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Full title: Systematic review: psychosocial factors associated with pain in Inflammatory Bowel

Disease

Authors

Louise Sweeney MSc BSc

PhD researcher

King's College London

Florence Nightingale Faculty of Nursing & Midwifery

London, United Kingdom

Rona Moss-Morris PhD MHSc BSc

Professor of Psychology as Applied to Medicine

King's College London

Health Psychology Section

London, United Kingdom

Wladyslawa Czuber-Dochan PhD RN

Lecturer

King's College London

Florence Nightingale Faculty of Nursing & Midwifery

London, United Kingdom

Laura Meade MA

PhD researcher

King's College London

School of Population Health Sciences

Faculty of Life Sciences and Medicine

London, United Kingdom

Gillian Chumbley PhD BSc (Hons) RN

Consultant Nurse – Pain Service

Imperial College Healthcare NHS Trust

London, United Kingdom

Christine Norton PhD RN

Florence Nightingale Professor of Clinical Nursing Research

King's College London

Florence Nightingale Faculty of Nursing & Midwifery

London, United Kingdom

Correspondence to:

Louise Sweeney

King's College London

Florence Nightingale Faculty of Nursing and Midwifery

James Clerk Maxwell Building

57 Waterloo Road

London SE1 8WA

Tel: 07745565349

Email: louise.sweeney@kcl.ac.uk

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Abstract

Background Pain is a frequently reported symptom of inflammatory bowel disease (IBD)

experienced by patients in active disease and remission. Psychological factors play a significant role in pain, but have not been systematically reviewed in IBD.

Aim To review psychosocial factors associated with pain in adults diagnosed with IBD.

Methods Electronic (PsycInfo, MEDLINE, EMBASE, Cochrane Library, CINAHL, Web of Science) and hand-searching were conducted February-May 2017. Two authors carried out screening and data extraction.

Results Fifteen studies including 5539 IBD patients were identified. Emotional, cognitive-behavioural and personality factors were associated with IBD-pain. Depression and anxiety were the most commonly explored constructs, followed by perceived stress and pain catastrophising, all of which were positively associated with greater pain. Greater abdominal pain was associated with a concurrent mood disorder over fivefold (OR 5.76, 95% CI 1.39, 23.89). Coping strategies and pain fear avoidance correlated with pain levels. Perceived social support ($r = .26$) and internal locus of control ($r = .33$) correlated with less pain. Patients reporting pain in IBD remission more frequently had an existing diagnosis of a mood disorder, a chronic pain disorder and irritable bowel syndrome. Six studies controlled for disease activity, of which 4 found that psychosocial factors significantly predicted pain. The majority of studies ($n=10$) were of high quality.

Conclusion Psychosocial factors appear to play a significant role in IBD-pain. Further research is required to explore psychosocial constructs in relation to IBD-pain, with use of validated pain measures, large sample sizes and clearer characterisation of disease activity.

Key words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, pain, psychosocial, psychological factors, systematic review

Short title: Psychosocial factors and pain in IBD

Introduction

Abdominal pain is a commonly experienced and debilitating symptom of IBD, with up to 70% of patients experiencing pain when the disease is active¹⁻³. Common causes of IBD-related abdominal pain include acute inflammation, strictures, adhesions, small-bowel obstruction and bowel dysmotility⁴. Reducing abdominal pain is a key therapeutic target for IBD therapy, however pain severity does not always correlate with endoscopic and clinical biomarkers, and a significant proportion of patients (20-50%) report ongoing pain during periods of remission^{3, 5-7}. Bodily pain, cramps and extra intestinal manifestations of IBD such as arthralgia are also reported by patients^{3, 8}. In an IBD population-based cohort, peripheral arthritis and non-inflammatory joint pain were reported by 0.4% and 16% of patients, respectively⁹. The prevalence of chronic widespread pain or fibromyalgia has ranged between 3.5-30% in adults with IBD^{10, 11}. Suggested causes of extra intestinal manifestations of pain in IBD include genetic predisposition, such as polymorphisms of the NOD2 gene involved in the transcription of proinflammatory cytokines and chemokines, or the migration of gut lymphocytes^{9, 12}. Research has shown the capacity of activated intestinal lymphocytes to enter the joints and adhere to inflamed synovial vessels¹³. Such processes within the ‘joint-gut axis’ are suggested to explain the high co-occurrence of IBD and arthropathies, however research into this area of IBD-pain has received much less attention.

Chronic pain in IBD is a complex phenomenon driven by a range of peripheral and central nervous system (CNS) processes. In the case of acute pain, noxious signalling is processed by sensory afferent nerves that innervate the gut wall and send signals from the lower gastrointestinal tract to the CNS via the dorsal spinal horn¹⁴. However, recurrent inflammation and release of mucosal signalling molecules (e.g. nerve growth factor, glial cell-lined derived neurotrophic factor and ion channel expression TRPV1/TRPA1) in the context of chronic IBD can result in visceral hypersensitivity^{1, 14}. In

CNS processing, recurrent visceral stimulation can lead to the activation of the N-methyl-D-aspartate receptor and influx of calcium in higher/second-order sensory neurons, resulting in long-lasting neuronal excitability in the absence of inflammation¹⁵. Central processing within the brain such as stress and arousal may also have a role in pain perception and aetiology of chronic IBD-pain, such as via mechanisms along the ‘brain-gut’ axis. Stress can exacerbate IBD symptoms by the production of cortisol and catecholamines from the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axis and thereby the release of circulating inflammatory cytokines (e.g IL-6)^{16, 17}. Emotional and cognitive processes can also amplify perception of incoming visceral signals by modulating descending inhibitory processes¹⁸. Similar mechanisms have been recognised in irritable bowel syndrome (IBS), and functional symptoms in quiescent IBD are frequently entangled with a diagnosis of IBS^{19, 20}. However, there is mixed support as to whether conceptualising symptoms in quiescent IBD as IBS is useful.

