Systematic Review

Mindfulness Meditation for Fibromyalgia Syndrome: A Systematic Review and Meta-analysis

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Disclaimer: S. Meng and C. Cao contributed equally and should be considered as co-first authors. This research was supported in part by research grants from the Yongchuan Natural Science Foundation of Chongqing, People's Republic of China (2023yc-jckx20059 to CFC). The Chongqing Science and Technology Commission and Chongqing Health and Family Planning Commission jointly funded the TCM science and technology project (ZY201802055).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Article received: 03-28-2024
Revised article received: 04-30-2024

Background: The effectiveness of mindfulness meditation (MM) for the treatment of fibromyalgia syndrome (FMS) is unknown and needs to be updated.

Objective: This study aimed at investigating the effectiveness of MM for the treatment of FMS.

Study Design: A systematic review and meta-analysis.

Methods: A comprehensive search of relevant studies published from the databases' inception through April 12, 2023 was conducted within the following databases: Cochrane Library, Embase, MEDLINE, PubMed, Clinicaltrials.gov, and PsycINFO. We included randomized controlled trials that reported at least one of the following outcome indicators: the Fibromyalgia Impact Questionnaire (FIQ), the Pittsburg Sleep Quality Index (PSQI), the Beck Depression Inventory (BDI), and the Perceived Stress Scale (PSS). Results are presented in terms of mean difference (MD), supplemented by 95% CIs The I^2 statistic assessed heterogeneity across 3 distinct observational time frames. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to appraise the robustness of the evidence.

Results: Ten randomized controlled trials were selected from 1,377 citations (n = 818). Various MM regimens were reported (type of mindfulness, duration, schemes, and ingredients). Among 818 patients, very low to moderate evidence indicated that MM could reduce FIQ in the short-term (MD = -6.20; 95% CI,-8.51 to -3.89; $P < 0.05$; GRADE: moderate); a lower PSQI score (MD = -1.84; 95% CI, -3.35 to -0.33; $P < 0.05$; GRADE: very low); a reduce BDI score (MD = -3.26; 95% CI, -5.77 to -0.76; $P < 0.05$; GRADE: moderate); and a decreased PSS score (MD = -4.85; 95% CI, -8.22 to -1.49; $P < 0.05$; GRADE: very low). At medium-term follow-up, MM consistently reduced the BDI score (MD = -2.88; 95% CI, -4.98 to -0.79; $P < 0.05$; GRADE: moderate) and decreased the PSS score (MD = -2.76; 95% CI, -4.82 to -0.70; $P < 0.05$; GRADE: moderate) but there was no significant difference in FIQ scores (MD = -2.78; 95% CI, -6.32 to 0.76; $P > 0.05$; GRADE: low) and PSQI scores (MD = -1.28; 95% CI, -3.35 to -0.80; $P > 0.05$; GRADE: very low). However, at long-term follow-up, MM still reduced FIQ scores (MD = -6.09; 95% CI, -9.01 to -3.16; $P < 0.05$; GRADE: moderate).

Limitations: The relatively small sample size and the average quality of the included studies may have introduced biases. The time and method of meditation in the included studies were not completely unified, and there were confounding factors. Additionally, the limited amount of available literature is a challenge. Despite focusing on randomized controlled trials, there is heterogeneity among these studies. Future research should aim for larger, higher-quality studies to address these limitations and provide a more comprehensive understanding of MM's effectiveness in fibromyalgia management.

Conclusions: Very low to moderate evidence shows that MM improves quality of life, relieves stress, and relieves insomnia and depression in patients with FMS in the short-term. Notably, the improvement in depression and stress levels continued into the medium-term period. Furthermore, quality of life improvement was discernible at long-term follow-up. This suggests that MM can be used as an adjunct therapy for FMS.

Accepted for publication:
07-09-2024

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International Prospective Register of Systematic Reviews (PROSPERO) Registration Number: CRD42023442356

Key words: Fibromyalgia, fibromyalgia syndrome, mindfulness meditation, meta-analysis, systematic review, musculoskeletal disease

Pain Physician 2024: 27:479-494

Fibromyalgia syndrome (FMS) is a multifaceted syndrome characterized by heightened pain responses, musculoskeletal aches, and an array of systemic manifestations (1). Clinically, it emerges as the second most prevalent rheumatologic ailment following osteoarthritis, affecting between 2%-8% of the general populace, with a marked predominance in women. This condition can manifest at any time, spanning from early childhood to mature adulthood (2).

Delving into its pathogenesis, the underpinnings remain enigmatic. Hypotheses include potential dysfunctions in the autonomic, central, and peripheral nervous systems, coupled with aberrations in cerebral function, discernible neuroimaging anomalies, and interplay of genetic and environmental determinants (3). While a subset of patients with fibromyalgia predominantly contend with pain, a broader spectrum faces auxiliary challenges, including fatigue, sleep disturbances, cognitive lapses, and depression (4). Consequently, fibromyalgia causes a pronounced deficiency in social and occupational responsibilities, alongside a substantial strain on health care systems.

In managing fibromyalgia, the foremost emphasis is placed on alleviating symptoms. The typical pharmacological regimen encompasses antidepressants, pain relievers, and sedatives. Given its pervasive nature and the ramifications of sustained pain medication usage, there is an increasing movement toward exploring adjunctive therapeutic strategies and medication-free alternatives (5).

Currently, the most advocated treatment approach for managing fibromyalgia is physical exercise, with both strength training and aerobic workouts demonstrating effectiveness (6-8). Additionally, augmenting with vitamin D, engaging in myofascial relaxation therapy, experimenting with hydrotherapy, and receiving psychological education have also shown some effectiveness in mitigating fibromyalgia symptoms (9-12).

Clinical research on mindfulness meditation (MM) as a therapeutic intervention for fibromyalgia is sparse, necessitating further investigation. Mindfulness, defined as the intentional act of directing one's awareness to the present moment and accepting the evolving experience without judgment (13), was originally introduced by Jon Kabat-Zinn and his colleagues at the University of Massachusetts Medical School in 1979, primarily to alleviate the profound stress experienced by outpatients (14,15). Central to mindfulness-based stress reduction is an 8-week structured course, where patients engage in weekly sessions ranging from 2.5 to 3.5 hours, typically within a group of 10 to 20 individuals (16). Central to MM is the cultivation of acute awareness and minimized distraction in relation to one's mental processes. This is achieved through a variety of mechanisms, including heightened emotional awareness, modified emotional responses, exposure and extinction practices, and the enhancement of cognitive reappraisal (17). Furthermore, long-term meditation and mindfulness practices have been linked to significant neurobiological modifications within the brain, leading to improved bodily functions (18).

In 2013, Lauche, et al (19) performed a meta-analysis revealing that mindfulness-based stress reduction has a discernible short-term supporting role in alleviating pain and enhancing the quality of life for patients with fibromyalgia. Nevertheless, the corpus of pertinent studies is relatively small; Lauche, et al (19) analyzed only 5 randomized controlled trials (RCTs); there are no intermediate- and long-term follow-up studies. Consequently, additional research and investigation are imperative to acquire a thorough understanding of this subject.

Recently, a number of studies on treating fibromyalgia with MM have been updated. Therefore, we designed our study to undertake a systematic review and meta-analysis to reevaluate the clinical effectiveness of MM in treating fibromyalgia. Our hypothesis posits that MM exerts a substantial therapeutic impact on fibromyalgia. Our objective was to rigorously investigate this area, with the aim of furnishing more compelling evidence in order to enhance clinical practice.

Methods

Protocol and Registration

This systematic review and meta-analysis was con-

ducted in strict adherence to the guidelines described in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2020 (PRISMA-P) (20). The research is duly registered with the International Prospective Registry of Systematic Reviews (PROSPERO) bearing the registration number CRD42023442356.

