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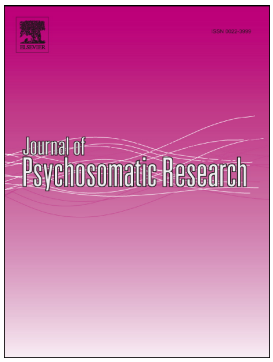

A systematic review and meta-analysis of mindfulness based interventions and yoga in inflammatory bowel disease

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A SYSTEMATIC REVIEW AND META-ANALYSIS OF MINDFULNESS BASED INTERVENTIONS AND YOGA IN INFLAMMATORY BOWEL DISEASE

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Abstract

Background

Mindfulness interventions are increasingly used as a part of integrated treatment in inflammatory bowel disease (IBD) but there are limited data and a lack of consensus regarding effectiveness.

Objectives

We explored the efficacy of mindfulness interventions compared to treatment as usual (TAU), or other psychotherapeutic interventions, in treating physical and psychosocial symptoms associated with IBD.

Methods

We conducted a systematic review and meta-analysis of relevant randomised controlled trials (RCTs). We included a broad range of mindfulness interventions including mindfulness-based interventions and yoga, with no restrictions on date of publication, participants' age, language or publication type. We searched the following electronic databases: MEDLINE, EMBASE, PsycINFO, CINAHL and WHO ICTRP database. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines in conducting the review.

Results

We included eight studies in the meta-analysis. Mindfulness interventions showed a statistically significant effect on stress in both the short(SMD=-0.48; 95%CI:-0.97, 0.00; P=0.05), and long term(SMD=-0.55; 95%CI:-0.78, -0.32; P< 0.00001), significant long term effects on depression (SMD=-0.36; 95%CI:-0.66, -0.07; P=0.02) and quality of life (SMD=0.38; 95%CI:0.08, 0.68; P=0.01),and small

but not statistically significant improvements in anxiety (SMD=-0.27; 95%CI:-0.65, 0.11; P=0.16).Effects on physical outcomes were equivocal and not statistically significant.

Conclusions

Mindfulness interventions are effective in reducing stress and depression and improving quality of life and anxiety, but do not lead to significant improvements in the physical symptoms of IBD. Further research involving IBD-tailored interventions and more rigorously designed trials is warranted.

Key words: IBD, mindfulness, systematic review.

Registration details: International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42017080632

Introduction

Rationale

IBD is an immune-mediated disease associated with chronic inflammation of the gastrointestinal tract and frequent extra-intestinal manifestations [1-3]. Individuals with IBD experience high burden of disease and significant mental health comorbidities [4]. Rates of depression and anxiety in periods of remission are two to three times higher than in age matched individuals in the general population [4, 5]. During active disease, rates of depression rise to over 60% with wide ranging implications in all areas of life[6]. Despite this, treatment of depression and anxiety is not routinely included in standard IBD care, although there are recommendations for screening and treatment of depression and anxiety to be embeded in integrated IBD care [7].

There has been increasing research evidence outlining the impact of stress [8], anxiety and depression on the course of IBD [5], with a recent systematic review showing that depression and anxiety were independently associated with clinical recurrence of IBD [9].Mindfulness based interventions have been of particular interest in IBD due to their effectiveness in attenuating stress and treating depression and anxiety [10-12],as well as their potential to improve the course of IBD related to emerging evidence of their salutogenic impact on the immune system [13].

Mindfulness is defined as an experiential practice of focussing one's attention with intention and without judgement[14]. While this definition of mindfulness is generally accepted, there is ongoing debate in the literature regarding the measuring and operationalization of mindfulness [15, 16]. Mindfulness Interventions include manualised mindfulness-based programs such as Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT), mindfulness-informed interventions such as Dialectical Behaviour Therapy (DBT) and Acceptance and Commitment Therapy (ACT), modified mindfulness interventions and yoga.

To our knowledge, there has been only one systematic review to date examining the efficacy and use of mindfulness interventions in IBD [17], published in 2015. The review included manualised and adapted mindfulness programs published in English and German and it was restricted to adults. It found that no study showed significant group differences regarding physical or psychological variables in the main analysis, and that only a subset of patients with additional irritable bowel syndrome (IBS)

symptoms experienced significant improvements in quality of life. The review reported that the findings about the efficacy of mindfulness interventions in IBD were inconclusive, that these interventions might be useful in subgroup of IBD patients with IBS symptoms and that further research of higher methodological quality was needed.Two narrative reviews reported similar findings [18, 19]. Since then, there have been several further RCTs of mindfulness interventions in IBD This systematic review therefore addresses the evidence gap by exploring a wide range of mindfulness interventions and including papers published in languages other than English and German and conducted in individuals of any age.

Methods

Objectives

The aim of this systematic review was to evaluate the effectiveness of mindfulness interventions in the management of psychosocial and physical symptoms associated with IBD. We aimed to answer the following questions:

1. Can mindfulness interventions improve psychological symptoms in IBD including depression, anxiety, stress and coping?
2. Can mindfulness interventions improve quality of life (QoL) in IBD?
3. Are mindfulness interventions effective in improving biological markers in IBD and other measures of IBD activity?

Protocol and registration

This systematic review was registered with PROSPERO , an international database of prospectively registered systematic reviews (CRD42017080632) [20]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines in designing this systematic review [21]. Ethical approval was not required as all included primary data had been previously published with ethical approval.

Eligibility criteria

We included RCTs of participants with IBD that compared interventions based on core mindfulness principles with TAU, waitlist or other psychosocial interventions using validated psychosocial and physical outcomes.

Design of included studies

Single-, double- or triple-blind RCTs were considered for inclusion. Studies published as abstracts were only included if the authors were contactable and further information provided to allow evaluation of study quality and main outcomes. Studies with a non RCT design and studies using non-validated outcome measures were excluded.

Participants

Patients of any age, including paediatric populations, with a diagnosis of IBD were included. We specified that the IBD diagnosis was based on established criteria, such as the Montreal classification system, including confirmation with ileocolonoscopy and biopsies of the affected tissues [20]. Montreal classification is an integrated IBD diagnostic and classification system involving clinical, serological and genetic parameters, which has been widely used in clinical and research settings [22].

