



**REVIEW ARTICLE**

# Epidemiology of Musculoskeletal Manifestations in Pediatric Inflammatory Bowel Disease: A Systematic Review

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**Objective.** Pediatric inflammatory bowel disease (p-IBD) is a chronic relapsing gastrointestinal disorder of childhood with long-term morbidity. Several extraintestinal manifestations are described, the most common being joint pain and/or inflammation. However, patient and disease characteristics, treatments, and outcomes of p-IBD-associated musculoskeletal disease are not well established. Our study aims to summarize the recent literature on the epidemiology of musculoskeletal manifestations in p-IBD in the era of biologics.

**Methods.** A systematic search of PubMed, Embase, Cochrane Library, Web of Science Core Collection, and Cumulative Index to Nursing and Allied Health Literature databases was performed with relevant keywords. Studies in English published from January 1, 2000, to December 21, 2020, were included. In total, 3893 articles were identified and screened. Study and population characteristics and outcomes of interest were recorded. Risk of bias assessment was performed using the Joanna Briggs Institute Critical Appraisal Tools.

**Results.** Thirteen studies were included for full review, which were primarily single-center observational studies with retrospective or cross-sectional designs. The diagnostic criteria and definitions used for musculoskeletal manifestations varied. Musculoskeletal manifestation prevalence ranged from 2% to 35%. Only one study assessed the response of musculoskeletal manifestations to biologics. Risk of bias demonstrated heterogeneity in study quality.

**Conclusion.** This is the first systematic review of musculoskeletal manifestations in p-IBD. Analysis was limited because of variability in study design and data-reporting methods. Definitions varied among included studies, with a clear lack in standardization. Our study demonstrates the need for standardized assessment of musculoskeletal manifestations of p-IBD and further research to explore optimal management to advance care for this group of children.

## INTRODUCTION

Pediatric inflammatory bowel disease (p-IBD) is a group of chronic inflammatory disorders that primarily affect the gastrointestinal tract and include Crohn disease (CD), ulcerative colitis (UC), and unclassified inflammatory bowel disease (IBD-U) (1,2). This disorder can present in childhood, has significant associated morbidity, and has been shown to negatively impact quality of life (3). The burden of inflammatory bowel disease (IBD) is growing worldwide, and in Canada specifically, the prevalence is expected

to increase by 35% by the year 2030 to about 1:100 individuals (4). Although p-IBD is primarily a gastrointestinal disorder, it is a systemic disease with the ability to affect nearly any organ system. The most common extraintestinal manifestations (EIMs) are those affecting the musculoskeletal (MSK) system, namely joint pain and/or inflammation (5,6).

Though it is well described that IBD can have systemic manifestations, the exact mechanism of joint disease and its relation to intestinal disease is still unclear. Genes such as those involved in the interleukin 17 and interleukin 23 pathway, nuclear factor κB

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pathway, or T helper 17 pathway are implicated (7). Gut inflammation is also believed to play a role in the pathology of arthritis through mechanisms such as alterations in the gastrointestinal microbiome, increased intestinal permeability, molecular mimicry, and immune responses (8,9). It is unclear whether this relationship between gut inflammation and arthropathies is causative or associative, but there is an indisputable link between the two. Overall, the precise pathogenesis has yet to be elucidated.

There are several studies that characterize the MSK EIMs in adult IBD; however, data for p-IBD are sparse. In 1986, Passo et al (10) were the first to describe the association of arthritis in patients with p-IBD. In this retrospective study, arthritis was described in 9% of children with UC and in 15.5% of children with CD. Arthralgia was more common than arthritis, occurring in 32% of patients with UC and 22% with CD. Since the initial description, few studies have been published on this topic. Classification criteria for MSK EIMs in p-IBD are not defined and rely on adult literature. The European Crohn's and Colitis Organisation has created an evidenced-based consensus on EIMs in adult IBD, and the definitions of arthropathies are described (11) (see Supplementary Table 1). These definitions have not been validated in children and, despite this, are commonly used nomenclature in the pediatric gastroenterology literature. This classification system is not commonly used in the pediatric rheumatology literature, which instead uses the International League of Associations for Rheumatology (ILAR) criteria (12). However, IBD-related arthritis is not considered under the ILAR criteria.

