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ORIGINAL RESEARCH

Adverse Childhood Experiences and Disease Activity Are Associated with Post-Traumatic Stress Symptoms in Crohn's Disease

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ABSTRACT

***Introduction*:** Crohn's disease (CD) is a chronic inflammatory bowel disease associated with a substantial psychological burden, including post-traumatic stress symptoms (PTSS). However, PTSS do not develop in all patients, suggesting individual vulnerability factors. Adverse childhood experiences (ACEs) are a transdiagnostic risk factor for stress-related psychopathology and may influence psychological responses to chronic disease. We examined whether ACEs moderate the relationship between clinical disease activity and PTSS in patients with CD.

***Methods*:** In this cross-sectional study, outpatients with CD completed self-report measures assessing PTSS and ACEs. Clinical disease activity was assessed using the Harvey–Bradshaw Index. Data were analyzed using Pearson correlation coefficients and hierarchical moderated regression analyses.

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Results: A total of 161 outpatients with CD were included. Clinically significant PTSS were observed in 32.1% of the sample. Disease activity was positively associated with PTSS (r=.33, p<.01), as was cumulative ACE exposure (r=.38, p<.01). In regression analyses, both disease activity (β=.22, p=.013) and ACEs (β=.35, p<.001) independently predicted PTSS, whereas disease duration was inversely associated (β=−.19, p=.047). A significant interaction between disease activity and ACEs emerged (ΔR^2=.034, p=.013), indicating a stronger association between disease activity and PTSS among patients with greater childhood adversity.
Conclusion: Early-life adversity appears to increase vulnerability to PTSS in the context of active CD. ACE-informed assessments may help identify patients at higher psychological risk and guide trauma-informed clinical care.

Keywords: Crohn's disease; Gut–brain axis; Post-traumatic stress symptoms; Adverse childhood experiences; Psychological distress

Key Summary Points

Why carry out this study?

Patients with CD often experience PTSS related to the experience of Crohn's disease, but not all individuals are equally vulnerable. Adverse childhood experiences are known risk factors for stress-related psychopathology and may modulate psychological responses to chronic illness.

What have we learned from this study?

Both CD activity and adverse childhood experiences independently predicted PTSS. Moreover, childhood adversity strengthened the association between disease activity and psychological distress.

Early-life adversity appears to increase vulnerability to PTSS in CD. Screening for adverse childhood experiences may help identify patients at higher psychological risk and may support trauma-informed models of care in IBD clinics.

INTRODUCTION

Crohn's disease (CD) is a chronic, relapsing–remitting inflammatory bowel disease (IBD) characterized by transmural inflammation that may affect any segment of the gastrointestinal tract [1]. Its pathogenesis is multifactorial and arises from a complex interplay between immune dysregulation, genetic susceptibility, alterations in the gut microbiota, and environmental factors [2, 3].

The unpredictable clinical course of CD and its substantial impact on daily functioning are associated with a significant psychological burden, including elevated levels of anxiety [4] and depressive symptoms [5], as well as trauma-related responses such as post-traumatic stress symptoms (PTSS) and, in some cases, post-traumatic stress disorder (PTSD) [6]. PTSD represents a formal psychiatric diagnosis, whereas PTSS refer to trauma-related psychological distress that may not fulfil the full diagnostic criteria for PTSD. Although PTSS can be clinically meaningful and negatively affect quality of life, they are typically assessed dimensionally and do not necessarily imply the presence of a confirmed psychiatric disorder. PTSD is defined by the presence of intrusive symptoms, avoidance of trauma-related stimuli, negative alterations in cognition and mood, and persistent psychophysiological arousal, including irritability and sleep disturbances [7].

While PTSD has traditionally been associated with discrete traumatic events such as violence, accidents, or natural disasters, increasing evidence suggests that the chronic, unpredictable, and invasive nature of medical conditions such as CD may be experienced as psychologically traumatic by patients [8]. This perspective is supported by recent findings on PTSS associated with cancer diagnosis [9] and other chronic illnesses [10]. In line with this view, previous studies have indicated that clinically significant PTSD affect approximately 10–32% of patients with IBD, with a higher prevalence observed among individuals with CD [6, 11]. These rates are substantially higher than the estimated 11% prevalence of PTSD reported in individuals with other chronic,

non-gastrointestinal medical conditions [11]. Notably, previous studies indicate that a substantial proportion of patients with IBD report PTSS specifically associated with their experience of CD [6].

