Technology and Health Care 32 (2024) S385–S402
DOI 10.3233/THC-248034
IOS Press

Review Article

Effectiveness and safety of thoracic manipulation in the treatment of neck pain: An updated systematic review and meta-analysis

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Abstract.
BACKGROUND: The purpose of this meta-analysis was to evaluate the effectiveness and safety of thoracic manipulation (TM) in patients with neck pain (NP).
OBJECTIVE: The purpose of this meta-analysis was to evaluate the effectiveness and safety of thoracic manipulation (TM) in patients with neck pain (NP).
METHODS: Seven electronic databases were searched from their inception through October 2023 by two authors. The methodological quality assessments were performed with the Physiotherapy Evidence Database (PEDro) scale. Pain, cervical range of motion (ROM), disability, and quality of life (QOL) were estimated for TM treatment in patients with NP.
RESULTS: Eighteen randomized controlled trials (RCTs) with 914 patients were included with a PEDro score of 6.923 ± 3.120. Pooled effect sizes of pain (SMD $= -0.481$, 95% CI -0.653 to -0.309, $P = 0.000$), disability (SMD $= -1.435$, 95% CI -2.480 to -0.390, $P = 0.007$), QOL-physical component score (PCS) (SMD $= 0.658$, 95% CI 0.290 to 1.025, $P = 0.000$), ROM of flexion (SMD $= 0.921$, 95% CI 0.287 to 1.555, $P = 0.000$), ROM of extension (SMD $= 0.572$, 95% CI 0.321 to 0.822, $P = 0.000$), ROM of left lateral flexion (SMD $= 0.593$, 95% CI 0.075 to 1.112, $P = 0.025$) and ROM of left rotation (SMD $= 0.230$, 95% CI 0.010 to 0.450, $P = 0.04$) were favored by the TM group.
CONCLUSIONS: TM provides short-term effect on relieving neck pain, increasing cervical ROM, and disability in patients with NP without serious side effects. Continuous therapy and distraction therapy are recommended as optimal choice on reducing pain and improving cervical ROM, especially in patients with chronic NP (> 3 months). The TM-induced improvements in the QOL of patients with NP should be verified by more further high-quality RCTs.

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Keywords: Thoracic manipulation (TM), thoracic spine manipulation, chronic neck pain, neck pain, cervical range of motion (ROM), disability

1. Introduction

Neck pain (NP) is a common disease and a potential cause of disability. The annual prevalence of NP is approximately 15%–20% in general population and 15%–60% in the workforce. Based on the duration of the symptoms, NP is divided into acute NP (less than 7 days), subacute NP (between 7 days and 3 months) and chronic NP (more than 3 months) [1]. The main symptom of NP is cervical pain and stiffness which usually radiate to the occiput, nuchal muscles, shoulders and upper limbs [2]. These symptoms affect patients' daily life and work, cause disability, increase social burden, and even affect patients' mood, leading to anxious or depression. According to the Global Burden of Disease 2010 Study, NP is the fourth leading cause of disability, rank behind back pain, depression, and arthralgias [3].

NP management may be applied using a different treatment approach's like; acupuncture, massage therapy, exercise therapy, traction, yoga and spinal manipulation. Although these interventions have some effects on patients with NP, the evidence for these methods is insufficient [4]. Furthermore, the use of cervical manipulation can cause side effects, such as neurological deficits, and headache. Due to the safety of thoracic mobilization or manipulation (TM), the use of TM has gradually increased [5,6]. TM is defined as the mobilization or manipulation technique acting on any segment of the thoracic spine, including the cervicothoracic junction. TM include both passive and skilled manual therapy techniques that are applied to joints and associated soft tissues at different speeds and amplitudes using interactive physiological or assistive movements to achieve therapeutic purposes [7]. TM is commonly used in the treatment of pain near to thoracic vertebrae, especially in patients with NP [8]. A meta-analysis pointed out that thoracic manipulation has short term effect on the treatment of specific neck pain [9]. However, less previous meta-analysis evaluated the long-term effect and improvement of cervical range of motion (ROM) of TM [10,11,12]. The Neck Pain Guidelines (2017) recommended TM as Grade B or C evidence for the treatment of NP [13]. While, a lot of new research have published since 2017 which may change the results. Therefore, an updated meta-analysis is needed to re-evaluate the effect of TM. Hence, the aim of this review was to reassess the long - and short-term effects of TM on pain, disability and ROM in the management of NP.

2. Method

2.1. Search strategy

An electronic search of the databases PubMed, Ovid, Embase, Medline, Cochrane Library, Wiley Online Library, and Science Direct was performed from their inception to October 1, 2022. We have registered in the PROSPERO database as (CRD42023426480) accessed at https://www.crd.york.ac.uk/PROSPERO.

The search was restricted to published articles written in English. The keywords for Science Direct were as follows: ("cervical vertebra" OR "neck pain" OR "spondylosis" OR "cervical spondylopathy") AND ("thoracic manipulation" OR "thoracic spine manipulation" OR "thoracic thrust manipulation" OR "thoracic spine mobilization" OR "thoracic spine mobility"). The keywords used in the other databases were ("cervical vertebra" OR "neck pain" OR "spondylosis" OR "cervical spondylosis" OR "cervical spondylopathy" OR "cervical vertebra disease"), ("thoracic manipulation" OR "thoracic spine manipulation" OR "thoracic thrust manipulation" OR "thoracic nonthrust manipulation" OR "thoracic spine mobilization" OR "thoracic spine mobility" OR "thoracic nonthrust mobilization" OR "thoracic spine joint mobilization") and ("randomized controlled trial" OR "RCT" OR "randomized" OR "controlled" OR "trial" OR "clinical"). The Boolean operator "AND" linked the three phrases. Titles and abstracts found in searches from the above databases were examined by two authors, and full texts of potentially eligible studies were subsequently screened.

To be as comprehensive as possible, reference lists of relevant reviews were manually searched by two separate authors to identify additional randomized controlled trials (RCTs). Final eligibility was determined through discussion when a discrepancy existed.

2.2. Selection criteria

Two authors came to a consensus regarding the selection criteria applied independently. Studies were included if they met the following criteria: (1) Patients complained of NP or were diagnosed with NP; (2) The ages were between 18 and 60 years; (3) The articles were randomized controlled trials (RCTs); (4) The treatment group received treatment that included TM, and the comparison group received treatment that included manipulations/mobilization in other regions, sham TM, exercise or physiotherapy; (5) There was at least one measurement of pain or cervical ROM; (6) NP caused by cervical spinal disorder.

Studies were excluded if they met the following criteria: (1) Diagnosed with a specific NP, such as cervical radiculopathy, myelopathy, and fibromyalgia syndrome, or had a history of whiplash or cervical surgery; (2) The purpose of comparison between the experimental group and the control group was not to test the effectiveness of TM; (3) The language was not English; (4) The full text was not available; (5) Data were not extracted. A consensus was reached by the authors through discussion if a discrepancy existed.

