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REVIEW

Manual Therapy in Primary Dysmenorrhea: A Systematic Review and Meta-Analysis

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Objective: This research aimed to assess the effectiveness of manual therapy in alleviating pain among women undergoing primary dysmenorrhea (PD).

Methods: All randomized controlled trials (RCTs) regarding manual therapy for PD were searched from online databases, spanning from their inception to July 2023. The identified literature underwent a thorough screening process, and the data were meticulously extracted and analyzed using RevMan 5.3. Subsequently, the included studies underwent Cochrane's quality assessment and meta-analysis. The evidence obtained was then assessed using the grading of recommendations, assessment, development, and evaluation (GRADE) approach.

Results: 32 RCTs, involving 2566 women were finally included for analysis. The overall quality of the concluding evidence was generally rated as low or very low. Performance bias and blind bias were found to be the main risk of bias of the included studies. In comparison to no treatment, manual therapy demonstrated a significant increase in pain relief in short-term (n=191, MD=1.30, 95% CI: 0.24~2.37). The differences in the effects of manual therapy and the placebo on pain intensity may not be statistically significant (n=255, MD=0.10, 95% CI: −0.37~0.58). In contrast to NSAIDs, manual therapy exhibited superior pain alleviation (n=507, MD=3.01, 95% CI: 1.08~4.94) and a higher effective rate (n=1029, OR=4.87, 95% CI: 3.29~7.20). Importantly, no severe adverse events were reported across all studies, indicating a relatively safe profile for manual therapy.

Conclusion: Manual therapy presented promise in effectively relieving menstrual pain with minimal adverse events in short term, outperforming both no treatment and NSAIDs. However, this conclusion is tempered by the low quality of the included RCTs, highlighting the necessity for more robust trials to validate it.

Keywords: primary dysmenorrhea, manual therapy, meta-analysis, systematic review

Introduction

Primary dysmenorrhea (PD) is defined as painful menstruation in the absence of pelvic pathology and is characterized by recurrent, crampy, lower abdominal pain during menstruation, affecting 50–90% of women.[1] Among them, 15–50% of women with moderate to severe symptoms find their daily activities, including work, school, or other activities, disrupted.[2] The adverse effects of PD extend beyond physical discomfort, affecting performance by reducing attention and productivity.[3,4] The guidelines recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs) as the primary therapeutic approach for PD.[5] Nevertheless, a subset of individuals fails to relieve their pain with NSAIDs and, instead, may experience undesirable side effects such as nausea, dyspepsia, headaches, or insomnia.[6]

The non-pharmacological and non-invasive therapies are endorsed to manage dysmenorrhea symptoms, including acupuncture, biofeedback, heat treatments, transcutaneous electrical nerve stimulation, exercises, and manual therapy.[7,8] Manual therapy, a specialized branch of physical therapy, employing skilled hands-on techniques to assess, diagnose, and treat musculoskeletal and neuromuscular conditions. This therapeutic approach encompasses a variety of hands-on techniques, including massage, acupressure, holographic therapy, spinal manipulative therapy and more.

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The utilization of manual treatment for PD remains controversial. Manual therapy, either in isolation or in combination with other treatment modalities, has demonstrated potential advantages for overall health with a low reported risk of adverse effects.[9] In contrast, in 2006, a Cochrane systematic review indicated inadequate evidence to substantiate the efficacy of manual therapy in alleviating pain for women with dysmenorrhea.[10] Given these divergent viewpoints, this research was to evaluate the efficacy and safety of manual therapy for PD, utilizing updated data and comparing its effects with no treatment, placebo or first-line treatment.

Methods

This meta-analysis adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Table S1).[11] The study protocol was registered in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO/; registration number CRD42023443160) and fully conducted in this research.

Search Strategy

A thorough search was conducted across multiple databases, including PubMed, EMBASE, MEDLINE, Cochrane Central Register of Controlled Clinical Trials, CNKI, Wanfang, SinoMed, and VIP, covering the period from inception to July 2023. The search strategy employed a combination of medical subject headings (MeSH) terms with free words such as dysmenorrhea, menstrual pain, massage, manipulation, manual therapy, and was adjusted based on the specific requirements of each database (Table S2).

Eligibility Criteria

Types of Participants

The inclusion criteria included female patients of reproductive age who were experiencing PD. PD was defined as cyclic pelvic pain occurring during menstruation without the presence of gynecological pathologies such as endometriosis, adenomyosis, or uterine myoma. Furthermore, patients with secondary dysmenorrhea or significant medical conditions were excluded.

Types of Studies

All randomized controlled trials (RCTs) assessing pain intensity and associated outcomes were systematically included to evaluate the efficacy of manual therapy in females with PD. The treatment duration spanned a minimum of 2 menstrual cycles.

Types of Interventions

In this research, the intervention group comprised various forms of manual therapies, while combinations of manual therapy with other interventions were excluded. The control group encompassed sham or placebo treatments, no treatment, and oral NSAIDs.

Types of Outcomes

The primary outcome measures were centered on a direct assessment of pain intensity or severity, utilizing assessment tools such as the *Visual Analogue Scale* (VAS) or *Numeric Rating Scale* (NRS) and *McGill Pain Questionnaire* (MPQ). The secondary outcomes included the *Moos Menstrual Distress* (MDQ) questionnaire, adverse events, and the effective rate. The effective rate was determined by applying specific evaluation criteria, including the improvement in clinical symptoms or other measurable outcomes. Participants were classified as "cured", "significantly improved", "improved", or "non-responders" following therapy. The effective rate was computed using the following formula: Effective Rate $=(N1+N2+N3)/N$, where N, N1, N2, and N3 represent the total sample size and the number of patients who were cured, significantly improved, and improved, respectively.[12]

Study Selection and Data Extraction

Two researchers (LX and WYH) independently conducted searches, integrating the results using NoteExpress software to eliminate duplicates and identify potentially eligible articles through a review of titles and abstracts. The full texts of the selected articles were subsequently assessed against predetermined inclusion and exclusion criteria. Data were extracted

in a standardized manner, with any discrepancies resolved through consultation with a senior reviewer (YCH). The data collection form included recorded information such as the first author, publication year, sample size, age, course of PD, intervention regimen, treatment duration, and follow-up.

Quality Assessment

Two reviewers (LX and SYN) employed Cochrane Handbook of Systematic Reviews to assess the potential for bias in each included RCT.[13] This assessment encompassed seven items categorized by the risk of bias, with each item being assigned to one of three risk categories: low risk, unknown risk, and high risk. The evidence quality was then rated as good, moderate, low, and very low using the grading of recommended assessment development and evaluation tool (GRADEpro GDT).[14] If any of the following conditions were met: 1) risk of bias; 2) inconsistency; 3) indirectness; 4) imprecision; and 5) publication bias, the GRADE grading downgraded quality of each study from excellent.

Interpretation of Treatment Effects

To gauge the clinical significance of each treatment effect, a comparison was made with the minimum clinically important difference (MCID): 1.3 points for pain intensity on NRS,[15] 10 points for MDQ,[16] and a 19.9% improvement for the effect rate.[12]

Data Synthesis

The outcomes were classified into short-term (2–3 months), intermediate (3–12 months), and long-term (>12 months). In cases where multiple time frames fell within the same category, data closest to 3 months (short-term), 6 months (intermediate), and 12 months (long-term) were considered.

Meta-analysis was performed using the RevMan 5.3. Heterogeneity was assessed through I-square (I^2) statistics and Cochrane Q test.[17] $I^2 < 50\%$ statistics or P-value > 0.01 indicated a low heterogeneity. When possible, a random-effects model was adopted for meta-analysis. In cases where substantial heterogeneity was observed, sources of heterogeneity were explored through subgroup or sensitivity analysis. For dichotomous variables, odds ratios (ORs) with 95% confidence intervals (CIs) were utilized, and other binary data were converted into OR values. Continuous variables were analyzed using the Hedges' g method and expressed as standardized mean difference (SMD) or mean difference (MD) with 95% CIs.

The findings were descriptively synthesized if there was only one relevant study or when the data were inappropriate for quantitative synthesis. To assess publication bias, a funnel plot was employed when more than ten papers were available for pooling.

Results

Study Selection

A total of 6068 citations were retrieved initially. After excluding 2367 duplicate studies, a further 3603 studies were excluded based on the screening of titles and abstracts, as they did not align with the study purpose. Subsequently, the full texts of 98 studies were carefully reviewed, and 65 were found not to meet the inclusion criteria. Finally, 32 RCTs that met the specified criteria were included in the analysis. All studies were published between January 1999 and 2019, with 18 studies published in Chinese[18–35] and 14 in English.[36–49] The PRISMA flowchart of the screening process is shown in Figure 1.