Definitions for MSK EIMs in p-IBD are lacking, cohorts are not well characterized, and much of the data are either based on extrapolation from adult data or individual case reports. Our study aims to summarize the more recent literature on the epidemiology of MSK EIMs in p-IBD in the era of biologic therapies, focusing on presentation, diagnosis, and disease course of MSK EIMs in p-IBD.

## MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (13), and the protocol for this systematic review was preregistered with PROSPERO identifier CRD42021244021 (14).

**Search strategy.** A limited electronic search of PubMed was used to identify relevant keywords for the concepts: "pediatric," "paediatric," "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "arthritis," and "joint disease." In line with this, synonyms were used for respective databases for an extensive search of the literature (see Supplementary File 1). An electronic search of the databases PubMed, Embase, Cochrane Library, Web of Science Core Collection, and Cumulative Index to Nursing and Allied Health Literature was conducted by the author AA, and the search strategy was reviewed by a librarian.

The search was limited to between January 2000 and December 2020, with the last search performed on December 22, 2020. The search was limited to studies published after 2000 because of the introduction of biological therapies in the management of p-IBD, demonstrating a shift in the paradigm of treatment of p-IBD.

**Study eligibility criteria.** Included studies were observational or interventional in design, published in the English language and after 2000, and had MSK EIMs as primary or secondary outcome variables in patients diagnosed with p-IBD (<18 years of age). The MSK EIMs of interest were arthralgia, enthesitis, and peripheral or axial arthritis. Studies were included when full-text articles were available, the p-IBD population was described separately from adult-onset IBD, and MSK EIMs were reported in more detail beyond incidence and prevalence.

**Exclusion criteria.** Studies were excluded if they 1) included only patients 18 years of age or older diagnosed with IBD or did not distinguish between pediatric-onset IBD and adult-onset IBD, 2) only reported prevalence or incidence of MSK EIMs without further description of the MSK EIMs, and 3) were review articles, case reports or series, or conference abstracts. Rheumatologic and MSK manifestations of osteopenia, osteoporosis, vasculitides, chronic recurrent multifocal osteomyelitis, psoriasis, or periodic fever syndromes were not evaluated in this review.

**Study selection.** Results from the searches were inserted into the Covidence software (15), in which automatic processes removed duplicates. Screening processes were performed by two reviewers (AA and MS) independently. The first screening was performed based on titles and abstracts, and if a study had information related with MSK EIMs, it was retained for the full-text review. The second screening phase involved a full-text review to select the relevant articles for quality assessment and data extraction. Discrepancies in reviewer selections were resolved by a third and/or fourth reviewer (EC and RB).

**Data extraction and synthesis.** Two reviewers (AA and MS) independently performed data extraction using a data extraction form. Information on the descriptive and quantitative characteristics were recorded and included clinical features as well as 1) publication details (year of publication, publication status), 2) characteristics of the study (study design, methods, country, setting, sample size, etc), and 3) characteristics of the population (age, sex, ethnicity, etc). Odds ratios or standardized mean differences were calculated when possible, and when not, data were summarized with frequencies and percentages.

**Quality assessment.** The risk of bias was assessed independently by two reviewers (AA and MS) using the Joanna Briggs Institute Critical Appraisal Tool for prevalence, analytical

cross-sectional, case-control, and cohort studies, corresponding to methodology used by the authors (16,17). Discrepancies between the reviewers were adjudicated by a third reviewer (DP).

