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Efficacy of acupuncture for whiplash injury: A systematic review and meta-analysis

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ABSTRACT

Objectives: Acupuncture is used for the treatment of various musculoskeletal disorders, including whiplash injury or whiplash-associated disorder (WAD). However, there is a lack of consensus regarding its effectiveness. This study aimed to establish clinical evidence for acupuncture by analyzing data from randomized controlled trials (RCTs) that demonstrated the efficacy of acupuncture for the treatment of WAD.

Design: A systematic review and meta-analysis.

Setting: Eleven online databases were searched for RCTs on the efficacy of acupuncture for WAD since their inception to June 2022.

Participants: The participants diagnosed with WAD, regardless of their race, age, or sex, were identified.

Interventions: The treatment interventions were acupuncture treatment, including electroacupuncture and dry needling, and acupuncture combined with active treatment(s), which were compared with the same active treatment(s) in the control group.

Primary and secondary outcome measures: The primary outcome was the pain visual analog scale (VAS) score or numerical rating scale score for neck pain, and the secondary outcomes were the range of motion (ROM) of the neck, the neck disability index, and safety.

Results: A total of 525 patients with WAD from eight RCTs were included in this study. The meta-analysis revealed that the outcomes showed significant differences in the pain VAS scores (standard mean difference [SMD]: -0.48 [-0.67 to -0.28], p< 0.001), ROM-extension (SMD: 0.47 [0.20 to 0.75], p< 0.001), and ROM-left lateral flexion (SMD: 0.61 [0.01 to 1.21], p= 0.05). The risk of bias assessment revealed that most studies published after 2010 showed low bias. Moreover, the pain VAS score and ROM-extension were graded as having high certainty.

Conclusion: Acupuncture may have clinical value in pain reduction and increasing the ROM

for patients with WAD. High-quality RCTs must be conducted to confirm the efficacy of acupuncture in treating patients with WAD.

Trial registration number: PROSPERO CRD42021261595.

Keywords: Acupuncture; Whiplash injuries; Whiplash-associated disorder; Systematic review; Meta-analysis; Randomized controlled trial

Word Count: 3731

Article Summary

Strengths and limitations of this study

- This systematic review and meta-analysis were conducted as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.
- Data regarding acupuncture were collected to appraise the acupuncture procedure as part of the Standards for Reporting Interventions in Clinical Trials of Acupuncture.
- Subgroup analysis was performed according to the type of acupuncture treatment to analyze the cause of heterogeneity.
- The Grading of Recommendations Assessment, Development and Evaluations method was used to evaluate the quality of the outcomes.
- Since fewer than ten studies were included, the publication bias could not be examined, and the original text of one study could not be accessed.

INTRODUCTION

Whiplash injury or whiplash-associated disorder (WAD) is caused by rapid hyperextension or hyperflexion of the patient's head due to sudden acceleration or deceleration during a vehicle crash [1]. WAD can cause musculoskeletal symptoms, such as neck pain, stiffness, and headache, as well as systemic symptoms, such as dizziness, psychological distress, depression, and sleep disturbances [2, 3]. Kim et al. [4] reported that 57% of patients involved in traffic accidents present with neck and back pain. Several conservative therapies can be used to relieve pain and discomfort in the cervical region, such as nerve block on the dysfunctional spinal articular process [5, 6]; however, it is difficult to predict the course and sequelae of WAD due to its unique mechanism [7, 8].

Acupuncture is used for the treatment of various musculoskeletal disorders, such as WAD [9-11], as it can target the neurological mechanisms to relieve physical pain via the release of opioids and 5-hydroxytryptamine in the brain reward/motivation circuit [12]. However, its effectiveness is yet to be recognized despite its usefulness in clinical practice [13]. The Canadian and Australian WAD clinical practice guidelines (CPGs) do not recommend acupuncture for treating WAD [14]; moreover, one of the guidelines does not conclude that acupuncture is effective [15]. This lack of consensus can be attributed to the lack of research or evidence on acupuncture at the time of formulating these CPGs.

Therefore, this study aimed to establish clinical evidence for acupuncture by analyzing data from randomized controlled trials (RCTs) that demonstrated the efficacy of acupuncture for the treatment of WAD. Moon et al. [16] published their systematic review (SR) in 2014; however, a meta-analysis was not conducted as part of their study. Lee et al. [17] published a protocol of an SR to verify the effect of acupuncture on WAD; however, no follow-up studies have been published. Therefore, in this study, we updated the previous SR [16] by adding clinical studies published after 2014 and evaluated the quality of evidence on acupuncture

through a meta-analysis and sensitivity analysis. Herein, an SR and meta-analysis were conducted as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines [18].

MATERIALS and METHODS

Database selection and search strategy

The protocol of this SR was registered in the Prospective Register of Systematic Reviews (PROSPERO) database on July 18, 2021 (CRD42021261595) [19]. Online databases, including PubMed, Ovid Medline, Embase, The Cochrane Library, China National Knowledge Infrastructure, ScienceOn, KMBASE, Korean Studies Information Service System, Korea Med, Oriental Medicine Advanced Searching Integrated System, and Research Information Sharing Service were searched for studies on the efficacy of acupuncture for WAD from their inception to June 2022. Terms related to acupuncture and WAD from the Medical Subject Headings were used in the search strategy; the terms were translated into the language suitable for each database (online supplemental table S1).

Eligibility criteria

The studies included in this study were selected according to the following five criteria: study design, participants, intervention, comparison, and outcomes. RCTs that used acupuncture on patients with WAD were included regardless of their reporting type, blinding, and language. In contrast, RCTs that did not target WAD or use acupuncture as an intervention were excluded. Additionally, non-RCTs, single-arm pre- and post-clinical trials, case–control studies, case reports, laboratory studies (including in vivo and in vitro studies), letters, and reviews were also excluded. Thereafter, the participants diagnosed with WAD, regardless of their race, age, or sex, were identified. The treatment interventions were acupuncture treatment, including electroacupuncture (EA) and dry needling, and acupuncture combined with active treatment(s), which were compared with the same active treatment(s) in the control group. The treatments administered to the control group were limited to usual care, such as physiotherapy, medications, conventional treatments other than acupuncture, and sham treatments. The

primary outcome was the pain visual analog scale (VAS) score or numerical rating scale score for neck pain, and the secondary outcomes were the range of motion (ROM) of the neck, the neck disability index (NDI), and safety [20].

Data collection and analysis

Study selection

Two independent researchers (SHL and MSH) were involved in the study selection process. In the case of disagreements during the process, the researchers proceeded to the next step after reaching a consensus through a discussion. After removing duplications, the titles and abstracts of the studies were screened to exclude those that did not meet the eligibility criteria. Subsequently, the full text of each selected study was fully reviewed for the final selection.

Data extraction and management

Two independent researchers (SHL and MSH) analyzed and extracted the data from the selected literature. Data regarding the country of origin, study design, sample size, participants, intervention, comparison, outcomes, and results were summarized in a table. In addition, data regarding the type of acupuncture, acupoints, depth of needling, stimulation response, total sessions, frequency of sessions, and retention time were collected to appraise the acupuncture procedure as part of the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [21, 22].

Quality assessment

Two independent researchers (SHL and MSH) evaluated the quality of the selected studies according to the risk of bias in the Cochrane Handbook for Systematic Reviews of Interventions [23]. In the case of "other sources of bias," the statistical homogeneity of

demographic information between the groups at the baseline was evaluated [24]. The risk of bias assessment was performed based on the content described in the original text and the characteristics of the intervention. The Grading of Recommendations Assessment, Development and Evaluations (GRADE) method was used to evaluate the quality of the outcomes [25]. Each outcome was classified as not serious, serious, or very serious according to the study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The certainty of the outcomes was categorized as high, moderate, low, or very low.

Statistical analysis

The meta-analysis was performed using the Review Manager version 5.4.1 (Cochrane) software. To determine the value of the effect size, standard mean difference (SMD) was used for continuous data and relative risk for dichotomous data. All data, including dichotomous and continuous data, were presented with a 95% confidence interval (CI). Fixed-effects or random-effects models were used for the synthesis of data according to the heterogeneity of each meta-analysis. Heterogeneity (I^2) of less than 50% was considered negligible, and a fixed-effects model was used in such cases. If the heterogeneity exceeded 50%, a random-effects model was used to estimate the effect size. Subgroup analysis was performed according to the type of acupuncture treatment to analyze the cause of heterogeneity (I^2). The "leave-one-out" approach, where the meta-analysis is performed repeatedly while excluding the included literature individually, was performed for sensitivity analysis [26]. In addition, funnel plots were generated to determine the presence of publication bias when more than 10 studies were included [27].

Patient and public involvement

No patient involved.

RESULTS

Study selection

A total of 802 articles were retrieved. After excluding 146 duplications, 261 studies unrelated to WAD, 147 non-RCT studies, 39 in vitro and in vivo studies, and 141 irrelevant studies were excluded while screening of the title and abstract. Thus, 588 articles were excluded from the screening process. The full text of the remaining 68 articles was reviewed, and 60 articles were excluded, including 49 articles that did not use acupuncture as an intervention, 6 articles without full text, 3 articles without a valid control group, and 2 articles for other reasons. Thus, 8 studies were included in the final analysis (Figure 1).

Study characteristics

A total of 525 patients with WAD were included in this study. The country of origin of the studies varied: three in Korea [30, 32, 34], two in Australia [28, 33], one each in Belgium [29], UK [31], and Austria [16]. The recruitment period was less than one year in five studies [29-32, 34], more than four years in two studies [28, 33], and not reported in one study [16]. Among the eight studies, one [29] was designed as a crossover RCT. Regarding the intervention, five studies [16, 28-31] compared acupuncture with sham acupuncture, usual care, or medication, whereas two [32, 33] compared EA with sham EA. One study [34] compared motion-style acupuncture treatment (MSAT) with usual care. The pain VAS scores were recorded in six studies [29-34], and the ROM was recorded in four studies [16, 28, 30, 34]. The NDI was recorded in six studies [28, 29, 31-34]. The study by Aigner et al. was described based on its reference in the SR by Moon et al. [16], as the original text could not be accessed (Table 1).

Table 1. Data of clinical studies on acupuncture for whiplash-associated disorder

First author (year)	Country of origin (period)	Design	Sample size	Participants	Intervention	Comparison	Outcomes	Results
Sterling et al (2015) [28]	Australia (2009 – 2012)	RCT	Total: 80 Exp.: 40 Con.: 40	WAD Ⅱ	Atx. + exercise	Sham atx. + exercise	1) NDI 2) ROM (1) Flex. (2) Ext. (3) Rt. Rot. (4) Lt. Rot.	1) Sig. (P<0.01) 2) (1) NS (2) NS (3) NS (4) NS
Tobbackx et al (2012) [29]	Belgium (01/2011 – 12/2011)	Crossover RCT	Total: 39	WAD Ⅰ or Ⅱ or Ⅲ (chronic WAD persisting more than 3 months)	Atx.	Relaxation	1) NDI 2) pain VAS	1) Sig. (P<0.05) 2) Sig. (P<0.05)
Kwak et al (2012) [30]	Korea (12/2009 – 10/2010)	RCT	Total: 40 Exp.: 20 Con.: 20	WAD (persisting more than 3 months)	Atx. + UC	UC (PTx. + exercise)	1) pain VAS 2) ROM (1) Flex.	1) Sig. (P<0.001) 2)

							(2) Ext.	(1) NS
							(3) Rt. Rot.	(P=0.961)
							(4) Lt. Rot.	(2) Sig.
							(5) Rt. Lat.	(P=0.015)
							Flex.	(3) NS
							(6) Lt. Lat.	(P=0.113)
							Flex.	(4) NS
								(P=0.137)
								(5) NS
								(P=0.908)
								(6) NS
								(P=0.075)
Tough et al (2010) [31]	UK (05/2007 – 12/2007)	RCT	Total: 34 Exp.: 17 Con.: 17	WAD Ⅱ (WAD persisting 2-16 weeks)	Atx. + Ptx.	Sham Atx. + Ptx.	1) pain VAS 2) NDI	1) NS (P=0.67) 2) NS (P=0.43)
Aigner et al (1998) [16]	Austria (NR)	RCT	Total: 61 Exp.: 28 Con.: 33	WAD Ⅰ or Ⅱ	Atx.	Med.	1) ROM	1) NR
Han et al	Korea	RCT	Total: 58	WAD	EA + HM	Sham EA + HM	1) pain VAS	1) Sig.

(2011) [32]	(03/2011 – 07/2011)		Exp.: 29 Con.: 29				2) NDI	(P=0.043) 2) NS
Cameron et al (2011) [33]	Australia (03/2001 – 10/2004)	RCT	Total: 116 Exp.: 52 Con.: 64	WAD Ⅰ or Ⅱ (subacute or chronic WAD persisting more than 1 month)	EA	Sham EA	1) pain VAS 2) NDI	1) Sig. (P=0.05) 2) NS
Kim et al (2020) [34]	Korea (07/2019 – 09/2019)	RCT	Total: 97 Exp.: 48 Con.: 49	WAD (within 7 days)	MSAT + IKM	IKM (Atx. + pharm. + EM + HM)	1) pain VAS 2) NDI 3) ROM (1) Flex. (2) Ext. (3) Rt. Rot. (4) Lt. Rot. (5) Rt. Lat. Flex. (6) Lt. Lat. Flex.	1) Sig. (P=0.005) 2) NS (P=0.197) 3) (1) Sig. (P=0.001) (2) Sig. (P=0.003) (3) Sig. (P<0.001) (4) Sig.

(P<0.001)
(5) Sig.
(P<0.001)
(6) Sig.
(P<0.001)

RCT: Randomized controlled trial; Exp.: Experimental; Con.: Control; WAD: Whiplash-associated disorder; MSAT: Motion style acupuncture treatment; IKM: Integrative Korean medicine treatment; Pharm.: Pharmacopuncture; CMT: Chuna manual therapy; HM: Herbal medicine; VAS: Visual analog scale; NDI: Neck disability index; ROM: Range of motion; Flex.: Flexion; Ext.: Extension; Rt.: Right; Rot.: Rotation; Lt.: Left; Lat.: Lateral; Sig.: Significant; NS: Non-significant; Atx.: Acupuncture therapy; UC: Usual care; PTx.: Physiotherapy; EA: Electroacupuncture; Med.: Medication

Standard for reporting acupuncture according to STRICTA

The eight studies were analyzed using STRICTA (online supplemental table S2). Regarding the type of acupuncture, five studies [16, 28-31] used general acupuncture, two used EA [32, 33], and one used MSAT [34]. Five studies [16, 29, 30, 32, 33] used specific acupoints, and three [28, 31, 34] used muscle trigger points instead of acupoints. The depth of needling was mentioned only in four studies [30, 32-34]. For stimulation response, two studies [29, 30] induced a *deqi* sensation, two [28, 31] used pecking, two [28, 30] used techniques such as twirling and rotation, and two [32, 33] used electrical stimulation. Regarding the total number of sessions, more than six sessions were performed in most studies [28, 30, 32-34], only one session was performed in one study [29], and two to six sessions were performed in one study depending on the degree of improvement in the symptoms [31]. The frequency of sessions was unreported in one study [16], whereas sessions were performed one to three times a week in the remaining seven studies. The number of weeks varied from one to six weeks, and the retention time varied from 15 to 60 min.

Risk of bias assessment

The eight selected studies were analyzed using the Cochrane Risk of Bias tool. Seven studies used an appropriate allocation procedure for random sequence generation [28-34]; one study could not be evaluated as the full text was not available [16]. Allocation concealment was performed in six studies [28-31, 33, 34]; however, it was unclear for the remaining two studies [16, 32]. Blinding of the participants and personnel was conducted in four studies using methods such as sham acupuncture and sham EA [28, 31-33]. The performance bias was high in one study in which MSAT was used only in the experimental group [34], one that was designed as a crossover RCT [29], one in which acupuncture was performed only in the experimental group [30], and one in which acupuncture and medication were compared [16].

Blinding of the outcome assessment was low in four studies [28-30, 34]. Attrition bias was classified as low in six studies with intention-to-treat analysis [28-31, 33, 34] and one with no dropouts [32]. Attrition bias was categorized as unclear in one study as it was not mentioned [16]. Selective reporting bias was classified as low in four studies as the protocol was previously announced [28-30, 34]. Other sources of biases were classified as low in four studies [29, 30, 32, 34], unclear in three [16, 28, 31], and high in the remaining one [33]. In the studies by Tobbackx et al. [29], Kwak et al. [30], Han et al. [32], and Kim et al. [34], no significant difference was observed between the baseline characteristics of the groups; hence, the other sources of bias were classified as low. There was no mention of related information in the study by Aigner et al. [16]. In contrast, in the studies by Sterling et al. [28] and Tough et al. [31], the baseline characteristics were presented, but a comparison between groups was not performed; therefore, the other sources of bias were classified as unclear. In the study by Cameron et al. [33], a significant difference was observed between the groups in terms of the current analgesic medication, the pain rating index-total of the short-form McGill Pain Questionnaire, and the NDI at the baseline; therefore, the other sources of bias were classified as high (Figure 2).

Meta-analysis

A meta-analysis was performed with seven studies [28-34] according to the outcomes, after excluding one study [16] in which no comparison was made between the groups. The subgroups were divided into general acupuncture, EA, and MSAT according to the type of acupuncture treatment.

Pain VAS score

The result of the meta-analysis for the pain VAS score revealed that acupuncture was effective

in treating patients with WAD (SMD: -0.48 [-0.67 to -0.28], p< 0.001). The fixed-effects model was used for the analysis as the heterogeneity (I^2) was 13%. Subgroup analysis revealed that general acupuncture, EA, and MSAT were all effective in treating patients with WAD (Figure 3).

ROM

Kwak et al. [30] and Kim et al. [34] recorded the ROM for all directions, whereas Sterling et al. [28] recorded the ROM for four directions: flexion, extension, right rotation, and left rotation. The results of the meta-analysis for ROM revealed that acupuncture was effective in improving extension and left lateral flexion in patients with WAD (extension - SMD: 0.47 [0.20 to 0.75], p< 0.001; left lateral flexion - SMD: 0.61 [0.01 to 1.21], p= 0.05). The fixed-effects model was used to analyze extension as the heterogeneity (I^2) was 45%. In contrast, the random-effects model was used to analyze flexion, right lateral flexion, left lateral flexion, right rotation, and left rotation as the heterogeneity (I^2) was > 50%. Subgroup analysis showed that MSAT was effective in treating patients with WAD in all directions of ROM. However, general acupuncture was not effective for ROM in any direction (Figure 4).

NDI

The results of the meta-analysis for NDI revealed that acupuncture was ineffective in improving the NDI. The fixed-effects model was used for the analysis as the heterogeneity (I^2) was 13%. Subgroup analysis revealed that all treatments were ineffective in improving the NDI (online supplemental figure S1).

Adverse events

Five studies [28, 30, 31, 33, 34] reported adverse events (AEs), whereas three [16, 29, 32] did not. Except for one case of moderate AE, all reported AEs were mild. Pruritus of unknown cause was reported in the study by Kim et al. [34], necessitating the administration of antihistamines by injection, cream, and oral route. Other AEs caused by acupuncture included hives, dizziness, exacerbation of neck pain, bruising, fatigue, and somatic reactions (sweating and low blood pressure); however, these AEs were mild and were cured within a few days. AEs such as diarrhea, soft stools, nausea, heartburn, and vesicles were also reported; however, these were confirmed to be caused by interventions other than acupuncture.

Sensitivity analysis

A sensitivity analysis for the pain VAS score, ROM-flexion, ROM-extension, ROM-right rotation, and ROM-left rotation, and NDI was performed,whereas ROM-right lateral flexion and ROM-left lateral flexion were excluded as they were included only in two studies (online supplemental table S3).

Pain VAS score

The results of the meta-analysis of the pain VAS score were maintained with the p-values < 0.05 even after removing the included studies individually. The overall heterogeneity (I^2) of the pain VAS score was negligible (13%) and was maintained at < 50% even after removing the included studies individually.

ROM

The results of the meta-analysis of ROM-extension were maintained when the study by Kwak et al. [30] or Sterling et al. [28] was removed; however, the results were not maintained when

the study by Kim et al. [34] was removed. In particular, there was no heterogeneity when the study by Sterling et al. [28] was excluded. However, the results of the meta-analysis of ROM-flexion, ROM-right rotation, and ROM-left rotation were not significantly affected as the p-value was > 0.05 even after removing the included studies one by one.

NDI

The result of the meta-analysis of NDI changed to the p-value < 0.05 and no heterogeneity, when the study by Cameron et al. [33] was removed (SMD: -0.22 [-0.43 to -0.01], p= 0.04, I^2: 0%).

Evidence quality

The quality of evidence of the outcomes was assessed using GradePro GDT (online supplemental table S4).

Pain VAS score

Six studies (n = 423) provided data regarding the pain VAS score. The risk of bias evaluation revealed high bias in four studies; however, the effect on the estimate was considered inconclusive in all studies, and the confidence level of the evidence was not lowered. Thus, the quality of evidence on the pain VAS score was graded as "high."

ROM

Three studies (n = 215) provided data regarding ROM-flexion, ROM-extension, ROM-right rotation, and ROM-left rotation. Two studies (n = 137) provided data regarding ROM-right lateral flexion and ROM-left lateral flexion. The risk of bias evaluation revealed high bias in

three studies; however, the effect on the estimate was considered inconclusive in all studies, and the confidence level of the evidence was not lowered. In the evaluation of consistency, ROM-flexion and ROM-left lateral flexion were downgraded by one level as their heterogeneity (I^2) was 71% and 62%, respectively. Similarly, ROM-right lateral flexion, ROM-right rotation, and ROM-left rotation were downgraded by two levels as their heterogeneity (I^2) was > 75%. In the evaluation of imprecision, ROM-extension and ROM-left lateral flexion were downgraded by one level as the number of participants was less than 400. Similarly, ROM-flexion, ROM-right lateral flexion, ROM-right rotation, and ROM-left rotation were degraded by two levels as the number of participants was less than 400, and their CI overlapped with no effect. The Z-score of ROM-extension was 3.41, and it was upgraded by one level in other considerations. Thus, ROM-extension was graded as "high," ROM-left lateral flexion was graded as "low," and ROM-flexion, ROM-lateral flexion, ROM-right rotation, and ROM-left rotation were graded as "very low."

NDI

Six studies (n = 461) reported data regarding the NDI. The risk of bias evaluation revealed high bias in three studies; however, the effect on the estimate was considered inconclusive in all studies, and the confidence level of the evidence was not lowered. In the evaluation of imprecision, the NDI was downgraded by one level as the CI overlapped with no effect. Thus, the NDI was graded as "moderate."

Publication bias

In accordance with the proposed protocol, publication bias was not examined as fewer than 10 studies were included [19].

DISCUSSION

This study revealed that acupuncture is effective in improving the pain VAS score, ROM-extension, and ROM-left lateral flexion in patients with WAD. The analgesic effect of acupuncture is thought to relieve pain in patients with WAD. In addition, patients with WAD were able to effectively improve ROM-extension following acupuncture, as acupoints GB20, GB21, SI11, SI14, SI15, and TE15, which are used extensively in patients with WAD, are located in the posterior muscles of the cervical spine and upper thoracic spine. However, further studies are required to validate the findings of ROM-left lateral flexion, as there were few participants and high heterogeneity (I^2). Notably, the NDI, ROM-flexion, ROM-right lateral flexion, ROM-right rotation, and ROM-left rotation did not show significant differences; thus, future studies are required to prove the effectiveness of acupuncture for these outcomes.

In the risk of bias assessment, except for one study published before 2010 [16], seven studies published after 2010 showed low bias in most domains [28-34]. In addition, although participant blinding is difficult owing to the nature of acupuncture [35], many studies have attempted to minimize this effect by utilizing placebo interventions. Moreover, two studies [28, 34] published after 2015 showed high bias in only one domain and low bias in all other domains, indicating that recent studies on acupuncture interventions are consistently designed with high quality.

In the sensitivity analysis of the pain VAS score, a significant effect was maintained even when the included studies were removed one by one. In this context, acupuncture showed significant effects in patients with WAD, despite differences in design, participants, interventions, and comparisons among the studies. For ROM-extension, there was no heterogeneity when the study by Sterling et al. [28] was removed; thus, it could be assumed that the study was a potential source of heterogeneity. In the study by Sterling et al. [28], high-intensity ROM exercises, including craniocervical flexion training, neck extensor training, scapular training,

posture re-education, and sensorimotor exercises, were performed for 1 h, which may have been the cause of heterogeneity. For the NDI, a significant effect appeared, and no heterogeneity was obtained when the study by Cameron et al. [33] was removed; therefore, the study was considered responsible for the between-study heterogeneity. It was presumed that the NDI SMD of the study favored the control group since it was > 0, affecting the overall effect size and heterogeneity.

A previous study [16] that analyzed the effectiveness of acupuncture in patients with WAD included studies published before 2014. This study differs from the previous study in the following ways: first, including two RCTs published after 2014, we analyzed a total of eight RCTs. Accordingly, this study provided more objective and quantitative evidence by synthesizing data on the efficacy of acupuncture for treating WAD. Second, the effect size of the pain VAS score, ROM, and NDI was verified by performing a meta-analysis. The directionality of the treatment effect and whether the CI of the individual studies overlapped was assessed using a forest plot. Third, sensitivity analysis was performed to confirm the robustness of the results. The effect of individual studies on heterogeneity (I^2) and effect size was analyzed using the leave-one-out approach method. Fourth, a subgroup analysis was conducted according to the type of acupuncture treatment. The effect size of each type of acupuncture treatment was verified by dividing them into general acupuncture, EA, and MSAT subgroups. Fifth, the evidence quality of the pain VAS score, ROM, and NDI was assessed using the GRADE method. By presenting the certainty for each outcome, this study provided criteria that can be clinically referred to when using acupuncture for patients with WAD.

However, this study has some limitations. First, since fewer than ten studies were included, the publication bias could not be examined. Second, the original text of one study could not be accessed. Third, except for ROM-extension and ROM-left lateral flexion, the efficacy of acupuncture in improving ROM in other directions was evaluated as being “very low.” This is

an area that needs to be verified through further studies.

CONCLUSION

The results of this study suggest that acupuncture has clinical value in the treatment of patients with WAD. In the future, high-quality RCTs, based on the aforementioned data, must generate evidence of higher quality than that in the present study to confirm the efficacy of acupuncture in treating patients with WAD.

AUTHOR CONTRIBUTIONS

Sang-Hyun Lee: Conceptualization

Sun-Young Park: Funding acquisition

Sang-Hyun Lee and Man-Suk Hwang: Investigation

In Heo and Byung-Cheul Shin: Methodology

Eui-Hyuoung Hwang and Man-Suk Hwang: Project administration

Man-Suk Hwang: Supervision

Sang-Hyun Lee: Writing – original draft

Sang-Hyun Lee and Man-Suk Hwang: Writing – review & editing

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DISCLAIMER

The funding source had no role in the design of the protocol, study search and selection, data

extraction and management, data interpretation, report writing, or the decision to submit the report for publication.

COMPETING INTERESTS

None.

PATIENT CONSENT FOR PUBLICATION

Not required.