Study Characteristics

The study population comprised a total of 2566 participants who were randomly assigned to one of the 32 comparator groups. Among these, 18 studies were conducted in the Chinese mainland,[18–35] 5 in Iran,[36,37,39,40,47] 2 in Germany,[45,46] 3 in Taiwan,[41–43] and 1 each in HongKong,[48] America,[44] Italy,[38] and Turkey.[49] The age of participants ranged from 14 to 41 years, and the duration of symptoms varied from a mean of 3 months to 17 years. Across the 32 studies, manual therapy consisted various techniques, with 15 studies focusing on massage, 10 on acupressure, 2 on foot reflexology, 2 on holographic therapy, 2 on spinal manipulative therapy, and 1 on neuromuscular therapy. In the control group, 8 studies employed no treatment, 3 used sham therapy, and 21 involved oral medications. Details are presented in Table 1.

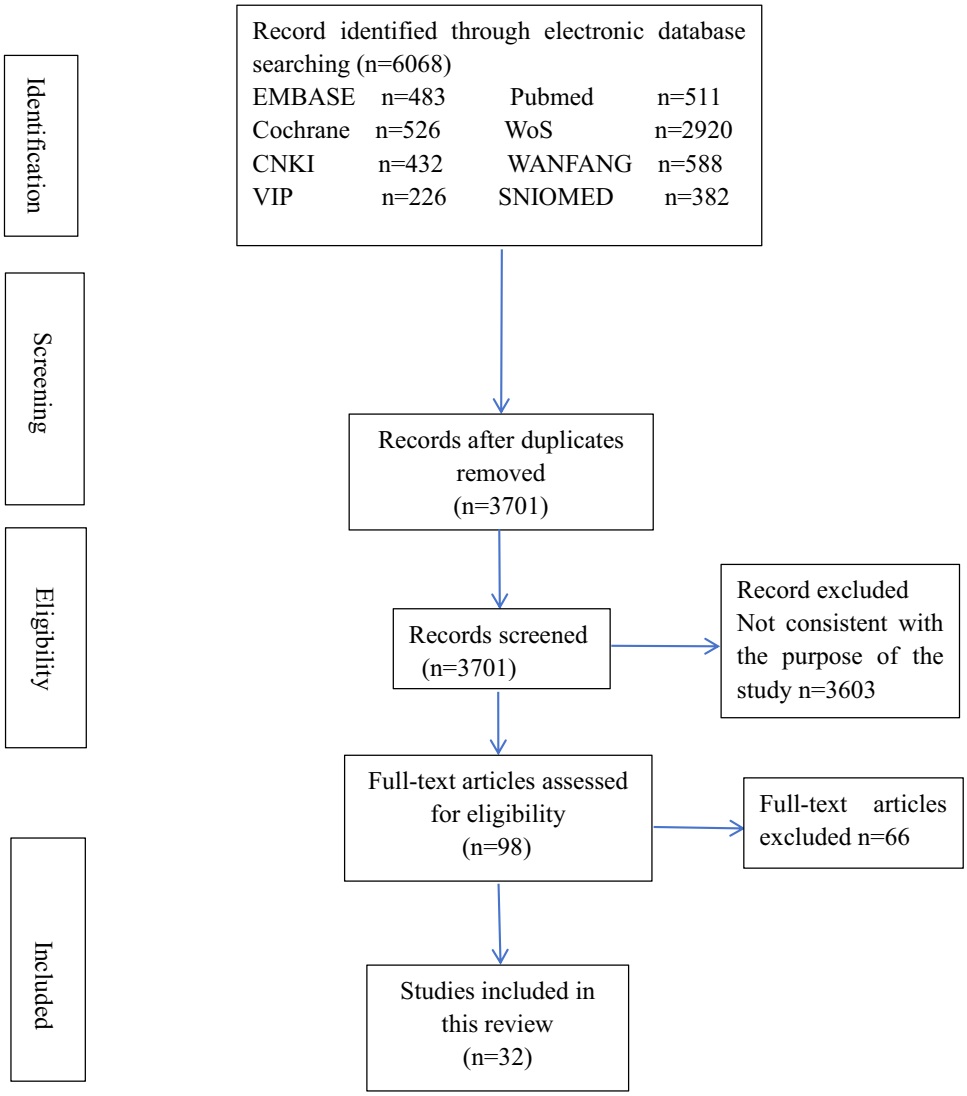

Figure 1 PRISMA flowchart. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 2021;134:178–189. Creative Commons.[11]

In terms of outcome reporting, the VAS was the most frequently utilized, with 15 studies[18,24,28,30,33,36–38,41–44,47–49] providing relevant data. Following closely, 14 studies[19,20,22–24,26,27,29–35] reported effect rates, all originating from China. Additionally, 4 studies,[22,25,26,30] reported pain scores, 4[41–43,48] reported outcomes using the MDQ, 3[21,45,46] mentioned outcomes using the NRS, and 2[40,47] demonstrated outcomes using the MPQ. Adverse events were documented in two studies.[28,45] The duration of most treatments lasted 2 to 4 menstrual cycles, with 6 studies having follow-ups of up to 6 months and one study extending to 12 months. Details are presented in Table 2.

Risk of Bias

Figures 2 and 3 illustrated the risk of bias observed in the included studies. Notably, in 4 studies,[27,30,33,36] the randomization methods were considered to pose a high risk of bias, whereas the randomization methods were deemed appropriate in 13 studies.[18,23–25,37,39,40,43–47,49] Additionally, 15 studies[19–22,26,28,29,31,32,34,35,38,41,42,48] did not provide specific details regarding the generation of random sequences. Allocation concealment was implemented in 4 studies.[36,43,45,49] Except for 1 study[36] reporting blinding of participants, the remaining studies[18–20,22–27,31,33–35,44–46,21,28–30,32,37–43,48,49,47] did not furnish information on blinding. Notably, details of missing data were not reported in any of the enrolled studies, suggesting an absence of selective reporting bias. With the exception of 1 study[28] with uncertainty, all other studies[18–27,31,33–46,29,30,32,47–49] did not exhibit any other biases.

Table 1 Summary of Included Trials Basic Information

Study	Country	Study Design	Number of Participants		Age, Mean (SD)/Range		Intervention	Control
			Intervention	Control	Intervention	Control		
Atrian 2013[36]	Iran	RCT	27	32	21.40 (2.45)	21.95 (3.01)	Acupressure	No treatment
Azima 2015[37]	Iran	RCT	34	34	21.41 (0.95)	21.08 (1.21)	Massage	No treatment
Barassi 2018[38]	Italy	RCT	30	30	31.56 (7.44)		Neuromuscular therapy	NSAIDs
Bazarganipour 2017[39]	Iran	RCT	30	30	22 (1.71)	21.76 (1.73)	Acupressure	Placebo
Behbahani 2016[40]	Iran	RCT	40	40	20.02 (1.44)	20.37 (1.54)	Acupressure	NSAIDs
Chen 2004[41]	Taiwan	RCT	35	34	17.78 (1.43)		Acupressure	No treatment
Chen 2010[42]	Taiwan	RCT	36	35	16.75 (1.36)	16.77 (1.19)	Acupressure	No treatment
Chen 2011[18]	China	RCT	30	30	22.47 (4.58)	23.70 (4.56)	Massage	NSAIDs
Chen 2015[43]	Taiwan	RCT	65	64	18.75 (1.74)	18.73 (0.63)	Acupressure	No treatment
Chen 2016[19]	China	RCT	25	25	20.44 (1.54)	20.44 (1.8)	Massage	No treatment
Guo 2015[20]	China	RCT	34	34	14–30	14–30	Acupressure	NSAIDs
Hondras 1999[44]	America	RCT	69	69	31.1	29.7	Spinal manipulative therapy	Placebo
Hu 2015[21]	China	RCT	40	40	22.61 (1.63)	22.83 (1.72)	Massage	NSAIDs
Jia 2011[22]	China	RCT	16	16	21–27	21–27	Holographic therapy	No treatment
Lin 2010[23]	China	RCT	20	20	14–41		Massage	NSAIDs
Lin 2017[24]	China	RCT	20	20	17.45 (1.13)		Massage	NSAIDs
Lin 2018[25]	China	RCT	20	20	20.2 (1.43)	20.93 (1.53)	Massage	NSAIDs
Liu 2012[26]	China	RCT	55	55	22.46 (7.21)	23.51 (6.98)	Massage	NSAIDs
Ru 2015[27]	China	RCT	50	50	26.62 (2.14)	26.77 (2.21)	Massage	NSAIDs
Susanne 2018[45]	Germany	RCT	111	110	24.4 (3.3)	23.7 (3.9)	Acupressure	No treatment
Tang 2012[28]	China	RCT	30	30	21.41 (1.58)	21.39 (1.03)	Spinal manipulative therapy	NSAIDs
Vagedes 2019[46]	Germany	RCT	23	17	30.22 (7.72)	26.65 (8.4)	Massage	NSAIDs
Valiani 2010[47]	Iran	RCT	32	36	21.6 (1.79)		Foot reflexology	NSAIDs
Wang 2003[29]	China	RCT	62	30	17–35	15–32	Massage	NSAIDs
Wong 2010[48]	Hong Kong	RCT	19	21	22	21.57	Acupressure	No treatment
Wu 2017[30]	China	RCT	12	12	22.41 (1.56)	22.6 (1.72)	Massage	No treatment
Xu 2008[31]	China	RCT	62	47	20.3		Holographic therapy	NSAIDs
Yilmaz 2019[49]	Turkey	RCT	29	29	20.3	19.7	Foot reflexology	Placebo
Zhao 2015[32]	China	RCT	30	30	22 (3.6)	21 (4.1)	Massage	NSAIDs
Zhou 2016[33]	China	RCT	34	30	26.2 (2.59)	25.3 (3.1)	Massage	NSAIDs
Zhu 2012[34]	China	RCT	50	46	–	–	Massage	NSAIDs
Zhu 2015[35]	China	RCT	125	125	18–27	18–27	Acupressure	NSAIDs