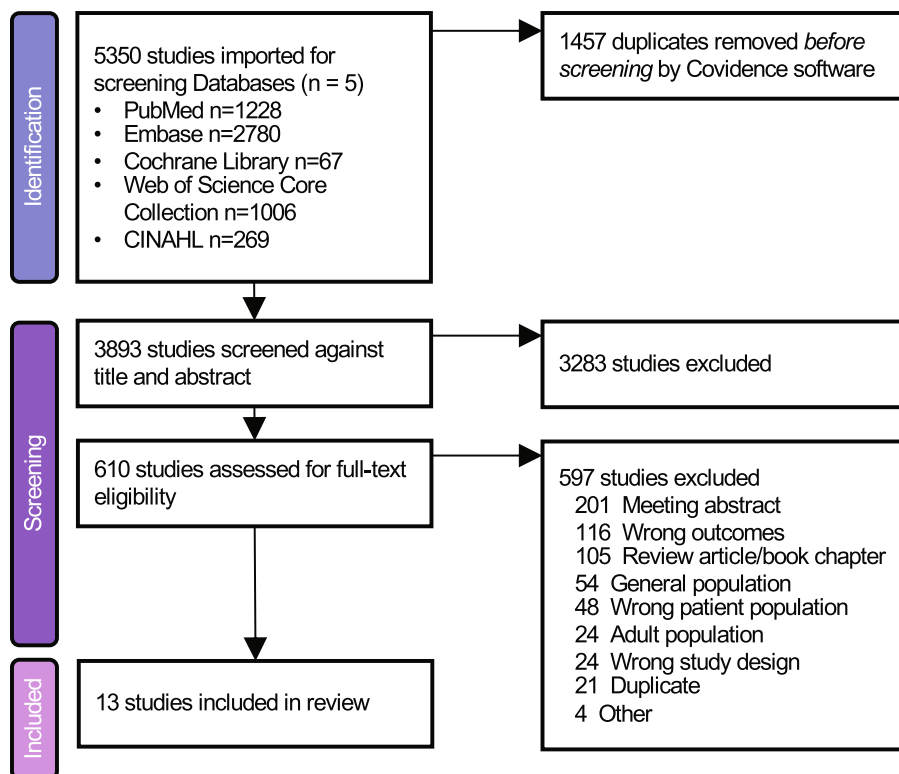
## RESULTS

The literature searches identified a total of 5350 articles (Figure 1). After removal of duplicates, 3893 records were screened for relevance. A total of 3283 records were excluded by screening the title and abstract, and the remaining 610 full-text articles were assessed for eligibility. Five hundred ninety-seven articles were excluded, and 13 studies met the inclusion criteria for full-text review. Because of the heterogeneity, odds ratios or standardized mean differences were not calculated, and data were summarized with frequencies and percentages in a narrative form.

**Study characteristics.** Included studies were primarily observational single-center studies (18–30) (Table 1). These were most commonly retrospective cohort studies with limited prospective follow-up. Only seven studies focused on MSK EIMs as their primary outcome, whereas the remainder reported on multiple p-IBD-associated EIMs. The study sample sizes were small, with only a few studies encompassing larger numbers of study participants.

**Study population and definitions.** There was a wide range in the prevalence of MSK EIMs (Figure 2). The reported prevalence varied depending on the definitions used and whether arthralgia was included in the definition. More studies demonstrated a larger number of patients with CD with MSK EIMs, as opposed to UC or IBD-U. There was a relatively equal number of males and females with MSK EIMs in the seven studies that reported these data, except for one, which found that all five patients with radiographic sacroiliitis were male (21). Three studies reported on age comparisons between those with MSK EIMs and those without, and all demonstrated a younger patient group in those with MSK EIMs (21,23,30). Data on intestinal disease extent and location were limited, and of the studies that did record differences between MSK EIM and non-MSK EIM groups relative to the intestinal disease, there were no significant differences noted in disease location, per Paris classification (28–30).

The method of diagnosis for MSK EIMs varied greatly between studies, with only four studies stating the involvement of a rheumatologist in the diagnosis and five studies not stating the method of diagnosis at all. The definitions used also varied, with MSK-related features, such as peripheral arthritis, axial arthritis, enthesitis, and arthralgia, included (Table 2, see Supplementary Table 2 for further definition information). The most commonly reported joints affected by peripheral arthritis and arthralgia were the knees and ankles (25,27,29).