These associations are increasingly interpreted within the framework of the brain–gut axis, a bidirectional communication system through which psychological states and gastrointestinal function influence each other. Experimental evidence from murine models of quiescent colitis suggests that even in the absence of overt clinical symptoms, intestinal inflammation may elicit behavioral alterations resembling psychological distress, likely mediated by activation of the hypothalamic–pituitary–adrenal (HPA) axis and systemic immune responses [12, 13]. Conversely, psychological stress has been identified as a contributor to both the onset and exacerbation of IBD [14, 15]. A recent meta-analysis further identified PTSD as a significant predictor of IBD onset, suggesting that trauma-related stress may disrupt immune homeostasis through chronic inflammation, HPA axis dysregulation, and alterations in the gut microbiome [16].

Notably, not all patients with CD develop PTSS, suggesting that the psychological impact of the disease may depend on individual vulnerability factors, including resilience [17]. One potential moderator that may account for this variability is exposure to adverse childhood experiences (ACEs), defined as early-life stressors such as physical, emotional, or sexual abuse, neglect, or household dysfunction [18]. Within IBD populations, ACEs are commonly reported and have been associated with poorer mental health outcomes, greater disease activity, and reduced quality of life [19, 20].

ACEs are known to disrupt the development of biological stress regulation systems, particularly the HPA axis, and to sensitize neuroimmune and affective circuits involved in fear processing, stress reactivity, and pain perception [21, 22]. Neuroimaging evidence further supports this association. For example, Xie et al. [23] demonstrated that exposure to ACEs is associated with reduced thalamic volume in adults following trauma, a structural alteration that correlates with greater severity of PTSS and an increased risk of developing PTSD. These findings highlight the long-term neurobiological consequences of childhood adversity and its potential role in increasing vulnerability to trauma-related psychopathology across the lifespan.

In addition, accumulating evidence suggests that ACEs differ not only in severity but also in qualitative characteristics, potentially exerting distinct effects on neurobiological development and long-term psychological functioning. Dimensional models of adversity propose that specific forms of early-life stress, such as abuse, neglect, or family dysfunction, may differentially influence neurobiological systems involved in stress regulation, emotional processing, and fear learning [24].

Building on this literature, the present study aimed to investigate the role of ACEs as a source of vulnerability to PTSS in CD. The primary objective was to examine whether exposure to ACEs moderates the association between clinical disease activity and the severity of PTSS. Secondary objectives were to assess whether ACEs are independently associated with PTSS regardless of disease activity and, in line with dimensional models of adversity, to exploratorily examine whether distinct ACE domains—abuse, neglect, and household dysfunction—differentially influence this moderating relationship.

METHODS

This cross-sectional study included consecutive outpatients with CD attending the Digestive Disease Center at Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy. Eligible participants were aged between 18 and 75 years, were able to read and understand Italian, and provided written informed consent. A diagnosis of CD was confirmed according to the 2019 ECCO-ESGAR guidelines [25].

Exclusion criteria included a prior diagnosis of schizophrenia or other psychotic disorders, as well as current or past substance use disorders, including alcohol or other psychoactive substances, as defined by DSM-5 criteria [26]. After providing informed consent, participants were welcomed by a psychologist who explained

the study procedures and remained available for clarification while the self-report questionnaires were completed independently. Clinical data and medical history were collected by experienced gastroenterologists specializing in inflammatory bowel disease.

The study protocol was approved by the Ethics Committee Lazio Area 3 (No. 4054) (Rome) and was conducted in accordance with the principles of the Declaration of Helsinki and European Good Clinical Practice guidelines. Written informed consent was obtained from all individual participants included in the study.

Measures

Participants were asked to complete a questionnaire including socio-demographic data and two self-reported scales, to assess PTSS and ACEs. Sociodemographic information, including age, sex, marital status, level of education, and employment condition, was gathered through self-report in the first section of the questionnaire.

Impact of Event Scale–Revised

The Impact of Event Scale–Revised (IES-R) is a 22-item self-report measure designed to assess the severity of trauma-related psychological symptoms experienced during the previous 7 days [26]. Items are rated on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("extremely"). The scale comprises three symptom clusters: intrusion, avoidance, and hyperarousal. Higher total scores indicate greater levels of PTSS. Participants were instructed to refer their responses to the experience of living with CD and its clinical course.