Data Synthesis

Manual Therapy versus No Treatment

Pain Intensity

To synthesize pain scores, a meta-analysis was conducted, incorporating 8 studies.[30,36,37,41–43,45,48] The pooled data exhibited significant heterogeneity (I^2=57%), as depicted in Figure 4. In the short term (n=191, MD=1.30, 95% CI:

Table 2 Summary of Included Trials' Outcome Measures and Follow-Up Period

Study	Outcomes	Course of Disease, Range/Mean±SD		Intervention Period (Menstrual Cycle)	Follow-Up Period (Menstrual Cycle)
		Intervention	Control		
Atrian 2013[36]	VAS	–		3	3
Azima 2015[37]	VAS, Anxiety Level	–		3	3
Barassi 2018[38]	VAS, Number of days with pain	–		4	4
Bazarganipour 2017[39]	Wong-Baker faces pain scale, SF12	–		3	3
Behbahani 2016[40]	MPQ	–		2	2
Chen 2004[41]	VAS, VASA, MDQ	–		3	6
Chen 2010[42]	VAS, VASA, MDQ	–		3	6
Chen 2011[18]	VAS, PGF2a, UHD, PGE2	4.46±3.44 year	5.51±3.38 year	3	3
Chen 2015[43]	VAS, MDQ	–		4	12
Chen 2016[19]	Traditional Chinese Medicine Symptom Score, Effective Rate	–		2	2
Guo 2015[20]	Effective Rate	6 month-5 year		3	3
Hondras 1999[44]	VAS, PGF2a	-		4	4
Hu 2015[21]	NRS	5.63±2.51 year	6.21 ±1.89 year	3	3
Jia 2011[22]	Effective Rate, Pain score, UHD	2–6 year		3	3
Lin 2010[23]	Effective Rate	0.5–5 year		3	6
Lin 2017[24]	VAS, Effective Rate, Clinical Symptom Scoring for Dysmenorrhea	3.75±0.67 year		2	5
Lin 2018[25]	Pain score, Hormone levels, emotional factors	3.7±0.62 year		3	3
Liu 2012[26]	Effective Rate, Pain score	0.5–10 year		3	3
Ru 2015[27]	Effective Rate	7.26±3.15 month	7.13±3.04 month	3	3
Susanne 2018[45]	NRS, Number of days with pain	-		3	6
Tang 2012[28]	VAS	63.89±30.36 month	68.32±15.58 month	3	3
Vagedes 2019[46]	NRS, SF12	–		3	3
Valiani 2010[47]	VAS, MPQ, PRI	–		3	3
Wang 2003[29]	Effective Rate	3 month-5 year		3	3
Wong 2010[48]	VAS, MDQ	–		3	3
Wu 2017[30]	VAS, Effective Rate, Pain score, PPI, Traditional Chinese Medicine Symptom Score	6.33±2.05 year	6.25±1.76 year	3	3
Xu 2008[31]	Effective Rate	0.7–4.3 year		3	3
Yilmaz 2019[49]	VAS	–		2	4
Zhao 2015[32]	Effective Rate	3±2.4 year	3±2.4 year	3	3
Zhou 2016[33]	VAS, Effective Rate	2.7±2.03 year	2.6±1.66 year	3	3
Zhu 2012[34]	Effective Rate	–		3	3
Zhu 2015[35]	Effective Rate	2–8 year		3	3

Abbreviations: VASA, Visual Analog Scale for Anxiety; SF12, Short Form 12-Item Health Survey; PRI, Pain Rating Index; PPI, Pain Pressure Threshold; PGF2a, Prostaglandin F2 alpha; UHD, Uterine hemodynamics; PGE2, Prostaglandin E2.

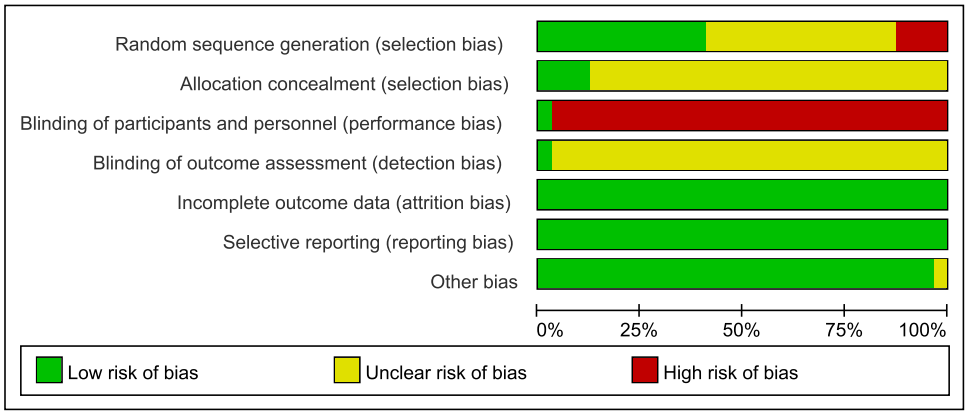

Figure 2 Risk of bias graph: review of the authors' judgments regarding each risk of bias item presented as percentages across all included studies.

0.24~2.37), manual therapy was preferred over no treatment by subgroup analysis; however, this effect was not seen in the intermediate term (n=361, MD=0.91, 95% CI: −0.18~1.99) or long term (n=129, MD=0.33, 95% CI: −0.33~1.09). Another subgroup analyses revealed that both acupressure (n=589, MD=0.61, 95% CI: 0.22~1.00) and massage (n=92, MD=2.48, 95% CI: 0.92~3.99) were superior to no treatment group, as depicted in Figure 5.

Effective Rate

3 studies[19,22,30] reported that the short-term effective rate in the manual therapy group was significantly higher than that in the no treatment control group (n=106, OR=8.73, 95% CI: 3.03~25.19), with no observed heterogeneity (I^2=0), as illustrated in Figure 6. A subgroup analysis showed that, in terms of improving effective rate, massage was superior to no treatment (n=74, OR=11.15, 95% CI: 3.40~36.58), but holographic therapy was not as beneficial (n=32, OR=3.46, 95% CI: 0.32~37.47).

MDQ

Additionally, 4 studies[41–43,48] reported MDQ scores. The results indicated that acupressure can lead to a greater reduction in MDQ scores compared to no treatment (n=309, MD=3.84, 95% CI: 2.27~5.40), as depicted in Figure 7. The subgroup analysis demonstrated that the benefit might extend from short-term, intermediate to long- term.

Manual Therapy versus Placebo

Pain Intensity

3 studies[39,44,49] comparing manual therapy to a placebo reported outcomes related to pain, suggested that the differences in the effects of manual therapy and the placebo on pain may not be statistically significant in short term (n=255, MD=0.01, 95% CI: −0.37~0.58), as depicted in Figure 8. The interventions in these three studies were acupressure, spinal manipulative therapy, and foot reflexology. The meta-analysis results are consistent with the findings of the original studies but lack clinical significance.

Manual Therapy versus NSAIDs

Pain Intensity

A total of 9 studies[18,21,24,25,28,33,38,46,47] were subjected to meta-analysis to synthesize pain intensity findings between manual therapy and NSAIDs. Due to substantial heterogeneity (I^2=99%), subgroup analyses were performed based on different types of manual therapy. As illustrated in Figure 9, 1 study[47] suggested that foot reflexology might yield greater pain relief than NSAIDs (n=68, MD=1.24, 95% CI: 0.41~2.07), although the difference did not attain statistical significance. 6 studies[18,21,24,25,33,46] indicated that massage therapy proved more effective in alleviating pain compared to NSAIDs (n=324, MD=3.85, 95% CI: 1.60~6.10). Furthermore, 1 study[28] reported that the spinal manipulative therapy could potentially offer superior pain relief compared to NSAIDs (n=55, MD=3.26, 95% CI: 2.21~4.40). Conversely, another study[38] found that Neuromuscular therapy demonstrated no remarkable difference in pain relief in comparison to NSAIDs (n=60, MD=−0.47, 95% CI: −1.35~0.41).