PROVENANCE AND PEER REVIEW

Not commissioned; extremally peer reviewed.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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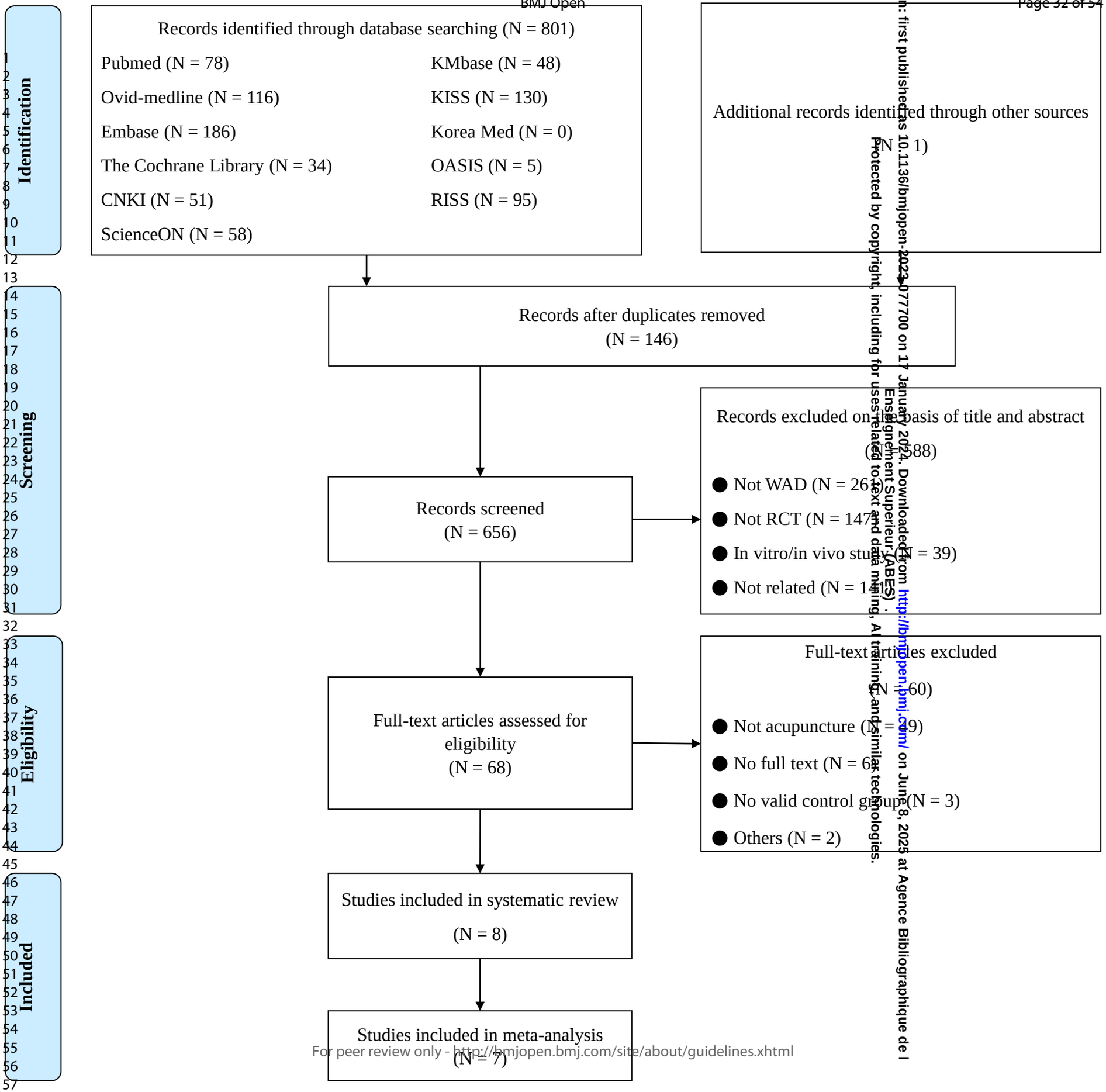
FIGURE LEGENDS

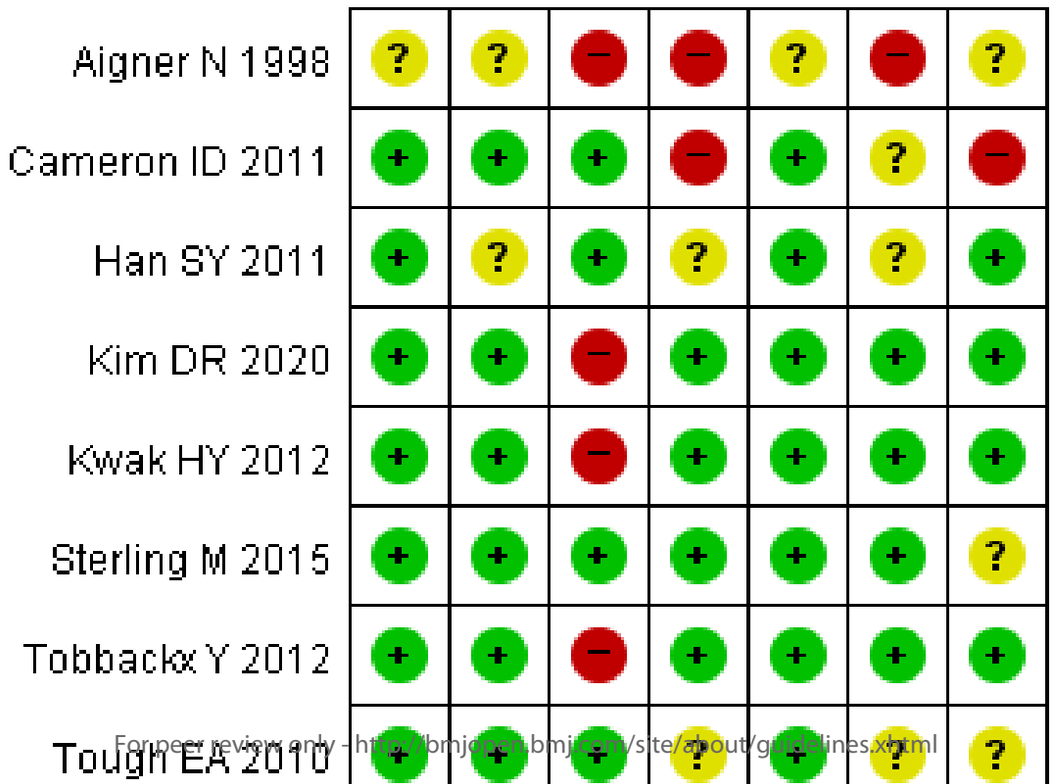
Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart of the included studies

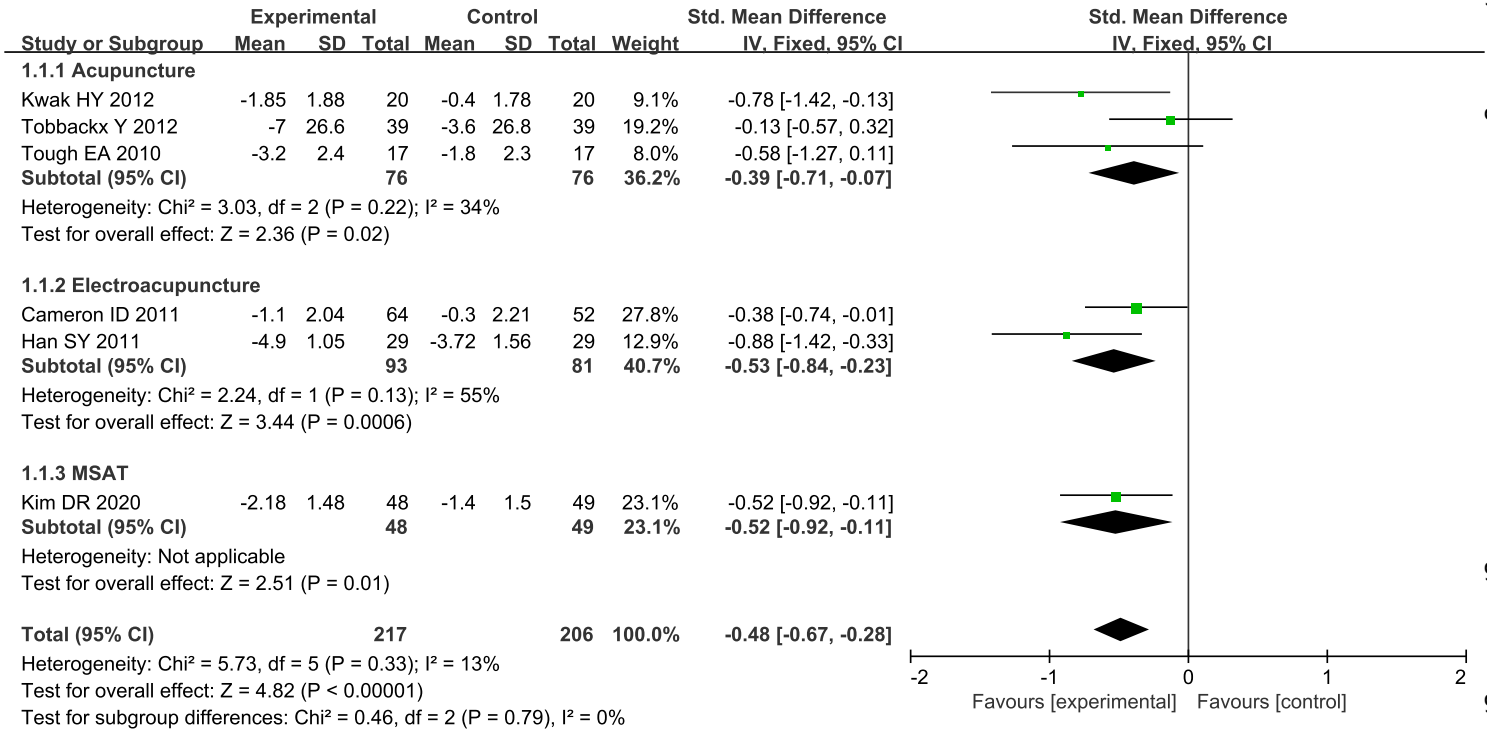
Figure 2. Risk of bias summary

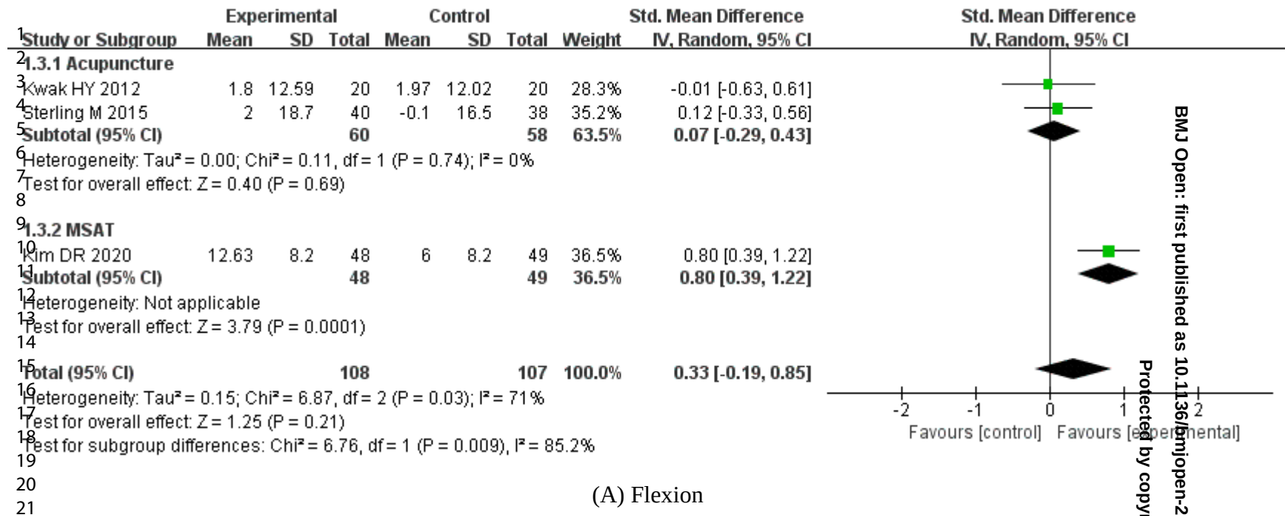
Figure 3. Forest plot of the meta-analysis for the pain visual analog scale

Figure 4. Forest plot of the meta-analysis for the range of motion

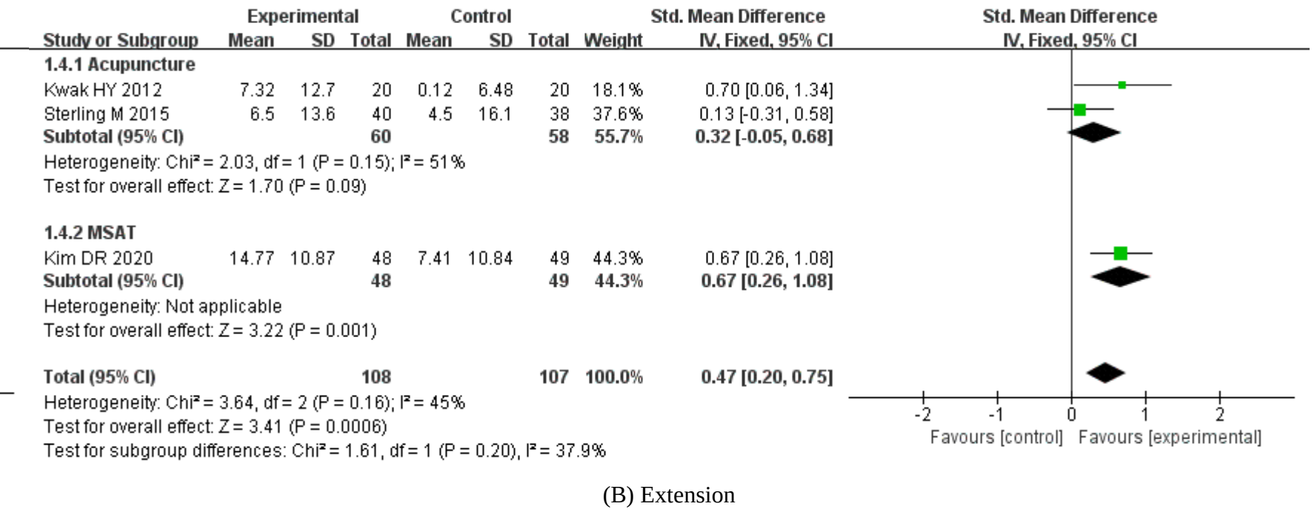




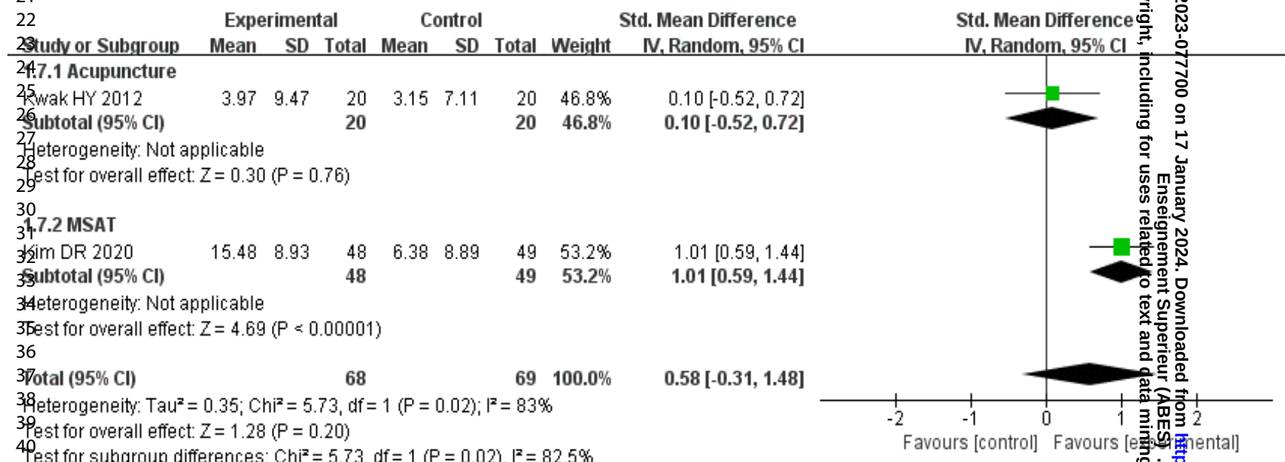




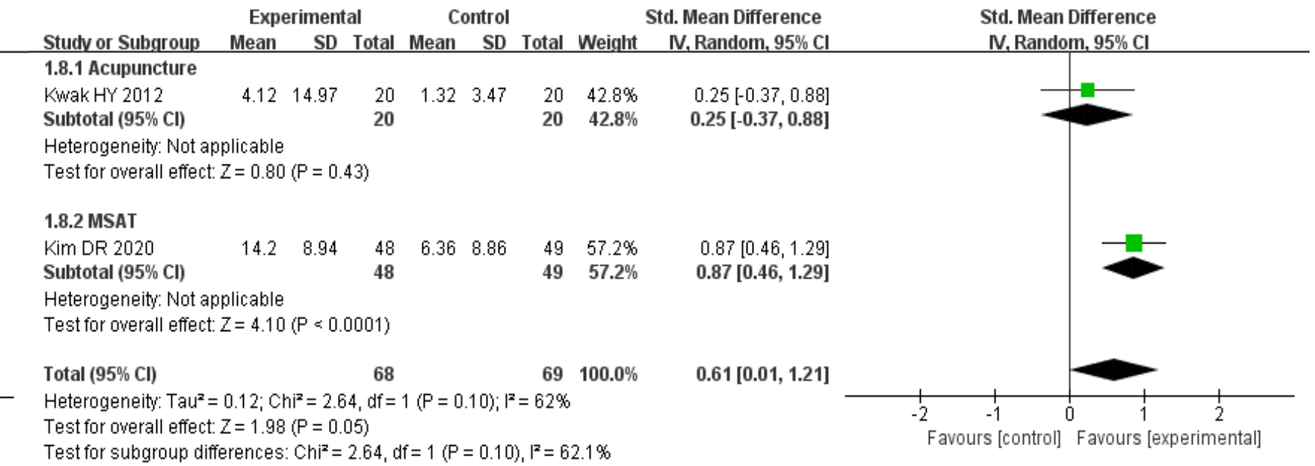
(A) Flexion



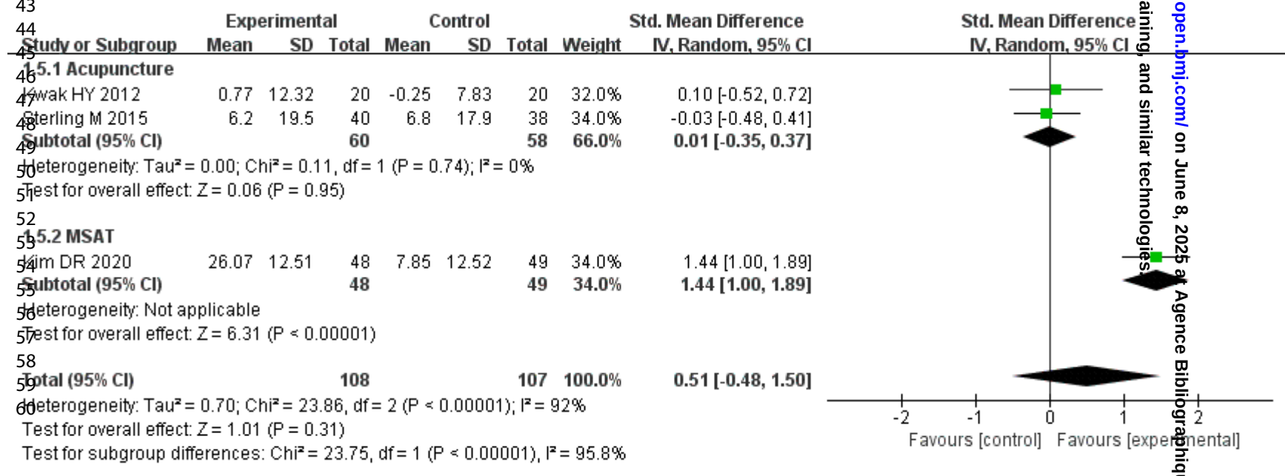
(B) Extension



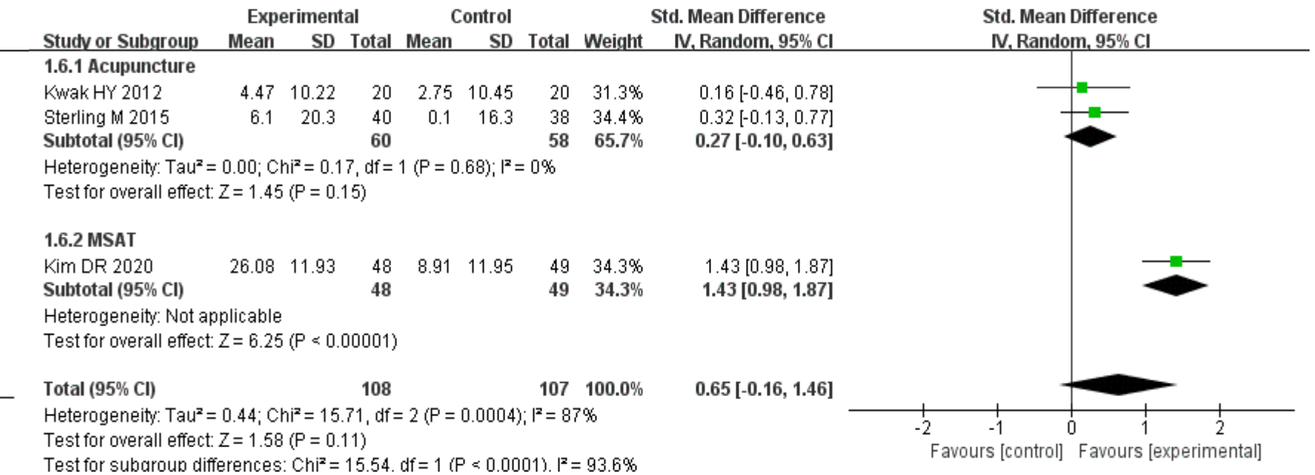
(C) Right lateral flexion



(D) Left lateral flexion



(E) Right rotation



(F) Left rotation

Supplemental table S1. Search strategy and terms used

Database: PubMed		
No.	Search strategy	Results
#1	whiplash OR acute whiplash injury* OR acute whiplash associated disorder* OR acute WAD OR acute whiplash associated disorder* II OR acute WAD II OR whiplash associated disorder* OR WAD OR whiplash associated disorder* II OR WAD II, OR whiplash OR whiplash injury* OR whiplash patient* OR whiplash syndrome* OR cervical spine disorder* OR cervical spine injury* OR "Accidents, Traffic" [Mesh] OR (("Motor Vehicles"[Mesh:NoExp] OR "Automobiles"[Mesh] OR "Motorcycles"[Mesh] OR traffic[tiab] OR vehicle[tiab] OR vehicular[tiab] OR car[tiab] OR cars[tiab] OR automobile[tiab] OR automobiles[tiab] OR motorcycle[tiab] OR motorcycles[tiab] OR taxi[tiab] OR cab[tiab] OR road[tiab] OR pedestrian[tiab] OR pedestrians[tiab]) AND (accident[tiab] OR accidents[tiab] OR injury[tiab] OR injuries[tiab] OR crash[tiab] OR crashes[tiab] OR "Wounds and Injuries"[Mesh] OR "injuries"[Subheading])) AND (cervic* OR thoracic* OR lumba*)	23,007
#2	acupuncture	38,405
#3	electroacupuncture	6,738
#4	acupressure	1,629
#5	((((((((((((((((((((((meridian) OR acupoint) OR acupuncture [mh]) OR acupuncture Analgesia [mh]) OR acupuncture Therapy [mh]) OR acupuncture points [mh]) OR acupuncture, ear [mh]) OR acupuncture [Text Word]) OR acupressure [Text Word]) OR electroacupuncture) OR electro acupuncture) OR electro-acupuncture) OR meridian* [Text Word]) OR needling [Text Word]) OR acu-point*) OR acu point* [Text Word]) OR acupoint* [Text Word]) OR Acupuncture [mh]) OR electroacupuncture [mh]) OR acupuncture* [Text Word]) OR elctroacupuncture* [Text Word]) OR (acupuncture AND th[sh])) OR acupuncture[tiab]) OR acupuncture[mh]) OR acupuncture/th[mh]	46,250
#6	#2 or #3 or #4 or #5	48,241
#7	#1 and #6	78
Database: Ovid Medline		
1	exp Whiplash Injuries/	3,371
2	whiplash.tw.	3,187
3	acute whiplash injury*.tw.	74
4	acute whiplash associated disorder*.tw.	66
5	acute WAD.tw.	59
6	WAD.tw.	977

7	whiplash patient*.tw.	198
8	whiplash syndrome*.tw.	182
9	cervical spine disorder*.tw.	216
10	cervical spine injury*.tw.	1,478
11	exp Accidents, Traffic/	46,806
12	exp Motor Vehicles/	23,048
13	exp Automobiles/	7,529
14	exp Motorcycles/	2,777
15	traffic.tw.	53,702
16	vehicle.tw.	125,682
17	vehicular.tw.	3,603
18	car.tw.	31,854
19	cars.tw.	8,493
20	automobile.tw.	6,131
21	automobiles.tw.	1,239
22	motorcycle.tw.	3,529
23	motorcycles.tw.	860
24	taxi.tw.	1,135
25	cab.tw.	3,401
26	road.tw.	43,424
27	pedestrian.tw.	4,658
28	pedestrians.tw.	3,434
29	accident.tw.	51,240
30	accidents.tw.	45,962
31	injury.tw.	737,087
32	injuries.tw.	236,793
33	crash.tw.	10,917
34	crashes.tw.	9,213
35	exp "Wounds and Injuries"/	977,757
36	or/29-35	1,579,963
37	or/11-28	275,281
38	or/1-10	6,147

39	36 and 37	75,471
40	38 or 39	80,163
41	acupuncture.mp.	32,013
42	electroacupuncture.mp.	6,378
43	acupressure.mp.	1,612
44	meridian.mp.	4,543
45	acupoint.mp.	3,677
46	exp acupuncture/	1,936
47	acupuncture.tw.	24,901
48	acupressure.tw.	1,338
49	electro acupuncture.mp.	907
50	meridian*.tw.	6,052
51	needling.tw.	3,536
52	acu-point*.mp.	33
53	acu point*.tw.	33
54	acupoint*.tw.	6,295
55	elctroacupuncture*.tw.	1
56	(acupuncture and th).mp.	75
57	or/41-56	41,125
58	40 and 57	116
Database: Embase		
1	'automobiles'/exp	11,192
2	'motor vehicle'/exp	45,809
3	'accident, traffic'/exp	70,722
4	'motorcycle'/exp	3,328
5	vehicle:ta,ab,de	189,288
6	traffic:ta,ab,de	142,366
7	vehicular:ta,ab,de	4,470
8	car:ta,ab,de	68,570
9	cars:ta,ab,de	11,495
10	automobile:ta,ab,de	6,968
11	automobiles:ta,ab,de	1,389

12	motorcycle:ta,ab,de	5,453
13	motorcycles:ta,ab,de	1,025
14	taxi:ta,ab,de	1,393
15	cab:ta,ab,de	4,574
16	road:ta,ab,de	43,386
17	pedestrian:ta,ab,de	6,804
18	pedestrians:ta,ab,de	3,770
19	accident:ta,ab,de	546,272
20	accidents:ta,ab,de	52,651
21	injury:ta,ab,de	1,791,998
22	injuries:ta,ab,de	258,946
23	crash:ta,ab,de	11,746
24	crashes:ta,ab,de	9,529
25	'wounds and injuries'/exp	2,627,209
26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	3,381,722
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	404,965
28	#26 AND #27	127,597
29	acupuncture	60,077
30	electroacupuncture	9,565
31	acupressure	2,813
32	acupoint	5,720
33	acupoint:ta,ab,de	5,143
34	'acupuncture analgesia'	2,299
35	'acupuncture therapy'	2,221
36	'acupuncture points'	2,228
37	'acupuncture, ear'	38
38	acupuncture:ta,ab,de	52,539
39	acupressure:ta,ab,de	2,724
40	electroacupuncture	9,565
41	'electro acupuncture'	1,386
42	meridian*:ta,ab,de	8,264

43	needling:ta,ab,de	4,587
44	'acu point*'	49
45	acu AND point*:ta,ab,de	884
46	acupoint*:ta,ab,de	8,170
47	'acupuncture'/exp	53,544
48	'electroacupuncture'/exp	8,255
49	acupuncture*:ta,ab,de	52,567
50	electroacupuncture*:ta,ab,de	9,111
51	acupuncture.:ta,ab,de	52,539
52	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	70,449
53	#28 AND #52	186
Database: The Cochrane Library		
#1	whiplash	552
#2	acute whiplash injury*	130
#3	acute whiplash associated disorder*	91
#4	acute WAD	97
#5	acute whiplash associated disorder* II	33
#6	acute WAD II	34
#7	whiplash associated disorder*	275
#8	WAD	348
#9	whiplash associated disorder* II	58
#10	WAD II	63
#11	whiplash patient*	399
#12	whiplash syndrome*	94
#13	cervical spine disorder*	529
#14	cervical spine injury*	555
#15	MeSH descriptor: [Accidents, Traffic] explode all trees	447
#16	MeSH descriptor: [Motor Vehicles] explde all trees	282
#17	MeSH descriptor: [Automobiles] this term only	58
#18	MeSH descriptor: [Motorcycles] this term only	25
#19	traffic:ti,ab,kw	2,358

#20	vehicle:ti,ab,kw	7,637
#21	vehicular:ti,ab,kw	53
#22	car:ti,ab,kw	3,677
#23	cars:ti,ab,kw	370
#24	automobile:ti,ab,kw	1,031
#25	automobiles:ti,ab,kw	75
#26	motor cycle*:ti,ab,kw	1,024
#27	taxi*:ti,ab,kw	227
#28	cab*:ti,ab,kw	10,072
#29	road*:ti,ab,kw	1,838
#30	pedestrian*:ti,ab,kw	213
#31	accident*:ti,ab,kw	22,223
#32	injur*:ti,ab,kw	67,393
#33	crash*:ti,ab,kw	696
#34	MeSH descriptor: [Wounds and Injuries] explode all trees	28,670
#35	Any MeSH descriptor in all MeSH products and with qualifier(s): [injuries - IN]	3,495
#36	cervic$ or thoracic$ or lumba$	30,341
#37	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	1,588
#38	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30	25,765
#39	#31 or #32 or #33 or #34 or #35	97,366
#40	#38 and #39	4,200
#41	#37 or #40	5,649
#42	#41 and #36	386
#43	acupuncture	18,418
#44	electroacupuncture	2,970
#45	acupressure	1,812
#46	meridian	1,222
#47	acupoint	2,903
#48	MeSH descriptor: [acupuncture] explode all trees	163
#49	MeSH descriptor: [acupuncture Analgesia] explode all trees	302
#50	MeSH descriptor: [acupuncture Therapy] explode all trees	5,269

#51	MeSH descriptor: [acupuncture points] explode all trees	2,244
#52	MeSH descriptor: [acupuncture, ear] explode all trees	216
#53	acupuncture:ti,ab,kw	16,436
#54	acupressure:ti,ab,kw	1,708
#55	electro acupuncture	923
#56	electro-acupuncture	712
#57	meridian*:ti,ab,kw	1,162
#58	needling:ti,ab,kw	2,606
#59	acu-point*	37
#60	acu point*:ti,ab,kw	231
#61	acupoint*:ti,ab,kw	4,417
#62	MeSH descriptor: [electroacupuncture] explode all trees	884
#63	elctroacupuncture*:ti,ab,kw	2
#64	acupuncture AND th	1,218
#65	#43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64	22,881
#66	#42 and #65	34
Database: China National Knowledge Infrastructure (CNKI)		
1	(SU='traffic accident' OR SU='交通事故' OR SU='whiplash injury' OR SU='颈椎屈伸损伤' OR SU='whiplash associated disorder' OR SU='挥鞭样损伤' OR SU='cervical spine disorder' OR SU='颈椎功能紊乱' OR SU='cervical spine injury' OR SU='颈椎损伤') AND (SU='acupuncture' OR SU='針' or SU='electro acupuncture' OR SU='电針' or SU='meridian' OR SU='经穴' or SU='acupoint' or SU='acupuncture-ear' OR SU='耳针')	51
Database: ScienceOn		
1	전체=(교통사고 | 편타성 손상 | 채찍질 손상 | 경항통 | 경추부 염좌) AND 전체=(침 | 전침 | 경혈 | 이침)	58
Database: KMBASE		
1	[ALL=교통사고]	852
2	[ALL=편타성 손상]	25