2.3. Data collection and quality assessment

Data extracted independently by two authors included characteristics of the study and population, details of the interventions for the experimental group and control group separately, outcomes, and side effects. Outcomes for this review were pain, cervical ROM, neck disability, and QOL. Pain was assessed by Numeric Pain Rating Scale (NPRS) or the Visual Analog Scale (VAS), disability was assessment by Neck Disability Index (NDI) or the Northwick Park Pain Questionnaire (NPQ), while, QOL were assessed via the SF36 health-related quality of life questionnaire (SF36). As one of a main outcome, cervical ROM were collected in all planes. The data we needed that were not mentioned are represented by "no report" (NR).

The 11-item Physiotherapy Evidence Database (PEDro) scale was used to assess the methodological quality of the articles, with sufficient reliability for evaluating the physical therapy RCT quality based on consensus judgments [14]. The scores of eligible RCTs were cited as the available scores from the PEDro database or were assessed manually by two authors separately. The PEDro scale score item consisted of random allocation, concealed allocation, baseline similarity, blinding of subjects, therapists and assessors, measures of key outcomes from more than 85% of subjects, intention-to-treat analysis, between-group statistical comparisons, point measures and measures of variability. An article that scored seven or above was considered high quality, a score of five to six was considered fair quality, and a score of four or below was considered poor quality [9].

Table 1
The methodological quality of the included studies

ID	1	2	3	4	5	6	7	8	9	10	Score	Eligibility criteria
[1]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	Y
[15]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	Y
[16]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	Y
[17]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	N
[18]	Y	N	Y	N	N	N	N	N	Y	Y	4	Y
[19]	Y	N	Y	N	N	N	Y	N	Y	Y	5	Y
[20]	Y	N	Y	N	N	Y	Y	N	Y	Y	6	N
[21]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7	Y
[22]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	Y
[23]	Y	Y	Y	N	N	N	Y	N	Y	Y	6	Y
[24]	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8	Y
[25]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9	Y
[26]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	Y
[27]	Y	Y	Y	N	N	Y	N	N	Y	Y	6	Y
[28]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7	Y
[29]	Y	Y	Y	N	N	Y	N	Y	Y	Y	7	Y
[30]	Y	Y	Y	N	N	Y	N	Y	Y	Y	7	Y
[31]	Y	Y	Y	N	Y	Y	Y	N	Y	Y	8	Y

Notes: 1, Random allocation; 2, Concealed allocation; 3, Baseline similarity; 4, Blinding of subjects; 5, Blinding of therapists; 6, Blinding of assessors; 7, Measures of key outcomes from more than 85% of subjects; 8, Intention to treat analysis; 9, Between-group statistical comparisons; 10, Point measures and measures of variability.

2.4. Statistical analyses

For continuous data, the standard mean difference (SMD) with 95% confidence interval (CI) was used. The I^2 statistic was used to assess statistical heterogeneity in the included studies, while $P < 0.10$ and $I^2 > 50\%$ represented substantial heterogeneity. In case of any heterogeneity, the following methods were applied to explain: (1) sensitivity analysis using influence analysis, metan-based (mataninf); (2) meta-regression and subgroup analysis; and (3) a random-effects model using the DerSimonian-Laird method. Funnel plots and Begg's test/Egger's test, a trim-and-fill adjusted analysis or the fail-safe number (Nfs) represented publication bias. Subgroup analyses were performed according to duration, course of treatment, direction, and comparison.

Statistics Data Analysis Special Edition software (Stata SE, V.12.0; Stata Corp LP, College Station, Texas, USA) was applied in the statistical analysis.

3. Computer simulation and results

3.1. Statistical analyses study selection

A total of 468 articles retrieved from 7 electronic databases and manual searches were identified based on the predefined search strategy. After removing duplicates and ineligible articles by screening titles and abstracts, 132 potentially eligible articles were identified. The full texts of these articles were scrutinized, leading to the final inclusion of 18 eligible studies included in this review [1,15,16,17,18,19,20,21,22,23, 24,25,26,27,28,29,30,31]. The search flowchart is shown in Fig. 1.

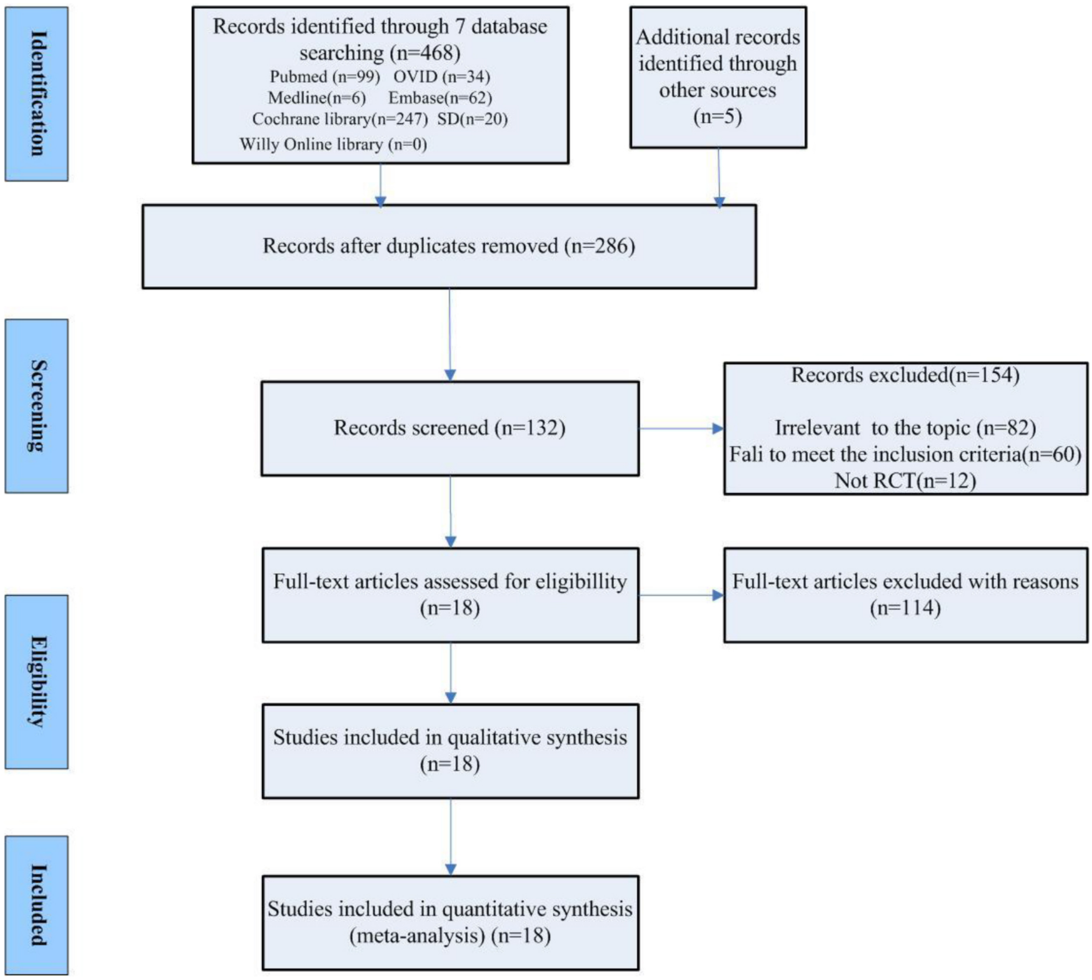


Fig. 1. Search flowchart of the meta-analysis. Flow diagram illustrating search strategy.