Interventions

We adopted a broad definition of mindfulness interventions to include any therapy or program based on mindfulness principles and involving mindfulness practices. Interventions of interest included mindfulness-based programs, mindfulness-informed programs, adapted and shortened mindfulness interventions and yoga. Mindfulness-based programs included MBSR and MBCT which are evidence-based, 8-week-long manualised group programs taught in weekly 2-2,5 hours sessions encompassing multiple mindfulness components, homework exercises and usually a day of silent practice [14, 23-25]. Mindfulness-informed interventions included DBT, an experiential therapy using mindfulness as a foundation of key DBT skills of distress tolerance, emotion regulation and interpersonal effectiveness[26], and ACT, a psychological intervention using acceptance and mindfulness strategies to increase psychological flexibility and commit to behaviour changes [27].

Abbreviated and adapted mindfulness Interventions such as Multi-Convergent Therapy (MCT) and Breath-Body-Mind-Workshop (BBMW) were also included in the review. MCT is a psychotherapeutic intervention combining mindfulness with cognitive behavioural techniques, usually delivered in six sessions over 16 weeks [28]. BBMW is an adapted program combining mindful movement, breathing practices, and meditation, delivered as a two-day workshop followed by six weekly sessions and monthly booster sessions [29]. For the purposes of this review, we divided the interventions into yoga studies and mindfulness programs involving MBSR, MBCT, adapted mindfulness programs and mindfulness informed interventions.

Comparators and context

Controls in the review included wait list, standard medical treatment or treatment as usual (TAU), and other evidence-based psychological interventions. Studies in any clinical setting were included.

Outcomes

Studies examining IBD related psychological outcomes, quality of life and physical outcomes, assessed by validated screening tools were included. Psychological outcomes of interest included the following: rates of depression, anxiety and stress as assessed by validated screening tools such as Depression, Anxiety and Stress Scale (DASS), Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) and coping as measured by the Brief Cope Questionnaire (COPE). Quality of life was assessed by IBDQ or WHO-QoL. Physical outcomes included IBD activity as measured by biological markers of disease including local inflammatory markers such as faecal calprotectin (FCP), systemic inflammatory markers such as C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR),

White Cell Count (WCC) and haematocrit, investigations such as intestinal ultrasound, gastroscopy, endoscopy and colonoscopy, and IBD disease activity questionnaires such as a Simple Clinical Colitis Activity Index (SCAI) and Harvey Bradshaw Index (HBI). We extracted definitions of outcomes as reported in individual studies and recorded them in the data sheets in Covidence software [30] .

Sources of information

The following databases were searched: MEDLINE, EMBASE, PsycINFO and CINAHL. These electronic databases searches were supplemented by searches of trial protocols and systematic reviews in the Cochrane Central Register of Controlled Trials (CENTRAL), Australian and New Zealand Clinical Trials Register (ANZCTR), WHO International Clinical Trials Registry Platform (ICTRP) and the PROSPERO register of systematic reviews. We also scanned the reference and citation lists of included studies to improve literature coverage. We contacted the study authors for clarification and additional information when this was needed. The searches were re-run prior to review completion to ensure currency.

Search strategies

The specific search strategies were created by a health clinical librarian with expertise in systematic review searching (KR). Literature search strategies were developed using controlled vocabulary and text words related to mindfulness and IBD. MEDLINE (EBSCO) search including the following terms:

1. MH "Inflammatory Bowel Diseases"
2. Crohn*
3. Ulcerat* N3 Colitis
4. IBD
5. "Inflammatory Bowel Disease*"
6. 1 OR 2 OR 3 OR 4 OR 5
7. MH "Cognitive Therapy+"
8. Dialectic* N3 (therap* OR intervention* OR treatment* OR training OR counsel*)
9. Mindful*
10. (accept* OR commit*) N3 (therap* OR intervention* OR treatment* OR training)
11. MH Yoga
12. MH Meditation
13. Yoga
14. Meditat*
15. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16. PT "Randomized Controlled Trial"
17. Random* N3 (allocat* OR trial*)
18. RCT
19. control* N3 trial*
20. (singl* OR doubl* OR treb* OR tripl*) N3 blind*

21. 16 OR 17 OR 18 OR 19 OR 20
22. 6 AND 15 AND 21

Study records

Data were managed by using EndNote and Covidence online software for conducting systematic reviews [30]. Literature search results were uploaded to EndNote and Covidence. Duplicate publications were excluded by visually inspecting abstracts and using EndNote. To reduce data entry errors, data were entered into pre-created adapted data extraction forms in Covidence and exported directly into RevMan statistical analysis software [31]. Data were extracted by one reviewer (TE) and checked for errors by a second (KR). We used RevMan software to create a PRISMA flow diagram following the completion of the screening and data extraction. Figure 1 shows the PRISMA diagram depicting the flow of studies through the systematic review.

