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A review of the link between psychological stress and inflammatory bowel disease exacerbation

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Abstract

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting illness characterized by episodes of inflammation in the gastrointestinal tract. This condition affects several million people worldwide and has become more prevalent in recent decades. It frequently manifests in individuals aged 15–35 and is observed among high school-aged adolescents and college-aged adults. Despite extensive research, the root cause of IBD remains unknown. The largely unknown etiology of the illness, variability of symptoms, and the need for improvement in the efficacy of IBD treatment underscore the significance of psychosocial factors on the influence of the condition. This review examines three lines of stress research—stressful life events, daily stress, and perceived stress—to evaluate the association between psychological stress and IBD exacerbation. A review of empirical evidence shows a robust link between psychological stress and disease activity in IBD, suggesting that psychological stress is a risk factor for disease exacerbation. Four major limitations involving psychological stress in the IBD literature are identified: (1) the influence of daily stress on IBD exacerbation, (2) stress conceptualization and the operationalization of disease activity, (3) directionality between stress and IBD activity, and (4) moderators of the link between stress and disease exacerbation. Future directions for stress research in IBD are proposed.

Keywords: *psychological stress, inflammatory bowel disease, disease activity, relapse, exacerbation, symptoms*

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1. Introduction

Inflammatory bowel disease (IBD) is a group of incurable gastrointestinal disorders involving chronic inflammation of the gastrointestinal tract and ulceration of the bowels [1, 2]. IBD disorders include Crohn's disease (CD) and ulcerative colitis (UC) [1, 2] which are characterized by unforeseeable relapsing and remitting periods of flare-up symptoms throughout life, including diarrhea, rectal bleeding, abdominal pain, urgent bowel movements, nausea, and fatigue. Immunosuppressive drug therapies, such as corticosteroids, natalizumab, mesalamine compounds, and biologics, are common treatments used to manage symptoms and achieve remission by suppressing abnormal immune responses in the intestinal tract [3]. In recent decades, the prevalence of IBD has significantly increased, particularly in Western regions, with rates of early- and very-early-onset IBD in children increasing worldwide [4]. This rising trend in IBD presents substantial challenges in both medical and psychological care because the disease most commonly presents itself in adolescents and young adults, resulting in patients facing a lifetime of illness [4]. IBD impairs the gastrointestinal tract's ability to absorb nutrients and water, leading to malnutrition, anemia, weight fluctuations, fatigue, and extraintestinal manifestations affecting the skin and musculoskeletal system [5, 6]. CD is a transmural inflammatory disease that can impair any area of the gastrointestinal tract, whereas UC is a non-transmural disease restricted to the colon that compromises the entire colon or the lining of any of its segments [5, 6]. Some patients need strict adherence to dietary plans and intensive drug therapy to manage active flares [1, 2, 7], while others with treatment resistance and severe disease may require the surgical removal of the large intestine and insertion of an ileostomy [8]. This makes the experience of IBD highly unique to the individual and challenging to treat. Thus, the need for improvement in the efficacy of IBD treatment makes psychosocial factors such as stress and well-being particularly important to consider in the exacerbation of symptoms. This review covers three lines of stress research in relation to IBD exacerbation: (1) stressful life events, (2) daily stress, and (3) perceived stress. This link is examined based on clinical and biological assessments of IBD activity. The evidence for these links is examined from a mixture of case–control, cross-sectional, and longitudinal studies using samples of IBD-diagnosed adults. A range of databases and search engines were utilized to collect articles primarily within the past two decades, including university libraries, PubMed, Google Scholar, and ResearchGate. These studies are synthesized into a cohesive narrative, which critiques the research findings and highlights key trends in the literature. This review integrates these research outcomes and examines the theoretical framework that explores the relationship between stre-

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ss and IBD exacerbation, offering an in-depth analysis of how stress may influence the pathogenesis of IBD. This narrative approach outlines the major findings, critically assesses the methodologies used in the studies, and provides a nuanced understanding of the current state of knowledge on this topic.

1.1. The importance of psychosocial factors in inflammatory bowel disease

IBD research has consistently suggested the role of a dysregulated immune system and the enteric nervous system (ENS) in the generation of gastrointestinal (GI) inflammation and IBD symptoms [9, 10]. The ENS is a component of the autonomic nervous system that controls all aspects of the gastrointestinal tract and parts of the local immune system that regulate gut motility, blood flow, and epithelial barrier functions [11, 12]. While a normal ENS delegates a balance between protecting the gut from harmful bacteria and modulating inflammatory responses, an altered ENS may reduce the ability of immunomodulatory agents in the intestinal tract to regulate inflammatory responses which results in the breakdown of intestinal barrier function and reduced diversity in the gut microbiome [13–15]. Although these mechanisms are known, there is no definitive cause for IBD onset or a clear understanding of why these immune dysregulations occur. Additionally, reasons why certain patients achieve remission while others experience persistent disease and relapse are not fully understood.

Two major frameworks, known as the biomedical model of health and the biopsychosocial model of health, have been utilized to explore the origin of gastrointestinal inflammatory illnesses. A biomedical perspective of illness explains that illness solely stems from biological abnormalities [16]. Researchers who employ this framework contend that IBD is influenced by abnormalities in the gut microbiome, immune cells, inflammation, and visceral hypersensitivity. For example, researchers have previously proposed that exposure to certain environmental agents, such as infections and bacteria, may be involved in the pathology of abnormal immune processes in individuals who are genetically predisposed to IBD and may worsen its progression and course. However, this biomedical view has faced criticism because it overlooks a person's life experiences, behaviors, and mental health [16]. A biopsychosocial model of illness proposes that health and illness are the result of complex interactions between biological, psychological, and social/environmental factors [17, 18]. Biological factors refer to genetic influences, brain chemistry, immune system function, or any physical aspect that could predispose an individual to certain illnesses. Psychological factors are the mental and emotional aspects that influence how a person responds and copes with challenges, impacting overall well-being. Social factors refer to the influence of relationships, culture, community, family, and resources, all of which can shape behavior and influence health. Due to the relapsing and remitting course of IBD, researchers have utilized the biopsychosocial model to examine the unknown causes of IBD relapse. Given that IBD has no known definitive physiological cause or cure, there is an opportunity for psychosocial factors to be investigated as potential contributors to understanding the development and progression of IBD. Given that stress can affect emotional regulation, health behavior, and hormone levels in the body, which play an individualized psychosocial role in disease risk [19], this review explores stress as a psychosocial risk factor of IBD exacerbation and examines three lines of psychological stress research and their associations with IBD exacerbation.