Search Strategy

Comprehensive searches were undertaken across prominent databases: the Cochrane Library, Embase, MEDLINE, PubMed, Clinicaltrials.gov, and PsycINFO. The search spanned from the databases' inception through April 12, 2023, aiming to systematically gauge the collective influence of MM on FMS. Two experienced reviewers (Meng and Cao) with a rich history of identifying pertinent studies, meticulously crafted the search strategies. Key search terminologies encompassed "FMS," "fibromyalgia," "fibromyalgia syndrome," "musculoskeletal disease," "chronic pain syndrome," "mindfulness," "meditation," "mindfulness meditation," and "meditation awareness training." The search was unbounded by language barriers, as detailed in Table 1. The focus remained steadfast on retrieving and assessing only RCTs. For a more comprehensive approach, both authors also scrutinized the reference sections of relevant articles to identify additional potential studies for consideration.

Selection of Studies

The inclusion criteria for the study were as follows: 1) RCTs that used an FMS diagnosis based on the criteria set by the American College of Rheumatology (21-23); 2) comparisons between MM interventions and either no treatment or alternative treatment modalities; 3) the inclusion of at least one outcome measure pertinent to FMS symptoms, such as quality of life, sleep quality, depression levels, and stress levels; 4) accessibility to the full, original published article; 5) emphasis on offline instructional methodologies, excluding online formats; 6) follow-up duration—the study imposed no restrictions on the follow-up duration. Short-term effects were identified as outcomes assessed immediately postintervention. Medium-term effects were determined based on evaluations conducted nearest to 3 months postrandomization, while long-term effects were gauged from measurements taken at the closest point to 6 months following postrandomization (19,24).

Our analysis omitted retrospective, clinically controlled, and cohort studies. Two authors (Meng and Cao) conducted an independent scrutiny of the identified studies. In the initial phase, titles were evaluated, and any duplicate entries were discarded. Thereafter, a comprehensive review of full papers and their corresponding abstracts was undertaken to filter out articles unrelated to our study's central theme. Data Extraction

We extracted data from all studies meeting the inclusion criteria. Independently, 2 authors (Meng and Cao) scrutinized the data from each publication. If there were no raw data available, we requested it from the original authors via email. If the data were unattainable, the study was excluded. Throughout the study inclusion process, we meticulously screened them according to our predetermined criteria to guarantee the study's quality and its alignment with our research objectives. Any arising discrepancies were reconciled through mutual agreement. If consensus proved elusive, a third author (Zhang) provided a decisive evaluation and facilitated further discussion to reach consensus.

Risk-of-Bias Assessement of Included Studies

Two independent authors (Meng and Cao) evaluated the risk-of-bias for each study, employing the Cochrane Collaboration's Risk-of-Bias 2 tool. This tool incorporates optional judgments regarding the direction of bias across various domains. The evaluation centered on 5 pivotal domains: the process of randomization, adherence to intended interventions, instances of missing outcome data, the accuracy of outcome measurement, and the selectivity of reported outcomes. Discrepancies between the 2 reviewers were addressed through deliberation. If a consensus remained in doubt, a third author (Zhang) arbitrated the final decision.

Treatment Effect Assessment

We conducted our meta-analysis with RevMan RevMan 5.4.1 software (The Nordic Cochrane Centre for The Cochrane Collaboration) and Stata 12 (StataCorp, LLC). For continuous data, when the heterogeneity was less than 50%, we used a fixed-effects model to reduce the potential influence of confounding variables on the results. If the heterogeneity was ≥ 50%, we used a random-effects model to assess the heterogeneity among different studies. Additionally, we established a 95% CI for each effect size in order to more accurately assess the credibility of the research results. In order to evaluate the robustness of the evidence, the online iteration of GRADEpro GDT software (https://www.gradepro.org/) was deployed; evidence strength was stratified as high, moderate, low, or very low.

Table 1. *Search strategy and results.*

Database	Step	Search Algorithm	Items Found
PubMed	#1	fibromyalgia	9,781
	#2	fibromyalgia syndrome	13,829
	#3	musculoskeletal disease	1,222,442
	#4	chronic pain syndrome	23,118
	#5	FMS	11,360
	#6	1 OR 2 OR 3 OR 4 OR 5	1,252,027
	#7	mindfulness	25,756
	#8	meditation	9,344
	#9	mindfulness meditation	3,292
	#10	meditation awareness training	444
	#11	7 OR 8 OR 9 OR 10	31,808
	#12	6 AND 11	621
Embase	#1	'fibromyalgia'/exp	25,178
	#2	'fibromyalgia syndrome':ab,ti	3,344
	#3	'musculoskeletal disease':ab,ti	1,858
	#4	'chronic pain syndrome':ab,ti	1,347
	#5	'fms':ab,ti	11,606
	#6	1 OR 2 OR 3 OR 4 OR 5	37,761
	#7	'mindfulness':ab,ti	15,005
	#8	'meditation':ab,ti	8,693
	#9	'mindfulness meditation':ab,ti	1,628
	#10	'meditation awareness training':ab,ti	6
	#11	7 OR 8 OR 9 OR 10	20,718
	#12	6 AND 11	257
Cochrane	#1	MeSH descriptor: [Fibromyalgia] explode all trees	1,950
	#2	fibromyalgia syndrome	1,300
	#3	musculoskeletal disease	7,767
	#4	chronic pain syndrome	5,549
	#5	FMS	943
	#6	1 OR 2 OR 3 OR 4 OR 5	10,181
	#7	mindfulness	8,347
	#8	meditation	4,257
	#9	mindfulness meditation	2,199
	#10	meditation awareness training	335
	#11	7 OR 8 OR 9 OR 10	10,405
	#12	6 AND 11	189

Database	Step	Search Algorithm	Items Found
MEDLINE	#1	"Fibromyalgia"	8,654
	#2	"fibromyalgia syndrome"	2,214
	#3	"musculoskeletal disease"	1,361
	#4	"chronic pain syndrome"	788
	#5	"FMS"	10,787
	#6	#1 OR #2 OR #3 OR #4 OR #5	20,707
	#7	"mindfulness"	12,961
	#8	"meditation"	7,912
	#9	"mindfulness meditation"	1,297
	#10	"meditation awareness training"	6
	#11	#7 OR #8 OR #9 OR #10	17,794
	#12	#6 AND #11	99
PsycINFO	#1	"Fibromyalgia"	3,612
	#2	"fibromyalgia syndrome"	1,295
	#3	"musculoskeletal disease"	444
	#4	"chronic pain syndrome"	1,313
	#5	"FMS"	1,120
	#6	#1 OR #2 OR #3 OR #4 OR #5	5,581
	#7	"Mindfulness"	18,273
	#8	"Meditation"	8,854
	#9	"mindfulness meditation"	2,507
	#10	"meditation awareness training"	40
	#11	#7 OR #8 OR #9 OR #10	23,709
	#12	#6 AND #11	101
Clinicaltrials.gov	#1	"Fibromyalgia"	3,612
	#2	"fibromyalgia syndrome"	1,295
	#3	"musculoskeletal disease"	444
	#4	"chronic pain syndrome"	1,313
	#5	"FMS"	1,120
	#6	#1 OR #2 OR #3 OR #4 OR #5	5,581
	#7	"Mindfulness"	18,273
	#8	"Meditation"	8,854
	#9	"mindfulness meditation"	2,507
	#10	"meditation awareness training"	40
	#11	#7 OR #8 OR #9 OR #10	23,709
	#12	#6 AND #11	101

Heterogeneity Assessment

The heterogeneity among comparison trials was rigorously assessed using the standard Cochran's Q tests in conjunction with the I^2 statistic, prior to conducting the meta-analysis. The interpretation of I^2 values strictly adhered complied to the established guidelines delin-

eated by Deeks (25). $P < 0.05$ was considered statistically significant.