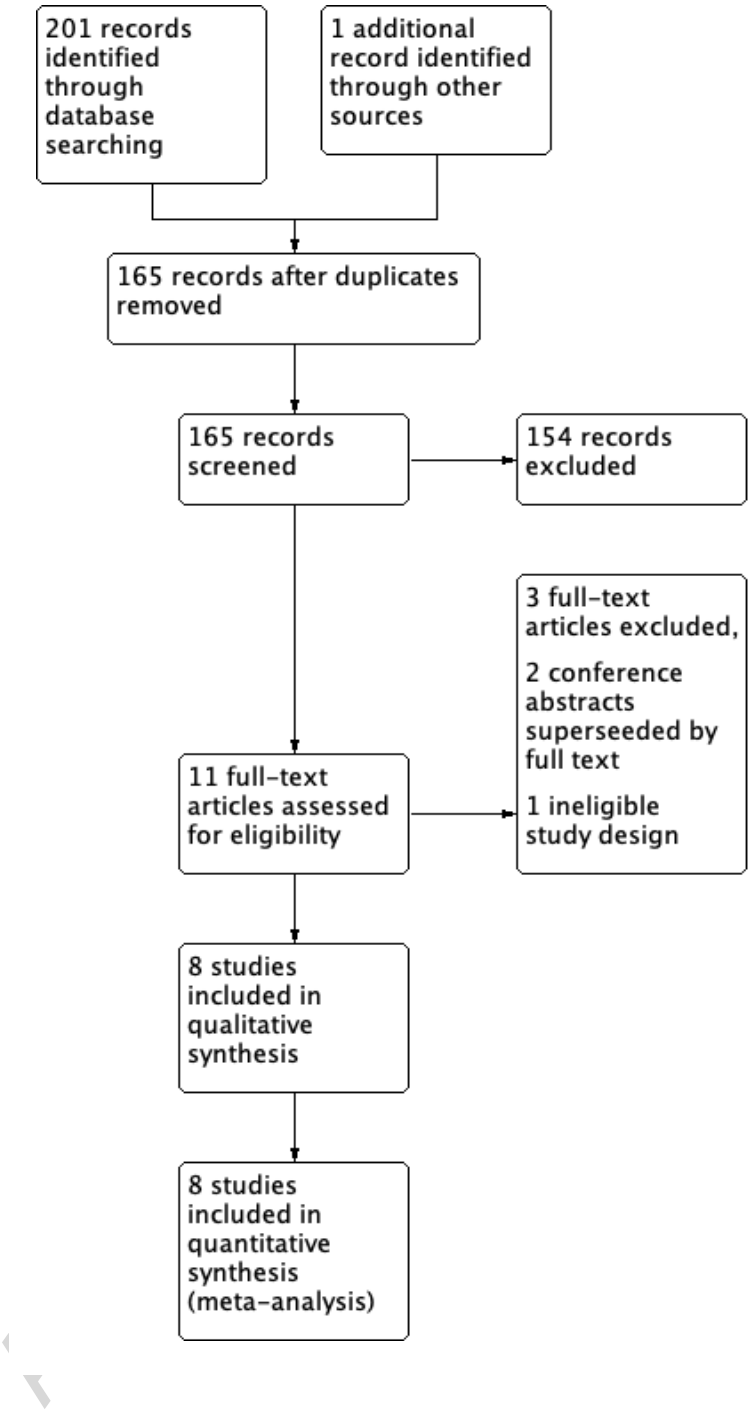

Figure 1: PRISMA flow diagram of the systematic review

Data selection and extraction

Two reviewers worked independently through all stages of the review, including screening papers for eligibility, examining full-text versions of studies for eligibility and inclusion in meta-analysis (TE, KR). Any disagreements were resolved through discussion with the third author (SK) and reasons for decisions documented.

We extracted the following:

- general information (authors, year and country of origin)
- trial methodology (study design, inclusion and exclusion criteria, study sample size and a priori sample size calculation)
- participant characteristics (demographic information, IBD subtype and diagnosis and mental health diagnosis)
- intervention characteristics (name, type, description, frequency, number and duration of sessions, length of the intervention, fidelity measures, therapists' training)
- types of control (wait-list, standard medical treatment or TAU, other psychological interventions)
- outcome measures
- results of main outcome measures including effect sizes
- type and source of financial support

Risk of bias (quality) assessment

The methodological quality of the included trials was assessed independently by two reviewers using the Cochrane Collaboration's Assessment of Risk of Bias Tool [32]. We assessed risk of bias in the included studies against the six criteria from the Cochrane Risk of Bias Tool, including random sequence generation, allocation concealment, blinding of the participants and the outcome assessors, incomplete data reporting, selective data reporting and other bias. We used risk of bias tables embeded in Covidence and adapted them by creating additional criteria involving interventions' fidelity, validity of the outcome measures, inclusion and exclusion criteria and similarity of participants' baseline characteristics. We evaluated each of the criteria in the risk of bias tool as low, high or unclear risk of bias and provided decisions justification. We did not assess publication bias due to having insufficient number of studies included in the review.

Data synthesis

We used statistical software RevMan 5.2, according to the guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions [32]. The populations, interventions, controls and outcomes of the included studies were assessed as being sufficiently similar to combine for inclusion in meta-analyses to estimated pooled estimates of effect. Comparable outcome measures were identified and data on the mean and standard deviation were extracted for each outcome for each time-point of interest for each study. Because different instruments were used across studies, standardised mean differences were specified as the effect of interest. Because there were differences in the study populations, type of intervention and measures of effect, we assumed the effects being estimated by different studies were not identical and random-effects models were specified. Thus, the effect estimates provide an estimate of the average effect and the 95% confidence intervals reflect the degree of heterogeneity between studies. Heterogeneity was assessed using the I^2 statistic, with scores 50% or greater indicating possible heterogeneity,and scores of 75– 100% indicating considerable heterogeneity [33]. Results were presented by the two subgroups of

mindfulness-based programs (MBPs) and yoga. Where possible, we conducted sensitivity analyses for study quality or type of control. If any meta-analysis included 10 or more studies, we planned to test for publication bias using funnel plot asymmetry, but only eight studies were included. In addition to quantitative analysis, we created an additional narrative summary, by using PICOS framework to explain the characteristics and findings of the included studies, in keeping with PRISMA statement recommendations [21].

Results

We identified 202 records and removed 37 duplicates (Figure 1). We excluded a further 154 after screening titles and abstracts of the remaining 165 records. We examined the remaining 11 articles for eligibility and excluded 3 of them, two because of being conference abstracts which were superseded by the full text articles and one because of not having the RCT design. The remaining 8 studies [34-41] were included in qualitative and quantitative analysis. Seven were full text articles and one was a conference abstract (Rowan 2017) which was assessed from the abstract content and by enlarging the reported graphs and then measuring and analysing the illustrated outcomes.

Study characteristics

Table 1 shows the characteristics of included studies. Studies were published between 2014 and 2017.