Current treatments for pain management in IBD carry a number of risks and limitations. Escalating pharmacotherapy or exploratory surgery for pain in the absence of inflammation can have iatrogenic side effects, potentially exacerbating disease activity, psychological distress and worsening quality of life for patients. Alternative options such as antispasmodics, anticonvulsants, tricyclic antidepressants and cyclooxygenase-2 (COX-2) inhibitors may provide pain relief, yet their long-term use can exacerbate gut symptoms and bowel dysmotility¹⁷. A significant number of patients use opioids or marijuana for pain control despite psychological and disease-related risks²¹⁻²⁴. In a European IBD cohort (n = 2831), 21.5% and 14.7% of patients were reported to take antidepressant or opioid medication, respectively²⁵. Norton et al.²⁶ recently reviewed abdominal pain management interventions in IBD and found promising evidence for psychological approaches for IBD pain. For example, self-directed and therapist-led stress management²⁷, coping skills²⁸ and disease anxiety-related cognitive behavioural therapy (CBT)²⁹, all appear to attenuate abdominal pain symptoms, albeit in predominantly small samples. Adjuvant psychological therapy may be particularly effective for individuals with IBD in pain, at risk of psychological distress and who are experiencing ongoing

symptoms in the absence of active disease³⁰. Yet the review highlighted the need for evidence-based theory to aid the development of effective psychosocial interventions for IBD-pain.

Bielefeldt et al have proposed a biopsychosocial model of IBD-pain¹. This identifies two key processes of hypersensitivity and hypervigilance in the aetiology of chronic pain, summarising the role of inflammation and visceral hypersensitivity in increasing central processing of pain, and the influence of emotional responses and mood disorders that can act to amplify the pain experience by disinhibition of descending signals¹ (Figure 1). The model has provided a useful insight into the possible mechanisms of chronic IBD-pain, however it is yet to be thoroughly investigated.

Figure 1. Bielefeld et al.'s (2009, p. 20) conceptual model of pain in IBD. Two distinct processes of hypervigilance and hypersensitivity are suggested to underlie greater pain. Recurrent inflammatory activity can lead to hypersensitivity of visceral neurons, resulting in increased central input of pain signals. Emotional reactivity to the affective dimension of pain (valence) can cause an individual to become hypervigilant, leading to disinhibition of descending pathways and further increase of sensory input.

Despite pain being rated as one of patients' most bothersome symptoms in IBD^{31,32}, this remains an area of limited research. In addition to the disease, the symptom of pain specifically has a profound impact on the quality of life and functioning of IBD patients³. To date, systematic reviews in IBD have explored the role of psychosocial factors on the course of IBD and associated psychotherapeutic approaches³³, psychosocial correlates of adjustment in IBD³⁴ and pain management interventions in IBD²⁶. However, a systematic review of psychosocial factors in IBD-pain specifically is lacking. A comprehensive profile of psychological and social factors associated with pain in IBD will provide a basis for developing a theory of IBD pain to underpin a psychosocial intervention, as has been applied in other conditions such as multiple sclerosis and paediatric chronic fatigue syndrome^{35,36}.

The specific aims of the study are to

- I) To systematically review psychological and social factors associated with pain in adults diagnosed with IBD.
- II) To assess the association of pain and clinical and sociodemographic factors within included studies of psychosocial investigations.

Methods

The protocol for this review was prospectively registered on 23/03/2017 (PROSPERO 42016052479).

Eligibility criteria

Studies were eligible if they reported on pain in an adult IBD population and measured at least one psychosocial factor. Studies including paediatric populations were not included, as it was contended that psychological processes compared to adult IBD-pain were likely to be different, for example the role of parent-child dyads. A focus on adult IBD-pain would therefore yield greater clarity in identifying key targets for a self-management intervention. Pain measures included any pain measure such as pain intensity, severity, diagnosis of chronic pain (> 3 months), pain-associated disability or interference. Inclusion and exclusion criteria for this review are presented in Table 1.

Information sources, search and study selection

Studies were identified through multiple online database and hand searching. Online searches were conducted in January and February 2017, and a final search was conducted on 24 May 2017.

Databases included EMBASE (1974 to 2017 Week 2), Medline (1946 to 2017 Week 2) PsycInfo (1806 to 2017 Week 1), Web of Science, CINAHL and the Cochrane Library. Additional articles were identified manually by the first author through reference lists. Authors of abstracts and those known to be working in the field of IBD pain were contacted directly for any unpublished data. Search terms were tailored for each database and included terms for 'inflammatory bowel disease', 'pain' and 'psychosocial factors' and combined using the set operators OR and AND (Table 2). MeSH and explode terms were utilised to maximise search results. Cross-sectional, prospective, longitudinal and experimental studies (reporting a baseline association of psychosocial factors and pain) were included. Only studies presented in English were selected (no scope for translation) however no restrictions were applied with regards to publication date due to the limited number of studies on psychosocial factors and pain in IBD. L.S. and L.M. independently carried out abstract and full-text screening using predetermined criteria. Any disagreements between reviewers were resolved through discussion utilising inclusion criteria.

Data collection

Predefined data extraction criteria were used by two authors (L.S. and L.M.) to extract relevant data. Any discrepancies were again resolved by consensus or inclusion of a third author (C.N). Extracted information from each study included (1) study design (2) number of participants, (3) characteristics of patient sample (age, IBD diagnosis), (4) comparator group (if applicable) (5) recruitment source (6) type of (correlate) psychosocial measure, (7) type of (outcome) pain measure, (8) key findings (9) key quantitative data (10) additional clinical/demographic correlates with pain. Due to variety in pain and psychosocial measures used, meta-analyses were not possible and so a narrative review was conducted.

Quality assessment

Methodological quality of studies was assessed using the Critical Appraisal Skills Programme (CASP) guidelines, selected by the specific methodological design of included studies³⁷. The same criteria have been applied in previous reviews on IBD populations^{38, 39}. Studies were assessed by L.S. and L.M. and points were deducted for a lack of defined objectives and hypothesis; non-validated measurement tools; inappropriateness or limited data regarding methodological design and statistical analysis; selective reporting of results and limitations not addressed. Assessment of studies yielded a low, medium or high quality rating. Any disagreement between reviewers was resolved through consensus or inclusion of C.N. Studies were classified as High (n =10), Medium (n=4) and Low quality (n=1) (see Supplementary Table 1). As all papers were considered to contribute to the topic of interest, no studies were excluded on the basis of quality.