1.2. Brain–gut mechanisms by which stress influences inflammatory bowel disease

IBD is influenced by the interplay of non-genetic and genetic factors. These include abnormalities in the composition of the gut microbiota and intestinal epithelial barrier function, genes encoding proteins that trigger maladaptive immune responses, autonomic dysfunction, and uncontrolled immune responses to antigens that are derived from normal gut microbiome. Other factors include stress, diet, infection, and early-life antibiotic exposure [20, 21]. Psychological factors, such as mood disorders, emotional distress, or maladaptive coping mechanisms such as drinking, smoking, or an unhealthy diet, can worsen IBD. Stress, a physiological response, becomes pathological when the body cannot adapt to environmental demands, leading to abnormalities in functional, metabolic, and immune-related processes. The HPA axis and CRF are key mediators of this process. The hypothalamic–pituitary–adrenal (HPA) axis is central to the stress response, which links perceived stress to physiological reactions. It interacts with the autonomic nervous system (ANS), the central nervous system (CNS), the gut's corticotropin-releasing factor system (CRF), and immune responses in the brain–gut axis. High stress has been shown to alter gut microbe, fecal metabolite, and plasma metabolite profiles, biomarkers that are strongly predictive of IBD flare risk [22]. Moreover, stress leads to the worsening of IBD symptoms [21]. Recent studies have shown the gut microbiota's role in IBD, where stress influences microbial populations and immune responses [23–26]. Stress-induced changes in the gut microbiota and cytokine levels demonstrate the interaction between stress, changes in the gut microbiome, and immunity. The sympathetic nervous system's release of norepinephrine stimulates bacterial growth, impacting gut bacterial colonization. Therefore, stress may contribute to the development of IBD by altering and disrupting gut mucosal integrity through brain–gut connections.

The diagram in **Figure 1** illustrates the pathway from psychological stress to IBD development. The diagram depicts the following sequence and relationships: At the top, "Psychological Stress" is shown as the starting point, with a downward arrow pointing to "Brain Response". From "Brain Response", the diagram branches into two parallel pathways, "HPA Axis Activation" and "Autonomic Nervous System". Both of these pathways converge at "Gut Changes", showing how the stress response systems affect the gut. From "Gut Changes", the diagram branches again into three parallel pathways, "Altered Microbiota", "Impaired Barrier Function", and "Immune Response". Finally, three of these pathways converge at the bottom of the diagram to "IBD Development", indicating that the various gut changes collectively contribute to the development of IBD.

1.3. Conceptualization of psychological stress and inflammatory bowel disease exacerbation

Psychological stress refers to emotional and physiological reactions to an event or situation that is challenging or threatening and exceeds an individual's regulatory capacity. Stress has been conceptualized in three primary ways: stressful life events, daily stress, and perceived stress [27, 28]. Stressful life events are major life events that require substantial adaptation, such as the death of a spouse, an illness, or a job loss [28]. Daily stress consists of minor hassles or situations that disturb or interrupt everyday activities which can negatively impact a person's well-being [28]. Examples

include arguments with significant others, work deadlines, or managing finances. Individuals are more likely to report psychological distress and physical symptoms on days where they experience daily stressors compared to stress-free days [29]. Demographic factors and individual differences can influence the level of resilience and vulnerability to daily stress. Finally, perceived stress is the subjective experience of stressful events, encompassing the extent to which an individual feels stressed by these events [28].

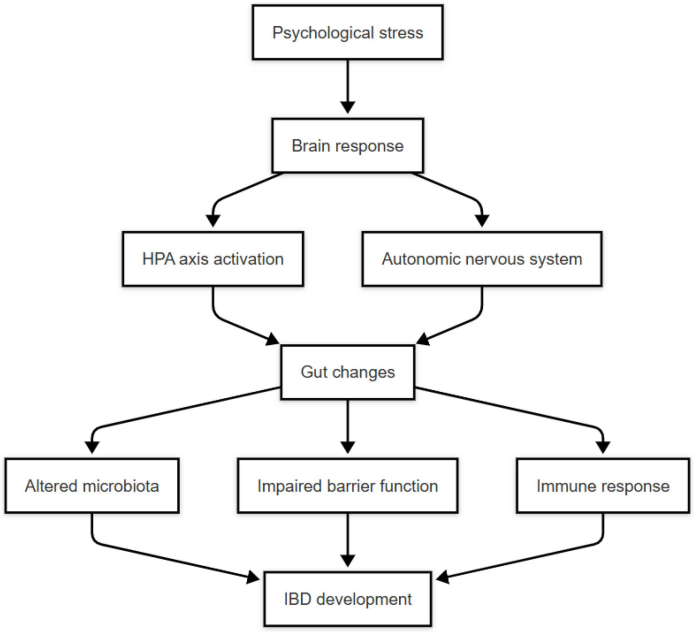

Figure 1 • An illustration of pathways linking psychological stress to the development of inflammatory bowel disease. Psychological stress activates brain responses via the hypothalamic-pituitary-adrenal axis (HPA) and autonomic nervous system (ANS), leading to gut changes. These gut changes include altered microbiota, impaired barrier function, and immune responses, contributing to the development of inflammatory bowel disease (IBD).

Disease exacerbation has not been well-defined in the IBD literature; however, many authors use the term exacerbation in IBD to refer to a worsening of the disease such as a relapse and/or an intensification of symptoms. It signifies a period when the disease becomes more active or severe, often leading to increased discomfort, complications, or the need for intensive treatment. A relapse of IBD is a change in disease status that occurs when a patient who was previously inactive transitions to an active disease phase [30]. During inactive phases, symptoms of the disease are significantly reduced or disappear entirely, and biological indices detect no signs of active inflammation. When the illness is active, the individual may experience more symptoms or the onset of flares, sudden episodes characterized by intensified and uncontrollable symptoms that detrimentally impact the well-being and daily functioning of the individual [31]. A clinical relapse in patients with quiescent IBD has been defined in many studies as patients' onset of symptoms or disease flares along with biological indications of a flare (e.g., endoscopic grade of 2, 3, or 4; Crohn's Disease Activity Index greater than score of 150). IBD has been assessed through the level of disease activity and constitutes the presence of (1) clinical markers of IBD such as the patient's report of a relapse and symptoms and/or (2) biological markers of IBD such as the presence of intestinal inflammation found in medical imaging. Self-reported questionnaires and daily symptom diaries are often used to evaluate symptom severity and frequency, the onset of flares, and the need for enhanced therapy to induce remission [32, 33]. Biological assessments in clinical practice have included the observation of endoscopic colonic inflammation, elevated plasma C-reactive protein (CRP) concentrations, fecal calprotectin levels, the erythrocyte sedimentation rate (ESR), and mucosal inflammatory cytokine production [34–36]. Levels of biomarkers above normal levels such as elevated plasma C-reactive protein (CRP), fecal calprotectin levels, the erythrocyte sedimentation rate (ESR), and mucosal inflammatory cytokine production have been shown to be predictive of a clinical relapse in adults with IBD [36] and, thus, are indicative of IBD exacerbation.