Sensitivity Analysis

A sensitivity analysis was undertaken to discern the influence of studies characterized by both high-risk and low-risk biases. Furthermore, the potential effect of studies manifesting significant shortcomings in one or multiple pivotal domains was evaluated.

Results

Included Studies

The search strategies for the literature and the corresponding results are illustrated in Fig. 1. An initial screen identified 1,377 pertinent studies, comprising 621 citations from PubMed, 189 from Cochrane, 257 from Embase, 99 from MEDLINE, 101 from PsycINFO, and 110 from clinicaltrials.gov. From this pool, 12 RCTs met the inclusion criteria, with 10 being incorporated into the meta-analysis. Two studies were excluded during the primary screening since they centered on online modalities rather than offline interventions.

Trial Locations

The included RCTs primarily originated from North America and Europe. Specifically, 5 studies were from the United States, 3 from Spain, one from Germany, and the remaining one from the United Kingdom.

Patient Data

A total of 818 patients were encompassed in the analysis: 434 were allocated to an MM intervention group, and 384 were in a control group. The average age for the MM groups was 49.5 years, with a range of 44.3 to 53.4 years. Conversely, the control groups had an average age of 50.0 years, ranging between 47.3 and 52.7 years. Gender distribution was reported in all studies, revealing a significant predominance of women. In the MM groups, there were 418 women and 16 men, while the control groups had 371 women and 13 men. The average follow-up period was 4.1 months, with a range from 2 to 12 months. The mean disease duration, based on data from 10 studies, was 8.9 years, ranging from 3.8 to 22.5 years. The detailed overview of the above-mentioned study attributes is listed in Table 2.

Risk-of-Bias of Included Studies

Two studies (26,27) were assessed as having a low risk-of-bias (Fig. 2). Four studies (28-31) raised risk-of-bias concerns: an unclear randomization process (29), deviations from intended interventions (30,31), and missing outcome data (28,30,31). The remaining 4 studies were deemed to have a high risk-of-bias (32-35).

Mindfulness Meditation Intervention Sessions and Data Analysis Time Points

From the 10 considered studies, 9 implemented MM interventions over an 8-week period, while one study spanned 7 weeks. Table 3 shows the detailed information about the specifics of the MM interventions, including duration, sessions, and integral components. For the purposes of the pooled analysis, we incorporated the 9 studies with 8-week sessions as the endpoint for treatment completion.

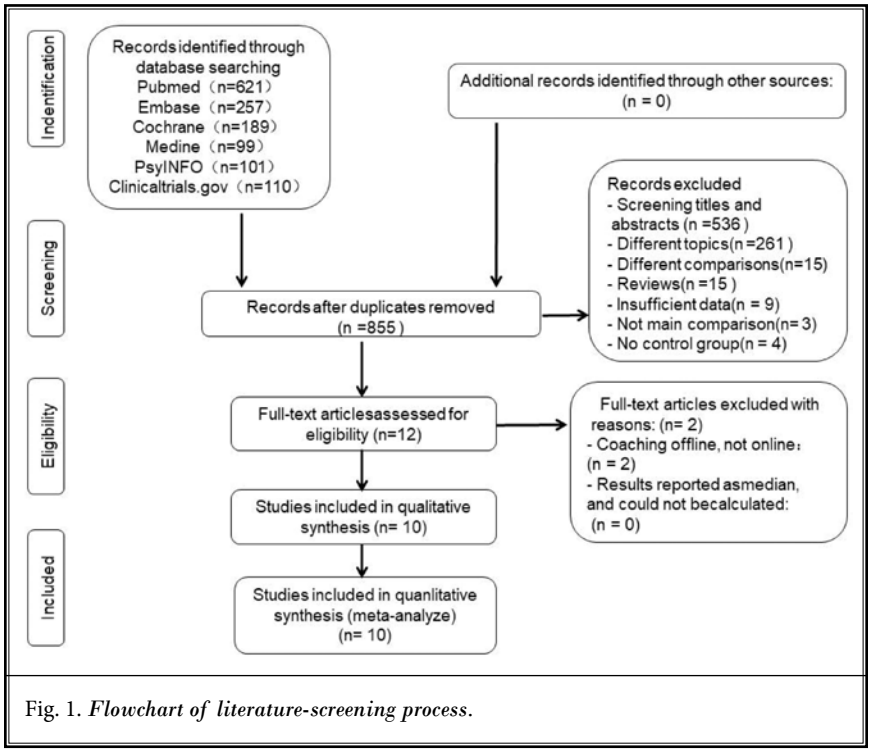

Fig. 1. *Flowchart of literature-screening process.*

Table 2. *Detailed information and characteristics of included studies.*

Studies	Country	Age (y)		Women/Men		Sample Size		Duration (y)		Follow-up (mo)
		MM	Control	MM	Control	MM	Control	MM	Control	
Astin, et al 2003 (32)	United States	47.7 ± 10.6	47.7 ± 10.6	63/1	64/0	64	64	4.9 ± 4.15	5.2 ± 7.31	6
Amutio, et al 2018 (28)	Spain	NA	NA	20/0	19/0	20	19	NA	NA	3
Cash, et al 2014 (33)	United States	NA	DNA	51/0	40/0	51	40	NA	NA	2
Carson, et al 2016 (29)	United States	49.7 ± 17.0	NA	7/0	NA	7	NA	8.4 ± 7.6	NA	3
Lush, et al 2009 (34)	United States	44.3 ± 11.25	NA	24/0	NA	24	NA	NA	NA	2
Schmidt, et al 2011 (26)	Germany	53.4 ± 8.7	51.9 ± 9.2	53/0	56/0	53	56	4.6 ± 4.06	3.8 ± 3.64	2
Sephton, et al 2007 (30)	United States	48.4 ± 8.9	47.6 ± 11.5	51/0	40/0	51	40	4.5 ± 3.6	4.9 ± 5.2	2
Van Gordon, et al 2016 (27)	United Kingdom	46.41 ± 9.06	47.34 ± 9.83	61/13	62/12	74	74	NA	NA	6
Perez-Aranda, et al 2019 (35)	Spain	52.96 ± 7.98	52.65±8.52	73/2	74/1	75	75	NA	NA	12
Parra-Delgado, et al 2013 (31)	Spain	53.1 ± 10.50	52.6 ± 10.58	15/0	16/0	15	16	21.7 ± 16.64	22.5 ± 13.84	3

MM: mindfulness meditation; NA: not available

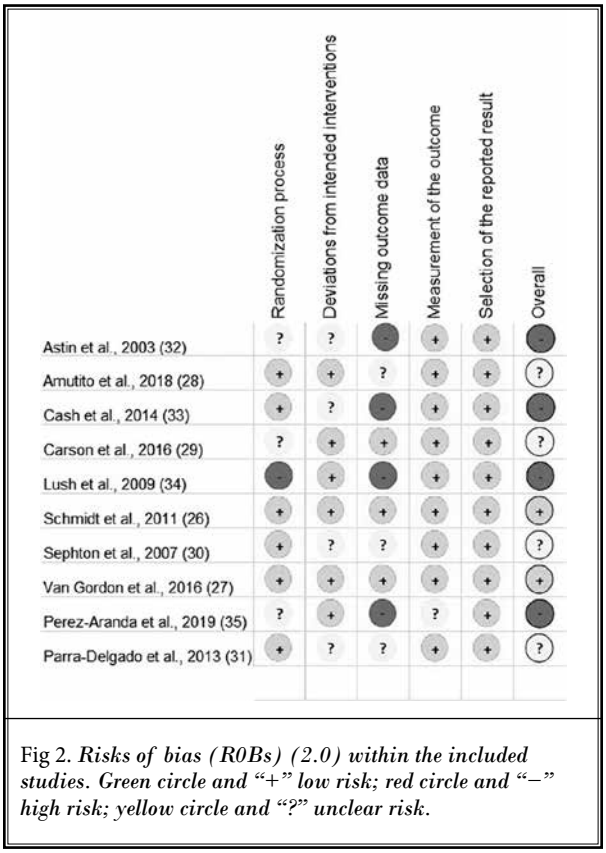

Fig 2. *Risks of bias (R0Bs) (2.0) within the included studies. Green circle and "+" low risk; red circle and "–" high risk; yellow circle and "?" unclear risk.*

Primary Outcome Measures

Fibromyalgia Impact Questionnaire (FIQ)

Six studiescompared FIQ scores between the MM and control groups at preintervention (26,27,31-33,35) (Fig. 3a). Test statistics revealed relatively low heterogeneity across these studies (I^2 = 29%). Utilizing a fixed-effects model, the findings demonstrated no statistically significant disparity between the 2 groups (mean difference [MD] = 1.69; 95% CI, -0.33 to 3.7; P > 0.05; Grading of Recommendations Assessment, Development, and Evaluation [GRADE]: moderate; Table 4). This suggests that the data from both groups were homogenous prior to the intervention, thereby facilitating further analysis and comparison.