3	[ALL=채찍질 손상]	0
4	[ALL=경항통]	88
5	[ALL=경추부 염좌]	4
6	[ALL=침]	13,948
7	[ALL=전침]	371
8	[ALL=이침]	78
9	[ALL=경혈]	322
10	(((([ALL=교통사고] OR [ALL=편타성 손상]) OR [ALL=채찍질 손상]) OR [ALL=경항통]) OR [ALL=경항통])	930
11	((([ALL=침] OR [ALL=전침]) OR [ALL=이침]) OR [ALL=경혈])	14,543
12	((((([ALL=교통사고] OR [ALL=편타성 손상]) OR [ALL=채찍질 손상]) OR [ALL=경항통]) OR [ALL=경항통]) AND ((([ALL=침] OR [ALL=전침]) OR [ALL=이침]) OR [ALL=경혈]))	48
Database: Korean Studies Information Service System (KISS)		
1	교통사고 and 침	126
2	교통사고 and 전침	4
3	교통사고 and 이침	0
4	교통사고 and 경혈	0
Database: Korea Med		
1	((((((“traffic”[ALL])) OR (“automobile”[ALL])) OR (“whiplash injury”[ALL])) OR (“whiplash associated disorder”[ALL])) OR (“cervical spine disorder”[ALL])) OR (“cervical spine injury”[ALL])	1,648
2	((((“acupuncture”[ALL])) OR (“electroacupuncture”[ALL])) OR (“meridian”[ALL])) OR (“acupoint”[ALL])	526
3	(((“((((((“traffic”[ALL])) OR (“automobile”[ALL])) OR (“whiplash injury”[ALL])) OR (“whiplash associated disorder”[ALL])) OR (“cervical spine disorder”[ALL])) OR (“cervical spine	0

	injury"[ALL])"[ALL])) AND ("((((("acupuncture"[ALL])) OR ("electroacupuncture"[ALL])) OR ("meridian"[ALL])) OR ("acupoint"[ALL])"[ALL])	
Database: Oriental Medicine Advanced Searching Integrated System (OASIS)		
1	교통사고 침	1
2	교통사고 전침	4
3	교통사고 이침	0
4	교통사고 경혈	0
Database: Research Information Sharing Service (RISS)		
1	전체 : 교통사고 <AND> 전체 : 침	90
2	전체 : 교통사고 <AND> 전체 : 전침	4
3	전체 : 교통사고 <AND> 전체 : 이침	0
4	전체 : 교통사고 <AND> 전체 : 경혈	1

Supplemental table S2. Appraisal of acupuncture procedure based on the revised SRICTA criteria (2010)

First author (year)[ref]	Type of acupuncture	Acupoints	Depth of needling	Stimulation response	Total sessions	Frequency and Retention
Sterling et al (2015) [28]	General acupuncture	Posterior muscles of the cervical spine and upper thoracic spine	NR	Pecking, Twirling	6	Frequency: 2 times/week X 3 weeks Retention: 30 minute
Tobbackx et al (2012) [29]	General acupuncture	Choose from GV14, C1-C7, GB20, SI11, GB21, TE15, SI14, BL17, SP10, SI3, BL64, TE5, GB41, Shiqizhuixia, Ear Zero point, Ear Jerome point, Ear C0.	NR	Deqi sensation	1	Frequency: 1 time/week X 1 week Retention: 20 minute
Kwak et al (2012) [30]	General acupuncture	SI2, SI3, SI5, SI7, SI14, SI15, LI11, BL10, BL12, BL13, BL14, BL60, BL62, BL66, GB20, GB21, GB40,	1.0-2.0 cm	Deqi sensation, Rotating	6	Frequency: 3 times/week X 2 weeks Retention: 15 minute

		GB41, TE5, TE15				
Tough et al (2010) [31]	General acupuncture	Myofascial trigger points in muscles in and around the neck	NR	Pecking (6-7 times)	2-6	Frequency: 1 time/week X 2-6 times Retention: NR
Aigner et al (1998) [16]	General acupuncture	TB5, SI6 bilaterally	NR	NR	NR	NR
Han et al (2011) [32]	Electroacupuncture	ST25, GB20, GB21, SI11, SI14, SI15, Ashi points	1.0-2.0 cm	Electrical frequency 300 Hz	8	Frequency: 2 times/week X 4 weeks Retention: 15 minute
Cameron et al (2011) [33]	Electroacupuncture	GB39, GB20, LI14, SI6 bilaterally	1.0-1.5 cm	Electrical frequency 2-5 Hz Electrical intensity 1.5 volts	12	Frequency: 2 times/week X 6 weeks Retention: 20 – 60 minutes
Kim et al (2020) [34]	MSAT	3 points at trapezius muscle	0.5-1.0 cm	NR	6	Frequency: 2 times/day X 3 days Retention: 15 minute

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture; MSAT: Motion-style acupuncture treatment; NR: Not reported

Supplemental table S3. Sensitivity analysis of whiplash-associated disorder

Study omitted	Pooled estimate	95% Confidence interval		p-value	I^2(%)
		Lower	Upper		
Pain VAS					
Kwak HY 2012	-0.45	-0.65	-0.24	<0.0001	17
Tobbackx Y 2012	-0.56	-0.78	-0.35	<0.00001	0
Tough EA 2010	-0.47	-0.67	-0.27	<0.00001	29
Cameron ID 2011	-0.52	-0.75	-0.29	<0.00001	25
Han SY 2011	-0.42	-0.63	-0.21	<0.0001	0
Kim DR 2020	-0.47	-0.69	-0.24	<0.0001	30
ROM – flexion					
Kwak HY 2012	0.46	-0.21	1.14	0.17	79
Sterling M 2015	0.43	-0.37	1.22	0.29	78
Kim DR 2020	0.07	-0.29	0.43	0.69	0
ROM – extension					
Kwak HY 2012	0.42	0.12	0.73	0.006	67
Sterling M 2015	0.68	0.34	1.03	0.0001	0
Kim DR 2020	0.32	-0.05	0.68	0.09	51
ROM – right rotation					
Kwak HY 2012	0.71	-0.74	2.15	0.34	95
Sterling M 2015	0.79	-0.53	2.11	0.24	92
Kim DR 2020	0.01	-0.35	0.37	0.95	0
ROM – left rotation					
Kwak HY 2012	0.87	-0.21	1.96	0.11	91
Sterling M 2015	0.81	-0.42	2.05	0.20	90
Kim DR 2020	0.27	-0.10	0.63	0.15	0
NDI					
Sterling M 2015	-0.14	-0.34	0.06	0.18	30
Tobbackx Y 2012	-0.14	-0.34	0.06	0.16	29

Tough EA 2010	-0.12	-0.32	0.07	0.20	30
Cameron ID 2011	-0.22	-0.43	-0.01	0.04	0
Han SY 2011	-0.07	-0.26	0.13	0.51	0
Kim DR 2020	-0.08	-0.29	0.12	0.44	18

VAS: Visual analog scale; ROM: Range of motion; NDI: Neck disability index

Supplemental table S4. Evidence quality assessment according to GRADE

Certainty assessment							No. of patients		Effect	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Experimental	Control	Absolute (95% CI)	Certainty
Pain VAS										
6	RCT	Not serious	Not serious	Not serious	Not serious	Strong association	217	206	SMD 0.48 lower (0.67 lower to 0.28 lower)	⊕⊕⊕⊕ High
ROM-flexion										
3	RCT	Not serious	Serious*	Not serious	Very serious†	None	108	107	SMD 0.33 higher (0.19 lower to 0.85 higher)	⊕◯◯◯ Very low
ROM-extension										
3	RCT	Not serious	Not serious	Not serious	Serious‡	Strong association	108	107	SMD 0.47 higher (0.2 higher to 0.75 higher)	⊕⊕⊕⊕ High
ROM-right lateral flexion										
2	RCT	Not	Very serious§	Not serious	Very	None	68	69	SMD 0.58 higher	⊕◯◯◯

		serious			serious†				(−2.31 lower to 1.48 higher)	Very low
ROM-left lateral flexion										
2	RCT	Not serious	Serious*	Not serious	Serious‡	None	68	69	SMD 0.61 higher (0.01 higher to 1.21 higher)	⊕⊕◯◯ Low
ROM-right rotation										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	107	SMD 0.51 higher (−0.48 lower to 1.5 higher)	⊕◯◯◯ Very low
ROM-left rotation										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	107	SMD 0.65 higher (−0.16 lower to 1.46 higher)	⊕◯◯◯ Very low
NDI										
6	RCT	Not serious	Not serious	Not serious	Serious¶	None	237	224	SMD 0.13 lower (−0.31 lower to 0.06 higher)	⊕⊕⊕◯ Moderate

*: Downgraded one level due to inconsistency (I^2, 50–75%)

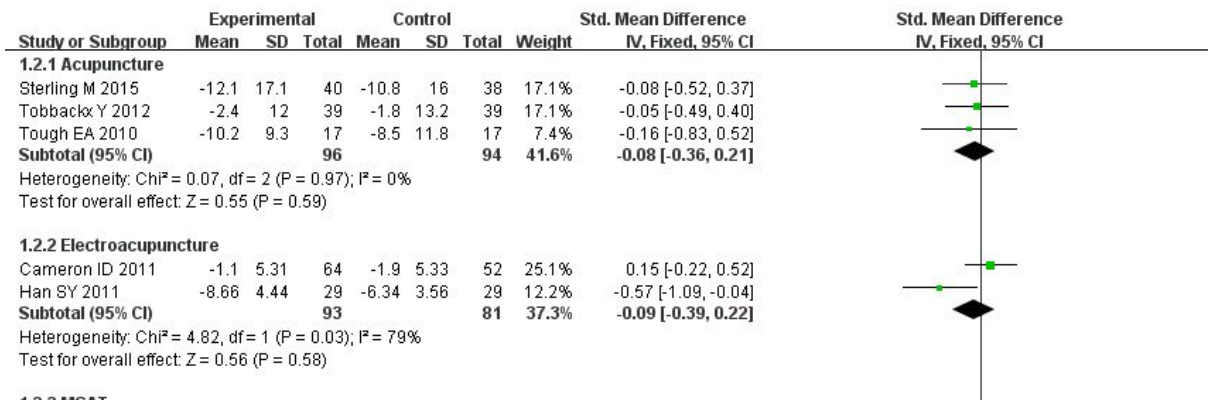
†: Downgraded two levels due to imprecision (fewer than 400 participants and CI overlaps with no effect)

‡: Downgraded one level due to imprecision (fewer than 400 participants)

§: Downgraded two levels due to inconsistency (I^2>75%)

¶: Downgraded one level due to imprecision (CI overlaps with no effect)

CI: Confidence interval; SMD: Standard mean difference; VAS: Visual analog scale; ROM: Range of motion; NDI: Neck disability index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation



Supplemental figure S1. Forest plot of the meta-analysis for the neck disability index

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4-5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6 Supple table 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 Supple table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Figure 1.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10 Figure 1.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	10 Figure 1.
Study characteristics	17	Cite each included study and present its characteristics.	10 Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	15-16 Figure 2.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	16-17 Figure 3,4. Supple figure 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	15-17 Figure 2,3,4. Supple figure 1.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	16-17 Figure 3,4. Supple figure 1
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	18-19 Supple table 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	18-19 Supple table 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	20
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	19-20 Supple table 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	21-22
	23b	Discuss any limitations of the evidence included in the review.	22-23
	23c	Discuss any limitations of the review processes used.	22-23
	23d	Discuss implications of the results for practice, policy, and future research.	21-23
OTHER INFORMATION			
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	23-24
Competing interests	26	Declare any competing interests of review authors.	24
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	24

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Efficacy of acupuncture for whiplash injury: A systematic review and meta-analysis

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Secondary Subject Heading:	Complementary medicine
Keywords:	Systematic Review, Randomized Controlled Trial, COMPLEMENTARY MEDICINE, PAIN MANAGEMENT

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Efficacy of acupuncture for whiplash injury: A systematic review and meta-analysis

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ABSTRACT

Objectives: This study aimed to establish clinical evidence for acupuncture by analyzing data from trials that demonstrated the efficacy of acupuncture for whiplash-associated disorder (WAD) with the following research question: Is acupuncture treatment effective for symptom alleviation in patients with WAD compared to other usual care?

Design: A systematic review and meta-analysis.

Data sources: PubMed, Ovid Medline, Embase, The Cochrane Library, China National Knowledge Infrastructure, ScienceOn, KMBASE, Korean Studies Information Service System, Korea Med, Oriental Medicine Advanced Searching Integrated System, and Research Information Sharing Service were searched from their inception to October 1, 2023.

Eligibility criteria: We included randomized controlled trials (RCTs) using acupuncture on patients with WAD. The outcomes were the pain visual analog scale (VAS) score or numerical rating scale score for neck pain, the range of motion (ROM) of the neck, the neck disability index, and safety.

Data extraction and synthesis: Two independent researchers analyzed and extracted data from the selected literatures. The risk of bias and the quality of evidence were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions and the Grading of Recommendations Assessment, Development, and Evaluation method, respectively.

Results: A total of 525 patients with WAD from eight RCTs were included in this study. The meta-analysis revealed that the outcomes showed significant differences in the pain VAS score (standard mean difference [SMD]: -0.57 [-0.86 to -0.28], p<0.001) and ROM-extension (SMD: 0.47 [0.05 to 0.89], p=0.03). The risk of bias assessment revealed that four studies published after 2012 (50%, 4 out of 8 studies) showed low bias in most domains. The pain VAS score was graded as having moderate certainty.

Conclusion: Acupuncture may have clinical value in pain reduction and increasing the ROM for patients with WAD. High-quality RCTs must be conducted to confirm the efficacy of acupuncture in patients with WAD.

Trial registration number: PROSPERO CRD42021261595.

Keywords: Acupuncture; Whiplash injuries; Whiplash-associated disorder; Systematic review; Meta-analysis; Randomized controlled trial

Word Count: 3788

Article Summary

Strengths and limitations of this study

- This systematic review was reported as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.
- Data regarding acupuncture were collected to appraise the acupuncture procedure as part of the Standards for Reporting Interventions in Clinical Trials of Acupuncture.
- Subgroup analysis was performed according to the type of acupuncture treatment to verify the effect size of each subgroup.
- The Grading of Recommendations Assessment, Development and Evaluations method was used to evaluate the quality of the outcomes.
- Grey literature and other supplementary searches were not conducted, which may result in missing studies and the risk of publication bias.

INTRODUCTION

Whiplash injury or whiplash-associated disorder (WAD) is caused by rapid hyperextension or hyperflexion of the patient's head due to sudden acceleration or deceleration during a vehicle crash [1]. WAD can cause musculoskeletal symptoms, such as neck pain, stiffness, and headache, as well as systemic symptoms, such as dizziness, psychological distress, depression, and sleep disturbances [2, 3]. Kim et al. [4] reported that 57% of patients involved in traffic accidents present with neck and back pain. Several conservative therapies can be used to relieve pain and discomfort in the cervical region, such as nerve block on the dysfunctional spinal articular process [5, 6]; however, it is difficult to predict the course and sequelae of WAD owing to its unique mechanism [7, 8].

Acupuncture is used for the treatment of various musculoskeletal disorders, such as WAD [9-11], as it can target the neurological mechanisms to relieve physical pain via the release of opioids and 5-hydroxytryptamine in the brain reward/motivation circuit [12]. However, its effectiveness is yet to be recognized despite its usefulness in clinical practice [13]. The Canadian and Australian WAD clinical practice guidelines (CPGs) do not recommend acupuncture for treating WAD [14]; moreover, one of the guidelines does not conclude that acupuncture is effective [15]. This lack of consensus can be attributed to the lack of research or evidence on acupuncture at the time of formulating these CPGs.

Therefore, this study aimed to establish clinical evidence for acupuncture by analyzing data from trials that demonstrated the efficacy of acupuncture for the treatment of WAD with the following research question: Is acupuncture treatment effective for symptom alleviation in patients with WAD compared to other usual care? Moon et al. [16] published their systematic review (SR) in 2014; however, a meta-analysis was not conducted as part of their study. Lee et al. [17] published a protocol of an SR to verify the effect of acupuncture on WAD; however, no follow-up studies have been published. Therefore, in this study, we updated the previous

SR [16] by adding clinical studies published after 2014 and evaluated the quality of evidence on acupuncture through a meta-analysis and sensitivity analysis. Herein, this SR was reported as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and referred to the Cochrane Handbook [18, 19].

MATERIALS and METHODS

Database selection and search strategy

The protocol of this SR was registered in the Prospective Register of Systematic Reviews (PROSPERO) database on July 18, 2021 (CRD42021261595) [20]. Online databases, including PubMed, Ovid Medline, Embase, The Cochrane Library, China National Knowledge Infrastructure, ScienceOn, KMBASE, Korean Studies Information Service System, Korea Med, Oriental Medicine Advanced Searching Integrated System, and Research Information Sharing Service were searched for studies on the efficacy of acupuncture for WAD from their inception to October 1, 2023. Terms related to acupuncture and WAD from the Medical Subject Headings were used in the search strategy; the terms were translated into the language suitable for each database (online supplemental table S1). In addition, we checked the reference lists of all previously published SRs identified by the above methods, looking for cited relevant studies. However, we did not review conferences because of its potential to introduce bias.

Eligibility criteria

The studies included in this study were selected according to the following five criteria: study design, participants, intervention, comparison, and outcomes. Randomized controlled trials (RCTs) that used acupuncture on patients with WAD were included regardless of their reporting type, blinding, and language. In contrast, RCTs that did not target WAD or use acupuncture as an intervention were excluded. Additionally, non-RCTs, single-arm pre- and post-clinical trials, case-control studies, case reports, laboratory studies (including in vivo and in vitro studies), letters, and reviews were also excluded. Thereafter, the participants diagnosed with WAD, regardless of their race, age, or sex, were identified. The diagnostic criteria for WAD were based on those of the Quebec Task Force, which classified patients according to their severity of signs and symptoms [21]. The Quebec Task Force's diagnostic criteria are as

follows:

Grade I: Neck complaint of pain, stiffness or tenderness only. No physical sign(s).

Grade II: Neck complaint AND musculoskeletal sign(s). Musculoskeletal signs include decreased range of motion and point tenderness.

Grade III: Neck complaint AND neurological sign(s). Neurological signs include decreased range of motion and point tenderness.

Grade IV: Neck complaint AND fracture or dislocation.

The treatment interventions were acupuncture treatment, including electroacupuncture (EA) and dry needling, and acupuncture combined with active treatment(s), which were compared with the same active treatment(s) in the control group. The treatments administered to the control group were limited to usual care, such as physiotherapy, medications, conventional treatments other than acupuncture, and sham treatments. The primary outcome was the pain visual analog scale (VAS) score or numerical rating scale score for neck pain, and the secondary outcomes were the range of motion (ROM) of the neck, the neck disability index (NDI), and safety [22].

Data collection and analysis

Study selection

Two independent researchers (SHL and MSH) were involved in the study selection process. Study selection and deduplication were performed using Excel. In the case of disagreements during the process, the researchers proceeded to the next step after reaching a consensus through a discussion. After removing duplications, the titles and abstracts of the studies were screened to exclude those that did not meet the eligibility criteria. Subsequently, the full text of each selected study was fully reviewed for the final selection.

Data extraction and management

Two independent researchers (SHL and MSH) analyzed and extracted the data from the selected literature. Data extraction and management were performed using Excel. Data regarding the country of origin, study design, sample size, participants, intervention, comparison, outcomes, and results were summarized in a table. In addition, data regarding the type of acupuncture, acupoints, depth of needling, stimulation response, total sessions, frequency of sessions, and retention time were collected to appraise the acupuncture procedure as part of the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [23, 24]. In the case of missing standard mean difference (SMD) for changes from baseline, we tried to contact the original investigators to request further data. However, if it was impossible, we calculated a correlation coefficient from a study reported in considerable detail and imputed missing data in accordance with the established method [25, 26].

Quality assessment

Two independent researchers (SHL and MSH) evaluated the quality of the selected studies according to the Cochrane RoB 2 tool in the Cochrane Handbook for Systematic Reviews of Interventions [19]. The risk of bias assessment was performed based on the content described in the original text and the characteristics of the intervention. The Grading of Recommendations Assessment, Development and Evaluations (GRADE) method was used to evaluate the quality of the outcomes [27]. Each outcome was classified as not serious, serious, or very serious according to the study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The certainty of the outcomes was categorized as high, moderate, low, or very low. In the case of disagreements between researchers, agreement was reached through discussion with third and fourth researchers (BCS, IH).

Statistical analysis

The meta-analysis was performed using the Review Manager version 5.4.1 (Cochrane) software. To determine the value of the effect size, SMD was used for continuous data and relative risk for dichotomous data. All data, including dichotomous and continuous data, were presented with a 95% confidence interval (CI). Fixed-effects or random-effects models were used for the synthesis of data according to the heterogeneity of each meta-analysis. Heterogeneity (I^2) of less than 50% was considered negligible, and a fixed-effects model was used in such cases. If the heterogeneity exceeded 50%, a random-effects model was used to estimate the effect size. Subgroup analysis was performed according to the type of acupuncture treatment to verify the effect size of each subgroup. The "leave-one-out" approach, where the meta-analysis is performed repeatedly while excluding the included literature individually, was performed for sensitivity analysis [28]. When a fixed-effects model was used for data synthesis, sensitivity analysis using a random-effects model was additionally performed to eliminate confounding effects. In addition, a funnel plot was generated to determine the presence of publication bias for the primary outcome.

Patient and public involvement

No patient involved.

RESULTS

Study selection

A total of 877 articles were retrieved from databases. After excluding 154 duplications, 295 studies unrelated to WAD, 163 non-RCT studies, 42 in vitro and in vivo studies, and 154 irrelevant studies were excluded while screening of the title and abstract. The full text of the remaining 69 articles was reviewed, and 62 articles were excluded, including 51 articles that did not use acupuncture as an intervention, 6 articles without full text, 3 articles without a valid control group, and 2 articles for other reasons. In addition, we included 1 study through reference tracking [16]. Thus, 8 studies were included in the final analysis (Figure 1).

Study characteristics

A total of 525 patients with WAD were included in this study. Five studies [16, 29-32] compared acupuncture with sham acupuncture, usual care, or medication, whereas two [33, 34] compared EA with sham EA. One study [35] compared motion-style acupuncture treatment (MSAT) with usual care. The country of origin of the studies varied: three in Korea [31, 33, 35], two in Australia [29, 34], one each in Belgium [30], UK [32], and Austria [16]. The recruitment period was less than one year in five studies [30-33, 35], more than four years in two studies [29, 34], and not reported in one study [16]. Among the eight studies, one [30] was designed as a crossover RCT. The pain VAS score was recorded in six studies [30-35], and the ROM was recorded in four studies [16, 29, 31, 35]. The NDI was recorded in six studies [29, 30, 32-35]. The study by Aigner et al. was described based on its reference in the SR by Moon et al. [16], as the original text could not be accessed (Table 1).

Table 1. Data of clinical studies on acupuncture for whiplash-associated disorder

First author (year)	Country of origin (period)	Design	Sample size	Participants	Intervention	Comparison	Outcomes	Results (Effect size, P-value)
Sterling et al (2015) [29]	Australia (2009 – 2012)	RCT	Total: 80 Exp.: 40 Con.: 40	WAD Ⅱ	Atx. + exercise	Sham atx. + exercise	1) NDI 2) ROM (1) Flex. (2) Ext. (3) Rot. (4) Lat.	1) 0.10, P=0.67 2) (1) -0.14, P=0.54 (2) 0.08, P=0.71 (3) -0.32, P=0.16 (4) 0.26, P=0.24
Tobbackx et al (2012) [30]	Belgium (01/2011 – 12/2011)	Crossover RCT	Total: 39	WAD Ⅰ or Ⅱ or Ⅲ (chronic WAD persisting more than 3 months)	Atx.	Relaxation	1) NDI 2) pain VAS	1) 0.17, P=0.47 2) 0.16, P=0.47
Kwak et al (2012) [31]	Korea (12/2009 – 10/2010)	RCT	Total: 40 Exp.: 20 Con.: 20	WAD (persisting more than 3 months)	Atx. + UC	UC (PTx. + exercise)	1) pain VAS 2) ROM (1) Flex.	1) 0.78, P=0.02 2) (1) -0.01, P=0.97

							(2) Ext.	(2) 0.73, P=0.03
							(3) Rt. Lat. Flex.	(3) 0.10, P=0.76
							(4) Lt. Lat. Flex	(4) 0.25, P=0.43
							(5) Rt. Rot.	(5) 0.10, P=0.76
							(6) Lt. Rot.	(6) 0.16, P=0.61
Tough et al (2010) [32]	UK (05/2007 – 12/2007)	RCT	Total: 34 Exp.: 17 Con.: 17	WAD Ⅱ (WAD persisting 2-16 weeks)	Atx. + Ptx.	Sham Atx. + Ptx.	1) pain VAS 2) NDI	1) 0.76, P=0.03 2) 0.61, P=0.08
Aigner et al (1998) [16]	Austria (NR)	RCT	Total: 61 Exp.: 28 Con.: 33	WAD Ⅰ or Ⅱ	Atx.	Med.	1) RCM	1) NR
Han et al (2011) [33]	Korea (03/2011 – 07/2011)	RCT	Total: 58 Exp.: 29 Con.: 29	WAD	EA + HM	Sham EA + HM	1) pain VAS 2) NDI	1) 0.88, P=0.002 2) 0.57, P=0.03
Cameron et al (2011) [34]	Australia (03/2001 – 10/2004)	RCT	Total: 116 Exp.: 52 Con.: 64	WAD Ⅰ or Ⅱ (subacute or chronic WAD persisting more than 1 month)	EA	Sham EA	1) pain VAS 2) NDI	1) 0.21, P=0.25 2) -0.49, P=0.009

							1) pain VAS	1) 0.85, P<0.0001
							2) NDI	2) 0.29, P=0.15
							3) ROM	3)
Kim et al (2020) [35]	Korea (07/2019 – 09/2019)	RCT	Total: 97 Exp.: 48 Con.: 49	WAD (within 7 days)	MSAT + IKM	IKM (Atx. + pharm. + CMT + HM)	(1) Flex.	(1) 0.80, P=0.0001
							(2) Ext.	(2) 0.67, P=0.001
							(3) Rt. Rot. Flex.	(3) 1.01, P<0.001
							(4) Lt. Rot. Flex	(4) 0.88, P<0.001
							(5) Rt. Lat.	(5) 1.44, P<0.001
							(6) Lt. Lat.	(6) 1.43, P<0.001

CI: Confidence interval; RCT: Randomized controlled trial; Exp.: Experimental; Con.: Control; WAD: Whiplash-associated disorder; MSAT: Motion-style acupuncture treatment; IKM: Integrative Korean medicine treatment; Pharm.: Pharmacopuncture; CMT: Chuna manual therapy; HM: Herbal medicine; VAS: Visual analog scale; NDI: Neck disability index; ROM: Range of motion; Flex.: Flexion; Ext.: Extension; Rt.: Right; Rot.: Rotation; Lt.: Left; Lat: Lateral; Atx.: Acupuncture therapy; UC: Usual care; PTx.: Physiotherapy; EA: Electroacupuncture; Med.: Medication

Standard for reporting acupuncture according to STRICTA

The eight studies were analyzed using STRICTA (online supplemental table S2). Regarding the type of acupuncture, five studies [16, 29-32] used general acupuncture, two used EA [33, 34], and one used MSAT [35]. Five studies [16, 30, 31, 33, 34] used specific acupoints, and three [29, 32, 35] used muscle trigger points instead of acupoints. The depth of needling was mentioned only in four studies [31, 33-35]. For stimulation response, two studies [30, 31] induced a *deqi* sensation, two [29, 32] used pecking, two [29, 31] used techniques such as twirling and rotation, and two [33, 34] used electrical stimulation. Regarding the total number of sessions, more than six sessions were performed in most studies [29, 31, 33-35], only one session was performed in one study [30], and two to six sessions were performed in one study depending on the degree of improvement in the symptoms [32]. The frequency of sessions was unreported in one study [16], whereas sessions were performed one to three times a week in the remaining seven studies. The number of weeks varied from one to six weeks, and the retention time varied from 15 to 60 min.

Risk of bias assessment

The eight selected studies were analyzed using the Cochrane RoB 2 tool. Six out of eight studies were identified as having low risk of bias with appropriate procedures for random sequence generation and allocation concealment [29-32, 34, 35]. Regarding deviations from the intended interventions, four studies were rated as having low risk of bias [29, 31, 34, 35], three as having some concerns [30, 32, 33], and one as having high risk of bias [16]. For missing outcome data, four studies were rated as having low risk of bias [30, 31, 33, 35]. In terms of bias in measurement of the outcome, except for one study that did not provide full text [16], all seven studies were identified as having low risk of bias. In terms of the selection of the reported result, studies that reported a pre-specified analysis plan were rated as having low risk of bias

[29-31, 35]. Overall, two studies showed low risk of bias in all five components [31, 35] (Figure 2, online supplemental figure S1).

Meta-analysis

A meta-analysis was performed with seven studies [29-35] according to the outcomes, after excluding one study [16] in which no comparison was made between the groups. The subgroups were divided into general acupuncture, EA, and MSAT according to the type of acupuncture treatment.

Pain VAS score

The result of the meta-analysis for the pain VAS score revealed that acupuncture was effective in treating patients with WAD (SMD: -0.57 [-0.86 to -0.28], p<0.001). The random-effects model was used for the analysis, as the heterogeneity (I^2) was 51%. Subgroup analysis revealed that general acupuncture and MSAT were effective in treating patients with WAD, whereas EA was ineffective (Figure 3).

ROM

Kwak et al. [31] and Kim et al. [35] recorded the ROM for all directions, whereas Sterling et al. [29] recorded the ROM for four directions: flexion, extension, right rotation, and left rotation. The results of the meta-analysis for ROM revealed that acupuncture was effective in improving extension in patients with WAD (SMD: 0.47 [0.05 to 0.89], p=0.03). The random-effects model was used for all directions of ROM, as the heterogeneity (I^2) was > 50%. Subgroup analysis showed that MSAT was effective in treating patients with WAD in all directions of ROM. However, general acupuncture was not effective for ROM in any direction

(Figure 4).

