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Mindfulness-Based Cognitive Therapy for Patients with Medically Unexplained Symptoms: A Randomized Controlled Trial

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Key Words
Medically unexplained symptoms · Mindfulness · Randomized controlled trial · Somatoform disorders

Abstract
Background: Patients with medically unexplained symptoms make heavy demands on the health care system. An offer for psychological treatment is often declined. There is a need for acceptable and effective treatments. We assessed the acceptability and effectiveness of mindfulness-based cognitive therapy (MBCT) for patients with persistent medically unexplained symptoms. ***Method:*** A randomized controlled trial comparing MBCT (n = 64) to enhanced usual care (EUC; n = 61). Participants were the 10% most frequently attending patients in primary care. The primary outcome measure was general health status at the end of treatment. Secondary outcome measures were mental and physical functioning. Assessments took place at the end of treatment and at the 9-month follow-up. ***Results:*** Health status and physical functioning did not significantly differ between groups. However, participants in the MBCT group reported a significantly greater improvement in mental functioning at the end of treatment (adjusted mean difference, 3.9; 95% CI, 0.24–7.6), in particular with regard to vitality and social functioning. In addition, at 9 months of follow-up, the mindfulness skills 'observing' and 'describing' were significantly higher in the MBCT group. Within the MBCT group, almost half of the outcome measures had significantly improved at the end of treatment, whereas in the EUC group none had. ***Conclusions:*** MBCT was feasible for frequently attending patients with persistent medically unexplained symptoms in primary care. Although MBCT did not lead to a significant difference in general health status between the two groups, it did result in a significant improvement in mental functioning.

Introduction

Patients with medically unexplained symptoms are common. About 1 in 5 patients presenting to the general practitioner (GP) has medically unexplained symptoms [1, 2]. Often, these symptoms resolve spontaneously [3]. However, in 10–16% of primary care patients, the symptoms persist and result in functional impairment [1, 4]. Uncertainty regarding the diagnosis often leads to unnecessary and unproductive investigations, resulting in high health care costs [5, 6]. Thus, effective interventions for patients with persistent medically unexplained symptoms are needed.

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At present, cognitive behavioral therapy is the intervention of choice for persistent medically unexplained symptoms. Several studies have shown modest improvements in somatic symptoms, psychological distress and functional impairment [7–9]. However, many patients with medically unexplained symptoms do not easily accept psychological treatment [10]. Consequently, there is still a need for more acceptable treatment options.

Mindfulness-based cognitive therapy (MBCT) is a relatively recent development in the field of medicine. It consists of meditation, yoga exercises and psycho-education [11]. MBCT is a group-based skills training program intended to enable participants to become more aware of their bodily sensations, thoughts, and feelings. It has a body-focused and experiential approach, which is different from the more cognitive approaches which are used in cognitive behavioral therapy and in the reattribution model [12]. Mindfulness training is a promising line of research as it helps participants in developing the ability to tolerate symptoms while at the same time not letting the symptoms dictate behavior [8].

MBCT might be acceptable to patients with medically unexplained symptoms because it is offered as a skills training rather than as a psychological treatment. Positive effects of MBCT have been demonstrated in patients with anxiety and mood disorders [13], sleep disorders [14], fibromyalgia [15], chronic pain [16], hypochondriasis [17] and chronic fatigue syndrome [18]. The aim of this study was to examine the acceptability and effectiveness of MBCT in patients who frequently attend their GP with medically unexplained symptoms. We hypothesized that MBCT would lead to an improvement of the general health status.

Methods

Design

We used a randomized controlled design comparing MBCT in addition to enhanced usual care (EUC), with EUC only. Inclusion was carried out by a three-step procedure. First, a selection was made of the 10% most frequently attending male and female patients of the participating GPs. Second, the GPs were asked to exclude patients on the basis of the exclusion criteria for the study and we invited the remaining patients to participate in the trial. Third, the researchers determined whether patients fulfilled the inclusion criteria in a research interview. Assessments took place at baseline, at the end of treatment and at the 9-month follow-up.

Participants

We invited GPs in the area of Nijmegen, a medium-sized city in the Netherlands, to participate in the trial. Nineteen GPs agreed to participate, their practices being located in neighborhoods with both low and higher socioeconomic standards. Patients aged 18–70 and belonging to the 10% most frequently attending male and female patients of their GP were eligible for the study. Frequent attendance was calculated over a period of 1 year. Exclusion criteria were: frequent attendance for other reasons than physical symptoms, physical symptoms fully explained by somatic diseases, no significant distress or functional impairment due to the symptoms, psychosis or bipolar disorder in medical history, current alcohol or drug abuse, cognitive impairment, problems with the Dutch language, and previous MBCT. Inclusion criteria were: having had physical symptoms for at least 6 months which were not (fully) explained by a physical disease or by substance abuse, and experiencing functional impairment due to these physical symptoms.

Procedure

At first, we provided the GPs with a list of their 10% most frequently attending male and female patients, which we retrieved from the computerized database of the GP's practice. To control for gender and age differences, we selected the 10% most frequently consulting women, and the 10% most frequently consulting men in two age groups (18–44 and 45–70 years) [19]. Secondly, the GPs applied the exclusion criteria to the list of frequently attending patients. The remaining patients were sent an invitation letter which described the study, signed by their own GP. Thirdly, if interested, patients were invited by phone for a research interview. The researcher and trainee psychiatrist (H.R.) conducted the research interviews under the supervision of an experienced psychiatrist (A.S.) to assess eligibility and to gain informed consent. Patients were asked about the main physical complaint and current physical diseases. The interview included the Mini-International Neuropsychiatric Interview [20] and the section on somatoform disorders of the Structured Clinical Interview for DSM-IV Axis I disorders [21]. All GPs were informed about the assessment by a letter including the results of the psychiatric assessment. If patients were randomized to the EUC group, they were offered to participate in the MBCT after completion of the study and requested to refrain from attending an MBCT course during the study period.

