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ORIGINAL PAPER

Mindfulness-Based Cognitive Therapy for Fatigue in Patients with Inflammatory Bowel Disease: Results of a Randomized Controlled Trial

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Abstract

Objectives Fatigue is a prevalent and burdensome problem in patients with inflammatory bowel disease (IBD), even when the disease is in remission. Evidence-based psychological interventions for managing IBD-related fatigue are still lacking. This study aimed to examine the efficacy of Mindfulness-Based Cognitive Therapy (MBCT) for reducing fatigue in patients with IBD in remission.

Method A two-arm multicenter randomized controlled trial was conducted in 113 IBD outpatients in remission with elevated levels of fatigue (i.e., Checklist Individual Strength — subjective fatigue ≥ 27). Patients were randomly assigned to an 8-week MBCT program ($n = 56$) or a waiting-list condition ($n = 57$). All participants completed questionnaires at baseline and directly post-intervention. The primary outcome was fatigue, assessed with the Checklist Individual Strength-20. Secondary outcomes included fatigue interference in daily life, depression, anxiety, and IBD-specific quality of life. Analysis of covariance (ANCOVA) was performed to examine treatment outcomes.

Results Intention-to-treat analyses showed significant reductions in the subjective experience of fatigue in patients receiving MBCT, compared to the waiting-list control condition ($p = 0.03$; Cohen's $d = 0.46$; clinically relevant improvement in 36% vs. 10%). No significant effects were found on other fatigue aspects or secondary outcomes.

Conclusions An 8-week MBCT group program effectively reduced the subjective experience of fatigue in patients with IBD in remission. Results do not support effects for other aspects of fatigue or secondary outcomes.

Preregistration ClinicalTrials.gov Identifier: NCT03162575.

Keywords Inflammatory bowel disease · Fatigue · Mindfulness-Based Cognitive Therapy · Randomized controlled trial

Inflammatory bowel disease (IBD) is a lifelong disease that includes Crohn's disease and ulcerative colitis, two inflammatory conditions of the gastrointestinal tract with a relapsing-remitting course. Fatigue is one of the most dominant complaints in patients with IBD, often experienced irrespective of disease status and despite standard disease management (Farrell et al., 2016). Fatigue can have an extensive impact on patients' lives, as it is associated with a lower quality of life (QoL), functional impairments, absence from work, and mood disorders (Cohen et al., 2014; Schreiner et al., 2021). Fatigue is often described as a sense of continuing tiredness, with periods of sudden and overwhelming lack of energy or a feeling of exhaustion that is not relieved through rest or sleep (Czuber-Dochan et al., 2014a). The prevalence of fatigue in patients with IBD ranges from 22 to 77% (Grimstad & Norheim, 2016). Although fatigue is in general more common in patients with active disease in comparison to patients in remission, the prevalence in IBD patients in remission remains considerably high (i.e., 41–48%) (van Langenberg & Gibson, 2010). Moreover, qualitative research revealed that IBD patients in remission report fatigue as the most burdensome problem (Farrell et al., 2016).

IBD-related fatigue is only identified and well managed in a small proportion of affected patients (Nocerino et al., 2020; van Langenberg & Gibson, 2010). Especially for

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patients in remission, health care professionals find it challenging to treat fatigue (Czuber-Dochan et al., 2014b). As these patients already receive medication and their disease activity is reduced, clinicians run out of treatment options for the remaining fatigue.

Research has shown that disease-related variables, such as disease activity or anemia, only contribute to a limited extent to the occurrence and risk of developing fatigue, whereas cognitive, emotional, and behavioral factors are found to contribute most to IBD-related fatigue (Artom et al., 2017; Chavarria et al., 2019). Specifically, negative cognitions about fatigue (e.g., the idea of not having control) and avoidance behaviors (e.g., avoidance of physical activity) have been associated with the severity and impact of fatigue on patients' lives (Artom et al., 2017). Moreover, anxiety and depression have often been reported as factors maintaining and worsening IBD-related fatigue (Borren et al., 2019; Chavarria et al., 2019). Psychological interventions aiming to change these factors might thus be promising for treating IBD-related fatigue, especially when the disease is already in remission.

In patient groups other than IBD, mindfulness-based interventions have been proven beneficial for reducing fatigue (Johns et al., 2021; Simpson et al., 2020; Xie et al., 2020), even for people who still experience severe chronic fatigue after receiving cognitive behavior therapy (Rimes & Wingrove, 2013). One promising intervention in this context is Mindfulness-Based Cognitive Therapy (MBCT; Segal et al., 2002). MBCT is an evidence-based group program, focused on cultivating non-judgmental awareness of the present moment through meditation and cognitive-behavioral exercises (Segal et al., 2002). MBCT might lead to reductions in fatigue, by helping patients to develop a more non-judgmental awareness of fatigue experiences, to learn to decenter from negative feelings and perceptions of fatigue, to become more aware of unhelpful automatic reactions, and to make conscious choices about doing physical activity, taking rest, performing daily activities, and communicating their boundaries to others. Given the significant overlap in the experience of fatigue between patients with IBD and other chronic diseases (Czuber-Dochan et al., 2013), we hypothesized that MBCT might also be helpful for IBD patients.

Previous studies have shown that MBCT is perceived as an acceptable and feasible intervention by patients with IBD and positive effects on various psychological outcomes have been reported (Ewais et al., 2021; Schoultz et al., 2016). Moreover, preliminary results of a pilot study in patients with IBD have suggested that mindfulness-based interventions can also reduce fatigue (Drent et al., 2016). The current study examined the efficacy of MBCT for IBD-related fatigue using a randomized controlled design.

The primary purpose of this randomized controlled trial was to examine the efficacy of MBCT for reducing fatigue in adult patients with IBD in remission, when compared to a waiting-list control group. In addition, we examined improvements of fatigue interference in daily life, depression, anxiety, and IBD-related QoL (i.e., secondary outcomes) in patients following MBCT, when compared to the waiting-list control condition.