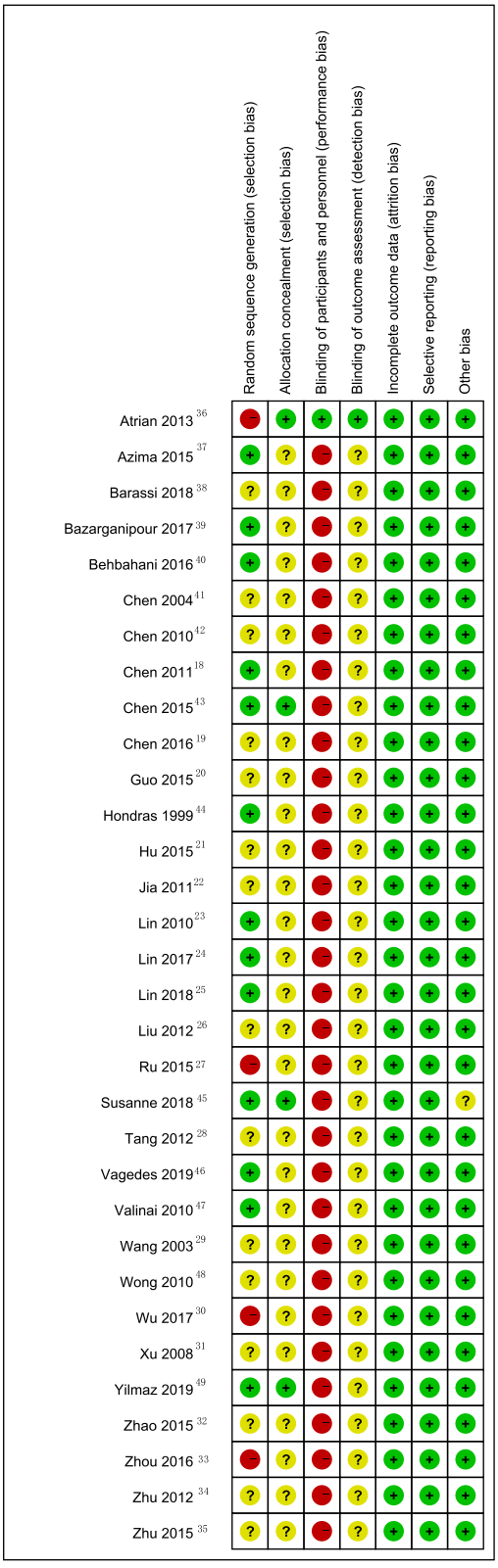

Figure 3 Risk of bias summary: review of the authors' judgments regarding each risk of bias item in each included study.

Subgroup analysis based on different follow-up durations reveals that manual therapy, in both short-term (n=467, MD=2.48, 95% CI: 0.79~4.18) and intermediate-term (n=40, MD=7.18, 95% CI: 6.75~7.61), may provide more pain relief compared to the NSAIDs group, as depicted in Figure 10.

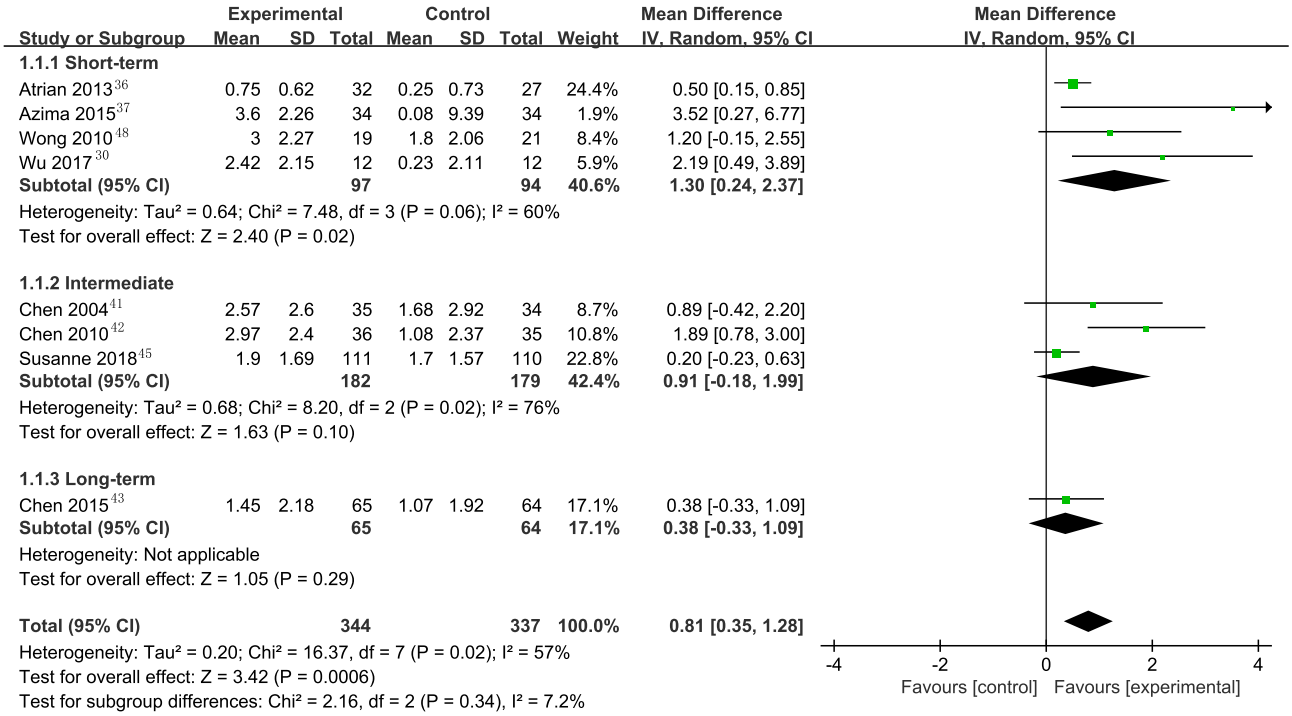

Figure 4 Overall and different follow-up times subgroup forest plot of weighted mean difference (95% CI) for pain intensity for manual therapy versus no treatment.

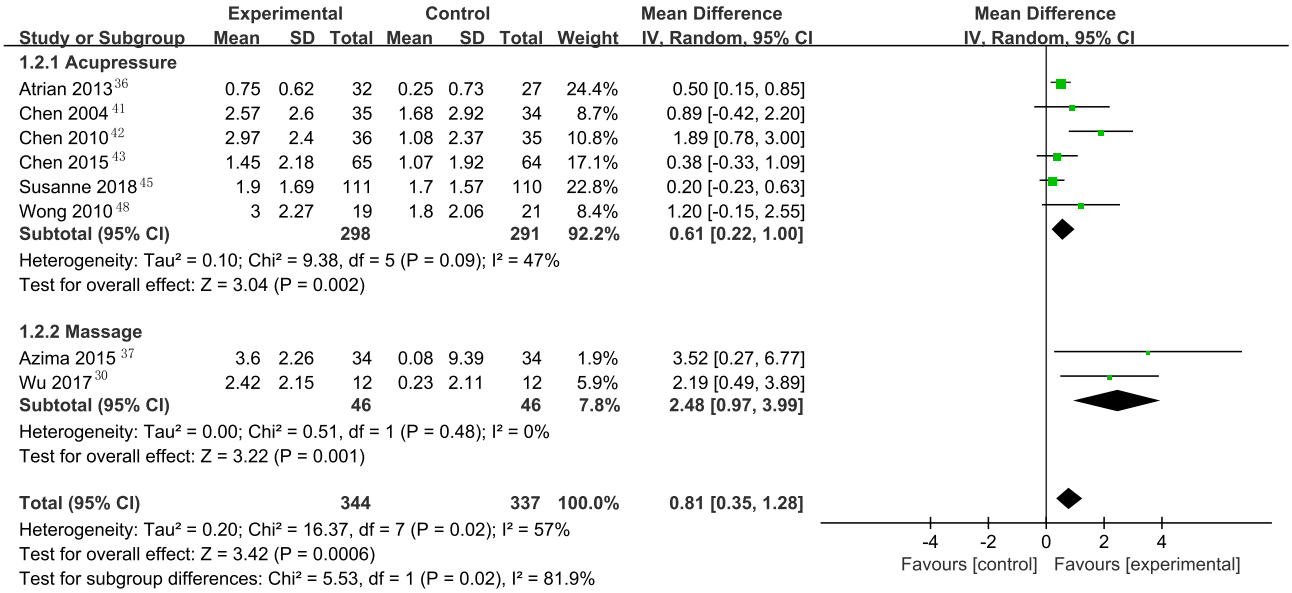

Figure 5 Overall and various manual therapies subgroup forest plot of weighted mean difference (95% CI) for pain intensity for manual therapy versus no treatment.