1.4. Empirical support for psychological stress and inflammatory bowel disease exacerbation

1.4.1. Stressful life events and the risk of relapse

Stressful life events have been evaluated using severity grades on life stressor checklists [37–42]. For example, a 2007 study [40] computed life event scores based on summed severity grades over all reported life events and the summed perceived stress impact across all events. Self-reported measures of stressful life events have included the Life Stressor Checklist—Revised (LSC-R), Schedule of Recent Experiences (SRE), Paykel Life Experiences Interview (PLEI), Social Readjustment Rating Scale (SRRS), and Psychiatric Epidemiology Research Interview Life Events Scale (PERI). These assessments measure major life events, with some focusing on recent life events. The Life Stressor Checklist—Revised (LSC-R) has been validated as a clinically useful tool for detecting situations subjected to the concept of psychological trauma. It captures traumatic experiences during childhood and adulthood and measures personal feelings and meanings of the event that are specific to the patient [37].

Longitudinal investigations on stressful life events and the risk of relapse suggests that recent stressful life events tend to precede the onset of a flare or the clinical relapse of IBD [38, 41–44]. Singh et al. [44] found consistent patterns in their examination of life events and disease activity over a year in both UC and CD patients; in any 3-month period, roughly 50% of patients with UC and CD experienced a previous significant life event. Moreover, this percentage was higher among patients with persistently active disease than those with inactive disease. Bernstein et al. [38] yielded comparable results to those of Singh et al. [44], showing that the experience of a major stressful event predicted a future flare within a several-month period. Moreover, Bitton et al. [41] evaluated a sample of 60 inactive UC patients and found that patients who had experienced more recent stressful life events had earlier relapses than patients with fewer recent stressful life events. A recent retrospective case–control research study examining IBD patients in active and inactive disease phases showed that patients with active IBD had significantly higher stress levels than inactive IBD patients (mean scores of 65.42 ± 8.88 in CD and 65.42 ± 8.88 in UC compared with 45.97 ± 13.23 and 41.79 ± 13.49, respectively, in those with inactive disease). Additionally, patients with active disease were more likely to use maladaptive coping mechanisms such as avoidance coping and emotional-response coping [45]. Together, the findings on stressful life events and relapse support that recent preceding stressful events are associated with a subsequent relapse.

In contrast, a few studies have found no support for a link between stressful life events and disease activity [39, 40, 46, 47]. For example, a study carried out by Lerebours et al. [40] did not reveal a significant association between life event occurrence and disease onset after adjusting for depression and anxiety scores, smoking status, and sociodemographic features, which suggests that stressful life events may not be independent risk factors for IBD onset and other factors such as the mental health and coping mechanisms of patients are important to consider. In a prospective study of 163 inactive patients, the number of previous stressful life events was not associated with a risk of a future relapse [46]. A 1990 prospective cohort study of 92 UC patients aiming to identify factors contributing to relapse found that there were no significant differences in stressful life events between relapsing and non-relapsing patients; however, patients who had relapsed had a higher occurrence of previous relapses and were in remission for a shorter time since their last relapse [47]. A recent meta-analysis examining predictors of clinical relapse in IBD revealed that patients with active histological disease (based on histological markers) have twice the risk of a clinical relapse compared to those in remission [48]. Relapse rates are hard to predict; however, research has shown that a younger age and multiple previous relapses are associated with future relapses [49]. Therefore, there is evidence suggesting that having a higher previous relapse frequency is associated with an increased risk of repeated relapses. In a recent systematic review examining the relationship between stress, the locus of control, and disease flare-ups in Crohn's disease patients, it was found that stress levels are significantly higher during flare-ups, which in turn increases the likelihood of future flare-ups. Additionally, individuals with a high external locus of control tend to experience higher stress during flare-ups [50]. These findings suggest that while stress is linked to relapse risk, the relationship between stressful life occurrences and the risk of disease flares is complex and varies by individual circumstances, and personal factors influence disease outcomes both directly and indirectly through increased stress. Factors such as previous relapses, a younger age at IBD onset, and active histological disease can also contribute to the increased risk of IBD relapse.

1.4.2. Daily stress and the risk of relapse

Self-reported measures in these studies have included the Daily Psychosocial Stress Diary (DPSD), the Daily Hassles Scale (DHS),and the Daily Stress Inventory (DSI). The Daily Stress Inventory (DSI) is a common measure used to assess the frequency of daily hassles and computes daily stress scores based on minor stressful occurrences in the past 24 h and the perceived stress ratings of these occurrences. Other measures include a person's perceived stress levels of the most bothersome daily problem using a scaled rating from 1 to 100 and the use of coping strategies [51, 52]. Researchers [53] have utilized the Daily Hassles Scale (DHS) to assess exposure to everyday stressors related to relational challenges (e.g., conflicts with family members), work hassles, time pressure, financial strain, and difficulties with social acceptance.

Daily stress studies on IBD suggest a significant positive link between daily hassles and symptoms in IBD. An early longitudinal study by Greene et al. [51] showed that stress related to daily life hassles was linked with greater IBD symptom severity at any given time during a month; however, a separate study found this positive relationship to be strong and significant for only 3 of 10 patients who were diagnosed with CD [54], and in another study, this was found for 55% of patients with active CD [55]. Greene et al. [51] also found that higher daily stress in the previous month predicted greater symptom severity in the following month. Interestingly, this stress predicted lower symptom severity several months later. The observed rebound effects and split findings suggest the possibility that the link between stress and symptoms varies by each individual and their daily management of IBD. Following the initial onset of an IBD flare-up and subsequent diagnosis, the resulting level of disability and impairments often lead to increased stressors and anticipation about the severity and interference of bowel symptoms in one's daily life. Individuals with inactive disease may have learned to effectively control symptoms to minimize their daily interference which may lessen daily stress; however, individuals with active disease may face challenges in managing both their illness and stressful aspects of daily life. For example, a daily stress comparison study showed no significant differences in daily stress levels between IBD patients and healthy controls; however, patients with active disease flares reported more daily stress than inactive patients [52]. A more recent study [53] that examined daily hassles in Crohn's disease patients found that daily hassles were linked to increased psychological stress, disease activity, lower socioeconomic status, and reduced quality of life. Moreover, patients' daily hassle scores were significantly linked to the duration of the disease, which suggests that patients do not necessarily improve their ability to adapt to the disease and manage stress well, even with the passage of time. This study also found that daily hassle scores and disease activity were mediated by psychological distress. Overall, the limited research on daily stress and stressful life events supports a link between daily stress and IBD exacerbation but should be interpreted with caution due to fewer studies on daily stress than on stressful life events and perceived stress. While daily hassles are not serious major events, the way an individual reacts and responds to daily hassles may affect their daily stress. In studies that focus on daily stress, there needs to be a better understanding of individual variability that plays a role in this link. This may be achieved by including more robust assessments of daily hassles in longitudinal studies, given that there is greater individual variability in responses to stressors. Other studies that show support for the individual variability in responses to stress and life changing events are the findings of an early longitudinal study [56] which showed a significant group-level correlation between life change scores and urinary adrenaline output in patients with a myocardial infarction. However, the study also revealed considerable individual differences: one-third of patients showed strong correlations, another third showed moderate correlations, and the final third showed no correlations. A 2022 study [57] identified distinct clusters of individuals with differences in heart-rate variability and magnitudes of reactivity during job stress. Finally, a stress-induced colitis mouse study showed individual differences in IL-6 levels from leukocytes which predicted individual susceptibility and resilience to stress-induced anxiety and depressive behavioral responses [58]. Moreover, the study showed that the presence of certain pathobionts shaped individual variability in vulnerability to stress/trauma-associated gut pathology. These studies highlight individual differences in stress sensitivity and vulnerability; hence, there is a need for novel therapeutic approaches for conditions affected by the interplay of stress exposure and individual environmental factors.