Table 1, Summary of included studies characteristics

Studies, country	Design, control, setting	Participants dg, n, age,	MBIs	Intervention length, N of sessions	Primary outcome	Psychological Outcomes	Physical outcomes	Collection time points	Data Complete, ITT
AminPur 2015, Iran	RCT, waitlist, outpatient	UC, n=37, mean age=37.3	ACT	8 weeks, weekly	CISS, problem-oriented scale	CISS, emotion & avoidance scales	Nil	8 weeks	No, No
Berril 2014, UK	RCT, waitlist, outpatient	UC, CD; n=66, mean age=44.9	MCT	16 weeks, 6 sessions	IBDQ	PSQ, HADS, WCC, RDHS	Cumul. Relapse rate	4M 8M 12M	No, No
Cramer 2017, Germany	RCT, written self-care, outpatient	UC, n=77, mean age=45.5	Yoga	12 weeks, weekly	IBDQ	PSS, HADS, PSQ, PANAS, BAQ, BRS	CAI, FCP ESR, CRP	12 weeks 24 weeks	Yes, Yes
Gerbarg 2015, USA	RCT, educational seminar, outpatient	IBD, UC, CD, n=29, mean age 54	BBMW	6 weeks, weekly sessions, Monthly boosters till week 26	BSI-18	IBDQ, BAI, BDI, PDS, PSQ, BIPQ	FCP, CRP, T, BP, pulse	6 weeks 26 weeks	No, No

Jedel 2014, USA	RCT, time attention control, outpatient	UC (in remission), n=53	MBSR	8 weeks, weekly	UC-DAI	IBDQ, PSQ, BDI, STAI, MAAS	CRP, FCP, IL6,8,1, ACTH, cortisol	8 weeks 6M 12M	No, No
Rowan 2017, Ireland	RCT, waitlist/TAU, outpatient	IBD, n=95	ACT	8 weeks, weekly	DASS-stress subscale	DASS, anxiety, depression subscales	FCP, CRP	8 weeks 20 weeks	No, No
Schoultz 2015, UK	RCT, waitlist, outpatient	IBD, n=44	MBCT	8 weeks, weekly	IBDQ	BDI, STAI	CDAI, SCCAI	8 weeks 6M	Yes, No
Sharma 2015, India	RCT, waitlist, outpatient	UC + CD, n=100	Yoga	8 weeks, 1 week daily practice then 7 weeks home daily practice	HRV	STAI	ECP, Cardio-vascular reactivity	1M 2M	Yes, No

MBIs: Mindfulness Based Interventions, CISS: Coping Inventory for Stressful Situations, IBDQ: Inflammatory Bowel Disease Questionnaire, PSQ: Perceived Stress Questionnaire, HADS: Hospital Anxiety and Depression Scale, WCC: Ways of Coping Checklist, RDHS: Revised Daily Hassle Scale, PSS: Perceived Stress Scale, PANAS: Positive and Negative Affect Scale, BAQ: Body Awareness Questionnaire, BRS: Body Responsiveness Scale, CAI: Clinical Activity Index, ESR: Erythrocyte Sedimentation Rate, CRP: C Reactive Protein, FCP: Faecal Calprotectin, BSI-18: Brief Symptom Inventory, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, PDS: Perceived Disability Scale, BIPQ: Brief Illness Perception Questionnaire, BP: Blood pressure, T: temperature, UC DAI: Ulcerative Colitis Disease Activity Index, STAI: State and Trait Anxiety Inventory, MAAS: Mindful Attention Awareness Scale, HRV: Heart Rate Variability, ECP: serum eosinophilic cationic protein, CDAI: Crohn's Disease Activity Index, SCCAI: Simple Clinical Colitis Activity Index

Study quality (Risk of Bias)

Although all studies were described as RCTs, allocation concealment was not adequately described in 5 out of the 8 included studies. Due to the nature of the intervention, it was difficult to blind the participants as they were aware of their group allocation in studies with waitlist and TAU controls. One of the studies who had control group comparable in both time and attention to the intervention, achieved participants blinding (Jedel 2014). Blinding of the assessors was not attempted in 2 out of 8 studies, 4 studies did not provide sufficient information about assessors' blinding and 2 of the studies explained how assessors were blinded to group assignment. There was also a significant proportion of studies with incomplete reporting with 6 studies having inadequate or incomplete data reporting. Only one of the studies employed Intention to Treat (ITT) analysis (Cramer 2017), while another employed modified ITT where participants who dropped out before the intervention onset were excluded (Jedel 2014). All the others used complete case or per protocol population analysis. The reasons for incomplete reporting were either omitting data reporting at certain time points, for example not reporting outcomes at therapy end and six months' time points but reporting them at one-year follow-up (Jedel 2014), or not reporting certain outcomes, for example not reporting HADS scores after baseline (Berril 2014).

Three out of eight studies described fidelity measures, both of the yoga studies and the MBCT study. The recorded fidelity measures included description of the intervention manual, facilitators adherence

to the manual, participants' attendance and homework logs, and facilitators' training and experience. Risk of bias assessment is presented in Table 2.

Table 2, Risk of bias table

	Amin Pur 2015	Berril 2014	Cramer 2017	Gerbarg 2015	Jedel 2014	Rowan 2017	Schoultz 2015	Sharma 2015
Random sequence generation (selection bias) (high, low or unclear)	Unclear	Low	Low	High	Low	Unclear	Low	Low
Allocation concealment (selection bias) (high, low or unclear)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low
Blinding of participants, personnel (performance bias) (high, low or unclear)	Unclear	High	High	Unclear	Low	Unclear	High	High
Blinding of outcome assessment (detection bias) (high, low or unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	High	High
Incomplete outcome data (attrition bias) (high, low or unclear)	Unclear	High	Low	High	Low	Unclear	High	High
Selective outcome reporting (reporting bias) (high, low or unclear)	High	Low	Low	Low	Low	Unclear	Low	High
Other sources of bias (high, low or unclear)	Unclear	Low	Unclear	Unclear	High	Unclear	Low	Unclear
Fidelity measures (high, low or unclear)	Unclear	High	Low	Unclear	Unclear	Unclear	Low	Low
Validity of outcomes (high, low or unclear)	Low	Low	Low	Low	Low	Low	Low	Low
Inclusion & exclusion criteria (high, low or unclear	Low	Low	Low	High	Low	Unclear	Low	Low
Similarity of participants at baseline (high, low or unclear)	Unclear	Low	Low	Unclear	High	Unclear	Unclear	Low

Participants' characteristics

All the participants were adults as no paediatric studies met the inclusion criteria. In all the studies, IBD was diagnosed with a combination of clinical, laboratory and endoscopic findings as per the widely accepted criteria. All studies enrolled individuals with quiescent IBD or IBD in remission and excluded individuals with significant mental health diagnoses.

Interventions Characteristics

Two studies involved Mindfulness Based Programs (MBPs) , one MBSR [38] and one MBCT[42] , two of the studies used ACT, one MCT, one BBMW and two studies delivered yoga. Duration of therapy was between 6 and 12 weeks (Table 1). The shortest mindfulness intervention was BBMW with only 6 weeks duration, however it had an intensive two-day start and was followed by monthly booster sessions up till 26 weeks. The longest intervention was MCT of 16 weeks duration but with only 6 sessions delivering a similar "dose" of mindfulness practices to the other interventions.