Method

Participants

Patients were eligible for inclusion if they had a diagnosis of either Crohn's disease or ulcerative colitis, as confirmed by a medical specialist. In addition, patients needed to report elevated levels of fatigue, i.e., a score ≥ 27 on the subjective fatigue scale of the Checklist Individual Strength (CIS-20), indicating at least mild fatigue (Vercoulen et al., 1994). Their disease had to be in remission at the start of the intervention, as defined by a score < 4.99 on the mHealth Index Colitis Ulcerosa or < 6.38 on the mHealth Index Crohn's Disease (Van Deen et al., 2016). Patients also needed to report a need for care concerning their fatigue and indicate motivation to participate in MBCT, which was assessed by open-ended questions during the intake. Additionally, eligible patients were aged between 18 and 75 years old, able to attend the eight weekly group sessions of 2.5 hr, and able to read, write, and speak Dutch and had no expectation of surgery in the upcoming 3 months. Exclusion criteria were severe cognitive, neurological, and psychiatric co-occurring conditions that could interfere with patients' participation or warranted other treatment, specifically psychotic complaints or diagnosis of schizophrenia, neurological disorders including severe cognitive limitations, substance use disorder, and acute suicidal ideations or behavior. These comorbidities were examined separately via open-ended questions during the intake. Other exclusion criteria were pregnancy, anemia (i.e., Hb < 7.4 for women, Hb < 8.1 for men), change in IBD medication within 1 month before study entry, and receiving psychological treatment for fatigue or psychological/psychiatric problems at the time of recruitment. The latter was implemented in order to minimize possible confounding by other psychological treatments.

Procedure

This two-arm multicenter randomized controlled trial (RCT) was conducted in the outpatient gastroenterology departments of the University Medical Centre Groningen, Medisch Spectrum Twente, and Isala Clinics Zwolle in the Netherlands, between July 2017 and September 2018. A consecutive sample was recruited via treating physicians in the three hospitals. All IBD patients who were under treatment in one

of the three hospitals at the time of recruitment received a short screening questionnaire by mail, including the subscale subjective fatigue of the CIS-20, the mHealth Index, and a question about their current need for care, with an accompanying letter from their physician. Based on this screening, patients with IBD in remission, elevated levels of fatigue, and a possible need for care to manage their fatigue were invited for an intake by telephone. During the intake, patients were informed about the goals and setup of the study and intervention, and assessed for eligibility by a brief standardized interview. Patients who fulfilled our criteria received an information letter and informed consent form, as well as the baseline questionnaire. Those patients that provided written informed consent for participation were included in the study. Assessments in both groups were performed before randomization (i.e., baseline) and directly after the intervention period (i.e., post-measurement, approximately 3 months after baseline).

Randomization Participants were randomly assigned to an 8-week MBCT or waiting-list control condition. The latter was chosen for ethical considerations, as all patients experienced elevated levels of fatigue at baseline. A research assistant not actively involved in the design and data analysis of the study generated a random allocation sequence and assigned participants to one of the two conditions (1:1 ratio). In order to ascertain balanced and equally sized groups, randomization was carried out using covariate adaptive randomization. Gender, IBD diagnosis, fatigue severity, and depressive symptoms at baseline were included as matching variables because of assumed interactions with post-measurement fatigue levels. Patients, mindfulness trainers, and researchers were all aware of group allocation.

Intervention Mindfulness-Based Cognitive Therapy (MBCT) is a structured group intervention developed by Segal et al. (2002). The intervention consisted of eight weekly 2.5-hr sessions and one 3-hr silent session. Key aspects of the program were group meditation, cognitive-behavioral exercises, psycho-education, and daily homework. The intervention in our study closely followed the original manual, with a few adaptations. First, psycho-education focused on fatigue symptoms and management, as well as on stress-management, the relation between stress and fatigue, and the importance of recognizing personal boundaries in activities, rather than on depression. In addition, experiences related to fatigue or IBD in general were a central and recurring topic during inquiry. Patients received homework assignments, including audio CDs with formal exercises, and were asked to practice for 30 min per day. The MBCT courses were delivered by three licensed and experienced mindfulness trainers (one trainer per center), who all received an additional training and supervision during the research period from an experienced MBCT trainer, in order to secure the adherence to the specific mindfulness-based treatment protocol.

All sessions were audiotaped to examine therapists' adherence to the protocol. Protocol adherence was defined as the extent to which each session component was implemented. Based on ratings of a random selection of one-third of the audiotaped sessions by one of the authors (Q.M.B.), therapists' adherence was considered sufficiently good (88%).

Patients reported their daily home practice on weekly evaluation forms. Homework compliance, defined as the proportion of given homework exercises completed per week, was rated for all weeks except the last two, as patients were then encouraged to develop their own homework plan. Seventy-five percent of the patients receiving MBCT completed the forms. Patients' homework compliance was sufficient, with patients completing on average 70% of the homework exercises each week.

Waiting-list Control Condition Patients in the waiting-list control condition were informed that they would receive MBCT after a waiting period of 3 months. Meanwhile, no psychological intervention was offered.

Measures

The baseline questionnaire included questions regarding demographic, socioeconomic, and disease-specific information. All psychological outcomes were assessed at baseline and post-measurement (on average, 3 months after the baseline assessment).

Primary Outcome Measure Fatigue was assessed with the self-report questionnaire Checklist Individual Strength (CIS-20; Vercoulen et al., 1994). The CIS-20 includes 20 statements scored on a 7-point Likert scale from 0 (*Yes, that is true*) to 7 (*No, that is not true*). The statements address fatigue in the last 2 weeks and refer to four subscales: (1) subjective feeling of fatigue, (2) concentration, (3) motivation, and (4) activity level. A total CIS-20 sum score between 20 and 140 can be obtained, with higher scores indicating more fatigue. We reversed items for which a higher score indicated less fatigue. For the total CIS-20, a cutoff point of > 76 has been established for severe fatigue (Bültmann et al., 2000). The CIS-20 has good reliability and is validated within the Dutch general population and clinical settings (Worm-Smeitink et al., 2017). In the current study, the scale's internal consistency at baseline was good ($\alpha = 0.87$). Similar reliability was found for the subscales subjective fatigue, concentration, and activity level ($\alpha = 0.86$–0.89). Reliability for the subscale motivation was lower, yet acceptable ($\alpha = 0.68$).

