Systematic Review: Psychosocial Correlates of Pain in Pediatric Inflammatory Bowel Disease

Lexa K. Murphy, PhD,*⊙ Rocio de la Vega, PhD,* Sara Ahola Kohut, PhD,†,‡ Joy S. Kawamura, PhD,§,¶ Rona L. Levy, PhD,‖ and Tonya M. Palermo, PhD*,**,⊙

Background: Pain is a common symptom in pediatric inflammatory bowel disease (IBD) and is associated with poor health outcomes, yet additional knowledge about the psychosocial correlates of pain is needed to optimize clinical care. The purpose of this study is to systematically review the psychosocial factors associated with pain and pain impact in youth diagnosed with IBD within a developmentally informed framework.

Methods: Manual and electronic searches yielded 2641 references. Two authors conducted screening (98% agreement), and data extraction was performed in duplicate. Average study quality was rated using the National Institutes of Health Quality Assessment Tool.

Results: Ten studies (N = 763 patients; N = 563 Crohn disease, N = 200 ulcerative/ indeterminate colitis) met the inclusion criteria. Findings showed consistent evidence that higher levels of child depression symptoms and child pain catastrophizing were associated with significantly greater pain and pain impact (magnitude of association ranged from small to large across studies). Greater pain and pain impact were also associated with higher levels of child anxiety symptoms, child pain threat, child pain worry, and parent pain catastrophizing. Within the included studies, female sex and disease severity were both significantly associated with pain and pain impact. Study quality was moderate on average.

Conclusions: There is evidence that child psychosocial factors are associated with pain and pain impact in pediatric IBD; more studies are needed to examine parent- and family-level psychosocial factors. Youth with IBD should be routinely screened for pain severity, pain impact, and psychosocial risk factors such as anxiety/depression.

Key Words: inflammatory bowel disease, pain, psychosocial, children, parents, depression, anxiety

INTRODUCTION

Pain is a common symptom in pediatric inflammatory bowel disease (IBD), with 30% of children and adolescents with IBD reporting chronic abdominal pain.[1] Pain is associated with poor psychological and disease outcomes in pediatric IBD[2-4] and increased health care utilization and costs.[5, 6] Although abdominal pain in IBD has traditionally been attributed to disease activity, such as increased inflammation in the gastrointestinal tract, an increasing body of research indicates that pain is not entirely driven by inflammation.[3, 7] Therefore, this study aims to review the evidence for psychosocial correlates for pain in pediatric IBD within a developmentally informed framework of pediatric pain to inform clinical care and future research.

Pain is increasingly being recognized as an important target in the clinical care of youth with IBD.[8, 9] Although the pediatric IBD literature is still nascent, recent studies have reported that 10%-61% of youth with quiescent disease and 42%-100% of youth with active disease report the presence of abdominal pain.[1, 2, 4, 10] It is well documented that recurrent and chronic pain are associated with poor outcomes for youth and families. Pediatric chronic pain is associated with missed school days, deficits in social functioning, decreased quality of life, and increased symptoms of anxiety/depression,[11-16] along with missed work days and increased distress for parents.[13-15] Further, a recent study estimated that the annual cost of pediatric chronic pain in the United States is $19.5 billion annually.[15]

Current conceptual models of pain in IBD emphasize that pain is multifactorial, involving both peripheral and central nervous system processes and contextual psychosocial factors.[6, 17, 18] The presence of pain during quiescent IBD is sometimes referred to as IBD-IBS,[19, 20] but it is important to note that in both conditions (IBD and irritable bowel syndrome [IBS]), pain is biopsychosocially determined.[21, 22] Because research is increasingly acknowledging that psychosocial factors play a role in both modulating and increasing risk for the experience of pain in IBD, greater attention is

being given to specific psychosocial risk factors for pain. For example, within the pediatric IBD literature, recent research has focused on both child psychosocial factors (eg, depression symptoms[3] and catastrophizing[4]) and parent psychosocial factors (eg, parental protective responses[23]) as correlates of pain. In addition, recent reviews and expert opinions have recommended that clinicians consider psychosocial processes when managing pain in IBD.[6, 8]

However, current approaches to pain management in pediatric IBD often neglect psychosocial factors and are typically limited to exploratory surgery or escalation of pharmacotherapy. Both of these approaches include risk for adverse effects and potentially limited efficacy for pain management.[6, 24] At the same time and in the absence of other treatment options, recent research has found that a significant subset of adolescents and young adults (AYAs) with IBD rely on opioids or marijuana for pain control,[25, 26] despite the associated risks. Specifically, one-third of AYAs with IBD reported using marijuana in a recent study; the most common medical reason reported was pain relief. It is also expected that marijuana use may increase with legalization. In a large national sample of patients, one-fifth of AYAs received chronic opioid therapy over a 2-year period with the annual prevalence of chronic opioid therapy rising over time,[26] which is of particular concern given the negative consequences of opiates on the gastrointestinal system.[9] Factors associated with opioid use in pediatric IBD include older age[17, 18] and male sex[26]; in adults, use is associated with a diagnosis of IBS and psychiatric history.[27]

Although a recent systematic review revealed promising evidence for nonpharmacologic psychological treatments for pain management in patients with IBD,[28] the evidence base in pediatrics is more limited. Prior studies that have tested psychological interventions for youth with IBD have not evaluated pain as a primary outcome.[29-34] Therefore, there is limited literature on the possible benefit of psychological therapies for the management of pain and pain impact in pediatric IBD, and additional knowledge about key psychosocial correlates of pain in pediatric IBD is needed to inform intervention development and optimization in this population. However, existing models of psychosocial risk factors for pain in youth with IBD are limited in 2 ways. First, these factors are not developmentally sensitive to psychosocial factors specific to children and adolescents (ie, they do not consider the influence of parent and family factors). Second, they do not separate emotional and cognitive-behavioral processes that are known risk factors for pediatric chronic pain (eg, anxiety and depression symptoms, pain-specific cognitive-behavioral factors such as pain catastrophizing). Therefore, the application of a developmental framework is needed to move the field forward.

Within the pediatric chronic pain literature, Palermo and colleagues[14] outlined a developmental framework for pediatric chronic pain such that a child's pain perception and response are influenced by individual factors (ie, emotional factors, cognitive-behavioral factors), parent factors (ie, parent emotional functioning, parent behaviors, and parent medical history), and family factors (ie, family functioning, environment, and stress) within the developmental context. Consistent with this framework, and relevant to pediatric IBD, previous studies have identified individual-level (eg, child anxiety, coping), parent-level (eg, parental anxiety, parental solicitous responses, modeling), and family-level (eg, family stress, parent-child interactions) correlates of pain and disability in youth with recurrent or functional abdominal pain.[35-38] This review therefore applies Palermo and colleagues'[14] 2014 framework to classify psychosocial risk factors for pain in pediatric IBD ([Fig. 1]).