All patients seen for the research interview were given a unique patient identification number. After the interview, this number was given to the research assistant who was blinded for the interview data. For randomization, the assistant used a computer-generated permuted-block randomization table with block size 20. The patient identification number was matched with the corresponding name to inform each participant about the allocation.

Assessments were done at baseline (2 weeks before start of the MBCT), at the end of treatment (within 3 months from baseline assessment) and 9 months after the end of treatment (12 months after baseline). We described the study using the CONSORT guidelines [22].

Mindfulness-Based Cognitive Therapy

Participants in the MBCT group received EUC and 8 weekly sessions of 2.5 h plus a 6-hour silent day. In addition to the group sessions, participants were instructed to practice 6 days a week for approximately 45 min a day. Our training protocol was based on the MBCT format for patients with recurrent depression [11]. We made minor adaptations to the MBCT training protocol to make it more suitable for patients with physical symptoms. The program consisted of formal meditation exercises such as body scan, sitting meditation, walking meditation and mindful movement. Partici-

pants were also encouraged to cultivate awareness of everyday activities, such as eating or taking a shower. In addition, the program included cognitive techniques such as psychoeducation, monitoring and scheduling of activities, identification of negative automatic thoughts and devising a relapse prevention plan. In the section on psychoeducation, we included information about respecting physical and mental boundaries and dealing with impairments. In line with the original Mindfulness-Based Stress Reduction format [23], we incorporated a silent day to give participants the opportunity to deepen their mindfulness practice [24]. To support home practice, patients received a folder with information about the individual sessions, homework assignments and forms to keep a record of their practice, together with CDs with guided meditations and movement exercises.

Group size varied between 7 and 14 participants. The MBCT groups were instructed by 2 experienced mindfulness trainers, who had both participated in an intensive 2-year teacher training course for mindfulness teachers and had many years of ongoing personal meditation practice. They have both taught more than 30 MBCT or Mindfulness-Based Stress Reduction courses to patients with psychiatric disorders and/or physical conditions.

In line with previous MBCT trials, an adequate dose of MBCT for the participants (i.e. the treated 'per protocol' cases) was defined as participation in at least 4 MBCT group sessions [11, 25].

Outcome Measures

Our primary outcome was the general health status assessed with the visual analogue scale (VAS) of the EuroQol 5D (EQ-5D), which ranges from 0 (worst imaginable) to 100 (best imaginable) [26].

Mental and physical functioning were measured with the summary measures [mental component summary (MCS); physical component summary] of the Medical Outcomes Study 36-Item Short Form (SF-36). MCS and physical component summary scores range from 0 to 100, higher scores corresponding to better health status [27]. We used the 8 subscales of the SF-36 to measure specific health domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health [27]. To assess physical and mental symptoms, we used the Patient Health Questionnaire (PHQ) scales for somatization (PHQ-15, scale 0–30, higher scores indicating more and/or more severe symptoms) and depressive disorder (PHQ-9, scale 0–27, higher scores indicating more and/or more severe symptoms) [28]. We used the 14-item Whitely Index to assess health anxiety (scale 0–56, higher scores indicating more anxiety) [29]. For the assessment of mindfulness skills, we used the Five-Facet Mindfulness Questionnaire, consisting of: observing, describing, acting with awareness, nonjudging of inner experience and nonreactivity to inner experience (scales 8–40; nonreactivity to inner experience scale 7–35, higher scores indicating higher levels of mindfulness skills) [30]. To assess health care use, we requested all patients to fill in monthly diaries concerning all health care contacts during the year of the study (e.g. GP visits, physiotherapy, homoeopathist, cardiologist). The research interview and the MBCT sessions were not included in the counts of health care contacts.

Sample Size

The power calculation is based on an estimate of the treatment effect on the general health status as measured with the VAS of the EQ-5D (range 0–100). We considered 10 units on the VAS as the minimum clinically relevant difference using a standard deviation of 20 points. We based this on the results of a randomized controlled trial by Blankenstein [31] with a similar study population as our population and a cross-sectional study in cancer patients [32]. Using an alpha of 0.05 and a power of 0.80, the sample size needed for an analysis of covariance (ANCOVA), controlling for baseline measurement and assuming a correlation of 0.7 ($R^2 = 0.5$), would be 64 patients in total and 32 patients per arm [33]. We also took account of the multilevel character of the data [estimated intraclass correlation coefficient (ICC) of 0.05] [34]. As a consequence, with a mean group size of 12, we needed 55% as many patients: 100 patients, 50 in each arm.

Statistical Analysis

The analysis was performed according to the principle of intention to treat, i.e. special care was taken to gather follow-up data on all patients regardless of whether they complied with the intervention they were randomized to or not [35]. A sensitivity analysis was performed with the multiple imputation technique to estimate missing values [36]. However, if patients were unable or unwilling to fill out the remaining questionnaires, we did not include these patients in the further analysis. A secondary per-protocol analysis was done with all participants who attended 4 or more sessions in the MBCT group and all of those not attending a mindfulness course in the EUC group. We assessed the heterogeneity across MBCT groups on the primary outcome measure by calculating the ICC.