Secondary Outcome Measures Fatigue interference was measured using the 7-item "fatigue interference" scale of the Fatigue Symptom Inventory (FSI) (Hann et al., 1998). Patients were asked to indicate to which degree fatigue interfered with their daily activities at home, work and

with others. Perceived interference was measured with an 11-point Likert scale ranging from 0 (*No interference*) to 10 (*Extreme interference*). These ratings were summed to obtain a total score, ranging from 0 to 70. The scale's reliability in this study at baseline was good ($\alpha = 0.89$).

Anxiety was assessed with the Generalized Anxiety Disorder 7-item (GAD-7) scale (Spitzer et al., 2006), measuring symptoms of general anxiety disorder. The GAD-7 is a self-report scale, on which patients indicate how often they have been bothered by anxiety symptoms over the past 2 weeks (e.g., feeling nervous, anxious, or on edge). Answers were given on a Likert scale from 0 (*Not at all*) to 3 (*Nearly every day*). A total sum score between 0 and 21 was calculated, with scores 5–10 indicating mild anxiety, 11–15 moderate anxiety, and > 15 severe anxiety (Spitzer et al., 2006). In this study, Cronbach's alpha of the scale at baseline was good ($\alpha = 0.89$).

The severity of depressive symptoms was measured by the 21-item Beck Depression Inventory II (BDI-II; Beck et al., 1996). This self-report questionnaire measures the severity of depressive symptoms (e.g., sadness, loss of interest, concentration) during the past 2 weeks, scored on a 4-point scale ranging from 0 (*No symptoms*) to 3 (*Severe symptoms*). The BDI-II yielded a total sum score between 0 and 63, with scores 0–13 indicating minimal, 14–19 mild, 20–28 moderate, and 29–63 severe depressive symptoms (Beck et al., 1996). Reliability in the current study at baseline was good ($\alpha = 0.88$).

Quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBD-Q; Guyatt et al., 1989), a scale specifically measuring QoL in IBD patients. This self-report questionnaire consists of 32 items that refer to four dimensions: (1) bowel symptoms, (2) systemic symptoms, (3) emotional function, and (4) social function. Item scores range from 1 (*Worst QoL*) to 7 (*Best QoL*). A total score (ranging between 32 and 224) was calculated by adding all item scores, with higher scores representing better QoL. Cronbach's alpha in this study at baseline was good ($\alpha = 0.89$).

Disease Activity Disease activity was measured with the mHealth Index Crohn's Disease (mHI-CD) and the mHealth Index Colitis Ulcerosa (mHI-CU) for Crohn's disease and ulcerative colitis, respectively (Van Deen et al., 2016). Both scales are patient-reported and consist of four items examining the number of stools, abdominal pain, disease control, rectal bleeding, and/or overall well-being. Active disease was defined as a score ≥ 4.99 on mHI-CU and ≥ 6.38 on mHI-CD (Van Deen et al., 2016).

Data Analyses

Sample size calculation for the primary research question was performed based on a pilot study (Drent et al., 2016), which assessed pre- and post-measurement fatigue levels in IBD patients participating in a mindfulness program similar to MBCT, specifically Mindfulness-Based Stress Reduction (MBSR) as developed by Kabat-Zinn (1990). The MBCT and MBSR program both involve eight weekly 2.5-hr sessions, focused on exercise and inquiry, one silent session of 3 hr, and homework exercises. Also, the content of the sessions is similar, except for the explicit focus on negative thoughts in MBCT. Given the similarities in the content, structure, and intensity of the two programs, we used this pilot study for the sample size calculation. With a statistical power of 0.80 and an alpha of 0.05, 64 patients were required per group (128 in total) to be able to detect differences with an effect size of at least 0.50.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 26). Descriptive statistics are presented as means and standard deviations, medians and interquartile, or numbers and percentages, as appropriate (Table 1). Independent samples *t*-tests (or Mann-Whitney *U* tests in case of non-parametric data) and χ^2 tests were used to examine group equivalence at baseline for demographic and clinical variables, as well as primary and secondary outcomes.

All inferential analyses were based on the intention-to-treat principle. To account for missing data, multiple imputations were performed with the use of predictive mean matching. Twenty imputed datasets were specified and results were pooled over all datasets. Based on Little's MCAR test and visual inspection of the data, we considered the data missing at random and multiple imputations were assumed to provide unbiased results. We performed sensitivity analyses in patients who completed both baseline and post-measurement questionnaires to demonstrate the robustness of the intention-to-treat findings (i.e., complete case analysis, see Supplementary Table 1).

Paired samples *t*-tests were conducted to examine within-group change in primary and secondary outcomes from baseline to post-measurement. Pooled standard deviations were calculated following Cohen's (1988) rule. Analysis of covariance (ANCOVA) was performed to examine the effect of MBCT on fatigue and secondary outcome variables. Post-measurement levels of the primary and secondary outcomes were used as dependent variables, condition as factor and baseline levels of the outcomes were considered covariates. Since no other possible confounding variables correlated significantly with the outcomes (e.g., changes in medication use and experiencing a flare-up during the study period), only these variables were entered in the model. Per-protocol analyses were performed in patients who completed five or more sessions of MBCT. Assumptions for all analyses were met and the impact of potential outliers was examined using winsorizing. Two-tailed *p*-values < 0.05 were considered statistically significant.