Results

Study characteristics

Combined database and manual searches identified 3336 references. After removing duplicates and undertaking title and abstract screening, full-texts of 65 studies were assessed by L.S and L.M. Fifteen studies reported in 16 papers were included (Figure 1). Studies excluded at the full-text screening stage, with reasons, are provided in Supplementary Table 2

Figure 2. PRISMA flow chart of included studies

Results of individual studies

The 15 studies included a total of 5539 IBD participants (including indeterminate colitis) and 993 non-IBD participants. A wide variety of pain measures were used in studies, with a significant proportion of studies relying on single-item questions or sub-scores to assess pain. Moreover, there was wide variability in study design and methodology. Eight studies were cohort studies and seven were case-control studies. One study was reported in two papers^{40, 41}. Three studies compared IBD with healthy controls⁴⁰⁻⁴³ and four studies involved other patient groups including back pain, IBS,

arthritis and gastroesophageal reflux disease⁴⁴⁻⁴⁷. One study was longitudinal and 14 studies were cross-sectional design, of which one was baseline data from an intervention study⁴⁸ and two were national cohort survey studies^{49, 50}. A summary of included studies is provided in Table 3, with detailed results of each included study presented in Supplementary Table 1.

25 psychosocial factors in relation to pain were identified, including emotional, cognitive, behavioural and personality factors. Ten and five studies conducted univariate and multivariate analyses, respectively (Table 4). A variety of pain presentations were investigated and different pain measures were used by the studies (Table 5). Two papers explored different pain presentations^{41, 51}, including joint pain, chronic pain with a neuropathic component and migraine⁵¹. Prevalence of probable migraine and chronic pain were significantly higher in the IBD cohort compared to the general population⁵¹. Prevalence of patients with IBD with chronic pain in studies ranged from 11.3-38%^{2, 51}. Percentages of patients experiencing pain of at least moderate intensity at the time of study, or who had experienced pain within the last three months, ranged from 20.5-82.5% across studies.

The 25 psychosocial factors identified were grouped into three broad categories; emotional, cognitive-behavioural and personality factors, and are reviewed below. Addressing the second aim of the review, clinical and sociodemographic factors associated with pain identified within the reviewed studies are then reported.

Emotional factors

One study investigated the presence of a mood disorder (by physician diagnosis) in relation to pain⁵². From multivariate analyses, a co-existing mood disorder increased the odds of pain frequency and pain severity fivefold (OR 5.76, 95% CI 1.39, 23.89).

Depression

10 of the 15 included studies explored depression in relation to pain, of which nine found that depression/depressive symptoms were significantly positively associated with higher pain intensity^{40-44, 47, 51, 53}, more locations of pain⁴¹ and reports that pain prevented and/or restricted activities⁵⁰. All but one of these studies were cross-sectional in design. Assessing different pain presentations, one study found that higher Hospital Anxiety Depression (HAD) depression scores (4th quartile vs 1st quartile) were associated with a 3.44 increased risk of probable migraine, but were not found to correlate with joint pain, abdominal pain or chronic pain with a neuropathic component⁵¹. In the only longitudinal study identified in this review, pain at baseline correlated with depressive symptoms at baseline and six months⁴⁷. Five of these studies used the Hospital Anxiety Depression Score (HADS) questionnaire. Two of these studies included a comparison group, namely IBS⁴⁴ and patients with arthritis⁵¹.

One study investigating depression stratified participants who had active and inactive disease, defined by colonoscopy and histological reports⁴³. Mucosal inflammation did not show a significant association with pain rating. Depression scores remained the only significant predictor of greater pain ratings in multivariate analyses, after controlling for age, growth factors levels (neurturin NRTN) and ion channel density (transient receptor potential Ankyrin TRPA1) in the colonic mucosa.

Anxiety

Of the seven included studies that explored anxiety and pain, all found a significant positive association between these variables in cross sectional analysis^{2, 43, 44, 49, 51, 53}. One study found that state but not trait anxiety significantly correlated with increased abdominal pain/tenderness, however this was deemed a low quality study⁴⁴. Exploring the association between anxiety and different pain presentations, HAD anxiety scores significantly correlated with joint and overall pain severity and probable migraine in an IBD cohort, but not abdominal or chronic pain with a neuropathic component in one longitudinal study⁵¹.

The HADS questionnaire was used in one study to assess factors associated with mood disorders in IBD⁴², and found that abdominal pain was significantly associated with HAD anxiety in CD. Active disease (SCCAI/endoscopic active disease Baron's score >1) and perceived stress independently predicted anxiety and depression scores in UC. Being an inpatient also predicted higher Fco HAD depression scores.

Stress

Four studies assessed levels of psychological stress, including perceived stress, in relation to pain^{46, 47, 53, 54}. All of these studies found significant and positive correlations between stress and pain intensity^{46, 47, 53, 54}, pain-related interference⁵³ and bodily pain⁵⁴. In regression analyses, odds ratio for psychological stress (OR lowest 2.26, highest 12.17) and female gender (OR highest 3.19) increased with greater pain using three pain sub-scores⁵⁴. Three out of four studies were cross-sectional in design, however one longitudinal study found only baseline pain scores correlated with baseline perceived stress⁴⁷.