NDI

The results of the meta-analysis for NDI revealed that acupuncture was ineffective in improving the NDI. The random-effects model was used for the analysis as the heterogeneity (I^2) was > 50%. Subgroup analysis revealed that all treatments were ineffective in improving the NDI (online supplemental figure S2).

Adverse events

Five studies [29, 31, 32, 34, 35] reported adverse events (AEs), whereas three [16, 30, 33] did not. Except for one case of moderate AE, all reported AEs were mild. Pruritus of unknown cause was reported in the study by Kim et al. [35], necessitating the administration of antihistamines by injection, cream, and oral route. Other AEs caused by acupuncture included hives, dizziness, exacerbation of neck pain, bruising, fatigue, and somatic reactions (sweating and low blood pressure); however, these AEs were mild and were cured within a few days. AEs such as diarrhea, soft stools, nausea, heartburn, and vesicles were also reported; however, these were confirmed to be caused by interventions other than acupuncture.

Sensitivity analysis

A sensitivity analysis for the pain VAS score, ROM-flexion, ROM-extension, ROM-right rotation, ROM-left rotation, and NDI was performed, whereas ROM-right lateral flexion and ROM-left lateral flexion were excluded as they were included only in two studies (online supplemental table S3).

Pain VAS score

The results of the meta-analysis of the pain VAS score changed to moderate heterogeneity when the study by Tobbackx et al. [30] was removed (SMD: -0.65 [-0.96 to -0.35], p<0.001, I^2: 44%).

ROM

The result of the meta-analysis of ROM-extension was maintained when the study by Sterling et al. [29] was removed; however, the results were not maintained when the study by Kwak et al. [31] or Kim et al. [35] was removed. In particular, there was no heterogeneity when the study by Sterling et al. [29] was excluded. However, the results of the meta-analysis of ROM-flexion, ROM-right rotation, and ROM-left rotation were not significantly affected as the p-value was > 0.05 even after removing the included studies one by one.

NDI

The result of the meta-analysis of NDI changed to the p-value < 0.05 and no heterogeneity when the study by Cameron et al. [34] was removed (SMD: -0.29 [-0.51 to -0.08], p= 0.007, I^2: 0%).

Evidence quality

The quality of evidence of the outcomes was assessed using GradePro GDT (online supplemental table S4).

Pain VAS score

Six studies (n = 423) provided data regarding the pain VAS score. The risk of bias evaluation

revealed high bias in one study; however, the effect on the estimate was considered inconclusive, and the confidence level of the evidence was not lowered. For inconsistency, the pain VAS score was downgraded by one level as its heterogeneity (I^2) was 51%. Thus, the quality of evidence on the pain VAS score was graded as "moderate."

ROM

Three studies (n = 216) provided data regarding ROM-flexion, ROM-extension, ROM-right rotation, and ROM-left rotation. Two studies (n = 137) provided data regarding ROM-right lateral flexion and ROM-left lateral flexion. The risk of bias evaluation revealed some concerns in one study; however, the effect on the estimate was considered inconclusive, and the confidence level of the evidence was not lowered. In the evaluation of consistency, ROM-extension and ROM-left lateral flexion were downgraded by one level as their heterogeneity (I^2) was higher than 50% but lower than 75%. Similarly, ROM-flexion, ROM-right lateral flexion, ROM-right rotation, and ROM-left rotation were downgraded by two levels as their heterogeneity (I^2) was > 75%. In the evaluation of imprecision, ROM-extension was downgraded by one level as the number of participants was less than 400. Similarly, ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation were degraded by two levels as the number of participants was less than 400 and their CI overlapped with no effect. Thus, ROM-extension was graded as "low," and ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation were graded as "very low."

NDI

Six studies (n = 462) reported data regarding the NDI. The risk of bias evaluation revealed high bias in one study; however, the effect on the estimate was considered inconclusive, and the

confidence level of the evidence was not lowered. For inconsistency, the NDI was downgraded by one level as its heterogeneity (I^2) was 69%. In the evaluation of imprecision, the NDI was downgraded by one level as the CI overlapped with no effect. Thus, the NDI was graded as "low."

Publication bias

Publication bias was evaluated using the funnel plot for the pain VAS score (online supplemental figure S3). The outcome was slightly asymmetric, meaning there was a little publication bias. However, as fewer than 10 studies were included, the power of the test is expected to be low.

DISCUSSION

This study revealed that acupuncture is effective in improving the pain VAS score and ROM-extension in patients with WAD. The analgesic effect of acupuncture is thought to relieve pain in patients with WAD. In addition, patients with WAD were able to effectively improve ROM-extension following acupuncture, as acupoints GB20, GB21, SI11, SI14, SI15, and TE15, which are used extensively in patients with WAD, are located in the posterior muscles of the cervical spine and upper thoracic spine. However, the NDI, ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation did not show significant differences; thus, future studies are required to prove the effectiveness of acupuncture for these outcomes.

In the risk of bias assessment, except for one study published before 2010 [16], seven studies published after 2010 showed low bias in most domains [29-35]. In addition, although participant blinding is difficult owing to the nature of acupuncture [36], many studies have attempted to minimize this effect by utilizing placebo interventions. Moreover, four studies [29-31, 35] published after 2012 showed some concerns in only two domains and low bias in all other domains, indicating that recent studies on acupuncture interventions are consistently designed with high quality.

In the sensitivity analysis of the pain VAS score, a significant effect was maintained even when the included studies were removed one by one. In this context, acupuncture showed significant effects in patients with WAD, despite differences in design, participants, interventions, and comparisons among the studies. In addition, when the study by Tobbackx et al. [30] was removed, moderate heterogeneity was observed, meaning it was accountable for the substantial heterogeneity of the overall result. The crossover RCT design of Tobbackx et al. [30] is presumed to be the reason for the low effect size and high heterogeneity. For ROM-extension, there was no heterogeneity when the study by Sterling et al. [29] was removed; thus, it could

be assumed that the study was a potential source of heterogeneity. In the study by Sterling et al. [29], high-intensity ROM exercises, including craniocervical flexion training, neck extensor training, scapular training, posture re-education, and sensorimotor exercises, were performed for 1 h, which may have been the cause of heterogeneity. For the NDI, a significant effect appeared, and no heterogeneity was obtained when the study by Cameron et al. [34] was removed; therefore, the study was considered responsible for the between-study heterogeneity. It was presumed that the NDI SMD of the study favored the control group since it was > 0, affecting the overall effect size and heterogeneity.

A previous study [16] that analyzed the effectiveness of acupuncture in patients with WAD included studies published before 2014. This study differs from the previous study in the following ways. First, including two RCTs published after 2014, we analyzed a total of eight RCTs. Accordingly, this study provided more objective and quantitative evidence by synthesizing data on the efficacy of acupuncture for treating WAD. Second, the effect size of the pain VAS score, ROM, and NDI was verified by performing a meta-analysis. The directionality of the treatment effect and whether the CI of the individual studies overlapped were assessed using a forest plot. Third, a sensitivity analysis was performed to confirm the robustness of the results. The effect of individual studies on heterogeneity (I^2) and effect size was analyzed using the leave-one-out approach method. Fourth, a subgroup analysis was conducted according to the type of acupuncture treatment. The effect size of each type of acupuncture treatment was verified by dividing them into general acupuncture, EA, and MSAT subgroups. Fifth, the evidence quality of the pain VAS score, ROM, and NDI was assessed using the GRADE method. By presenting the certainty for each outcome, this study provided criteria that can be clinically referred to when using acupuncture for patients with WAD.

However, this study has some limitations. First, grey literature and other supplementary searches were not conducted, which may result in missing studies and the risk of publication

bias. However, we attempted to minimize publication bias by reviewing the references of a previously published SR. Second, the original text of one study could not be accessed. Third, except for ROM-extension, the efficacy of acupuncture in improving ROM in other directions was evaluated as being "very low." This is an area that needs to be verified through further studies.

CONCLUSION

The results of this study suggest that acupuncture may have clinical value in the treatment of patients with WAD. In the future, high-quality RCTs, based on the aforementioned data, must generate evidence of higher quality than that in the present study to confirm the efficacy of acupuncture in patients with WAD.

AUTHOR CONTRIBUTIONS

Sang-Hyun Lee: Conceptualization

Sun-Young Park: Funding acquisition

Sang-Hyun Lee and Man-Suk Hwang: Investigation

In Heo and Byung-Cheul Shin: Methodology

Eui-Hyuoung Hwang and Man-Suk Hwang: Project administration

Man-Suk Hwang: Supervision

Sang-Hyun Lee: Writing – original draft

Sang-Hyun Lee and Man-Suk Hwang: Writing – review & editing

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DISCLAIMER

The funding source had no role in the design of the protocol, study search and selection, data extraction and management, data interpretation, report writing, or the decision to submit the report for publication.

COMPETING INTERESTS

None.

PATIENT CONSENT FOR PUBLICATION

Not required.

PROVENANCE AND PEER REVIEW

Not commissioned; extremally peer reviewed.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

AMENDMENT

In accordance with the reviewer's comment for revision, the RoB 2 tool and funnel plot were added to this review, unlike the proposed protocol. In addition, conference tracking was not conducted.

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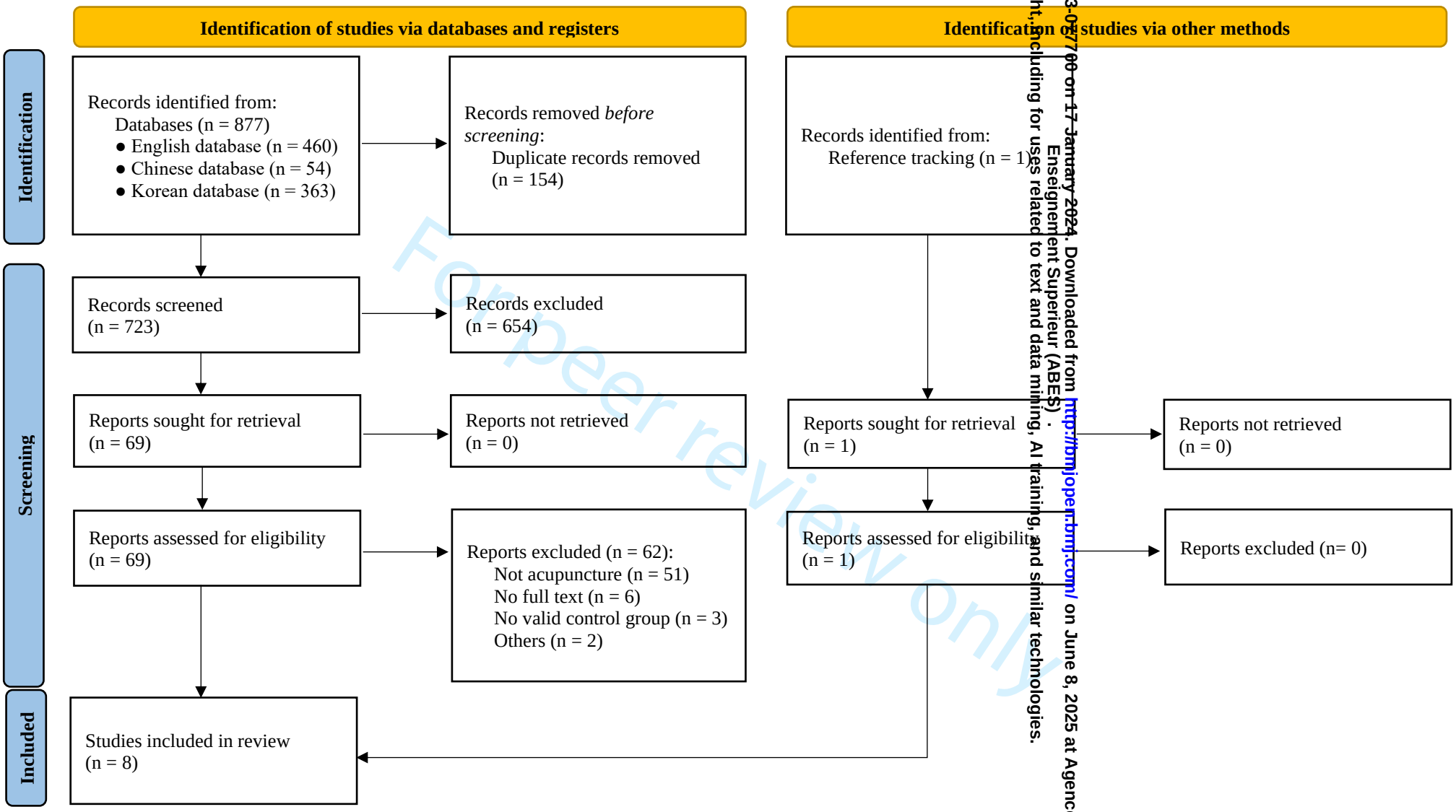
FIGURE LEGENDS

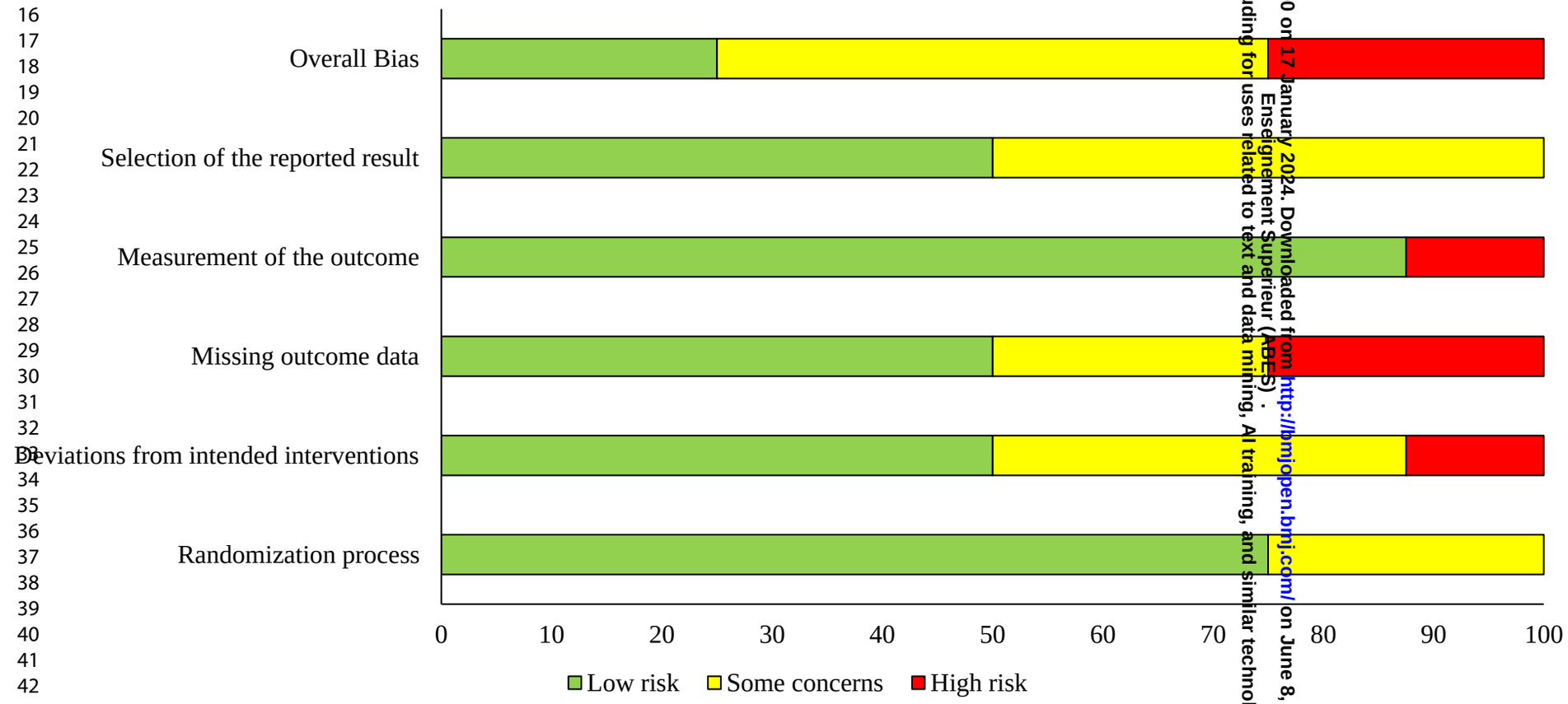
Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart of the included studies

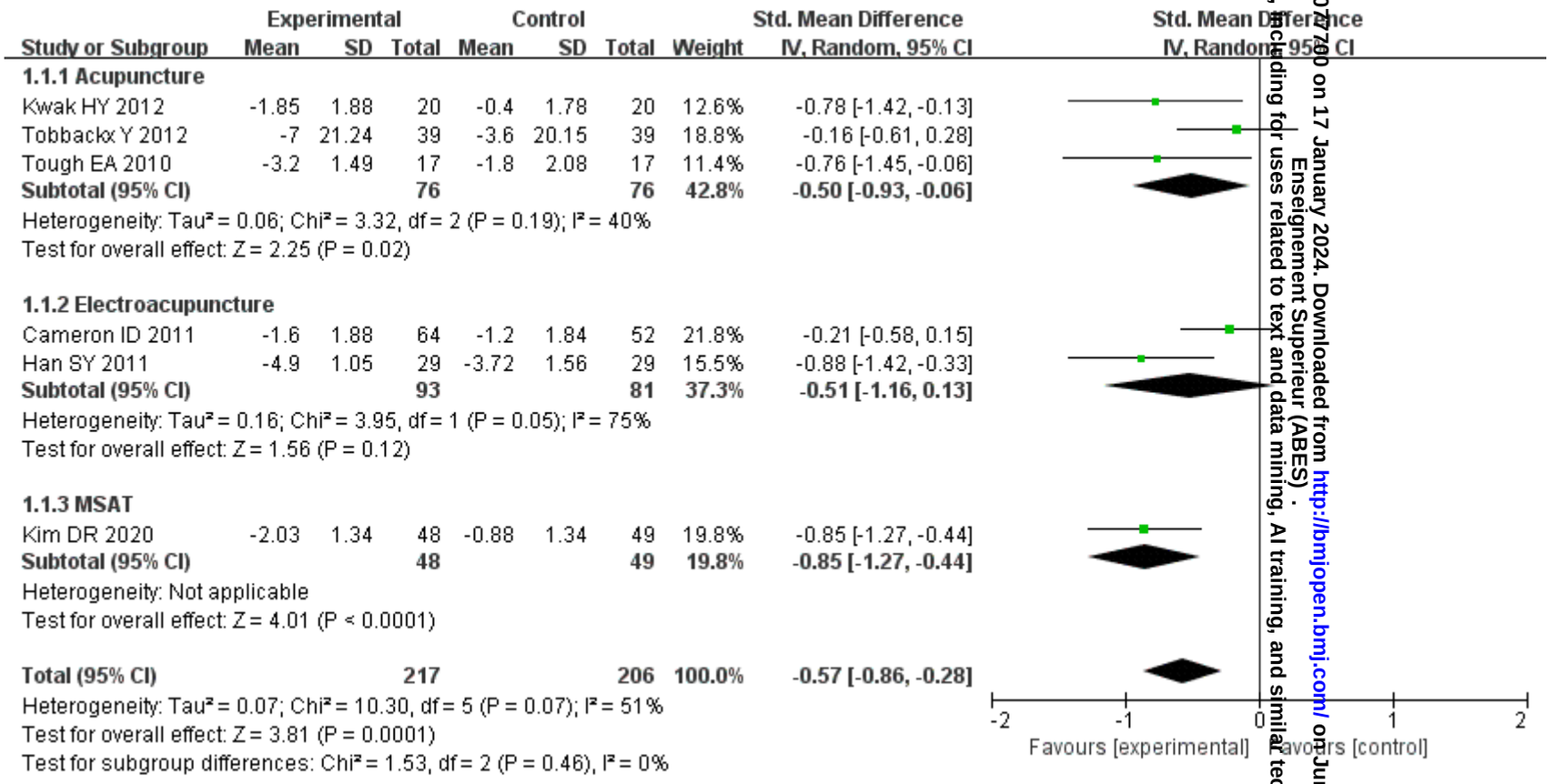
Figure 2. Summary in risk of bias 2

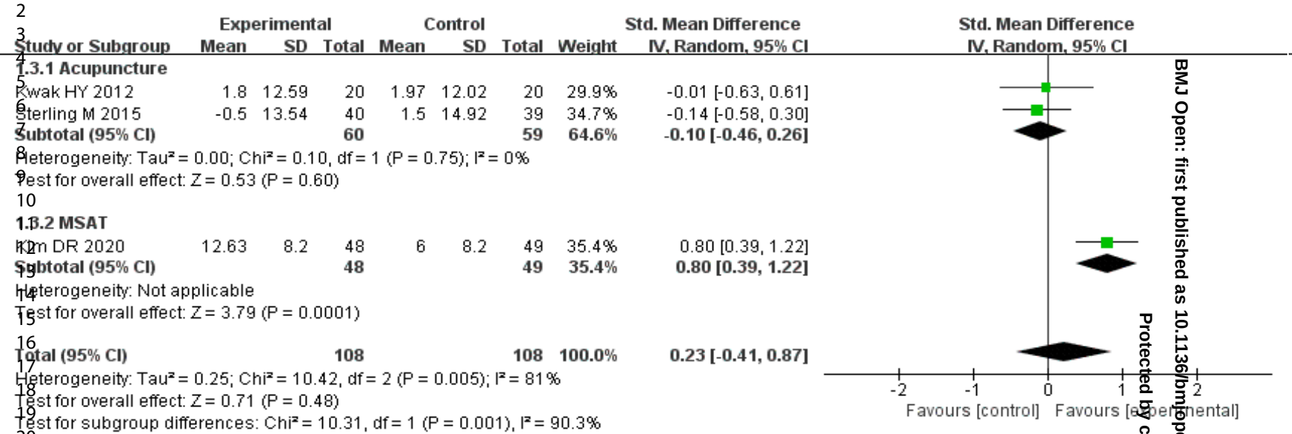
Figure 3. Forest plot of the meta-analysis for the pain visual analog scale score

Figure 4. Forest plot of the meta-analysis for the range of motion

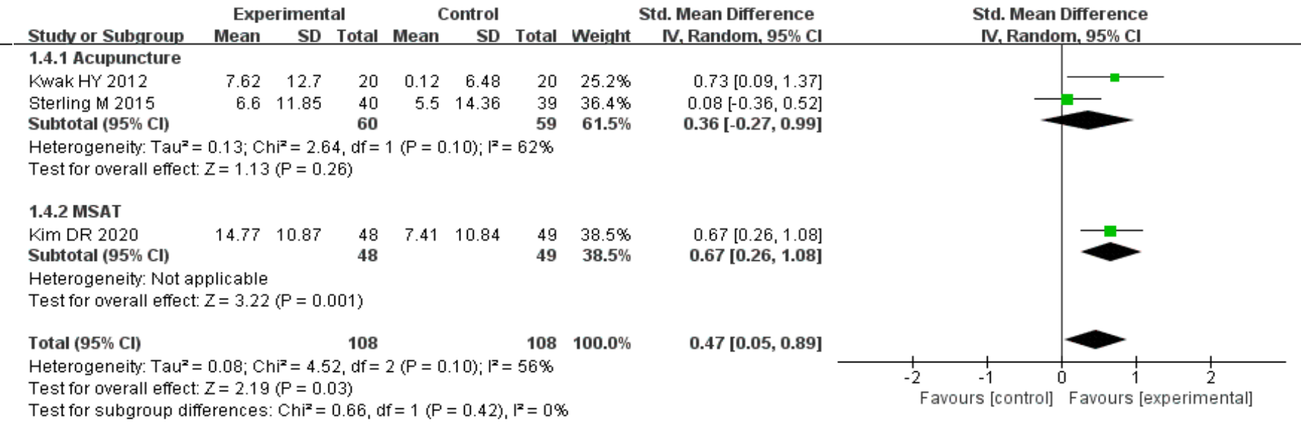




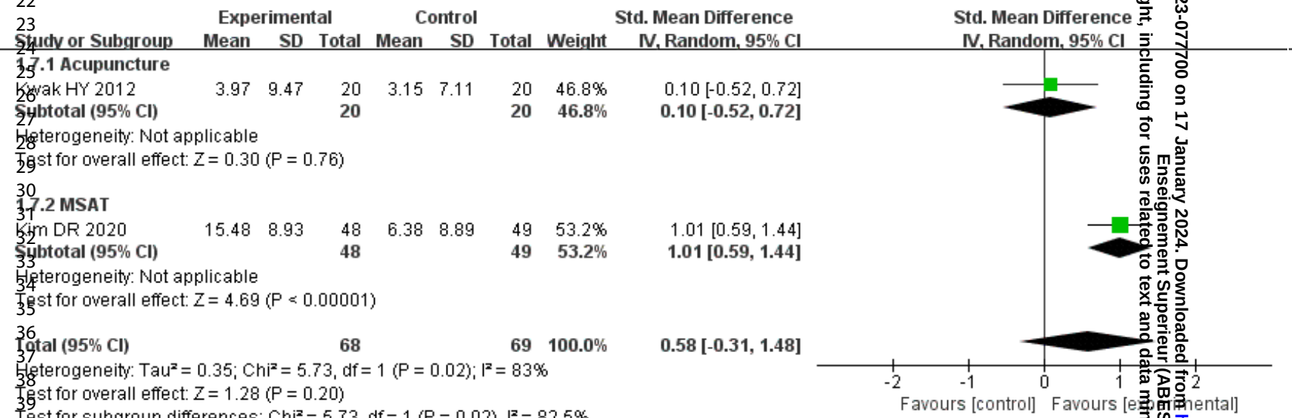




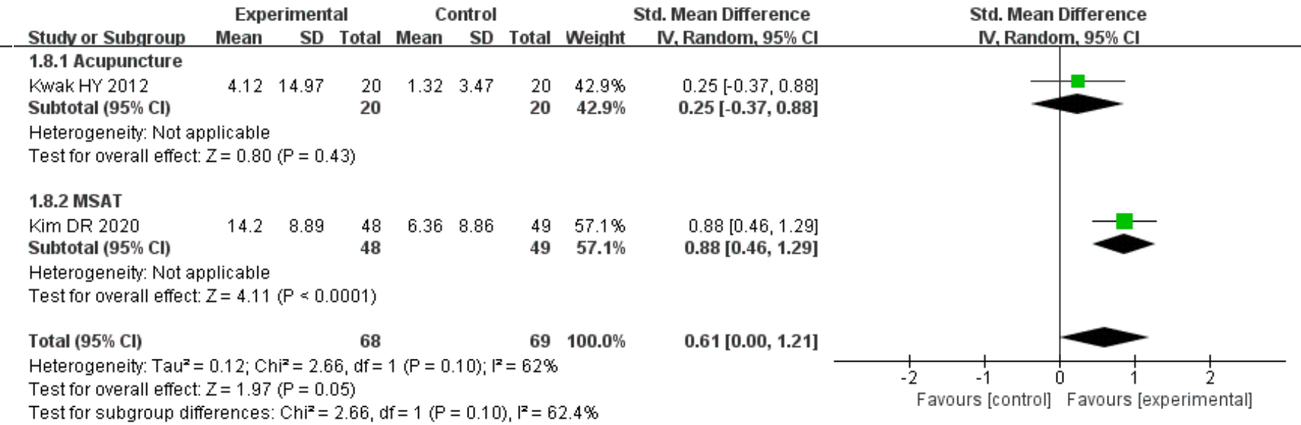
(A) Flexion



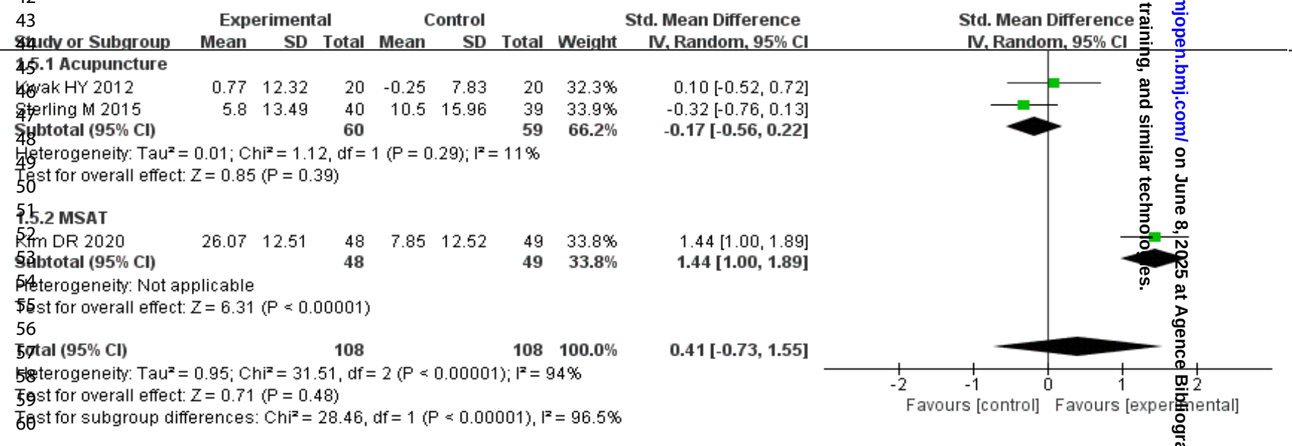
(B) Extension



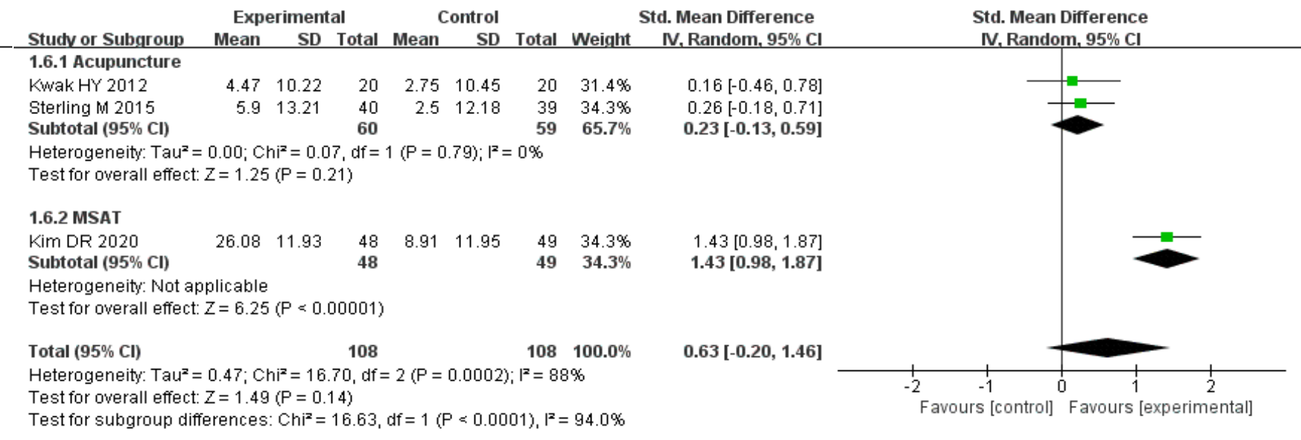
(C) Right lateral flexion



(D) Left lateral flexion



(E) Right rotation



(F) Left rotation

Supplemental table S1. Search strategy and terms used

Database: PubMed (pubmed.ncbi.nlm.nih.gov; 1996-2023)		
No.	Search strategy	Results
#1	whiplash OR acute whiplash injury* OR acute whiplash associated disorder* OR acute WAD OR acute whiplash associated disorder* II OR acute WAD II OR whiplash associated disorder* OR WAD OR whiplash associated disorder* II OR WAD II, OR whiplash OR whiplash injury* OR whiplash patient* OR whiplash syndrome* OR cervical spine disorder* OR cervical spine injury* OR "Accidents, Traffic" [Mesh] OR (("Motor Vehicles"[Mesh:NoExp] OR "Automobiles"[Mesh] OR "Motorcycles"[Mesh] OR traffic[tiab] OR vehicle[tiab] OR vehicular[tiab] OR car[tiab] OR cars[tiab] OR automobile[tiab] OR automobiles[tiab] OR motorcycle[tiab] OR motorcycles[tiab] OR taxi[tiab] OR cab[tiab] OR road[tiab] OR pedestrian[tiab] OR pedestrians[tiab]) AND (accident[tiab] OR accidents[tiab] OR injury[tiab] OR injuries[tiab] OR crash[tiab] OR crashes[tiab] OR "Wounds and Injuries"[Mesh] OR "injuries"[Subheading])) AND (cervic* OR thoracic* OR lumba*)	24,250
#2	acupuncture	42,653
#3	electroacupuncture	7,448
#4	acupressure	1,832
#5	((((((((((((((((((((((meridian) OR acupoint) OR acupuncture [mh]) OR acupuncture Analgesia [mh]) OR acupuncture Therapy [mh]) OR acupuncture points [mh]) OR acupuncture, ear [mh]) OR acupuncture [Text Word]) OR acupressure [Text Word]) OR electroacupuncture) OR electro acupuncture) OR electro-acupuncture) OR meridian* [Text Word]) OR needling [Text Word]) OR acu-point*) OR acu point* [Text Word]) OR acupoint* [Text Word]) OR Acupuncture [mh]) OR electroacupuncture [mh]) OR acupuncture* [Text Word]) OR elctroacupuncture* [Text Word]) OR (acupuncture AND th[sh])) OR acupuncture[tiab]) OR acupuncture[mh]) OR acupuncture/th[mh]	51,277
#6	#2 or #3 or #4 or #5	54,150
#7	#1 and #6	89
Database: Ovid Medline (ovidsp.ovid.com; 1946-2023)		
1	exp Whiplash Injuries/	3,423
2	whiplash.tw.	3,292
3	acute whiplash injury*.tw.	75
4	acute whiplash associated disorder*.tw.	71
5	acute WAD.tw.	66
6	WAD.tw.	1,038