Comparators' characteristics

All included studies had a parallel group allocation design. Control groups were wait list patients in five out of eight studies, one had a written self-care control group and two studies had active controls. In both studies with active controls, participants in the control group were receiving treatment that mimicked the amount of time and attention received by the treatment group but thought not to have significant therapeutic effect, referred to as attention placebo control [43].

Outcomes characteristics and outcomes collection time points

Seven of the eight included studies measured both psychological and biological outcomes and all studies measured psychological outcomes. For the purpose of this review, we classified post treatment outcomes collection point as a short-term follow-up which occurred 6-16 weeks post baseline, depending on the length of the intervention. We defined long-term follow-up point as being between five months (20 weeks) and one-year post baseline, with one study assessing long-term outcomes at 20 weeks (Rowan 2017), three at six months (Cramer 2017, Gerbarg 2015 and Schoultz 2015) and two at 12-months post baseline (Berril 2014 and Jedel 2014).

Psychological Outcomes Changes in Response to Mindfulness Interventions

Eight studies were included in the meta-analysis, providing data for 251 participants who received mindfulness interventions and 249 waitlist, TAU or active controls (Table 1). Tables 3 and 4 show short and long-term changes in psychological outcomes.

Table 3: Short-term psychological symptoms

Outcome or Subgroup	Studies	Participants	**Standardised mean difference** [95% CI]
Depression scores at therapy end	3	127	-0.29 [-0.87, 0.29]
MBPs	2	50	0.01 [-0.55, 0.57]
Yoga	1	77	-0.68 [-1.14, -0.22]
Anxiety scores at therapy end	4	179	-0.19 [-0.62, 0.24]
MBPs	2	51	0.06 [-0.86, 0.98]
Yoga	2	128	-0.36 [-0.76, 0.05]

Stress scores at therapy end	**4**	**256**	**-0.48 [-0.97, 0.00]**
MBPs	3	179	-0.51 [-1.20, 0.18]
Yoga	1	77	-0.36 [-0.81, 0.09]
QoL scores at therapy end	4	185	0.22 [-0.07, 0.51]
MBPs	3	108	0.11 [-0.27, 0.49]
Yoga	1	77	0.37 [-0.08, 0.82]
Coping scores at therapy end			
MBPs	2	97	6.02 [-5.67, 17.72]

Table 4 Long-term psychological symptoms

Outcome or Subgroup	Studies	Participants	**Standardised mean difference** [95% CI]
Depression scores	4	179	-0.36 [-0.66, -0.07]
MBPs	3	102	-0.19 [-0.58, 0.20]
Yoga	1	77	-0.61 [-1.06, -0.15]
Anxiety scores	4	179	-0.27 [-0.65, 0.11]
MBPs	3	102	-0.07 [-0.46, 0.32]
Yoga	1	77	-0.66 [-1.12, -0.20]
Stress scores	**5**	**301**	**-0.55 [-0.78, -0.32]**
MBPs	4	224	-0.51 [-0.77, -0.24]
Yoga	1	77	-0.67 [-1.13, -0.21]
QoL scores	4	175	0.38 [0.08, 0.68]
MBPs	3	98	0.33 [-0.07, 0.74]
Yoga	1	77	0.45 [-0.01, 0.90]
Coping scores			
MBPs	1	51	0.64 [0.07, 1.20]

Depression

Depression scores were measured in four studies, three studies involving MBPs and one yoga study. There was no significant difference in depression scores between people who received mindfulness and those in the control group in the short-term. However, on subgroup analysis, it was apparent that the three studies of MBP showed no effect while the single yoga study was significantly better than TAU (Table 3). By contrast, in the long-term, all the mindfulness interventions were significantly better than the control condition (Table 4 and Figure 2) although, again, the best result was for the single study of yoga.