Five studies conducted a comparative analysis of FIQ scores post the culmination of the MM sessions (26,27,31,33,35) (Fig. 3b). The heterogeneity among the studies is relatively low (I^2 = 25%). Employing a fixed-effects model, the results revealed that, relative to the control group, there was a significant improvement in the symptoms of patients in the intervention group over the short-term (MD = -6.20; 95% CI, -8.51 to -3.89; P < 0.05; GRADE: moderate).

Four studies conducted a comparative analysis of FIQ scores between the MM and control groups at

Table 3. *Detailed information and characteristics of mindfulness meditation.*

Studies	Intervention		Duration (h)	Sessions	Ingredients
	MM	Control			
Astin, et al 2003 (32)	MM with qigong	education support	2.5	8 wk of treatment, once a week, each time 2.5 h	body scan, sitting meditation, the practice of qigong
Amutio, et al 2018 (28)	Flow-Meditation	education support	0.67	7 wk of treatment, 40 min/d	mindful body-scan, full awareness of breathing exercises
Cash et al 2014 (33)	MBSR	wait	no intervention	8 wks of treatment, 6 d/wk, 45 min a day	attention-focusing technique, sitting meditation, a series of yoga positions
Carson, et al 2016 (29)	Mindful Yoga	NA	2	8 wk of treatment	gentle stretching poses, mindfulness meditation, breathing techniques
Lush, et al 2009 (34)	MBSR	NA	2.5	8 wk of treatment, once a week, 2.5 h each time	body scan, sitting meditation, hatha yoga
Schmidt, et al 2011 (26)	MBSR	wait	no intervention	8w of treatment, 45-60 min/d	mindfulness practice, mindful awareness of dynamic yoga postures, social interactions
Sephton, et al 2007 (30)	MBSR	wait	no intervention	8 wk of treatment, 6 d/wk, 30-45 min each time	stress management
Van Gordon, et al 2016 (27)	MAT	cognitive behaviour theory	2	8 wk of treatment, once a week, 2 h each time	meditatively observing, compassion meditation, engage in mindfulness
Perez-Aranda, et al 2019 (35)	MBSR+TAU	Treatment as usual	2	8 wk of treatment, once a week, 2 h each time	Hatha yoga, sitting and walking meditation, body scan
Para-Delgado, et al 2013 (31)	MBCT	treatment as usual	NA	8 weeks of treatment, 6 times a week	body scan, sitting meditation, walking meditation or mindful breathing

MM: mindfulness meditation; MBSR: Mindfulness-based Stress Reduction; MAT: meditation awareness training; MBCT: Mindfulness-based Cognitive Therapy; TAU: Treatment as usual

medium-term (26,31-33) (Fig. 3c). Importantly, these studies exhibited no heterogeneity (I^2 = 0). Utilizing a fixed-effects model, the difference in scores did not achieve statistical significance (MD = -2.79; 95% CI, -6.33 to 0.74; P > 0.05; GRADE: low]. This outcome implies that during the intermediate follow-up period post-MM intervention, there was a resurgence of symptoms among the patients.

Additionally, 2 studies offered an assessment of FIQ scores in the MM and control groups at long-term (27,32) (Fig. 3d). Similar to the previous analysis, these studies demonstrated no heterogeneity (I^2 = 0). However, in the long-term follow-up, the results again indicated that, compared to the control group, patients who received the intervention exhibited a notable improvement in symptoms (MD = -6.09; 95% CI, -9.01 to -3.16; P < 0.05; GRADE: moderate).

Pittsburg Sleep Quality Index (PSQI)

Among the ten RCTs in our analysis, 3 assessed the preintervention PSQI (26-28) (Fig. 4a). The heterogeneity among these studies was none (I^2 = 0), leading to the adoption of a fixed-effects model. The results showed no statistically significant difference between the 2 groups (MD = 0.10; 95% CI, -0.55 to 0.75; P > 0.05; GRADE: moderate). This indicates that the baseline differences between the 2 groups are comparable.

Of the 10 RCTs, 3 evaluated the PSQI in the short-term (26-28) (Fig. 4b). These studies exhibited substantial heterogeneity (I^2 = 70%), prompting the use of a random-effects model. The results indicated a marked improvement in sleep quality in the intervention group compared to the control group (MD = -1.84; 95% CI. -3.35 to -0.33; P < 0.05; GRADE: very low).

Two studies compared the PSQI scores between the MM and control groups at medium-term (26,28) (Fig. 4c). The studies exhibited a substantial degree of heterogeneity (I^2 = 62%), necessitating the use of a random-effects model. The findings revealed no statistically significant difference between the 2 groups (MD = -1.28; 95% CI, -3.35 to -0.80, P > 0.05; GRADE: very low).

Beck Depression Inventory (BDI)

Three studies assessed preintervention BDI scores (30-32) (Fig. 5a). Heterogeneity was absent (I^2 = 0). The analysis revealed no statistically significant effect on the BDI (MD = 0.74; 95% CI, -1.36 to 2.85; P > 0.05;