Post-treatment and follow-up scores were compared between the two groups, controlling for baseline measurements. We used an ANCOVA to compare the groups with respect to changes in primary and secondary outcomes at the end of treatment and the 9-month follow-up. The ANCOVA model also included age, gender and level of education as covariates, as these might influence the effectiveness of MBCT.

In addition, in each group, we tested the difference between baseline measurements and the post-treatment and 9-month follow-up measurements using paired t tests. Effect sizes were calculated with the adjusted differences between the groups using Cohen's d formula. For the analysis of predicting factors, we have examined the effects of age, gender, level of education and the presence of physical diseases and additional psychiatric disorders on the primary outcome measure. These analyses were restricted to the patients who adhered to the study protocol.

The trial was registered at Trialregister.nl, No. NTR2222. The study obtained ethics approval from the CMO Arnhem-Nijmegen, CMO dossier No. 2009/164, ABR No. NL27551.091.09. Participants gave informed consent before taking part in the study.

Results

GPs in the region of Nijmegen were readily willing to offer MBCT to their frequently attending patients with persistent medically unexplained symptoms. Participants were recruited from December 2009 to August 2010. Of the 2,231 frequently attending patients, 1,546 (69%) were excluded by their GP, most often because they had symp-

toms which were fully explained by physical diseases or did not have physical symptoms (anymore) (fig. 1). GPs excluded significantly more men (n = 859, 77%) than women (n = 692, 62%; $p < 0.05$).

Of the 685 eligible patients, 500 (73%) were not interested in participation or did not answer the invitation letter. More than a quarter (n = 185; 27%) of the invited patients was interested in participation. From the 153 patients interviewed, 18 (12%) were excluded because they did not meet the inclusion criteria (fig. 2). Ten patients (7%) declined to participate, mostly because of a lack of time. As a result, 125 patients were included in the trial: 94 women and 31 men. The inclusion of participants ended at the scheduled date of closure.

About half of the participants were unemployed (table 1). Education levels were evenly divided among low, middle and high. In addition to the persistent medically unexplained symptoms, 95 patients (81%) had at least 1 physical disease and 34 (29%) had 3 or more physical diseases. The most frequent physical complaint was fatigue (n = 31, 26%). According to the psychiatric interview, somatization disorder was diagnosed in 15 (13%) and pain disorder in 23 (20%) patients. One third of the patients (n = 41, 35%) had a comorbid anxiety disorder, depressive disorder, or both. More than half of the patients (n = 71, 61%) used 3 or more medicines, including both prescribed and over-the-counter medication. In the year preceding participation in this study, the average number of visits to their GP was 9.8 (SD 4.8) (n = 117). Female patients had an average of 10.4 (SD 4.9) visits and males 8.1 (SD 4.0) visits, the difference being nonsignificant. Patients who withdrew before baseline assessment (n = 8) or were lost to follow-up (n = 10) did not significantly differ on baseline characteristics from the others. One patient withdrew due to a severe physical condition (newly diagnosed cancer).