Effect sizes were calculated using Cohen's *d*. Values of 0.20–0.50 indicated small effects, 0.50–0.80 moderate effects, and > 0.80 large effects (Cohen, 1988). For

the subscale subjective fatigue, we defined clinically relevant outcomes as having improved and being recovered. Improvement was calculated by the Reliable Change Index (RCI), which refers to the difference between an individuals' baseline and post-measurement score, divided by the standard error of the difference (Jacobson & Truax, 1991). Each participant was categorized as improved (RCI > 1.96), no change (−1.96 to 1.96), or deteriorated (RCI < −1.96). Recovery was defined as a post-measurement score of subjective fatigue < 27, i.e., a level of fatigue comparable to healthy people (Vercoulen et al., 1994). χ^2 tests were used to compare the number of clinically relevant improved and recovered patients between the MBCT and waiting-list control conditions.

Results

Recruitment and Attrition

In total, 3896 patients were approached for screening (Fig. 1). Of the 2376 patients who returned the screening questionnaire, 1440 patients reported an elevated fatigue score (CIS — subjective fatigue ≥ 27). Around one-third of

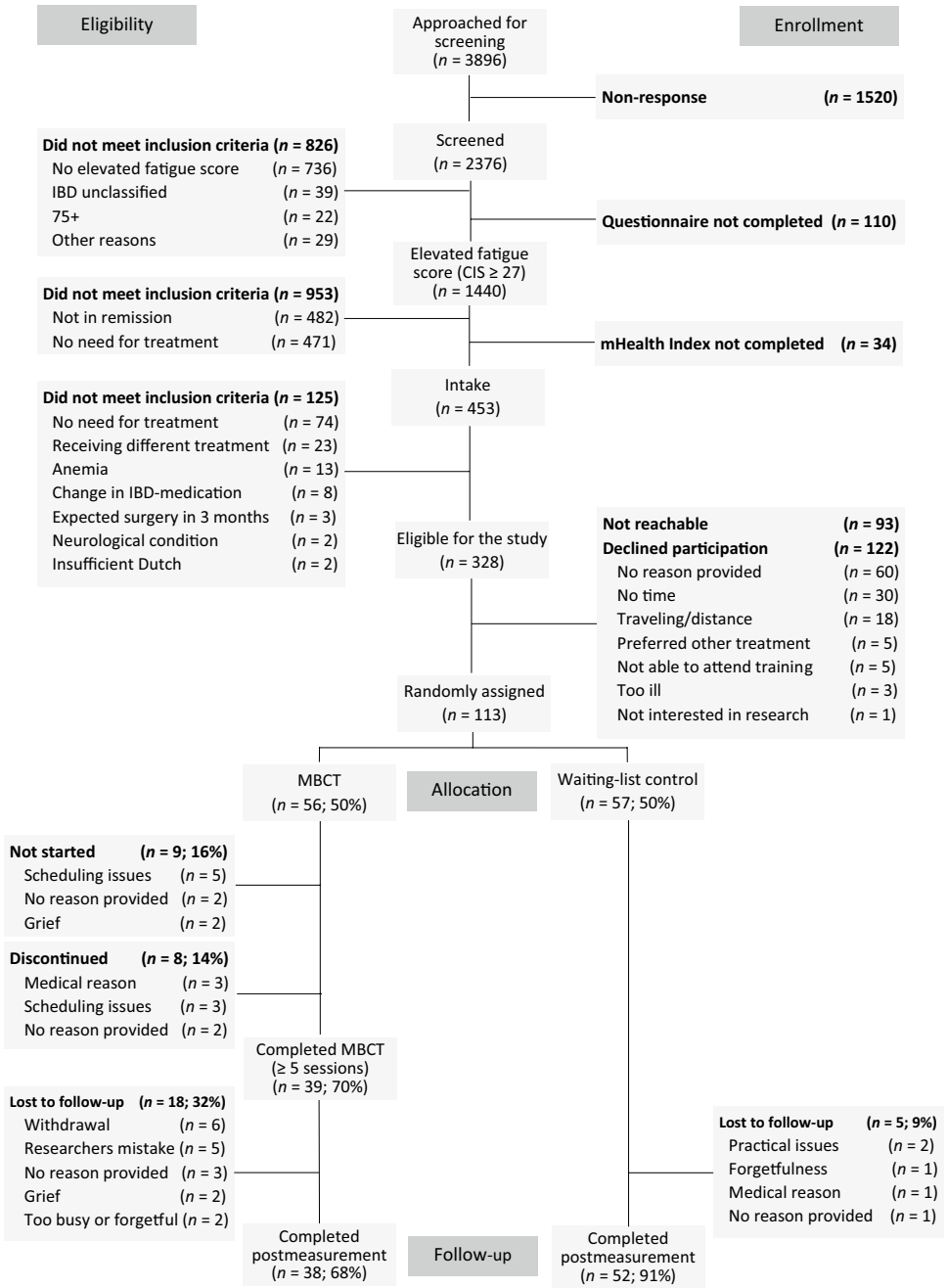

Fig. 1 CONSORT flow diagram —— Participant recruitment and attrition through the study

the patients with elevated fatigue could be approached for the intake ($n = 453$). Based on the intake, 125 patients were not eligible for participating in the study, mostly because they did not feel the need for treatment after all. Half of the eligible patients ($n = 215$) declined participation because of various reasons.

In the end, 113 patients gave consent and were randomized into either the MBCT condition or the waiting-list control condition ($n = 56$ and 57, respectively). Although the overall response rate was 3% (i.e., approached vs. randomized), 34% of the eligible patients participated in the study. Patients included in the study did not differ significantly in age, gender, and type of IBD compared to all approached patients ($n = 3896$). Eighteen patients (32%) in the MBCT condition did not complete the post-measurement questionnaire, in contrast to five patients (9%) in the waiting-list condition ($\chi^2(1, n = 113) = 9.52, p < .01$). Within the intervention group, seventeen patients (30%) did not complete MBCT (i.e., participated in less than five sessions). Reasons for dropout were mainly medical or related to scheduling; four patients did not provide any reason. Patients did not report any harm related to the study. Dropout of the intervention was only significantly associated with being a female ($\chi^2(1, n = 56) = 6.10, p = .01$) and not with other demographic or clinical variables, nor with fatigue or secondary outcomes.