3.2. *Methodological quality*

All eligible articles assessed the methodological quality according to the PEDro scale. The quality score ranged from 4 [18] to 9 [25] points (6.923 ± 3.120), which indicated that the referenced studies were of fair quality. Twelve articles [1,16,17,21,22,24,25,26,28,29,30] were rated as high quality, four [19, 20,23,27] as fair, and one [18] as poor. In all of the included studies, the reasons for score deductions primarily involved the blinding of subjects and therapists, the intention-to-treat analysis and the blinding of assessors. The scores of 15 articles [1,16,17,18,19,20,21,22,23,24,25,26,27,28,29] were obtained from the PEDro database website, while 2 articles [15,30] were scored independently by two authors, who then reached a consensus. The details of the PEDro scores are shown in Table 1.

3.3. *Study characteristics*

This review involved 18 studies with 914 subjects (471 in the experimental group, 443 in the control group). The characteristics of the population, interventions, comparison and outcomes are presented as follows, and more details are given in Table 2.

Table 2
The characteristics of the included studies

Author year	Cases E/C	NPT	Duration	D	Course of treatment	E vs C	Measures
Paulo 2015	32 16/16	Pain or fatigue	> 6 m	NR	a single session	TM vs placebo	VAS
Gonzalez 2009	45 23/22	AMNP	E, 18 d ± 6; C, 17 d ± 5	Distraction	TM: 1 session/w, Electro/ thermal: 2 session/w; 3 w	TM + electro/thermal vs electro/thermal	NPRS; NPQ ROM
Herman 2011	120 60/60	CMNP	>3 m	AP	15 min/session, 2 sessions/w, 4 w	TM + IRR/education vs IRR/education	NPRSROM NPQ SF36
Suvarnnato 2013	26 13/13	CMNP	> 3 m	Screw thrust	A single session	TM vs placebo	VAS; ROM
Aslak 2004	41 24/17	Neck shoulder	NR	NR	4 sessions/1 w	TM vs exercise	VAS
Jinmo 2015	30 15/15	CMNP	>12 w	AP	30 min/sessions, 3 sessions/w, 6 w	TM + CST vs CST	VAS
Kwan- 2016	31 16/15	CMNP	> 3 m	NR	35 min/d, 3 d/w, 10 w	TM + DCF vs DCF	VAS;NDI; ROM NDI
Joshua 2010	140 70/70	NP	E, 62.5 d ± 53.3 C, 64.4 d ± 61.3	Distraction AP	2 session/w, 1 w 1 session/w, 3 w	TM + exercise vs exercise	NPRS;
Raquel 2012	62 33/29	Bilateral CMNP	E, 3.8 y ± 1.5 C, 3.7 y ± 1.5	AP	A single session	TM vs cervical thrust	NPRS; ROM
Rob Sillevis 2010	100 50/50	CMNP	E, 23.3 m; C, 25.3 m	AP	A single session	TM vs placebo	sVAS
Joshua 2005 .	36 19/17	MNP	E, 12.2 w ± 3.5; C, 13.2 w ± 4.2	AP	A single session	TM vs placebo	VAS
Cheryl L 2017.	24 12/12	MNP	Less than 6 w	AP	A single session	TM vs placebo	NPRS
González 2009	45 23/22	MNP	E, 19.5 d ± 4.5 C, 18.7 d ± 3.9	Distraction	2 session/w; 5 session	TM + electro/thermal vs electro/thermal	VAS, NPQ ROM;
John 2008	32 22/10	MNP	NR	AP	A single session	TM vs placebo	ROM
Masaracchio 2013	66 34/32	MNP	E, 37.3 d ± 25.3 C, 34.5 d ± 26.9	AP	3 sessions	TM + HEP vs CM + HEP	NPRS; NDI
Puentedura 2011	24 10/14	MNP	18.8 d ± 9.3	distraction; AP	1–3 sessions, 1 w 4–5 sessions, 1 w	TM + exercise Vs CM + exercise	NPRS; NDI
Khoja 2015	18 10/8	MNP	> 3 m	NR	2 sessions /1 w; 6 w	TM + multimodal vs multimodal	NPRS, NDI ROM
Shriya 2020	4221/21	MNP	NR	NR	A single session	TM VS CT junction mobilization	NRS ROM

Notes:; D, duration; HEP, home exercise program; M, month; NDI, neck disability index; NPQ, the Northwick Park Neck Pain Questionnaire; NPRS, numeric pain rating scale; NR, no reported; ROM, range of motion; VAS, visual analogue scale; W, week; NPT,neck pain Type; P, position; MNP, mechanical neck pain; NP, neck pain; CM,cervical mobilization; AP, anterior-posterior; D, distraction.

3.3.1. Patients

The age of the participants ranged from 18 to 65 years. Only two articles explicitly stated gender differences, one of which consisted of all female patients and the other of which had more female patients than male patients [1,27]. In terms of duration, the participants in 3 articles [15,26,29] were in the acute phase, and those in 3 articles [25,28,31] were in the acute and subacute phases. Seven articles reported the chronic phase [1,16,17,19,20,22,23]. Participants in 2 articles [21,30] were in all three phases, and the phase was not clearly mentioned in 3 articles [18,24,27].

3.3.2. Interventions

TM techniques varied substantially in the included studies in terms of the patient position, segment, range, velocity, amplitude, direction of TM and course of treatment. The patient position included seated (2 articles) [15,26], supine (6 articles) [1,16,20,22,23,24], prone (2 articles) [17,31] and seated plus supine (3 articles) [19,21,29]. Ten articles [1,20,21,22,23,24,25,28,29,31] mentioned that the velocity of TM was high, while other articles did not report the velocity. Six articles [1,20,24,25,28,31] mentioned that the amplitude of TM was low, while others did not clearly report the amplitude. This review subgrouped the TM technique using the direction of TM classification into anterior-posterior [16,19,22,23,24,25,27, 28] distraction [15,26] or screw thrust [17] directions and performed a subgroup analysis.

3.3.3. Comparison

In the included studies, six articles [1,17,23,24,25,27] compared TM to placebo TM, six articles [18,19, 20,21,29,31] compared TM plus exercise to exercise, and the others compared TM plus comprehensive physical therapy to comprehensive physical therapy.

3.3.4. Outcomes

The outcomes included pain (VAS in 7 studies [1,17,19,20,23,24,26], NPRS in 9 studies [15,16,21,22, 25,28,29,30,31], CROM in 9 articles) [15,16,17,20,22,26,27,30,31], disability (NPQ in 3 articles [15,16, 26], NDI in 5 articles [20,21,28,29,30], and QOL (in 1 article, 120 patients) [16]. Eight studies [1,17, 22,23,24,25,27,31] assessed immediate effects after a single session, and nine articles [15,16,18,19,20, 21,26,28,29,30] examined cumulative effects. One article [18] did not describe immediate or short-term results but only follow-up results (12 months). The follow-up varied from 24 hours to 12 months in 6 included studies. The follow-up visits were more than 6 months in only 4 studies [16,18,21,29].