Sweeney and colleagues[39] recently conducted a systematic review of psychosocial factors associated with pain in IBD, focusing exclusively on adults. This review found consistent associations between emotional and cognitive-behavioral factors (particularly anxiety and depression symptoms, catastrophizing, and certain coping strategies such as disengagement) and pain (intensity, duration, and impact). Although findings from this review can inform research and intervention efforts in adult IBD populations, to date there has been no systematic review of pain focusing on children and adolescents with IBD. Therefore, the purpose of this study is to systematically review the evidence for the psychosocial correlates of pain in pediatric IBD within a framework informed by the pediatric chronic pain literature.[14] This review is intended to identify gaps in knowledge, inform future observational and treatment research, and inform screening and clinical care in pediatric IBD.
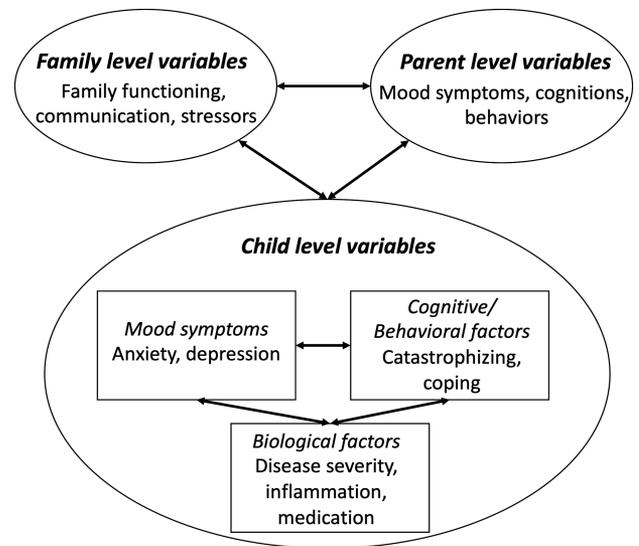

FIGURE 1. Developmental framework of child, parent, and family-level influences on pediatric chronic pain and disability, adapted from Palermo et al 2014.[14]

Aims

The primary aim of this review is to examine the psychosocial correlates of pain and pain impact in youth with IBD. It is expected that individual, parent, and family psychosocial factors are significantly related to pain and pain impact in pediatric IBD. The second aim, consistent with the recent review by Sweeney et al[39] of the psychosocial correlates of pain in adults with IBD, is to assess the association between pain and clinical and sociodemographic factors within the included studies.

METHODS

The protocol for this review was registered on Prospero on May 29, 2019 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019121162).

Inclusion and Exclusion Criteria

Eligible studies (1) reported at least 1 psychosocial factor (eg, child anxiety symptoms, parent pain catastrophizing) using a validated measure, (2) reported at least 1 aspect of pain (pain intensity, severity) or pain impact (interference, activity limitations, or disability) using a validated self-report measure, and (3) included a pediatric sample (samples including patients aged <19 years) with a diagnosis of IBD (ie, Crohn's disease [CD], ulcerative colitis [UC], and/or indeterminate colitis). Pain and psychosocial measures were considered valid and acceptable if they were rated as high methodologic quality in a recent review of outcome measures in pediatric functional abdominal pain.[40] Exclusion criteria were (1) pain that was only assessed within an IBD composite score and not reported separately (eg, the Pediatric Crohn's Disease Activity Index [PCDAI] or the Pediatric Ulcerative Colitis Activity Index [PUCAI]), (2) measurement validation studies, and (3) a study population with significant medical comorbidity (eg, cancer). We chose to exclude studies measuring pain with the PCDAI/PUCAI because this measure is not necessarily self-reported (eg, may be completed by caregivers) and 3-point Likert scales do not provide sufficient variability for adequate pain assessment.[41]

Of note, throughout this review we refer to individual psychosocial factors as "child" factors, which is inclusive of both children and adolescents.

Search Strategy

A search strategy was developed to search Ovid MEDLINE (1946 to present), Embase (1974 to present), and PsycINFO (1987 to present). The final search was conducted on March 1, 2019, and was limited to articles published in English. A combination of controlled vocabulary and keywords was used in the following areas: (1) IBD (IBD, CD, UC), (2) pain (pain, chronic pain, pain threshold, complex regional pain syndrome, fibromyalgia, IBS, functional abdominal pain, disability, functional disability, activity limitations, quality of life, health-related quality of life), and (3) psychosocial factors (psychological, psychosocial, biopsychosocial, social, illness beliefs, catastrophizing, anxiety, depression, trauma, internalizing, affective symptoms, affect, mood, coping, avoidance, fear, cognition, perception, acceptance, parenting, family, parent-child relations, communication, solicitousness, modeling, attitude to health, adaptation, internal-external control, neuroticism, hostility). Additional articles were identified by the first and second authors by searching all reference lists for included studies and review articles focused on psychosocial well-being in pediatric IBD.

Articles were first screened by title independently by the first and second authors (eg, reviews, commentaries, and drug trials were removed). The first author screened all remaining articles by abstract; the second author reviewed 20% for reliability, and agreement was 98%. The first author then reviewed the full text of all articles to screen for inclusion and exclusion criteria. All screening decisions were double-checked by the second author, and disagreements were resolved through discussion.

Data Extraction

The first and second authors extracted the following information independently: study design, sample size, age, psychosocial measure used, pain measure used, descriptive statistics for pain (M/SD or percentage) and psychosocial measure(s), and key findings (Table 1) along with the location of the sample, details characterizing the sample (number of patients with CD and UC, percentage of female patients), disease measurement (severity/activity, number of flares, illness duration), and additional findings related to disease/sociodemographic factors (Supplemental Table 1). Discrepancies were resolved through discussion. Psychosocial correlates were categorized into individual child–level, parent-level, or family-level factors. If the study reported results from a treatment/intervention, then only baseline data were extracted. Because of the small number of studies identified in the review and the variability of pain and psychosocial measures, results were summarized narratively and no meta-analysis was conducted.

