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Systematic review: the role of psychological stress in inflammatory bowel disease

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Summary

Background: Psychological stress is a possible factor in the disease course and poor psychosocial outcomes in inflammatory bowel disease (IBD). Understanding the exact relationship between stress and health has been hampered by methodological issues and how stress has been defined and measured.

Aims: To explore the association between stress and disease outcomes, investigate the impact of stress on psychosocial outcomes, and evaluate the efficacy of interventions in reducing stress for people with IBD

Methods: We performed a systematic review, searching Medline, CINAHL, Embase and PsycInfo databases on 21 January 2021. We included prospective studies that recruited people with IBD who were aged 16 or over and that measured psychological stress or distress. Analyses included Critical Appraisal Skills Programme quality assessments of included studies and narrative analyses against each research question.

Results: We reviewed 38 studies with 4757 people with IBD, and included 23 observational and 15 interventional studies using 36 different instruments to measure stress. Perceived stress was the most frequently studied concept and preceded IBD exacerbation. Only three studies examined the relationship between stress and psychosocial factors. Cognitive behavioural interventions may reduce stress and other interventions with disease-specific stress, but more studies are needed where groups have comparable baseline characteristics and potential harms are considered alongside benefits.

Conclusion: Psychological stress appears to precede IBD exacerbation, although what role it plays in psychosocial outcomes and how it is best managed is unclear. Further research needs to examine the differential effects of stress on disease subtypes and IBD in flare and remission.

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1 | INTRODUCTION

Inflammatory Bowel disease (IBD) is an autoimmune condition associated with fluctuating inflammation of the digestive system, the two main disease types being Crohn's Disease (CD) and Ulcerative Colitis (UC). It is a chronic condition typically diagnosed between 20 and 40 years old[1] and affects 6.8 million people worldwide.[2] The underlying cause of IBD is unknown, so treatment is focused on achieving and maintaining remission.

Previous systematic reviews have established that quality of life is lower in people with IBD compared to the general population,[3] when IBD is active rather than inactive, and those with CD rather than UC, improving over the disease's duration.[4] Anxiety and depression are common co-morbidities that interact with IBD.[5] Their exact relationship has yet to be established due to a lack of prospective designs.[6] A recent meta-analysis on whether there was a causal link between anxiety and depression, and symptom exacerbation was inconclusive.[7] Psychological interventions have limited beneficial effects on quality of life and depression in people with IBD, with more trials needed to determine their impact on disease activity.[8] There remains a need to better understand the psychological factors affecting people with IBD.

Lazarus and Folkman define stress as 'a relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her wellbeing'.[9] This relationship is multi-faceted and informed by personal and environmental antecedents, the nature of the stressor and our perception of it, how stressors are appraised and their immediate and long-term effects (see Figure 1 for more details). Latterly, emotions have been recognised as inherent to the appraisal of stress in both psychological[10] and physiological[11] models, leading some researchers to use the concepts of stress and distress interchangeably. Stress has been associated with increased disease activity[12] and lower quality of life[13] for people with IBD. It has been suspected of playing a role in disease onset since the 1930s[14] and as a potential trigger in disease flares.[15,16] Previous reviews have found a significant association between stress and IBD disease activity in 13/18 studies[17] and 6/11 studies[18] reviewed. These reviews have raised concerns about heterogeneity in study design, participant samples and disease activity and stress measures that have made establishing the relationship between stress and disease activity difficult.[7,17,18]

This review re-examines how stress relates to IBD activity. It focuses on prospective studies as the inclusion of cross-sectional designs in previous reviews has prevented a discussion of any temporal links between stress and disease activity. It explores the current literature on the relationship between stress and psychosocial outcomes to inform the potential role of stress in psychological disorders in adults with IBD. Psychosocial outcomes include psychological factors where individuals' cognitive processes affect their mental health, social factors where societal variables affect an individual's experiences, and the effect of the interaction between these two on a person's outlook and behaviour.[19]This review examines what preventative interventions may reduce stress in IBD, which has not been reviewed previously.

The review's specific research questions are

1. What association is there, if any, between psychological stress and IBD outcomes?
2. What association is there, if any, between psychological stress and IBD psychosocial outcomes?
3. What is the effect of interventions for people with IBD on psychological stress?

2 | METHODS

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021230143. This systematic review followed the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta Analysis] statement.[20]

Medline (1946–2021), CINAHL (1981–2021), Embase (1974–2021) and PsycInfo (1806–2021) were searched on 21 January 2021 with no restriction on years of publication. Key search terms used were variations on psychological stress or distress and IBD. An initial search strategy was developed for Medline (see Table S1) and then adapted as appropriate for other databases. Studies were included if they were published in English in peer-reviewed journals, had a prospective design, a measure of psychological stress or distress and IBD participants who were 16 years old or over. Paediatric, animal and laboratory studies were excluded as well as those with a cross-sectional design. References were searched from included studies and previous systematic reviews[17,18] to ensure all relevant papers were included. All studies were screened by one reviewer (J.B.) and papers reporting the same study were coalesced.

Quality assessments of included studies were conducted using the appropriate Critical Appraisal Skills Programme checklist,[21,22] assessing four specific domains: (1) validity of study design, (2) methodological validity, (3) reliability of the findings and (4) whether the findings can be applied locally. Quality assessments were conducted independently by two reviewers (J.B. and Y.Y.) and consensus was reached through discussion.

Data for synthesis were extracted by J.B. via Covidence, a systematic review management system (see Table S2 for data items). The extracted data of 20% of the included studies (randomised and stratified by design) were checked by a second reviewer (H.S.). Stress was conceptualised in a variety of ways amongst the reviewed studies and therefore could not be treated as a single, cohesive concept. Studies' stated definitions were compared with each other and against Lazarus and Folkman's transactional model of stress[9] (see Figure 1) to identify stress subtypes. Where no definition was stated, the study's choice of stress measures was used to determine the implied definition. Seven stress subtypes were identified, depending on whether they focused on external events (life events, daily hassles, stressors), self-reports of stress experienced (perceived stress), biological markers (stress reactivity),