Finally, findings suggest that stress is a positive predictor of relapse but do not provide sufficient evidence to establish a causal link between stress and IBD exacerbation due to the lack of large-scale

experimentally controlled trials. While many IBD individuals report a relapse after experiencing a recent major life event, factors such as lag time between stressful events and symptoms make it difficult to determine whether an initial flare initiates stressful events and increases relapse risk or stressful events initiate flares and increase the risk of a relapse (chicken or egg dilemma). It is also difficult to measure how quickly stress engages the gastrointestinal tract. The benefit of testing daily stress on disease activity in longitudinal research is that it provides a better window for evaluating causality. Daily stress studies can closely monitor the influence of daily patterns and types of stress on disease activity by testing the effects of daily hassles on the next-day severity of symptoms while controlling for baseline levels of daily stress and symptoms. Thus, there is a need for more longitudinal research on daily stress, stress management, and symptoms to evaluate a causal link between stress and IBD.

1.4.3. Perceived stress and the risk of relapse

Assessments of perceived stress have included the Perceived Stress Questionnaire (PSQ) and Cohen Perceived Stress Scale (CPSS). Several studies have utilized multiple indices of perceived stress such as the total stress impact of life events, short-term perceived stress, which evaluates perceived stress during the past month, or long-term perceived stress, which evaluates perceived stress within the previous two years [13, 32, 38, 39, 59–61]. According to the majority of research findings, perceived stress, referred to as feeling overwhelmed or threatened by life's demands, has been linked with a heightened risk of IBD relapse. Prospective studies and reviews revealed that high perceived stress in prior months significantly predicts the risk of relapse and the timing of relapse in subsequent months to years [32, 38, 39, 43, 44, 60]. However, Sexton et al. [32] revealed a bidirectional link between stress and IBD exacerbation such that their findings showed that baseline perceived stress predicted a change in later symptom activity from 0 to 3 months, and likewise, symptom activity at baseline predicted changes in later perceived stress from 0 to 3 months. In addition, a diagnosis before the age of 17, a history of surgery, and symptom activity were all significant predictors of perceived stress in month 0. It is important to note that multiple demographic variables that were not assessed in prior studies were accounted for in this study. These findings suggest that perceived stress and IBD activity may influence each other over a 3-month period and that further research should consider how an individual's experience with the disease and IBD-relevant stressors influence their perceived stress levels over time.

Additionally, patients who relapse tend to report greater perceived stress in recent months before their relapse compared to non-relapsed patients [14, 32, 38, 39, 43, 59, 60]. For example, an investigation executed by Langhorst et al. [60] showed that elevated short-term perceived stress at the last visit before a disease flare predicted a relapse; however, perceived stress, along with other risk factors, explained merely 10% of the variability in exacerbation. An extensive longitudinal investigation of 62 UC patients in clinical remission over 45 months [39] found that long-term perceived stress was positively related to the experience of IBD symptoms over months to years. However, there was no association found between recent perceived stress and symptom exacerbation in the following months, and exacerbation was not associated with stressful life events, depressive symptoms, short-term perceived stress, smoking, disease duration, or severity. When assessing stress every month, it was found that perceived stress during any visit significantly increased patients' likelihood of experiencing a flare in the subsequent 8 months. This may suggest that patients who perceive higher stress are at a greater risk of relapsing with IBD after several months of experiencing a higher stress burden. These results imply that high long-term perceived stress in IBD patients may contribute to the role of stressful life events in disease progression. Additionally, there may be many factors contributing to IBD that remain predominantly unidentified. For example, the unpredictable nature of the disease, interference of symptoms, and management of bowel issues may induce long-term anxiety and emotional distress, leading to high long-term perceived stress in IBD. Likewise, gut health conditions in IBD may be highly vulnerable to stressful conditions. Thus, symptom flares may be more likely to occur following high levels of psychological stress.

Future longitudinal studies examining the effects of relapse and disease course on perceived stress in later months are needed to evaluate the directionality of the stress–IBD link. Although there is ample evidence of an association between perceived stress and the risk of a relapse, few researchers have found that only a portion of relapsing individuals report higher perceived stress than their non-relapsing counterparts, suggesting within-cluster variation in relapse groups. For example, Bernstein et al. [38] surveyed 3110 IBD patients every 3 months for one year and found that when comparing the perceived stress scores of major events in flare and non-flare groups, the flare group was more likely to report greater perceived stress for major events compared to the non-flare group. However, of the patients who had experienced a flare, only 50% of them reported higher perceived stress levels in a three-month period preceding active disease compared to those who did not flare. One implication of this finding is that greater variability may exist for reported perceived stress than for reported major life events. Perceived stress is a subjective, broad, multidimensional concept of stress that does not explain individual differences in stress sensitivity, the duration of stressors, and resilience to stress. The perceived stressfulness of a situation may be generally low; however, it can easily become high if the individual catastrophizes stressful situations or if the stressful event becomes prolonged and chronic.

Given the limitations of the conceptualization of perceived stress, studies in later years have evaluated biological markers of IBD activity in conjunction with perceived stress scores as predictors of disease activity [13, 42, 60, 62]. Several studies have found greater perceived stress and heightened responses to stress (and anxiety and depression) to be associated with lower microbiome diversity and epithelial damage and greater concentrations of CRP, higher levels of cytokine production, and elevated levels of bacterial lipopolysaccharides in individuals with IBD [13, 59, 63]. One study in particular found that UC patients in remission exhibited higher chronic perceived stress, anxiety, depression, and concentrations of CRP compared to healthy controls. Second, signs of dysregulated anti-inflammatory cell production, systemic low-grade inflammation, and the adrenergic upregulation of IL-10 production were found in UC patients, suggesting that perceived stress in IBD is associated with stress-related changes in the responsiveness of immune cells in IBD. Humbel et al. [59] found that higher perceived stress (as well as anxiety and depression) was associated with lower microbiome diversity in IBD patients. Lastly, a stress-induction experimental study on a small sample of 15 IBD patients in remission found that heightened responses to stressors were

linked with greater epithelial damage [63] which suggests that high perceived stress is associated with more severe disease conditions in IBD. However, few studies have not found a link between perceived stress scores and biological markers of disease [42, 62]. For example, in an assessment of elevated fecal calprotectin and disease symptoms in IBD patients, the occurrence of life events in the preceding 3 months was positively associated with the presence of inflammation and clinical symptoms; however, the level of perceived stress was not [42]. In a cross-sectional study, researchers evaluated associations between perceived stress, intestinal inflammation, and IBD symptoms. They found that in both CD and UC patients, perceived stress was strongly and positively related to symptom complaints but was not related to intestinal inflammation in both UC and CD patients [62].