3.3.4.1. Effect size of pain

Pain data (16 articles, 840 subjects) were assessed with the VAS and NPRS, which showed a high correlation [33]. The pooled effect size indicated significant heterogeneity ($P = 0.000$, $I^2 = 86.6\%$) [1, 15,16,17,19,20,21,22,23,24,25,26,28,29,30,31]. After the sensitivity analysis, 7 articles [15,19,20,23, 25,29,31] were excluded, and the heterogeneity disappeared ($P = 0.100$, $I^2 = 40.2\%$). Then, a fixed-effects model was used for the remaining studies (9 articles, 545 subjects), and the results showed that TM reduced NP (SMD $= -0.481$, 95% CI -0.653 to -0.309, $P = 0.000$), which is shown in forest plots (Fig. 2A). Moreover, a random-effects model was used for the excluded studies (7 articles, 295 subjects), and the pooled effect size of pain indicated that TM cannot reduce NP (SMD $= -0.743$, 95% CI -1.837 to 0.352, $P = 0.183$) (detailed in S1 Table). According to the subgroup and regression analyses among all studies, no evidence indicated that the duration of NP, course of treatment, direction of TM and comparison had an impact on heterogeneity. Moreover, subgroup analysis of excluded studies also showed similar results. Details are shown in S2 Table. The publication bias performed by Egger's

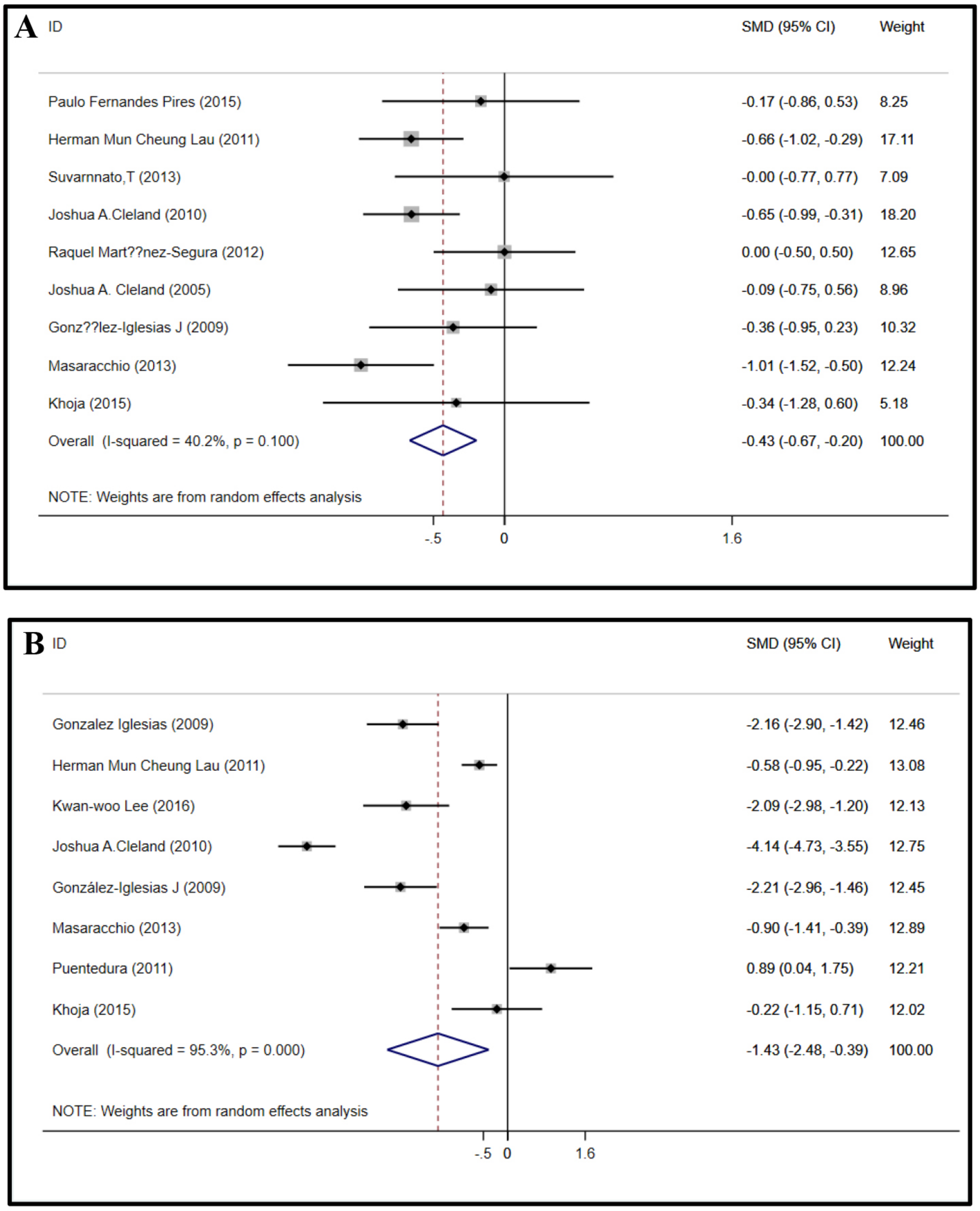


Fig. 2. Forest plots of pain and disability. Efficacy of TM vs placebo. Forest plot was built considering $p < 0.05$ as statistically significant effect.

tests (Fig. 3A) and Begg's tests revealed no large migration ($P = 0.685$; $P =$A 0.610, respectively); the details are shown in S3 Table.

Follow-up assessments for pain (at least six months) were reported in 4 articles with 325 subjects [16,18, 21,29]. The extracted data were pooled with a random-effects model and showed substantial heterogeneity and no statistical significance ($I^2 = 97.0\%$, $P = 0.000$; SMD $= -0.248$, 95% CI -1.923 to 1.427, $P = 0.772$), as detailed in S1 Table.