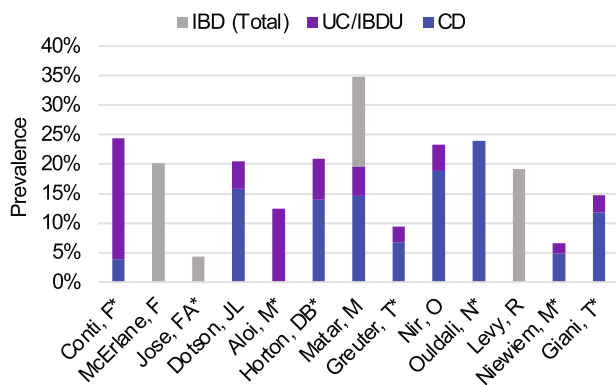
**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the study search and selection for inclusion in the systematic review. CINAHL, Cumulative Index to Nursing and Allied Health Literature.

**Table 1.** Study and sample characteristics

Study	Country	Sample source	Study type	Sample size	% female	IBD type, n (% total)			Age in years
						CD	UC	IBD-U/IC	
Conti et al (19), 2005	Italy	Single center	Cross-sectional	31	58.1	3 (9.7)	4 (12.9)	12 (38.7)	Median 11.4 (range 5-17)
McErlane et al (27), 2008	UK	Single center	Cross-sectional	124	57.3	67 (54.0)	55 (44.4)	2 (1.6)	Median 12.7 (range 6-16)
Jose et al (24), 2009	USA	Multicenter	Retrospective and prospective cohort	1649	45.8	1007 (61.1)	471 (28.6)	171 (10.4)	At diagnosis, mean 11.1 ± SD 4.14
Dotson et al (20), 2010	USA and Canada	Multicenter	Prospective cohort	1009	42.5	728 (72.2)	281 (27.8)	-	Mean 11.7 ± SD 3.1
Aloi et al (18), 2010	Italy	Single center	Retrospective cohort	32	50	-	32 (100.0)	-	Median 14 (range 8.3-19.8)
Horton et al (23), 2012	USA	Single center	Cross-sectional	43	48.8	32 (74.4)	1 (2.3)	10 (23.3)	Median 16 (IQR 12-18)
Matar et al (26), 2017	Israel	Single center	Retrospective cohort	184	42.9	129 (70.1)	46 (25.0)	9 (4.9)	Mean 13.2 ± SD 2.8
Greuter et al (22), 2017	Switzerland	Multicenter	Retrospective cohort	329	45	173 (52.6)	156 (47.4)	-	At enrollment, median 14 (IQR 11-15, range 0-17)
Nir et al (29), 2017	Israel	Single center	Retrospective cohort	430	42.8	301 (70.0)	112 (26.0)	17 (4.0)	At diagnosis, median 14.0 (IQR 11.2-16.2)
Ouldali et al (30), 2018	France	Single center	Retrospective and prospective cohort	272	43.8	272 (100.0)	-	-	At diagnosis, median 12.1 (IQR 10.1-14.2)
Levy et al (25), 2019	Israel	Single center	Nested case-control	69	56.5	20 (29.0)	2 (2.9)	1 (1.4)	NR
Niewiarn et al (28), 2019	Poland	Single center	Retrospective cohort	287	43.2	140 (48.8)	147 (51.2)	-	CD mean 14.1 (range 5-18), UC mean 12.9 (range 2-18)
Giani et al (21), 2020	Italy	Single center	Retrospective cohort	34	29.4	32 (94.1)	2 (5.9)	-	Mean 14.3, median 15.3

Note: Characteristics of included studies are based on sample size, source, study type, and subject characteristics.

Abbreviations: CD, Crohn disease; IBD-U, unclassified inflammatory bowel disease; IQR, interquartile range; NR, not reported; UC, ulcerative colitis.



**Figure 2.** Reported prevalence for musculoskeletal (MSK) extraintestinal manifestations (EIMs). MSK EIM prevalence reported by inflammatory bowel disease (IBD) subtype where data are available. \*Study did not include arthralgia in definition. CD, Crohn disease; IBUD, unclassified inflammatory bowel disease; UC, ulcerative colitis.