Cognitive-behavioural factors

Pain catastrophising

Three studies investigated pain catastrophising, which refers to an exaggerated negative cognitive and affective interpretation of actual pain or an expected pain experience. It includes magnifying potential negative factors associated with pain, feelings of helplessness and an inability to disengage from pain-related thoughts⁵⁵. All three cross-sectional studies found that pain catastrophising was associated with greater pain reporting in IBD^{2, 40, 41}. Participants who reported more than one location of pain also were found to catastrophise more about pain in one study that looked at pain phenotyping⁴¹. Phenotype 1, 2 and 3 represented abdominal pain, 1-2 locations (e.g. abdominal and lower back) and

3+ locations, respectively. In univariate analyses, all pain phenotype participants with IBD showed significantly higher scores for pain catastrophising compared to healthy controls. However, phenotype 1 showed significantly lower scores for these two psychosocial measures compared to phenotype 2 and 3, with no significant difference between the latter phenotypes⁴¹. One high quality study found that a tendency to catastrophise was a significant predictor of moderate to severe pain after controlling for active disease, measured by the Harvey Bradshaw Index (HBI) or SCCAI².

Coping

Coping is an important construct in the context of chronic illness, and refers to an individual's efforts to tolerate and resolve stressors that exceed his or her resources⁵⁶. Three cross-sectional studies assessed the association between pain and coping, using a variety of measures. As measured by the Coping Strategies Questionnaire, one study found that having a catastrophising tendency predicted moderate to severe pain in multivariate analyses, as aforementioned². However, in univariate analyses, ignoring sensations, praying and hoping, cognitive coping/suppression, helplessness and diverting attention/praying were all found to be significantly correlated to greater pain intensity and associated disability². In this study, chronic pain was present in 38% of patients, of which chronic abdominal pain was the most frequently reported (91%) followed by joint pain (33%), back pain (33%) and chronic headache (33%)². Moderate to severe pain was also associated with active disease according to the HBI or SCCAI. Excluding disease activity, there were no differences in other disease characteristics (medication, disease duration) between moderate-severe and mild pain reporters.

Coping strategies were investigated in one study, which assessed pain in participants recruited online and in clinics, through pain sub-scales in the HBI, Short Inflammatory Bowel Disease Questionnaire and Short-Form 36⁵⁴. These included emotion-focused coping (e.g. acceptance, humour, and emotional support use), problem-focused coping (e.g. active coping and planning) and unhelpful or 'dysfunctional' coping (e.g. self-blame, denial and substance use). For the whole cohort, use of 'dysfunctional' strategies was the only coping strategy that significantly correlated with severe pain

across all three pain-sub scores ($p < .001$). In logistic regression analyses, dysfunctional coping showed significant increased odd ratios with mild pain (OR 1.06 in HBI and SF-36) and moderate pain (OR 1.07 in SIBDQ) (both $p < .05$). From the SIBDQ pain sub-score, use of problem-focused coping was associated with a 15% reduced risk of experiencing severe pain ($p < .05$). Emotion-focused coping showed no significant association with pain across pain sub-scores. Both illness-focused (guarding, resting behaviours) and wellness-focused coping (task persistence, relaxation) were positively associated with pain in one high quality study⁴⁰ (Pearson $r = 7.2$ and 3.5 respectively).

Knowledge and beliefs, perceived social support

One study assessed participants' knowledge of IBD and found no association with pain levels⁵³. Most (70.6%) pain reporters said their doctor 'did not understand their pain symptoms'. Significantly more patients reporting pain had active disease (defined by physician assessment), however no significant associations were found between age, alcohol consumption or disease duration and pain⁵³. Lower beliefs in the effectiveness of pain medication was found to be associated with greater pain in multivariate analyses in another study². In univariate analyses of this study, the extent to which participants believed that they were disabled by pain (disability score) significantly correlated with pain. A positive psychological factor, perceived social support, was significantly associated with less pain in one high quality cross-sectional study⁴⁰, however this was not supported in a prospective study which found no association with social support and pain levels⁴⁷.

Pain fear avoidance

Pain fear avoidance was investigated in IBD patients diagnosed with chronic pain, along with patients with back pain and heterogonous pain conditions (e.g. fibromyalgia and spinal pain syndromes)⁴⁵. This construct explores individual's beliefs of fearful or threatening situations, and is argued to exacerbate deconditioning and disability in the context of chronic pain⁵⁷. In a cross-sectional design,

pain intensity correlated with pain fear avoidance across all three groups. No data were provided on disease activity.

Personality factors

Personality factors and bodily pain within a health-related quality of life (HRQoL) measure was investigated in one study⁴⁸. Patients were recruited on the basis of a disease activity index for CD or UC of >4 (active disease) and perceived stress questionnaire score of > 60 . In CD patients only, greater scores on a bodily pain sub-scale (demonstrating better pain-related quality of life) was associated with internal locus of control ($p = .04$). In regression analyses, although the overall model (including control variables) was not found to be significant in explaining bodily pain, the personality variable of internal locus of control remained significant. Pain levels were not associated with positive personality traits of gratitude, benefit finding or thriving in the only included longitudinal study⁴⁷.

Clinical and sociodemographic factors

Addressing the second aim of this review, clinical or sociodemographic correlates of pain reported within included papers were extracted. Six out of 15 studies controlled for disease activity and/or clinical factors^{2, 43, 48, 51-53}. Within these, four found an association between active disease and pain (three out of four measured by physician-reported disease activity index)^{2, 48, 51, 53}, and one found an association between an inflammatory marker (C-reactive protein) and pain⁵². Abdominal pain showed no association with disease activity in two studies^{43, 51} and active disease only predicted pain in UC but not CD patients in another study⁴⁸. Three studies found that psychosocial factors remained significant predictors of pain alongside active disease or markers of inflammation^{2, 43, 51, 52}. One study found that depression remained the only significant predictor of pain ratings when controlling for clinical factors ($r > .50$)⁴³. This study investigated the influence of ion channel density and neurotrophic factors on pain, which are upregulated as a result of inflammatory activity and can lead

to visceral hypersensitivity¹. In univariate analyses, higher NRTN and lower TRPA1 levels in the mucosa correlated with higher pain ratings. Endoscopic findings and cytokine inflammatory markers (IL 1b, IL6, IL17) did not correlate with pain ratings⁴³. Disease duration was associated with probable migraine⁵¹, but not found to be significantly associated with pain ratings in another study⁵³. With regards to medication use, two studies found that no IBD-specific medications were associated with overall pain risk^{2, 51} and one found that only use of NSAIDS was significantly greater in the abdominal pain group⁵². As expected, opiate and paracetamol use increased in relation to pain severity groups in two^{2, 52} and three studies, respectively^{2, 52, 53}.