Baseline Characteristics

Table 1 shows an overview of the baseline characteristics of our sample. Patients in the MBCT and waiting-list condition did not differ significantly on demographic and clinical baseline characteristics. Averages of primary and secondary outcome measures at baseline are presented in Table 2. Descriptive statistics show severe levels of fatigue and reduced QoL, whereas levels for fatigue interference, depressive symptoms, and anxiety indicate little impairments. No significant differences in these outcome measures were found between the two conditions.

Primary Outcome Measure

Intention-to-treat analyses revealed significant differences in post-measurement subjective fatigue scores between the MBCT and waiting-list control conditions (Table 2). Patients in the intervention group reported significantly lower subjective fatigue scores at post-measurement than patients in the waiting-list control group, when adjusted for baseline values of the outcome ($p = 0.03$). The effect size was small to moderate (Cohen's $d = 0.46$). Although within-group time effects were significant for both conditions, the decline in subjective fatigue was stronger in the intervention group compared to the control group (Cohen's $d = 0.62$ and 0.19, respectively). Regarding the other aspects of fatigue, no significant differences were found between the two conditions in the post-measurement scores (neither in the total fatigue score, nor in the other subscales). Per-protocol analyses (i.e., in patients who completed five or more sessions of MBCT) yielded similar results, except for an additional significant effect on total fatigue ($p < 0.05$), with a small to moderate effect size (Cohen's $d = 0.40$) (Table 3).

Secondary Outcome Measures

Intention-to-treat analyses showed no significant differences between the two conditions in the post-measurement scores of fatigue interference, anxiety, depression, and QoL, when controlled for baseline levels of the outcome (Table 2). Effect sizes were small (Cohen's $d < 0.25$). Per-protocol analyses showed that patients receiving MBCT reported significantly lower depression at post-measurement than patients in the waiting-list control condition, when adjusted for baseline levels. The effect size was small ($p = 0.04$; Cohen's $d = 0.29$; Table 3).

Clinically Relevant Outcome

Clinically relevant improvement of subjective fatigue (i.e., RCI score > 1.96) was found in 36% of the participants after MBCT versus 10% in the waiting-list control condition ($\chi^2(1, n = 86) = 9.37, p < 0.01$) (Table 4). After the intervention period, 21% of the patients in the MBCT condition were considered recovered (i.e., CIS — subjective fatigue < 27), compared to 9% in the control condition ($\chi^2(1, n = 90) = 4.54, p = 0.03$). Sixteen percent of patients in the MBCT condition both improved and recovered, whereas no patients in the waiting-list control group fulfilled this criterion ($\chi^2(1, n = 90) = 10.39, p < 0.01$). Rates of improvement and recovery in patients completing five or more MBCT sessions were similar (see Supplementary Table 2).

Discussion

In the past decade, an increasing number of studies demonstrated the efficacy of mindfulness-based interventions for improving psychological outcomes such as affect and reducing symptoms of distress, anxiety, and depression. To a much lesser extent, studies examined whether mindfulness-based interventions can also reduce fatigue. Particularly in patients with cancer (Johns et al., 2021; Xie et al., 2020) and multiple sclerosis (Simpson et al., 2020), recent meta-analyses suggested positive results regarding the acceptability, feasibility, and benefits for fatigue. To our knowledge, this is the first randomized controlled trial investigating the efficacy of MBCT for reducing fatigue in severely fatigued patients

Table 1 Sociodemographic and clinical patient characteristics at baseline ($n = 113$)

	MBCT ($n = 56$)	WAIT ($n = 57$)	Total ($n = 113$)
Sex, *n* (%)			
Female	36 (64)	34 (60)	70 (62)
Male	20 (36)	23 (40)	43 (38)
Age, mean (SD)	47.3 (12.7)	46.0 (14.8)	46.6 (13.8)
Education, *n* (%)			
Lower level vocational school	7 (12)	10 (18)	17 (15)
Secondary education/advanced level vocational school	29 (52)	27 (47)	56 (50)
Higher or university education	20 (36)	20 (35)	40 (35)
Employment, *n* (%)			
Paid employment	33 (59)	32 (56)	65 (57)
Unemployed/unpaid employment	23 (41)	24 (42)	47 (42)
Relationship status, *n* (%)			
In a relationship	45 (80)	46 (81)	91 (81)
Not in a relationship	11 (20)	9 (16)	20 (18)
Disease type, *n* (%)			
Crohn's disease	26 (46)	34 (60)	60 (53)
Ulcerative colitis	30 (54)	23 (40)	53 (47)
Disease activity, median (IQR)			
Crohn's disease	4.3 (2.1–5.7)	4.3 (2.1–4.8)	4.3 (2.1–5.5)
Ulcerative colitis	1.4 (0.0–2.8)	1.4 (0.0–2.8)	1.4 (0.0–2.8)
Time since diagnosis (years), median (IQR)	12.0 (6.0–23.0)	10.5 (6.3–20.0)	11.0 (6.0–21.0)
Age at diagnosis (years), median (IQR)	29.0 (20.0–36.0)	29.0 (20.0–45.0)	29.0 (20.3–41.8)
Doctor visits in the past year, *n* (%)			
0 visits	5 (9)	3 (5)	8 (7)
1–2 visits	32 (57)	37 (65)	69 (61)
≥ 3 visits	16 (29)	17 (30)	33 (29)
Surgery, *n* (%)			
No surgery	38 (68)	39 (68)	77 (68)
One surgery	9 (16)	6 (10)	15 (13)
More than one surgery	9 (16)	11 (20)	20 (18)
Hemoglobin in mmol/l, median (IQR)	8.7 (8.2–9.2)	8.7 (8.1–9.2)	8.7 (8.2–9.2)
IBD–related medication, *n* (%)			
Mesalazine	13 (23)	17 (30)	30 (27)
Immunosuppressive/biological agents	24 (43)	19 (34)	43 (38)
Mesalazine + immunosuppressive/biological agents	3 (5)	3 (5)	6 (5)
Immunosuppressive/biological agents + corticosteroids	0 (0)	3 (5)	3 (3)
None	16 (29)	15 (26)	31 (27)

WAIT, waiting-list; *SD*, standard deviation; *IQR*, interquartile range

Percentages may not add up to 100% due to missing data

with IBD in remission. Results indicated that MBCT was effective in reducing the subjective experience of fatigue, when compared to a waiting-list control group, with one-third of patients reporting clinically relevant improvement in fatigue. Contrary to our expectations, we found no significant effects of MBCT on other aspects of fatigue, nor on the interference of fatigue in daily life, depression and anxiety symptoms, and QoL.