**Disease course.** The relationship between onset and diagnosis of MSK EIMs and IBD onset and diagnosis was not established in most studies primarily because of the retrospective or

cross-sectional study design. Greuter et al (22) describe peripheral and axial arthritis appearing prior to IBD diagnosis in 28% and 40% of patients, respectively; however, peripheral arthritis was significantly more likely to present after IBD diagnosis rather than prior (64% vs 28%,  $P = 0.011$ ). This was not seen in axial arthritis, with presentation prior to and after IBD diagnosis occurring at a similar frequency (22). In the study by Jose et al (24), arthritis was reported in 26% of patients prior to IBD diagnosis, with the cumulative proportion of peripheral arthritis at 10 years of 4.2%;. Ouldali et al (30) found that only 4 of 65 (6.2%) patients developed arthritis prior to IBD diagnosis with, the majority developing arthritis in the first year after CD diagnosis.

Data on disease activity, flares, and severity were poorly defined in relation to MSK EIMs. Prospective data collection were limited, resulting in missing data. Many studies documented symptoms or severity at initial data collection, with the follow-up flares of either intestinal or extraintestinal disease not reported. There was no patient self-reported relationship between intestinal disease flares and the severity of joint symptoms for the majority of patients, and of 30, only 12 had MSK EIMs preceding or

**Table 2.** Descriptive characteristics of MSK EIMs

Study	MSK manifestation	Frequency % (n/N)
Rheumatologist involved in diagnosis		
Conti et al (19), 2005	Axial arthritis	29.0 (9/31)
	Peripheral arthritis	9.6 (3/31)
	Enthesitis	25.8 (8/31)
McErlane et al (27), 2008	Arthralgia	17.1 (22/124)
	Arthritis	2.4 (3/124)
Horton et al (23), 2012	Arthritis	2.3 (1/43)
	Enthesitis	23.2 (10/43)
Greuter et al (22), 2017	Axial arthritis	1.5 (5/329)
	Peripheral arthritis	7.9 (26/329)
Rheumatologist not involved in diagnosis or not stated		
Jose et al (24), 2009 <sup>a</sup>	Axial arthritis	0.7 (12/1649)
	Peripheral arthritis	2.7 (45/1649)
	Axial and peripheral arthritis	0.8 (14/1649)
Dotson et al (20), 2010	Arthralgia	16.5 (166/1009)
	Axial arthritis	0.3 (4/1009)
	Peripheral arthritis	3.6 (37/1009)
Aloi et al (18), 2010	Spondyloarthropathy	12.5 (4/32)
	Arthralgia	12.5 (23/184)
Matar et al (26), 2017	Arthritis	22.3 (41/184)
	Arthralgia	13.9 (60/430)
Nir et al (29), 2017	Axial arthritis	1.1 (5/430)
	Peripheral arthritis	6.3 (27/430)
	Axial and peripheral arthritis	1.8 (8/430)
	Arthritis	6.3 (17/272)
Ouldali et al (30), 2018	Peripheral arthritis	17.6 (48/272)
	Arthralgia (with arthritis)	8.7 (6/69)
Levy et al (25), 2019	Axial arthritis	11.6 (8/69)
	Arthritis (all)	33.3 (23/69)
	Arthritis	6.6 (19/287)
Niewiem et al (28), 2019	Arthritis	6.6 (19/287)
Giani et al (21), 2020	Sacroiliitis (radiologic)	14.7 (5/34)

Abbreviations: EIMs, extraintestinal manifestations; MSK, musculoskeletal.

<sup>a</sup>Frequency is based on the number of first chronological EIM presentations, as the total MSK EIM frequency in the sample is not reported.

concurrent with their intestinal disease (27). Nir et al (29) define luminal disease activity using a Harvey-Bradshaw Index score of 5 or more for CD and a Pediatric UC Activity Index (PUCAI) score of 10 or more for UC. In the UC group, patients with arthralgia were more likely to have higher disease activity during follow-up compared with those without joint disease, but this was only significant in univariate analyses ( $P = 0.005$ ), not multivariate analyses ( $P = 0.628$ ). There was an overall trend toward more hospitalizations in the MSK disease groups for both CD and UC, but this did not reach statistical significance. This is also demonstrated in the study by Ouldali et al (30), in which arthritis was significantly associated with increased hospitalizations for intestinal disease over a 4-year period ( $P = 0.007$ ). For Pediatric CD Activity Index and PUCAI scores, there was no significant difference between groups with MSK EIMs and those without; however, these scores were only reported at one time point (20,28,29).