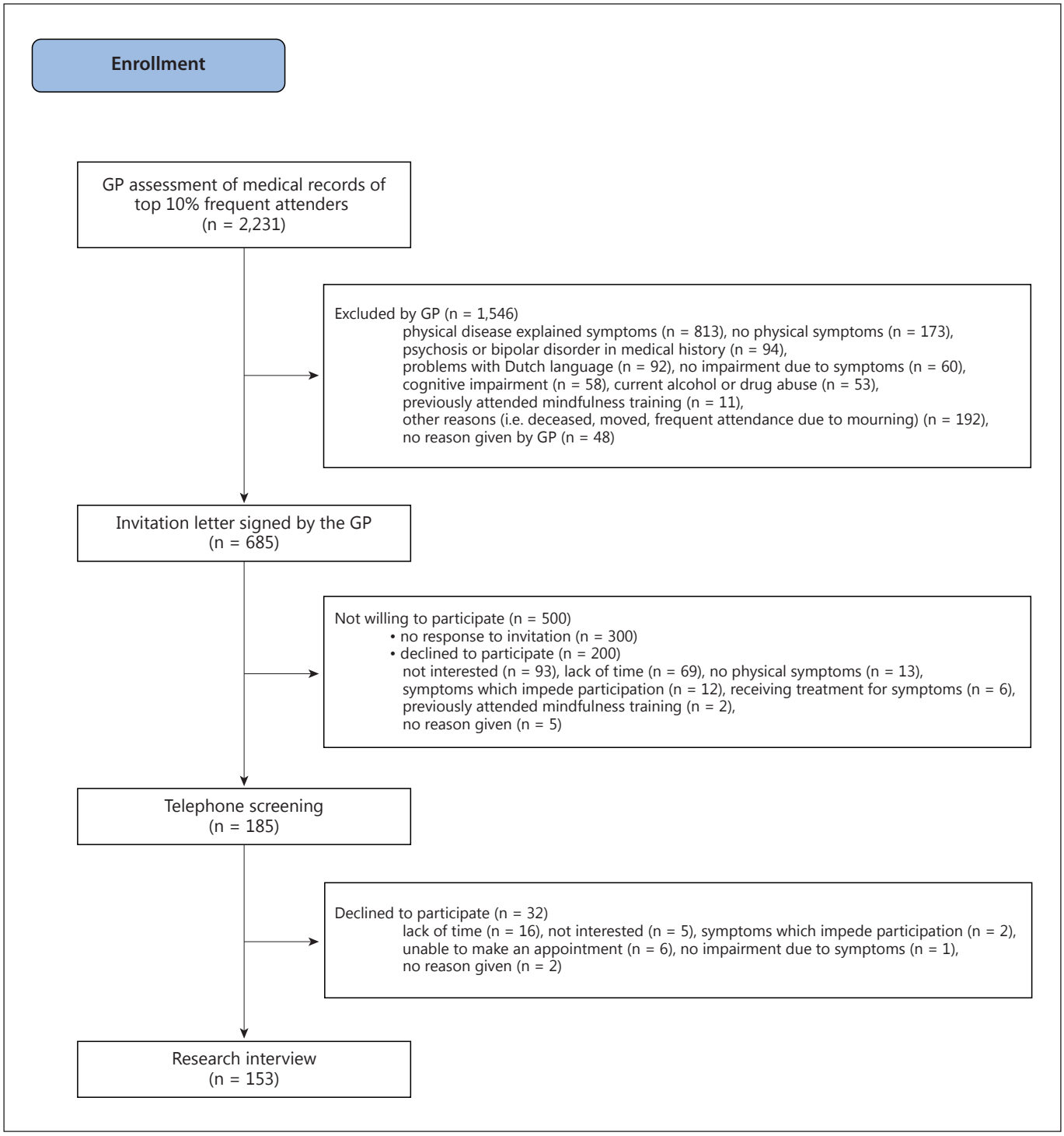
Comparing patients in the MBCT and EUC groups, there were no important differences regarding sociodemographic characteristics. With regard to somatic morbidity, patients in the MBCT group more often suffered from hypertension and joint problems, and those in the EUC group reported more neurological symptoms as their main physical symptom. Of all patients randomized to MBCT, 3 (5%) withdrew after the research interview and before the baseline questionnaire, 8 (13%) completed the questionnaire but did not start MBCT and 4 (8%) did start but did not complete 4 or more treatment sessions. Those who did not start or did not complete the training were slightly older than the completers, although this difference was not statistically significant. One patient in the EUC group received MBCT within the follow-up period.

We assessed the heterogeneity across training groups on the primary outcome measure by calculating the ICC. The highest ICC was found to be 0.031, so adjustments for clustering were not deemed necessary. A sensitivity analysis was done by using the multiple imputation tech-

Table 1. Sociodemographic and baseline clinical characteristics

	MBCT (n = 61)	EUC (n = 56)
Demographic characteristics		
Female gender	49 (80)	38 (68)
Age, mean ± SD, years	47.6±11	46.5±12
Marital state		
Married	30 (49)	22 (39)
Single/unmarried	20 (33)	20 (36)
Divorced	11 (18)	11 (20)
Widowed	0	3 (5)
Employed	29 (48)	30 (54)
Level of education		
Low	18 (30)	20 (36)
Middle	28 (46)	20 (36)
High	15 (25)	16 (29)
Born in the Netherlands	53 (87)	48 (86)
Clinical characteristics		
Main physical symptom		
Fatigue	17 (28)	14 (25)
Joint problems	12 (20)	6 (11)
Back pain	7 (12)	9 (16)
Other musculoskeletal symptom	13 (21)	10 (18)
Gastrointestinal symptom	6 (10)	7 (13)
Neurological symptom	3 (5)	8 (14)
Impairment in daily functioning		
Moderate	29 (48)	27 (48)
Severe	32 (52)	29 (52)
Physical diseases		
Hypertension	18 (30)	11 (20)
Arthrosis	11 (18)	8 (14)
Asthma/bronchitis	11 (18)	6 (11)
Diabetes mellitus type II	6 (10)	5 (9)
Psychiatric disorders		
Somatization disorder	8 (13)	7 (13)
Pain disorder	11 (18)	12 (21)
Hypochondriasis	2 (3)	1 (2)
Depressive disorder	9 (15)	13 (23)
Anxiety disorder	15 (25)	14 (25)

Figures in parentheses are percentages. Education level was classified as low (primary and lower secondary education), middle (upper secondary education) and high (higher vocational training and university).



Color version available online

Fig. 1. CONSORT 2010 flow diagram. GP assessment of the medical records of the 10% most frequently attending patients.