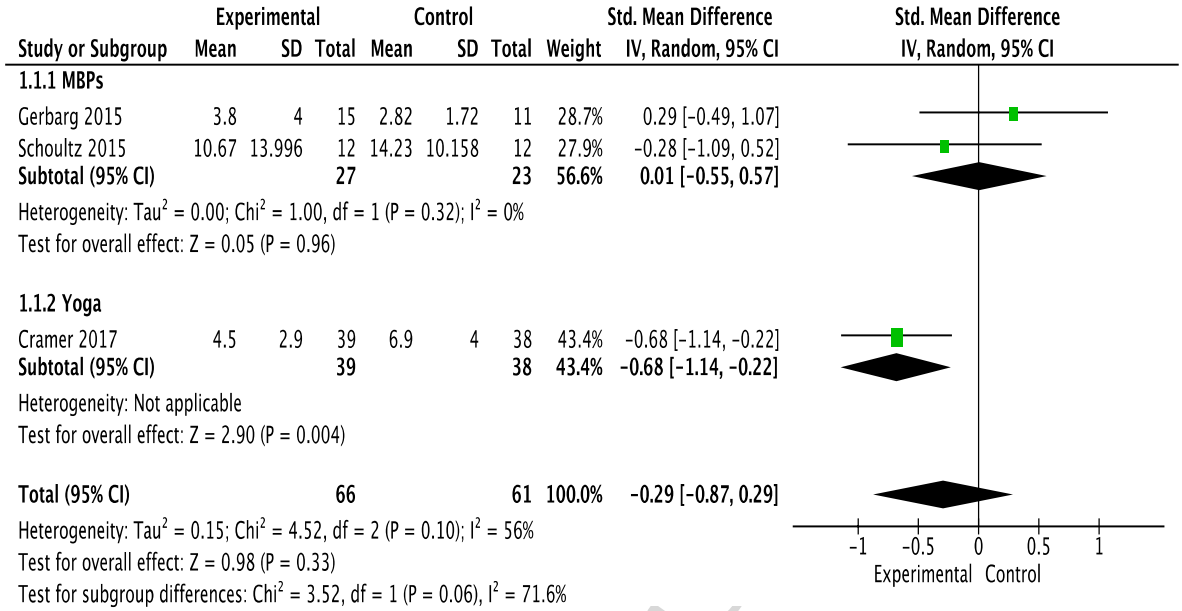

Figure 2: Forest plot of short-term depression

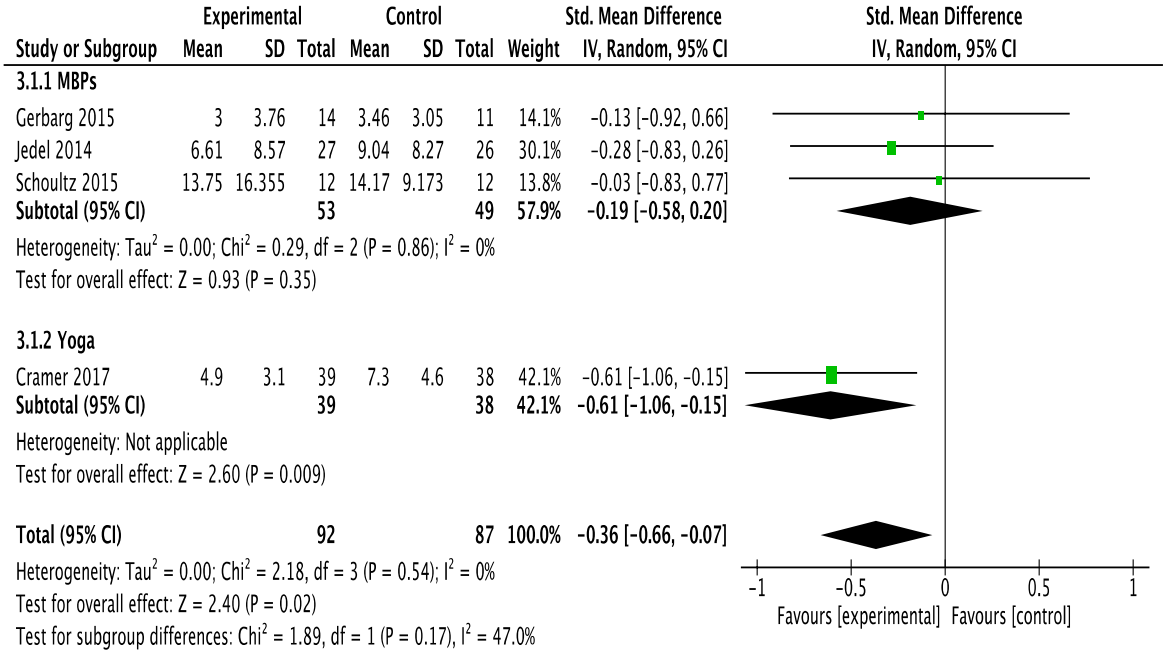

Figure 3: Forest plot of long-term depression

Anxiety

Four studies assessed anxiety as an outcome, with 2 MBPs and 2 yoga studies reporting short-term anxiety scores (Table 3), and 3 MBPs and 1 yoga study reporting long-term anxiety scores (Table 4). When results from all studies were pooled, estimates were consistent with a small reduction in anxiety, which did not reach statistical significance in either the short- (Table 3) or long-term (Table 4). Similarly, there were no significant differences between the intervention and control groups on subgroup analyses at any time point (Tables 3 and 4). The one exception was a single yoga study that reported a significantly greater improvement in anxiety at long-term follow-up (Table 4).

Stress

Of four studies assessing MBPs as the intervention and reporting stress as a long-term outcome, three included short-term measures at the end of the intervention period (Tables 3 and 4). Combining MBPs and yoga interventions in a single analysis resulted in statistically greater improvements in both the short-term (Table 3 and Figure 4) and long-term (Table 4 and Figure 5). These results were mirrored in the subgroup analyses of MBPs and yoga in the long-term (Table 4 and Figure 5) but not the short-term (Table 3 and Figure 4).