7	whiplash patient*.tw.	201
8	whiplash syndrome*.tw.	183
9	cervical spine disorder*.tw.	228
10	cervical spine injury*.tw.	1,571
11	exp Accidents, Traffic/	48,509
12	exp Motor Vehicles/	24,289
13	exp Automobiles/	7,798
14	exp Motorcycles/	2,900
15	traffic.tw.	58,851
16	vehicle.tw.	134,582
17	vehicular.tw.	4,046
18	car.tw.	36,938
19	cars.tw.	9,562
20	automobile.tw.	6,526
21	automobiles.tw.	1,392
22	motorcycle.tw.	3,814
23	motorcycles.tw.	931
24	taxi.tw.	1,261
25	cab.tw.	3,755
26	road.tw.	48,507
27	pedestrian.tw.	5,278
28	pedestrians.tw.	3,859
29	accident.tw.	53,887
30	accidents.tw.	48,861
31	injury.tw.	801,932
32	injuries.tw.	254,612
33	crash.tw.	11,757
34	crashes.tw.	9,905
35	exp "Wounds and Injuries"/	1,014,422
36	or/29-35	1,675,831
37	or/11-28	298,607
38	or/1-10	6,385

39	36 and 37	79,754
40	38 or 39	84,652
41	acupuncture.mp.	34,547
42	electroacupuncture.mp.	7,050
43	acupressure.mp.	1,813
44	meridian.mp.	4,833
45	acupoint.mp.	4,164
46	exp acupuncture/	2,043
47	acupuncture.tw.	27,126
48	acupressure.tw.	1,523
49	electro acupuncture.mp.	951
50	meridian*.tw.	6,456
51	needling.tw.	3,936
52	acu-point*.mp.	33
53	acu point*.tw.	33
54	acupoint*.tw.	7,040
55	elctroacupuncture*.tw.	1
56	(acupuncture and th).mp.	79
57	or/41-56	44,775
58	40 and 57	120
Database: Embase (embase.com; 1947-2023)		
1	'automobiles'/exp	11,661
2	'motor vehicle'/exp	28,069
3	'accident, traffic'/exp	75,665
4	'motorcycle'/exp	3,664
5	vehicle:ta,ab,de	203,388
6	traffic:ta,ab,de	153,433
7	vehicular:ta,ab,de	4,909
8	car:ta,ab,de	77,435
9	cars:ta,ab,de	12,857
10	automobile:ta,ab,de	7,368
11	automobiles:ta,ab,de	1,524

12	motorcycle:ta,ab,de	5,934
13	motorcycles:ta,ab,de	1,104
14	taxi:ta,ab,de	1,535
15	cab:ta,ab,de	5,070
16	road:ta,ab,de	48,308
17	pedestrian:ta,ab,de	7,726
18	pedestrians:ta,ab,de	4,183
19	accident:ta,ab,de	593,740
20	accidents:ta,ab,de	56,438
21	injury:ta,ab,de	1,928,938
22	injuries:ta,ab,de	280,812
23	crash:ta,ab,de	12,698
24	crashes:ta,ab,de	10,253
25	'wounds and injuries'/exp	2,824,750
26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	3,658,250
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	427,543
28	#26 AND #27	136,545
29	acupuncture	65,725
30	electroacupuncture	10,710
31	acupressure	3,180
32	acupoint	6,816
33	acupoint:ta,ab,de	6,154
34	'acupuncture analgesia'	2,374
35	'acupuncture therapy'	2,500
36	'acupuncture points'	2,351
37	'acupuncture, ear'	42
38	acupuncture:ta,ab,de	56,629
39	acupressure:ta,ab,de	3,077
40	electroacupuncture	10,710
41	'electro acupuncture'	1,442
42	meridian*:ta,ab,de	9,056

43	needling:ta,ab,de	5,115
44	'acu point*'	50
45	acu AND point*:ta,ab,de	968
46	acupoint*:ta,ab,de	9,351
47	'acupuncture'/exp	57,828
48	'electroacupuncture'/exp	9,355
49	acupuncture*:ta,ab,de	56,660
50	electroacupuncture*:ta,ab,de	10,236
51	acupuncture.:ta,ab,de	56,629
52	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	77,464
53	#28 AND #52	211
Database: The Cochrane Library (thecochranelibrary.com; 1993-2023)		
#1	whiplash	589
#2	acute whiplash injury*	139
#3	acute whiplash associated disorder*	97
#4	acute WAD	113
#5	acute whiplash associated disorder* II	37
#6	acute WAD II	44
#7	whiplash associated disorder*	297
#8	WAD	382
#9	whiplash associated disorder* II	69
#10	WAD II	76
#11	whiplash patient*	426
#12	whiplash syndrome*	98
#13	cervical spine disorder*	605
#14	cervical spine injury*	623
#15	MeSH descriptor: [Accidents, Traffic] explode all trees	547
#16	MeSH descriptor: [Motor Vehicles] explde all trees	361
#17	MeSH descriptor: [Automobiles] this term only	77
#18	MeSH descriptor: [Motorcycles] this term only	35
#19	traffic:ti,ab,kw	2,624

#20	vehicle:ti,ab,kw	8,257
#21	vehicular:ti,ab,kw	56
#22	car:ti,ab,kw	4,202
#23	cars:ti,ab,kw	463
#24	automobile:ti,ab,kw	1,157
#25	automobiles:ti,ab,kw	95
#26	motor cycle*:ti,ab,kw	1,169
#27	taxi*:ti,ab,kw	260
#28	cab*:ti,ab,kw	11,113
#29	road*:ti,ab,kw	2,087
#30	pedestrian*:ti,ab,kw	231
#31	accident*:ti,ab,kw	25,630
#32	injur*:ti,ab,kw	76,691
#33	crash*:ti,ab,kw	773
#34	MeSH descriptor: [Wounds and Injuries] explode all trees	35,004
#35	Any MeSH descriptor in all MeSH products and with qualifier(s): [injuries - IN]	3,961
#36	cervic$ or thoracic$ or lumba$	33,603
#37	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	1,770
#38	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30	28,521
#39	#31 or #32 or #33 or #34 or #35	112,456
#40	#38 and #39	4,739
#41	#37 or #40	6,352
#42	#41 and #36	429
#43	acupuncture	21,079
#44	electroacupuncture	3,539
#45	acupressure	2,174
#46	meridian	1,465
#47	acupoint	3,749
#48	MeSH descriptor: [acupuncture] explode all trees	713
#49	MeSH descriptor: [acupuncture Analgesia] explode all trees	339
#50	MeSH descriptor: [acupuncture Therapy] explode all trees	6,467

#51	MeSH descriptor: [acupuncture points] explode all trees	2,520
#52	MeSH descriptor: [acupuncture, ear] explode all trees	244
#53	acupuncture:ti,ab,kw	19,015
#54	acupressure:ti,ab,kw	2,062
#55	electro acupuncture	1,023
#56	electro-acupuncture	783
#57	meridian*:ti,ab,kw	1,399
#58	needling:ti,ab,kw	3,062
#59	acu-point*	43
#60	acu point*:ti,ab,kw	257
#61	acupoint*:ti,ab,kw	5,508
#62	MeSH descriptor: [electroacupuncture] explode all trees	1,161
#63	elctroacupuncture*:ti,ab,kw	4
#64	acupuncture AND th	1,248
#65	#43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64	26,713
#66	#42 and #65	40
Database: China National Knowledge Infrastructure (CNKI) (cnki.net; 1993-2023)		
1	(SU='traffic accident' OR SU='交通事故' OR SU='whiplash injury' OR SU='颈椎屈伸损伤' OR SU='whiplash associated disorder' OR SU='挥鞭样损伤' OR SU='cervical spine disorder' OR SU='颈椎功能紊乱' OR SU='cervical spine injury' OR SU='颈椎损伤') AND (SU='acupuncture' OR SU='針' or SU='electro acupuncture' OR SU='电針' OR SU='meridian' OR SU='经穴' or SU='acupoint' or SU='acupuncture-ear' OR SU='耳针')	54
Database: ScienceOn (scienceon.kisti.re.kr; 2001-2023)		
1	전체=(교통사고 | 편타성 손상 | 채찍질 손상 | 경항통 | 경추부 염좌) AND 전체=(침 | 전침 | 경혈 | 이침)	61
Database: KMBASE (kmbase.medric.or.kr; 1985-2023)		
1	[ALL=교통사고]	864

2	[ALL=편타성 손상]	25
3	[ALL=채찍질 손상]	0
4	[ALL=경항통]	89
5	[ALL=경추부 염좌]	4
6	[ALL=침]	14,195
7	[ALL=전침]	377
8	[ALL=이침]	80
9	[ALL=경혈]	326
10	(((([ALL=교통사고] OR [ALL=편타성 손상]) OR [ALL=채찍질 손상]) OR [ALL=경항통]) OR [ALL=경추부 염좌])	946
11	((([ALL=침] OR [ALL=전침]) OR [ALL=이침]) OR [ALL=경혈])	14,801
12	(((([ALL=교통사고] OR [ALL=편타성 손상]) OR [ALL=채찍질 손상]) OR [ALL=경항통]) OR [ALL=경항통]) AND ((([ALL=침] OR [ALL=전침]) OR [ALL=이침]) OR [ALL=경혈]))	48
Database: Korean Studies Information Service System (KISS) (kiss.kstudy.com; 1993-2023)		
1	교통사고 and 침	126
2	교통사고 and 전침	4
3	교통사고 and 이침	0
4	교통사고 and 경혈	0
Database: Korea Med (koreamed.org; 1992-2023)		
1	((((("traffic"[ALL])) OR ("automobile"[ALL])) OR ("whiplash injury"[ALL])) OR ("whiplash associated disorder"[ALL])) OR ("cervical spine disorder"[ALL])) OR ("cervical spine injury"[ALL])	1,706
2	((((("acupuncture"[ALL])) OR ("electroacupuncture"[ALL])) OR ("meridian"[ALL])) OR ("acupoint"[ALL])	553
3	#1 AND #2	22

Database: Oriental Medicine Advanced Searching Integrated System (OASIS) (oasis.kiom.re.kr; 1963-2023)		
1	교통사고 침	1
2	교통사고 전침	4
3	교통사고 이침	0
4	교통사고 경혈	0
Database: Research Information Sharing Service (RISS) (riss.kr; 1988-2023)		
1	전체 : 교통사고 <AND> 전체 : 침	92
2	전체 : 교통사고 <AND> 전체 : 전침	4
3	전체 : 교통사고 <AND> 전체 : 이침	0
4	전체 : 교통사고 <AND> 전체 : 경혈	1

Supplemental table S2. Appraisal of acupuncture procedure based on the revised SRICTA criteria (2010)

First author (year)	Type of acupuncture	Acupoints	Depth of needling	Stimulation response	Total sessions	Frequency and Retention
Sterling et al (2015)	General acupuncture	Posterior muscles of the cervical spine and upper thoracic spine	NR	Pecking, Twirling	6	Frequency: 2 times/week X 3 weeks Retention: 30 minute
Tobbackx et al (2012)	General acupuncture	Choose from GV14, C1-C7, GB20, SI11, GB21, TE15, SI14, BL17, SP10, SI3, BL64, TE5, GB41, Shiqizhuixia, Ear Zero point, Ear Jerome point, Ear C0.	NR	Deqi sensation	1	Frequency: 1 time/week X 1 week Retention: 20 minute
Kwak et al (2012)	General acupuncture	SI2, SI3, SI5, SI7, SI14, SI15, LI11, BL10, BL12, BL13, BL14, BL60, BL62, BL66,	1.0-2.0 cm	Deqi sensation, Rotating	6	Frequency: 3 times/week X 2 weeks Retention: 15 minute

		GB20, GB21, GB40, GB41, TE5, TE15				
Tough et al (2010)	General acupuncture	Myofascial trigger points in muscles in and around the neck	NR	Pecking (6-7 times/s)	2-6	Frequency: 1 time/week X 2-6 times Retention: NR
Aigner et al (1998)	General acupuncture	TB5, SI6 bilaterally	NR	NR	NR	NR
Han et al (2011)	Electroacupuncture	ST25, GB20, GB21, SI11, SI14, SI15, Ashi points	1.0-2.0 cm	Electrical frequency: 300 Hz	8	Frequency: 2 times/week X 4 weeks Retention: 15 minute
Cameron et al (2011)	Electroacupuncture	GB39, GB20, LI14, SI6 bilaterally	1.0-1.5 cm	Electrical frequency: 2-5 Hz Electrical intensity: 1.5 volts	12	Frequency: 2 times/week X 6 weeks Retention: 20 – 60 minutes
Kim et al (2020)	MSAT	3 points at trapezius muscle	0.5-1.0 cm	NR	6	Frequency: 2 times/day X 3 days Retention: 15 minute

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture; MSAT: Motion-style acupuncture treatment; NR: Not reported

Supplemental table S3. The "leave-one-out" approach for sensitivity analysis of whiplash-associated disorder

Study omitted	Pooled estimate	95% Confidence interval		p-value	I^2(%)
		Lower	Upper		
Pain VAS score					
Kwak HY 2012	-0.54	-0.87	-0.21	0.001	59
Tobbackx Y 2012	-0.65	-0.96	-0.35	<0.0001	44
Tough EA 2010	-0.55	-0.87	-0.22	0.001	59
Cameron ID 2011	-0.65	-1.01	-0.29	0.0005	53
Han SY 2011	-0.47	-0.84	-0.11	0.01	61
Kim DR 2020	-0.45	-0.81	-0.10	0.01	53
ROM – flexion					
Kwak HY 2012	0.33	-0.59	1.26	0.48	89
Sterling M 2015	0.43	-0.37	1.22	0.29	78
Kim DR 2020	-0.10	-0.46	0.26	0.60	0
ROM – extension					
Kwak HY 2012	0.38	-0.19	0.96	0.19	73
Sterling M 2015	0.69	0.34	1.03	<0.0001	0
Kim DR 2020	0.36	-0.27	0.99	0.26	62
ROM – right rotation					
Kwak HY 2012	0.56	-1.16	2.29	0.52	97
Sterling M 2015	0.79	-0.53	2.11	0.24	92
Kim DR 2020	-0.17	-0.56	0.22	0.39	11
ROM – left rotation					
Kwak HY 2012	0.85	-0.29	1.98	0.15	92
Sterling M 2015	0.81	-0.42	2.05	0.20	90
Kim DR 2020	0.23	-0.13	0.59	0.21	0
NDI					
Sterling M 2015	-0.19	-0.61	0.23	0.37	75

Tobbackx Y 2012	-0.18	-0.59	0.24	0.40	75
Tough EA 2010	-0.11	-0.46	0.25	0.56	71
Cameron ID 2011	-0.29	-0.51	-0.08	0.007	0
Han SY 2011	-0.09	-0.45	0.26	0.61	68
Kim DR 2020	-0.15	-0.56	0.26	0.48	73

VAS: Visual analog scale; ROM: Range of motion; NDI: Neck disability index

Supplemental table S4. Evidence quality assessment according to GRADE

Certainty assessment							No. of patients		Effect	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Experimental	Control	Absolute (95% CI)	Certainty
Pain VAS score										
6	RCT	Not serious	Serious*	Not serious	Not serious	None	217	206	SMD 0.57 lower (0.86 lower to 0.28 lower)	⊕⊕⊕○ Moderate
ROM-flexion										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	108	SMD 0.23 higher (0.41 lower to 0.87 higher)	⊕○○○ Very low
ROM-extension										
3	RCT	Not serious	Serious*	Not serious	Serious‡	None	108	108	SMD 0.47 higher (0.05 higher to 0.89 higher)	⊕⊕○○ Low
ROM-right lateral flexion										

2	RCT	Not serious	Very serious[§]	Not serious	Very serious[†]	None	68	69	SMD 0.58 higher (0.31 lower to 1.48 higher)	⊕○○○ Very low
ROM-left lateral flexion										
2	RCT	Not serious	Serious[*]	Not serious	Very serious[†]	None	68	69	SMD 0.61 higher (0.01 to 1.21 higher)	⊕○○○ Very low
ROM-right rotation										
3	RCT	Not serious	Very serious[§]	Not serious	Very serious[†]	None	108	108	SMD 0.41 higher (0.73 lower to 1.55 higher)	⊕○○○ Very low
ROM-left rotation										
3	RCT	Not serious	Very serious[§]	Not serious	Very serious[†]	None	108	108	SMD 0.63 higher (0.21 lower to 1.46 higher)	⊕○○○ Very low
NDI										
6	RCT	Not serious	Serious[*]	Not serious	Serious[¶]	None	237	225	SMD 0.17 lower (0.51 lower to 0.17 higher)	⊕⊕○○ Low

*: Downgraded one level due to inconsistency (I^2, 50–75%)

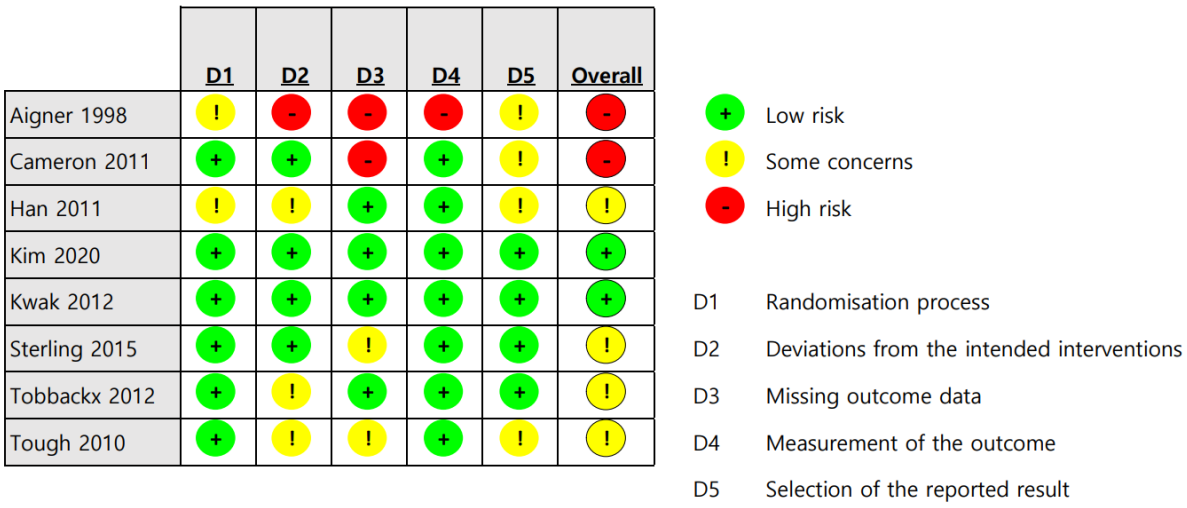
†: Downgraded two levels due to imprecision (fewer than 400 participants and CI overlaps with no effect)

‡: Downgraded one level due to imprecision (fewer than 400 participants)

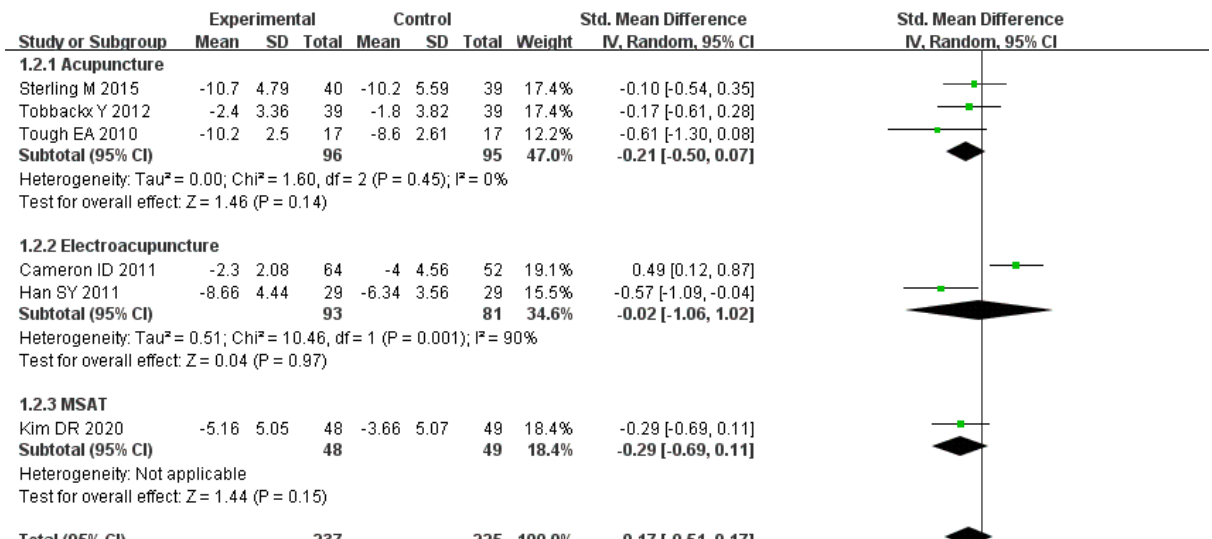
§: Downgraded two levels due to inconsistency (I^2>75%)

¶: Downgraded one level due to imprecision (CI overlaps with no effect)

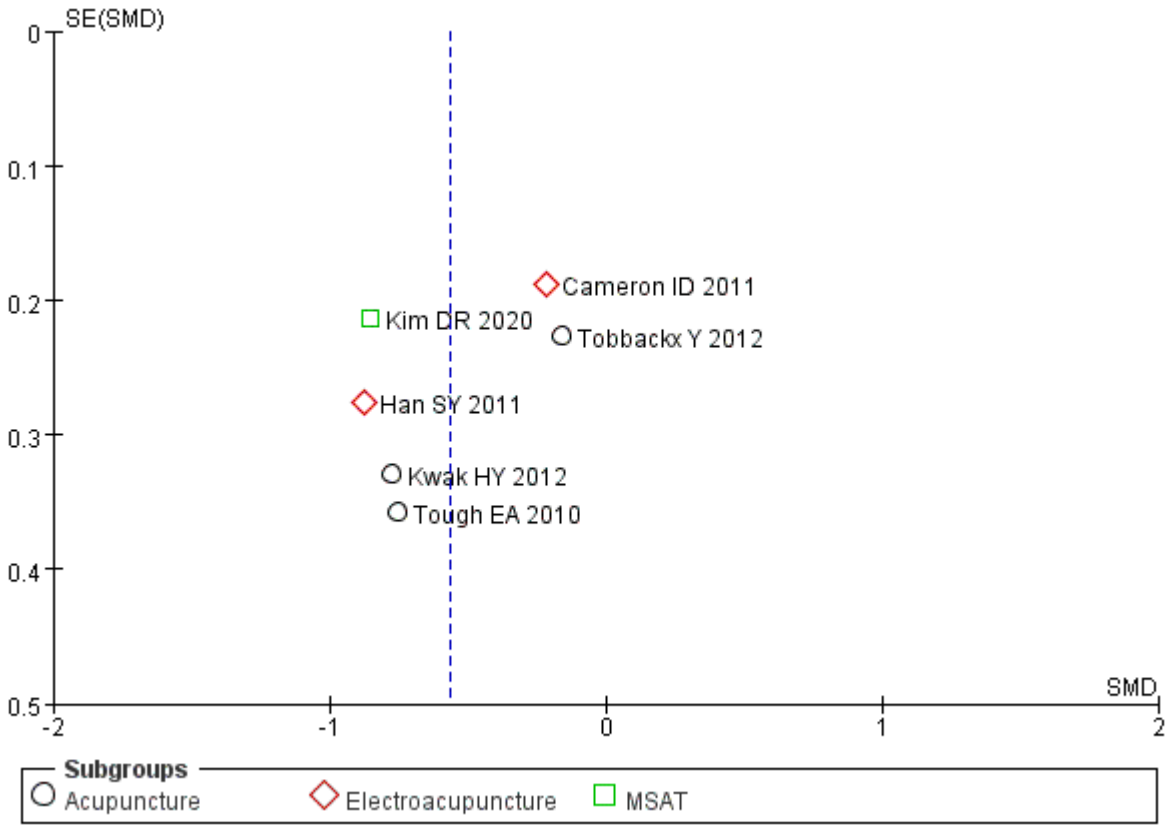
CI: Confidence interval; SMD: Standard mean difference; VAS: Visual analog scale; ROM: Range of motion; NDI: Neck disability index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation



Supplemental figure S1. Individual data of RoB 2



Supplemental figure S2. Forest plot of the meta-analysis for the neck disability index



Supplemental figure S3. Funnel plot for the pain visual analog scale score

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4-5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6 Supple table 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 Supple table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8-9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8-9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8-9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10 Figure 1.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	10 Figure 1.
Study characteristics	17	Cite each included study and present its characteristics.	10 Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	14-15 Figure 2. Supple figure 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	15-16 Figure 3,4. Supple figure 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	15-17 Figure 2,3,4. Supple figure 1,2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	15-16 Figure 3,4. Supple figure 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	16-17 Supple table 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	16-17 Supple table 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	19 Supple figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	17-19 Supple table 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	20-21
	23b	Discuss any limitations of the evidence included in the review.	21-22
	23c	Discuss any limitations of the review processes used.	21-22
	23d	Discuss implications of the results for practice, policy, and future research.	20-22

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	23
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	22-23
Competing interests	26	Declare any competing interests of review authors.	23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	23

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Efficacy of acupuncture for whiplash injury: A systematic review and meta-analysis

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Efficacy of acupuncture for whiplash injury: A systematic review and meta-analysis

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ABSTRACT

Objectives: This study aimed to establish clinical evidence for acupuncture by analyzing data from trials that demonstrated the efficacy of acupuncture for whiplash-associated disorder (WAD) with the following research question: Is acupuncture treatment effective for symptom alleviation in patients with WAD compared to other usual care?

Design: A systematic review and meta-analysis.

Data sources: PubMed, Ovid Medline, Embase, The Cochrane Library, China National Knowledge Infrastructure, ScienceOn, KMBASE, Korean Studies Information Service System, Korea Med, Oriental Medicine Advanced Searching Integrated System, and Research Information Sharing Service were searched from their inception to October 1, 2023.

Eligibility criteria: We included randomized controlled trials (RCTs) using acupuncture on patients with WAD. The outcomes were the pain visual analog scale (VAS) score or numerical rating scale score for neck pain, the range of motion (ROM) of the neck, the neck disability index, and safety.

Data extraction and synthesis: Two independent researchers analyzed and extracted data from the selected literatures. The risk of bias and the quality of evidence were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions and the Grading of Recommendations Assessment, Development, and Evaluation method, respectively.