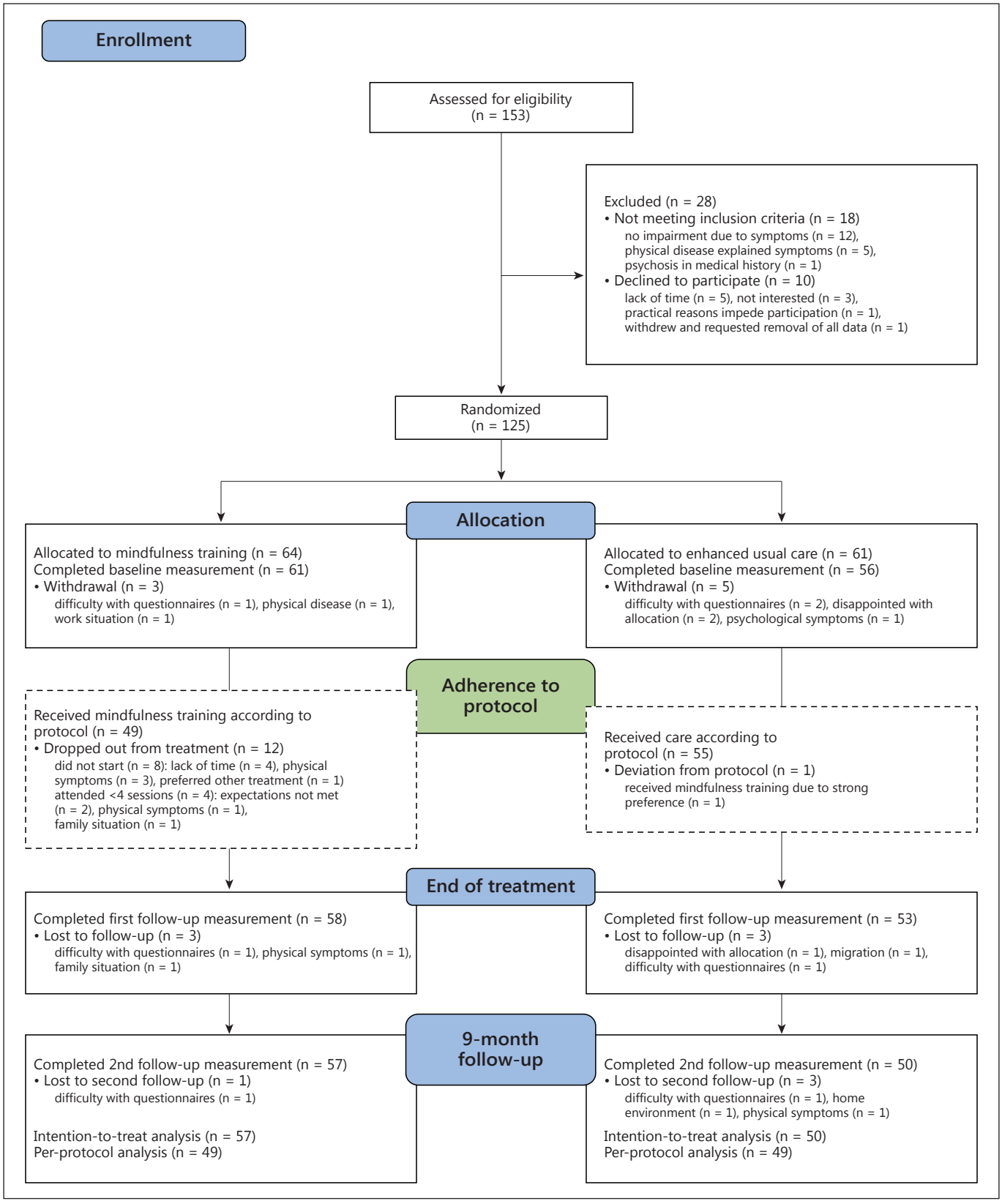


Fig. 2. CONSORT 2010 flow diagram. Patient assessment for eligibility.

Table 2. Effects of MBCT and EUC at the end of treatment and at the 9-month follow-up

	Baseline		End of treatment		9-month follow-up	
	MBCT (n = 61)	EUC (n = 56)	MBCT (n = 58)	EUC (n = 53)	MBCT (n = 57)	EUC (n = 50)
Health status						
General health status (VAS)	58.2 (17.4)	62.9 (14.4)	63.8 (17.1)[b]	64.2 (16.7)	63.5 (18.3)[b]	66.7 (16.9)
Physical functioning						
Physical functioning (PCS)	36.3 (9.62)	40.7 (9.60)	38.2 (11.0)	41.4 (11.5)	39.6 (12.1)[b]	42.7 (10.2)
Physical functioning	65.2 (22.9)	70.3 (23.0)	68.4 (24.8)	71.3 (24.9)	69.1 (27.8)	73.4 (22.6)
Physical role	27.1 (33.9)	35.7 (38.4)	36.6 (39.8)[b]	38.9 (37.8)	43.9 (42.9)[b]	56.0 (41.2)[b]
Bodily pain	48.8 (18.5)	54.2 (19.5)	53.1 (18.6)	57.8 (20.5)	56.2 (23.6)[b]	59.3 (22.1)
General health	46.3 (16.4)	50.0 (20.2)	50.6 (21.5)	51.0 (20.0)	51.7 (21.6)[b]	54.3 (19.9)
Mental functioning						
Mental functioning (MCS)	44.3 (11.5)	41.5 (11.7)	47.4 (11.6)[a, b]	42.2 (12.3)	47.0 (12.3)[b]	46.3 (10.5)[b]
Vitality	40.0 (21.3)	45.2 (21.7)	47.7 (24.3)[a, b]	45.4 (21.6)	48.3 (25.8)[b]	52.5 (22.0)[b]
Social functioning	59.4 (27.7)	64.7 (21.6)	69.6 (23.7)[a, b]	63.9 (24.5)	68.2 (28.3)[b]	72.5 (23.4)[b]
Emotional role	56.3 (41.5)	47.0 (42.5)	67.2 (40.2)[b]	52.6 (43.0)	70.2 (39.7)[b]	66.0 (39.5)[b]
Mental health	66.0 (19.1)	59.7 (20.5)	67.9 (19.6)	61.2 (18.2)	66.9 (20.1)	66.6 (17.9)[b]
Symptoms						
Physical symptoms	12.6 (4.68)	12.7 (5.15)	10.9 (4.90)[b]	12.6 (6.10)	11.0 (5.44)[b]	11.8 (5.46)[b]
Depressive symptoms	8.50 (5.11)	8.77 (5.44)	7.61 (5.92)	7.87 (5.35)	7.26 (5.61)	7.66 (5.33)[b]
Health anxiety	23.1 (8.61)	23.3 (10.3)	20.6 (9.16)[b]	21.9 (9.26)	20.6 (9.19)[b]	22.6 (10.1)
Mindfulness skills						
Observing	25.7 (6.53)	24.8 (5.08)	26.5 (5.68)	24.5 (5.22)	26.7 (5.34)[a]	24.4 (5.53)
Describing	27.1 (6.52)	26.8 (6.00)	26.9 (7.13)	26.9 (6.20)	28.5 (6.52)[a, b]	26.3 (6.93)
Acting with awareness	25.6 (6.36)	24.4 (5.44)	26.1 (6.83)	25.3 (6.37)	26.3 (6.00)	25.1 (6.19)
Nonjudging of inner experience	27.8 (6.59)	26.2 (5.47)	28.8 (6.82)	27.1 (6.53)	28.8 (5.96)	27.4 (6.25)
Nonreactivity to inner experience	20.3 (5.33)	20.2 (4.03)	21.7 (4.53)[b]	20.5 (4.68)	21.5 (4.98)[b]	21.0 (4.80)