Quality Assessment for Included Studies

Study quality was assessed with the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, adapted for the current review.[42] Each study was assessed on the following criteria: (1) research question/objective was clear; (2) study population was specified and defined; (3) participation rate was reported and ≥50%; (4) exclusion criteria were clear and all participants came from the same sample; (5) sample size justification, power description, or variance and effect estimates were provided; (6) both pain and (7) other primary independent/dependent variables were defined and assessed with valid and reliable tools; and (8) potential confounding variables were measured and adjusted for their impact on study variables. Studies were assigned 1 point

TABLE 1. Summary of Findings From Included Studies

Reference	Study Design	N	Diagnosis	Age Range (y), M	Pain Measure	Pain M (SD) or %	Psychosocial Factor(s)	Key Findings
Claar et al 2017[72]	Baseline of RCT	116	100% CD	8-18 M = 13.8	FPS-R	27.6% of patients in sample reported any pain (14.7% were in remission, 12.9% were in flare)	Depression sx (CDI); Anxiety sx (MASC)	One-way ANOVAS conducted to compare 4 groups (remission with and without pain, flare with and without pain) with posthoc testing: Children in a flare with pain reported increased depression sx vs both children in a flare without pain and children in remission without pain (M = 13.95 vs 6.02, 5.82; $P < 0.05$). Children in a flare with pain reported increased anxiety sx compared to children in remission without pain (M = 51.78 vs. 38.10; $P < 0.05$).
Crandall et al 2007[63]	Cross-sectional	20	75% CD, 25% UC	11-16 M = 13.3	NRS-11 "usual" pain severity	M = 5.33 (SD = NR)	Anxiety sx (STAI-C)	Anxiety sx significantly predicted pain in linear regression ($F(1,16) = 13.29$, $P = 0.002$, $\beta = 0.226$).
Langer et al 2014[23]	Baseline of RCT	184	68% CD, 32% UC	8-18 M = 13.7	FPS-R	M = 0.51 (SD = 1.46)	Parent protective responses (ARCS-P); Parent catastrophizing (PCS-P)	In bivariate correlations, parental protective responses was not significantly correlated with pain ($r = 0.04$, $P = $ ns) and parental catastrophizing was not significantly correlated with pain ($r = 0.02$, $P = $ ns).
Srinath et al 2014[3]	Baseline of RCT	163	74% CD, 26% UC	9-17 M = 14.3	API	M = 20.89 (SD = 10.21)	Depression sx (CDRS); Anxiety sx (SCARED)	Univariate analyses were conducted predicting pain severity separately by diagnosis. Crohn's Disease group: Depression sx was significantly associated with pain ($r = 0.33$, $P < 0.001$; $R^2 = 10.9$, B = 0.022, 95% CI 0.011, 0.034, $P < 0.0001$). Anxiety sx was not significantly associated with pain severity ($R^2 = 0.7$, B = 0.006, 95% CI −0.007, 0.018, $P < 0.36$). Ulcerative Colitis group: Depression sx was significantly associated with pain severity ($r = 0.46$, $P = 0.002$; $R^2 = 21.5$, B = 0.031, 95% CI 0.012, 0.050, $P < 0.002$). Anxiety sx was not significantly associated with pain severity ($R^2 = 2.2$, B = 0.010, 95% CI −0.012, 0.033, $P < 0.36$).
Szegethy, Youk et al 2014[62]	Baseline of RCT	226	75% CD, 25% UC	9-17 M = 14.3	API	NR, z-scores used	Depression sx (CDRS)	Latent Profile Analysis identified depression subgroups. Pain severity significantly predicted membership in "somatic depression" subgroup compared to "mild depression" subgroup in logistic regression, controlling for demographic and clinical variables (OR = 1.78, $P = 0.012$).
van Tilburg et al 2015[61]	Cross-sectional	189	67% CD, 33% UC	7-18 M = 13.8	FDI	M = 6.48 (SD = 7.1)	Catastrophizing (PRI); passive and active coping (PRI)	In linear regression controlling for age, sex, and IBD symptom severity, only catastrophizing significantly predicted disability ($F = 20.9$, $P < 0.001$, $R^2 = 0.54$; $\beta = 0.24$).

TABLE 1. Continued

Reference	Study Design	N	Diagnosis	Age Range (y), M	Pain Measure	Pain M (SD) or %	Psychosocial Factor(s)	Key Findings
van Tilburg et al 2017[7]	Baseline of RCT	127	100% CD	8-18 M = 13.8	FDI	M = 6.23 (SD = 7.2)	Depression sx (CDI); anxiety sx (MASC); pain beliefs—pain threat (PBQ); catastrophizing (PRI)	Univariate analyses with manifest variables: Depression sx was significantly correlated with disability ($r = 0.60$, $P < 0.01$). Anxiety sx was significantly correlated with disability ($r = 0.42$, $P < 0.01$). Pain beliefs (pain threat) was significantly correlated with disability ($r = 0.69$, $P < 0.01$). Catastrophizing was significantly correlated with disability ($r = 0.54$, $P < 0.01$). Multivariate analyses with latent variables: Psychological factors (depression, anxiety, pain beliefs, catastrophizing) significantly predicted disability ($\beta = 0.75$, $P < 0.001$).
Varni, Shulman et al 2018[64]	Cross-sectional	172	74% CD, 26% UC	13-18 M = 15.8	Stomach pain and hurt (PedsQL GI Symptoms Scale)	M = 67.66 (SD = 21.31)	Stomach pain worry (PedsQL Gastrointestinal Worry Scale)	Stomach pain worry was significantly correlated with stomach pain and hurt in a bivariate correlation ($r = 0.65$, $P < 0.001$).
Watson et al 2017[65]	Cross-sectional	81	77% CD, 23% UC	8-18 M = 14.4	FAPD diagnosis per report of abdominal pain on QPGS-III and ROME criteria	26% met criteria for FAPD	Depression sx (CDI-2); anxiety sx (STAIC-C2); T-scores >64 used as clinical cutoff	Children with IBD and FAPD reported significantly greater depression sx ($P = 0.003$) but not anxiety sx ($P = 0.213$) than those with just IBD. Children with IBD and FAPD were more likely to be above the cut-off for depression sx (23.8% vs. 2%; $P = 0.006$) but not for anxiety sx (14.3% vs. 2%; $P = 0.06$) compared to those with just IBD.
Wojtowitz et al 2014[4]	Baseline of RCT	75	73% CD, 24% UC, 3% IC	11-18 M = 14.5	API;FDI	API NR, only z-scores used; FDI = 2.84 (4.98)	Parent pain catastrophizing (PCS-P)	In bivariate correlations, parent pain catastrophizing was significantly correlated with abdominal pain severity ($r = 0.44$, $P < 0.001$) and functional disability ($r = 0.31$, $P < 0.001$).