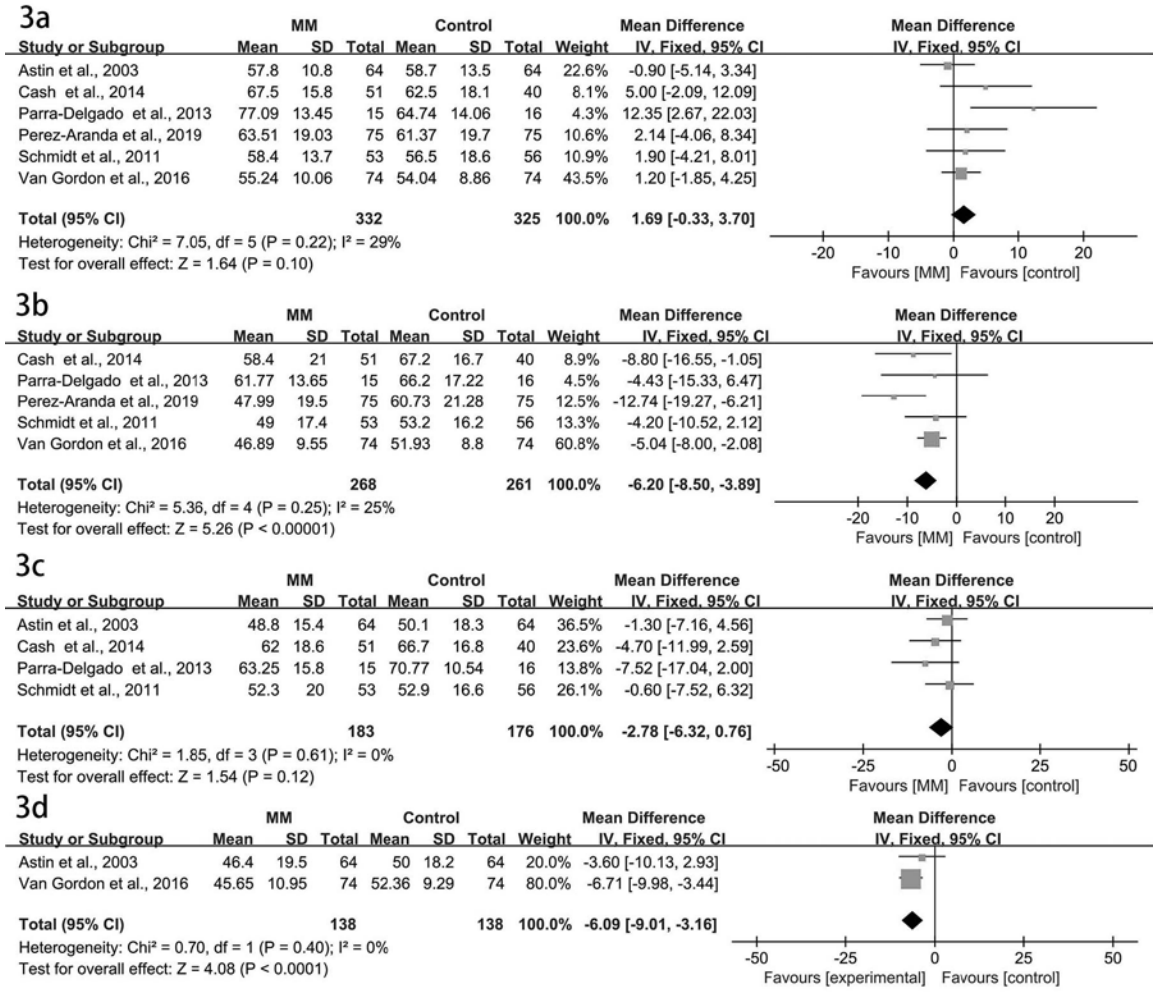

Fig. 3. *Forest plot for the comparison of the Fibromyalgia Impact Questionnaire (3a) at preintervention, showing no difference between the 2 groups; (3b) after the end of MM sessions (short-term), showing the effect favoring mindfulness meditation; (3c) at medium-term, showing no difference between the 2 groups; and (3d) at long-term, showing the effect favoring mindfulness meditation. Green square represents the standard mean difference, bars represent the 95% CI, and black diamond represents the pooled analysis for each pain score.*

GRADE: moderate), suggesting that the baseline data of the 2 groups were comparable.

Two studies evaluated the short-term BDI score (30,31) (Fig. 5b). No heterogeneity was noted across these studies ($I^2 = 0$), so a fixed-effects model was used. The results demonstrated that, in the short-term follow-up, patients in the intervention group experienced significant improvements in depressive symptoms compared to those in the control group (MD = -3.62,; 95% CI, -5.77 to -0.76; $P < 0.05$; GRADE: moderate).

Two studies evaluated the medium-term BDI scores (30-32) (Fig. 5c). They reported no heterogeneity ($I^2 = 0\%$), so a fixed-effects used. The findings indicated that, in the intermediate follow-up phase, patients undergoing the MM intervention exhibited a notable decrease in depression symptoms compared to those in the control group (MD = -2.88; 95% CI, -4.98 to -0.79; $P < 0.05$; GRADE: moderate).

Perceived Stress Scale (PSS)

Three studies evaluated preintervention PSS scores (26,33,35) (Fig. 6a). These studies displayed no heterogeneity ($I^2 = 0$), so a fixed-effects model was applied. The analysis revealed no statistically significant differences in PSS scores (MD = 0.41; 95% CI, -1.34 to 2.16; *P*

Table 4. *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings.*

Outcome	Certainty Assessment							No. of Patients		Effect		Certainty
	No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	meditation	Control	Relative (95% CI)	Absolute (95% CI)	
FIQR at preintervention	6	Randomized trials	Serious	Not serious	Not serious	Not serious	None	332	325	-	SMD 1.69 higher (0.33 lower to 3.7 higher)	⊕⊕⊕◯ MODERATE
FIQR at short-term	5	Randomized trials	Serious	Not serious	Not serious	Not serious	None	268	261	-	SMD 6.2 lower (8.51 lower to 3.89 lower)	⊕⊕⊕◯ MODERATE
FIQR at medium-term	4	Randomized trials	Serious	Serious	Not serious	Not serious	None	183	176	-	SMD 2.76 lower (6.33 lower to 0.74 higher)	⊕⊕◯◯ LOW
FIQR at long-term	2	Randomized trials	Serious	Not serious	Not serious	Not serious	None	138	138	-	SMD 6.09 lower (9.01 lower to 3.16 lower)	⊕⊕⊕◯ MODERATE
PSQI at preintervention	3	Randomized trials	Serious	Not serious	Not serious	Not serious	None	147	149	-	SMD 0.1 higher (0.55 lower to 0.75 higher)	⊕⊕⊕◯ MODERATE
PSQI at short-term	3	Randomized trials	Serious	Very serious	Not serious	Not serious	None	147	149	-	SMD 1.84 lower (3.35 lower to 0.33 lower)	⊕◯◯◯ VERY LOW
PSQI at medium-term	2	Randomized trials	Serious	Very serious	Not serious	Not serious	None	73	75	-	SMD 1.28 lower (3.35 lower to 0.8 higher)	⊕◯◯◯ VERY LOW
BDI at preintervention	3	Randomized trials	Serious	Not serious	Not serious	Not serious	None	97	88	-	SMD 0.75 higher (1.31 lower to 2.82 higher)	⊕⊕⊕◯ MODERATE
BDI at short-term	2	Randomized trials	Serious	Not serious	Not serious	Not serious	None	66	55	-	SMD 2.62 lower (5.82 lower to 0.05 higher)	⊕⊕⊕◯ MODERATE
BDI at medium-term	3	Randomized trials	Serious	Not serious	Not serious	Not serious	None	97	88	-	SMD 2.23 lower (4.38 lower to 0.08 lower)	⊕⊕⊕◯ MODERATE
PSS at preintervention	3	Randomized trials	Serious	Not serious	Not serious	Not serious	None	179	174	-	SMD 0.41 higher (1.34 lower to 2.16 higher)	⊕⊕⊕◯ MODERATE
PSS at short-term	3	Randomized trials	Serious	Very Serious	Not serious	Not serious	None	179	174	-	SMD 4.85 lower (8.22 lower to 1.49 lower)	⊕◯◯◯ VERY LOW

Table 4 cont. *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings.*

Outcome	Certainty Assessment							No. of Patients		Effect		Certainty
	No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	meditation	Control	Relative (95% CI)	Absolute (95% CI)	
PSS at medium-term	2	Randomized trials	Serious	Not serious	Not serious	Not serious	None	104	99	-	SMD 2.76 lower (4.82 lower to 0.7 lower)	⊕⊕⊕◯ MODERATE

SMD: standardized mean difference; FIQR: Fibromyalgia Impact Questionnaire; PSQI: Pittsburg Sleep Quality Index; BDI, Beck Depression Index; PSS: Perceived Stress Scale. ⊕⊕⊕⊕: High quality—We are very confident that the true effect lies close to that of the estimate of the effect; ⊕⊕⊕◯: Moderate quality—We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; ⊕⊕◯◯: Low quality—Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; ⊕◯◯◯: Very low quality—We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

> 0.05; GRADE: moderate), suggesting that the baseline data of both groups were comparable.

Two studies assessed the short-term PSS scores (26,33,35) (Fig. 6b). These studies showed considerable heterogeneity (I^2 = 74%), so a random-effects model was used. The results indicate that MM led to a significant reduction in PSS scores for the intervention groups compared to control groups soon after treatment (MD = -4.85; 95% CI, -8.22 to -1.49; P <0.05; GRADE: very low).