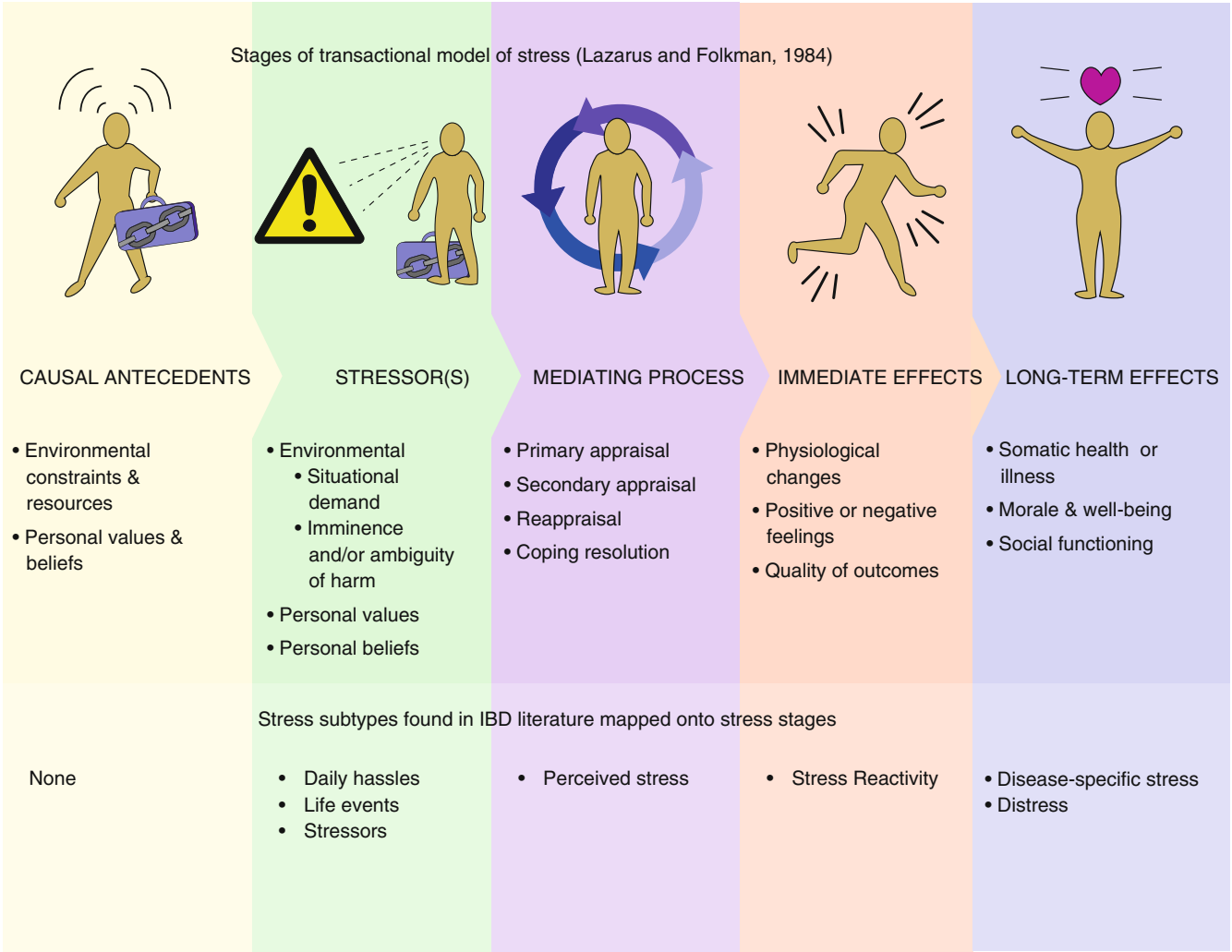

FIGURE 1 Stages of the transactional model of stress (Lazarus and Folkman[9]).

concerns about IBD's impact on lifestyle (disease-specific stress) or mood ratings (distress). Some studies looked at more than one subtype of stress and these results were analysed separately. Narrative analyses were undertaken using these subtypes against each of the research questions. A meta-analysis was not possible due to the heterogeneity of the studies.

Any measure explicitly described by the authors as measuring stress or that was designed to measure stress was eligible for inclusion. All outcome measures could be self-reported (e.g. questionnaire, diary) or investigative (e.g. blood test, endoscopy) and no measures were excluded due to lack of previous evidence of validity or reliability assessment. As this review focused on prospective studies, outcome measures were only included if they were collected at baseline and at least one subsequent time point. However, there was no limitation on either the number of time points or the length of follow-up. Additional data were collected on the publications' details, the study (including how stress was defined), the participants' characteristics, the research design and outcomes, analyses used and recommendations for research and clinical practice.

3 | RESULTS

3.1 | Study selection

The search strategy led to 7651 initial hits and 6861 after de-duplication. Using the inclusion and exclusion criteria, 6760 records were screened out at the title and abstract stage, leaving 101 reports to assess for eligibility at the full-text stage. This led to the further exclusion of 60 reports. Three studies[15,16,23] were reported in two papers each, so the 41 identified reports coalesced into 38 studies for inclusion (Figure 2). A manual search of citations in previous systematic reviews[17,18] and included studies did not result in any additional inclusions.

3.2 | Studies' overview

Thirty-eight included studies[12,15,23–58] are summarised in Table 1 and their participant characteristics, design and stress measures are outlined below. Tables 2–4 outline the studies' findings and, where

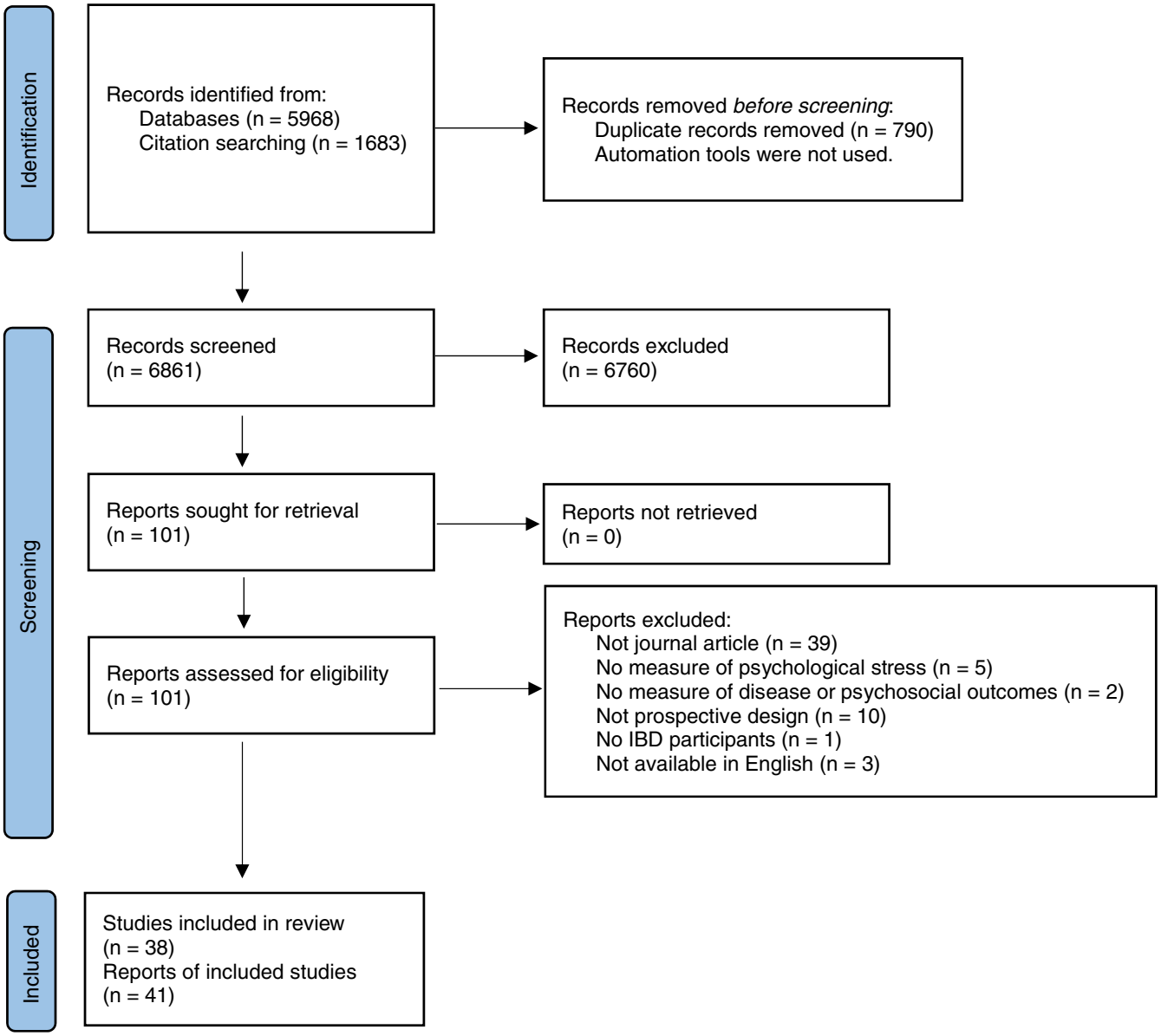

FIGURE 2 PRISMA flow chart. Adapted from: Page et al.[20] For more information, visit: http://www.prisma-statement.org/.

