate that approximately 5% of patients may be excluded due to these exclusion criteria. Finally, although these exclusions may limit the generalisability of findings to the entire IBD population, they are necessary to ensure accuracy and reliability of biomarker measurements and psychological assessment, which represent the core focus of the current study.

Measures

All patients will undergo clinical evaluation through the collection of demographics, biological, clinical and psychological variables. Data will be anonymised using numerical codes, ensuring patient confidentiality. Demographic, clinical and disease-related data will be extracted from medical records following informed consent.

Demographic data

- Age (years).
- Sex (male or female).

Disease characteristics and history

- Disease type (CD or UC).
- Diagnosis date (month and year).
- Age at diagnosis (years).
- Disease duration (months).
- Current pharmacological treatment (conventional or biologic therapy).

Clinical parameters

Disease activity status:

- HBI for CD (remission: <5).[45]
- SCCAI for UC (remission: <5).[46]

Presence of IBS:

- Rome IV Criteria.[81]

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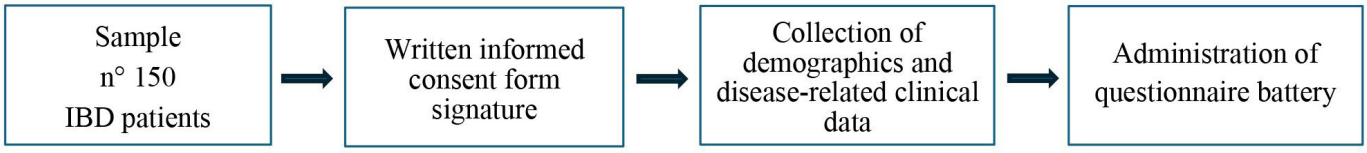

Figure 1 Graphical representation of the study design. Flowchart illustrating the main study steps: recruitment of at least 150 consecutive IBD patients, signing of written informed consent, collection of demographic and clinical data, and finally administration of the psychological questionnaire battery. IBD, Inflammatory Bowel Disease.

Laboratory parameters

Laboratory parameters will be collected from medical records as part of routine clinical care. Only patients with tests performed within 30 days of enrolment will be included. Laboratory data will be analysed as continuous variables and included in the k-means cluster analysis.

- FC: intestinal inflammation marker (mg/kg).[82]
- CRP: systemic inflammation marker (mg/L).[83]
- CRP (mg/L)/Albumin (g/L) ratio (CAR): systemic inflammation index (higher values indicate inflammation).[43 44]
- Haemoglobin (Hb): anaemia indicator (g/L).[84]

Psychological assessments

Subsequently, a standardised psychological battery composed of 7 psychological tests with available Italian validation will be administered. Psychological scale results will be analysed as continuous variables and used as inputs for the k-means cluster analysis.

- Generalised Anxiety Disorder-7 (GAD-7)[85]: evaluation of anxiety symptom severity (DSM-IV criteria).
- Patient Health Questionnaire-9 (PHQ-9)[86]: evaluation of depression symptom severity.
- Perceived Stress Scale (PSS)[87 88]: evaluation of perceived stress levels.
- Central Sensitivity Index (CSI)[89]: evaluation of CS-related symptoms.
- Visceral Sensitivity Index (VSI-IT)[90]: evaluation of visceral sensitivity and GI-specific anxiety.
- ACEs Questionnaire[91 92]: assessment of early-life ACEs.
- Fatigue Severity Scale (FSS)[93]: evaluation of fatigue severity.

Procedures

Study design

This study will follow a cross-sectional design. Participants will be consecutively recruited during routine clinical visits at the Regional Referral Centre for IBDs. Eligible patients are individuals diagnosed with IBD, as defined in the 'Study sample' section. Patients meeting eligibility criteria will be informed about the study aims and procedures and invited to participate. Those who agree to participate will provide written informed consent before data collection. Figure 1 presents a representation of the study design. All clinical and psychological assessments outlined in this protocol will be conducted after recruitment and informed consent, in a private room to ensure participants' privacy. To ensure methodological transparency, a participant flow diagram will be included in the final manuscript, summarising the number of individuals screened for eligibility, excluded with reasons, and finally enrolled and analysed.