[a] $p < 0.05$ for difference between MBCT and EUC group (ANCOVA, function score adjusted for baseline, age, gender, level of education). [b] $p < 0.05$ for difference within the MBCT or EUC group (paired-samples t test). Figures are means with SD in parentheses. MCS = Mental component summary; PCS = physical component summary.

nique [36] to assess whether missing data affected the outcomes; however, no differences were revealed.

End of Treatment

With regard to the primary outcome measure, the general health status, as measured with the EQ-5D VAS at the end of treatment, the MBCT and EUC groups did not significantly differ (table 2). However, mental functioning as assessed with the SF-36 MCS was significantly better in the MBCT than in the EUC group (adjusted difference, 3.91; 95% CI, 0.24–7.59). This also applied to 2 subscales of the SF-36: vitality (adjusted difference, 7.38; 95% CI, 1.08–13.7) and social functioning (adjusted difference, 9.45; 95% CI, 1.37–17.5). These were all small to moderate effects, with effect sizes d = 0.34 for mental functioning, d = 0.34 for vitality and d = 0.38 for social functioning. Additional information concerning the adjusted differences between the groups (ANCOVA, adjusted for baseline, gender and level of education; 95% CI) and the difference within the groups (paired-samples t test; 95% CI) is provided in table 3.

Looking at within-group differences, however, a broader picture arises. In the MBCT group, general health status significantly improved over the course of treatment, as did physical symptoms and the subscale physical role of the SF-36. Mental functioning according to the SF-36 improved, alongside the subscales vitality, social functioning and emotional role. In addition, both health anxiety and the mindfulness skill nonreactivity to inner experience (e.g. 'When I have distressing thoughts or images, I just notice them and let them go') improved. In contrast, in the EUC group, none of the outcome measures showed any significant improvement over the course of this 3-month period.

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Table 3. Differences between and within MBCT and EUC groups at the end of treatment and at the 9-month follow-up