ARCS indicates Adult Responses to Children's Symptoms; ANOVA, analysis of variance; CDI, Child Depression Inventory; CDRS, Clinicians Depression Rating Scale; IC, indeterminate colitis; FPS-R, Faces Pain Scale-Revised; MASC, Multidimensional Anxiety Scale for Children; NR, not reported; NRS-11, Numerical Rating Scale-11; PBQ, Pain Behavior Questionnaire; PCS, Pain Catastrophizing Scale; PRI, Pain Response Inventory; QPGS-III, Questionnaire on Pediatric Gastrointestinal Symptoms: Rome III version; RCT, randomized controlled trial; SCARED, Screen for Anxiety Related Emotional Disorders; STAI-C2, State Trait Anxiety Inventory for Children; sx, symptoms.

per each criterion met, which were summed for a total quality score of 0 (lowest quality) to 8 (highest quality).[42, 43]

RESULTS

Study Selection

Combined database and manual searches resulted in 2641 references. After removing duplicates and screening at the level of title and abstract, the full text of 154 articles was assessed. Of these, 144 studies were excluded for the following reasons: 6 did not report original data (eg, commentaries, reviews), 4 did not include samples of patients with IBD diagnoses or patients in samples had a significant medical comorbidity, 23 did not include children (patients in sample were aged >18 years), 65 did not measure pain, 14 did not measure psychosocial correlates, 20 did not include a valid pain measure, and 12 did not analyze psychosocial and pain measures together. Ten studies met the inclusion criteria. Fig. 2 shows the details in a PRISMA flowchart.

Pain and pain impact measures

Among the studies measuring pain, the Abdominal Pain Index (API)[44] was used most frequently, followed by the Faces Pain Scale-Revised.[45] One study each used the 11-point Numerical Rating Scale,[46] the Stomach Pain and Hurt subscale from the PedsQL,[47] and diagnostic criteria for functional abdominal pain disorder (FAPD) based on pain intensity, frequency, and duration ratings.[48] All studies assessed abdominal pain specifically. Of the studies measuring pain impact, all used the Functional Disability Inventory (FDI).[49] Table 1 contains details.

Given that a relatively large number of studies were excluded because they did not include a valid measure of pain (n = 20), we reviewed the reasons for their exclusion further in Supplemental Table 2. The most common reasons for exclusion were (1) combining pain measurement with a different construct (eg, combined pain and nausea scales), (2) measuring pain as part of a composite disease severity index (eg, the PCDAI), and (3) utilizing dichotomous variables to assess pain (eg, yes/no
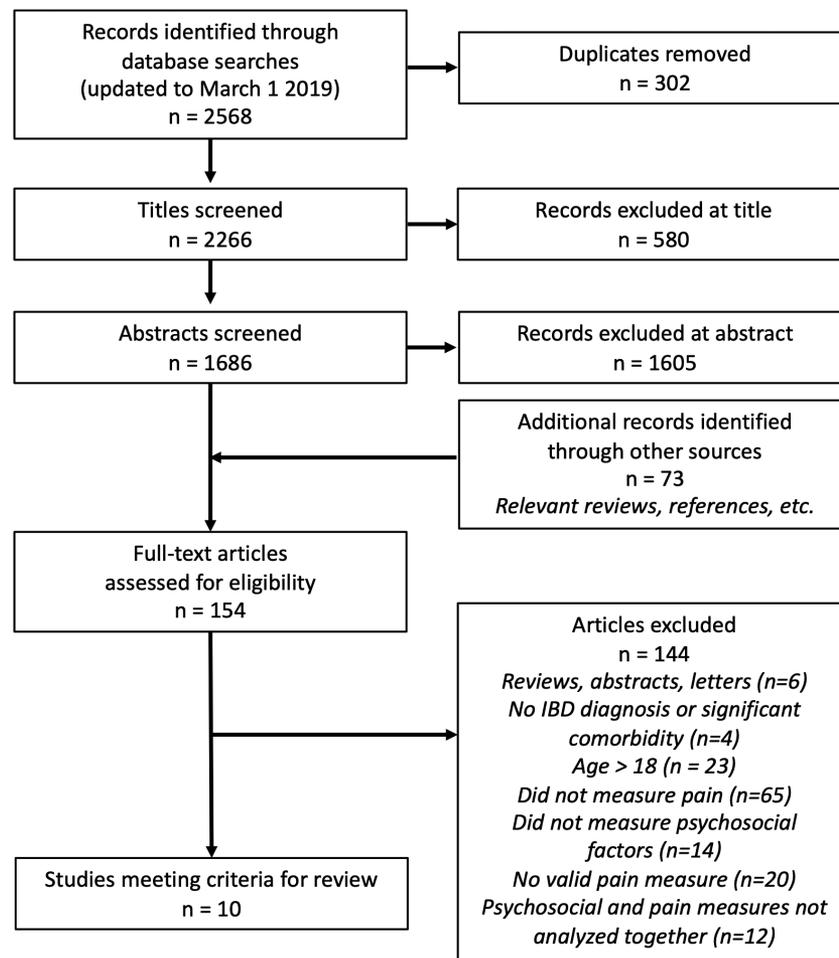

FIGURE 2. PRISMA flowchart of included studies.

reporting whether pain was a problem). Supplemental Table 2 contains further detail.

Psychosocial factors

Psychosocial measures in included studies assessed both child psychosocial factors and parent psychosocial factors. Child anxiety symptoms were measured via self-report (ie, State-Trait Anxiety Inventory for Children, Multidimensional Anxiety Scale for Children, and Screen for Child Anxiety Related Disorders[50-52]) and child depression symptoms were measured via both child self-report and clinician rating of symptoms (ie, Children's Depression Inventory—2nd Edition and Children's Depression Rating Scale[53, 54]). Child pain catastrophizing, pain coping, pain threat, and stomach pain worry were all measured via child self-report (Pain Catastrophizing Scale for Children,[55] Pain Response Inventory,[56] Children's Pain Beliefs Questionnaire,[57] and PedsQL Gastrointestinal Worry Scale[58]). Parent pain catastrophizing was measured with the Pain Catastrophizing Scale—Parent version[59] and parent protective behaviors were measured with the Protect subscale of the Adult Responses to Children's Symptoms scale.[60] Table 1 contains further details.