Seven studies assessed the relationship between gender and pain, and three found a significant association with pain and female gender^{51, 52, 54}, including greater prevalence of migraine in females⁵¹. Younger age was associated with greater pain^{43, 52} and probable migraine⁵¹. In quiescent IBD, one study found that patients reporting frequent to constant levels of pain were significantly more likely to have a co-existing diagnosis of a mood disorder, a chronic pain syndrome, a diagnosis of IBS, were more likely to be female, be younger and have higher ESR (mm/hour) values⁵².

Discussion

This systematic review investigated psychosocial factors associated with pain in adults diagnosed with IBD. Emotional, cognitive-behavioural and personality factors were found to be associated with pain. The majority of studies were of high quality and had moderate to large sample sizes, lending weight to the conclusions of the review. Depression and anxiety were the most commonly explored psychosocial constructs in relation to IBD-pain. Findings indicate that higher levels of depression and anxiety are associated with greater pain severity/intensity. A recent systematic review identified prevalence rates of 15% and 20% for depression and anxiety in over 150,000 IBD patients,

respectively⁵⁸. Prospective studies with IBD patients have demonstrated that depression and anxiety are associated with symptom exacerbation and onset of active disease⁵⁹⁻⁶². The current review suggests that pain may be one of the symptoms associated with these psychological factors. Higher levels of perceived stress were also a significant correlate of IBD-pain^{44, 46, 53, 54}, which supports previous evidence demonstrating the effects of stress on symptom exacerbation via the gut-brain axis^{16, 63}. Negative emotional arousal may exacerbate pain in IBD directly through amplification of descending pain signals in higher order processing or by exacerbating inflammation via the production of cortisol¹. Alternatively, greater negative affect may contribute to unhelpful behaviours such as withdrawal or poor medication adherence, which can affect pain levels. The negative emotional factors identified in this review have been recognised in the IBS literature and served as targets for therapeutic change in non-pharmacological interventions for patients with IBS^{64, 65}, supporting the view that IBS and IBD may share some similar pain mechanisms.

Exacerbation of pain symptoms from emotional arousal may also link to cognitive-behavioural factors. Greater catastrophising was associated with pain across several studies, which has been recognised as a contributing factor to chronic pain in conditions such as multiple sclerosis and fibromyalgia^{66, 67}. Moreover, research in IBS has shown a mediating role of pain catastrophising between depression and abdominal pain⁶⁸. A number of studies examined coping strategies in relation to pain levels^{40, 54}. Greater use of behaviours such as self-distraction, behavioural disengagement, denial, venting and self-blame (labelled ‘dysfunctional’ coping) and less use of active coping and planning (labelled ‘problem-focused’ coping) were related to increased pain severity. Emotionally-focused coping strategies (acceptance, humour, positive framing) showed no relation to pain levels. In another reviewed study, both ‘wellness’ and ‘illness’-focused coping were investigated. Wellness-focused coping addresses behaviours that aim to facilitate pain control, such as exercise/stretching, task persistence and relaxation, whereas illness-focused coping includes withdrawal behaviours and giving up on an attempt to control the pain, such as guarding, resting and asking for assistance. Both types of coping were positively associated with increased pain intensity. These conflicting results suggest that the relation of over-arching coping styles to IBD-pain is unclear. One could argue that the

use of emotionally focused techniques, such as acceptance and humour, may be adaptive or ‘functional’ for an individual in a given context. In this regard, identifying specific unhelpful thoughts and behaviours in relation to pain, such as denial, self-blame and fear avoidance⁴⁵, may be more effective targets than overarching coping styles for intervention development.

A number of positive psychological factors were explored in studies identified in the current review. Perceived social support and problem-focused coping were negatively associated with pain^{40, 54}. An internal locus of control⁴⁸, namely the perception that one’s behaviour can control events and outcomes was associated with better pain-related quality of life. Research on chronic back pain has shown that individuals with an external locus of control are more likely to rely on maladaptive coping strategies such as low levels of activity and a lack of belief in recovery^{69, 70}. This has been supported in research on IBD cohorts with back and joint pain⁷¹. Perceived controllability of stressful life events has been investigated in individuals with functional gastrointestinal disorders, and has demonstrated that developing skills of coping flexibility, in particular learning to identify and respond adaptively to controllable versus uncontrollable stressors, may be a useful tool for patients with more complex symptoms⁷². One study found that acceptance of pain significantly positively correlated with resilience and negatively correlated with low mood in IBD patients with chronic pain⁴⁹. This may suggest that targeting pain-related thoughts such as pain acceptance may indirectly reduce pain symptoms by improving mood. Positive psychological factors such as pain acceptance and resilience may be important avenues to explore with regards to pain adaptation, and as possible therapeutic mechanisms for future psychological interventions for IBD-related pain.

The review did not find a clear relationship between active disease/inflammation and pain. Previous studies have demonstrated an association between mucosal signalling molecules, such as an increase in pain nerve fibres TRPA1/TRPN1, and greater pain^{73, 74}. However this was not supported by one reviewed study⁴³. This demonstrates the complexity of identifying clinical factors related to pain in IBD, and requires further clarification. The majority of studies that controlled for disease activity found that psychosocial factors remained significant predictors of pain levels regardless of disease

activity. This supports the role of a biopsychosocial approach to IBD-pain, and highlights the need to take an integrative approach when assessing patients' symptoms and quality of life, in periods of both active and inactive disease.

The review identified that females and younger adults may be at particular risk of experiencing or reporting pain^{43, 51, 52, 54}. However, no gender differences were noted for different types of pain presentations which has been highlighted in a study by Schirbel and colleagues, who found greater rates of arthralgia in females³. This study by Schirbel et al. was not eligible for the review as no explicit psychosocial measure was included separate from HRQoL. However, in 400 IBD patients, 87.9% reported pain, 48.2% reported persistent pain and 38.3% of patients reported that pain was intensified by mental stress³.