In sum, these results suggest that greater perceived stress may increase the risk of disease exacerbation in IBD. High perceived stress may sustain existing IBD biological abnormalities that facilitate symptoms which may lead to the overall worsening of the condition. Inconsistent findings between perceived stress and the biological presence of IBD inflammation may be suggestive of inconsistent methods used to evaluate stress as well as the use of outdated measures to evaluate one's perceived stress and the need for evaluating types of stress. Lastly, perceived stress may also increase after a flare because of the stressful nature of IBD. For instance, the stress of the condition may have negative long-term effects on the mental and physical well-being of the patient, perpetuating existing gut sensitivities and increasing emotional reactivity to stress. Evidence has shown that IBD patients are burdened by psychological symptoms, particularly during active disease. A study found that in addition to experiencing bowel symptoms of urgency, bloating, and diarrhea, psychological symptoms such as worry and fatigue were identified as the most burdensome [64]. Another study evaluating IBD patients, a majority of whom were in remission, revealed that a significant proportion of them suffered from anxiety (41%) and expressed worry about their condition [65]. A two-year longitudinal study of 405 adult IBD patients conducted by Gracie et al. [66] found evidence for bidirectional effects of disease activity and the risk of psychological disorders. Patients with evidence of disease activity at baseline had higher rates of developing abnormal anxiety and depression scores, and similarly, patients with abnormal anxiety scores and inactive disease at baseline had higher rates of developing a future flare. Considering the greater need for attention to psychological factors in IBD patients, future longitudinal studies are needed to examine the daily influence of IBD on subsequent stress levels.

2. Discussion

The findings of the current literature support a link between psychological stress and IBD exacerbation. Studies on psychological stress provide sufficient evidence that more frequent stressful life events and higher levels of daily stress and perceived stress are associated with an increased risk of disease flares and IBD relapse. Thus, experiencing high psychological stress in prior months predicts an increased risk of IBD exacerbation by aggravating existing disease conditions. Due to longitudinal evidence revealing a stronger significant relationship between perceived stress and increased IBD activity within a proximal timeframe, conclusions can be drawn about a temporal link between stress and IBD exacerbation. However, there is not sufficient evidence to establish a causal link between stress and exacerbation. In addition, there is less support for the link between daily stress and disease exacerbation compared to stressful life events and perceived stress. Managing IBD may amplify daily stressors, potentially increasing levels of perceived stress that contribute to both psychological and physical symptoms of IBD. IBD patients have been shown to exhibit heightened psychological distress, anxiety, and tendencies towards pain catastrophizing [37, 67, 68]. This suggests that a relapse or increased disease activity may heighten stress reactivity and vulnerability via brain–gut connections. In turn, high stress can sustain existing gut sensitivities and IBD immune dysregulation in response to increased stress hormones. Additionally, daily stress levels may stem from the cumulative impact of daily emotional, social, and physical challenges associated with IBD. Relapsed and non-relapsed patients may experience similar levels of non-related IBD stress; however, relapsed patients likely experience more disease-related stress than non-relapsed patients, which, theoretically, should indicate a greater severity of stressful life events, daily hassles, and perceived stress. Thus, more research is needed to examine the bidirectional relationship between stress and IBD activity. Finally, inconsistencies and within-cluster variations in IBD relapse suggest that individual differences play a role in the link between stress and IBD exacerbation. Four major limitations of the research on psychological stress and disease activity are identified and discussed in detail below.

2.1. Study limitations

2.1.1. Limitation 1: the influence of daily stress on disease exacerbation in inflammatory bowel disease

The effects of daily hassles on disease progression and exacerbation in IBD are understudied because very few studies have been conducted on the topic of daily stress and hassles. In earlier research in the 1990s, daily stress influenced disease symptoms after controlling for the effect of major life events in a study looking at 10 CD patients followed for 28 days [54]. Another early 1990 study found that both daily strains and major life events independently contributed to the variance in symptoms of Crohn's disease and UC [69]. This research has not been replicated despite the recent events in our society such as the COVID-19 pandemic, the rise of technology and social media, social and political polarization, the rise in mental health awareness, a shift in the normalization of remote work culture, and environmental concerns. These life-changing events in our fast-paced, evolving society may have redefined stress in people's lives and may affect the way people experience daily hassles.

Second, the IBD literature lacks a complete exploration of the daily stress introduced by the disease process itself. Inventory checklists of stressful life events and global perceived stress measures have been the predominant metric for evaluating the amount of psychological stress linked to increased disease activity in IBD patients. It is important to note that individuals with IBD contend with both everyday life stressors and the stress of their disease. Across multiple studies, managing the illness's symptoms are commonly cited stressors [37]. IBD is stigmatized and a difficult disease to control in public [70], leading to an individual's daily challenges of locating suitable bathrooms at work or school, navigating dietary restrictions, concealing uncontrollable bowel symptoms, and coping with bowel stigma following their transparency about their illness [31, 71, 72]. A recent qualitative investigation into eating

habits among individuals with IBD revealed that managing symptoms involves the daily strain of identifying foods that are safe versus those that worsen the condition. Patients' limited understanding of how food affects bowel symptoms and abdominal pain tends to adversely affect their food selection, consumption habits, and enjoyment of communal dining [73]. Consequently, patients with IBD experience the stress of facing challenges in receiving accommodations or social support services due to being expected to prove their disability [74]. A lack of social support is also linked to worse health outcomes in IBD patients, which exacerbate the negative impact of IBD on quality of life and social interactions [74]. The effective management of IBD requires continuous medical treatment and lifestyle modifications, all of which are significant daily time commitments. In consideration of the psychosocial challenges of IBD, the daily stress that is associated with relapse and the exacerbation of symptoms may be quite significant and unique.