Effective Rate

11 studies[20,23,24,26,27,29,31,33–35,49] reported that the manual therapy group exhibited a significantly higher effective rate to the NSAIDs (n=1029, OR=4.87, 95% CI: 3.29~7.20), showing no heterogeneity (I^2=19%). When compared to NSAIDs, the subgroup analysis revealed that acupressure, massage, and a holographic treatment are more beneficial in increasing effective rate. These findings were summarized in Figure 11. Subgroup analysis based on different follow-up durations

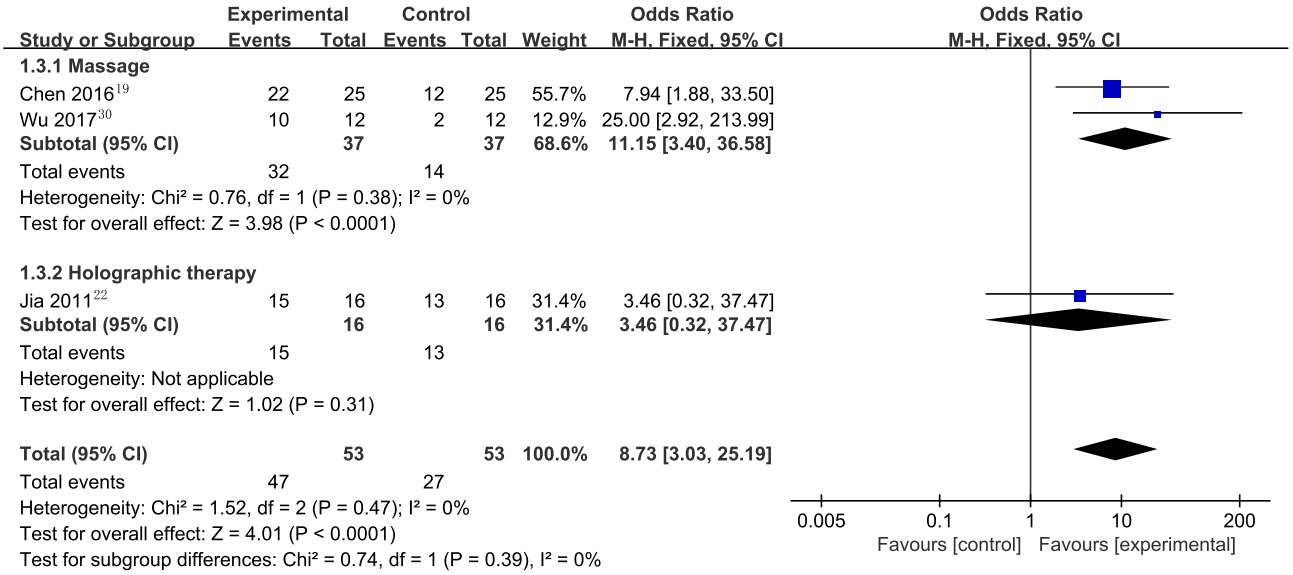

Figure 6 Overall and various manual therapies subgroup forest plot of weighted OR (95% CI) for effective rate for manual therapy versus no treatment.

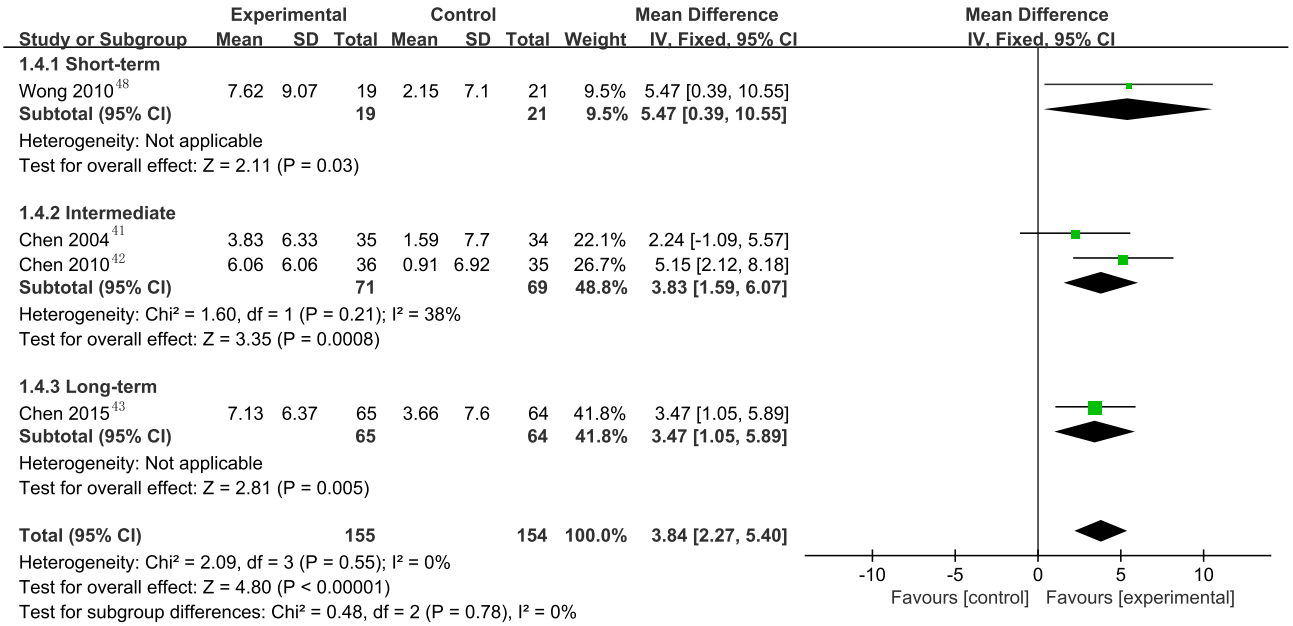

Figure 7 Overall and different follow-up times subgroup forest plot of weighted mean difference (95% CI) for MDQ for manual therapy versus no treatment.

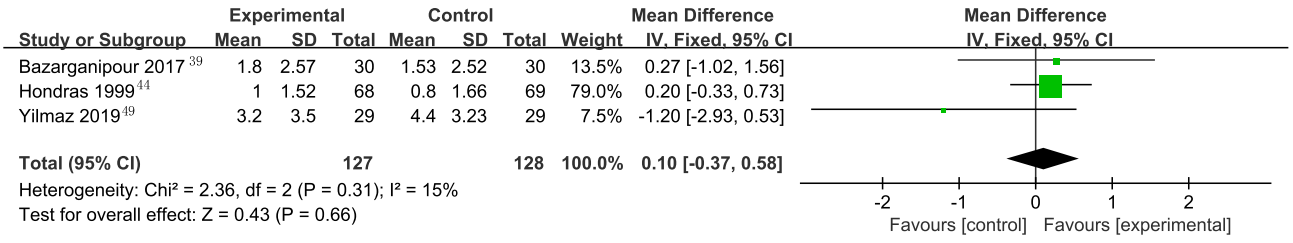

Figure 8 Forest plot of weighted mean difference (95% CI) for pain intensity for manual therapy versus place control.