The current review confirms the role of emotional and cognitive factors in relation to pain in IBD, as proposed by Bielefeldt et al¹ in their model of IBD-pain. However, their model has a particular focus on anxiety and mood disorders, rather than addressing pain-specific emotions, cognitions and behaviours. This review has identified pain-specific psychosocial processes that may be important mechanisms of chronic pain in IBD, such as pain catastrophising and pain fear avoidance. In addition, results from the review suggest that positive psychological factors such as active coping, internal locus of control, resilience and pain acceptance may be buffering or 'protective' factors against more severe or chronic IBD-pain^{40, 53, 54}. Psychological therapies may therefore be beneficial to patients with chronic pain in IBD and particularly those with psychological distress and unhelpful thought processes. CBT has a large evidence-base for treatment in IBS and other functional gastrointestinal disorders⁷⁵⁻⁷⁸, as well as positive outcomes for quality of life and coping skills in IBD populations^{30, 65}. Further research is required to confirm the role of negative psychological factors, including depression and anxiety, and pain-specific cognitive-behavioural factors in relation to chronic pain in IBD. Additionally, the potential buffering effects of positive psychological factors on pain identified in the review warrants further investigation.

Limitations

Despite identification of key factors associated with pain in IBD, limitations must be acknowledged. Although a number of studies controlled for disease activity, only one stratified results based on patients with active and inactive disease⁵². Patients with active disease were included in the review as studies examining patients only in remission and fulfilling eligibility criteria were sparse in preliminary searches. Therefore, investigation of pain in patients in remission specifically was limited in this review. A substantial number of reviewed studies lacked the inclusion of a specific validated pain measure; eight out of 15 studies used either the pain sub-measure from HRQoL, disease activity index questionnaires or single items in questionnaire surveys^{49, 50}. The use of validated pain scales with broader profile of pain is recommended for pain assessment, including pain location, intensity/severity, pain interference and pain-related beliefs^{79, 80}. These constructs are also recommended as key outcome measures in pain clinical trials⁸¹.

Ongoing pain in IBD remission has been discussed in relation to IBS and conceptualised as IBS-IBD or more recently ‘irritable inflammatory bowel syndrome’⁸². In support, one study found that patients with quiescent UC but reporting frequent to constant levels of pain were more likely to have a diagnosis of IBS (and chronic pain syndromes), alongside a mood disorder⁵². As IBS and IBS-IBD were not the main focus of this review, these were not included in the search terms. In addition, it was felt by the authors that exploration of IBD-pain in isolation rather than the addition of IBS-IBD would have yielded a purer review on IBD pain, rather than with accompanying gastrointestinal or functional symptoms. At the screening stage, studies were not excluded if they involved IBS-IBD patients, but were excluded if pain was measured only within an IBD or IBS composite score. Therefore, although studies on IBS-IBD were considered for this review pending eligibility criteria, a large number of papers on IBS-IBD or functional symptoms in IBD may have provided a more comprehensive profile of psychosocial factors associated with pain in IBD. In addition, it may have yielded more studies examining IBD patients exclusively in remission.

All but one of the included studies were observational studies, therefore direction of causality cannot be determined. Future research would benefit from longitudinal studies to assess whether psychosocial factors can predict variation in pain ratings over time. Lastly, only one of the 15 included studies carried out a power calculation⁵¹. Further exploration of psychosocial factors and pain in would be strengthened by prospective studies and use of statistical power analyses. Further recommendations for observational and intervention studies are summarised in Table 6.

Clinical implications of key findings

The review suggests a number of implications for clinical practice. A recent systematic review on chronic abdominal pain management in IBD presented promising findings for psychosocial interventions, including stress management techniques and coping skills training²⁶. Results from this review support the application of a psychosocial intervention, alongside IBD medication, for pain management. In particular, the consistent association identified between depression and anxiety and pain in the present review suggests that treatment of mood-related issues may improve pain levels and pain-related quality of life. Additionally, targeting pain-specific thoughts and behaviours such as pain catastrophising and fear avoidance may in turn show beneficial effects on mood as well as pain. The review also indicates that positive psychology may be an important avenue to explore in relation to treatment for pain. Active coping and perceptions of control and social support were associated with lower pain levels in this review. In addition, pain acceptance and resilience/psychological well-being may be useful targets for an intervention in buffering the impact of pain on patients with IBD. Further research is required to explore the role of negative ‘risk’ factors and positive ‘protective’ psychological factors in relation to IBD-pain, to aid the development of effective and disease-specific psychological treatment.

Conclusions and recommendations

This is the first review to systematically explore the role of psychosocial factors related to IBD-pain. The emotional, cognitive, behavioural and personality factors identified here are consistent with other systematic reviews on disease-specific pain and the chronic pain literature. In addition, the review has presented similarities between IBD and IBS pain, and supports the view that application of IBS-pain management approaches may be useful in the context of IBD, such as cognitive behavioural therapy. It is recommended that further research aims to confirm the importance of emotional factors and explore both negative and positive cognitive content and behavioural responses to pain. Further research in this area, with use of power calculation of sample sizes and validated pain measures, should help to build a more comprehensive understanding of IBD-related pain.

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Authorship Statement

- (i) **Guarantor of the article:** Louise Sweeney
- (ii) **Specific author contributions:** LS, CN, WCD and RMM designed the study and drafted the protocol; LS conducted the searches; LS and LM extracted data; LS, LM and CN conducted quality appraisal of included studies. All authors contributed to manuscript preparation.
- (iii) All authors approved the final version of the manuscript.