Given the majority of evidence linking perceived stress and stressful life events to an increased risk of subsequent relapses of IBD, it is clear that IBD patients who are under high levels of stress are at a greater risk of relapsing. However, it is not clear as to how daily stress contributes to an increased risk of disease exacerbation. While there is limited research on daily stress and IBD exacerbation, research has shown support for daily hassles being linked to greater physical health complaints. For example, a study examining the temporal relationship between daily hassles and physical health complaints among 255 undergraduate students [75] found the following patterns of daily hassles: (1) daily hassles from the previous day predicted current daily hassles, and daily hassles significantly predicted subsequent symptom complaints; (2) there was no bidirectional relationship, meaning that health complaints were not a significant predictor of future hassles; and (3) both daily hassles and health complaints showed daily stability. Understanding the nature of unique and emerging forms of daily stress in IBD patients is needed to understand the unique factors of daily stress that contribute to the disease course. Although daily hassles are construed as less significant, minor annoyances that occur in everyday life, we may be underestimating their effect. When daily hassles multiply and persist overtime, they can lead to chronic stress and have negative impacts on well-being. There may also be greater individual variability in daily stress because individuals respond differently to daily challenges. Therefore, there is an emphasis on the need for more robust assessments of daily hassles and more longitudinal designs to better understand the time dimensions and cumulative impact of stress on symptoms and the disease course.

The existing literature predominantly addresses stress experienced during the post-diagnosis of IBD, neglecting to elucidate the various stresses that occur before and after the onset of the disease. Distinguishing between types of daily stress precipitating IBD and stress coinciding with exacerbation poses a challenge. The most closely related assessment for stress stemming directly from IBD is the Quality of Life in Inflammatory Bowel Disease Questionnaire [76]. This instrument evaluates various dimensions of psychosocial impairments relevant to IBD, including emotional stress in daily life, work stress, disability, experiences of discrimination, and support from the social care system. Although developed by Kubesch et al. [76] for assessing IBD-related impacts in a German IBD patient cohort, its validity and reliability remain untested, limiting its application to pilot studies.

Together with the above findings and conclusions, IBD induces daily stress in social, interpersonal, and occupational contexts which can have a "wear-and-tear" effect, ultimately leading to the deterioration of both psychological and physical health and increase the risk of exacerbation. A case–control study found that active IBD was associated with greater IBD-related post-traumatic stress (PTS), hyperarousal symptoms, avoidance behavior, and alterations in mood and cognition among South Asian patients [77]. Daily stress can have significant connections to IBD-related post-traumatic stress by increasing sleep disturbance, fatigue, pain sensitivity, and treatment-avoidance behaviors (e.g., missing medical appointments, reduced medication adherence). Noteworthy findings from studies [38, 44, 52] indicate that everyday non-IBD stressors are more common than IBD stressors among individuals with IBD. However, the physical health aspect constitutes a more significant stressor for IBD patients compared to those without the condition. Therefore, research is needed to assess the influence of daily stress in IBD on disease activity and progression such as disease-related trauma and societal hurdles posed by the condition. A daily stress assessment covering both symptom-related and unrelated facets of IBD would help clinicians create effective interventions to help patients cope with daily hassles, speeding remission, and prolonging symptom relief as well as potentially reducing the risk of IBD onset in genetically predisposed individuals who are highly reactive to stress.

2.1.2. Limitation 2: stress conceptualization and disease activity operationalization

Another limitation is the lack of clarity regarding what constitutes stress. The way objective life events are interpreted depends on the individual perceiver, who holds their own subjective view of stress. Individuals may have their unique definition of stress based on their sensitivities, reactivity, and beliefs and attitudes about stress, shaping how stress impacts their physical state in distinctive ways. The stress of an event is governed by how it is perceived, interpreted, and reacted to [78]. Eustress and distress are two constructs of stress that have been widely studied in occupational contexts and are differentiated by the extent to which a stressor is appraised as a challenge or threat. Distress refers to stress that induces negative arousal associated with discomfort, dissatisfaction, disengagement, and impairment, whereas eustress refers to a state of positive emotional arousal associated with beneficial outcomes [79]. Eustress arises from situations that are perceived as challenging, manageable, and rewarding such as starting a new job, getting married, or participating in a thrilling activity. However, distress tends to arise when challenges become threatening, unmanageable, and unrewarding. Most studies have equated stress with negative aspects of life changes and subjective distress; however, the impacts of eustress on health outcomes have been largely ignored in the literature. Future studies should employ explicit stress definitions and reexamine the stress methodology to understand how eustress and distress are associated with IBD relapse.

Overall, studies have measured disease activity in multiple ways to understand IBD exacerbation. When a mixture of clinical and biological indexes are utilized as the operational definition of disease activity in IBD, studies may yield differing or conflicting results. Biological markers such as intestinal inflammation are considered a reliable method of confirming active disease and symptoms. However, they do not capture the entire exacerbation experience

of IBD. Alternatively, clinical indicators such as reported symptom severity and frequency may overestimate the presence of relapses, particularly when individuals remain symptomatic despite biological markers indicating no signs of an active flare. In a study executed by Singh et al. [44], a percentage of participants during periods of inactive disease reported aching joints (17%), diarrhea (13%), abdominal pain (9%), and fatigue (15%), suggesting that patients in remission can still have symptoms of IBD. Increasing evidence suggests that irritable bowel syndrome (IBS) can co-occur with IBD in some patients. IBS is a chronic functional gastrointestinal disorder that shares many symptoms with IBD but lacks the structural and physiological characteristics of IBD. IBS-type symptoms commonly occur in IBD patients without active inflammation. Between 11% and 35% of IBD patients in clinical remission have reported IBS-type symptoms [14], potentially explaining why symptoms may persist in IBD individuals who are in clinical remission. This further adds complexity to the obstacle of identifying IBD exacerbation, indicating that a more standardized and comprehensive approach is needed to evaluate disease activity in IBD.

In longitudinal studies, it is proposed that forthcoming studies employ a single-dimensional conceptual measure of IBD symptom activity. This may involve tracking changes in combined self-reported symptom activity by calculating the sum of the standardized scores of each symptom complaint for symptom severity, frequency, and duration from the initial assessment to subsequent time points across a sample. Symptom severity should be based on the rated intensity of each symptom complaint present. Frequency should be determined by the number of times each symptom complaint occurs. Lastly, symptom duration should be determined by the length of time (e.g., hours, days, weeks) each symptom is present from start to end.

2.1.3. Limitation 3: evaluating the directionality between stress and disease activity

Most studies have assessed whether elevated levels of stressful events, daily stress, and perceived stress predict exacerbation in subsequent months to years. However, there is a scarcity of research investigating the bidirectionality between subsequent stress and disease activity. The bulk of studies have evaluated a one-directional link: whether higher levels of perceived stress, daily stress, and stressful life events increase the future risk of disease activity. High stress levels may perpetuate existing immune dysfunction and aggravate disease which generates more severe physical symptoms that become the main source of stress and contribute to more stressful events and daily problems and greater perceived stress in later months. The specified interferences of the illness intensify discomfort, increase stress, and may have long-term impacts on stress reactivity.