Results: A total of 525 patients with WAD from eight RCTs were included in this study. The meta-analysis revealed that the outcomes showed significant differences in the pain VAS score (standard mean difference [SMD]: -0.57 [-0.86 to -0.28], p<0.001) and ROM-extension (SMD: 0.47 [0.05 to 0.89], p=0.03). The risk of bias assessment revealed that four studies published after 2012 (50%, 4 out of 8 studies) showed low bias in most domains. The pain VAS score was graded as having moderate certainty.

Conclusion: Acupuncture may have clinical value in pain reduction and increasing the ROM for patients with WAD. High-quality RCTs must be conducted to confirm the efficacy of acupuncture in patients with WAD.

Trial registration number: PROSPERO CRD42021261595.

Keywords: Acupuncture; Whiplash injuries; Whiplash-associated disorder; Systematic review; Meta-analysis; Randomized controlled trial

Word Count: 3831

Article Summary

Strengths and limitations of this study

- This systematic review was reported as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.
- Data regarding acupuncture were collected to appraise the acupuncture procedure as part of the Standards for Reporting Interventions in Clinical Trials of Acupuncture.
- Subgroup analysis was performed according to the type of acupuncture treatment to verify the effect size of each subgroup.
- The Grading of Recommendations Assessment, Development and Evaluations method was used to evaluate the quality of the outcomes.
- Grey literature and other supplementary searches were not conducted, which may result in missing studies and the risk of publication bias.

INTRODUCTION

Whiplash injury or whiplash-associated disorder (WAD) is caused by rapid hyperextension or hyperflexion of the patient's head due to sudden acceleration or deceleration during a vehicle crash [1]. WAD can cause musculoskeletal symptoms, such as neck pain, stiffness, and headache, as well as systemic symptoms, such as dizziness, psychological distress, depression, and sleep disturbances [2, 3]. Kim et al. [4] reported that 57% of patients involved in traffic accidents present with neck and back pain. Several conservative therapies can be used to relieve pain and discomfort in the cervical region, such as nerve block on the dysfunctional spinal articular process [5, 6]; however, it is difficult to predict the course and sequelae of WAD owing to its unique mechanism [7, 8].

Acupuncture is used for the treatment of various musculoskeletal disorders, such as WAD [9-11], as it can target the neurological mechanisms to relieve physical pain via the release of opioids and 5-hydroxytryptamine in the brain reward/motivation circuit [12]. However, its effectiveness is yet to be recognized despite its usefulness in clinical practice [13]. The Canadian and Australian WAD clinical practice guidelines (CPGs) do not recommend acupuncture for treating WAD [14]; moreover, one of the guidelines does not conclude that acupuncture is effective [15]. This lack of consensus can be attributed to the lack of research or evidence on acupuncture at the time of formulating these CPGs.

Therefore, this study aimed to establish clinical evidence for acupuncture by analyzing data from trials that demonstrated the efficacy of acupuncture for the treatment of WAD with the following research question: Is acupuncture treatment effective for symptom alleviation in patients with WAD compared to other usual care? Moon et al. [16] published their systematic review (SR) in 2014; however, a meta-analysis was not conducted as part of their study. Lee et al. [17] published a protocol of an SR to verify the effect of acupuncture on WAD; however, no follow-up studies have been published. Therefore, in this study, we updated the previous

SR [16] by adding clinical studies published after 2014 and evaluated the quality of evidence on acupuncture through a meta-analysis and sensitivity analysis. Herein, this SR was reported as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and referred to the Cochrane Handbook [18, 19].

MATERIALS and METHODS

Database selection and search strategy

The protocol of this SR was registered in the Prospective Register of Systematic Reviews (PROSPERO) database on July 18, 2021 (CRD42021261595) [20]. Online databases, including PubMed, Ovid Medline, Embase, The Cochrane Library, China National Knowledge Infrastructure, ScienceOn, KMBASE, Korean Studies Information Service System, Korea Med, Oriental Medicine Advanced Searching Integrated System, and Research Information Sharing Service were searched for studies on the efficacy of acupuncture for WAD from their inception to October 1, 2023. We did not limit our search by language or by publication date. Terms related to acupuncture and WAD from the Medical Subject Headings were used in the search strategy; the terms were translated into the language suitable for each database (online supplemental table S1). In addition, we checked the reference lists of all previously published SRs identified by the above methods, looking for cited relevant studies. However, we did not review conferences because of its potential to introduce publication bias [21].

Eligibility criteria

The studies included in this study were selected according to the following five criteria: study design, participants, intervention, comparison, and outcomes. Randomized controlled trials (RCTs) that used acupuncture on patients with WAD were included regardless of their reporting type, blinding, and language. In contrast, RCTs that did not target WAD or use acupuncture as an intervention were excluded. Additionally, non-RCTs, single-arm pre- and post-clinical trials, case-control studies, case reports, laboratory studies (including in vivo and in vitro studies), letters, and reviews were also excluded. Thereafter, the participants diagnosed with WAD, regardless of their race, age, or sex, were identified. The diagnostic criteria for WAD were based on those of the Quebec Task Force, which classified patients according to

their severity of signs and symptoms [22]. The Quebec Task Force's diagnostic criteria are as follows:

Grade I: Neck complaint of pain, stiffness or tenderness only. No physical sign(s).

Grade II: Neck complaint AND musculoskeletal sign(s). Musculoskeletal signs include decreased range of motion and point tenderness.

Grade III: Neck complaint AND neurological sign(s). Neurological signs include decreased range of motion and point tenderness.

Grade IV: Neck complaint AND fracture or dislocation.

The treatment interventions were acupuncture treatment, including electroacupuncture (EA) and dry needling, and acupuncture combined with active treatment(s), which were compared with the same active treatment(s) in the control group. The treatments administered to the control group were limited to usual care, such as physiotherapy, medications, conventional treatments other than acupuncture, and sham treatments. The primary outcome was the pain visual analog scale (VAS) score or numerical rating scale score for neck pain, and the secondary outcomes were the range of motion (ROM) of the neck, the neck disability index (NDI), and safety [23].

Data collection and analysis

Study selection

Two independent researchers (SHL and MSH) were involved in the study selection process. Study selection and deduplication were performed using Excel. In the case of disagreements during the process, the researchers proceeded to the next step after reaching a consensus through a discussion. After removing duplications, the titles and abstracts of the studies were screened to exclude those that did not meet the eligibility criteria. Subsequently, the full text of each selected study was fully reviewed for the final selection.

Data extraction and management

Two independent researchers (SHL and MSH) analyzed and extracted the data from the selected literature. Data extraction and management were performed using Excel. Data regarding the country of origin, study design, sample size, participants, intervention, comparison, outcomes, and results were summarized in a table. The outcomes of the primary endpoint were extracted. However, if the study did not present the primary endpoint, the outcomes of the first follow-up after the treatment were extracted. In addition, data regarding the type of acupuncture, acupoints, depth of needling, stimulation response, total sessions, frequency of sessions, and retention time were collected to appraise the acupuncture procedure as part of the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [24, 25]. In the case of missing standard mean difference (SMD) for changes from baseline, we tried to contact the original investigators to request further data. However, if it was impossible, we calculated a correlation coefficient from a study reported in considerable detail and imputed missing data in accordance with the established method [26, 27].

Quality assessment

Two independent researchers (SHL and MSH) evaluated the quality of the selected studies according to the Cochrane RoB 2 tool in the Cochrane Handbook for Systematic Reviews of Interventions [19]. The risk of bias assessment was performed based on the content described in the original text and the characteristics of the intervention. The Grading of Recommendations Assessment, Development and Evaluations (GRADE) method was used to evaluate the quality of the outcomes [28]. Each outcome was classified as not serious, serious, or very serious according to the study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The certainty of the outcomes was categorized as high,

moderate, low, or very low. In the case of disagreements between researchers, agreement was reached through discussion with third and fourth researchers (BCS, IH).

Statistical analysis

The meta-analysis was performed using the Review Manager version 5.4.1 (Cochrane) software. To determine the value of the effect size, SMD was used for continuous data and relative risk for dichotomous data. All data, including dichotomous and continuous data, were presented with a 95% confidence interval (CI). Fixed-effects or random-effects models were used for the synthesis of data according to the heterogeneity of each meta-analysis. Heterogeneity (I^2) of less than 50% was considered negligible, and a fixed-effects model was used in such cases. If the heterogeneity exceeded 50%, a random-effects model was used to estimate the effect size. Subgroup analysis was performed according to the type of acupuncture treatment to verify the effect size of each subgroup. The "leave-one-out" approach, where the meta-analysis is performed repeatedly while excluding the included literature individually, was performed for sensitivity analysis [29]. When a fixed-effects model was used for data synthesis, sensitivity analysis using a random-effects model was additionally performed to eliminate confounding effects. In addition, a funnel plot was generated to determine the presence of publication bias for the primary outcome.

Patient and public involvement

No patient involved.

RESULTS

Study selection

A total of 877 articles were retrieved from databases. After excluding 154 duplications, 295 studies unrelated to WAD, 163 non-RCT studies, 42 in vitro and in vivo studies, and 154 irrelevant studies were excluded while screening of the title and abstract. The full text of the remaining 69 articles was reviewed, and 62 articles were excluded, including 51 articles that did not use acupuncture as an intervention, 6 articles without full text, 3 articles without a valid control group, and 2 articles for other reasons. In addition, we included 1 study through reference tracking [16]. Thus, 8 studies were included in the final analysis (Figure 1).

Study characteristics

A total of 525 patients with WAD were included in this study. Five studies [16, 30-33] compared acupuncture with sham acupuncture, usual care, or medication, whereas two [34, 35] compared EA with sham EA. One study [36] compared motion-style acupuncture treatment (MSAT) with usual care. The country of origin of the studies varied: three in Korea [32, 34, 36], two in Australia [30, 35], one each in Belgium [31], UK [33], and Austria [16]. The recruitment period was less than one year in five studies [31-34, 36], more than four years in two studies [30, 35], and not reported in one study [16]. Among the eight studies, one [31] was designed as a crossover RCT. The pain VAS score was recorded in six studies [31-36], and the ROM was recorded in four studies [16, 30, 32, 36]. The NDI was recorded in six studies [30, 31, 33-36]. The study by Aigner et al. was described based on its reference in the SR by Moon et al. [16], as the original text could not be accessed (Table 1).

Table 1. Data of clinical studies on acupuncture for whiplash-associated disorder

First author (year)	Country of origin (period)	Design	Sample size	Participants	Intervention	Comparison	Outcomes	Results (Effect size, P-value)
Sterling et al (2015) [30]	Australia (2009 – 2012)	RCT	Total: 80 Exp.: 40 Con.: 40	WAD Ⅱ	Atx. + exercise	Sham atx. + exercise	1) NDI 2) ROM (1) Flex. (2) Ext. (3) Rot. (4) Lat.	1) 0.10, P=0.67 2) (1) -0.14, P=0.54 (2) 0.08, P=0.71 (3) -0.32, P=0.16 (4) 0.26, P=0.24
Tobbackx et al (2012) [31]	Belgium (01/2011 – 12/2011)	Crossover RCT	Total: 39	WAD Ⅰ or Ⅱ or Ⅲ (chronic WAD persisting more than 3 months)	Atx.	Relaxation	1) NDI 2) pain VAS	1) 0.17, P=0.47 2) 0.16, P=0.47
Kwak et al (2012) [32]	Korea (12/2009 – 10/2010)	RCT	Total: 40 Exp.: 20 Con.: 20	WAD (persisting more than 3 months)	Atx. + UC	UC (PTx. + exercise)	1) pain VAS 2) ROM (1) Flex.	1) 0.78, P=0.02 2) (1) -0.01, P=0.97

							(2) Ext.	(2) 0.73, P=0.03
							(3) Rt. Lat. Flex.	(3) 0.10, P=0.76
							(4) Lt. Lat. Flex	(4) 0.25, P=0.43
							(5) Rt. Rot.	(5) 0.10, P=0.76
							(6) Lt. Rot.	(6) 0.16, P=0.61
Tough et al (2010) [33]	UK (05/2007 – 12/2007)	RCT	Total: 34 Exp.: 17 Con.: 17	WAD Ⅱ (WAD persisting 2-16 weeks)	Atx. + Ptx.	Sham Atx. + Ptx.	1) pain VAS 2) NDI	1) 0.76, P=0.03 2) 0.61, P=0.08
Aigner et al (1998) [16]	Austria (NR)	RCT	Total: 61 Exp.: 28 Con.: 33	WAD Ⅰ or Ⅱ	Atx.	Med.	1) ROM	1) NR
Han et al (2011) [34]	Korea (03/2011 – 07/2011)	RCT	Total: 58 Exp.: 29 Con.: 29	WAD	EA + HM	Sham EA + HM	1) pain VAS 2) NDI	1) 0.88, P=0.002 2) 0.57, P=0.03
Cameron et al (2011) [35]	Australia (03/2001 – 10/2004)	RCT	Total: 116 Exp.: 52 Con.: 64	WAD Ⅰ or Ⅱ (subacute or chronic WAD persisting more than 1 month)	EA	Sham EA	1) pain VAS 2) NDI	1) 0.21, P=0.25 2) -0.49, P=0.009

							1) pain VAS	1) 0.85, P<0.0001
							2) NDI	2) 0.29, P=0.15
							3) ROM	3)
Kim et al (2020) [36]	Korea (07/2019 – 09/2019)	RCT	Total: 97 Exp.: 48 Con.: 49	WAD (within 7 days)	MSAT + IKM	IKM (Atx. + pharm. + CMT + HM)	(1) Flex.	(1) 0.80, P=0.0001
							(2) Ext.	(2) 0.67, P=0.001
							(3) Rt. Rot. Flex.	(3) 1.01, P<0.001
							(4) Lt. Rot. Flex	(4) 0.88, P<0.001
							(5) Rt. Lat.	(5) 1.44, P<0.001
							(6) Lt. Lat.	(6) 1.43, P<0.001

CI: Confidence interval; RCT: Randomized controlled trial; Exp.: Experimental; Con.: Control; WAD: Whiplash-associated disorder; MSAT: Motion-style acupuncture treatment; IKM: Integrative Korean medicine treatment; Pharm.: Pharmacopuncture; CMT: Chuna manual therapy; HM: Herbal medicine; VAS: Visual analog scale; NDI: Neck disability index; ROM: Range of motion; Flex.: Flexion; Ext.: Extension; Rt.: Right; Rot.: Rotation; Lt.: Left; Lat.: Lateral; Atx.: Acupuncture therapy; UC: Usual care; PTx.: Physiotherapy; EA: Electroacupuncture; Med.: Medication

Standard for reporting acupuncture according to STRICTA

The eight studies were analyzed using STRICTA (online supplemental table S2). Regarding the type of acupuncture, five studies [16, 30-33] used general acupuncture, two used EA [34, 35], and one used MSAT [36]. Five studies [16, 31, 32, 34, 35] used specific acupoints, and three [30, 33, 36] used muscle trigger points instead of acupoints. The depth of needling was mentioned only in four studies [32, 34-36]. For stimulation response, two studies [31, 32] induced a *deqi* sensation, two [30, 33] used pecking, two [30, 32] used techniques such as twirling and rotation, and two [34, 35] used electrical stimulation. Regarding the total number of sessions, more than six sessions were performed in most studies [30, 32, 34-36], only one session was performed in one study [31], and two to six sessions were performed in one study depending on the degree of improvement in the symptoms [33]. The frequency of sessions was unreported in one study [16], whereas sessions were performed one to three times a week in the remaining seven studies. The number of weeks varied from one to six weeks, and the retention time varied from 15 to 60 min.

Risk of bias assessment

The eight selected studies were analyzed using the Cochrane RoB 2 tool. Six out of eight studies were identified as having low risk of bias with appropriate procedures for random sequence generation and allocation concealment [30-33, 35, 36]. Regarding deviations from the intended interventions, four studies were rated as having low risk of bias [30, 32, 35, 36], three as having some concerns [31, 33, 34], and one as having high risk of bias [16]. For missing outcome data, four studies were rated as having low risk of bias [31, 32, 34, 36]. In terms of bias in measurement of the outcome, except for one study that did not provide full text [16], all seven studies were identified as having low risk of bias. In terms of the selection of the reported result, studies that reported a pre-specified analysis plan were rated as having low risk of bias

[30-32, 36]. Overall, two studies showed low risk of bias in all five components [32, 36] (Figure 2, online supplemental figure S1).

Meta-analysis

A meta-analysis was performed with seven studies [30-36] according to the outcomes, after excluding one study [16] in which no comparison was made between the groups. The subgroups were divided into general acupuncture, EA, and MSAT according to the type of acupuncture treatment.

Pain VAS score

The result of the meta-analysis for the pain VAS score revealed that acupuncture was effective in treating patients with WAD (SMD: -0.57 [-0.86 to -0.28], p<0.001). The random-effects model was used for the analysis, as the heterogeneity (I^2) was 51%. Subgroup analysis revealed that general acupuncture and MSAT were effective in treating patients with WAD, whereas EA was ineffective (Figure 3).

ROM

Kwak et al. [32] and Kim et al. [36] recorded the ROM for all directions, whereas Sterling et al. [30] recorded the ROM for four directions: flexion, extension, right rotation, and left rotation. The results of the meta-analysis for ROM revealed that acupuncture was effective in improving extension in patients with WAD (SMD: 0.47 [0.05 to 0.89], p=0.03). The random-effects model was used for all directions of ROM, as the heterogeneity (I^2) was > 50%. Subgroup analysis showed that MSAT was effective in treating patients with WAD in all directions of ROM. However, general acupuncture was not effective for ROM in any direction

(Figure 4).

NDI

The results of the meta-analysis for NDI revealed that acupuncture was ineffective in improving the NDI. The random-effects model was used for the analysis as the heterogeneity (I^2) was > 50%. Subgroup analysis revealed that all treatments were ineffective in improving the NDI (online supplemental figure S2).

Adverse events

Five studies [30, 32, 33, 35, 36] reported adverse events (AEs), whereas three [16, 31, 34] did not. Except for one case of moderate AE, all reported AEs were mild. Pruritus of unknown cause was reported in the study by Kim et al. [36], necessitating the administration of antihistamines by injection, cream, and oral route. Other AEs caused by acupuncture included hives, dizziness, exacerbation of neck pain, bruising, fatigue, and somatic reactions (sweating and low blood pressure); however, these AEs were mild and were cured within a few days. AEs such as diarrhea, soft stools, nausea, heartburn, and vesicles were also reported; however, these were confirmed to be caused by interventions other than acupuncture.

Sensitivity analysis

A sensitivity analysis for the pain VAS score, ROM-flexion, ROM-extension, ROM-right rotation, ROM-left rotation, and NDI was performed, whereas ROM-right lateral flexion and ROM-left lateral flexion were excluded as they were included only in two studies (online supplemental table S3).

Pain VAS score

The results of the meta-analysis of the pain VAS score changed to moderate heterogeneity when the study by Tobbackx et al. [31] was removed (SMD: -0.65 [-0.96 to -0.35], p<0.001, I^2: 44%).

ROM

The result of the meta-analysis of ROM-extension was maintained when the study by Sterling et al. [30] was removed; however, the results were not maintained when the study by Kwak et al. [32] or Kim et al. [36] was removed. In particular, there was no heterogeneity when the study by Sterling et al. [30] was excluded. However, the results of the meta-analysis of ROM-flexion, ROM-right rotation, and ROM-left rotation were not significantly affected as the p-value was > 0.05 even after removing the included studies one by one.

NDI

The result of the meta-analysis of NDI changed to the p-value < 0.05 and no heterogeneity when the study by Cameron et al. [35] was removed (SMD: -0.29 [-0.51 to -0.08], p= 0.007, I^2: 0%).

Evidence quality

The quality of evidence of the outcomes was assessed using GradePro GDT (online supplemental table S4).

Pain VAS score

Six studies (n = 423) provided data regarding the pain VAS score. The risk of bias evaluation

revealed high bias in one study; however, the effect on the estimate was considered inconclusive, and the confidence level of the evidence was not lowered. For inconsistency, the pain VAS score was downgraded by one level as its heterogeneity (I^2) was 51%. Thus, the quality of evidence on the pain VAS score was graded as "moderate."

ROM

Three studies (n = 216) provided data regarding ROM-flexion, ROM-extension, ROM-right rotation, and ROM-left rotation. Two studies (n = 137) provided data regarding ROM-right lateral flexion and ROM-left lateral flexion. The risk of bias evaluation revealed some concerns in one study; however, the effect on the estimate was considered inconclusive, and the confidence level of the evidence was not lowered. In the evaluation of consistency, ROM-extension and ROM-left lateral flexion were downgraded by one level as their heterogeneity (I^2) was higher than 50% but lower than 75%. Similarly, ROM-flexion, ROM-right lateral flexion, ROM-right rotation, and ROM-left rotation were downgraded by two levels as their heterogeneity (I^2) was > 75%. In the evaluation of imprecision, ROM-extension was downgraded by one level as the number of participants was less than 400. Similarly, ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation were degraded by two levels as the number of participants was less than 400 and their CI overlapped with no effect. Thus, ROM-extension was graded as "low," and ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation were graded as "very low."

NDI

Six studies (n = 462) reported data regarding the NDI. The risk of bias evaluation revealed high bias in one study; however, the effect on the estimate was considered inconclusive, and the

confidence level of the evidence was not lowered. For inconsistency, the NDI was downgraded by one level as its heterogeneity (I^2) was 69%. In the evaluation of imprecision, the NDI was downgraded by one level as the CI overlapped with no effect. Thus, the NDI was graded as "low."

Publication bias

Publication bias was evaluated using the funnel plot for the pain VAS score (online supplemental figure S3). The outcome was slightly asymmetric, meaning there was a little publication bias. However, as fewer than 10 studies were included, the power of the test is expected to be low.

DISCUSSION

This study revealed that acupuncture is effective in improving the pain VAS score and ROM-extension in patients with WAD. The analgesic effect of acupuncture is thought to relieve pain in patients with WAD. In addition, patients with WAD were able to effectively improve ROM-extension following acupuncture, as acupoints GB20, GB21, SI11, SI14, SI15, and TE15, which are used extensively in patients with WAD, are located in the posterior muscles of the cervical spine and upper thoracic spine. However, the NDI, ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation did not show significant differences; thus, future studies are required to prove the effectiveness of acupuncture for these outcomes.

In the risk of bias assessment, except for one study published before 2010 [16], seven studies published after 2010 showed low bias in most domains [30-36]. In addition, although participant blinding is difficult owing to the nature of acupuncture [37], many studies have attempted to minimize this effect by utilizing placebo interventions. Moreover, four studies [30-32, 36] published after 2012 showed some concerns in only two domains and low bias in all other domains, indicating that recent studies on acupuncture interventions are consistently designed with high quality.

In the sensitivity analysis of the pain VAS score, a significant effect was maintained even when the included studies were removed one by one. In this context, acupuncture showed significant effects in patients with WAD, despite differences in design, participants, interventions, and comparisons among the studies. In addition, when the study by Tobbackx et al. [31] was removed, moderate heterogeneity was observed, meaning it was accountable for the substantial heterogeneity of the overall result. The crossover RCT design of Tobbackx et al. [31] is presumed to be the reason for the low effect size and high heterogeneity. For ROM-extension, there was no heterogeneity when the study by Sterling et al. [30] was removed; thus, it could

be assumed that the study was a potential source of heterogeneity. In the study by Sterling et al. [30], high-intensity ROM exercises, including craniocervical flexion training, neck extensor training, scapular training, posture re-education, and sensorimotor exercises, were performed for 1 h, which may have been the cause of heterogeneity. For the NDI, a significant effect appeared, and no heterogeneity was obtained when the study by Cameron et al. [35] was removed; therefore, the study was considered responsible for the between-study heterogeneity. It was presumed that the NDI SMD of the study favored the control group since it was > 0, affecting the overall effect size and heterogeneity.

A previous study [16] that analyzed the effectiveness of acupuncture in patients with WAD included studies published before 2014. This study differs from the previous study in the following ways. First, including two RCTs published after 2014, we analyzed a total of eight RCTs. Accordingly, this study provided more objective and quantitative evidence by synthesizing data on the efficacy of acupuncture for treating WAD. Second, the effect size of the pain VAS score, ROM, and NDI was verified by performing a meta-analysis. The directionality of the treatment effect and whether the CI of the individual studies overlapped were assessed using a forest plot. Third, a sensitivity analysis was performed to confirm the robustness of the results. The effect of individual studies on heterogeneity (I^2) and effect size was analyzed using the leave-one-out approach method. Fourth, a subgroup analysis was conducted according to the type of acupuncture treatment. The effect size of each type of acupuncture treatment was verified by dividing them into general acupuncture, EA, and MSAT subgroups. Fifth, the evidence quality of the pain VAS score, ROM, and NDI was assessed using the GRADE method. By presenting the certainty for each outcome, this study provided criteria that can be clinically referred to when using acupuncture for patients with WAD.

However, this study has some limitations. First, grey literature and other supplementary searches were not conducted, which may result in missing studies and the risk of publication

bias. However, we attempted to minimize publication bias by reviewing the references of a previously published SR. Second, the original text of one study could not be accessed. Third, except for ROM-extension, the efficacy of acupuncture in improving ROM in other directions was evaluated as being "very low." This is an area that needs to be verified through further studies.

CONCLUSION

The results of this study suggest that acupuncture may have clinical value in the treatment of patients with WAD. In the future, high-quality RCTs, based on the aforementioned data, must generate evidence of higher quality than that in the present study to confirm the efficacy of acupuncture in patients with WAD.

AUTHOR CONTRIBUTIONS

Conceptualization: Sang-Hyun Lee

Formal analysis: Sun-Young Park and In Heo

Funding acquisition: Sun-Young Park and Eui-Hyuoung Hwang

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Methodology: Sun-Young Park, In Heo, Eui-Hyuoung Hwang, and Byung-Cheul Shin

Project administration: Sun-Young Park, In Heo, Eui-Hyuoung Hwang and Man-Suk Hwang

Supervision: Byung-Cheul Shin and Man-Suk Hwang

Writing – original draft: Sang-Hyun Lee

Writing – review & editing: Sang-Hyun Lee, Eui-Hyuoung Hwang, Byung-Cheul Shin and Man-Suk Hwang

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DISCLAIMER

The funding source had no role in the design of the protocol, study search and selection, data extraction and management, data interpretation, report writing, or the decision to submit the report for publication.

COMPETING INTERESTS

None.

PATIENT CONSENT FOR PUBLICATION

Not required.

PROVENANCE AND PEER REVIEW

Not commissioned; extremally peer reviewed.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

AMENDMENT

In accordance with the reviewer's comment for revision, the RoB 2 tool and funnel plot were added to this review, unlike the proposed protocol. In addition, conference tracking was not

conducted.