Given the high prevalence and burden of fatigue in IBD patients, a key finding is that MBCT effectively reduced the subjective experience of fatigue. This finding is in line with outcomes of previous studies demonstrating the beneficial effect of mindfulness-based interventions, including MBCT and MBSR, for fatigue in patients with cancer or multiple sclerosis, reporting similar effect sizes (Johns et al., 2021; Simpson et al., 2020; Xie et al., 2020). In our study,

Table 2 Mean scores at baseline and post-measurement and group differences for primary and secondary outcome measures — intention-to-treat ($n = 113$)

				Time effect			Group effect			
Measure	Group	Baseline Mean (SD)	Post Mean (SD)	*t*	*p*	Cohen's *d* (95% CI)	Mean difference[a] (95% CI)	t^a	p^a	Cohen's d^a (95% CI)
Fatigue (CIS-20)										
Subjective	MBCT	41.5 (7.5)	36.1 (9.8)	3.78	<0.001*	0.62 (0.24 to 1.00)	3.71 (0.47 to 6.94)	2.27	0.03*	0.46 (0.09 to 0.84)
	WAIT	41.6 (8.3)	39.9 (9.3)	2.28	0.02*	0.19 (−0.18 to 0.56)				
Concentration	MBCT	20.4 (7.6)	19.8 (6.7)	0.61	0.54	0.08 (−0.29 to 0.45)	0.23 (−2.05 to 2.52)	0.20	0.84	0.04 (−0.33 to 0.41)
	WAIT	18.8 (6.9)	19.1 (6.9)	−0.29	0.77	−0.04 (−0.41 to 0.32)				
Motivation	MBCT	15.8 (4.6)	15.4 (4.9)	0.45	0.65	0.08 (−0.29 to 0.50)	0.21 (−1.70 to 2.12)	0.21	0.83	0.07 (−0.30 to 0.44)
	WAIT	15.9 (4.5)	15.7 (4.6)	0.44	0.66	0.04 (−0.32 to 0.41)				
Activation	MBCT	13.6 (4.3)	12.1 (4.9)	2.64	0.01*	0.33 (−0.05 to 0.70)	1.13 (−0.34 to 2.60)	1.52	0.13	0.27 (−0.10 to 0.64)
	WAIT	13.5 (4.5)	13.1 (4.5)	0.83	0.41	0.09 (−0.28 to 0.46)				
Total	MBCT	91.4 (17.0)	83.5 (20.3)	2.63	0.01*	0.42 (0.05 to 0.80)	5.45 (−1.51 to 12.41)	1.55	0.12	0.33 (−0.04 to 0.70)
	WAIT	89.9 (16.0)	87.8 (18.9)	1.20	0.23	0.12 (−0.25 to 0.49)				
Fatigue interference (FSI)	MBCT	29.2 (12.9)	25.7 (12.1)	1.88	0.06	0.28 (−0.09 to 0.65)	0.86 (−3.37 to 5.09)	0.40	0.69	0.07 (−0.30 to 0.44)
	WAIT	26.1 (14.1)	24.8 (13.2)	0.81	0.42	0.10 (−0.27 to 0.46)				
Anxiety (GAD)	MBCT	7.2 (5.1)	6.2 (3.9)	1.70	0.09	0.22 (−0.15 to 0.59)	0.65 (−0.69 to 2.00)	0.96	0.34	0.14 (−0.23 to 0.51)
	WAIT	5.9 (4.7)	6.1 (4.4)	−0.41	0.68	−0.04 (−0.41 to 0.32)				
Depression (BDI-II)	MBCT	16.5 (10.7)	14.4 (9.6)	1.77	0.08	0.21 (−0.17 to 0.58)	2.18 (−0.54 to 4.89)	1.57	0.12	0.21 (−0.16 to 0.58)
	WAIT	15.4 (9.1)	15.7 (10.1)	−0.41	0.68	−0.03 (−0.40 to 0.34)				
Quality of life (IBD-Q)	MBCT	171.4 (22.7)	172.1 (22.2)	−0.23	0.82	−0.03 (−0.40 to 0.34)	−0.51 (−7.21 to 6.19)	−0.15	0.88	−0.02 (−0.39 to 0.35)
	WAIT	172.6 (21.8)	172.4 (23.4)	0.07	0.95	0.01 (−0.36 to 0.38)				

WAIT, waiting-list; *SD*, standard deviation; *CI*, confidence interval

[a]Estimate based on adjusted means

*$p < 0.05$

Table 3 Mean scores at baseline and post-measurement and group differences for primary and secondary outcome measures — per-protocol ($n = 96$)