Study Characteristics

The 10 published studies that met the inclusion criteria were drawn from 6 separate samples of youth with IBD. Four studies published data from the baseline assessment of a randomized clinical trial of a psychological intervention.[2, 7, 23, 61] Two of these studies focused on a subsample of youth with only CD, and 2 focused on youth with CD and UC; each study presented unique variables and analytic approaches. Two studies published data from the baseline assessment of a randomized clinical trial comparing psychotherapeutic interventions.[3, 62] These studies also presented unique variables and analytic approaches. The remaining 4 studies were cross-sectional.[4, 63-65]

The 10 studies included a total of 763 participants. Sample sizes ranged from 20 to 226. All samples were drawn from pediatric gastroenterology departments in children's hospitals located in the United States. Ages ranged from 7 to 18 years. Eight studies included youth with either CD or UC/indeterminate colitis; 2 studies focused exclusively on youth with CD. Seven studies measured pain, 2 measured pain impact, and 1 study measured both. Eight studies examined child psychosocial factors, 2 studies examined parent psychosocial factors, and none of the studies focused on broader family-level factors. Findings are reviewed separately below for each of the aims of this study.

Aim 1: Psychosocial Correlates of Pain and Pain Impact

Eight psychosocial correlates of child pain or pain impact were examined: 6 child-level factors and 2 parent-level factors. No studies reported on family-level psychosocial correlates. A variety of analyses were conducted to assess the relation between psychosocial factors and pain. Key findings and study characteristics are listed in Table 1. A summary of factors associated with pain, along with the magnitude of associations and significance,[66] are summarized in Table 2.

Child psychosocial correlates

Of the studies examining child psychosocial factors as correlates of pain or pain impact, 5 studies examined child anxiety, 5 studies examined child depression, 2 studies examined pain catastrophizing, and 1 study each examined active coping, stomach pain worry, and pain threat. Findings are reviewed separately here for mood (anxiety and depression) and pain-specific cognitive-behavioral factors (pain catastrophizing, pain coping, stomach pain worry, pain threat).

Anxiety and depression

Five studies examined the association between anxiety symptoms and pain or pain impact, and 3 found significant associations with either pain intensity (n = 2) or pain impact (n = 1). Across these studies, the magnitude of associations ranged from small to large. Crandall et al[63] examined the association between anxiety symptoms and pain intensity in a small sample of youth with IBD and found that anxiety was a significant correlate of pain. Similarly, van Tilburg et al[7] found a significant association between higher anxiety symptoms and higher functional disability in youth with CD. Claar et al[2] compared psychosocial functioning in 4 groups of youth with CD: those in disease remission with and without pain and those in a flare with and without pain. In posthoc testing, youth in a flare with pain reported significantly more anxiety symptoms than did youth in remission without pain, although there were no significant differences between the other groups. In contrast, Srinath et al[3] examined associations between anxiety symptoms and abdominal pain severity in CD and UC groups separately and found that anxiety was not significantly correlated with pain in either subgroup. Watson et al[65] examined anxiety symptoms in youth with IBD with and without a FAPD diagnosis. Youth with IBD and FAPD did not have significantly greater anxiety symptoms than youth with IBD without FAPD. When clinical cutoffs for anxiety symptoms were considered, the FAPD group was 7 times more likely to be above the clinical cutoffs, although the difference was not significant.

Five studies examined the association between depression symptoms and pain (n = 4) and pain impact (n = 1) and all found significant associations; the magnitude of associations ranged from small to large. Van Tilburg et al[7] found a significant bivariate association in 2017 between depression symptoms and functional disability in youth with CD. Similarly, Srinath et al[3] examined bivariate associations between depression symptoms and abdominal pain severity in CD and UC groups separately in 2014 and found that

TABLE 2. Summary of Factors Associated With Pain Identified in Included Studies

Psychosocial Factor	Claar et al 2017[2]	Crandall et al 2007[63]	Langer et al 2014[23]	Srinath et al 2014[3]	Szigethy et al 2014[62]	van Tilburg et al 2015[61]	van Tilburg et al 2017[7]	Varni, Shulman et al 2018[64]	Watson et al 2017[65]	Wojtowitz et al 2014[4]
Child factors										
Anxiety symptoms	M*	S**		S (NS); S (NS)			M**		ND, NS; L (NS)	
Depression symptoms	L*			M***; M**	S*		L**		ND**; L**	
Pain catastrophizing						S***	L**			
Coping						S (NS)				
Stomach pain worry								L***		
Pain threat							L**			
Parent factors										
Protective responses			S (NS)							
Pain catastrophizing			S (NS)							M**; M**

Direction of all associations is positive. Where multiple analyses in same domain were conducted in the same article, findings are separated by a semicolon.

L, large magnitude; M, moderate to large magnitude; ND, magnitude could not be described from data reported per Cohen's guidelines;[96] NS, not significant; S, small to moderate magnitude.

*P < 0.05, **P < 0.01, ***P < 0.001, (n.s.), not significant

depression symptoms were significantly correlated with pain in both subgroups; the magnitude of associations was consistent across groups. Claar et al[2] found that youth in a flare with pain reported significantly increased depression symptoms compared to both youth in a flare without pain and youth in remission without pain. Similarly, Watson et al.[65] reported that youth with IBD and FAPD had significantly greater depression symptoms and were significantly more likely to be above the clinical cutoff for depression symptoms than youth with IBD who did not meet the criteria for FAPD. Finally, Szigethy, Youk, and colleagues[62] used latent profile analysis to identify depression subgroups and then examined pain severity as a predictor of group membership in multivariate analyses. Controlling for other demographic and clinical variables, pain severity was significantly associated with membership in the "somatic depression" subgroup (characterized by the highest depression symptoms) compared with the "mild depression" subgroup.

Pain-specific cognitive-behavioral factors

Child pain catastrophizing, pain coping, pain threat, and stomach pain worry were examined in 3 separate studies in relation to pain or pain impact. With the exception of pain coping, each factor was significantly associated with pain or pain impact.

Pain catastrophizing is a cognitive process that involves magnifying or exaggerating the threat or seriousness of painful sensations.[67] Two studies examined child self-reported pain catastrophizing, and both found significant associations (1 of small magnitude, 1 of large magnitude). Van Tilburg et al[7] examined the association between pain catastrophizing and functional disability in youth with CD in 2017 and found a significant bivariate correlation of large magnitude. In a 2015 study of youth with both CD and UC, van Tilburg et al[61] tested the association between multiple types of pain responses and functional disability in a multivariate linear regression. Controlling for age, sex, and IBD symptom severity, pain catastrophizing was significantly associated with disability; the magnitude of the association was small.