Figure legend

Figure 1: Bielefeldt et al. (2009) model of pain in IBD

Figure 2: PRISMA flow chart of included studies

Tables

Table 1. Inclusion and exclusion criteria for studies

	Inclusion criteria	Exclusion criteria
Population	Adults ≥ 18 years with IBD Active and inactive disease	Patients < 18 years Adults without a diagnosis of IBD
Exposure/correlate	Psychological factors Personality factors Social factors	Demographic/clinical factors only
Control/comparison	No comparator IBD without pain Chronic pain associated with another condition	
Outcomes	Pain intensity/severity Pain-related interference Pain-related quality of life Chronic pain Bodily pain Abdominal pain Joint/musculoskeletal pain	Pain assessed only within IBS or IBD composite score and not reported separately Post-operative pain Experimentally induced pain/pain threshold study
Study design	Prospective, longitudinal and experimental studies (if reporting baseline associations)	Non-empirical, qualitative or review papers Studies not published in English

Table 2. Search terms entered into databases

IBD terms	AND	Pain terms	AND	Psychosocial factors terms
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Inflammatory	Pain (OR)	Psycholog* (OR)
bowel disease	Chronic pain (OR)	Psychosocial* (OR)
IBD (OR)	Chronic abdominal	Social* (OR)
Ulcerative	pain (OR)	Illness beliefs (OR)
Colitis (OR)	Abdominal pain	Catastrophizing (OR)
UC (OR)	(OR)	Anxi* (OR)
Crohn's	Persistent pain	Depress* (OR)
Disease (OR)	(OR)	Affect* (OR)
CD (OR)	Pain interference	Mood* (OR)
	(OR)	Cop* (OR)
	Pain-related* (OR)	Avoid* (OR)
		Fear* (OR)
		Cogniti* (OR)
		Perception (OR)
		Accept* (OR)
		Biopsychosocial (OR)

Table 3. Summary of results from included studies

Reference	Study design	Psychosocial factor investigated	Pain measure <i>Pain location</i>	Key findings	Quality
Boye 2008 ⁴⁸	Cross-sectional	BussPerry Aggression Eysenck Personality Questionnaire Multidimensional Health Locus of Control Scale Toronto Alexithymia Scale	Short Form-36 <i>Bodily pain</i>	High internal locus of control associated with higher pain-related quality of life in CD.	High
Boyle 2015 ⁵³	Cross-sectional	Stress - Anxiety -Depression (21 score) Crohn's and Colitis Knowledge	Brief Pain Inventory <i>Abdominal pain</i>	Mean scores in the SAD-21 for anxiety, depression and stress were significantly greater in pain reporters.	Medium
Coates 2013 ⁵²	Cross-sectional	Mood disorder	SIBDQ Pain Score Modified ulcerative colitis disease activity index survey <i>Abdominal pain</i>	Patients with higher pain more frequently carried a concurrent diagnosis of a mood disorder. (OR 5.76, 95% CI 1.39–23.89)	High
Deberry 2014 ⁴³	Cross-sectional	Hospital Anxiety and Depression Scale	VAS McGill Short Form Questionnaire <i>Abdominal pain</i>	Patients with UC with pain had significantly higher HADS when compared with controls and patients with UC without pain - UC with pain. Higher depression scores independently predicted pain in UC patients ($r > 0.5$)	High
Edman 2017 ⁴⁶	Cross-sectional	Perceived Stress Scale	Self-report numerical rating scale of pain <i>Unspecified location</i>	Perceived stress significantly positively correlated with average pain ($r = 0.32$, $p < .0001$) and worst pain ($r = 0.35$, $p < .01$) in the IBD group.	High
Esteve 2013 ⁴⁵	Cross-sectional	Acceptance and Action Questionnaire	SF-36 bodily pain Pain intensity scale <i>Chronic pain</i> <i>Bodily pain</i>	Across all three groups, pain intensity (and experiential avoidance) correlated with pain fear avoidance ($\beta = .19$, $p < .05$)	High
Fuller-Thomson & Sulman 2006 ⁵⁰	Cross-sectional	Depression (Kessler and Mroczek scale)	Pain items in survey questionnaire <i>Unspecified location</i>	Respondents whose activities were limited by pain (depressed = 35.1% vs non-depressed = 58.4%, $p < .001$) and who were in severe pain were much more likely to be depressed. Those who reported that activities were prevented by pain were significantly more depressed.	Medium
Fuller-Thompson 2015 ⁴⁹	Cross-sectional	Generalised anxiety disorder	Pain items in survey questionnaire <i>Unspecified location</i>	Anxiety was predicted by chronic pain (OR 2.43)	Medium
Goodhand 2012 ⁴²	Cross-sectional	Hospital Anxiety and Depression Scale	Harvey Bradshaw Index <i>Abdominal pain</i>	Chi-squared analyses showed a significant association between abdominal pain and HADS-A scores in CD patients.	High