Two studies compared the 2-month PSS scores (26,33) (Fig. 6c). Heterogeneity was absent between these studies (I^2 = 0), so a fixed-effects model was utilized. The results showed that there was a significant reduction in stress among patients during the intermediate follow-up period (MD = -2.76; 95% CI, -4.82 to -0.70; P < 0.05; GRADE: moderate).

Sensitivity Analyses

On the one hand, for the indicators such as the short-term FIQ, medium-term FIQ, preintervention PSQI, preintervention BDI, and preintervention PSS sensitivity analyses did not alter the results, by excluding one study at a time from each meta-analysis (Tables S2-S4, Table S6, Table S8). On the other hand, for other indicators such as the preintervention FIQ, short-term PSQI medium-term BDI, and short-term PSS, the results were not as robust (Table S1, Table S5, Table S7, Table S9). The main reason for the change of results at preintervention FIQ and during medium-term BDI follow-up may be related to Astin, et al's study (32) using mindfulness yoga as the intervention method.

In addition, the short-term follow-up results of PSQI and the short-term follow-up results of PSS had high heterogeneity (I^2 > 50%); sensitivity analysis was performed to find the source of heterogeneity (Fig. 7). This analysis revealed that the heterogeneity in the short-term follow-up results of PSQI predominantly originated from the study by Amutito, et al (27). After excluding this study, heterogeneity was none (I^2 = 0). The revised results bolstered the effectiveness of the MM group over the control group (MD = -1.29; 95% CI, -2.03 to -0.54; P < 0.05) (Fig. 8a).

Our analysis found that heterogeneity in the short-term follow-up results of PSS was mainly due to the study by Schmidt, et al (26). After excluding this study, the heterogeneity decreased (I^2 = 52%). Even with this adjustment, the results continued to show that the MM group had a superior reduction in stress levels compared to the control group (MD = -6.31; 95% CI, -9.32 to -3.30; P < 0.05) (Fig. 8b).

Discussion

Our systematic review and meta-analysis examined the effect of MM on FMS at various time points, providing a precise level of evidence as reflected by the GRADE assessment. With a total of 818 patients, there is moderate to low evidence that MM has a positive effect on patients with fibromyalgia, particularly in the short term, with moderate to low evidence indicating improvements in quality of life, sleep quality, depression, and stress levels. However, in the medium-term follow-up, while improvements in depression and stress

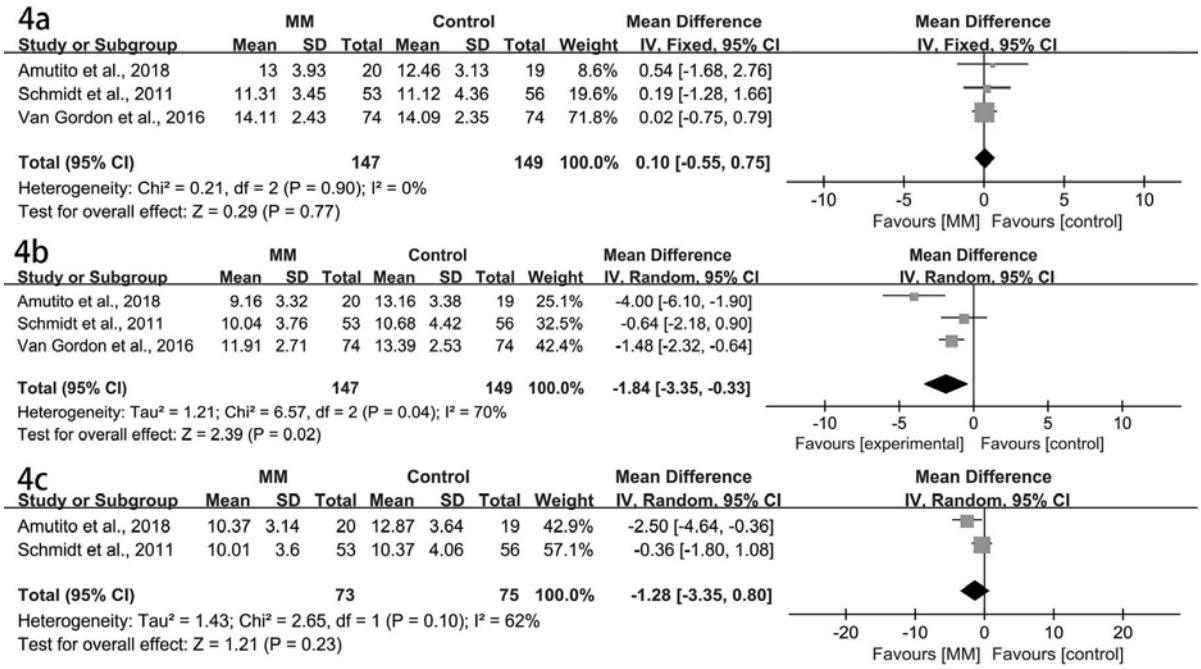

Fig. 4. *Forest plot for the comparison of the Pittsburg Sleep Quality Index (4a) at preintervention, showing no difference between the 2 groups; (4b) after the end of MM sessions (short-term), showing the effect favoring mindfulness meditation; (4c) at medium-term, showing no difference between the 2 groups. Green square represents the standard mean difference, bars represent the 95% CI, and black diamond represents the pooled analysis for each pain score.*

are maintained, the effects on quality of life and sleep quality are not significant. In the long term, due to limited data, our study concludes there is an improvement in quality of life, but the effects on sleep quality, depression, and stress remain unclear, highlighting the need for more comprehensive long-term research to fully understand the sustained effects of MM on these aspects.

In a 2013 meta-analysis, Langhorst, et al (36) examined 7 RCTs in order to assess the effect of qigong, tai chi, yoga, and body awareness therapies on fibromyalgia symptoms. This analysis found that tai chi and yoga might improve sleep, fatigue, depression, and health-related quality of life in the short term. However, it's important to note that their meta-analysis primarily concentrated on meditative movement therapies. Among the studies included, only one was directly related to mindfulness meditation. Additionally, there was significant heterogeneity in the literature they reviewed, and the level of evidence was not thoroughly evaluated.

Another significant piece of research in 2013 was conducted by Lauche, et al (19). This team performed a meta-analysis of 6 studies focusing on mindfulness interventions. Their findings suggested that mindfulness could positively affect patients' pain symptoms and quality of life in the short-term. However, it's important to note some limitations in their meta-analysis. First, of the 6 studies analyzed, only 5 were RCTs. Furthermore, there was a lack of assessment regarding the level of evidence provided by these studies. Another critical limitation of this meta-analysis was the scarce inclusion of studies that looked at medium and long-term follow-up periods.

The meta-analysis by Pei, et al (37) included 8 RCTs demonstrating the effectiveness of mindfulness in managing chronic pain syndromes in the short term. However, its applicability to fibromyalgia is limited, as only one of these trials specifically focused on patients with fibromyalgia, with others involving conditions like rheumatoid arthritis and migraine. Furthermore, this analysis did not investigate the combined effects of meditation and mindfulness within the context of fibromyalgia, highlighting a gap in research and under-