Coping is defined as purposeful and volitional efforts in response to stress.[68] The 2015 van Tilburg et al[61] examined various types of passive coping (eg, self-isolation, behavioral disengagement) and active coping (eg, problem-solving, seeking social support, rest, massage/guard) efforts in response to stomach pain specifically. Controlling for age, sex, and IBD symptom severity, the study found that active and passive coping were not significantly associated with disability.

One study examined perceived pain threat, which assesses the extent to which youth find pain threatening or worrisome (eg, "my stomachaches mean I'm really sick"). Van Tilburg et al[7] found a significant bivariate correlation of large magnitude in 2017 between pain threat and disability in a sample of youth with CD.

Stomach pain worry specifically assesses worry about abdominal pain. Varni, Shulman et al[64] examined the bivariate association between stomach pain worry and abdominal pain severity in a sample of youth with IBD in 2018 and found a significant association of large magnitude.

Parent psychosocial correlates

Regarding the parent psychosocial factors examined in relation to pain, 2 studies examined parent pain catastrophizing[4, 23] and 1 examined parent protective responses.[4, 23] Parent pain catastrophizing assesses parents' catastrophizing about their child's pain,[59] and parent protective responses assess parents' behavior in response to their child's pain (eg, letting children stay home from school, giving special treats when their child has pain).[60] Wojtowicz et al[4] examined pain catastrophizing in parents of adolescents with IBD and found a significant bivariate association with both child pain severity and child functional disability. Both associations were of moderate magnitude. In contrast, Langer et al[23] examined the association between pain intensity and both parent pain catastrophizing and parent protective responses in a sample of youth with IBD in 2014 and found no significant correlations.

Aim 2: Clinical and Sociodemographic Correlates of Pain and Pain Impact

We also examined associations between pain and clinical and sociodemographic factors in the included studies. These findings are summarized in Supplemental Table 1. Sociodemographic factors included sex and age. Four of the 5 studies that examined sex differences found that girls reported significantly greater pain or pain impact than did boys[2, 4, 61, 65]; the other study did not find significant sex differences.[23] Of the 3 studies that examined age as a correlate of pain or pain impact, none found a significant association. No other sociodemographic factors were examined in relation to pain.

Only 7 studies reported on disease status, and the majority of the patients in these studies had quiescent disease (Supplemental Table 1). Six studies examined the relation between disease factors and pain and pain impact. Four studies examined disease activity/severity, and all found significant associations with pain or pain impact[3, 4, 7, 61]; 3 studies used disease activity indexes that included pain ratings. Two studies examined time elapsed since IBD was diagnosed and found no significant association with pain.[3, 65] One study examined medication and found that youth taking anti-tumor necrosis factor treatments were significantly less likely to report pain.[2] Watson et al[65] found that similar numbers of youth with CD and UC met the criteria for FAPD. Of note, only 3 studies examined both psychosocial factors and IBD disease severity as predictors of pain in the same multivariable model, and all measures of disease severity were composites that included pain ratings. Of these studies, 2 found that psychosocial factors were stronger predictors of pain or pain impact[3, 64] and 1 found that disease severity was a stronger predictor of pain impact.[61]

Study Quality

All of the included studies met the criteria of providing a clear research question or objective and clearly defining and assessing pain and other variables with valid and reliable tools. However, no study provided a sample size justification, power description, or variance and effect estimates and most (n = 8) failed to report on participation rates. Global quality scores ranged from 4 to 7 (out of 8), with an average of 5.4 (Fig. 3).
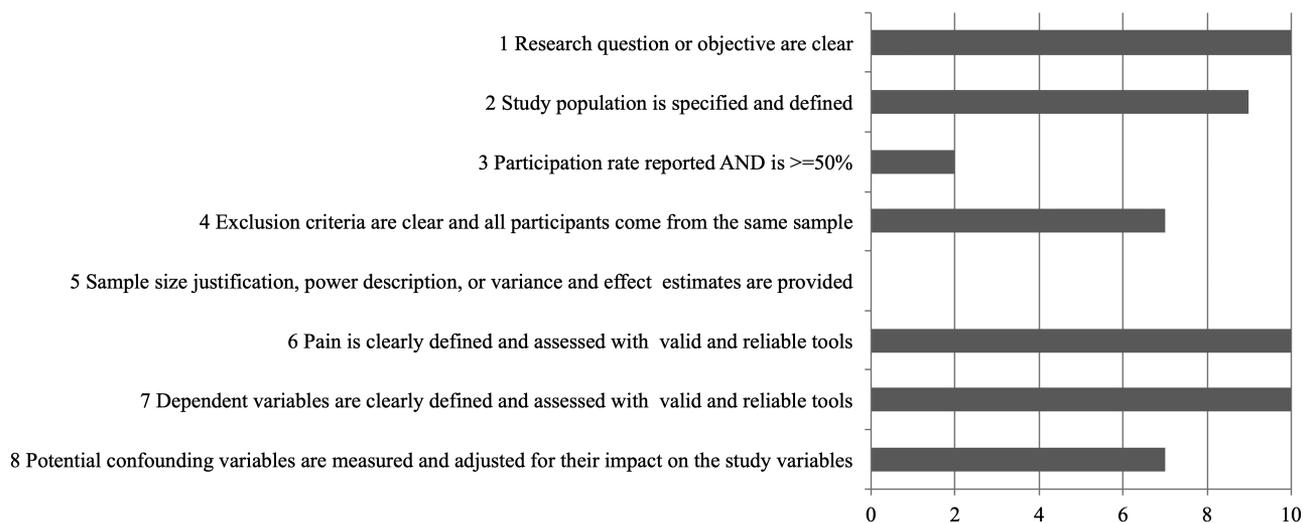
FIGURE 3. Summary of quality ratings across all the studies (n = 10) included.

DISCUSSION

This is the first study to systematically review the psychosocial correlates of pain and pain impact in youth with IBD. Building on a recent review of the psychosocial correlates of pain in adults with IBD,[39] this review applied a developmental framework to classify psychosocial risk. Results indicate that this topic is an emerging area of research in pediatric IBD, with only 8 studies examining child psychosocial correlates, 2 studies examining parent psychosocial correlates, and no studies examining family-level psychosocial correlates of child pain or pain impact. All studies were cross-sectional, and all were of moderate to high quality. Taken together, there is consistent evidence that individual child and parent psychosocial risk factors are associated with pain and pain impact. Specifically, we found that child depression, anxiety, and pain-specific threat, worry, and catastrophizing are associated with significantly greater pain and impact and that parent pain catastrophizing is also associated with greater child pain and impact.