reported, strengths of associations. A narrative synthesis relating to each research question follows with observational studies informing analysis for research questions one and two, and interventional studies for research question three. These analyses look specifically at the findings in relation to the seven stress subtypes identified (see Section 2). Perceived stress was researched in 22 studies,[12,15,24–32,34,37–39,41,42,46,48,49,55,58] typically using the Perceived Stress Questionnaire (PSQ), Perceived Stress Scale (PSS) or a visual analogue scale. Distress was measured in 10 studies[23,24,35,37,40,44,47,51,52,58] using 11 different instruments and life events were measured in eight studies[15,24,26,30,32,36,53,57] with seven different instruments. Fifteen studies[12,15,24,26,30,32,34,36,37,39,48,49,51,54,58] examined more than one type of stress. While perceived stress was researched in cohort, experimental and interventional study designs, life events were measured in cohort designs only, and stress reactivity and disease-specific stress in only interventional and experimental designs.

3.2.1 | Participant characteristics

The studies reported on a total of 4757 people with IBD, with individual study sizes ranging from 10 to 704 participants. The proportion of female participants ranged from 36% to 83%, except in one study,[43] which had an exclusively female sample, and the average age per study was between 31 and 56 years old. Six studies[26,27,40,41,46,55] reported participants' ethnicity.

Five studies[28,44,50,52,55] did not report participant numbers by IBD subtype (i.e. CD and UC), 11 studies[24,25,28–30,34,39,41,42,49,57] included only participants with inactive IBD at baseline, and eight

TABLE 1 Overview of included studies

Study ID (recent–oldest), country	Study design	Follow-up (months)	Stress type	Participants (% female)	Disease activity at baseline	Age, mean years (SD)
Hirten 2020, USA	Cohort	10	PS	UC: 16 (60%)	Mixed	33[a] (not reported)
Koch 2020, Germany	Intervention	6	PS	UC: 77 (72%[b])	Inactive	45 (13.3)[b]
Jordan 2019, UK	Intervention	Not reported	D	CD: 12, UC: 15 (70%)	Not reported	37.4 (12.6)
Lores 2019, Australia	Intervention	13	D	IBD: 183[c] (54%)[d]	Inactive: 44%, active: 56%	40 (15.1)[d]
Wintjens 2019, Netherlands	Cohort	>12	PS, LE	CD: 248, UC: 169 (not reported)	Not reported	Not reported
Wynne 2019, Ireland	Intervention	5	PS, S, D	CD: 38, UC: 41 (54%)[b]	Inactive: 95%[b], active: 5%	40.6 (11.2)[b]
Luo 2018, China	Cohort	12	PS	UC: 229 (49%)	Inactive: 25.8%, active: 74.2%	40.4 (12.6)
Sexton 2017, Canada	Cohort	6	PS	CD: 238, UC: 179 (64%)	Inactive: 52%, active: 48%	CD: 54.7 (13.0), UC: 56.9 (13.1)
Sirois 2017, Various[e]	Cohort	7	PS	IBD: 144[c], Arthritis: 163 (78%)	Not reported	38.3 (12.7)
Berding 2016, Germany	Intervention	3	DS	CD:100, UC: 81 (69%)	Inactive/low activity	39.9 (12.7)
Bernstein 2016, Canada	Cohort	3	PS, S	CD: 233, UC: 199 (63%)	Mixed	55.4 (13.16)
Neilson 2016, Australia	Intervention	7	D	IBD: 58[c] (55%)	Inactive: 60%, active: 40%	36.38 (11.49)
Gerbarg 2015, USA	Intervention	6	PS, D	CD: 18, UC: 9, IC/LP: 2[f] (59%)	Not reported	56 (not reported)
Berrill 2014, UK	Intervention	13	PS, DH	CD: 21, UC: 45 (77%)	Inactive	44.4 (11.7)[b]
Jedel 2014, USA	Intervention	13	PS, SR	UC: 53 (44%)[b]	Inactive	46.04 (12.80)[b]
Jaghult 2013, Sweden	Case-Crossover	6.2	PS	IBD: 50[c] (60%)	Inactive	40 (1.31)
Keefer 2013, USA	Intervention	12.2	PS	UC: 50 (54%)	Inactive	38 (not reported)
Langhorst 2013, Germany	Cohort	12[g]	PS	UC: 75 (not reported)	Inactive	Not reported
Boye 2011, Norway/Germany	Intervention	20	D	CD: 56, UC: 58 (68%)	Active	40.4 (11.0)[b]
Camara 2011, Switzerland	Cohort	20	PS	CD: 468 (51%)	Inactive	41.83 (14.42)
Bernstein 2010, Canada	Cohort	12	PS, LE	CD: 426, UC: 278 (61%)	Mixed	52.1 (13.0)
Langhorst 2007, Germany	Experimental	Same day	SR	UC: 22, Healthy: 24 (100%)	Inactive: 77% active: 23%	37.8 (1.4)[h]
Maunder 2006, Canada	Experimental	7–37	PS, SR	UC: 93 (48%)	Inactive: 71%, active: 29%	44.23 (10.74)
Mawdsley 2006, UK	Experimental	Same day	PS, SR	UC: 35, Healthy: 22 (48%)[b]	Inactive	44 (not reported)[b]
Vidal 2006, Spain	Cohort	11[g]	LE	CD: 79, UC: 76 (48%)	Inactive	Not reported
Mardini 2004, USA	Cohort	48	D	CD: 20 (67%)	Not reported	31[a] (not reported)
Bitton 2003, USA	Cohort	12	PS, LE, D	UC: 60 (62%)	Inactive	39 (9.4)
Mussell 2003, Germany	Intervention	10	D, DS	CD: 14, UC:14 (57%)	Inactive/low activity	CD: 44.9 (11.3), UC: 39.7 (11.9)
Levenstein 2000, Italy	Cohort	45[g]	PS, LE	UC: 62 (47%)	Inactive	38.8 (13.0)
Loudon 1999, Canada	Intervention	3	DS	CD: 12 (83%)	Inactive/low activity	38.3 (7.5)

(Continues)

TABLE 1 (Continued)