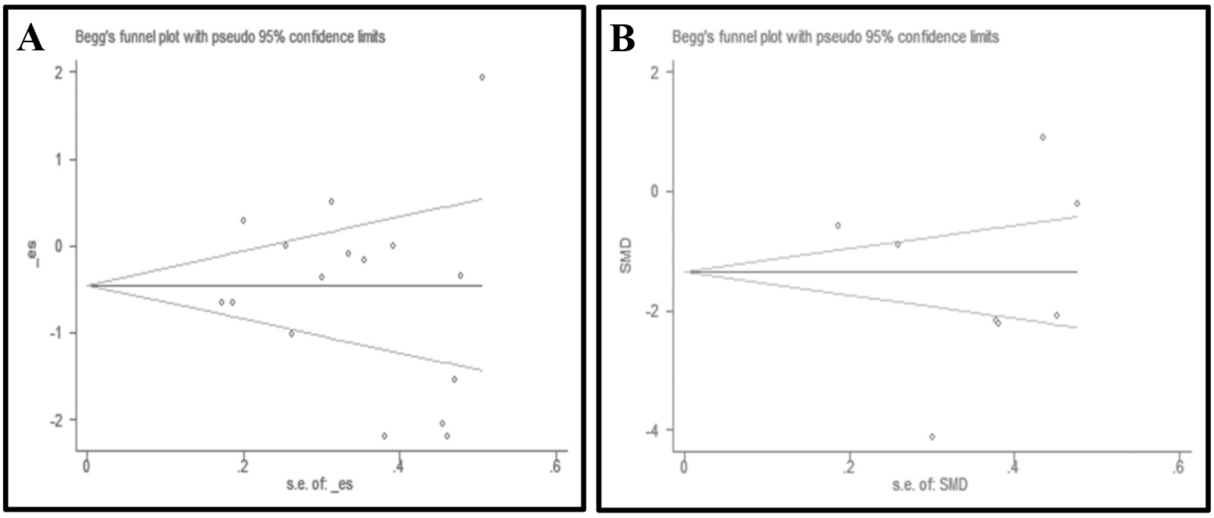


Fig. 3. Funnel plots of pain and disability.

3.3.4.2. Effect size of ROM

The cervical ROM was measured across all 9 studies (421 patients) [15,16,17,20,22,26,27,30,31]. Separate meta-analyses were conducted to evaluate the changes in cervical ROM in all planes. Meta-analysis of 8 studies [15,16,17,20,22,26,30,31] ($n = 389$) that evaluated the change in cervical flexion showed significant heterogeneity ($P = 0.000$, $I^2 = 87.3\%$), which still existed after the sensitivity analysis. The results indicated that TM improved the cervical ROM of flexion in patients with NP (SMD = 0.921, 95% CI 0.287 to 1.555, $P = 0.000$, S1 Table). The forest plot of the ROM of flexion is shown in Fig. 4A1. Subgroup analysis showed that the course of treatment was the main cause of heterogeneity. Moreover, the pooled data demonstrated that TM had a better effect on cervical ROM of flexion in patients with distraction direction (SMD = 2.39, 95% CI 1.71 to 3.07, $P = 0.000$) (Fig. 4A2). Subgroup analysis of the course of treatment demonstrated that TM improved the cervical ROM of flexion in patients undergoing continued treatment (SMD = 1.269, 95% CI 0.994 to 1.544, $P = 0.000$) (Fig. 4A3). Details are shown in S2 Table. Meta-analysis of 8 studies [15,16,17,20,22,26,30,31] ($n = 389$) that evaluated the change in cervical extension showed significant heterogeneity ($P = 0.000$, $I^2 = 81.1\%$). After the sensitivity analysis, 3 studies [15,26,31] were excluded, and the heterogeneity disappeared ($P = 0.551$, $I^2 = 0\%$). Then, a fixed-effects model was used for the remaining studies (5 studies, 257 subjects), and the results showed that TM improved the cervical ROM of extension (SMD = 0.572, 95% CI 0.321 to 0.822, $P = 0.000$), which is shown in forest plots (Fig. 4B). Moreover, a random-effects model was used for the excluded studies (3 studies, 132 subjects), and the pooled effect size indicated that TM did not improve cervical ROM of extension (SMD = 1.620, 95% CI -0.033 to 3.273, $P = 0.055$) (detailed in S1 Table). Subgroup analysis revealed that duration of disease and direction of TM were the main causes of heterogeneity. The pooled data showed that TM had a better effect on patients undergoing continued treatment and distraction direction ($P = 0.000$, $P = 0.000$, respectively), which are shown in S2 Table. Meta-analysis of 7 studies [15,16,17,22,26,30,31] ($n = 358$) that evaluated the change in cervical left lateral flexion showed significant heterogeneity ($P = 0.000$, $I^2 = 80.4\%$), which still existed after the sensitivity analysis, while the results indicated that TM improved the cervical ROM of left lateral flexion (SMD = 0.593, 95% CI 0.075 to 1.112, $P = 0.025$, S2 Table). The forest plot of the ROM of left lateral flexion is shown in Fig. 4C. Subgroup analysis indicated that heterogeneity was caused by the course of