Child depression and anxiety symptoms were the most commonly examined psychosocial factors, and both were associated with significantly higher levels of pain intensity and pain impact. This is consistent with findings from the Sweeney et al review[39] of the psychosocial correlates of pain in adults in that mood symptoms were also commonly examined and consistently associated with greater pain. Previous reviews have highlighted that anxiety and depression are common comorbidities in pediatric IBD[69] and that youth with IBD are at heightened risk compared with healthy youth.[70, 71] Mood symptoms such as depression and anxiety may serve as risk factors for pain by amplifying descending pain pathways (ie, increasing pain signals). Specifically, there is evidence that brain regions associated with depression and anxiety, such as the anterior cingulate cortex and amygdala, interact with sensory input such as pain to influence pain perception.[72] Further, depression symptoms are known to negatively impact medical adherence behaviors in pediatric IBD,[73] which may result in greater IBD symptoms such as pain, and anxiety symptoms may serve to increase attention to and experience of pain itself.[74, 75] Although this review provides evidence that anxiety/depression symptoms and pain are significantly associated concurrently, causation cannot be assumed; longitudinal studies are needed to better understand the temporal relationship of these symptoms. For example, it is unclear if anxiety and depression symptoms predict risk for maintenance or worsening of pain and disability in pediatric IBD over time or whether higher levels of pain and disability result in increased anxiety and depression symptoms.

This review also provides evidence for the association between pain-specific cognitive-behavioral factors and pain. Catastrophizing, pain threat, and pain worry are fear-related constructs and each were significantly positively associated with increased pain and pain impact. Each of these factors may contribute to the experience of pain itself and to the avoidance of activities and increased disability.[74] In the context of pediatric

IBD, pediatric patients and their parents may be told by physicians that pain is a sign of disease activity or recurrence and be cautioned to remain hypervigilant to pain.[6] Therefore, youth with IBD may be especially prone to show fear of pain, which is well known to increase risk for pain-related disability across other chronic pain conditions.[74, 76] Only 1 study included in our review examined coping and it did not find a significant association with pain; however, additional data are needed and we encourage the inclusion of coping measures in future studies. Previous reviews have highlighted that coping efforts that involve adapting to uncontrollable stress associated with chronic illness and pain are consistently associated with lower levels of pain and disability.[77, 78]

Only 2 studies examined parent psychosocial factors in relation to child pain and pain impact, and 1 found significant associations between parent pain catastrophizing and child pain intensity and disability. Of note, the authors of the study that found nonsignificant associations administered the Faces Pain Scale-Revised[45] over the phone to participants, which may have influenced findings. Within the pediatric pain literature, it is well established that parent psychosocial factors are important influences on child pain and disability.[14] In the context of pediatric IBD, parent pain catastrophizing may be driven by parents' worries that their child's pain is indicative of a worsening disease process. This catastrophizing may lead to parent behaviors (eg, checking in frequently about the child's pain) that serve to increase the child's attention to and experience of pain.[79] Within the framework of social learning theory, parent behaviors such as attending to pain symptoms and allowing their children to avoid undesired activities when they are in pain may result in increased disability.[79-81] Limited data are available on parent protective responses as a correlate of child pain, and further studies are needed in pediatric IBD.

In addition, it is a notable gap that none of the included studies measured broader family functioning or family environment (eg, family conflict, family stress). In other pediatric chronic pain conditions, poorer family functioning has been associated with increased pain and disability.[14, 81] We encourage future studies to include broad measures of family-level functioning. When considering social factors in pediatric pain more broadly, it is important to note that the role of peers and social functioning is expected to increase with age.[14] Given that prior research has found decrements in social functioning in youth with IBD[70, 71] and that peer victimization has been tied to increased pain and disability in both clinical and community samples of youth with pain,[12, 82] future studies examining psychosocial influences on pain should also consider the role of peers.

Although we cannot draw conclusions on directionality from the cross-sectional findings reviewed here, psychosocial risk factors such as mood symptoms and pain-specific cognitive-behavioral factors are theoretically posited to both amplify descending pain pathways and to increase attention to

and experience of pain itself.[74, 75] There is also clear evidence in the pediatric chronic pain literature that psychosocial interventions targeting mood symptoms and pain-specific cognitive-behavioral factors can lead to subsequent reductions in pain and disability. A recent Cochrane review[83] examining the evidence for psychological therapies in the management of chronic and recurrent pain in children and adolescents showed that psychological therapies significantly reduce pain intensity, disability, and anxiety. Consequently, despite the direction of the association between pain symptoms and psychological symptoms that is yet to be determined, it seems clear that targeting psychological symptoms in youth can be beneficial for pain management. We discuss this element further below in Clinical Implications.

This review also examines the clinical and sociodemographic correlates of pain and pain impact within included studies. Findings showed that female sex is significantly associated with increased pain and pain impact, which is consistent with the general pediatric pain literature and with findings from the adult IBD pain review.[39] Although most studies did not examine differences between patients with CD and patients with UC, 2 studies conducted analyses separately by diagnosis, and findings were consistent across disease groups.[3, 65]

Regarding the role of disease activity, it is important to note that many of the studies included samples in which the majority of youth had quiescent disease and had been diagnosed with IBD more than a year before the study. Although disease activity/severity was commonly assessed in relation to pain, note that several of these disease indexes included abdominal pain ratings within their composite assessment of IBD symptoms (eg, the PCDAI and the PUCAI[84, 85]), which could artificially inflate the association with pain ratings (ie, the 2 measures assess the same construct). Given that only 3 studies examined both psychosocial factors and disease factors together in the same multivariate model, and all used disease activity indexes that included pain ratings, it is premature to conclude whether disease factors or psychosocial factors are stronger predictors of pain in pediatric IBD. Going forward, future studies examining pain in IBD should measure clinical and psychosocial constructs separately (ie, they should use disease severity measures that do not include pain ratings). In addition, it will be important to examine psychosocial factors in patients nearer the time of diagnosis and with more active disease. Given that optimizing medication may take some time after diagnosis, this may be an ideal window to deliver psychological services targeting pain management skills.