Study ID (recent–oldest), country	Study design	Follow-up (months)	Stress type	Participants (% female)	Disease activity at baseline	Age, mean years (SD)
Traue 1999, Germany	Cohort	5	DH	CD: 20 (60%)	Active	33.4 (not reported)
Porcelli 1996, Italy	Cohort	8	D	CD: 23, UC: 81 (38%)	Mixed	37.8 (1.1)[g]
Greene 1994, USA	Cohort	12	PS	CD: 6, UC: 5 (36%)	Not reported	48 (not reported)
Duffy 1992, USA	Cohort	8	PS, LE, DH	CD: 73, UC: 50 (47%)	Inactive: 70%, active: 30%	Not reported
Garrett 1991, USA	Cohort	1	LE, DH	CD: 10 (60%)	Not reported	41.2 (10.55)
North 1991, USA	Cohort	36	LE	CD: 24, UC: 8 (not reported)	Mixed	Not reported
Schwarz 1991, USA	Intervention	4	DH, DS	CD: 10, UC: 10, NK: 1[i] (57%)	Not reported	43.9 (12.45)
Milne 1986, Canada	Intervention	13	DS	IBD: 80[c] (60%)	Inactive: 71%, active: 29%	36.8 (10.37)[b]

Abbreviations: D, distress; DH, daily hassles; DS, disease specific; LE, life events; PS, perceived stress; S, stressors; SR, stress reactivity.
[a]Median.
[b]Intervention participants only.
[c]IBD numbers not reported by subtype.
[d]Screening stage.
[e]Online—participants from USA, Canada, UK and other countries.
[f]IC/LP indeterminate colitis or lymphocytic pancolitis.
[g]Or until relapse.
[h]Standard error of mean.
[i]NK Data not known for one participant.

studies[32,36–38,40,47,54,55] did not report whether participants had am active disease or not at baseline.

3.2.2 | Design

Nineteen prospective studies used cohort designs,[12,15,23–27,29–32,36,38,46,47,53,55–57] one a case-crossover design[28] and three experimental designs,[43,48,49] while measuring stress, psychosocial and/or disease outcomes, though that was not necessarily the study's primary aim. Fifteen studies trialled interventions for people with IBD and included a stress outcome measure.[33–35,37,39–42,44,45,50–52,54,58] All took place in either Europe or North America, except for two studies in Australia,[44,52] one in China[46] and one online study by researchers based on Canada and the UK and whose participants were from North America, UK and 'other' countries (not described).[55] Tables S3 and S4 summarise the quality assessments.

3.2.3 | Stress measures

The included studies used a combined total of 36 different instruments to measure stress with 23 instruments being used in only one of the included studies (Table S4). The most common stress measures used were the Perceived Stress Questionnaire (PSQ) in 10 studies[25,29,30,34,35,37,39,41,42,49] and the Perceived Stress Scale (PSS) in eight studies.[12,15,24,27,29,31,46,55]

3.3 | Research question 1: Stress and IBD outcomes

Twenty-two studies examined the relationship of stress with disease outcomes (Table 2),[12,15,23–32,36,38,43,46–49,53,56,57] with seven of these studies also examining psychosocial factors.[27,29,30,32,46,53,56] The most common disease outcome researched was the impact of stress on disease activity, although hospitalisation and inflammatory responses were also explored. Most studies used robust outcome measures with disease activity typically reported using indices (such as the Crohn's Disease Activity and Harvey-Bradshaw Indices), endoscopy or symptom diaries. There was a comprehensive follow-up of participants with nine studies including over 100 participants,[12,15,23,25,26,31,32,46,57] although five studies included 20 people or fewer.[27,36,38,47,56] The majority involved a mixture of people with active or inactive disease or did not report disease activity levels at baseline, with confounding factors such as medication and surgery not always being identified and/or accounted for in the design of the study (Tables S2 and S3).

3.3.1 | Disease activity

Nineteen studies examined the relationship between stress and disease activity,[12,15,23–32,36,38,47,48,53,56,57] with significant associations reported in 17 (Table 2). Stress preceded disease exacerbation in 11 studies[15,24,25,27–32,47,48] with two of these studies[27,31] reporting a bidirectional relationship. Two studies found no significant

TABLE 2 Summary of findings—psychological stress and disease outcomes

Study ID	Study design[a]	Stress type (measures)[b]	Disease outcomes (measure)[c]	Key findings[d]
Bernstein 2010	Cohort	PS (PSS), LE (AO)	Disease Activity (Index—MIBDI)	High PS in preceding 3 months was associated with exacerbation (OR 2.40 95% CI 1.35–4.26); LE more likely in preceding 3 months in flare group (OR = 1.31 95% CI 0.78, 2.19)
Bernstein 2016	Cohort	PS (PSS), S (SSS)	Disease Activity (Index—MIBDI)	Higher mean PS and stressors' ratings over 3 months in persistently active (PA) compared to persistently inactive (PI) disease group (month 0: 18.12 (PI) vs 23.62; month 3: 17.46 (PI) vs 23.64 (PA)
Bitton 2003	Cohort	PS (PSS), LE (PERI), D (SCL90R)	Disease Activity (Endoscopy)	PS (HR = 0.898, 95% CI 0.53–1.53, $p = 0.69$) and distress (HR = 1.038, 95% CI 0.95–1.14, $p = 0.43$) in preceding month not associated with time to relapse; LE in the past month associated with time to relapse (HR = 1.26, 95% CI 1.04–1.53, $p = 0.02$)
Camara 2011	Cohort	PS (PSQ)	Disease Activity (Index—CDAI)	High PS associated with exacerbation within 18 months (OR = 1.85 95% CI 1.43–2.40, $p < 0.001$), though removing depression and anxiety components negated the association
Duffy 1992	Cohort	PS (VAS), LE (SRE), DH (SRRS)	Disease Activity (Index—CDAI)	High PS ($r = 0.31$, $p < 0.001$) and LE ($r = 0.31$, $p < 0.001$) associated with exacerbation within 6 months, though not DH ($r = 0.20$, p = NS)
Garrett 1991	Cohort	LE (LES), DH (DSI)	Disease Activity (Index—CDAI)	DH positively correlated with disease activity over 28 days ($\beta = 0.18$, $p < 0.01$) but not LE
Greene 1994	Cohort	PS (DPSD)	Disease Activity (Diary)	PS positively correlated with daily disease activity ($\beta = 0.04$, $p < 0.01$) and the same month disease activity ($\beta = 0.015$, $p < 0.001$). High PS in the preceding month was associated with lower disease activity ($\beta = -0.02$, $p < 0.001$)
Hirten 2020	Cohort	PS (PSS)	Disease Activity (Index—SCCAI; blood tests; FC)	Blood markers ($p = 0.03$) but not FC ($p = 0.25$) is positively associated with subsequent PS. PS positively associated with subsequent exacerbation (SCCAI, $p = 0.02$)
Jaghult 2013	CC	PS (single item)	Disease Activity (Index—TWSI; diary)	'Quite a lot' PS the preceding day associated with exacerbation (OR = 4.8, 95% CI 1.09–21.10)
Langhorst 2007	Exp	Stress Reactivity (BM, STAI-S)	Neuroendocrine–immune interactions	Stress reactions comparable in UC and control groups during the study (not reported)
Langhorst 2013	Cohort	PS (PSQ, PSS)	Disease Activity (Index—CAI; endoscopy)	High short-term PS at last visit associated with exacerbation (HR = 1.05, 95% CI 1.01–1.10) but not long-term PS (HR = 0.20, 95% CI 0.01–3.31)
Levenstein 2000	Cohort	PS (PSQ), LE (PLEI)	Disease Activity (Endoscopy)	High PS associated with exacerbation within next 8 months (OR = 3.9, 95% CI 1.1–13, $p = 0.03$). LE in previous 6 months not associated with exacerbation (HR = 0.73, 95% CI 0.27–2.0, $p = 0.54$)
Luo 2018	Cohort	PS (PSS)	Hospitalisation	PS not associated with 1-year hospitalisation rate (OR = 1.04, 95% CI 0.97–1.11, $p = 0.27$)
Mardini 2004	Cohort	D (BAI, BDI, BHS, RLC)	Disease Activity (Index—CDAI)	Depression in the preceding 8–12 weeks is associated with exacerbation ($\beta = 6.08$, $p = 0.004$) but not anxiety or hopelessness
Maunder 2006	Exp	PS (VAS), Stress Reactivity (HR)	Disease Activity (Index—SMI)	Delayed response to stress (HR) associated with a lower probability of exacerbation ($F = 8.98$, $p = 0.004$) after 7–37 months; PS not compared to disease activity
Mawdsley 2006	Exp	PS (PSQ), Stress Reactivity (BM)	Systemic and rectal mucosal measures	Stress increased TNF-alpha by 54% (p = 0.004), IL-6 production by 11% ($p = 0.04$) and mucosal TNF-alpha release by 102% ($p = 0.03$); PS comparable in UC and control participants