Consistent with prior literature, a total score ≥ 24 indicates clinically relevant symptoms, whereas a score ≥ 33 suggests a probable diagnosis of PTSD [27, 28].

Adverse Childhood Experiences Questionnaire

The Adverse Childhood Experiences (ACE) Questionnaire is a retrospective 10-item self-report questionnaire assessing exposure to adverse events before the age of 18 years [29]. Items evaluate experiences of physical, emotional, and sexual abuse, physical and emotional neglect, and household dysfunction, including domestic violence, parental separation or divorce, household substance abuse, household mental illness, and incarceration of a household member [30].

Each item is coded dichotomously (yes/no), and a cumulative ACE score is calculated by summing endorsed items (range 0–10), with higher scores indicating greater cumulative childhood adversity. In line with previous studies, a score ≥ 1 was used to identify the presence of any adverse childhood experience, whereas a score ≥ 4 was used to indicate high-risk exposure associated with an increased likelihood of adverse mental and physical health outcomes [22, 29, 30].

Clinical Disease Characteristics

Clinical and disease-related information was extracted from medical records and included disease duration (years since diagnosis), disease location according to the Montreal classification, history of CD-related surgical interventions (coded as yes/no), and current pharmacological treatment. Medical therapies were categorized into corticosteroids, conventional immunosuppressive agents, biologic therapies, and small-molecule drugs.

Clinical disease activity at the time of assessment was evaluated using the Harvey–Bradshaw Index (HBI) [31]. The HBI assesses general well-being, abdominal pain, number of liquid stools per day, presence of abdominal mass, and disease-related complications. Total scores classify disease activity as remission (< 5), mild (5–7), moderate (8–16), or severe (> 16).

Statistical Analysis

A hierarchical moderated regression analysis was performed to examine the association between clinical disease activity and PTSS, with ACEs included as a moderating variable. In the first step, disease activity (HBI score) and ACE total

score were entered as predictors. Disease duration, prior intestinal surgery (coded as 0 = no, 1 = yes), and number of previous biological therapies were also included as covariates. In the second step, an interaction term between disease activity and ACE was added to test whether the relationship between disease activity and PTSS varied as a function of childhood adversity. The two predictors were mean-centered to reduce multicollinearity and facilitate interpretation of interaction effects. Significant interaction effects were probed using simple slope analyses, examining the association between disease activity and IES-R scores at low (− 1 SD), average (mean), and high (+ 1 SD) levels of ACE.

To further explore the potential differential impact of distinct forms of early-life adversity, additional moderated regression analyses were conducted using the three ACE domains—abuse, neglect, and household dysfunction—as separate moderators in independent models.

All analyses were conducted using SPSS version 27 (IBM, Armonk, NY, USA) and the PROCESS macro-version 4.2 [32]. Statistical significance was set at $p < 0.05$.

Table 1 Sociodemographic and clinical characteristics of the sample ($n = 161$)

Variables	$n = 161$
Age (years), mean ± SD	39.96 ± 14.24
Female sex, *n* (%)	89 (55.3%)
Disease duration (years), mean ± SD	11.14 ± 10.39
Clinical disease activity (HBI), *n* (%)	
Remission (< 5)	67 (41.6%)
Mild (5–7)	47 (29.2%)
Moderate (8–16)	38 (23.6%)
Severe (> 16)	9 (5.6%)
Concomitant pharmacological treatment, *n* (%)	
Steroids	43 (26.7%)
Conventional immunosuppressive	13 (8%)
Biologic therapy	56 (34.7%)

Data are presented as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Clinical disease activity was assessed using the Harvey–Bradshaw Index (HBI)

RESULTS

Sample Characteristics

The study included 161 outpatients diagnosed with CD, of whom 55.3% were female. Sociodemographic and clinical characteristics of the sample are summarized in Table 1. The mean age of participants was 39.96 ± 14.24 years, and the mean disease duration was 11.14 ± 10.39 years.

Based on the Harvey–Bradshaw Index, 41.6% of patients were in clinical remission, 29.2% had mild disease activity, 23.6% had moderate disease activity, and 5.6% had severe disease activity. With respect to pharmacological treatment, 26.7% of patients were receiving corticosteroids, 8.0% conventional immunosuppressive agents, and 34.7% biologic therapies.

Nine participants did not complete the ACE scale, two did not provide responses for the IES-R, and six had missing data on disease duration, resulting in a final sample of 144 patients with complete data for regression analyses.