	Difference between groups, end of treatment[a]	Difference within groups, end of treatment[b]		Difference between groups, 9-month follow-up[a]	Difference within groups, 9-month follow-up[b]	
		MBCT	EUC		MBCT	EUC
Health status						
General health status (VAS)	1.53 (–4.74 to 7.79)	6.04 (1.25 to 10.8)*	1.48 (–3.78 to 6.74)	0.68 (–6.54 to 6.68)	5.84 (1.13 to 10.3)*	2.00 (–3.22 to 7.22)
Physical functioning						
Physical functioning (PCS)	0.59 (–2.39 to 3.57)	2.00 (–0.10 to 4.09)	0.75 (–1.63 to 3.13)	–0.14 (–3.44 to 3.17)	3.20 (0.61 to 5.80)*	1.74 (–0.57 to 4.04)
Physical functioning	1.89 (–4.10 to 7.88)	3.53 (–1.07 to 8.14)	1.83 (–2.52 to 6.18)	–0.02 (–5.75 to 5.72)	3.86 (–0.69 to 8.41)	2.80 (–1.50 to 7.10)
Physical role	4.01 (–8.70 to 16.7)	9.91 (0.87 to 19.0)*	3.37 (–8.41 to 15.1)	–8.54 (–23.3 to 6.19)	16.7 (4.95 to 28.4)*	19.5 (7.21 to 31.8)*
Bodily pain	–0.73 (–6.52 to 5.07)	4.57 (–0.01 to 9.15)	3.25 (–1.39 to 7.89)	0.08 (–7.28 to 7.43)	7.54 (1.67 to 13.4)*	5.02 (–0.76 to 10.8)
General health	3.05 (–3.48 to 9.58)	5.02 (0.33 to 9.71)	0.87 (–4.23 to 5.96)	0.01 (–5.95 to 5.96)	5.86 (1.33 to 10.4)*	3.90 (–0.19 to 7.99)
Mental functioning						
Mental functioning (MCS)	3.91 (0.24 to 7.59)*	3.66 (1.00 to 6.33)*	0.69 (–2.21 to 3.59)	–0.94 (–4.66 to 2.78)	3.24 (0.27 to 6.20)*	5.28 (2.27 to 8.30)*
Vitality	7.38 (1.08 to 13.7)*	8.71 (4.06 to 13.4)*	0.77 (–3.82 to 5.36)	–1.15 (–8.42 to 6.12)	9.30 (3.88 to 14.72)*	8.90 (2.89 to 14.9)*
Social functioning	9.45 (1.37 to 17.5)*	11.4 (4.64 to 18.2)*	0.48 (–7.09 to 6.13)	–0.19 (–8.64 to 8.27)	9.21 (1.94 to 16.5)*	7.50 (0.65 to 14.4)*
Emotional role	9.41 (–4.83 to 23.6)	11.5 (1.04 to 22.0)*	5.77 (–6.38 to 17.9)	–0.25 (–13.1 to 12.6)	15.2 (5.17 to 25.2)*	18.0 (6.48 to 29.5)*
Mental health	4.15 (–1.29 to 9.58)	2.76 (–1.33 to 6.84)	1.31 (–3.18 to 5.80)	–4.05 (–9.82 to 1.73)	1.61 (–2.63 to 5.86)	8.32 (3.05 to 13.6)*
Symptoms						
Physical symptoms	–1.17 (–2.57 to 0.23)	–1.61 (–2.50 to –0.71)*	–0.54 (–1.63 to 0.56)	–0.40 (–1.99 to 1.20)	–1.44 (–2.60 to –0.28)*	–1.24 (–2.37 to –0.11)*
Depressive symptoms	–0.031 (–1.70 to 1.64)	–1.23 (–2.52 to 0.06)	–1.10 (–2.25 to 0.06)	0.22 (–1.19 to 1.63)	–0.05 (–0.16 to 0.05)	–0.16 (–0.27 to –0.05)*
Health anxiety	–1.62 (–4.00 to 0.77)	–2.36 (–4.09 to –0.63)*	0.81 (–2.71 to 1.10)	–2.04 (–4.18 to 0.10)	–2.33 (–3.95 to –0.72)*	–0.54 (–2.07 to 0.99)
Mindfulness skills						
Observing	0.92 (–0.55 to 2.39)	0.57 (–0.72 to 1.86)	–0.15 (–1.18 to 0.87)	1.40 (0.038 to 2.76)*	0.70 (–0.45 to 1.86)	–0.44 (–1.30 to 0.42)
Describing	0.05 (–1.31 to 1.41)	0.04 (–1.00 to 0.93)	–0.02 (–0.95 to 0.91)	1.80 (0.107 to 3.50)*	1.54 (0.35 to 2.74)*	–0.32 (–1.59 to 0.95)
Acting with awareness	–0.18 (–1.83 to 1.48)	0.79 (–0.57 to 2.14)	0.90 (–0.07 to 1.88)	0.43 (–1.47 to 2.34)	0.93 (–0.50 to 2.36)	0.98 (–0.57 to 2.53)
Nonjudging of inner experience	0.89 (–0.92 to 2.71)	0.98 (–0.47 to 2.43)	0.63 (–0.60 to 1.87)	0.40 (–1.27 to 2.07)	1.11 (–0.09 to 2.30)	1.08 (–0.26 to 2.41)
Nonreactivity to inner experience	1.36 (–0.18 to 2.90)	1.55 (0.22 to 2.88)*	0.25 (–0.92 to 1.42)	0.30 (–1.29 to 1.87)	1.25 (0.09 to 2.40)*	1.14 (–0.11 to 2.39)

* $p < 0.05$. Figures in parentheses are 95% CI. PCS = Physical component summary.
[a] ANCOVA, function score adjusted for baseline, age, gender, level of education.
[b] Paired-samples t test.

The per-protocol analysis did not reveal relevant differences on the primary outcome. In the per-protocol analysis (n = 98), the level of health anxiety showed statistically significant differences between the MBCT and EUC group in terms of health anxiety (p = 0.05) and nonreactivity to inner experience (p = 0.04).

Nine-Month Follow-Up

At the 9-month follow-up (table 2), the MBCT and EUC groups showed some significant differences in terms of mindfulness skills: the MBCT group reported more observing skills (adjusted difference, 1.40; 95% CI, 0.038–2.76) (e.g. 'I pay attention to physical experiences, such as the wind in my hair or sun on my face') and describing skills (adjusted difference, 1.80; 95% CI, 0.107–3.50) (e.g. 'I'm good at finding words to describe my feelings') than the EUC group.

Again, the within-group differences give a fuller picture of the changes over time. In comparison with the start of treatment, the MBCT group reported significant improvements with regard to the general health status, physical and mental functioning according to the SF-36 and 6 out of 8 subscales of the SF-36: physical role, bodily pain, general health, vitality, social functioning and mental health. In addition, they reported lower levels of physical symptoms and health anxiety, alongside higher levels of the mindfulness skills describing and nonreactivity. This time, the EUC group also showed some improvements, particularly with regard to their mental functioning. They reported improvements in the MCS of the SF-36, the subscales vitality, social functioning, emotional role and mental health, and depression. They also experienced less physical symptoms and had lower scores on the physical role subscale of the SF-36.