(Continues)

TABLE 2 (Continued)

Study ID	Study design[a]	Stress type (measures)[b]	Disease outcomes (measure)[c]	Key findings[d]
North 1991	Cohort	LE (SRRS)	Disease Activity (Index—CRS; endoscopy)	LE not associated with intestinal symptoms 1 month ($\beta = -0.51$, 95% CI −1.90 to 0.89) or 2 months later ($\beta = -0.57$, 95% CI −2.44 to 1.29)
Porcelli 1996	Cohort	D (HADS)	Disease Activity (Index – TWSI and HBI)	Disease activity positively correlated with anxiety ($F = 89.6$, $p = 0.0001$) and depression ($F = 3.67$, $p = 0.03$) over 6 months
Sexton 2017	Cohort	PS (PSS)	Disease Activity (Index—MIBDI, HBI and PTI; FC)	PS at baseline associated with disease activity 3 months later in CD ($\beta = 0.32$, $p < 0.001$) and UC ($\beta = 0.22$, $p < 0.01$) and vice versa in CD ($\beta = 0.10$, $p < 0.05$) and UC ($\beta = 0.15$, $p < 0.05$)
Traue 1999	Cohort	DH (DSI)	Disease Activity (Diary)	Higher disease activity associated with high (rather than low) stress days ($t = 4.07$, $p = 0.001$)
Vidal 2006	Cohort	LE (SRRS)	Disease Activity (Index—HBI AND SCCAI)	LE in preceding month not associated with exacerbation (HR = 0.88, 95% CI 0.68–1.13, $p = 0.33$)
Wintjens 2019	Cohort	PS (VAS), LE (single item)	Disease Activity (Index—MIAH; FC; Endoscopy)	LE (OR = 1.81, 95% CI = 1.04–3.17) and novel PS (OR = 2.92; 95% CI = 1.44–5.90) in preceding 3 months associated with exacerbation

[a]CC, Case-Crossover; Exp, Experimental.

[b]AO, Authors' Own; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BHS, Beck Hopelessness Scale; BM, Biological Markers; D, Distress; DH, Daily Hassles; DPSD, Daily Psychosocial Stress Diary; DSI, Daily Stress Inventory; HADS, Hospital Anxiety and Depression Scale; HR, Heart Rate; LE, Life Events; LES, Life Experiences Survey; PERI, Psychiatric Epidemiology Research Interview Life Events Scale; PLEI, Paykel Life Experiences Interview; PS, Perceived Stress; PSQ, Perceived Stress Questionnaire; PSS, Perceived Stress Scale; RLC, Holmes Recent Life Changes; S, Stressors; SCL90R, Symptom Check List 90 Revised – Global Symptom Index; SRE, Schedule of Recent Experience; SRRS, Social Readjustment Rating Scale/Scaling of Life Change; SSS, Sources of Stress Scale; STAI-S, State Trait Anxiety Inventory; VAS, Visual Analogue Scale.

[c]CAI, Clinical Colitis Activity Index; CDAI, Crohn's Disease Activity Index; CRS, Clinical Rating Scale; FC, faecal calprotectin; HBI, Harvey-Bradshaw Index; MIAH, Monitor IBD At Home questionnaire; MIBDI, Manitoba Inflammatory Bowel Disease Index; PTI, Powell-Tucker Index; SCCAI, Simple Clinical Colitis Activity Index, St Mark's Index; TWSI, Truelove & Witts Severity Index.

[d]CI, confidence interval; HR, hazard ratio; OR, odds ratio.

associations between stress and disease activity.[53,57] Stress and disease activity covaried in six studies,[12,23,26,36,38,56] including a small study which found high stress in the preceding month was associated with lower disease activity.[38]

Thirteen studies measured perceived stress and disease activity[12,15,24–32,38,48] though one did not report on this relationship[48] (see Figure 3). High perceived stress was associated with subsequent disease exacerbation in nine studies[15,16,25,27–32] with one of these studies reporting a bidirectional relationship.[31] Perceived stress and disease activity covaried in two studies[12,38] with one study finding no significant association.[24]

Of the eight studies that compared life events and disease activity,[15,24,26,30,32,36,53,57] four studies found no association[30,36,53,57] and four studies found life events preceded IBD exacerbation.[15,24,26,32] Daily hassles covaried with disease activity in people with CD over 28 days[36] and 84 days[56] but not in a mixed IBD sample over 6 months.[26] One study found a positive correlation between ratings of stressors and disease activity[12] and an experimental study found stress reactivity preceded a lower probability of disease exacerbation in the following 7–37 months.[48] Distress did not exacerbate disease in the following month[24] but when distress was measured with separate depression, anxiety and hopelessness indices, depression was associated with disease exacerbation 8–12 weeks later.[47] Disease activity levels positively correlated with distress over 6 months.[23]

3.3.2 | Other disease outcomes

Three studies[43,46,49] looked at outcomes other than disease activity. Perceived stress was not associated with subsequent 1-year hospitalisation rates[46] nor mucosal release[49] in UC, though the latter study found stress reactivity preceded mucosal release. Another study found stress reactivity (measured using blood samples) had no significant association with neuroendocrine–immune interactions.[43]

3.4 | Research question 2: Stress and IBD psychosocial outcomes

While psychosocial measures were used in eight cohort studies,[27,29,30,32,46,53,55,56] only three studies[27,46,55] measuring perceived stress reported analyses on their associations (Table 3). Perceived stress was negatively correlated with resilience[27] and quality of life,[46] though another study found no association with the latter.[27] One study[55] found a bidirectional relationship between perceived