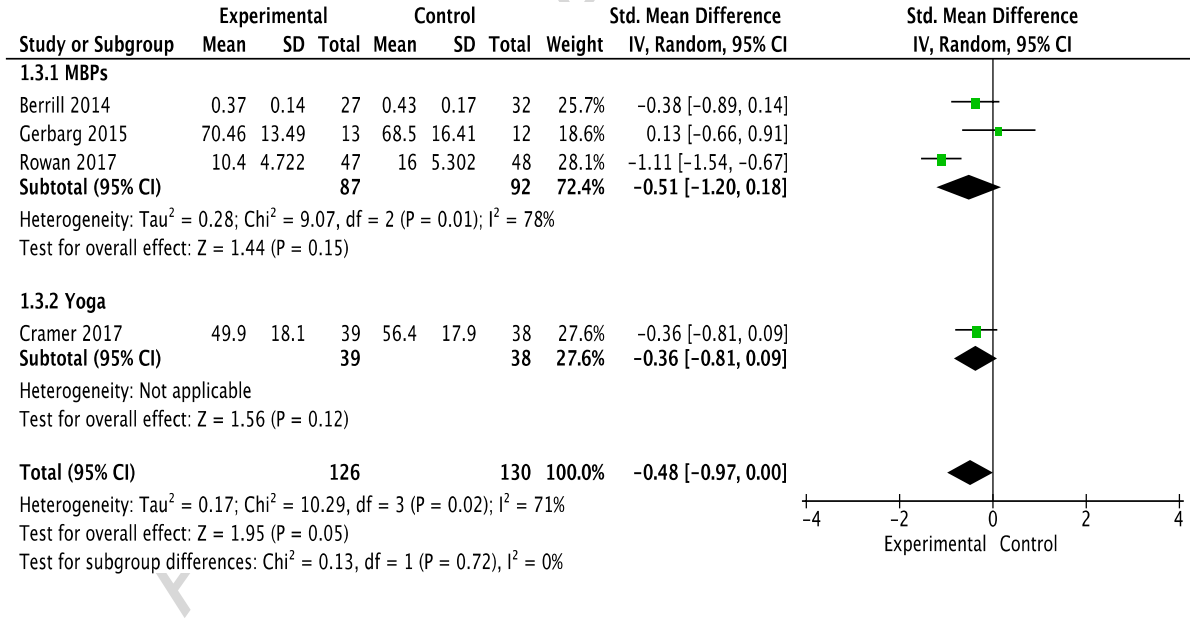

Figure 4: Forest plot short term stress

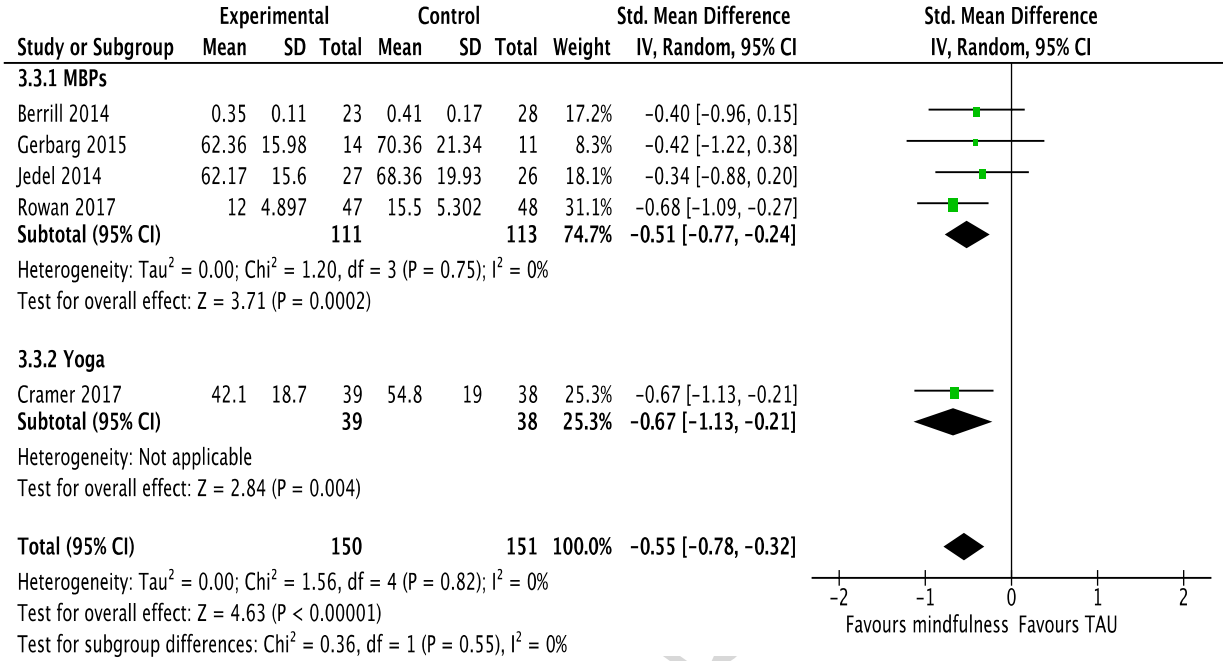

Figure 5: Forest plot long term stress

Coping scores

Two studies reported on short-term outcomes and one in long-term outcomes. There were no significant differences between mindfulness and TAU at both intervals (Tables 3 and 4)

Quality of Life Changes in Response to Mindfulness Interventions

Three studies reported on the QoL outcome at each time-point but only two were common to both times. When the mindfulness and yoga interventions were combined in a single analysis, there was evidence for a statistically greater improvement in the long-term effect estimates (Table 4 and Figure 6), but not the short-term (Table 3). None of the results in the subgroup analyses reached statistical significance (Tables 3 and 4).

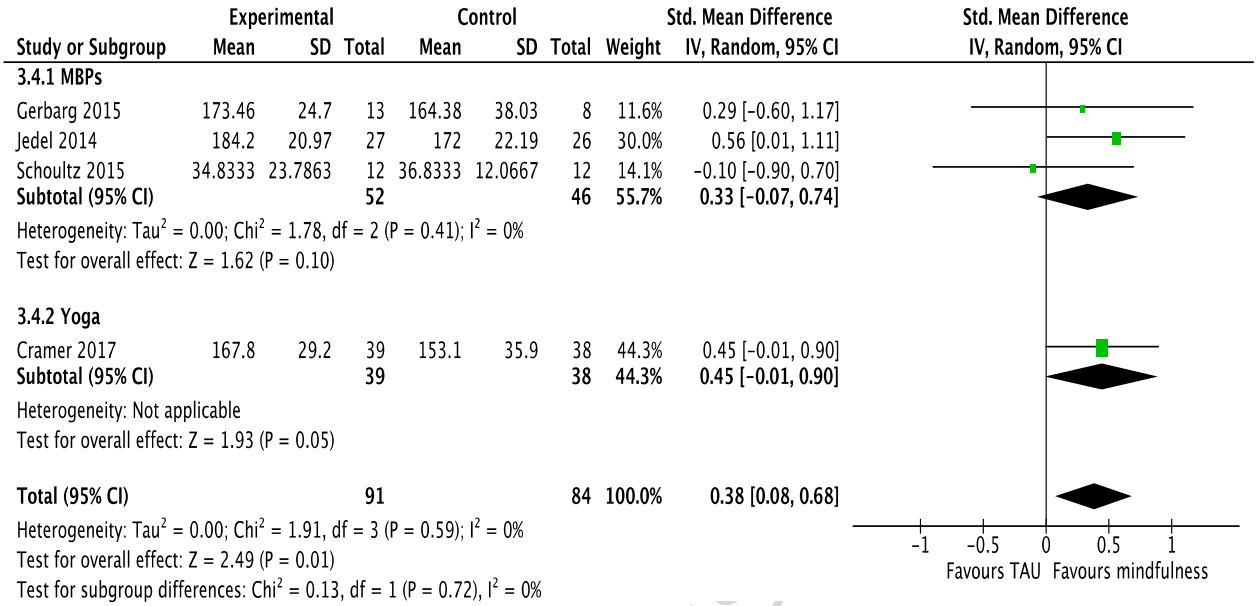

Figure 6: Quality of life long term

Physical Outcomes Changes in Response to Mindfulness Interventions

There was limited information on physical disease outcomes, including systemic inflammatory markers (ESR/CRP), local inflammatory markers (FCP) and clinical disease activity. Only one MBP and one yoga study reported short term physical outcomes, both reporting non-significant results. The MBP reported clinical disease activity (SMD= -0.42; 95% CI:-1.77, 0.92; P=0.54) while the yoga study reported ESR/CRP (SMD=0.03; 95% CI:-0.41, 0.48;P=0.88), FCP (SMD=0.36; 95% CI:-0.09, 0.81;P=0.12), and clinical disease activity (SMD=-0.08; 95% CI:-0.53, 0.36; P=0.72).