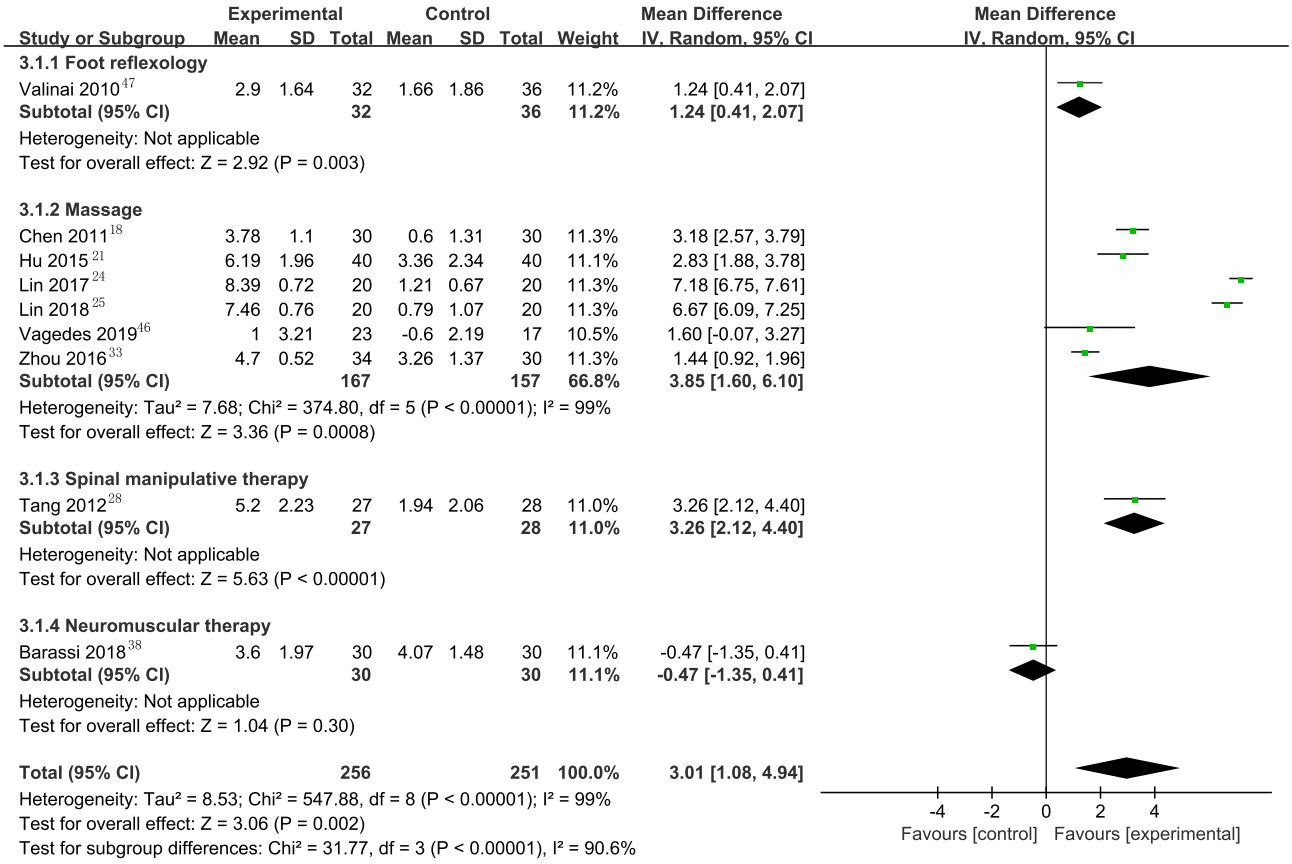

Figure 9 Overall and various manual therapies subgroup forest plot of weighted mean difference (95% CI) for pain intensity for manual therapy versus NSAIDs.

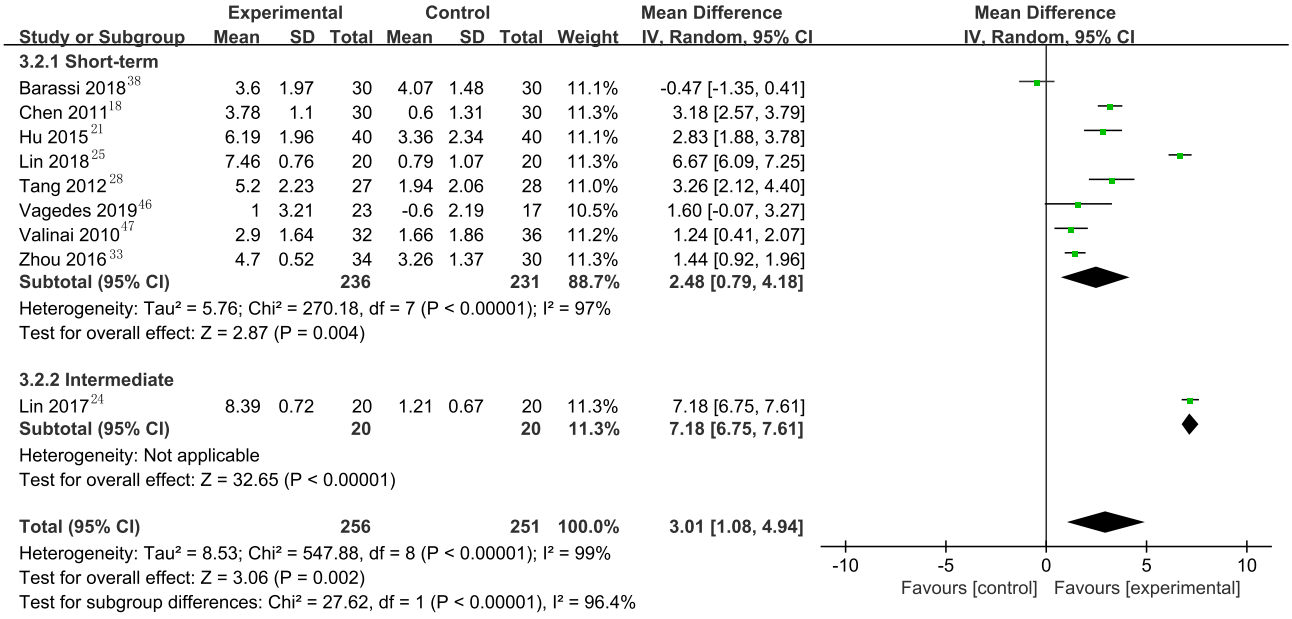

Figure 10 Overall and different follow-up times subgroup forest plot of weighted mean difference (95% CI) for pain intensity for manual therapy versus versus NSAIDs.

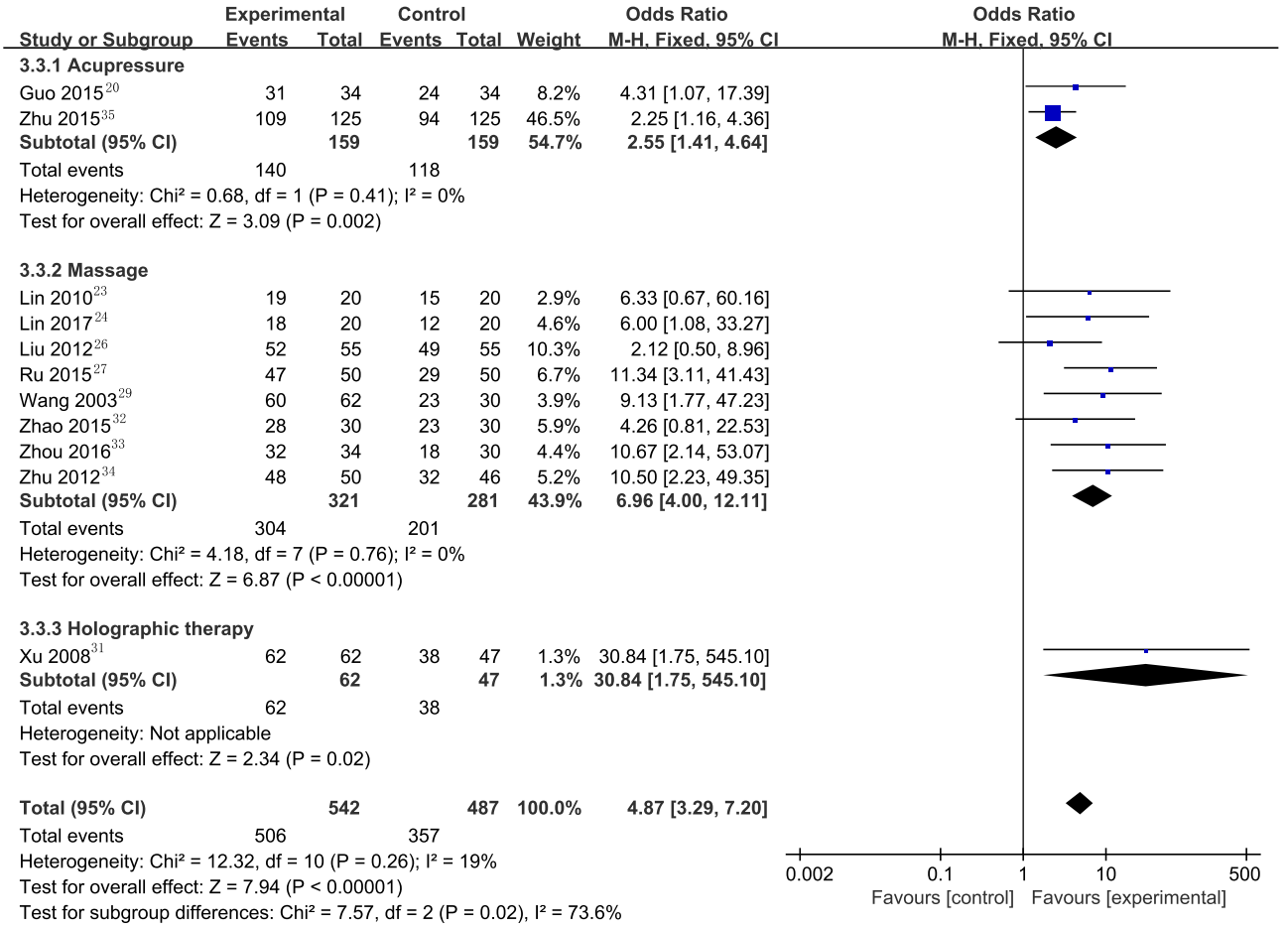

Figure 11 Overall and various manual therapies subgroup forest plot of weighted OR (95% CI) for effective rate for manual therapy versus NSAIDs.

indicates that manual therapy has an advantage over NSAIDs in improving effective rate, particularly in the short-term (n=949, OR=4.77, 95% CI: 3.17~7.17) and intermediate (n=80, OR=6.13, 95% CI: 1.57~23.98), as depicted in Figure 12.