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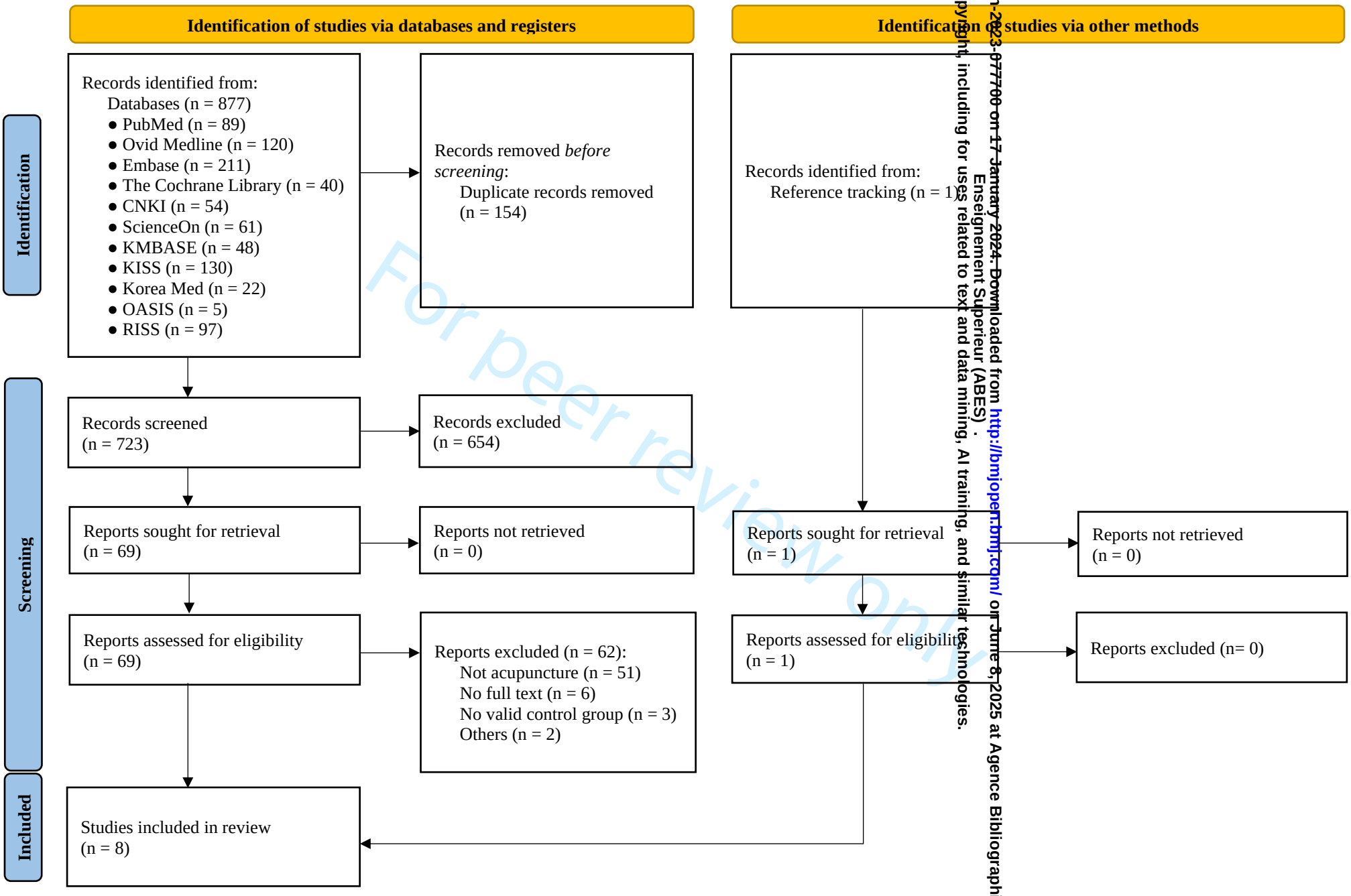
FIGURE LEGENDS

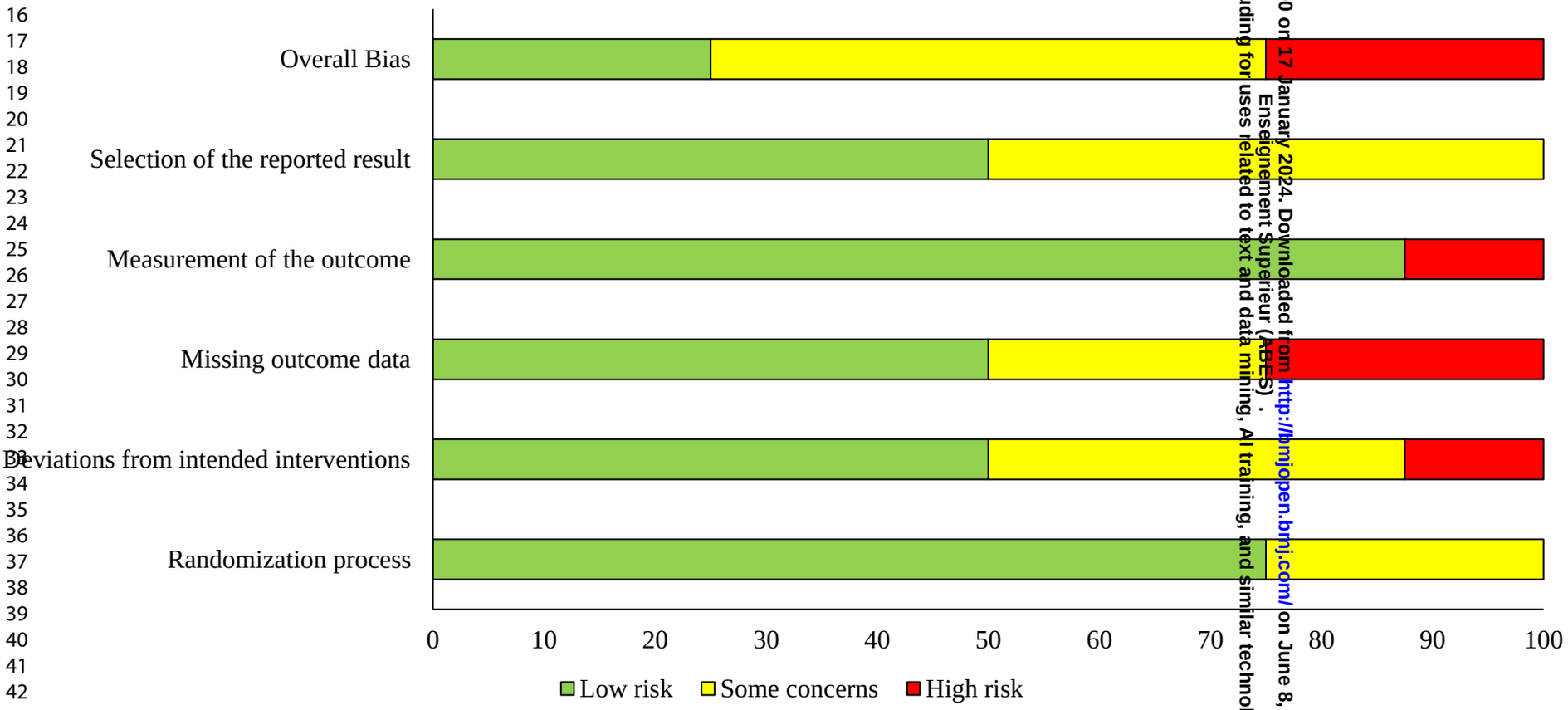
Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart of the included studies

Figure 2. Summary in risk of bias 2

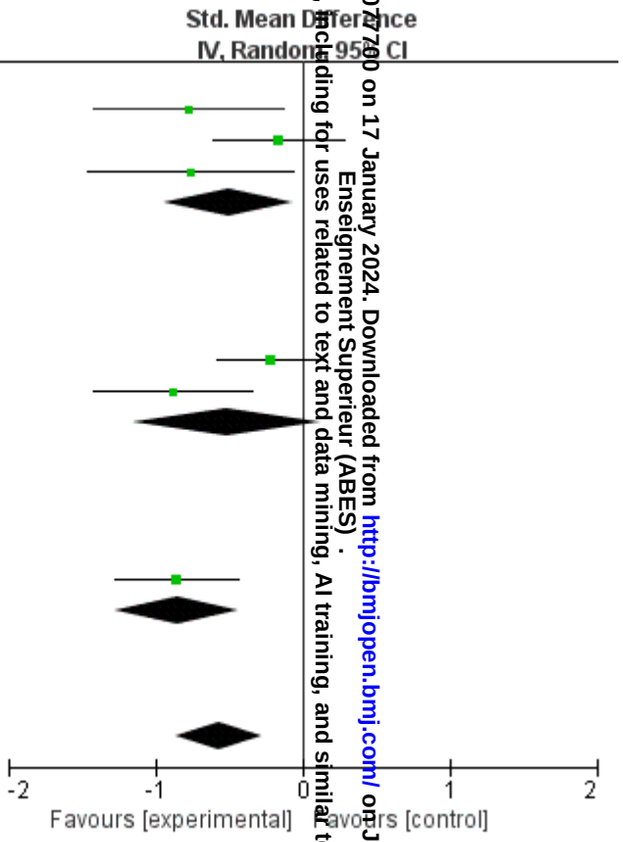
Figure 3. Forest plot of the meta-analysis for the pain visual analog scale score

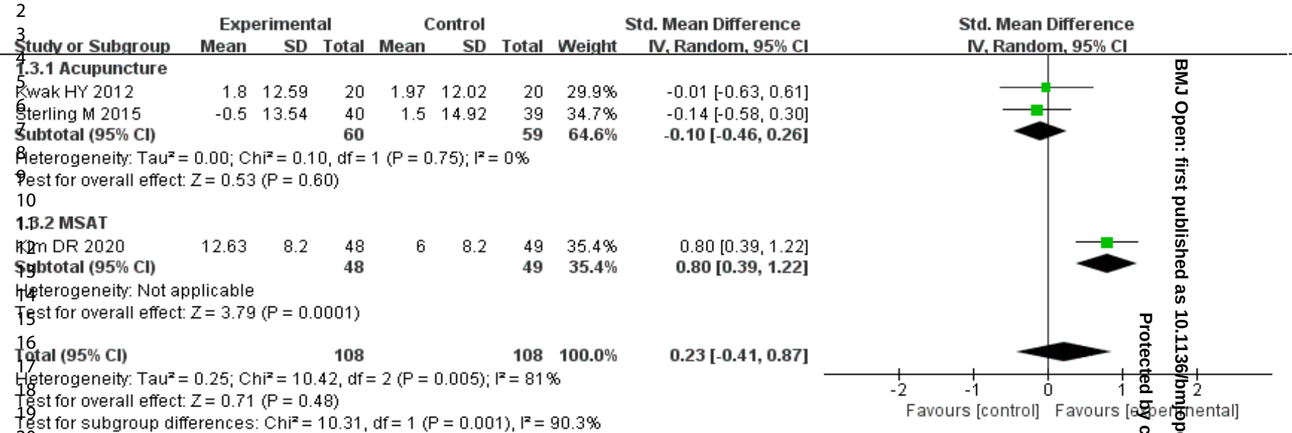
Figure 4. Forest plot of the meta-analysis for the range of motion



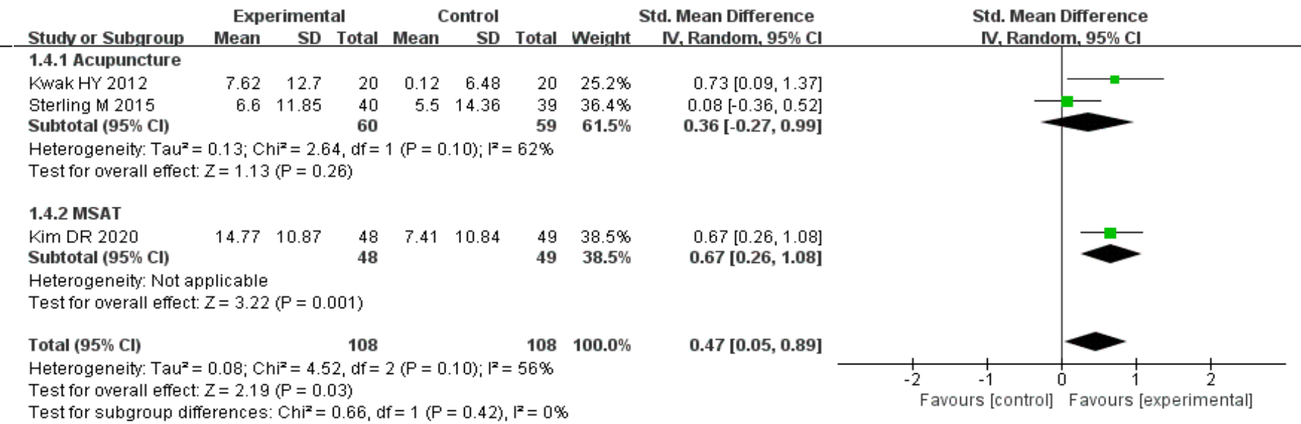


Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Acupuncture								
Kwak HY 2012	-1.85	1.88	20	-0.4	1.78	20	12.6%	-0.78 [-1.42, -0.13]
Tobbackx Y 2012	-7	21.24	39	-3.6	20.15	39	18.8%	-0.16 [-0.61, 0.28]
Tough EA 2010	-3.2	1.49	17	-1.8	2.08	17	11.4%	-0.76 [-1.45, -0.06]
Subtotal (95% CI)			**76**			**76**	**42.8%**	**-0.50 [-0.93, -0.06]**
Heterogeneity: Tau² = 0.06; Chi² = 3.32, df = 2 (P = 0.19); I² = 40%								
Test for overall effect: Z = 2.25 (P = 0.02)								
1.1.2 Electroacupuncture								
Cameron ID 2011	-1.6	1.88	64	-1.2	1.84	52	21.8%	-0.21 [-0.58, 0.15]
Han SY 2011	-4.9	1.05	29	-3.72	1.56	29	15.5%	-0.88 [-1.42, -0.33]
Subtotal (95% CI)			**93**			**81**	**37.3%**	**-0.51 [-1.16, 0.13]**
Heterogeneity: Tau² = 0.16; Chi² = 3.95, df = 1 (P = 0.05); I² = 75%								
Test for overall effect: Z = 1.56 (P = 0.12)								
1.1.3 MSAT								
Kim DR 2020	-2.03	1.34	48	-0.88	1.34	49	19.8%	-0.85 [-1.27, -0.44]
Subtotal (95% CI)			**48**			**49**	**19.8%**	**-0.85 [-1.27, -0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.01 (P < 0.0001)								
Total (95% CI)			**217**			**206**	**100.0%**	**-0.57 [-0.86, -0.28]**
Heterogeneity: Tau² = 0.07; Chi² = 10.30, df = 5 (P = 0.07); I² = 51%								
Test for overall effect: Z = 3.81 (P = 0.0001)								
Test for subgroup differences: Chi² = 1.53, df = 2 (P = 0.46), I² = 0%								

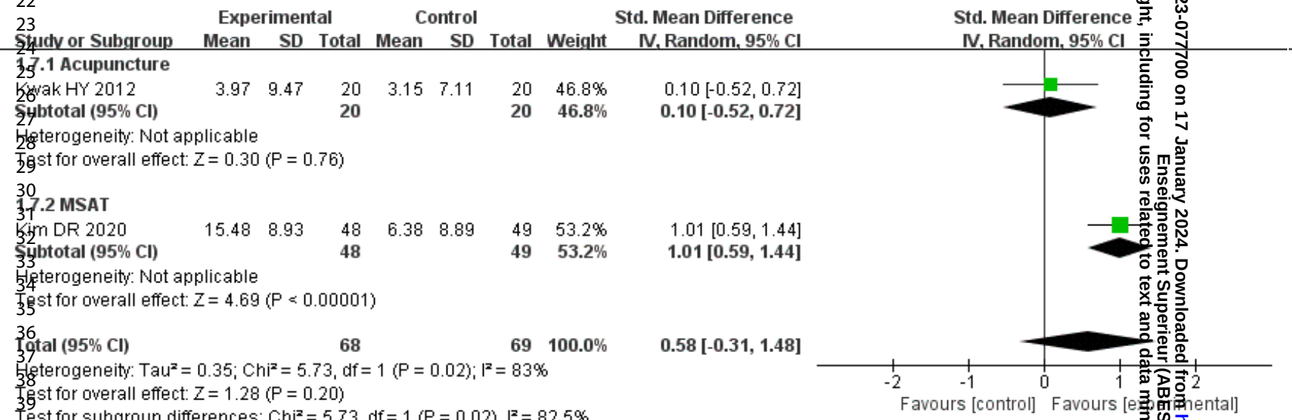




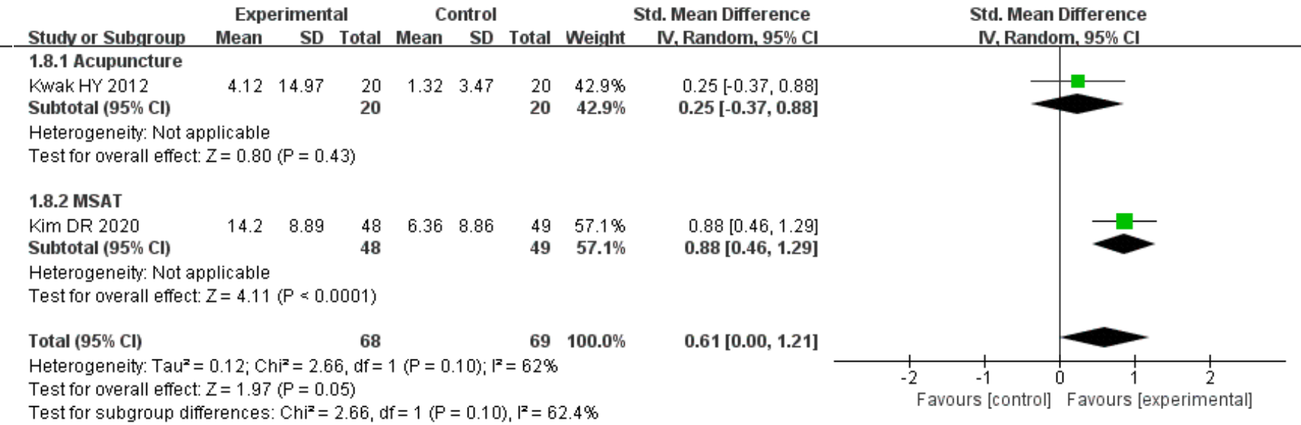
(A) Flexion



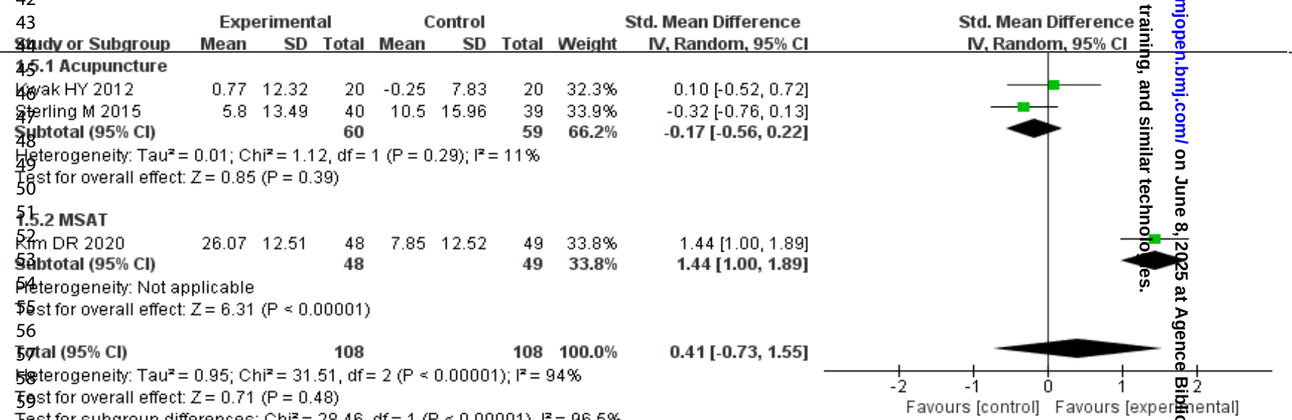
(B) Extension



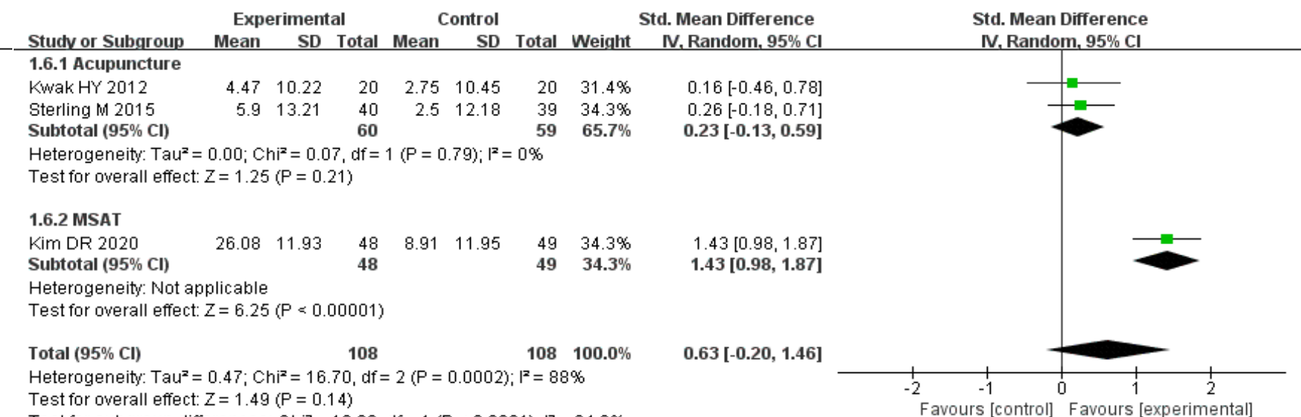
(C) Right lateral flexion



(D) Left lateral flexion



(E) Right rotation



(F) Left rotation

Supplemental table S1. Search strategy and terms used

Database: PubMed (pubmed.ncbi.nlm.nih.gov; 1946-2023)		
No.	Search strategy	Results
#1	whiplash OR acute whiplash injury* OR acute whiplash associated disorder* OR acute WAD OR acute whiplash associated disorder* II OR acute WAD II OR whiplash associated disorder* OR WAD OR whiplash associated disorder* II OR WAD II, OR whiplash OR whiplash injury* OR whiplash patient* OR whiplash syndrome* OR cervical spine disorder* OR cervical spine injury* OR "Accidents, Traffic" [Mesh] OR (("Motor Vehicles"[Mesh:NoExp] OR "Automobiles"[Mesh] OR "Motorcycles"[Mesh] OR traffic[tiab] OR vehicle[tiab] OR vehicular[tiab] OR car[tiab] OR cars[tiab] OR automobile[tiab] OR automobiles[tiab] OR motorcycle[tiab] OR motorcycles[tiab] OR taxi[tiab] OR cab[tiab] OR road[tiab] OR pedestrian[tiab] OR pedestrians[tiab]) AND (accident[tiab] OR accidents[tiab] OR injury[tiab] OR injuries[tiab] OR crash[tiab] OR crashes[tiab] OR "Wounds and Injuries"[Mesh] OR "injuries"[Subheading])) AND (cervic* OR thoracic* OR lumba*)	24,250
#2	acupuncture	42,653
#3	electroacupuncture	7,448
#4	acupressure	1,832
#5	((((((((((((((((((((((meridian) OR acupoint) OR acupuncture [mh]) OR acupuncture Analgesia [mh]) OR acupuncture Therapy [mh]) OR acupuncture points [mh]) OR acupuncture, ear [mh]) OR acupuncture [Text Word]) OR acupressure [Text Word]) OR electroacupuncture) OR electro acupuncture) OR electro-acupuncture) OR meridian* [Text Word]) OR needling [Text Word]) OR acu-point*) OR acu point* [Text Word]) OR acupoint* [Text Word]) OR Acupuncture [mh]) OR electroacupuncture [mh]) OR acupuncture* [Text Word]) OR elctroacupuncture* [Text Word]) OR (acupuncture AND th[sh])) OR acupuncture[tiab]) OR acupuncture[mh]) OR acupuncture/th[mh]	51,277
#6	#2 or #3 or #4 or #5	54,150
#7	#1 and #6	89
Database: Ovid Medline (ovidsp.ovid.com; 1946-2023)		
1	exp Whiplash Injuries/	3,423
2	whiplash.tw.	3,292
3	acute whiplash injury*.tw.	75
4	acute whiplash associated disorder*.tw.	71
5	acute WAD.tw.	66
6	WAD.tw.	1,038

7	whiplash patient*.tw.	201
8	whiplash syndrome*.tw.	183
9	cervical spine disorder*.tw.	228
10	cervical spine injury*.tw.	1,571
11	exp Accidents, Traffic/	48,509
12	exp Motor Vehicles/	24,289
13	exp Automobiles/	7,798
14	exp Motorcycles/	2,900
15	traffic.tw.	58,851
16	vehicle.tw.	134,582
17	vehicular.tw.	4,046
18	car.tw.	36,938
19	cars.tw.	9,562
20	automobile.tw.	6,526
21	automobiles.tw.	1,392
22	motorcycle.tw.	3,814
23	motorcycles.tw.	931
24	taxi.tw.	1,261
25	cab.tw.	3,755
26	road.tw.	48,507
27	pedestrian.tw.	5,278
28	pedestrians.tw.	3,859
29	accident.tw.	53,887
30	accidents.tw.	48,861
31	injury.tw.	801,932
32	injuries.tw.	254,612
33	crash.tw.	11,757
34	crashes.tw.	9,905
35	exp "Wounds and Injuries"/	1,014,422
36	or/29-35	1,675,831
37	or/11-28	298,607
38	or/1-10	6,385

39	36 and 37	79,754
40	38 or 39	84,652
41	acupuncture.mp.	34,547
42	electroacupuncture.mp.	7,050
43	acupressure.mp.	1,813
44	meridian.mp.	4,833
45	acupoint.mp.	4,164
46	exp acupuncture/	2,043
47	acupuncture.tw.	27,126
48	acupressure.tw.	1,523
49	electro acupuncture.mp.	951
50	meridian*.tw.	6,456
51	needling.tw.	3,936
52	acu-point*.mp.	33
53	acu point*.tw.	33
54	acupoint*.tw.	7,040
55	elctroacupuncture*.tw.	1
56	(acupuncture and th).mp.	79
57	or/41-56	44,775
58	40 and 57	120
Database: Embase (embase.com; 1947-2023)		
1	'automobiles'/exp	11,661
2	'motor vehicle'/exp	28,069
3	'accident, traffic'/exp	75,665
4	'motorcycle'/exp	3,664
5	vehicle:ta,ab,de	203,388
6	traffic:ta,ab,de	153,433
7	vehicular:ta,ab,de	4,909
8	car:ta,ab,de	77,435
9	cars:ta,ab,de	12,857
10	automobile:ta,ab,de	7,368
11	automobiles:ta,ab,de	1,524

12	motorcycle:ta,ab,de	5,934
13	motorcycles:ta,ab,de	1,104
14	taxi:ta,ab,de	1,535
15	cab:ta,ab,de	5,070
16	road:ta,ab,de	48,308
17	pedestrian:ta,ab,de	7,726
18	pedestrians:ta,ab,de	4,183
19	accident:ta,ab,de	593,740
20	accidents:ta,ab,de	56,438
21	injury:ta,ab,de	1,928,938
22	injuries:ta,ab,de	280,812
23	crash:ta,ab,de	12,698
24	crashes:ta,ab,de	10,253
25	'wounds and injuries'/exp	2,824,750
26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	3,658,250
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	427,543
28	#26 AND #27	136,545
29	acupuncture	65,725
30	electroacupuncture	10,710
31	acupressure	3,180
32	acupoint	6,816
33	acupoint:ta,ab,de	6,154
34	'acupuncture analgesia'	2,374
35	'acupuncture therapy'	2,500
36	'acupuncture points'	2,351
37	'acupuncture, ear'	42
38	acupuncture:ta,ab,de	56,629
39	acupressure:ta,ab,de	3,077
40	electroacupuncture	10,710
41	'electro acupuncture'	1,442
42	meridian*:ta,ab,de	9,056

43	needling:ta,ab,de	5,115
44	'acu point*'	50
45	acu AND point*:ta,ab,de	968
46	acupoint*:ta,ab,de	9,351
47	'acupuncture'/exp	57,828
48	'electroacupuncture'/exp	9,355
49	acupuncture*:ta,ab,de	56,660
50	electroacupuncture*:ta,ab,de	10,236
51	acupuncture.:ta,ab,de	56,629
52	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	77,464
53	#28 AND #52	211
Database: The Cochrane Library (thecochranelibrary.com; -2023)		
#1	whiplash	589
#2	acute whiplash injury*	139
#3	acute whiplash associated disorder*	97
#4	acute WAD	113
#5	acute whiplash associated disorder* II	37
#6	acute WAD II	44
#7	whiplash associated disorder*	297
#8	WAD	382
#9	whiplash associated disorder* II	69
#10	WAD II	76
#11	whiplash patient*	426
#12	whiplash syndrome*	98
#13	cervical spine disorder*	605
#14	cervical spine injury*	623
#15	MeSH descriptor: [Accidents, Traffic] explode all trees	547
#16	MeSH descriptor: [Motor Vehicles] explde all trees	361
#17	MeSH descriptor: [Automobiles] this term only	77
#18	MeSH descriptor: [Motorcycles] this term only	35
#19	traffic:ti,ab,kw	2,624

#20	vehicle:ti,ab,kw	8,257
#21	vehicular:ti,ab,kw	56
#22	car:ti,ab,kw	4,202
#23	cars:ti,ab,kw	463
#24	automobile:ti,ab,kw	1,157
#25	automobiles:ti,ab,kw	95
#26	motor cycle*:ti,ab,kw	1,169
#27	taxi*:ti,ab,kw	260
#28	cab*:ti,ab,kw	11,113
#29	road*:ti,ab,kw	2,087
#30	pedestrian*:ti,ab,kw	231
#31	accident*:ti,ab,kw	25,630
#32	injur*:ti,ab,kw	76,691
#33	crash*:ti,ab,kw	773
#34	MeSH descriptor: [Wounds and Injuries] explode all trees	35,004
#35	Any MeSH descriptor in all MeSH products and with qualifier(s): [injuries - IN]	3,961
#36	cervic$ or thoracic$ or lumba$	33,603
#37	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	1,770
#38	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30	28,521
#39	#31 or #32 or #33 or #34 or #35	112,456
#40	#38 and #39	4,739
#41	#37 or #40	6,352
#42	#41 and #36	429
#43	acupuncture	21,079
#44	electroacupuncture	3,539
#45	acupressure	2,174
#46	meridian	1,465
#47	acupoint	3,749
#48	MeSH descriptor: [acupuncture] explode all trees	713
#49	MeSH descriptor: [acupuncture Analgesia] explode all trees	339
#50	MeSH descriptor: [acupuncture Therapy] explode all trees	6,467

#51	MeSH descriptor: [acupuncture points] explode all trees	2,520
#52	MeSH descriptor: [acupuncture, ear] explode all trees	244
#53	acupuncture:ti,ab,kw	19,015
#54	acupressure:ti,ab,kw	2,062
#55	electro acupuncture	1,023
#56	electro-acupuncture	783
#57	meridian*:ti,ab,kw	1,399
#58	needling:ti,ab,kw	3,062
#59	acu-point*	43
#60	acu point*:ti,ab,kw	257
#61	acupoint*:ti,ab,kw	5,508
#62	MeSH descriptor: [electroacupuncture] explode all trees	1,161
#63	elctroacupuncture*:ti,ab,kw	4
#64	acupuncture AND th	1,248
#65	#43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64	26,713
#66	#42 and #65	40
Database: China National Knowledge Infrastructure (CNKI) (cnki.net; 1993-2023)		
1	(SU='traffic accident' OR SU='交通事故' OR SU='whiplash injury' OR SU='颈椎屈伸损伤' OR SU='whiplash associated disorder' OR SU='挥鞭样损伤' OR SU='cervical spine disorder' OR SU='颈椎功能紊乱' OR SU='cervical spine injury' OR SU='颈椎损伤') AND (SU='acupuncture' OR SU='針' or SU='electro acupuncture' OR SU='电針' OR SU='meridian' OR SU='经穴' or SU='acupoint' or SU='acupuncture-ear' OR SU='耳针')	54
Database: ScienceOn (scienceon.kisti.re.kr; 2001-2023)		
1	전체=(교통사고 | 편타성 손상 | 채찍질 손상 | 경항통 | 경추부 염좌) AND 전체=(침 | 전침 | 경혈 | 이침)	61
Database: KMBASE (kmbase.medric.or.kr; 1985-2023)		
1	[ALL=교통사고]	864