				Time effect			Group effect			
Measure	Group	Baseline Mean (SD)	Post Mean (SD)	*t*	*p*	Cohen's *d* (95% CI)	Mean difference[a] (95% CI)	*t*[a]	*p*[a]	Cohen's *d*[a] (95% CI)
Fatigue (CIS-20)										
Subjective	MBCT	41.9 (7.8)	36.4 (9.6)	3.70	<0.001*	0.63 (0.17 to 1.08)	3.75 (0.69 to 6.81)	2.41	0.02*	0.47 (0.06 to 0.88)
	WAIT	41.6 (8.3)	39.9 (9.3)	2.28	0.02*	0.19 (−0.18 to 0.56)				
Concentration	MBCT	21.1 (7.7)	20.1 (6.7)	1.15	0.25	0.14 (−0.31 to 0.58)	0.45 (−1.78 to 2.69)	0.40	0.69	0.07 (−0.34 to 0.48)
	WAIT	18.8 (6.9)	19.1 (6.9)	−0.29	0.77	−0.04 (−0.41 to 0.32)				
Motivation	MBCT	16.9 (4.5)	15.7 (4.6)	1.33	0.18	0.26 (−0.18 to 0.71)	0.43 (−1.39 to 2.26)	0.47	0.64	0.11 (−0.30 to 0.52)
	WAIT	15.9 (4.5)	15.7 (4.6)	0.44	0.66	0.04 (−0.32 to 0.41)				
Activation	MBCT	14.1 (4.2)	12.2 (4.8)	3.07	<0.01*	0.42 (−0.03 to 0.87)	1.35 (−0.09 to 2.79)	1.84	0.07	0.32 (−0.09 to 0.73)
	WAIT	13.5 (4.5)	13.1 (4.5)	0.83	0.41	0.09 (−0.28 to 0.46)				
Total	MBCT	94.0 (16.9)	84.4 (19.4)	3.21	<0.001*	0.53 (0.08 to 0.98)	6.59 (0.15 to 13.03)	2.01	<0.05*	0.40 (−0.01 to 0.81)
	WAIT	89.9 (16.0)	87.8 (18.9)	1.20	0.23	0.12 (−0.25 to 0.49)				
Fatigue interference (FSI)	MBCT	30.0 (13.3)	25.7 (12.6)	2.09	0.04*	0.48 (0.03 to 0.93)	1.38 (−3.01 to 5.77)	0.62	0.54	0.09 (−0.31 to 0.50)
	WAIT	26.1 (14.1)	24.8 (13.2)	0.81	0.42	0.10 (−0.27 to 0.46)				
Anxiety (GAD)	MBCT	7.7 (5.3)	6.3 (4.0)	2.10	0.04*	0.30 (−0.15 to 0.74)	0.87 (−0.53 to 2.27)	1.22	0.22	0.18 (−0.23 to 0.59)
	WAIT	5.9 (4.7)	6.1 (4.4)	−0.41	0.68	−0.04 (−0.41 to 0.32)				
Depression (BDI-II)	MBCT	17.9 (11.4)	14.7 (10.1)	2.35	0.02*	0.30 (−0.15 to 0.74)	2.94 (0.10 to 5.78)	2.03	0.04*	0.29 (−0.12 to 0.70)
	WAIT	15.4 (9.1)	15.7 (10.1)	−0.41	0.68	−0.03 (−0.40 to 0.34)				
Quality of life (IBD-Q)	MBCT	170.5 (23.2)	172.5 (23.8)	−0.64	0.52	−0.09 (−0.53 to 0.36)	−1.70 (−8.67 to 5.28)	−0.48	0.63	−0.08 (−0.48 to 0.33)
	WAIT	172.6 (21.8)	172.4 (23.4)	0.07	0.95	0.01 (−0.36 to 0.38)				

WAIT, waiting-list; *SD*, standard deviation; *CI*, confidence interval. $n_{MBCT} = 39$; $n_{WAIT} = 57$

[a]Estimate based on adjusted means

*$p < 0.05$

Table 4 Clinically relevant improvement[a] and recovery[c] — intention-to-treat ($n = 113$)

Improved, *n* (%)				Recovered, *n* (%)			
	MBCT	WAIT	*p*		MBCT	WAIT	*p*
Improved[a]	20 (36)	6 (10)	<0.01*	Recovered[c]	12 (21)	5 (9)	0.03*
No change	32 (57)	50 (88)		Unrecovered	44 (79)	52 (91)	
Deteriorated[b]	4 (7)	1 (2)					

WAIT, waiting-list

χ^2 Chi square test for between group differences ($p < 0.05$)

[a]Reliable Change Index score > 1.96

[b]Reliable Change Index score < −1.96

[c]Subjective fatigue score < 27

one-third of patients receiving MBCT reported a clinical meaningful reduction in fatigue and one-fifth of patients were considered to be recovered, given their low levels of fatigue after the intervention. Considering that fatigue is very difficult to treat and that IBD patients often suffer from fatigue for many years without experiencing alleviation of symptoms (Klusmann et al., 2021), the current results are encouraging and of clinical relevance in the treatment of IBD-related fatigue. A more in-depth examination regarding the benefits of MBCT for different aspects of fatigue is required, using RCTs as well as qualitative interviews, to examine whether our results are replicated and to provide more insight into patients' own perceptions of the benefits of MBCT for fatigue.

The finding that a considerable group of patients did not benefit from MBCT raises the question how these patients differ from the patients who experienced an improvement in fatigue. Studies in people with other chronic somatic diseases show inconsistent results regarding the moderating role of demographic, clinical, and psychological characteristics in MBCT. Specifically, some studies indicate that gender and education play a role in the effects of MBCT on psychological outcomes (Nyklíček et al., 2016; Tovote et al., 2017), suggesting that women and people with higher educational attainment may respond better to MBCT. Others show that personality traits and psychological factors can explain psychological outcomes of MBCT (Cillessen et al., 2018; Johannsen et al., 2017; Nyklíček et al., 2016; Tamura et al., 2022). For instance, it has been found that people reporting high levels of extraversion are less likely to benefit from MBCT than people low in extraversion (Nyklíček et al., 2016). Until now, research examining possible moderators of MBCT for fatigue is lacking.