MPQ

The reported results from the single study[40] indicated a greater reduction in pain for acupressure compared to NSAIDs in short-term (n=80, MD=−6.92, 95% CI: −10.90~-2.94), which was proven by MPQ scores.

Adverse Events

Among the 32 studies analyzed, adverse events associated with the interventions were documented in only 2 studies. 1 study[45] highlighted soreness in the lower back region associated with spinal manipulative therapy. In contrast, another study[28] reported adverse events linked to self-acupressure, including bruises, deterioration, hand pain, pressure pain, menstrual cycle shifts, dizziness, nausea, leg pain, and finger tingling. The majority of these adverse events were considered minor, as they either resolved spontaneously or were treated effectively.

Quality of Evidence

To assess quality, GRADEpro GDT was employed, incorporating outcomes from the enrolled studies. The evidence was generally appraised as being of low or very low quality based on GRADE criteria, attributable to the elevated risk of bias and pronounced heterogeneity. Notably, self-rating scales employed as a primary outcome for pain assessment were considered low-quality evidence. The summarized findings of interventions are presented in Table 3.

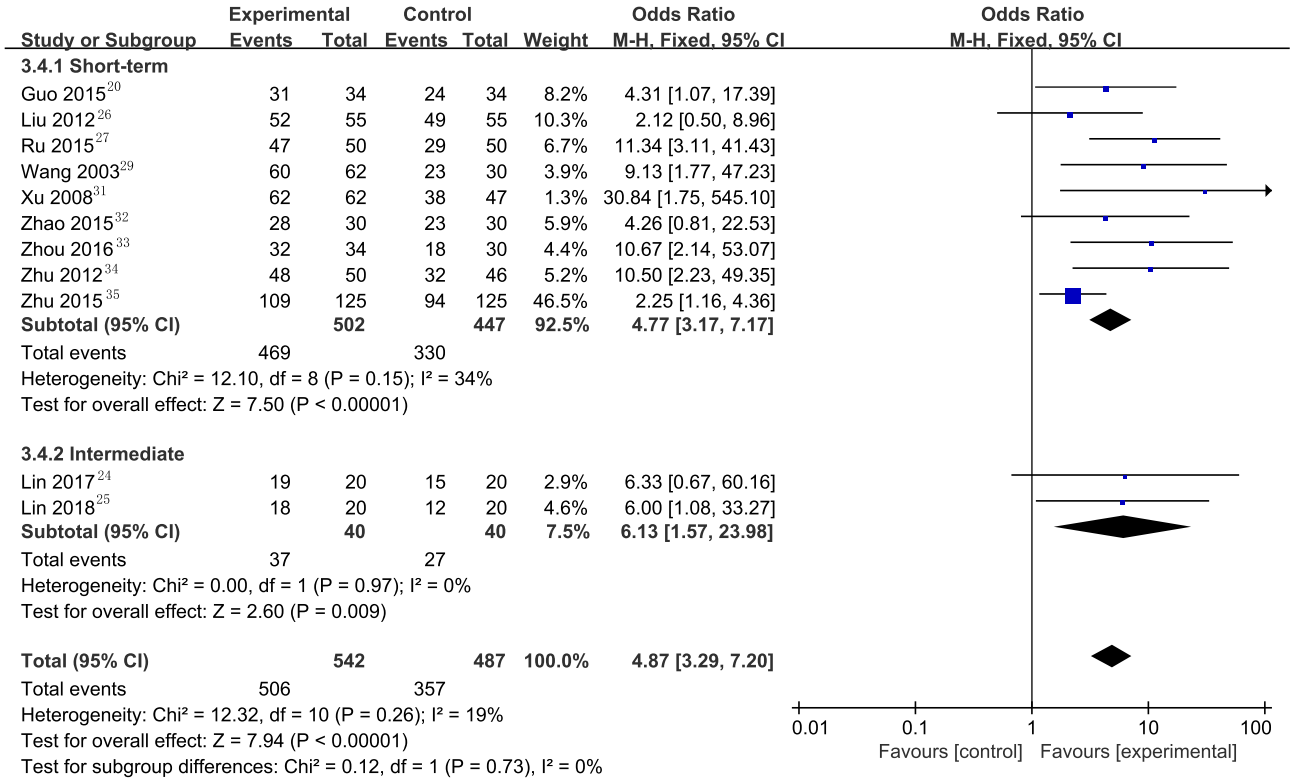

Figure 12 Overall and different follow-up times subgroup forest plot of weighted OR (95% CI) for effective rate for manual therapy versus NSAIDs.

Sensitivity Analysis

Sensitivity analyses demonstrated robustness by excluding those with a sample size less than 30, or those with unclear randomization procedures (Table S3).

Table 3 Summery of Finding

Outcome No of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty
		Without Manual Therapy	With Manual Therapy	Difference	
Manual therapy compared to no treatment for PD					
Pain intensity № of participants: 629 (8 RCTs)	–	–	–	MD **0.81 higher** (0.35 higher to 1.28 higher)	⊕◯◯◯ Very low[a,b,c]
Effective rate № of participants: 106 (3 RCTs)	**OR 8.73** (3.03 to 25.19)	50.9%	**90.1%** (86.1 to 97.6)	**39.1% more** (24.9 more to 45.4 more)	⊕⊕◯◯ Low[d]
MDQ № of participants: 309 (3 RCTs)	–	–	–	MD **3.84 higher** (2.27 higher to 5.4 higher)	⊕◯◯◯ Very low[a,d]
Manual therapy compared to placebo control for PD					
Pain intensity № of participants: 507 (9 RCTs)	–	–	–	MD 0.10 **higher** (0.37 lower to 0.58 higher)	⊕◯◯◯ Very low[a,b,c]

(*Continued*)

Table 3 (Continued).

Outcome No of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty
		Without Manual Therapy	With Manual Therapy	Difference	
Manual therapy compared to NSAIDs for PD					
Pain intensity № of participants: 507 (9 RCTs)	–	–	–	MD **3.01 higher** (1.08 higher to 4.94 higher)	⊕◯◯◯ Very low[a,b,c]
Effective rate № of participants: 1029 (11 RCTs)	**OR 4.87** (3.29 to 7.20)	73.3%	**93.0%** (90 to 95.2)	**19.7% more** (16.7 more to 21.9 more)	⊕⊕◯◯ Low[a,c]

Notes: The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. [a]Download one level for serious risk of bias: included studies did not conduct the blinding method, and unclear risk of bias in one or two domains. [b]Downgraded one level for serious inconsistent: interventions of included studies inconsistent, or the outcome indicators exist statistical heterogeneous. [c]Downgraded one level for wide confidence intervals. [d]Downgraded two level for serious imprecision: very small sample size.
Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio.

Publication Bias

As depicted in Figure 13, the likelihood of publishing bias appeared to be minimal, as indicated by the study of the funnel plot, which did not reveal any significant asymmetry. However, it is essential to approach the interpretation of funnel plot results with caution, considering inherent heterogeneity in the meta-analysis and acknowledging other potential sources of bias.