Moisset 2017⁵¹	Cross-sectional	Hospital Anxiety and Depression Scale	International Classification of Headache Disorders' diagnostic criteria Headache Impact Test DN4-interview questionnaire British Pain Inventory <i>Abdominal pain</i> <i>Arthralgia</i> <i>Migraine</i> <i>Chronic pain with neuropathic pain</i>	Depression significantly associated with probable migraine. HAD anxiety was significantly associated with arthralgia/joint pain. HAD anxiety was significantly associated with overall pain.	High
Morrison 2013²	Cross-sectional	Survey of Pain Attitudes Coping Strategies Questionnaire Hospital Anxiety and Depression Scale	von Korff Pain Intensity and Disability questionnaire <i>Chronic pain</i> <i>Abdominal, joint, headache, back pain</i> <i>(Results for overall pain score)</i>	Independent and significant associations with moderate-severe pain were catastrophising tendency (OR 34.69), depression (OR 1.8), medication beliefs (OR .05) and active disease (OR 48.54).	High
Odes 2017⁵⁴	Cross-sectional	Brief Symptom Inventory, Brief COPE Inventory, Family Assessment Device, Satisfaction with Life Scale, Work Productivity and Activity Impairment	Harvey Bradshaw Index Short Inflammatory Bowel Disease Questionnaire (SIBDQ) SF-36 bodily pain <i>Abdominal pain</i> <i>Bodily pain</i>	Higher pain scores significantly correlated with psychological stress, dysfunctional coping strategies, poor family relationships, work abstinence, presenteeism, productivity loss and activity impairments and all WPAI sub-measures.	High
Schwarz 1993⁴⁴	Cross-sectional	Beck Depression Inventory State-Trait Anxiety Psychosomatic Symptom Checklist	Daily symptom diary (0-4 scale) <i>Abdominal pain</i>	Pain/tenderness significantly correlated with all psychological measures excluding STAI-trait.	Low
Sirois & Wood 2017⁴⁷	Longitudinal	Gratitude (Q-6) Depression Scale Perceived Stress Scale Duke-UNC Functional Social Support questionnaire	Bowel Symptoms sub-scale (Inflammatory Bowel Disease Questionnaire) <i>Abdominal pain</i>	T1 pain significantly positively correlated with T2 depressive symptoms, T2 pain, perceived stress and helplessness, and negatively correlated with T1 self-rated health measured by SF-36 (all p <.01). T2 pain significantly correlated with T1 pain and perceived stress (all p <.01)	Medium
Tripp (paper 1) 2015⁴¹	Cross-sectional	Pain Catastrophising Scale Depression (PHQ-9) Short Inflammatory Bowel Disease Questionnaire	Short Form McGill Pain Questionnaire Pain body Diagram <i>Abdominal pain</i> <i>1, 2, >3 locations</i>	All IBD pain phenotype groups reported more pain catastrophising and depressive symptoms than controls. Patients with IBD abdominal pain reported significantly less pain catastrophising (p<.01) and depressive symptoms (p<.001) than IBD patients with 1-2/3+ pain locations.	High
Tripp (paper 2) 2015⁴⁰	Cross-sectional	Chronic Pain Coping Inventory Pain Catastrophizing Scale Depression (PHQ-9) Multidimensional Scale of Perceived Social Support Bowel Disease Questionnaire	Short Form McGill Pain Questionnaire Pain body Diagram <i>Unspecified location</i>	Pain associated with illness-focused coping (r =.7), pain catastrophising (r =.52), wellness-focused coping (r =.35), depressive symptoms (r =.68) and perceived social support -.26).	High

Table 4. Factors associated with pain identified in included studies

Factor associated with pain	Study - univariate/multivariate analysis (U/M)														
	1(M) Boye, 2008	2(U) Boyle, 2015	3(M) Coates, 2013	4(U) Deberry, 2014	5(U) Edman, 2017	6(U) Esteve, 2013	7(U) Fuller-Thompson, 2006	8(U) Fuller-Thompson, 2015	9(U) Goodhand, 2012	10(M) Moisset, 2017	11(M) Morrison, 2013	12(M) Odes, 2017	13(U) Schwarz, 1993	14(U) Sirois, 2017	15(U) Tripp, 2015
Psychosocial															
Depression		***		+			***			+	+		***	**	**
Anxiety		***		NS				+	+	+			+		
Mood disorder			+												
Stress		***			***							***		**	
Somatisation													***		
Pain catastrophising											**				***
Helplessness														**	+
Medication beliefs											**				
IBD knowledge		NS													
Dysfunctional coping												+			
Problem focused coping												-			
Emotion focused coping												+			
Illness focused coping															**
Wellness focused coping															**
Pain fear avoidance						+									
Internal locus of control	**														
Neuroticism	NS														
Hostility/aggression	NS														
Alexithymia	NS														
Conventionality	NS														
Perceived Social Support														NS	**
Benefit Finding														NS	
Illness Acceptance														NS	
Gratitude														NS	
Thriving														NS	
Clinical/demographic															
Disease activity index	***	+	**							**	+				
Disease duration		NS								+					
Female gender			+							+		***			
Age		NS	NS	-						-					
Inflammatory markers (ESR/CRP/calpro/endosc)			+	NS											
TRPV1/TRPVA1				NS											
Opioid use			**												
Antidepressant use			+												
Units of alcohol p/week		NS													
Chronic pain syndrome			+												

If provided, $p \leq .05$ *, $p \leq .01$ **, $p \leq .001$ ***. NB inflammatory markers include histology, endoscopy, calprotectin, C-reactive protein. TRPV1/TRPVA1 = transient receptor potential cation channel subfamily V1/ ankyrin 1 . +/- indicate positive or negative associations.

Table 5. List of pain presentations and pain measures in reviewed studies

Type of pain	Pain measure	No. of studies/reference
Abdominal pain	Short inflammatory bowel disease questionnaire pain item	2 ^{52, 54}
	Modified UC disease activity index	1 ⁵²
	Harvey Bradshaw Index pain item	2 ^{42, 54}
	Daily symptom diary	1 ⁴⁴
	Bowel Symptoms sub-scale (IBDQ)	1 ⁴⁷
	Visual analogue score	1 ⁴³
	Short Form McGill Questionnaire	1 ⁴³
Unspecified location of pain	Brief Pain Inventory	1 ⁵³
	Self-report numerical rating scale	1 ⁴⁶
	Pain intensity scale	1 ⁴⁵
	Single pain survey item	2 ^{49, 50}
	Von Korff Pain intensity and Disability	1 ²
	Short Form McGill Questionnaire	2 (papers) ^{40, 41}
Bodily pain/ pain-related quality of life	SF-36	3
Joint pain/arthritis	Brief Pain Inventory	1 ⁵¹
Migraine	International Classification of Headache Disorders	1 ⁵¹
Chronic pain	Participant screening item	2 ^{2, 51}
Chronic pain (neuropathic component)	DN4-interview questionnaire	1

Table 6. Recommendations for future observational and intervention studies

Study type	Recommendations
Observational studies	<ul style="list-style-type: none"> Validated pain measure Neuropathic pain measure Long-term follow up Objective marker of disease activity Exploration of positive and negative psychosocial factors Sample size power calculation
Intervention studies	<ul style="list-style-type: none"> Intervention based on theoretical principles Validated pain measure Clear stratification of active and remission patients (or recruitment of remission patients only) Control group Objective marker of disease activity Long term follow-up Sample size power calculation

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether	9-10 (QA)

		this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10 (QA)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23
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