Descriptive Statics and Correlations

Descriptive statistics and intercorrelations among study variables are presented in Table 2. Based on the recommended IES-R cut-off score of 33, 52 patients (32.1% of the sample) exhibited clinically significant PTSS.

Nineteen patients (7.2%) reported an ACE score of 4 or higher, a threshold previously associated with an increased risk of adverse mental and physical health outcomes. As expected, IES-R scores were positively correlated with disease activity ($r = 0.33$, $p < 0.01$) and ACE scores ($r = 0.38$, $p < 0.01$). The reliability coefficients for both the IES-R (Cronbach's $\alpha = 0.95$) and ACE (Kuder–Richardson 20 = 0.80) scale scores exceeded the conventional threshold of 0.70, indicating good internal consistency.

Table 2 Descriptive statistics, intercorrelations, and reliability coefficients for the study variables in the total sample ($n = 161$)

Variables	1	2	3	4	5	6
1. IES-R		.33**	.38**	– .02	.07	.10
2. Disease activity			.27**	.25**	.20*	.36**
3. ACE				.01	– .13	.10
4. Disease duration					.57**	.37**
5. Previous surgery						.26**
6. Previous biologic therapies						
M	24.77	4.73	1.32	11.14	.41	1.33
SD	19.48	4.81	1.96	10.39	.49	1.19

Pearson correlation coefficients are reported; *$p < .05$, **$p < .01$. Disease activity refers to the continuous Harvey–Bradshaw Index (HBI) total score. Higher scores indicate greater disease activity

Moderated Regression Analysis Results

The results of the hierarchical moderated regression analyses are presented in Table 3. In the first step, the model including disease activity, ACE, disease duration, IBD-related surgical history, and number of previous biological treatments as predictors was statistically significant ($F(5,138) = 8.01$, $p < 0.001$), accounting for 22.5% of the variance in IES-R scores.

Significant positive effects were observed for disease activity ($\beta = 0.22$, $p = 0.013$) and ACE ($\beta = 0.35$, $p < 0.001$), indicating that greater disease activity and higher levels of childhood adversity were associated with more severe PTSS. Disease duration was negatively associated with IES-R scores ($\beta = -0.19$, $p = 0.047$), whereas surgical history ($\beta = 0.17$, $p = 0.069$) and number of previous biological treatments ($\beta = 0.03$, $p = 0.735$) were not significant predictors.

In the second step, inclusion of the interaction term between disease activity and ACE resulted in a significant increase in explained variance ($\Delta R^2 = 0.034$, $p = 0.013$). The interaction effect indicated that the association between disease activity and PTSS was stronger among patients with higher levels of childhood adversity ($\beta = 0.20$, $p = 0.013$).

Simple slope analyses demonstrated that the relationship between disease activity and IES-R scores was significant at average ($b = 0.698$, $p = 0.048$) and high ($b = 1.508$, $p = 0.005$) levels of ACE, but not at low levels ($b = 0.148$, $p = 0.742$). This pattern is illustrated in Fig. 1.

Conversely, no significant interaction between ACEs and disease duration was observed ($\beta = -0.007$, $p = 0.927$). Therefore, this interaction term was not retained in the final models.

Domain-Specific Effects of Adverse Childhood Experiences

To explore whether specific domains of childhood adversity differentially moderated the association between disease activity and PTSS, the moderated regression analyses were repeated using the three ACE domains (abuse, neglect, and household dysfunction) in separate models (Supplementary Tables S1–S3).

All ACE domains showed significant main effects on IES-R scores, indicating that higher levels of childhood abuse, neglect, and household dysfunction were associated with greater PTSS. However, a significant interaction with disease activity emerged only for the abuse domain ($\Delta R^2 = 0.03$, $p = 0.016$), suggesting that the association between disease activity and PTSS was stronger at higher levels of childhood abuse.