TABLE 3 Summary of findings—psychological stress and psychosocial outcomes

Study ID	Study design	Stress type (measures)[a]	Psychosocial outcomes (measure)[b]	Key findings[c]
Hirten 2020	Cohort	PS (PSS)	Anxiety/Depression (PROMIS), IBD Quality of Life (SIBDQ), Resilience (CD-RISC)	PS negatively correlated with resilience ($p < 0.001$) over 14 days. No correlations found between PS and quality of life ($p = 0.32$), anxiety ($p = 0.65$) or depression ($p = 0.59$)
Langhorst 2013	Cohort	PS (PSQ)	Anxiety, Depression (HADS)	Not reported
Levenstein 2000	Cohort	PS (PSQ), LE (PLEI)	Depression (CES-D)	Not reported
Luo 2018	Cohort	PS (PSS)	IBD Quality of Life (IBDQ), Medical Coping (MCMQ)	PS negatively correlated with quality of life (OR: 1.13, 95% CI 1.07–1.19, $p < 0.001$) at baseline. PS associations with medical coping not reported
North 1991	Cohort	LE (SRRS)	Depression (BDI)	Not reported
Sirois 2017	Cohort	PS (PSS)	Depression (CES-D), Gratitude (GQ-6), Illness cognition (ICQ), Mental Health diagnosis (single item), Psychological Thriving (CTS), Social support (FSSQ)	Baseline PS positively associated with depression ($r = 0.57$, $p < 0.01$) and negatively associated with social support ($r = -0.34$, $p < 0.01$) at 6 months. PS at 6 months positively associated with baseline depression ($r = 0.51$, $p < 0.01$) and helplessness ($r = 0.23$, $p < 0.01$) and negatively associated with baseline gratitude ($r = -0.36$, $p < 0.01$), social support ($r = -0.22$, $p < 0.01$), illness acceptance ($r = -0.30$, $p < 0.01$) and thriving ($r = -0.39$, $p < 0.01$)
Traue 1999	Cohort	DH (DSI)	Coping (SVF)	Not reported
Wintjens 2019	Cohort	PS (VAS), LE (authors')	Anxiety, Depression, Fatigue (every single item)	Not reported

[a]DH, Daily Hassles; DSI, Daily Stress Inventory; LE, Life Events; PLEI, Paykel Life Experiences Interview; PS, Perceived Stress, PSQ, Perceived Stress Questionnaire; PSS, Perceived Stress Scale; SRRS, Social Readjustment Rating Scale; VAS, Visual Analogue Scale.

[b]BDI, Beck Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; CES-D, Center for Epidemiological Studies Depression; CTS, Carver Thriving Scale; FSSQ, Duke-UNC Functional Social Support questionnaire; GQ-6, Gratitude Questionnaire-6; HADS, Hospital Anxiety and Depression Scale; IBDQ, Inflammatory Bowel Disease Questionnaire; ICQ, Illness Cognition Questionnaire; MCMQ, Medical Coping Modes Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; SVF Coping and Stress Questionnaire (German).

[c]CI, confidence interval; OR, odds ratio.

stress, depression and social support, where high perceived stress preceded higher depression and lower social support levels 6 months later and vice versa. All these studies either did not collect data on possible confounders or did not control for disease activity at baseline in the analysis (Tables S2 and S3).

3.5 | Research question 3: Intervention studies' effects on stress

Fifteen studies trialled interventions and measured stress outcomes, including cognitive-behavioural (CB) techniques,[34,35,37,39,40,44,51,52,58] exercise,[42,45] education,[33,54] hypnotherapy[41] and stress management[50] interventions designed to improve psychosocial and/or disease outcomes, with 12 studies[33,37,39,40,42,44,45,50–52,54,58] reporting significant improvements in stress (Table 4). Reducing stress or distress was a stated aim (or an implied aim by targeting participants with high stress or distress or the use of a stress management programme) in 10 of the 15 studies.[33–35,37,39,40,42,45,50,51] The majority measured perceived stress, distress and disease-specific stress, amongst other outcomes. A randomised controlled trial design was used in seven studies[33–35,39,41,42,58] and no study replicated a previous study or intervention. Only three studies[34,41,58] confirmed that intervention and comparator groups had similar baseline characteristics and only one reported a cost–benefit analysis of whether intervention benefits outweighed harms (Table S3).[52] Intervention and stress types were too heterogenous to allow meta-synthesis.

3.5.1 | Cognitive behavioural intervention studies

Individualised Cognitive Behavioural Therapy[40,44] reduced distress levels in the intervention group (although in one study distress

TABLE 4 Summary of findings—Interventions' effect on psychological stress

Study ID	Intervention type	Stress type (measures)	Key findings
Berding 2016	Education (medical information, coping and self-management skills), Group, Weekend (11.5 h)	DS (RFIPC)	RFIPC decreased significantly 2 weeks ($\eta p^2 = 0.088$, $p < 0.001$) and 3 months ($\eta p^2 = 0.080$, $p < 0.001$) after intervention
Berrill 2014	CB (Behavioural/cognitive techniques, mindfulness), 1–2-1, 16 weeks (6 × 40-min)	PS (PSQ), DH (RDHS)	Decreases in PS and DH not significant
Boye 2011	CB (problem-solving, relaxation, CBT), Group: weekly (5 × 3 h), 1–2-1: 6–9 sessions	D (PSQ)	Decreases in distress are not significant
Gerbarg 2015	CB (breathing, meditation), Group, 2 consecutive days (9 h), Weekly (6 × 90 min), Monthly (4–5 × 90 min)	PS (PSQ), D (BSI-18)	PS ($p = 0.01$) and Distress ($p = 0.04$) decreased significantly 26 weeks after baseline
Jedel 2014	CB (mindfulness), Group, Weekly (8 × 2–2.5-h)	PS (PSQ), SR (BM)	Decreased PS scores at the last visit in those who flared in the intervention group vs the control ($p = 0.04$). Increased Serum ACTH levels over time for those who flared in the intervention group vs the control ($p = 0.007$). No significant difference in cortisol levels
Jordan 2019	CB (CBT) 1–2-1, Weekly (5–10 × 51-min)	D (GAD7, PHQ9)	Distress decreased after intervention ($p < 0.001$)
Keefer 2013	Hypnotherapy (gut-directed) 1–2-1, Weekly (7 × 40 min)	PS (PSQ)	PS not significantly different in intervention and control groups after 3 months ($t = 0.24$, p-ns)
Koch 2020	Exercise (Yoga) Group, Weekly (12 × 90 min)	PS (PSQ)	PS decreased significantly after 12 weeks ($t = -0.40$, $p < 0.001$) and 24 weeks ($t = -0.32$, $p < 0.01$) in the intervention group. PS at 12 weeks mediated intervention effects on HRQOL and disease activity at 24 weeks ($b = 14.74$, CI −0.08 to 29.56, $p = 0.05$)
Lores 2019	CB (CBT/ACT) 1–2-1, Various	D (K6)	Distress decreased in the intervention group ($t = 8.18$, $p < 0.001$) and the comparison group ($t = 2.08$, $p < 0.05$) after 12 months. Group × time interactions are not significant
Loudon 1999	Exercise (walking) Group, three times weekly (12 × 20–35 min)	DS (IBDSI)	DS significantly decreased after 12 weeks ($p = 0.0005$)
Milne 1986	Stress management (planning and communication skills, Autogenic training) Group (frequency not reported) (6 × 3 h)	DS (IBDSI)	DS decreased significantly in intervention group at 4 months ($p < 0.001$), 8 months ($p < 0.01$) and 12 months ($p < 0.01$), where control was unchanged
Mussell 2003	CB (cognition/emotions, coping, muscle relaxation) Group, Weekly (12 × 90 min)	D (SCL90R-R/GSI), DS (RFIPC)	Distress has no significant change over time. DS decreased significantly by 3 months ($t = 3.1$, $p < 0.05$) and maintained at 6- and 12-month follow-up
Neilson 2016	CB (meditation, mindfulness, discussion) Group, Weekly (8 × 2.5 h) + Weekend (1 × 7 h)	D (HADS)	Distress decreased significantly at 8 weeks for anxiety ($F = 1.82$, $p < 0.05$) and depression ($F = i1.75$, $p < 0.05$), and at 32 weeks for depression ($F = 2.61$, $p < 0.001$)
Schwarz 1991	Education (muscle relaxation, thermal biofeedback, coping, IBD symptoms) 1–2-1, Twice weekly (8 × 1-h) then Weekly (4 × 1-h)	DH (HS), DS (IBDSI)	DH no significant change post-treatment or 3 months later than controls. DS decreased post-intervention ($p < 0.05$)
Wynne 2019	CB (ACT) Group, Weekly (8 × 90-min)	PS (VAS), S (DMPL), D (DASS21)	PS and distress decreased in the intervention group compared to the control group over time ($p < 0.001$). Stressors consistent over time and between groups