**Biomarkers.** A trend toward an increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level in patients with MSK EIMs was seen in a few studies (20,21,23,29), but significance was only achieved in one study in which patients with UC with arthralgia had significantly higher CRP levels than those without joint involvement (29). Nir et al (29) also found that in patients with CD, joint disease was more likely to occur in women, those with a family history of IBD, and those with elevated liver enzyme levels and less likely to occur in those with perianal disease. They also found that patients with arthralgia at initial IBD diagnosis were more likely to later develop arthritis compared with those without arthralgia at IBD diagnosis. In a case-control study, it was demonstrated that in patients with arthritis associated with p-IBD, compared with those with arthritis of other causes, there was significantly increased ESR, CRP level, sacroiliac involvement, arthralgia, and additive arthritis and a significantly decreased white blood cell count and hemoglobin

level (25). Only one article looked at fecal calprotectin levels (25), which demonstrated elevated levels in the patients with p-IBD compared with the controls without known intestinal disease, but unfortunately no studies compared p-IBD with and without MSK EIMs.

**Therapeutic response.** Four studies reported on the therapeutic response of MSK EIMs to pharmacotherapy, and only three of those reported on biologic use. The study by Nir et al (29) was the only study that documented MSK response to biologic therapy; however, no specific definition was given for clinical response. For patients with CD receiving either infliximab or adalimumab, clinical improvement in MSK EIMs was seen, with a 78% response rate for peripheral arthritis and a 60% response rate for sacroiliitis. In three patients with UC who received infliximab, two patients had a positive clinical response for MSK EIMs, with one responding for peripheral arthritis and another for axial arthritis. Interestingly, two studies also found a greater likelihood of initiating biological therapy in those patients with arthritis compared with those without (29,30).

**Risk of bias.** Risk of bias demonstrated a large heterogeneity in the quality of included studies (Table 3). Most studies were prevalence studies and all of them had overall poor quality, with scores less than 5 of 9. The cohort studies followed, with large variability in their quality; one study was high quality (30), with the remainder having poor to moderate quality. The case-control and cross-sectional studies both had moderate to high quality.

## DISCUSSION

p-IBD is a systemic disease with the potential to affect any organ, with the most common EIM system affected being the MSK system. Despite this, the prevalence, presentation, accurate diagnosis and disease course, and response to treatment remain poorly characterized. Of the included articles ( $n = 13$ ), only seven focus on MSK EIMs as their primary objective, requiring inclusion of studies that more broadly described all EIMs. This systematic review highlights the a priori hypothesis that there remains a paucity of data on this topic. Though all the studies reported a prevalence, many failed to fully characterize the clinical features, onset, and progression of the MSK EIMs. Specifically, the relationship to intestinal disease activity and exacerbations, and laboratory findings were limited to only a few studies.

Extraction of data from the included studies was also challenging because of the lack of a standardized set of definitions and measurement tools used for the diagnosis of MSK EIMs. Clinical examination of the MSK system requires a systematic approach, and yet only four studies stated the involvement of a rheumatologist in the diagnosis of joint manifestations. Within the multicenter cohort studies, it was also acknowledged that standardization among the different centers was not achieved.