Taken together, findings from this review were largely similar to findings from the Sweeney et al[39] review of psychosocial correlates of pain in adults in that mood symptoms and pain-specific cognitive-behavioral factors seem to be key correlates of pain across age groups. A notable exception is the inclusion of parent psychological factors in this review, consistent with developmental models of pediatric chronic pain. In contrast to the current review, studies focused on pain in adults with IBD examined a wider variety of both clinical and psychosocial factors in relation to pain. For example, studies reviewed here did not examine antidepressant use and substance use in relation to pain in pediatric populations. In addition, positive psychological factors, such as benefit finding, gratitude, and acceptance, have been examined in adults with IBD but have not yet been examined in relation to pain and pain impact in pediatric IBD. This suggests that going forward it will be important to explore resiliency factors that may serve to protect pediatric patients with IBD from the negative consequences of pain.[86-88]

Limitations

Findings should be interpreted in light of several limitations, primarily because of the few studies included in this review and the variability among them. The samples are heterogeneous, with some focused on CD to the exclusion of UC, some stratified by disease severity/activity, and others that did not characterize disease severity. Few studies characterized time since IBD diagnosis, and those that did included samples of patients with a large variability in years since diagnosis. In addition, although this review focused on 10 papers with unique analytical approaches, the articles were drawn from only 6 studies. As a result of this, 2 of the samples were overrepresented across the review. Further, all studies were limited to cross-sectional analyses. Samples were drawn from pediatric gastroenterology departments in children's hospitals only in the United States. Therefore, findings may not generalize to pediatric patients from other countries where IBD presentation and treatment may differ.

To include a wider variety of studies and to match the inclusion criteria in the recent review of psychosocial correlates of pain in adults with IBD,[39] we focused on both pain (intensity, duration, frequency) and pain impact (ie, disability) as outcomes. However, note that these are distinct constructs. Indeed, psychosocial factors like the ones explored here have been posited to mediate the association between pain intensity and disability.[89] Therefore, in clinical and research contexts, pain severity and pain impact should both be measured to understand the experience of youth in their day-to-day life.

Clinical Implications

The results of this review suggest several important implications for clinical practice in both routine screening and referral for comprehensive evaluation and intervention. First, given the impact of pain and disability on quality of life in pediatric patients with IBD,[2-4] it is important for pain to be assessed routinely during clinic visits to the pediatric gastroenterologist. Although there are no current standardized methods of assessing pain in pediatric IBD, we recommend the use of brief, well-validated, and freely available measures, such as the API,[36] the FDI,[49] or the Pediatric PROMIS Pain Interference scale.[90] Furthermore, because child depression and anxiety symptoms are common

in pediatric patients with IBD[69, 70] and are significantly associated with pain, it is important for pediatric gastroenterologists to screen for psychological symptoms during clinic visits as well. There have been several recent calls for routine screening for mood disorders in pediatric IBD,[91-93] and toolkits have recently been published and disseminated that aid pediatric gastroenterologists in implementing procedures for screening and referral for mental health needs in clinic settings.[93]

Following routine clinic assessment, pediatric patients endorsing elevated pain or psychological symptoms that significantly interfere with daily functioning should be referred to a mental health provider for comprehensive psychological evaluation and subsequent treatment as indicated. Psychological treatment for mood disorders in youth typically includes cognitive-behavioral techniques, involves parents in treatment, and is well supported by research.[94] As we have described, there is also evidence from a recent Cochrane review that psychological therapies are effective in the management of chronic and recurrent pain in youth with pain disorders.[83] Results from this review suggest that both anxiety/depression symptoms and pain-specific cognitive-behavioral factors such as pain catastrophizing may be important treatment targets for pediatric patients with IBD and pain. Further, parents' thoughts about their child's pain, specifically parent pain catastrophizing, may also be a useful intervention target.

Research Implications

Findings of this review also suggest important recommendations to inform future research. First, the pediatric IBD literature would benefit from improved measurement of pain to guide not only future research but also future targeted interventions. In this current review, 20 studies were excluded for not using a valid measure of pain or for combining pain with different constructs in analyses. However, as we have noted, valid measures of pain and pain impact in pediatric populations exist (eg, API,[44] FDI;[49] see review of functional abdominal pain assessment measures[32]) and can be easily implemented. Further, all studies included in the present review were cross-sectional; large multisite longitudinal designs are needed to better understand the temporal relationships among pain and psychosocial functioning in pediatric IBD samples. It will also be critical for future research to use developmentally sensitive frameworks for categorizing risk factors for pain. Parent and family-level constructs are associated with pain and pain impact in other pediatric samples,[14] so the inclusion of more parent-level and family-level constructs such as parent distress, parent-child communication, and family conflict in pediatric IBD will be important. Finally, all samples in this review were located in the United States. It is essential for research to be completed internationally, with multiple collaborating centers, particularly given that the rates of pediatric IBD are increasing globally.[95]

Moving forward, results from this review and future research in this area will inform the development of more precise cognitive-behavioral interventions to reduce pain and disability among pediatric patients with IBD. These interventions may draw on elements from successful trials developed for older adolescents and adults with IBD (eg, targeting pain-related cognitions and depression/anxiety[28]). However, interventions need to be tailored developmentally for children with IBD by considering and directly targeting parent and family factors as well. This approach is consistent with pain management interventions that have been developed for other pediatric pain populations (eg, FAPD, sickle cell disease[83]).

CONCLUSIONS

This is the first study to systematically review and summarize the associations between pain and psychosocial factors in youth with IBD. Our findings suggest that psychosocial factors are associated with pain and pain impact. Whereas child depression, anxiety, and pain-specific threat, worry, and catastrophizing are associated with significantly greater pain and impact, parent pain catastrophizing is also associated with greater child pain and impact. These findings provide guidance on how to optimize clinical care for children with IBD; specifically, gastroenterologists should consider routinely screening for both pain and anxiety/depression symptoms in pediatric patients with IBD. Future research should direct efforts to better characterize the experience of pain separately from disease activity and to discern how (ie, mechanisms) and when (ie, causality) associations between psychosocial risk and pain take place. The results of such research may help inform the tailoring of pain management interventions for youth with IBD. This includes first-line cognitive-behavioral treatment to target psychosocial factors (such as depression/anxiety symptoms and pain catastrophizing) to reduce pain impact, prevent the need for escalating medical management, and improve the overall quality of life in youth with IBD. In summary, although research on psychosocial factors associated with pain in pediatric IBD is still nascent, findings from this systematic review may guide future research and clinical practice.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

References 2–4, 7, 23, and 61–65 reflect inclusion in the systematic review.

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