Abbreviations: ACT, Acceptance and Commitment Therapy; CB, Cognitive-Behavioural; CBT, Cognitive Behavioural Therapy; BM, Biological Markers; BSI-18, Brief Symptom Inventory; D, Distress; DASS21, Depression Anxiety Stress Scales; DH, Daily Hassles; DS, Disease Specific; DMPL, Distress Management Problem List, Generalised Anxiety Disorder questionnaire; HADS, Hospital Anxiety and Depression Scale; HS, Hassles Scale; IBDSI, IBD Stress Index; K6, Kessler 6 scale; PHQ9, Patient Health Questionnaire; PS, Perceived Stress; PSQ, Perceived Stress Questionnaire; RDHS, Revised Daily Hassle Scale; RFIPC, Rating Form of IBD Patient Concerns; S, Stressors; SCL90R-R/GSI, Symptom Check List 90 Revised/Global Symptom Index measure; SR, Stress Reactivity; VAS, Visual Analogue Scale.

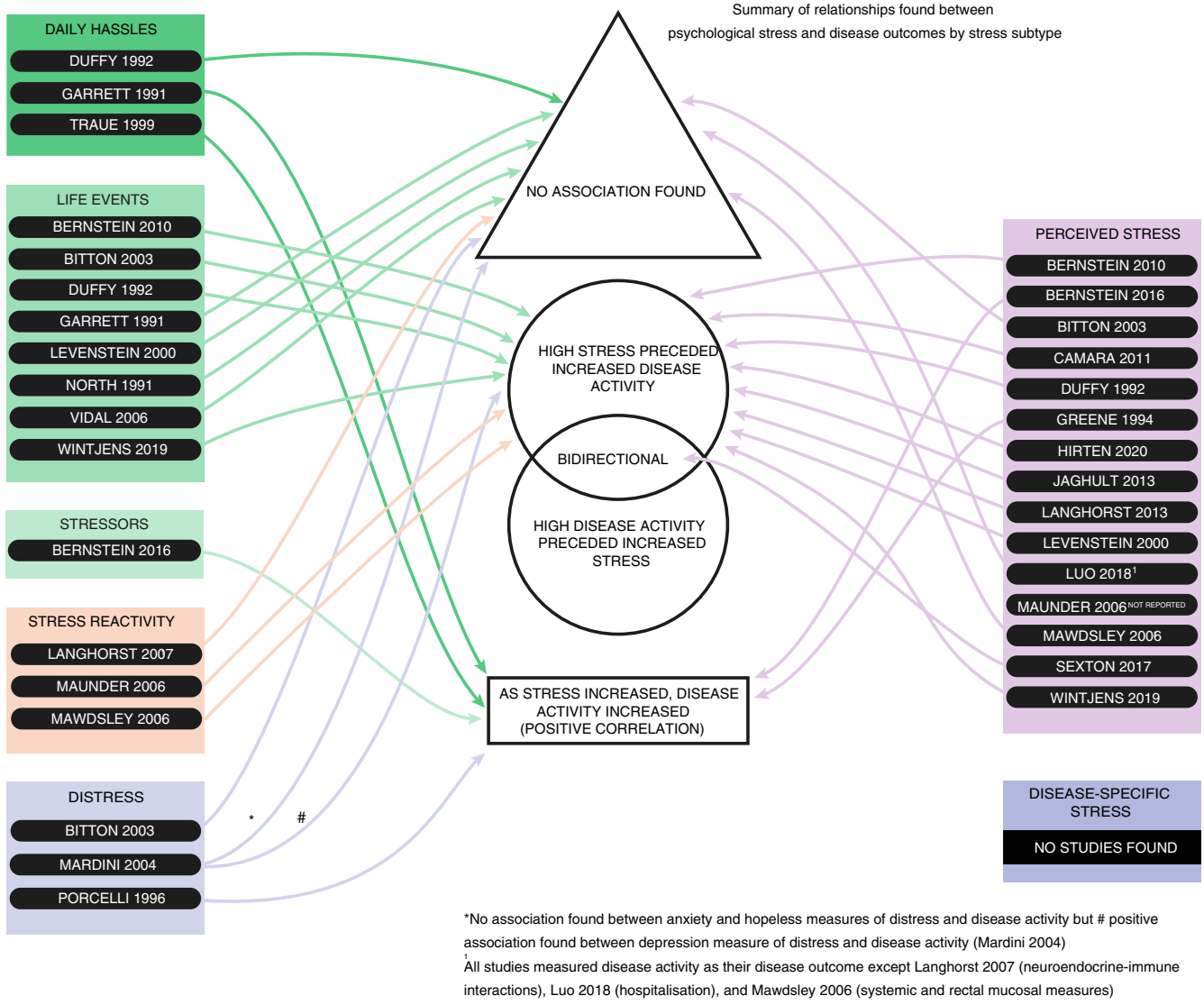

FIGURE 3 Summary of relationships found between psychological stress and disease outcomes by stress subtype. *No association was found between anxiety and hopeless measures of distress and disease activity but # positive association was found between depression measures of distress and disease activity.[47] [1]All studies measured disease activity as their disease outcome except Langhorst 2007 (neuroendocrine–immune interactions), Luo 2018 (hospitalisation) and Mawdsley 2006 (systemic and rectal mucosal measures).

also improved in the comparator group[44]), while one-to-one sessions on cognitive behavioural techniques and mindfulness[34] did not improve perceived stress or stress from daily hassles. Group programmes that included meditation or mindfulness[37,39,52] or Acceptance-Commitment Therapy[58] reduced distress and perceived stress. Multi-faceted programmes that included relaxation, coping or problem-solving elements found no improvement in distress[35,51] but sustained improvement in disease-specific stress.[51]

3.5.2 | Other intervention studies

Educational programmes on IBD, coping and relaxation or self-management skills reduced disease-specific stress[33,54] but not stress from daily hassles.[54] A stress management programme lowered disease-specific stress long term.[50] Group exercise decreased disease-specific stress[45] and perceived stress,[42] the latter having a mediating effect on subsequent quality of life and disease activity. Hypnotherapy did not affect perceived stress.[41]

4 | DISCUSSION

This systematic review investigated the associations between psychological stress and disease and psychosocial outcomes in people with IBD, as well as the impact of interventions on stress. The review demonstrated that perceived stress (though not other stress subtypes) generally preceded disease exacerbation, though one small study found stress preceded disease improvement.[38] This augments the findings of previous reviews,[17,18] which suggested that stress plays a

role in IBD disease activity, by establishing a temporal link. However, the exact nature of the temporal link remains unquantified, with the lag between high stress levels and disease exacerbation ranging from 1 day to 18 months and perceived stress being reported for the preceding month or year, depending on the measure. Further studies analysing the time to relapse after stress could clarify this relationship.