Health Care Use

Health care use during the year of the study was recorded each month by 55 (90%) patients in the MBCT group and 41 (73%) patients in the EUC group. Overall, health care use did not differ significantly between the two groups. In the MBCT group, the median of health care contacts was 26 (range 0–129, mean 38, SD 35) and in the EUC group it was 22 (range 0–166, mean 39, SD 41).

Predicting Factors

A subgroup analysis was performed on a per-protocol basis to check for relevant interactions. Gender, level of education, the presence of physical diseases and the presence of psychiatric disorders did not show significant interactions with any of the 3 main outcome measures (VAS EQ-5D, MCS and physical component summary). The only interaction that proved significant was that between age and physical functioning at the 9-month follow-up (estimated difference per year, –0.40; 95% CI, –0.69 to –0.10). This indicates that higher age had a stronger negative influence on physical functioning in the MBCT than in the EUC group.

Discussion

This is the first randomized controlled trial about MBCT in patients with persistent medically unexplained symptoms in primary care. The intervention seemed to be feasible for patients with unexplained symptoms, but MBCT did not result in an improvement in the general health status. However, mental functioning had significantly improved after the MBCT training, in particular vitality and social functioning had improved. Although the differences between the two groups were modest, the within-group comparisons were more revealing. After completing the MBCT course, participants reported improvements in 9 out of 19 outcome measures: general health status, physical symptoms, physical role, mental functioning, vitality, social functioning, emotional role, health anxiety and nonreactivity. In contrast, at the end of treatment, no significant changes in any of these outcome measures were demonstrated in the EUC group.

Although the validity of existing mindfulness measures, such as the Five-Facet Mindfulness Questionnaire, has recently been under scrutiny [37], we did demonstrate changes in mindfulness skills, such as observing, describing and nonreactivity to inner experience. This is particularly interesting in the light of the fact that patients with persistent medically unexplained symptoms are sometimes described as 'alexithymic', i.e. having difficulty with recognizing and describing emotions [38, 39]. In addition, although only 3 out of 117 patients had a diagnosis of hypochondriasis, there were significant decreases in health anxiety within the MBCT group both at the end of treatment and at the follow-up. So, cognitive processes such as mindfulness skills and health anxiety might be more addressed by MBCT than the physical symptoms themselves and their resulting impairment.

The effect size of MBCT on mental functioning after treatment was similar to that in studies of MBCT for chronic somatic conditions. In a recent review by Bohlmeijer et al. [40], MBCT appeared to have small effects on depression (d = 0.26) and on anxiety (d = 0.24). In our

study, the effect size of MBCT on mental functioning at the post-treatment measurement was d = 0.34. In Denmark, Fjorback et al. [41, 42] recently completed a randomized controlled trial on the effectiveness of mindfulness training for patients with somatization disorder and functional somatic syndromes in secondary care. In their severely affected population, mindfulness training was acceptable and feasible, and 88% completed the treatment. At the end of treatment, the mindfulness group showed more improvement in physical functioning (SF-36) than the control group. However, at the 15-month follow-up, the control group had improved as well. Although our population seemed to be less severe, our results are comparable. Our results concerning mental functioning, health anxiety and mindfulness skills show a greater improvement than the results in the studies by Fjorback et al. [41, 42].

With regard to the intervention itself, we did not systematically assess the treatment integrity and therapist competency. Instruments which have recently been developed to assess therapist competency in mindfulness-based interventions [43] were not available when we started the study. However, the trial therapists were both adequately trained and had a long-standing professional experience and personal meditation practice. They were both mindfulness trainers on an earlier trial of MBCT for recurrent depression [44], which demonstrated the effectiveness of MBCT with an effect size of d > 0.5. Their ratings based on videotaped therapy sessions of a current trial of MBCT [44] were competent or above. Another factor that might have influenced the effectiveness of the training is the compliance of the patients. Unfortunately, we did not keep a record of their compliance with the homework exercises. The fact that both groups showed improvements over time might be attributable to the selection of patients in a period when their symptoms were most severe, after which the symptoms generally gradually diminished. This phenomenon is known as 'regression to the mean'. In addition, in both groups, a proportion of the patients might have improved naturally, whether or not due to the unrestricted utilization of 'usual care' [45]. Health care use was similar in both groups, with a median of about 25 contacts (e.g. with physiotherapist, GP, specialist) per person per year.

In addition, it is not unlikely that the participation in the study itself led to an additional improvement in the control group. To begin with, these participants were willing to participate in this study, so they showed 'readiness for change'. A thorough research interview was done, which might have led to new insights in some patients. Also, GPs received a letter about the diagnostic assessment, which included a new psychiatric diagnosis in 30% of the patients. This might have led to a more effective treatment of psychiatric symptoms which could also affect their physical well-being. Moreover, the patients in the EUC group, just like those in the MBCT group, filled out many questionnaires over the year which might have made them more aware of their coping style.

It is encouraging that more than a quarter of the invited patients was interested in MBCT and that it was feasible for the participants to take part in MBCT, especially when taking into account the high level of patient involvement required in MBCT. Given the many improvements in the patients participating in the MBCT group over the course of treatment and at the 9-month follow-up, mindfulness has the potential to become a valuable contribution to the scarce therapeutic arsenal for persistent medically unexplained symptoms. Further research is needed to tailor the intervention to the particular needs of these patients and to select or develop more suitable outcome measures. It might be interesting to compare the MBCT to other interventions like cognitive behavioral therapy [46], acceptance and commitment therapy or other specific group interventions for medically unexplained symptoms [47].

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