Since fatigue can have an extensive impact on patients' daily life and mood (Cohen et al., 2014; Schreiner et al., 2021), we also examined a possible wider effect of MBCT on patients' functioning besides fatigue. Considering the well-established positive effects of mindfulness-based interventions on psychological health outcomes, also in patients with IBD (Ewais et al., 2019; Hood & Jedel, 2017), we hypothesized that perceived fatigue interference, anxiety, depressive symptoms, and QoL would also improve when addressing fatigue with MBCT. It was therefore unexpected to find no significant improvements in these outcomes, when compared to the control condition. One explanation for these results may be the relatively low levels of fatigue interference, anxiety, and depressive symptoms before the start of the MBCT intervention, making it difficult to find improvements (i.e., a floor effect). This was surprising, as all patients were screened and selected on the presence of moderate to severe levels of fatigue. Since the median time since diagnosis was 11 years, it can be reasoned that, over time, the patients who participated in our trial had adjusted to the persistent fatigue and learned to live with the impact of fatigue on their lives, therefore reporting little interference and mood problems, even while experiencing fatigue (Czuber-Dochan et al., 2013). Moreover, we might have missed IBD patients who experience both severe fatigue and severe psychological symptoms, partly because we excluded patients with severe psychiatric co-morbidity and those patients receiving psychological treatment at the time of recruitment. Especially patients with severe co-occurring conditions might be in need of a psychological intervention and benefit from such additional support.

Limitations and Future Research

Although our study was carefully designed, the findings should be considered in light of several limitations. First, as the current sample size allowed us to reveal medium to large effects, we might have overlooked small effects. Second, consistent with previous MBCT studies in IBD patients, only 70% of the patients completed the intervention (Schoultz et al., 2015). Most patients dropped out because of scheduling issues with the group sessions. Offering individual MBCT could solve this issue (Schroevers & Fleer, 2019). Previous studies have also suggested that treatment adherence could be increased by offering MBCT online, as

this type of treatment would be more accessible and flexible (Bruggeman-Everts et al., 2017; Compen et al., 2018). These studies showed, however, that dropout rates of online MBCT programs were higher compared to face-to-face MBCT. Blending face-to-face with online sessions might be a suitable alternative. Other reasons for dropout might have been the intensity and time-consuming nature of the program or a disease flare-up (Schoultz et al., 2015). As dropout was unrelated to the severity of fatigue and psychological symptoms at baseline, we assume that the results are not affected by attrition bias. Another limitation is that we were limited in examining the long-term effects of MBCT for IBD-related fatigue, since the waiting-list control condition received the intervention after the post-measurement. Long-term effects of MBCT should be assessed to examine stability of effects (Farrell et al., 2020). Moreover, although sleep problems are often associated with fatigue, we did not examine sleep disturbances and we thus do not know whether sleep quality has interfered with the effects of MBCT on fatigue. It can be hypothesized that severe sleep problems might hinder the effect of MBCT on fatigue, but it is also known that mindfulness can positively affect sleep disturbances (Shallcross & Visvanathan, 2016), which could have enhanced the effect of MBCT on fatigue. Future research is needed to examine these associations and effects. A last limitation concerns the self-report measurement of disease activity. Although the mHealth Indexes show reasonable measurement properties for use in clinical trials, they demonstrate limited validity compared to more recent self-report instruments or objective measures of inflammation (de Jong et al., 2018). We recommend the additional examination of fecal calprotectin or endoscopic assessment, or the use of a newly validated and reliable short screening instrument such as the Monitor IBD At Home questionnaire (MIAH; de Jong et al., 2019) for future research.

Together with other national and international IBD professionals and researchers, we emphasize the need and importance of appropriate psychological care for fatigue in IBD patients in remission. Fatigue is a multifaceted concept with a complex and multidimensional etiology. Therefore, the treatment of fatigue may require a multimodal and personalized approach, in which patients are screened for their symptoms, and different interventions can be offered that target not only fatigue, but also psychological functioning, sleep, nutrition, and physical activity, depending on the individual patients' complaints, needs, and wishes (Borren et al., 2019). Researchers in the Netherlands have developed and implemented the telemedicine tool MyIBDCoach (de Jong et al., 2017), which successfully monitors and screens for IBD symptoms, including fatigue, on a regular basis and from home. A next step is to provide suitable and effective interventions based on the outcomes of these screening tools.

Given the low uptake of care and high dropout rates when psychological interventions are offered to patients in a medical setting, the current literature, including our study, asks for a better understanding of patients' needs, wishes, and possibilities to participate in interventions when experiencing severe fatigue. When developing new interventions, content, format, and duration could be adjusted accordingly to increase beneficial outcomes, for instance, by offering one-on-one treatment or online sessions as part of the intervention (Bruggeman-Everts et al., 2017). Alternatively, including physical activity components to the treatment of fatigue seems promising (Davis et al., 2020). We also suggest replication studies with larger sample sizes to give more robust insights into the benefits of MBCT for treating fatigue, in comparison to other (psychological) interventions. In addition, the examination of demographic, clinical, and psychological moderators, as well as underlying mechanisms of the effects of MBCT, would allow us to better understand which IBD patients benefit most from MBCT and how MBCT reduces fatigue.

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Data Transparency Statement The data and syntaxes that support the research findings are available upon reasonable request to the corresponding author. Data are not publicly available due to privacy and ethical restrictions.

Author Contribution Maya Schroevers, Gerard Dijkstra, and Joke Fleer developed the study design. Ans Smink, Gerard Dijkstra, Marijn Visschedijk, Maurice Russel, Mark van der Lugt, Maarten Meijssen, and Egbert Jan van der Wouden were responsible for patient recruitment and data collection. Greetje Kuiken, Joke Potjewijd, and Marleen Laroy provided the Mindfulness-Based Cognitive Therapy. Quirine Bredero processed the data and performed data analyses. Quirine Bredero, Maya Schroevers, and Joke Fleer interpreted the data. Quirine Bredero wrote the first draft of the manuscript with support of Maya Schroevers and Joke Fleer. All authors critically reviewed and approved the final draft of the manuscript.

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Declarations

Ethics Approval The study was approved by the Medical Ethical Review Committee of the University Medical Center Groningen (METc no. 2016/316) and conducted according to the principles of the Declaration of Helsinki (version 2013) and the Dutch Medical Research Involving Human Subjects Act (WMO). Secondary approval of the study protocol was obtained from the three participating centers.

Informed Consent All participants provided written informed consent.

Competing Interests Gerard Dijkstra reports grant from DSM Nutritional Products LTD and speakers fees from Janssen Pharmaceuticals, AbbVie, and Takeda, outside the submitted work. The other authors declare that they have no conflict of interest.

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