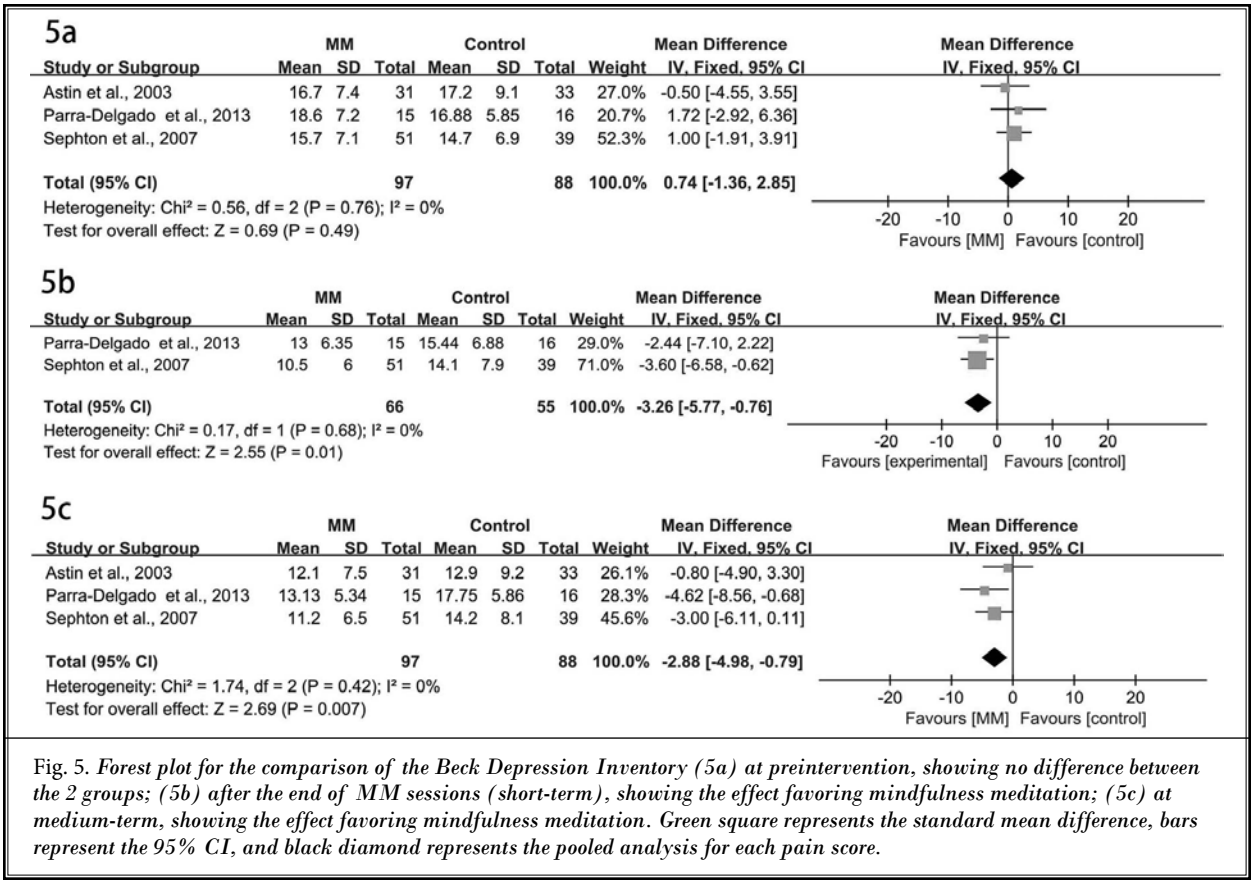

Fig. 5. *Forest plot for the comparison of the Beck Depression Inventory (5a) at preintervention, showing no difference between the 2 groups; (5b) after the end of MM sessions (short-term), showing the effect favoring mindfulness meditation; (5c) at medium-term, showing the effect favoring mindfulness meditation. Green square represents the standard mean difference, bars represent the 95% CI, and black diamond represents the pooled analysis for each pain score.*

scoring the need for more targeted studies in this area (38). Since then, there have been no systematic reviews regarding MM.

Our meta-analysis includes 10 studies involving 818 patients screened out based on our criteria. All of these studies were RCTs that aimed to investigate the effectiveness of MM in individuals with fibromyalgia and those with depression, anxiety, and insomnia. The data extraction points varied across the studies and included , 2 weeks, 2 months, 3 months, and 6 months posttreatment. Based on previous literature, we divided the follow-up time into 3 stages: short-term, medium-term and long-term (19,24). Short-term effects: these are outcomes measured immediately following the completion of the intervention. Medium-term effects: these are assessed approximately 3 months after the patients were randomized into the study. Long-term effects: These are evaluated around 6 months postrandomization.

Our study reinforces the positive effect of MM on improving patients' quality of life in the short term, as well as providing symptom relief. These findings align with previous research (19,36,37). However, in the medium-term follow-up, no significant effects of MM on enhancing quality of life and sleep quality were observed, a finding not reported in earlier meta-analyses (19). Interestingly, MM demonstrated a positive influence on quality of life again in the long-term follow-up. This pattern suggests a potential fluctuation in the effectiveness of MM over time, which could be due to a diminishing effect of the intervention or complex neuroregulatory mechanisms in patients. Further investigation is needed to fully understand these dynamics and the long-term effects of MM.

Additionally, our study found MM to be effective in reducing depressive symptoms and stress levels during the short-term follow-up, corroborating findings from Langhorst, et al (36) and Plemam, et al (39). Plemam, et al's research particularly supports MM's potential for alleviating depressive symptoms, in line with our study's results. At the medium-term follow-up, MM continued to positively affect patients' depression and stress levels, consistent with previous research (33). Each of the 2 programs was successful

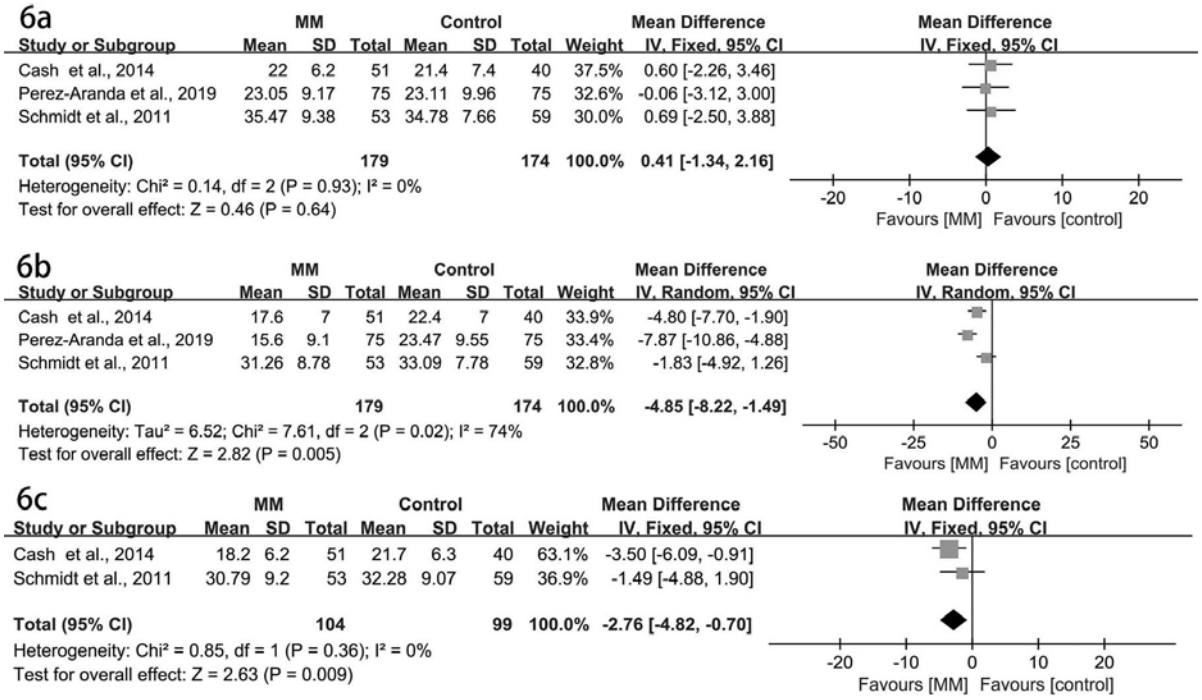

Fig. 6. *Forest plot for the comparison of the Perceived Stress Scale (6a) at preintervention, showing no difference between the 2 groups; (6b) after the end of MM sessions (short-term), showing the effect favoring mindfulness meditation; and (6c) at medium-term, showing the effect favoring mindfulness meditation. Green square represents the standard mean difference, bars represent the 95% CI, and black diamond represents the pooled analysis for each pain score.*