Furthermore, there is not enough evidence to suggest that stress causes the onset of IBD as there is a scarcity of studies examining whether stress leads to the development of IBD. A review examined the impact of stress interventions on reducing disease activity in IBD and concluded that while stress interventions can improve the mental well-being and quality of life of patients with IBD, there is insufficient evidence to definitively state that heightened stress is a causal factor of disease activity in IBD [12]. This is in line with a meta-analysis [80] which concluded that adverse childhood experiences (ACEs), stressful or traumatic events occurring during childhood, are not significantly linked to the development of immune-related disorders in adulthood; however, there is an association with specific variables, though their effect sizes are small (e.g., emotional abuse, neglect, and witnessing violence). Moreover, Cohen et al. [19] argued that most people who experience normative stressful events and traumatic events do not develop an illness. While it is possible that significant levels of stress can increase the risk for IBD, genetic risks, behaviors, mental health, and environmental factors may be other contributors to IBD. Nevertheless, there is sufficient evidence to verify that stressors occurring in IBD-diagnosed individuals can exacerbate discomfort, elevate stress levels, and potentially have enduring effects on disease activity.

Finally, there is a likelihood that additional undisclosed findings could yield comparable nonsignificant results akin to those observed in several studies such as those of Lerebours et al., Vidal et al., and Riley et al. [40, 46, 47]. Thus, significant findings regarding the temporal link between stress and IBD exacerbation should be considered with caution given the potential impacts of disease-induced stress and symptoms on this alleged connection. Recognizing the potential for unpublished studies with nonsignificant outcomes is important to consider.

2.1.4. Limitation 4: moderators of the stress—inflammatory bowel disease link

Little empirical attention has been given to moderators of the stress–IBD link. The overall severity level of disease, disease control, symptoms, prognosis, and treatment approaches can vary considerably between patients as demonstrated in studies revealing within-cluster variation in relapse groups. For example, in a study referenced earlier, only 50% of relapsing individuals reported higher perceived stress than those who did not relapse [38]. Elements of personality tendencies, psychological disorders, illness perceptions, and emotion regulation found in IBD patients [81] may be influential on how one experiences and copes with stressors and symptoms. These split findings may suggest individual variability in the relationship between stress and IBD exacerbation. While major events often require major changes that impact the well-being of most individuals, daily stress is often less significant; however, the impact of daily stress on physical well-being might hinge on individual sensitivities. For this reason, moderators are important to consider in the stress–IBD link, especially in daily stress studies where individual differences may be better captured.

2.1.5. Resilience

Future research studies should consider the role of resilience in the stress–IBD link, an individual characteristic that refers to an ability to psychologically and behaviorally adapt to a stressor [82, 83]. Highly resilient individuals tend to experience fewer negative consequences when facing stress and may learn to manage flare-ups more effectively during high stress [84]. By adopting effective daily resilience strategies, individuals may enhance their resilience, potentially reducing flare-up risk. It is also important that clinicians help patients apply adaptive coping strategies to support resilience to the impacts of IBD stigma. Resilience in chronic illness has shown to be associated with a variety of positive health outcomes including improved recovery, improved mental health, the adoption of health-promoting behaviors, improved quality of life, and effective coping strategies [85]. The role of resilience in stress and

IBD exacerbation has seldom been examined in IBD; however, a systematic review on resilience in pediatric IBD emphasized associations between resilience and improved quality of life, enhanced social functioning, and better mental health outcomes [86]. In a register-based cohort study [87], it was discovered that adolescents with low levels of resilience had a higher risk of developing IBD in adulthood. However, the magnitude of this effect was small, suggesting that stress alone is not a major contributor to IBD risk but likely influences conversion from subclinical to symptomatic disease among those with low stress resilience and a proinflammatory tendency. Moreover, recent studies revealed that high levels of resilience were associated with lower disease activity, better mental health outcomes, and fewer surgeries for IBD [88, 89]. Therefore, individuals with IBD who possess strong resilience when facing significant stressors may mitigate their risk of flares because their capacity to perceive positive outcomes and compartmentalize negative emotions could diminish the adverse impact of stress on gut health in IBD. However, there are key limitations of these resilience studies worth noting. One is the use of cross-sectional designs to evaluate associations between resilience and disease, which implies that resilience cannot be determined as a causal factor and greater disease burden could lead to lower resilience rather than vice versa. The second is the study of resilience and disease activity in a linear fashion. As individuals continue to live with the conditions of IBD, resilience to stress may change over time and either increase as disease sufferers learn to control their IBD or decrease during periods when the disease burden persists. Thus, the role of resilience in the temporal link between life stress, and IBD exacerbation should be tested longitudinally to fully understand how resilience promotes positive adaptation to stress.

2.1.6. Psychoeducation and clinical approaches to stress

Psychoeducation in GI offices about managing stress and mental health during and between flare-ups is essential for better overall care. A recent study highlighted that mental health disorders such as anxiety, depression, and impaired quality of life are common among IBD patients, particularly greater in women with newly diagnosed IBD [90]. This underscores the importance of addressing mental health needs in IBD, especially early in the disease course. Gastroenterologists should routinely assess the mental health of their patients and refer them to therapists, as needed. Healthcare providers, when interacting with patients, should focus on giving empathetic responses as a form of social support. Additionally, there is a need for culturally competent care in IBD and mental health services due to more frequent PTSD symptoms of IBD found in South Asian individuals compared to white individuals [77]).

It is also essential to educate family members about IBD. Stigma surrounding the condition, illness uncertainty, catastrophizing, and feelings of embarrassment often contribute to increased stress and reduced quality of life [21]. Misconceptions (e.g., the belief that IBD can be cured by food choices or that symptoms are exaggerated) can lead to increased stress and lower quality of life [74]. Patient advocacy groups have emerged to destigmatize IBD and help patients cope with the stigma of the condition [74]. A recent qualitative research synthesis exploring the lived experiences of stigma in individuals with inflammatory bowel disease [91] showed that IBD subjects reported feelings of otherness which fluctuated between feelings of exclusion and integration. Feelings of otherness created a sense of disconnection between their "ill" self and former healthy self, which led to social estrangement. Thus, education is critical to improve the understanding of IBD's psychosocial impact on health and prevent stigmatizing interactions with patients.