In contrast, the interaction terms for the neglect and household dysfunction domains were

Table 3 Hierarchical moderated regression analyses predicting Impact of Event Scale–Revised (IES-R) scores in patients with CD

Predictor	Model 1			Model 2		
	b	SE	β	*b*	SE	β
Disease activity	.88*	.35	.22	.70*	.35	.17
ACE	3.40**	.78	.35	3.27**	.76	.34
Disease duration	− .35*	.18	− .19	− .38*	.17	− .20
Surgical intervention	6.80	3.72	.17	6.74	3.65	.17
Previous biologic therapies	.46	1.37	.03	.01	1.36	.00
Disease activity × ACE				.40*	.16	.20
R^2	.22			.26		
F (df)	8.01 (5, 138)**			7.99 (6, 137)**		
ΔR^2				.03		
ΔF (df)				6.36 (1, 137)*		

Disease activity was assessed using the Harvey–Bradshaw Index (*HBI*). Adverse Childhood Experiences (*ACE*) was assessed using the ACE questionnaire; β represents standardized regression coefficients

* $p < .05$ ** $p < .01$

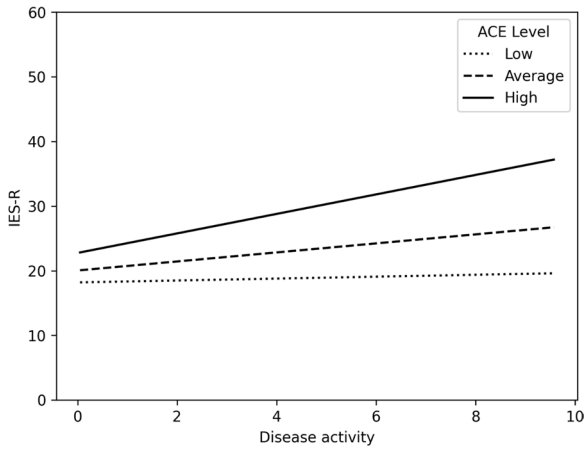

Fig. 1 Scatterplot representing the relationship between disease activity (*HBI*) and post-traumatic stress symptoms, as measured by the Impact of Event Scale–Revised (*IES-R*) at different levels of Adverse Childhood Experiences (*ACE*). Disease activity (HBI) and ACE scores were mean-centered for the purpose of the moderation analysis. Values on the *x*-axis represent deviations from the sample mean. Simple slopes were estimated at low (− 1 SD), average (mean), and high (+ 1 SD) levels of ACE

not statistically significant, indicating that these forms of adversity did not moderate the relationship between disease activity and IES-R scores.

DISCUSSION

The present study has examined whether ACEs increase vulnerability to PTSS related to the experience of CD in patients with CD and whether such experiences moderate the relationship between clinical disease activity and psychological distress.

The most relevant finding was the moderating role of ACEs in the association between clinical disease activity and disease-related PTSS. Specifically, a stronger relationship between disease activity and PTSS was observed among patients with higher levels of childhood adversity, whereas no significant association was detected among those with low ACE exposure. This pattern suggests that ACEs may function as sensitizing factors, amplifying emotional reactivity to somatic stressors. From a psychobiological

perspective, early-life adversity has been associated with long-lasting epigenetic modifications and dysregulation of the HPA axis, leading to heightened physiological and emotional responses to subsequent stressors and increased vulnerability to PTSS [33].

In addition, ACEs emerged as independent predictors of disease-related PTSS, even after adjustment for CD activity, disease duration, prior intestinal surgery, and number of previous biological therapies. This finding is consistent with previous evidence identifying childhood adversity as a transdiagnostic risk factor for psychopathology across a wide range of chronic medical conditions [29, 33, 34].

Clinical disease activity was also significantly associated with disease-related PTSS, with patients experiencing more active disease reporting higher levels of psychological distress. This result supports the hypothesis that CD, due to its unpredictable course, recurrent flare-ups, and invasive diagnostic and therapeutic procedures, may be perceived as a psychologically traumatic condition, contributing to the development of disease-related PTSS [35, 36].

Interestingly, disease duration was inversely associated with PTSS, suggesting a potential process of psychological adaptation over time. Patients with longer disease history may develop more effective coping strategies, greater illness acceptance, or improved emotional regulation, which could mitigate trauma-related distress. To further explore this finding, we tested whether disease duration modified the association between ACEs and PTSS. However, no significant interaction between ACEs and disease duration was observed, indicating that the relationship between ACEs and PTSS does not vary according to disease chronicity. These findings suggest that ACE-related vulnerability to distress is independent of disease duration.

An additional contribution of this study is the exploratory analysis of different domains of childhood adversity. Although abuse, neglect, and household dysfunction were all associated with higher levels of PTSS, only the abuse domain moderated the relationship between disease activity and psychological symptoms. This finding suggests that early experiences of interpersonal threat, such as physical, emotional, or sexual abuse, may represent a specific vulnerability factor for stress sensitization. This interpretation is consistent with dimensional models of childhood adversity, which distinguish experiences of "threat" from experiences of "deprivation" and attribute threat-related adversity to heightened reactivity of stress-response systems [24]. Moreover, psychoneuroimmunological evidence has linked childhood abuse to increased inflammatory reactivity in adulthood [33]. In line with this perspective, previous studies have reported associations between childhood abuse and both PTSD and chronic physical conditions [37, 38].