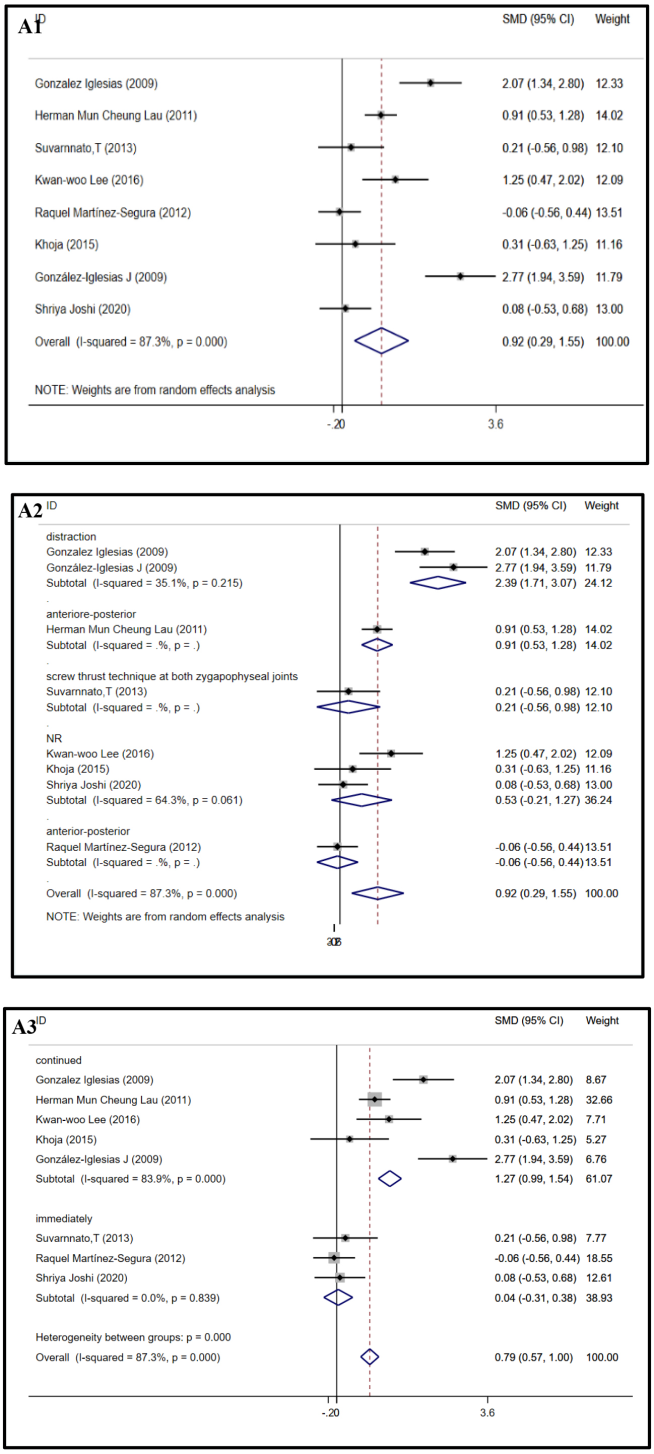
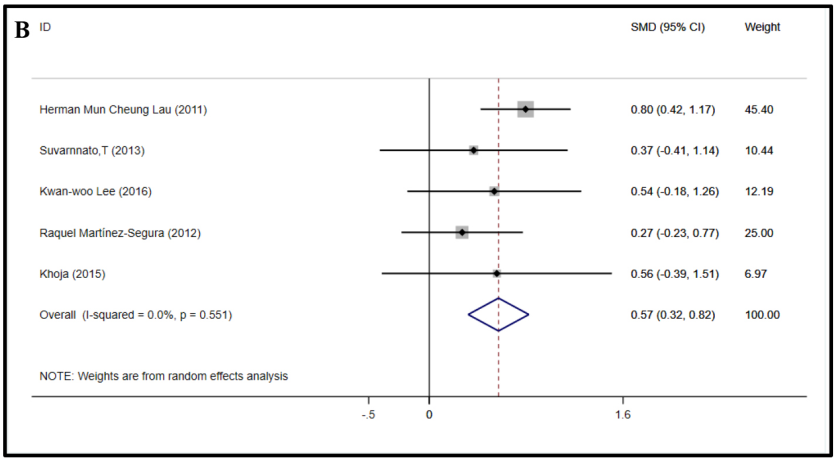
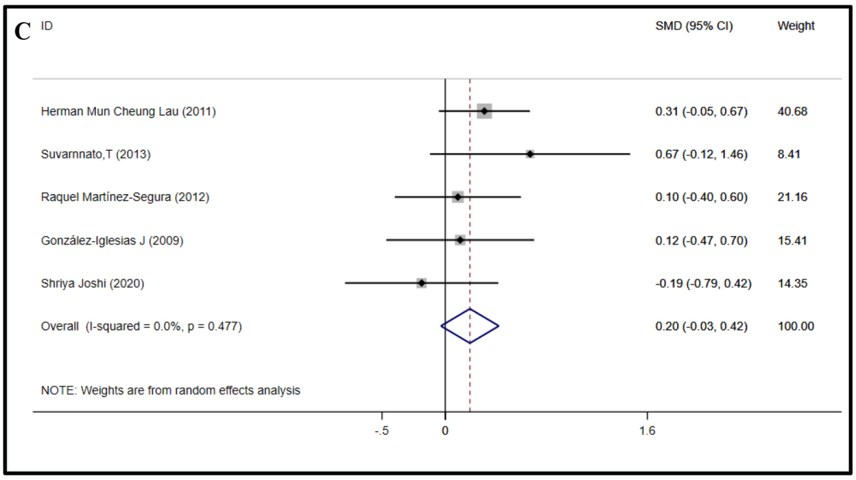
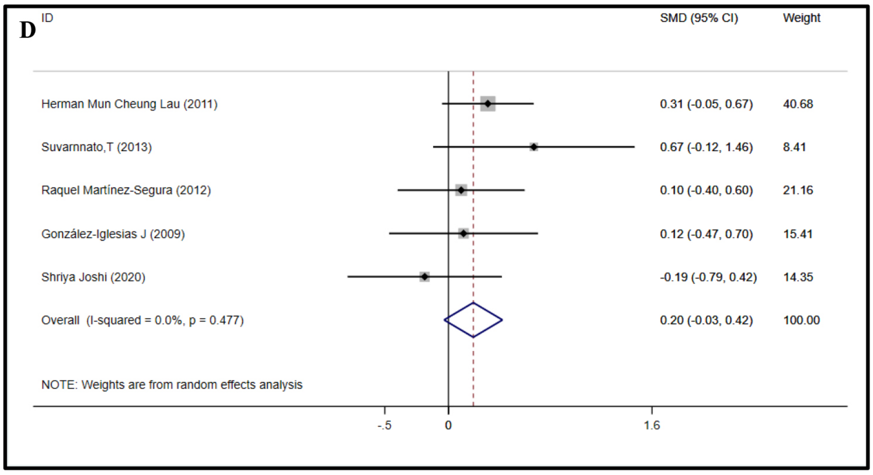


Fig. 4. Forest plots of ROM in all planes.







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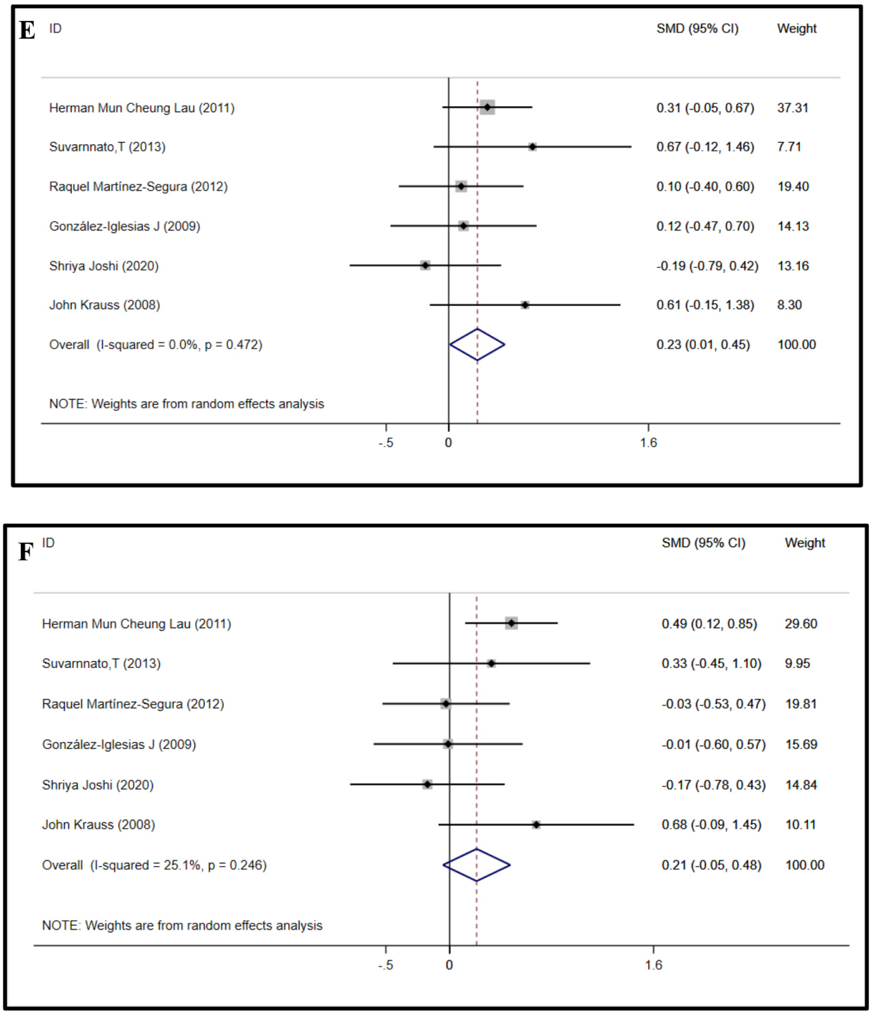