It is important for healthcare providers to standardize clinical approaches to reducing daily stress levels and enhancing social support in IBD. For example, individuals with IBD should work with rehabilitation professionals to identify work accommodations for IBD, allowing employers and supervisors to provide flexibility in work or school schedules [92]. This flexibility may significantly reduce stress, especially during flare-ups. Clinicians should teach IBD patients coping skills tailored to the condition, including deep breathing, mindfulness, meditation, and CBT techniques, such as reframing "I'm an ill person" to "my large intestine is sick, but other parts of my body are healthy". IBD-specific CBT has shown to be effective in improving the mental health and disease-specific quality of life for IBD patients [93, 94], demonstrating the effectiveness of managing emotional distress and depression associated with the disease. An evaluation of a multimodal mind–body–medicine-based stress management and comprehensive lifestyle modification program found that 79% of intervention-group patients showed improved disease-related quality of life immediately during post-intervention compared to 44% of control-group patients [95]. The study also found secondary benefits of the intervention, such as improved inflammatory biomarkers. Mindfulness-based therapy has shown to be related to reduced IBD inflammation by decreasing inflammatory biomarkers of IBD such as fecal calprotectin, C-reactive protein, and interleukin-6 [21]. Additionally, therapists should prioritize helping clients manage IBD symptoms directly, rather than attributing them solely to anxiety. Misunderstanding of the condition and its frequent confusion with IBS can lead to patients feeling invalidated, especially when therapists mistakenly associate the condition with anxiety.

Moreover, light- to moderate-intensity exercise can aid stress management, mental health, sleep quality, disease symptoms, fatigue, and cardiorespiratory fitness in IBD [96], although vigorous exercise should be avoided. Participation in support groups, both online and in person, can be valuable resources for patients learning to cope with IBD. For example, a 2013 study showed that online support groups can provide informational and emotional support for IBD [97] and that social support is linked to improvements in health and well-being [98]. However, it is important to be aware that while online social support is typically beneficial, online social interactions can also lead to negative experiences due to unwanted confrontation or undesirable forms of support [99]. Thus, clinicians should be aware of both the potential benefits and limitations of social support for IBD when assessing stress levels and management in IBD.

2.1.7. Other limitations: recall bias, sampling cohorts, patient compliance, and variability in study design and methodology

Most investigators included patients with a clinically determined IBD diagnosis identified from IBD research registries and/or healthcare professionals. In cross-sectional studies, the recall of life events after a diagnosis can make it likely for individuals to emphasize recent events that they believed caused their illness. For example, Levenstein et al. [39] found that symptomatic patients were more likely to recall major life events in the previous six months compared to asymptomatic patients. These patients were also more likely to attribute highly stressful life events as the cause

of their disease flare-ups. Hence, beliefs about stress and the effects it has on illness may actuate memory of recent stressful events and the overreporting of perceived stress in prior months in individuals with IBD who have relapsed. Therefore, it would be advantageous for future investigators to develop additional longitudinal studies that track daily stress levels and symptom activity using diary-based approaches to mitigate recall bias.

Second, inconsistency has been found in the criteria of sampling cohorts. For instance, certain researchers such as Zhang et al. [61] and Langhorst et al. [60] have concentrated solely on specific subsets of IBD patients, either with CD or UC, while others such as Larsson et al. [31] and Rogala et al. [52] have investigated a mixed cohort consisting of both CD and UC patients. While CD and UC both fall under the umbrella of IBD, they represent distinct conditions that may exhibit varied responses to stress. Thus, more future studies examining CD and UC patients distinctively are warranted. Additionally, many researchers such as Langhorst et al. [60] have limited their recruitment of IBD patients to individuals in clinical remission at the time of study enrollment, which consequently restricts the ability to observe bidirectional effects of relapse on subsequent stressful life events and perceived stress. Furthermore, studies on stress and IBD [38, 42, 60, 62] either exclude or control for patients with a history of IBD surgeries, pregnancies or breast-feeding, or psychiatric comorbidities. Having a more restrictive exclusion criterion can limit sample size, diversity, and statistical power as well as exploratory variables to consider in the stress–IBD link. Factors such as surgeries, treatment compliance, diet adherence, or substance dependence may be important to model in future studies to evaluate potential health behaviors by which stress may indirectly exacerbate IBD.

Understandably, methodological limitations are common in IBD studies. There are limited numbers of longitudinal studies on stress and exacerbation because it is difficult to follow patients over a long period to allow an adequate number of relapses to occur and to determine how quickly stress acts on the gastrointestinal tract. Furthermore, these studies require a high degree of patient compliance in the recording of detailed life events, daily stressors, and symptoms. As a result, there is variability in the study designs, methods, and inclusion/exclusion criteria. These studies lack clear methodologies, and cohort sampling is inconsistent (e.g., mixing Crohn's and colitis patients or varying control variables). The inclusion of multiple variables beyond the primary focus (such as depression, anxiety, and quality of life) further complicates the potential for a systematic review. Finally, given the complexity of IBD and the emerging nature of stress-related research in this field, rigorous studies suitable for a systematic review are still limited. Future investigations should implement more longitudinal designs and methods that increase patient compliance (such as the use of wearable tracking devices) to effortlessly track daily stress and symptom activity in IBD.

2.2. Future directions

In light of the major limitations, future research may benefit from the following directions in examining the link between stress and disease exacerbation. First, because the research lacks well-defined conceptualizations and operational definitions of psychological stress and disease activity, a standardized measure of disease activity and a new IBD stress measure are needed in future investigations to improve assessments of stress and disease exacerbation. The current assessments used in IBD research do not wholly reflect the different elements of stressors related to IBD. Differentiating the types of stress before and after relapse is an important avenue for understanding stressors that coexist with IBD versus those that precede the development of IBD. Second, the bulk of longitudinal research has focused on major life events and global perceived stress but less has been conducted on daily stress or hassles. Daily stress may provide the best assessment for evaluating the directionality of the link between stress and IBD. To improve this avenue, future studies should implement more well-executed and lengthier longitudinal designs of the influences of daily hassles on symptoms while also providing opportunities to optimize subject compliance.

Lastly, more empirical attention should be given to explore moderators of the link between stress and disease activity such as resilience, psychoeducation among GI providers, standardizing clinical approaches to reducing stress in IBD, and IBD education in families to destigmatize IBD. Longitudinal studies are also needed to understand the role of individual differences in perceived stress and disease activity as well as the effects of changes in symptoms on stress over time. Controlled clinical trials should examine mechanisms by which stress resilience orchestrates beneficial effects in IBD. Alongside resilience and other individual factors, the role of psychoeducation in GI offices and standardized clinical approaches to patient IBD care should be examined in the relationship between stress and exacerbation in IBD.

3. Conclusions

This review examined empirical evidence regarding the link between psychological stress and IBD exacerbation. Specifically, three lines of stress research were included in this review: stressful life events, daily hassles, and perceived stress. This review indicates that psychological stress is a risk factor for disease exacerbation in IBD patients. Additionally, the detrimental impacts of stress on disease may be moderated by individual differences such as one's resilience to stress and behaviors that safeguard one's health during stressful periods. This relationship may also be moderated by clinical approaches to mental health and stress in IBD and psychoeducation about IBD. In addition, more research is needed to fully understand the directionality of the link between stress and IBD, particularly how daily stress influences the clinical course and progression of IBD. The authors hope that this review will increase public awareness about stress as a risk factor for IBD exacerbation. IBD should be evaluated holistically, and specific disease-induced stressors ought to be considered in the disease course to increase social and mental well-being in patients.

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