Stress is thought to activate the hypothalamic–pituitary–adrenal (HPA) axis which has been implicated in gastrointestinal inflammation,[59] where changes such as neuroendocrine–immune system alterations make disease exacerbation more likely.[60] Stress may drive behavioural changes, such as medication nonadherence,[61] poor diet[62] and alcohol use[63] which increase the risk of disease exacerbation. Perceived stress measures may play a role in identifying those at risk of relapse and indicating a need to intercede when used in tandem with disease activity indices. Yet 60% of IBD patients reported in a recent UK survey that they were not asked about their mental health during medical appointments, so this may require changes in clinical practice.[64] Two studies found a bidirectional relationship between perceived stress and disease exacerbation, which warrants further investigation and inclusion in future prospective study designs given the relapsing–remitting nature of IBD.

The relationship between stress and psychosocial outcomes was unclear. Many studies measured a variety of psychosocial outcomes but analysed only disease outcomes, with only three reporting psychosocial associations with stress. One study suggested a cyclical relationship between perceived stress, social support and depressive symptoms and a positive association between stress and helplessness, while the other studies reported negative correlations between stress and resilience and quality of life. This suggests potential roles for psychological and situational characteristics as either protective or risk factors for stress. However, as only three studies examined this area,[27,46,55] more research is needed to identify protective characteristics and thus enhance physical and mental health.

The impact of interventions in general seemed to be positive with 12[33,37,39,40,42,44,45,50–52,54,58] of the 15 studies finding significant improvement in stress levels post-intervention. Individualised cognitive behavioural-based therapy and group programmes with mindfulness or Acceptance-Commitment Therapy components had a positive impact on distress. These therapeutic techniques may help manage the emotional aspects of stress. Educational, stress management and exercise group programmes reported improvements in disease-specific stress and suggest positive effects from time spent with others with IBD and greater information about the condition. This implies that psychological therapeutic techniques, stress management and greater knowledge of IBD can all have a positive impact on stress.

The included studies involved some large (100+) samples with comprehensive follow-up and used robust disease outcome measures. However, data on medication, surgery and other confounders were often not collected.

Researchers have recruited heterogeneous samples (both in terms of IBD subtypes and baseline disease activity), despite recommendations to the contrary.[7,17,18] This can obscure any differences that disease type may play in the association between stress and disease activity where studies are not sufficiently large to analyse these separately. Similarly, a mixed sample of people with the active and inactive disease could prevent analysis reflecting the relapsing–remitting nature of IBD over time. The majority of studies had more female participants than males, who may be more likely to report high stress levels[65]; female sex may play an independent role in stress-triggered disease exacerbation.[66] Further research may be required with an equal gender split, younger people, people from black and minority ethnic groups, and those recently diagnosed to ascertain whether their experience of stress and IBD is similar. Psychological comorbidity, such as depressive or anxiety disorders, is thought to be higher amongst those people who have IBS symptoms in addition to IBD or those in the relapse phase of the disease.[6] Researchers may consider targeting these groups to ensure their results inform interventions for those most at risk and to explore the potential impact of stress reduction on active disease.

Most intervention studies did not use a randomised controlled study design, some opting for a 'real-world' design where participants opted to be in intervention or control groups. These preference designs recognise the difficulty of blinding participants to their group assignment and mitigate against related behaviour change. However, few studies confirmed that the groups' baseline characteristics were comparable, and it is possible that people who self-select to participate may be guided by their disease activity. Whatever study design researchers choose, baseline between-group differences need to be reported.

4.1 | Defining and measuring stress

This review found a lack of consensus on what is meant by stress or distress in IBD research. Thirty-six different stress measures were used, from life event inventories to self-reported stress ratings, non-validated single-item measures to clinical measures designed to identify symptoms of anxiety and depression. Future research would benefit from studies explicitly defining the type of stress under investigation, outlining the rationale for the choice of measure, and being set within the context of a suitable model of stress (such as Lazarus and Folkman[9]). Perceived stress instruments may be influenced by IBD symptoms which can be pervasive even when clinical remission has been achieved, such as fatigue.[67] Stress instruments requiring participants to rate statements on their energy and tiredness[68] may not be suitable if unduly influenced by fatigue when intending to measure stress.

4.2 | Strengths and Limitations

This is the first systematic review to explore the relationship between psychological stress and psychosocial and disease outcomes for people with IBD over time, differentiating by the stress subtype studied. The latter permitted us to discuss specifically the nature of the stress affecting those outcomes, while including only

prospective longitudinal studies allowed us to draw conclusions on the temporal nature of the relationship. Moreover, we were able to update the findings of previous reviews[17,18] including 21 more recent studies from the last decade. The narrative synthesis gave a picture of the literature to date and suggests a temporal link between perceived stress and disease exacerbation.

The search strategy's focus on the English language and peer-reviewed journal articles has led to the inclusion of studies predominantly based in the US, Canada and Europe which found significant associations with stress. The effect of stress on disease activity may have been artificially amplified by the absence of published studies with non-significant associations; the studies' locations restrict the applicability of our findings to residents of North America and Europe. Initial screening was conducted by a single investigator, limiting the robustness of this process. The majority of studies used self-reported symptom indices, rather than investigative medical tests. Symptom self-reporting may be higher in those with co-morbidities, such as IBS[69,70] and mood disorders,[71] and so objective disease activity measures should be employed where possible and the presence of co-morbidities included in analyses.

The creation and use of seven subtypes to frame the review's analysis, while grounded in a well-established model of stress, cannot wholly reflect the interaction between the different elements of the stress process. The stress subtypes' measurement is likely to be affected by psychosocial factors and IBD symptoms, such as pain and fatigue.

In conclusion, there is evidence of a temporal link between the perceived stress levels of people with IBD and subsequent disease exacerbation. Patient care has changed considerably in the 35-year period these studies span with a growing focus on multidisciplinary teams. More remains to be done to integrate stress management into routine IBD care to prolong remission and improve psychosocial outcomes.

AUTHOR CONTRIBUTIONS

Jacqueline M A Black: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); writing – original draft (lead); writing – review and editing (lead). **Louise Sweeney:** Conceptualization (supporting); supervision (equal); writing – review and editing (supporting). **Yuhan Yuan:** Formal analysis (equal). **Harinder Singh:** Data curation (equal). **Christine Norton:** Conceptualization (supporting); supervision (equal); writing – review and editing (supporting). **Wladyslawa Janina Czuber-Dochan:** Conceptualization (supporting); supervision (equal); writing – review and editing (supporting).

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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