Fig. 4. continued.

treatment, and the pooled data showed that TM can improve the cervical ROM of left lateral flexion in patients receiving continued treatment. Details are shown in S2 Table. Meta-analysis of 7 studies [15,16, 17,22,26,30,31] ($n = 358$) that evaluated the change in cervical right lateral flexion showed significant heterogeneity ($P = 0.000$, $I^2 = 80.5\%$). After the sensitivity analysis, 2 studies [15,30] were excluded, and the heterogeneity disappeared ($P = 0.477$, $I^2 = 0\%$). Then, a fixed-effects model was used for the remaining studies (5 studies, 295 subjects), and the results showed that TM did not improve the cervical ROM of right lateral flexion (SMD $= 0.195$, 95% CI -0.034 to 0.425, $P = 0.095$), which is shown in forest plots (Fig. 4D). Moreover, a random-effects model was used for the excluded studies (2 studies, 63 subjects), and the pooled effect size indicated that TM improved the cervical ROM of right lateral flexion (SMD $= 1.893$, 95% CI 1.251 to 2.535, $P = 0.000$) (detailed in S1 Table). Subgroup analysis indicated that duration of disease, course of treatment and direction of TM are the causes of heterogeneity, and the results demonstrated that TM can improve cervical ROM of right lateral flexion in long duration (> 3 months) patients or patients undergoing continued TM treatment. Details are shown in S2 Table. Meta-analysis of 8 studies [15,16,17,22,26,27,30,31] ($n = 390$) that evaluated the change in cervical left rotation showed significant heterogeneity ($P = 0.002$, $I^2 = 77.4\%$). After the sensitivity analysis, 2 studies [15,30] were excluded, and the heterogeneity disappeared ($P = 0.472$, $I^2 = 0\%$). Then, a fixed-effects model was used for the remaining studies (6 studies, 327 subjects), and the results showed that TM improved the cervical ROM of left rotation (SMD = 0.230, 95% CI 0.010 to 0.450, $P = 0.04$), which is shown in forest plots (Fig. 4E). Moreover, a random-effects model was used for the excluded studies (2 studies, 63 subjects), and the pooled effect size indicated that TM can improve cervical ROM of left rotation (SMD = 1.893, 95% CI 1.251 to 2.535, $P = 0.000$) (detailed in S1 Table). Subgroup analysis demonstrated that duration of disease, course of treatment and direction contributed greatly to the heterogeneity, and the results showed that TM is prior to other treatment methods in patients with long duration (> 3 months) or undergoing continued or anteriore-posterior treatment (S2 Table). Meta-analysis of 8 studies [15,16,17,22,26,27,30,31] ($n = 390$) that evaluated the change in cervical right rotation showed significant heterogeneity ($P = 0.03$, $I^2 = 57.1\%$). After the sensitivity analysis, 2 studies [15, 30] were excluded, and the heterogeneity disappeared ($P = 0.246$, $I^2 = 25.1\%$). Then, a fixed-effects model was used for the remaining studies (6 studies, 327 subjects), and the results showed that TM did not improve the cervical ROM of right rotation (SMD = 0.212, 95% CI −0.053 to 0.477, $P = 0.117$), which is shown in forest plots (Fig. 4F). Moreover, a random-effects model was used for the excluded studies (2 studies, 63 subjects), and the pooled effect size indicated that TM improved cervical ROM of right rotation (SMD = 1.458, 95% CI 0.896 to 2.020, $P = 0.000$) (detailed in S1 Table). Subgroup analysis indicated that duration of disease and course of treatment were the main causes of heterogeneity. Moreover, the results demonstrated that TM did not benefit patients with a long duration (> 3 months) or who underwent immediate treatment (S2 Table).

The publication bias of cervical ROM in all planes was separately performed by Begg's tests and Egger's tests. The results showed that publication bias of cervical ROM in all planes was not identified in Begg's tests and Egger's tests, which is shown in S3 Table (Fig. 5).

3.3.4.3. Effect size of disability

Disability functions were assessed with NDI and NPQ in 8 articles (489 subjects) [15,16,20,21,26,28, 29,30]. The NDI and NPQ scores were merged due to the high correlation between them [34]. The pooled effect size of disability showed significant heterogeneity ($P = 0.000$, $I^2 = 95.3\%$) which still exist after the sensitivity analysis but showed positive results (SMD = −1.435, 95% CI −2.480 to −0.390, $P = 0.007$, S1 Table), and the forest plot is shown in Fig. 2B. The subgroup analysis showed that TM improved disability in NP patients regardless of disease duration and treatment direction. Regarding the variance in the duration of NP, the intervention of the control group and the course of treatment, no evidence showed that these factors were the cause of heterogeneity (S2 Table). Publication bias was assessed by Begg's tests (Fig. 3B) and Egger's tests and indicated no publication bias ($P = 0.902$ and $P = 0.700$, respectively), which is shown n S3 Table.

Meta-analysis of disability follow-up data for more than six months in 3 articles with 284 subjects showed no statistical significance (SMD = −1.512, 95% CI −4.859 to 1.835, $P = 0.376$, S2 Table) [16, 21,29].

3.3.4.4. Effect size of QOL

QOL was evaluated with the health-related quality of life questionnaire (SF36) in 1 study (120 subjects) [16] which consisted of a mental component score (MCS) and physical component score (PCS) [35]. Consequently, the meta-analysis was unable to perform. The SMD (−0.107) and 95% CI (−0.465 to 0.251) of the MCS indicated that the TM experimental group had a greater effect than the control group, but this was not statistically significant ($P = 0.558$). The SMD (0.658) and 95% CI (0.290 to 1.025) of PCS showed that TM improved the QOL-PCS ($P = 0.000$, S1 Table).