Overall, these findings support a biopsychosocial model in which early-life adversity and current disease activity interact to shape psychological outcomes in CD. The observed moderating effect of ACEs, in the absence of formal psychiatric diagnoses, suggests the presence of latent vulnerability to stress-related psychopathology in the context of CD.

It is also important to consider that other psychological factors may influence the relationship between disease-related stress and mental health outcomes. For example, recent evidence from similar clinical contexts indicates that psychological resilience may buffer the impact of disease activity on symptoms of anxiety and depression, acting as a protective resource [39]. These findings highlight the importance of integrative assessments that consider both vulnerability and protective factors in inflammatory bowel disease care.

From a clinical perspective, the assessment of ACEs may represent a valuable component of psychological evaluation in patients with inflammatory bowel disease. However, given the complexity of ACE-related constructs and the cross-sectional nature of the present study, the adoption of a universal screening approach may be premature. Instead, a more targeted assessment strategy may be more appropriate, particularly among patients reporting elevated emotional distress or difficulties in managing disease-related stressors. In this context, evaluating ACE exposure may help identify individuals at increased vulnerability to trauma-related symptoms and support more individualized, trauma-informed clinical care. Importantly, the

assessment of ACEs requires specific expertise and should be embedded within a multidisciplinary approach involving mental health professionals. The integration of psychologists within the clinical team may therefore represent a key element in ensuring appropriate assessment and management of patients' psychological needs. Further research is needed to clarify the clinical utility, timing, and implementation of ACE-informed approaches within gastroenterological settings.

Notwithstanding these considerations, several limitations should be acknowledged. Disease activity was assessed using a clinical index (Harvey–Bradshaw Index), a validated and widely used measure reflecting symptom burden of disease. While this approach is aligned with the study's focus on subjective psychological outcomes, it does not incorporate objective inflammatory markers (e.g., C-reactive protein or fecal calprotectin) or endoscopic assessment, which may provide a more comprehensive evaluation of the underlying inflammatory burden. In addition, the cross-sectional design precludes causal inference and does not capture the dynamic, relapsing–remitting course of CD over time. Accordingly, the present findings should be interpreted as reflecting a "snapshot" of disease activity rather than its longitudinal trajectory. Although we attempted to account for aspects of disease burden by including relevant clinical variables, such as disease duration, history of IBD-related surgery, and prior biologic exposure, these measures may not fully capture the complexity of disease course. Therefore, our findings should be interpreted within the context of these methodological considerations. Finally, the reliance on self-reported measures may have introduced recall and social desirability biases, and the limited sample may limit the generalizability of the findings. Future prospective, longitudinal, multicenter studies integrating objective biomarkers with psychological and clinical assessments are warranted to clarify the temporal and mechanistic relationships between childhood adversity, disease activity, and trauma-related psychological outcomes in CD.

CONCLUSION

In this cross-sectional study, both clinical disease activity and ACEs were independently associated with higher levels of PTSS related to the experience of CD. Moreover, the association between disease activity and PTSS was stronger among patients with greater exposure to childhood adversity, suggesting that early-life stress may confer increased vulnerability to disease-related psychological distress. These findings support a biopsychosocial model in which early environmental adversity and current disease burden jointly shape psychological outcomes in CD. The results underscore the potential clinical value of a more targeted, trauma-informed psychological assessment into patient management, particularly in patients with active disease and elevated emotional distress. Longitudinal studies are needed to clarify the temporal dynamics, mechanisms, and clinical implications of these associations.

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and Antonio Maria D'Onofrio, approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Giorgia Spagnolo, Daniele Ferrarese, Jacopo Iaccarino, Marco Murgiano, Michele Vecchione, Guglielmo Sicilia, Daniele Napolitano, Antonio Maria D'Onofrio, Antonio Gasbarrini, Giovanni Camardese, Daniela Pia Rosaria Chieffo and Franco Scaldaferri have nothing to disclose. Federica Di Vincenzo is an Editorial Board member of *Advances in Therapy*. Federica Di Vincenzo was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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