Statistical analysis

Study data will be incorporated into an Excel database and analysed using Jamovi V.2.7.9.0 with the snowCluster module (V.7.5.6), as well as Rstudio (V.4.5.1; Rcore Team, 2025) with clustMixType (V.0.42), car: companion to applied regression (V.3.1-3), factoextra (V.1.0.7) and ClusterBootstrap (V.2.0.0) packages. Processing will be performed on aggregated data to ensure anonymity. Regarding descriptive analyses, nominal and categorical variables will be reported as frequencies (n) and percentages (%). Finally, a k-means cluster analysis (Hartigan-Wong algorithm) will be conducted to identify potential subgroups among IBD patients based on distinct patterns of psychopathological and physical symptoms, stressful life events, clinical disease activity and biological markers. The selection of variables for the k-means cluster analysis is theory-driven, designed to capture the key domains of our research hypothesis. The input variables will encompass biological markers (FC, CRP, CAR, Hb) and scores from psychological questionnaires (GAD-7, PHQ-9, PSS, CSI, VSI-IT, ACE, FSS). All data will be standardised into Z-scores, to ensure that each variable contributes equally to the clustering analysis. No a priori dimension reduction is planned, as the clustering will be conducted directly on the standardised clinical and psychological variables to preserve their interpretability. The optimal number of clusters will be determined empirically once data is available, using the Elbow method, to visually determine the optimal number of clusters by identifying the point at which additional clusters minimally reduce within-cluster variance, and the Gap Statistic method which compares the within-cluster dispersion with the one expected under a null reference distribution, providing an objective criterion to identify the most appropriate cluster solution.[94 95] Internal validity will be assessed with a bootstrap-based, cluster-wise stability method (Jaccard), while sensitivity analysis will be conducted applying different clustering algorithms, variations in the number of clusters and random starts, with the aim of ensuring stability and guarding against overfitting.[96] All variables are expected to be complete for all participants; consequently, no missing data handling or imputation procedures will be required. Post hoc comparisons among clusters will be conducted using non-parametric procedures (ie, Kruskal-Wallis test,

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Dunn method, Bonferroni correction). The $\chi 2$ test and related post hoc comparisons[97] will be conducted to evaluate associations among subgroups identified by cluster analysis with external factors such as disease type (CD vs UC), clinical activity (Active vs Remission), IBS (Presence vs Absence). For all post hoc comparisons, multiplicity will be controlled using Bonferroni correction or false discovery rate where appropriate.

We anticipate identifying approximately three clusters, with participants expected to be similarly distributed across sub-groups. A sample of at least 150 participants seems appropriate, given that a recent simulation study demonstrated how, even with small subgroup samples (n=20), it is possible to detect small differences (d=0.30) among three groups.[98] Currently, there are no clear guidelines for the estimation of the best number of variables to include in a k-means cluster analysis. However, adopting a conservative approach, this study will apply at least a 10:1 observation/variables ratio.[99] To limit the risk of unstable or weakly separated partitions with many correlated measures, we will reduce redundancy through correlation screening or PCA on standardised values and quantify stability by applying 100 random starts. Variables such as age, sex, age at diagnosis, disease duration, current therapy class etc, will be collected and reported descriptively. These variables will not be included in the K-means cluster analysis, as the main aim is to identify patient subgroups based on integrated biological and psychological profiles. Clusters will be described using centroid values (mean value of each variable per cluster), and the relative contribution of variables will be summarised using differences from overall means. Clusters will be shown with profile plots to visually highlight differences between clusters. Notably, K-means cluster analysis should be considered exploratory, and no causal or predictive interpretations can be drawn. Results of sensitivity analyses will be reported in terms of reallocation rates, cluster size changes and centroid correlation.

Data monitoring and safety

The collected data will be retained for 5 years following the completion of the research. Paper-based questionnaires and signed informed consent forms will be stored at the Clinical Psychology Laboratory of the University of L'Aquila, under the responsibility of Professor Dina Di Giacomo. All data from studies will also be stored in password-protected electronic format. On computers, data will be saved in a separately password-protected folder accessible exclusively to the Principal Investigator (Professor Dina Di Giacomo). Access to the final anonymised dataset will be restricted to the principal investigator and members of the research team involved in data analysis.

Patient and public involvement

The patients and/or the public will not be involved in the design, conduct, reporting or dissemination plans of this research.

Access to data

The research data may be shared after de-identification on reasonable request to the Principal Investigator of the GastroPsy Project. Proposals to access the data must be reviewed and approved by the CEtRA Abruzzo Region (IT) Ethical Committee.

Data management

The participants' paper and electronic files will be maintained in secure storage on a password-protected computer throughout the completion of the project. Data will then be stored at the University of L'Aquila (IT) for at least 5 years after publication, after which these will be destroyed according to university protocols. Non-numerical data will be coded according to predefined coding definitions. Data entry screening will be conducted at the time of data entry to ensure that there are no inconsistencies between the paper-based and electronic data.

ETHICS AND DISSEMINATION

Ethical Committee Approval was obtained from the CEtRA Abruzzo Region (IT) (Protocol n° 243773/24; ID 228/2025). The results of the present project will be published in peer-reviewed journals, disseminated electronically and presented as abstracts and/or personal communications during national and international conferences. Written informed consent will be treated as a mandatory component of this research according to the guidelines of the Declaration of Helsinki ('World Medical Association Declaration of Helsinki 2013) National and international regulations on patient privacy will be followed.

Participants' safety and support

The questionnaire battery requires approximately 20 min to complete and doesn't expose participants to any direct physical risk. Participants may pause or stop the assessment at any time without any consequence. All questionnaires will be administered in the presence of a clinical psychologist. Participants reporting significant distress or any suicidal thoughts will be immediately supported by the attending psychologist and, if necessary, promptly referred to the hospital's psychiatric services. In addition, participants will be informed in advance about available psychological support resources. We consider that this approach is able to ensure participants' safety while allowing the collection of sensitive psychological data.

Contributors AC (Chief Investigator); DDG (Project Manager); GL and FG (Study management); AC and MC (Statistical oversight and analysis). All authors approved the final manuscript. Guarantor: DDG.

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