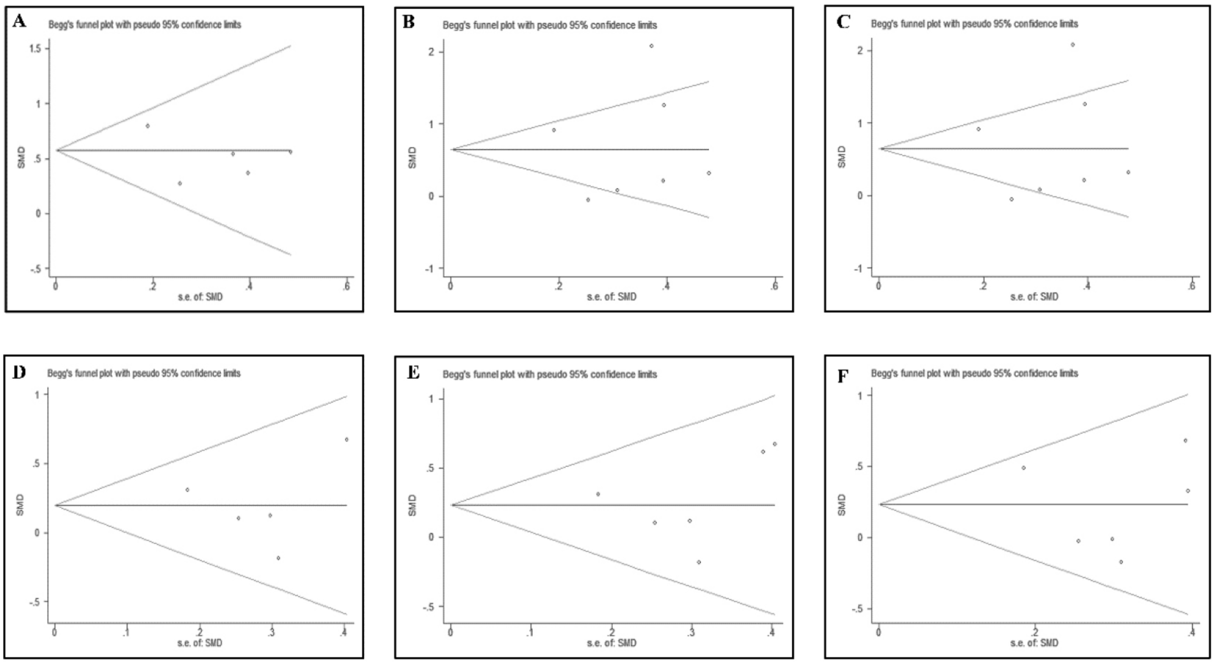

Fig. 5. Funnel plots of ROM in all planes.

3.4. Adverse events

Only 2 articles clearly stated that patients presented adverse reactions, one [22] reported fatigue after receiving TM and the another one [29] reported headache and upper back pain. Seven articles [16,20,21, 24,25,27,28] clearly reported that there were no adverse reactions after receiving TM. The remaining 8 articles [1,15,17,18,19,23,26,30] did not report whether adverse events had occurred.

4. Discussion

This meta-analysis evaluated the effect of TM in patients with NP. To the limit of our knowledge, this is a preliminary meta-analysis study that simultaneously assesses improving effects of TM on pain, cervical ROM, QOL and disability among subjects with NP. This review included 18 RCTs with 914 patients and demonstrated that TM provide a short-term effect on improving pain, ROM, QOL-PCS and neck disability among patients with NP.

The results of the present review demonstrated that TM provide a short-term effect on alleviating pain, especially in patients with a long duration ($>$ 3 months) or those undergoing continued treatment or distraction treatment method. This finding is consistent with the results of previous reviews investigating TM for NP [10,36]. Our further study found that patients undergoing continued treatment or distraction treatment method had better effect than immediately treatment or other direction treatment. Our follow-up study showed that TM didn't produce a long-term effect to improve pain among NP patients. In terms of improving cervical ROM, our results showed that TM improved the cervical ROM in all directions other than right rotation. Subgroup analysis showed that continued treatment was better than immediately treatment methods in improving cervical ROM. Compared with exercise, TM performed a better effect in cervical ROM on flexion, left lateral flexion, right lateral flexion. Moreover, better effects were also observed in patients with a long duration ($>$ 3 months) when evaluating the cervical ROM on right lateral flexion and left rotation. To the limit of our knowledge, this is a preliminary meta-analysis study assessing improving cervical ROM. In order to evaluate cervical ROM more accurately, we assessed the improving cervical ROM from all planes. Though, cervical ROM was not statistically significant at right rotation, TM was roughly considered to be effective in improving cervical ROM, which is consistent with the results of previous studies [20,30]. This review also indicated that TM improved disability when evaluating the outcomes by NDI and NPQ. Although the pooled effect sizes of follow-up disability data were not statistically significant, the NDI results exceeded the minimal clinically important differences (MCIDs), which were used to assess whether an intervention is clinically meaningful [21]. Therefore, the results demonstrated that patients with NP who received TM experienced long-term disability improvements. Our review only included one article assessing QOL, meta-analysis was unable to performed. The systematic review indicated that TM had a significantly improvement in QOL-PCS. Finally, our study proved that TM was a relatively safe method for NP, although meta-analysis of safety data was not conducted. In all included studies, only two reported mild adverse events, such as headache, upper back pain and fatigue after TM. Therefore, the clinician or physical therapist may use continuous therapy techniques or distraction therapy as treatment options for reducing pain and improving cervical ROM, especially in patients with chronic NP ($>$ 3 months).

Compared with previous meta-analyses focusing on this topic [9,12,37,38], although the benefits of TM on patients with NP remained similar, there were still differences from previous reviews. First, this study included more RCTs and a larger sample size. Second, the improving cervical ROM of TM on NP patients were first analyzed in this study. Third, this study analyzed the methodological quality with the PEDro scale but not the Cochrane Collaboration scale [39], which was not specifically targeted in physical therapy RCTs [12]. Finally, subgroup analyses according to the duration of NP, the course of treatment, comparison and the direction of TM were analyzed to optimize the clinical application of TM, while none of the others were analyzed.

Several limitations existed in this review. First, the influence of TM on the participation and environmental level in patients with NP was not investigated due to a lack of relevant data [40]. Second, considerable heterogeneities existed in our study due to the variations in the TM protocols and control interventions. In the included studies, the standardization of TM protocols was challenged by the treatment sessions, manipulation direction, and vertebral segment. The control interventions also varied and were diverse from each other. Moreover, two studies were proven to be the main causes of heterogeneity in sensitivity analysis when assessing cervical ROM of right lateral flexion, left rotation and right rotation, which were conducted by Gonzalez Iglesias et al. [32] and Shriya Joshi et al. [30] Compared with other studies, research led by Gonzalez Iglesias et al. [32] included patients with acute mechanical neck pain, which is different from other studies. However, a study led by Shriya Joshi et al. [30] did not demonstrate the details of duration, position, direction, segment, range velocity and amplitude. Third, the blinding of therapists and subjects was not well conducted in most of the included studies due to the nature of physical therapy [41]. Moreover, QOL was evaluated by only one article, which largely influenced our results. Therefore, future studies are strongly recommended to evaluate QOL and describe the intervention process in detail, including the operation segment, patient and therapist's position, frequency, amplitude, direction, range, course of treatment, etc.

5. Conclusion

TM provide a short-term effect on reducing neck pain, increasing cervical ROM, and disability in patients with NP without serious side effects. Continuous therapy and distraction therapy are recommended as an optimal choice on reducing pain and improving cervical ROM, especially in patients with chronic NP (>3 months). The TM-induced improvements in the QOL of patients with NP should be verified by further high-quality RCTs.

Acknowledgments

We would like to thank associate professor Deng kai of West China Hospital, Sichuan University, for providing valuable suggestions and comments. This research was supported by the Key Research and Development Project of the Science and Technology Department of Sichuan Province (No. 2016SZ0039; No. 2018SZ0082) and the Medical Association of Sichuan Province (No. S15063), Chengdu, China.

Conflict of interest

None to report.

Supplementary data

The supplementary files are available to download from http://dx.doi.org/10.3233/THC-248034.

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