**Table 3.** Quality assessment of included studies

Study	JBICritical Appraisal Tool	Score
Conti et al (19), 2005	Prevalence	4/9
McErlane et al (27), 2008	Prevalence	4/9
Jose et al (24), 2009	Cohort	4/11
Dotson et al (20), 2010	Cohort	5/11
Aloi et al (18), 2010	Prevalence	3/9
Horton et al (23), 2012	Analytical cross-sectional	7/8 <sup>a</sup>
Matar et al (26), 2017	Prevalence	2/9
Greuter et al (22), 2017	Cohort	6/11 <sup>a</sup>
Nir et al (29), 2017	Cohort	6/11 <sup>a</sup>
Ouldali et al (30), 2018	Cohort	10/11 <sup>a</sup>
Levy et al (25), 2019	Case-control	7/10 <sup>a</sup>
Niewiem et al (28), 2019	Prevalence	3/9
Giani et al (21), 2020	Prevalence	4/9

**Note:** Quality assessment performed using the appropriate JBI Critical Appraisal Tool. Score reflects positive answers to tool questions, with lower scores indicating poorer quality of evidence. Abbreviation: JBI, Joanna Briggs Institute.

<sup>a</sup>Moderate to high quality.



Diagnostic criteria for definition of MSK EIMs were also not stated in six studies, further limiting generalizability of study outcomes. Only one study explored clinical response of biologic use on MSK EIMs; however, the definitions of what constitutes clinical response were not clear, although validated tools are used to measure response for many current drug trials.

Further, our search was limited by the lack of interventional data and heavily relied on observational studies of small sample sizes. There were few multicenter studies (20,24); however, these did not have MSK EIM as the primary outcomes measure. Assessment by the critical appraisal tool demonstrated overall poor to moderate quality for the majority of studies, with only a few achieving good scores in quality assessment.

Of interest, a published abstract (excluded from systematic review) highlights the possible role of biomarkers in patients with MSK EIMs. Porfito et al (31) had findings to support the trend of greater MSK EIMs in the CD population. They also found that ESR, CRP, and calprotectin levels were elevated in the group with joint disease, with intestinal disease flares mirroring joint disease in about half of patients. Future prospective studies should aim to incorporate biomarkers with a detailed MSK assessment and description of luminal disease activity to accurately characterized the phenotype of these patients.

This systematic review highlights gaps in care for patients with MSK EIM and p-IBD, with accurate prevalence data, diagnosis, disease course, effect on pain and quality of life, and outcomes lacking. As demonstrated by Giani et al (21), subclinical joint inflammation can occur in asymptomatic patients with IBD, with MSK disease often going unaddressed as a result; this was also demonstrated in a further study by Rasheed et al (32). Several studies support the fact that clinical or subclinical enthesitis involvement may also occur in p-IBD (23,33,34). With the knowledge that MSK EIMs can often go unrecognized, and the decreased quality of life associated with arthritis in patients with p-IBD (35), it is essential that we both increase our research focus in this area and develop methods to appropriately screen for MSK EIMs in p-IBD. Screening tools are being developed for the adult IBD population to detect MSK EIMs, with some preliminary success (36–38). The use of appropriate screening in the p-IBD population would positively impact the detection, diagnosis, and treatment of MSK EIMs.

Recent consensus has been reached in the adult IBD literature to define end points for MSK EIMs for the assessment of these manifestations in IBD trials, allowing for prospective assessment of these manifestations and comparison between studies (39). A similar initiative is needed for p-IBD with close collaboration between pediatric gastroenterologists and rheumatologists to optimize care for this complex patient population.

This is the first systematic review of the literature for MSK EIMs in p-IBD. We highlight the challenges of combining data collected over this period due to limited between-study comparability. Included studies reported prevalence of MSK EIMs, but the ascertainment of MSK EIMs, both method and definition, varied and had

a clear lack in standardization. Our study demonstrates the need for additional research to define the presentation, diagnosis, management, and morbidity associated with MSK EIMs in p-IBD. Future studies should also be directed at validating appropriate screening tools in the p-IBD population for prompt recognition and management of MSK EIM to mitigate risk for long-term morbidity.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Ms. Ali had full access to all of the data and takes full responsibility for the integrity of the data and accuracy of the data analysis.

**Study conception and design.** Crowley, Berard.

**Acquisition of data.** Ali, Schmidt.

**Analysis and interpretation of data.** Ali, Schmidt, Piskin, Crowley, Berard.

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