Long-term physical outcomes were reported by two MBPs and one yoga study. Two MBPs did not find statistically significant improvement in ESR/CRP (SMD=-0.25; 95% CI:-0.79, 0.30; P=0.37), FCP (SMD=0.22; 95% CI: -0.32, 0.76; P=0.42), and clinical disease activity (SMD=-0.57; 95%CI:-1.99, 0.86; P=0.44).The yoga study did not find significant improvement in ESR/CRP (SMD= -0.18; 95%CI:-0.63, 0.27; P=0.44) and FCP (SMD=-0.18; 95%CI:-0.63, 0.26; P=0.42) but it did find statistically improved scores on the clinical disease activity index (SMD=-0.45; 95% CI:-0.90, 0.00; P=0.05).

Heterogeneity and publication bias

The short-term outcomes showed statistically significant heterogeneity, which is why we used random-effects models. By contrast, there was no evidence of heterogeneity in the long-term results. We were unable to test for publication bias as none of meta-analyses of outcomes included 10 or more studies.

Discussion

This review is the first systematic review to explore the efficacy of a broad range of mindfulness interventions in IBD while including all population ages and settings and posing no language or time and type of publication restrictions. It updates an earlier review of 2015 with more restrictive inclusion criteria and we were able to add six studies published since that meta-analysis. Broadening the definition of mindfulness interventions brought five additional studies, including 2 yoga studies, 2 studies involving ACT, and one study involving an adapted mindfulness program (BMBW). Expanding the language only brought one additional study, published in Farsi, because the study conducted in Germany (Cramer 2017) and the study conducted in India (Sharma 2015) were both published in English. One of the authors (BA) translated the Iranian study.

Expanding the age criteria did not bring any paediatric and adolescent studies as there were no RCTs in this age group despite a recent meta-analysis and a review showing that adolescents and young adults (AYAs) with IBD are particularly responsive to psychotherapy [18, 44], and that AYAs are responsive to mindfulness interventions [45, 46].

Overall findings of the review suggest that mindfulness interventions as a group are most effective in mitigating stress both the short- and long-term. In the short term, mindfulness interventions were only statistically superior to the control conditions in the case of stress (Table 3 and Figure 4). However, on subgroup analysis, patients receiving yoga were significantly less depressed (Figure 2). In the longer-term, symptoms of stress continued to improve with statistically significant differences in scores for both yoga and MBPs (Figure 5), and no differences for anxiety and depression in response to MBPs and mindfulness interventions as a group but only for yoga (Table 4). Improvements in quality of life were only statistically significant in the long-term. One of the yoga studies, Cramer et al, outperformed all other mindfulness interventions in depression, anxiety and stress scores changes both short and long-term and in stress scores long-term. Care needs to be taken however when interpreting these results as they could be related to high methodological quality of this study rather than the type of the intervention.

Interestingly, our results showed further decreases in stress scores on long term follow up, which is unusual in psychotherapy research where results usually fade with time. One explanation is that we were able to include one additional study in our long-term meta-analysis that may have increased precision by reducing 95% confidence intervals. Another explanation might be the effect of differential loss to follow-up. A third might be the long-term benefits of continuing with mindfulness practices. Reduction in stress offers a potential explanatory model for mindfulness mechanisms of action in IBD via the gut-brain axis and HPA axis modifications, leading to normalisation of psychological and biological markers via this pathway. This review, however, did not show significant improvement in biological markers for mindfulness interventions as a whole although both yoga studies showed reduction in inflammatory markers that did not reach statistical significance apart from clinical disease activity index which was statistically improved in yoga in comparison with the control group. It is important to consider these findings while keeping in mind that all of the studies excluded participants

with significant mental illness and active IBD. This resulted in enrolment of participants with low baseline levels of both psychological and biological parameters which made it more difficult to demonstrate improvement.

Strengths and Limitations of the Review

Strengths of this review are the inclusion of a broad range of mindfulness interventions and exploration the impact of mindfulness interventions on biological as well as psychological outcomes. Limitations of this review are that it has only eight included studies and with small sample sizes which resulted in limited sensitivity analysis and no assessment of publication bias. Furthermore, the quality of individual studies has been affected by poor blinding of the outcome assessors, incomplete data reporting and a relative lack of fidelity measures. The short-term outcomes showed statistically significant heterogeneity and should be viewed with caution even though we used random-effects models. An additional limitation is that included studies measured long-term outcomes at wide-ranging time frames, from 20 weeks (Rowan 2017) to one year (Jedel 2014 and Berril 2014). The review showed a relative lack of assessment of biological markers.

This review highlights the need for rigorously designed studies with improved allocation concealment and blinding, more uniform follow-up time frames, and use of the ITT analysis and imputing of the missing data. The review suggests the need for mindfulness interventions that are tailored for IBD which could improve participants' engagement and potentially increase their effect via a dose-response relationship. In view of the beneficial impact of yoga, use of yoga-based programs and increase in yoga component in mindfulness programs may convey further benefits. Careful consideration of expansion of inclusion criteria to include participants with more severe IBD and psychological symptoms might be appropriate although limited by the impact of these conditions on participants' ability to practice. Given the positive effect of mindfulness interventions on stress, depression and quality of life, and the impact of yoga on some physical outcomes, these therapies may be useful additions to integrative IBD care.

Contributions

Systematic review was conceived and designed by TE, SK and KR and critically revised by SK, MK, JB and KH. Drafting of the paper was completed by TE. All authors approved the final manuscript.

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Declarations of interests

None

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Highlights

- Mindfulness interventions are effective in reducing stress, depression and anxiety and improving quality of life in individuals suffering from inflammatory bowel disease
- Yoga-based programs are associated with significant improvements in depression, anxiety, stress and quality of life in inflammatory bowel disease, with moderate effect sizes on both short and long-term follow-up
- Effects of mindfulness interventions on physical outcomes in inflammatory bowel disease are equivocal and not statistically significant
- Mindfulness interventions may be useful additions to integrative IBD care
- Further research involving IBD-tailored interventions and more rigorously designed trials is warranted