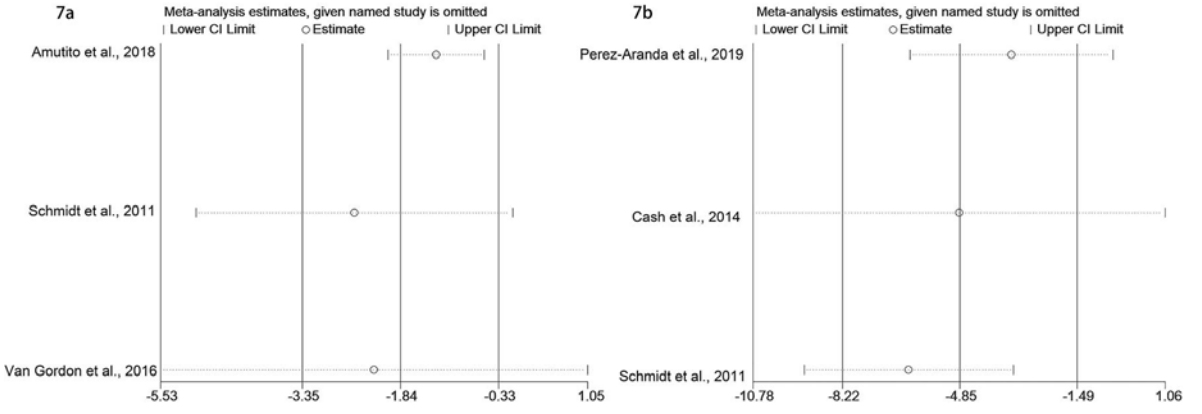

Fig. 7. *Sensitivity analysis of (7a) the Pittsburg Sleep Quality Index at short-term, (7b) Perceived Stress Scale at short-term.*

in stress reduction (26,33). MM could reduce the psychological burden on women, foster a positive mood, and relieve stress. This might be linked to an uptick in T cell production of the interleukin (IL)-4 cytokine. Notably, stress output correlates with a decline in IL-4 cytokine levels (40,41). By boosting IL-4 cytokines, MM can diminish anxiety in patients. Additionally, there are notable therapeutic advantages for breast cancer treatment (42).

The precise mechanism through which MM miti-

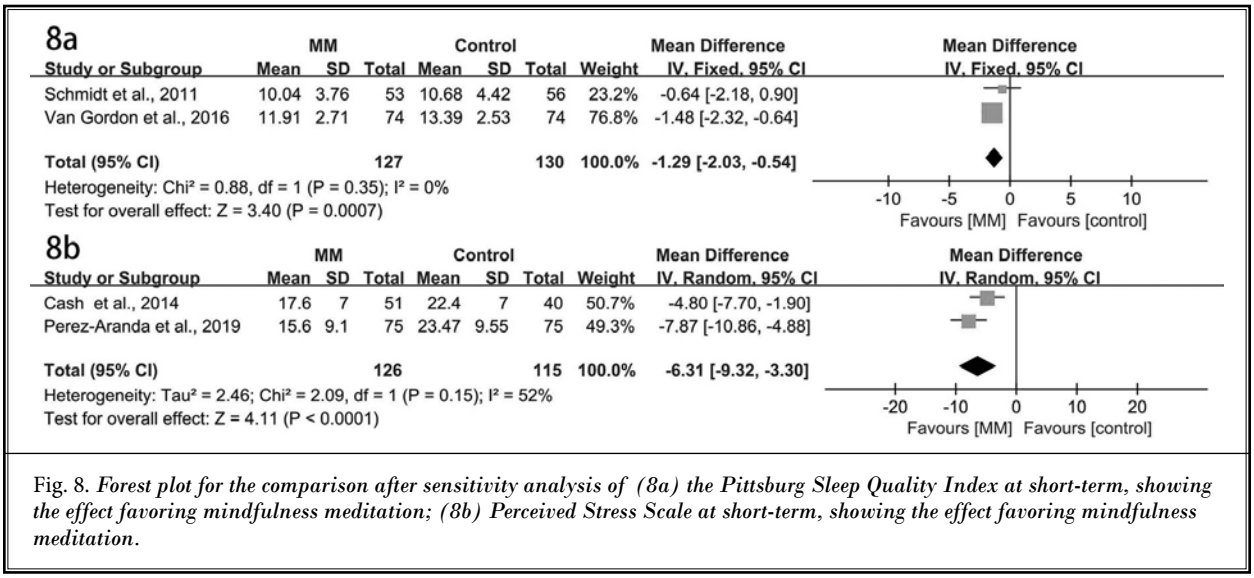

Fig. 8. *Forest plot for the comparison after sensitivity analysis of (8a) the Pittsburg Sleep Quality Index at short-term, showing the effect favoring mindfulness meditation; (8b) Perceived Stress Scale at short-term, showing the effect favoring mindfulness meditation.*

gates the effects of fibromyalgia requires further investigation. The present hypothesis posits that fibromyalgia intensifies pain primarily via central sensitization and cognitive/emotional processes. Central sensitization causes patients to experience heightened pain from equivalent pain stimuli. This phenomenon may be linked to activity in pain-associated brain regions, such as the insula, anterior/posterior cingulate cortex, cerebellum, and both primary and secondary somatosensory cortices, especially when contrasted with healthy controls matched by age and gender (43-46). Furthermore, there's enhanced connectivity within the default mode network in patients with fibromyalgia. This neural network, crucial for self-referential (47,48) and mind-wandering processes(49), shows robust connections to the insula, thus placing the patient in a particular mental state. In this state, the patient becomes more attuned to observing and assessing noxious stimuli, which may lead to pain "chronification" (50). MM appears to beneficially affect depression, pain, and anxiety. It achieves this by modulating the perception and routing of stimuli, dampening reactions based on past experiences, and subsequently reducing the symptoms experienced by patients (51).

Moderate heterogeneity was noted among the included studies due to several factors. First and foremost, the follow-up period varied, as listed in Table 2. The conclusions may be different in different follow-up stages. Secondly, the time and method of MM varied among the included studies. The selected research indicators are also different. Finally, almost all RCTs were imperfect regarding blinding. These factors may have contributed to intergroup differences, affecting the entire heterogeneity of the included studies.

This meta-analysis has some limitations. The relatively small sample size and the average quality of the included studies may introduce biases. The time and method of meditation in the included studies were not completely unified, and there were confounding factors. Additionally, the limited amount of available literature is a challenge. Despite focusing on RCTs, the reasons for heterogeneity among these studies remain unclear. Future research should aim for larger, higher-quality studies to address these limitations and provide a more comprehensive understanding of MM's effectiveness in fibromyalgia management.

Conclusion

Among the 818 patients studied, evidence ranging from very low to moderate indicates that MM can enhance quality of life in the short term for individuals with FMS. It also suggests MM's potential in alleviating stress, providing relief from insomnia, and mitigating depression. Notably, the improvements in depression and stress levels were maintained at the medium-term follow-up. Furthermore, an improvement in quality of life was still observable at the long-term follow-up. This suggests that MM can play a role in the complex treatment of fibromyalgia and can help improve the condition of patients. To solidify these findings, more established MM regimens, larger sample sizes, and extended observation periods are required.

Acknowledgments

We thank LetPub (www.letpub.com) for providing linguistic assistance during manuscript preparation.

Author Contributions

Conceptualization, Meng, Cao, and Dong; methodology, Meng, Cao, and Zhang; software, Meng and Cao; validation, Cao and Lu; formal analysis, Cao; investigation, Zhang; resources, Meng; data curation, Lu; writing—original draft preparation, Meng; writing—review and editing, all authors; visualization, Zhang; supervision, Dong; project administration, Dong; funding acquisition, Cao. All authors have read and agreed to the published version of the manuscript.

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