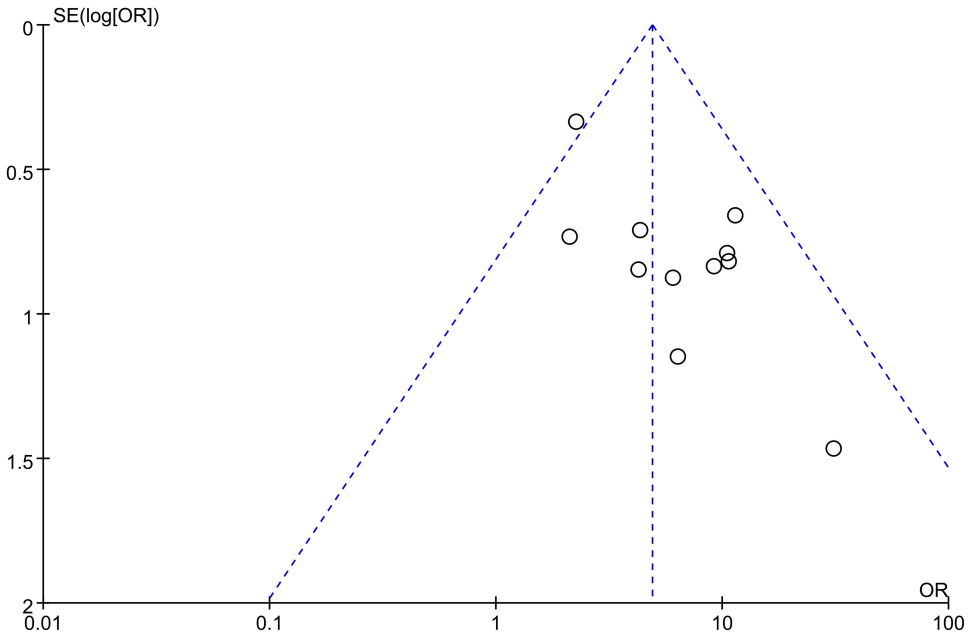

Figure 13 Funnel plot of effective rate for manual therapy versus NSAIDs.

Discussion

Summary of Main Results

We methodically examined and compiled the data from a diverse array of studies investigating manual therapy for PD in this meta-analysis. 32 studies included covered a wide variety of manual therapeutic techniques, such as massage, acupressure, foot reflexology, holographic therapy, spinal manipulative therapy, and neuromuscular therapy. By amalgamating data from these RCTs, our analysis provided a thorough overview of the effectiveness of manual therapy in addressing PD. Notably, the adverse events reported across the studies were predominantly minor in nature, with many resolving spontaneously or responding well to effective treatment.

The evidence, rated as low to very low, indicates that manual therapy for dysmenorrhea may demonstrate superior efficacy compared to both no treatment and oral NSAIDs, resulting in a more substantial alleviation of pain. These results endorse the preference for manual treatment over no treatment in patients with PD. The treatment impact estimates exceed the MCID threshold of 20%, with an effect rate of 39.1%. Nonetheless, our meta-analyses revealed that the treatment impact estimates for quality of life (MDQ, 3.84 points on a 30-to-150-point scale) and pain (NRS, 0.81 points on a 0-to-10-point scale) were marginally below thresholds of MCID thresholds among patients with PD. These results bolstered the case for utilizing manual treatment rather than oral medication in PD patients. The decrease in pain intensity by 3.01 points (95% CI: 1.08~4.94) surpassed the MCID of 2 points, while the improvement in effective rate by 19.7% (16.7~21.9) is close the MCID of 19.9%.

In studies comparing manual therapy with a placebo control (n=255, MD=0.10, 95% CI: −0.37~0.58), the results suggest that manual therapy did not exhibit superiority. Concerning this outcome, considerations arise on two fronts. Firstly, there is contemplation of the limited number of included studies and an insufficient sample size. Secondly, attention is drawn to the potential influence of the placebo effect. The placebo effect is defined as a genuine positive psychological or physiological response solely attributed to the knowledge of receiving a substance or undergoing a procedure, rather than the inherent efficacy of that substance or procedure.[50] This improvement is not initiated by the treatment itself but rather by the patient's beliefs and expectations. Previous research underscores the significance of acknowledging the placebo effect in the context of physical therapy, especially when compared with placebos associated with pharmaceuticals or other intervention measures.[51–53]

Subgroup analyses were conducted following significant heterogeneity in outcomes related to pain. In a subset characterized by a small sample size and a limited number of studies, conflicting results were observed. It is crucial to approach the interpretation of this specific subset with caution, considering its restricted representation and smaller study population, which could contribute to the observed discrepancies.

We discerned a prevalent trend of subpar research quality in the scrutinized papers, as evidenced by our comprehensive analysis of bias risk and evidence quality. The primary factor contributing to this observation is the lack of transparent data in most studies regarding the generation of random sequences and participant assignment. Furthermore, the application of blinding procedures proves challenging due to the distinctive nature of manual therapy interventions; nevertheless, a body of research[36] has demonstrated the feasibility of blinding in this context. These methodological deficiencies underscore the imperative for enhanced reporting guidelines and innovative approaches to address the challenges associated with blinding and randomization in studies focusing on manual therapy interventions.

Advantages of Manual Therapy for PD

Manual therapy provides a non-pharmacological option for addressing PD, catering to individuals who prefer non-drug interventions or seek complementary approaches alongside conventional medical treatments. The personalized nature of manual therapy allows for tailored interventions with therapists adjusting techniques based on pain severity, preferences, and overall health.

The specific mechanisms underlying the efficacy of manual therapy in addressing PD are not fully understood. However, a study by Chen et al[54] revealed that massage therapy was beneficial for PD. Because it may relieve pain by enhancing uterine blood flow and regulating aberrant levels of prostaglandin F2a (PGF2a) and prostaglandin E2 (PGE2). Farzaneh et al[55] suggested that acupressure at the *Sanyinjiao* point (SP6) can be an effective, feasible, and cost-effective

intervention for mitigating PD. The SP6 acupoint serves as the junction point of the liver, spleen, and kidney meridians. According to the traditional Chinese medicine, this intervention can strengthen the spleen function, resolve and expel dampness, and restore balance to Yin and blood, liver, and kidneys.[56] Furthermore, some individuals believe that manual therapy for dysmenorrhea is closely associated with reflex points. For instance, Mur et al[57,58] reported increased intestinal blood flow during stimulation of corresponding reflex points compared to subjects intervened with reflex stimulation on unrelated points. Similarly, Sudmeier et al[59] demonstrated increased renal blood flow, measured with Doppler sonography, with reflexology on foot points related to the kidney compared with individuals given placebo reflexology at points not associated with the kidney.

Strengths and Limitations

Prior to this research, a systematic review[60] evaluated the effect of manual therapy for PD, incorporating four studies published in 2017. In contrast to this earlier review, our study involved a more comprehensive search strategy, encompassing a greater number of studies meeting the criteria. Meanwhile, different analytical methods were employed herein. Our research aimed to extensively explore various manual therapy modalities and considered the cyclical nature of dysmenorrhea. Additionally, we defined a minimum treatment duration of at least two months, acknowledging the periodicity of menstrual pain. The control group exclusively comprised placebos and NSAIDs. This design, with a placebo control, facilitates the evaluation of the specific effects of manual therapy. Additionally, the comparison of manual therapy with NSAIDs offers insights into the relative effectiveness and potential advantages of manual therapy over standard pharmacological interventions.

This research was subjected to several limitations. Firstly, the included studies were of low quality, restricting the availability of high-quality evidence supporting the efficacy of manual therapy in treating dysmenorrhea. Secondly, various manual therapy modalities were not classified and quantified when assessing the overall effectiveness due to their diverse range. Lastly, despite conducting subgroup analyses to address significant heterogeneity observed in the meta-analysis, the issue persisted without resolution.

Implications for Clinical Practice and Research

In clinical practice, the findings underscored the potential efficacy of manual therapy in alleviating menstrual pain. Healthcare practitioners may contemplate incorporating manual therapy into their treatment protocols for individuals experiencing PD. From a research perspective, this research highlights the necessity for further investigating distinct manual therapy modalities and their comparative efficacy. Future research endeavors should strive to enhance the quality of evidence based on high-quality studies with rigorous methodologies. Additionally, exploring the mechanisms behind the effects of manual therapy on dysmenorrhea could contribute valuable insights to the field.

Conclusion

The results in this work suggested that manual therapy might alleviate menstrual pain in short-term, surpassing both no treatment and NSAIDs. However, it is impossible to rule off an effective placebo effect during manual therapy. Manual therapy demonstrated only mild adverse events, indicating a relatively safe profile. It's important to note that our study recommendations are constrained by limitations stemming from the low quality of the included RCTs. More rigorously designed trials are imperative to validate and confirm our findings.

Abbreviations

RCTs, randomized controlled trials; PD, primary dysmenorrhea; GRADE, grading of recommendations, assessment, development, and evaluation; NSAIDs, non-steroidal anti-inflammatory drugs; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; MeSH, medical subject headings; VAS, *Visual Analogue Scale*; NRS, *Numeric Rating Scale*; MPQ, *McGill Pain Questionnaire*; MDQ, *Moos Menstrual Distress* questionnaire; MCID, minimum clinically important difference; ORs, odds ratios; CIs, confidence intervals; SMD, standardized mean difference; MD, mean difference.

Ethics Approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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