2	[ALL=편타성 손상]	25
3	[ALL=채찍질 손상]	0
4	[ALL=경항통]	89
5	[ALL=경추부 염좌]	4
6	[ALL=침]	14,195
7	[ALL=전침]	377
8	[ALL=이침]	80
9	[ALL=경혈]	326
10	(((([ALL=교통사고] OR [ALL=편타성 손상]) OR [ALL=채찍질 손상]) OR [ALL=경항통]) OR [ALL=경추부 염좌])	946
11	((([ALL=침] OR [ALL=전침]) OR [ALL=이침]) OR [ALL=경혈])	14,801
12	(((([ALL=교통사고] OR [ALL=편타성 손상]) OR [ALL=채찍질 손상]) OR [ALL=경항통]) OR [ALL=경항통]) AND ((([ALL=침] OR [ALL=전침]) OR [ALL=이침]) OR [ALL=경혈]))	48
Database: Korean Studies Information Service System (KISS) (kiss.kstudy.com; 1993-2023)		
1	교통사고 and 침	126
2	교통사고 and 전침	4
3	교통사고 and 이침	0
4	교통사고 and 경혈	0
Database: Korea Med (koreamed.org; 1992-2023)		
1	((((("traffic"[ALL])) OR ("automobile"[ALL])) OR ("whiplash injury"[ALL])) OR ("whiplash associated disorder"[ALL])) OR ("cervical spine disorder"[ALL])) OR ("cervical spine injury"[ALL])	1,706
2	((("acupuncture"[ALL])) OR ("electroacupuncture"[ALL])) OR ("meridian"[ALL])) OR ("acupoint"[ALL])	553
3	#1 AND #2	22

Database: Oriental Medicine Advanced Searching Integrated System (OASIS) (oasis.kiom.re.kr; 1963-2023)		
1	교통사고 침	1
2	교통사고 전침	4
3	교통사고 이침	0
4	교통사고 경혈	0
Database: Research Information Sharing Service (RISS) (riss.kr; 1988-2023)		
1	전체 : 교통사고 <AND> 전체 : 침	92
2	전체 : 교통사고 <AND> 전체 : 전침	4
3	전체 : 교통사고 <AND> 전체 : 이침	0
4	전체 : 교통사고 <AND> 전체 : 경혈	1

Supplemental table S2. Appraisal of acupuncture procedure based on the revised SRICTA criteria (2010)

First author (year)	Type of acupuncture	Acupoints	Depth of needling	Stimulation response	Total sessions	Frequency and Retention
Sterling et al (2015)	General acupuncture	Posterior muscles of the cervical spine and upper thoracic spine	NR	Pecking, Twirling	6	Frequency: 2 times/week X 3 weeks Retention: 30 minute
Tobbackx et al (2012)	General acupuncture	Choose from GV14, C1-C7, GB20, SI11, GB21, TE15, SI14, BL17, SP10, SI3, BL64, TE5, GB41, Shiqizhuixia, Ear Zero point, Ear Jerome point, Ear C0.	NR	Deqi sensation	1	Frequency: 1 time/week X 1 week Retention: 20 minute
Kwak et al (2012)	General acupuncture	SI2, SI3, SI5, SI7, SI14, SI15, LI11, BL10, BL12, BL13, BL14, BL60, BL62, BL66,	1.0-2.0 cm	Deqi sensation, Rotating	6	Frequency: 3 times/week X 2 weeks Retention: 15 minute

		GB20, GB21, GB40, GB41, TE5, TE15				
Tough et al (2010)	General acupuncture	Myofascial trigger points in muscles in and around the neck	NR	Pecking (6-7 times/s)	2-6	Frequency: 1 time/week X 2-6 times Retention: NR
Aigner et al (1998)	General acupuncture	TB5, SI6 bilaterally	NR	NR	NR	NR
Han et al (2011)	Electroacupuncture	ST25, GB20, GB21, SI11, SI14, SI15, Ashi points	1.0-2.0 cm	Electrical frequency: 300 Hz	8	Frequency: 2 times/week X 4 weeks Retention: 15 minute
Cameron et al (2011)	Electroacupuncture	GB39, GB20, LI14, SI6 bilaterally	1.0-1.5 cm	Electrical frequency: 2-5 Hz Electrical intensity: 1.5 volts	12	Frequency: 2 times/week X 6 weeks Retention: 20 – 60 minutes
Kim et al (2020)	MSAT	3 points at trapezius muscle	0.5-1.0 cm	NR	6	Frequency: 2 times/day X 3 days Retention: 15 minute

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture; MSAT: Motion-style acupuncture treatment; NR: Not reported

Supplemental table S3. The "leave-one-out" approach for sensitivity analysis of whiplash-associated disorder

Study omitted	Pooled estimate	95% Confidence interval		p-value	I^2(%)
		Lower	Upper		
Pain VAS score					
Kwak HY 2012	-0.54	-0.87	-0.21	0.001	59
Tobbackx Y 2012	-0.65	-0.96	-0.35	<0.0001	44
Tough EA 2010	-0.55	-0.87	-0.22	0.001	59
Cameron ID 2011	-0.65	-1.01	-0.29	0.0005	53
Han SY 2011	-0.47	-0.84	-0.11	0.01	61
Kim DR 2020	-0.45	-0.81	-0.10	0.01	53
ROM – flexion					
Kwak HY 2012	0.33	-0.59	1.26	0.48	89
Sterling M 2015	0.43	-0.37	1.22	0.29	78
Kim DR 2020	-0.10	-0.46	0.26	0.60	0
ROM – extension					
Kwak HY 2012	0.38	-0.19	0.96	0.19	73
Sterling M 2015	0.69	0.34	1.03	<0.0001	0
Kim DR 2020	0.36	-0.27	0.99	0.26	62
ROM – right rotation					
Kwak HY 2012	0.56	-1.16	2.29	0.52	97
Sterling M 2015	0.79	-0.53	2.11	0.24	92
Kim DR 2020	-0.17	-0.56	0.22	0.39	11
ROM – left rotation					
Kwak HY 2012	0.85	-0.29	1.98	0.15	92
Sterling M 2015	0.81	-0.42	2.05	0.20	90
Kim DR 2020	0.23	-0.13	0.59	0.21	0
NDI					
Sterling M 2015	-0.19	-0.61	0.23	0.37	75

Tobbackx Y 2012	-0.18	-0.59	0.24	0.40	75
Tough EA 2010	-0.11	-0.46	0.25	0.56	71
Cameron ID 2011	-0.29	-0.51	-0.08	0.007	0
Han SY 2011	-0.09	-0.45	0.26	0.61	68
Kim DR 2020	-0.15	-0.56	0.26	0.48	73

VAS: Visual analog scale; ROM: Range of motion; NDI: Neck disability index

Supplemental table S4. Evidence quality assessment according to GRADE

Certainty assessment							No. of patients		Effect	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Experimental	Control	Absolute (95% CI)	Certainty
Pain VAS score										
6	RCT	Not serious	Serious*	Not serious	Not serious	None	217	206	SMD 0.57 lower (1.02 lower to 0.28 lower)	⊕⊕⊕○ Moderate
ROM-flexion										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	108	SMD 0.23 higher (0.41 lower to 0.87 higher)	⊕○○○ Very low
ROM-extension										
3	RCT	Not serious	Serious*	Not serious	Serious‡	None	108	108	SMD 0.47 higher (0.05 higher to 0.89 higher)	⊕⊕○○ Low
ROM-right lateral flexion										

2	RCT	Not serious	Very serious§	Not serious	Very serious†	None	68	69	SMD 0.58 higher (0.3 lower to 1.48 higher)	⊕○○○ Very low
ROM-left lateral flexion										
2	RCT	Not serious	Serious*	Not serious	Very serious†	None	68	69	SMD 0.61 higher (0.01 lower to 1.21 higher)	⊕○○○ Very low
ROM-right rotation										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	108	SMD 0.41 higher (0.73 lower to 1.55 higher)	⊕○○○ Very low
ROM-left rotation										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	108	SMD 0.63 higher (0.2 lower to 1.46 higher)	⊕○○○ Very low
NDI										
6	RCT	Not serious	Serious*	Not serious	Serious¶	None	237	225	SMD 0.17 lower (0.5 lower to 0.17 higher)	⊕⊕○○ Low

*: Downgraded one level due to inconsistency (I^2, 50–75%)

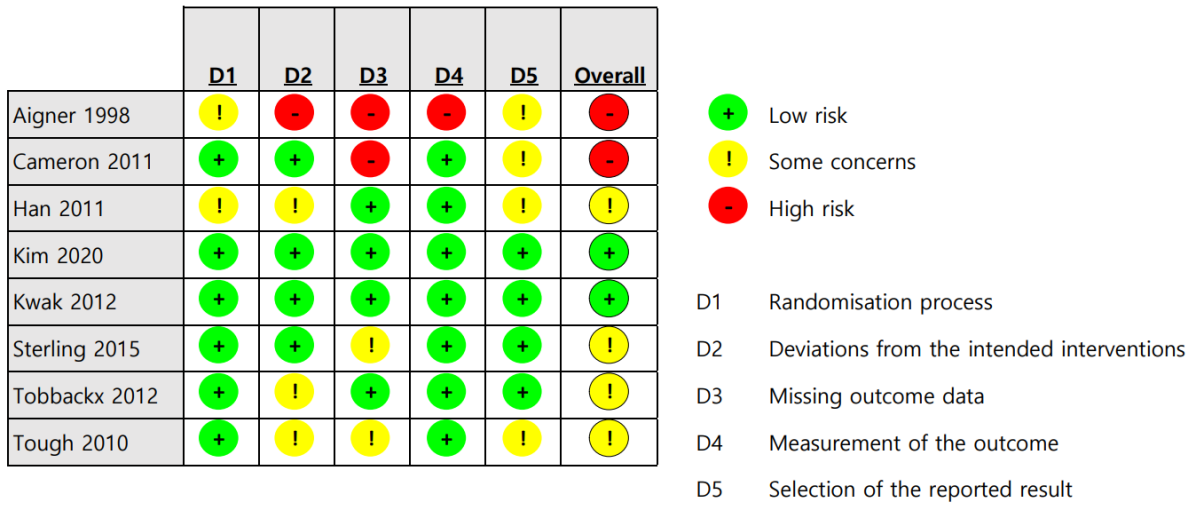
†: Downgraded two levels due to imprecision (fewer than 400 participants and CI overlaps with no effect)

‡: Downgraded one level due to imprecision (fewer than 400 participants)

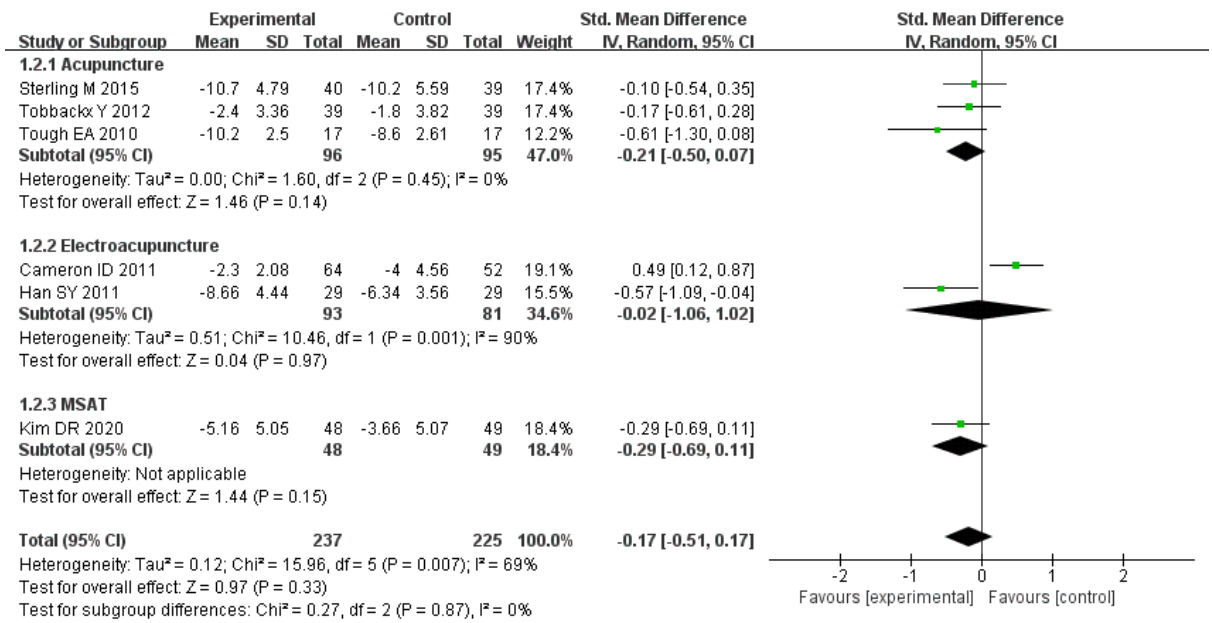
§: Downgraded two levels due to inconsistency (I^2>75%)

¶: Downgraded one level due to imprecision (CI overlaps with no effect)

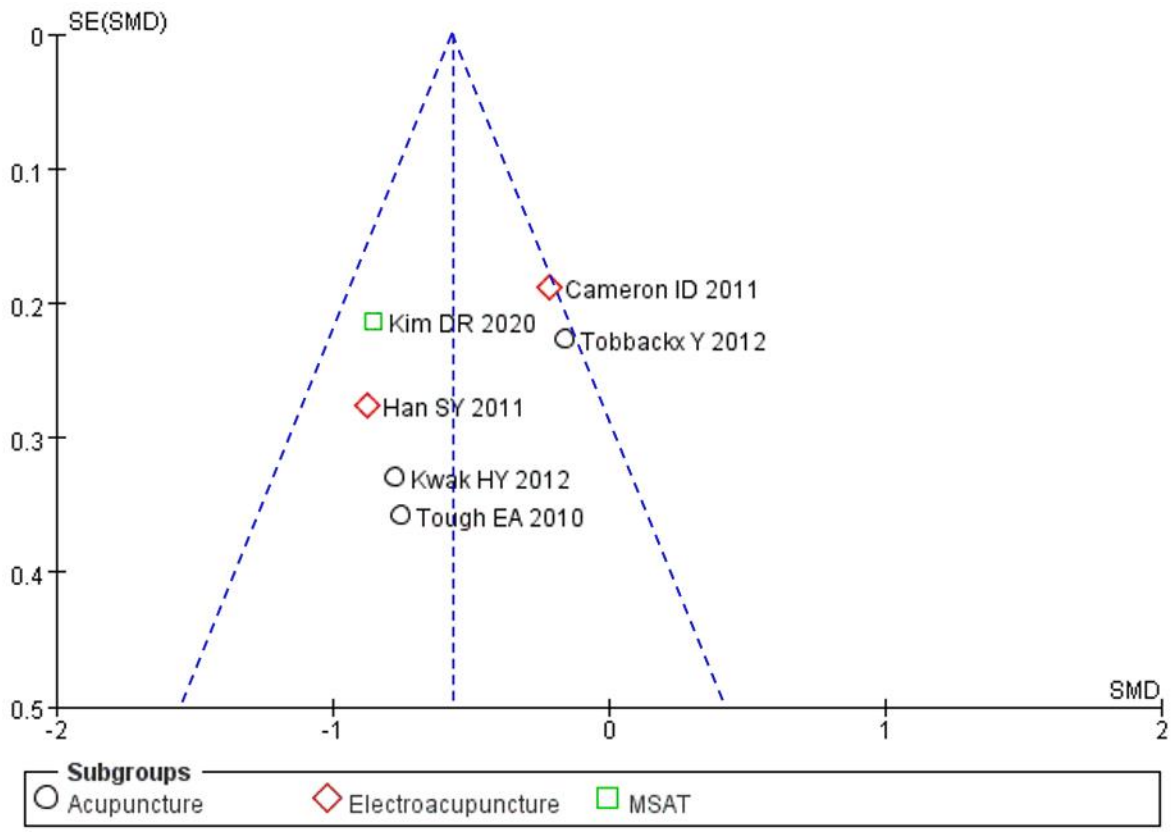
CI: Confidence interval; SMD: Standard mean difference; VAS: Visual analog scale; ROM: Range of motion; NDI: Neck disability index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation



Supplemental figure S1. Individual data of RoB 2



Supplemental figure S2. Forest plot of the meta-analysis for the neck disability index



Supplemental figure S3. Funnel plot for the pain visual analog scale score

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4-5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6 Supple table 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 Supple table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8-9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8-9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8-9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10 Figure 1.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	10 Figure 1.
Study characteristics	17	Cite each included study and present its characteristics.	10 Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	14-15 Figure 2. Supple figure 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	15-16 Figure 3,4. Supple figure 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	15-17 Figure 2,3,4. Supple figure 1,2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	15-16 Figure 3,4. Supple figure 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	16-17 Supple table 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	16-17 Supple table 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	19 Supple figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	17-19 Supple table 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	20-21
	23b	Discuss any limitations of the evidence included in the review.	21-22
	23c	Discuss any limitations of the review processes used.	21-22
	23d	Discuss implications of the results for practice, policy, and future research.	20-22

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	23
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	22-23
Competing interests	26	Declare any competing interests of review authors.	23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	23

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Efficacy of acupuncture for whiplash injury: A systematic review and meta-analysis

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ABSTRACT

Objectives: This study aimed to establish clinical evidence for acupuncture by analyzing data from trials that demonstrated the efficacy of acupuncture for whiplash-associated disorder (WAD) with the following research question: Is acupuncture treatment effective for symptom alleviation in patients with WAD compared to other usual care?

Design: A systematic review and meta-analysis.

Data sources: PubMed, Ovid Medline, Embase, The Cochrane Library, China National Knowledge Infrastructure, ScienceOn, KMBASE, Korean Studies Information Service System, Korea Med, Oriental Medicine Advanced Searching Integrated System, and Research Information Sharing Service were searched from their inception to October 1, 2023.

Eligibility criteria: We included randomized controlled trials (RCTs) using acupuncture on patients with WAD. The outcomes were the pain visual analog scale (VAS) score or numerical rating scale score for neck pain, the range of motion (ROM) of the neck, the neck disability index, and safety.

Data extraction and synthesis: Two independent researchers analyzed and extracted data from the selected literatures. The risk of bias and the quality of evidence were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions and the Grading of Recommendations Assessment, Development, and Evaluation method, respectively.

Results: A total of 525 patients with WAD from eight RCTs were included in this study. The meta-analysis revealed that the outcomes showed significant differences in the pain VAS score (standard mean difference [SMD]: -0.57 [-0.86 to -0.28], p<0.001) and ROM-extension (SMD: 0.47 [0.05 to 0.89], p=0.03). The risk of bias assessment revealed that four studies published after 2012 (50%, 4 out of 8 studies) showed low bias in most domains. The pain VAS score was graded as having moderate certainty.

Conclusion: Acupuncture may have clinical value in pain reduction and increasing the ROM for patients with WAD. High-quality RCTs must be conducted to confirm the efficacy of acupuncture in patients with WAD.

Trial registration number: PROSPERO CRD42021261595.

Keywords: Acupuncture; Whiplash injuries; Whiplash-associated disorder; Systematic review; Meta-analysis; Randomized controlled trial

Word Count: 3836

Article Summary

Strengths and limitations of this study

- This systematic review was reported as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.
- Data regarding acupuncture were collected to appraise the acupuncture procedure as part of the Standards for Reporting Interventions in Clinical Trials of Acupuncture.
- Subgroup analysis was performed according to the type of acupuncture treatment to verify the effect size of each subgroup.
- The Grading of Recommendations Assessment, Development and Evaluations method was used to evaluate the quality of the outcomes.
- Grey literature and other supplementary searches were not conducted, which may result in missing studies and the risk of publication bias.

INTRODUCTION

Whiplash injury or whiplash-associated disorder (WAD) is caused by rapid hyperextension or hyperflexion of the patient's head due to sudden acceleration or deceleration during a vehicle crash [1]. WAD can cause musculoskeletal symptoms, such as neck pain, stiffness, and headache, as well as systemic symptoms, such as dizziness, psychological distress, depression, and sleep disturbances [2, 3]. Kim et al. [4] reported that 57% of patients involved in traffic accidents present with neck and back pain. Several conservative therapies can be used to relieve pain and discomfort in the cervical region, such as nerve block on the dysfunctional spinal articular process [5, 6]; however, it is difficult to predict the course and sequelae of WAD owing to its unique mechanism [7, 8].

Acupuncture is used for the treatment of various musculoskeletal disorders, such as WAD [9-11], as it can target the neurological mechanisms to relieve physical pain via the release of opioids and 5-hydroxytryptamine in the brain reward/motivation circuit [12]. However, its effectiveness is yet to be recognized despite its usefulness in clinical practice [13]. The Canadian and Australian WAD clinical practice guidelines (CPGs) do not recommend acupuncture for treating WAD [14]; moreover, one of the guidelines does not conclude that acupuncture is effective [15]. This lack of consensus can be attributed to the lack of research or evidence on acupuncture at the time of formulating these CPGs.

Therefore, this study aimed to establish clinical evidence for acupuncture by analyzing data from trials that demonstrated the efficacy of acupuncture for the treatment of WAD with the following research question: Is acupuncture treatment effective for symptom alleviation in patients with WAD compared to other usual care? Moon et al. [16] published their systematic review (SR) in 2014; however, a meta-analysis was not conducted as part of their study. Lee et al. [17] published a protocol of an SR to verify the effect of acupuncture on WAD; however, no follow-up studies have been published. Therefore, in this study, we updated the previous

SR [16] by adding clinical studies published after 2014 and evaluated the quality of evidence on acupuncture through a meta-analysis and sensitivity analysis. Herein, this SR was reported as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and referred to the Cochrane Handbook [18, 19].

MATERIALS and METHODS

Database selection and search strategy

The protocol of this SR was registered in the Prospective Register of Systematic Reviews (PROSPERO) database on July 18, 2021 (CRD42021261595) [20]. Online databases, including PubMed, Ovid Medline, Embase, The Cochrane Library, China National Knowledge Infrastructure, ScienceOn, KMBASE, Korean Studies Information Service System, Korea Med, Oriental Medicine Advanced Searching Integrated System, and Research Information Sharing Service were searched for studies on the efficacy of acupuncture for WAD from their inception to October 1, 2023. We did not limit our search by language or by publication date. Terms related to acupuncture and WAD from the Medical Subject Headings were used in the search strategy; the terms were translated into the language suitable for each database (online supplemental table S1). In addition, we checked the reference lists of all previously published SRs identified by the above methods, looking for cited relevant studies. However, we did not review conferences because of the validity of the findings as reported as in conference abstracts [21].

Eligibility criteria

The studies included in this study were selected according to the following five criteria: study design, participants, intervention, comparison, and outcomes. Randomized controlled trials (RCTs) that used acupuncture on patients with WAD were included regardless of their reporting type, blinding, and language. In contrast, RCTs that did not target WAD or use acupuncture as an intervention were excluded. Additionally, non-RCTs, single-arm pre- and post-clinical trials, case-control studies, case reports, laboratory studies (including in vivo and in vitro studies), letters, and reviews were also excluded. Thereafter, the participants diagnosed with WAD, regardless of their race, age, or sex, were identified. The diagnostic criteria for

WAD were based on those of the Quebec Task Force, which classified patients according to their severity of signs and symptoms [22]. The Quebec Task Force's diagnostic criteria are as follows:

Grade I: Neck complaint of pain, stiffness or tenderness only. No physical sign(s).

Grade II: Neck complaint AND musculoskeletal sign(s). Musculoskeletal signs include decreased range of motion and point tenderness.

Grade III: Neck complaint AND neurological sign(s). Neurological signs include decreased range of motion and point tenderness.

Grade IV: Neck complaint AND fracture or dislocation.

The treatment interventions were acupuncture treatment, including electroacupuncture (EA) and dry needling, and acupuncture combined with active treatment(s), which were compared with the same active treatment(s) in the control group. The treatments administered to the control group were limited to usual care, such as physiotherapy, medications, conventional treatments other than acupuncture, and sham treatments. The primary outcome was the pain visual analog scale (VAS) score or numerical rating scale score for neck pain, and the secondary outcomes were the range of motion (ROM) of the neck, the neck disability index (NDI), and safety [23].

Data collection and analysis

Study selection

Two independent researchers (SHL and MSH) were involved in the study selection process. Study selection and deduplication were performed using Excel. In the case of disagreements during the process, the researchers proceeded to the next step after reaching a consensus through a discussion. After removing duplications, the titles and abstracts of the studies were screened to exclude those that did not meet the eligibility criteria. Subsequently, the full text

of each selected study was fully reviewed for the final selection.

Data extraction and management

Two independent researchers (SHL and MSH) analyzed and extracted the data from the selected literature. Data extraction and management were performed using Excel. Data regarding the country of origin, study design, sample size, participants, intervention, comparison, outcomes, and results were summarized in a table. The outcomes of the primary endpoint were extracted. However, if the study did not present the primary endpoint, the outcomes of the first follow-up after the treatment were extracted. In addition, data regarding the type of acupuncture, acupoints, depth of needling, stimulation response, total sessions, frequency of sessions, and retention time were collected to appraise the acupuncture procedure as part of the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [24, 25]. In the case of missing standard mean difference (SMD) for changes from baseline, we tried to contact the original investigators to request further data. However, if it was impossible, we calculated a correlation coefficient from a study reported in considerable detail and imputed missing data in accordance with the established method [26, 27].

Quality assessment

Two independent researchers (SHL and MSH) evaluated the quality of the selected studies according to the Cochrane RoB 2 tool in the Cochrane Handbook for Systematic Reviews of Interventions [19]. The risk of bias assessment was performed based on the content described in the original text and the characteristics of the intervention. The Grading of Recommendations Assessment, Development and Evaluations (GRADE) method was used to evaluate the quality of the outcomes [28]. Each outcome was classified as not serious, serious, or very serious according to the study design, risk of bias, inconsistency, indirectness,

imprecision, and other considerations. The certainty of the outcomes was categorized as high, moderate, low, or very low. In the case of disagreements between researchers, agreement was reached through discussion with third and fourth researchers (BCS, IH).

Statistical analysis

The meta-analysis was performed using the Review Manager version 5.4.1 (Cochrane) software. To determine the value of the effect size, SMD was used for continuous data and relative risk for dichotomous data. All data, including dichotomous and continuous data, were presented with a 95% confidence interval (CI). Fixed-effects or random-effects models were used for the synthesis of data according to the heterogeneity of each meta-analysis. Heterogeneity (I^2) of less than 50% was considered negligible, and a fixed-effects model was used in such cases. If the heterogeneity exceeded 50%, a random-effects model was used to estimate the effect size. Subgroup analysis was performed according to the type of acupuncture treatment to verify the effect size of each subgroup. The "leave-one-out" approach, where the meta-analysis is performed repeatedly while excluding the included literature individually, was performed for sensitivity analysis [29]. When a fixed-effects model was used for data synthesis, sensitivity analysis using a random-effects model was additionally performed to eliminate confounding effects. In addition, a funnel plot was generated to determine the presence of publication bias for the primary outcome.

Patient and public involvement

No patient involved.

RESULTS

Study selection

A total of 877 articles were retrieved from databases. After excluding 154 duplications, 295 studies unrelated to WAD, 163 non-RCT studies, 42 in vitro and in vivo studies, and 154 irrelevant studies were excluded while screening of the title and abstract. The full text of the remaining 69 articles was reviewed, and 62 articles were excluded, including 51 articles that did not use acupuncture as an intervention, 6 articles without full text, 3 articles without a valid control group, and 2 articles for other reasons. In addition, we included 1 study through reference tracking [16]. Thus, 8 studies were included in the final analysis (Figure 1).

Study characteristics

A total of 525 patients with WAD were included in this study. Five studies [16, 30-33] compared acupuncture with sham acupuncture, usual care, or medication, whereas two [34, 35] compared EA with sham EA. One study [36] compared motion-style acupuncture treatment (MSAT) with usual care. The country of origin of the studies varied: three in Korea [32, 34, 36], two in Australia [30, 35], one each in Belgium [31], UK [33], and Austria [16]. The recruitment period was less than one year in five studies [31-34, 36], more than four years in two studies [30, 35], and not reported in one study [16]. Among the eight studies, one [31] was designed as a crossover RCT. The pain VAS score was recorded in six studies [31-36], and the ROM was recorded in four studies [16, 30, 32, 36]. The NDI was recorded in six studies [30, 31, 33-36]. The study by Aigner et al. was described based on its reference in the SR by Moon et al. [16], as the original text could not be accessed (Table 1).

Table 1. Data of clinical studies on acupuncture for whiplash-associated disorder

First author (year)	Country of origin (period)	Design	Sample size	Participants	Intervention	Comparison	Outcomes	Results (Effect size, P-value)
Sterling et al (2015) [30]	Australia (2009 – 2012)	RCT	Total: 80 Exp.: 40 Con.: 40	WAD Ⅱ	Atx. + exercise	Sham atx. + exercise	1) NDI 2) ROM (1) Flex. (2) Ext. (3) Rot. (4) Lat.	1) 0.10, P=0.67 2) (1) -0.14, P=0.54 (2) 0.08, P=0.71 (3) -0.32, P=0.16 (4) 0.26, P=0.24
Tobbackx et al (2012) [31]	Belgium (01/2011 – 12/2011)	Crossover RCT	Total: 39	WAD Ⅰ or Ⅱ or Ⅲ (chronic WAD persisting more than 3 months)	Atx.	Relaxation	1) NDI 2) pain VAS	1) 0.17, P=0.47 2) 0.16, P=0.47
Kwak et al (2012) [32]	Korea (12/2009 – 10/2010)	RCT	Total: 40 Exp.: 20 Con.: 20	WAD (persisting more than 3 months)	Atx. + UC	UC (PTx. + exercise)	1) pain VAS 2) ROM (1) Flex.	1) 0.78, P=0.02 2) (1) -0.01, P=0.97

							(2) Ext.	(2) 0.73, P=0.03
							(3) Rt. Lat. Flex.	(3) 0.10, P=0.76
							(4) Lt. Lat. Flex	(4) 0.25, P=0.43
							(5) Rt. Rot.	(5) 0.10, P=0.76
							(6) Lt. Rot.	(6) 0.16, P=0.61
Tough et al (2010) [33]	UK (05/2007 – 12/2007)	RCT	Total: 34 Exp.: 17 Con.: 17	WAD Ⅱ (WAD persisting 2-16 weeks)	Atx. + Ptx.	Sham Atx. + Ptx.	1) pain VAS 2) NDI	1) 0.76, P=0.03 2) 0.61, P=0.08
Aigner et al (1998) [16]	Austria (NR)	RCT	Total: 61 Exp.: 28 Con.: 33	WAD Ⅰ or Ⅱ	Atx.	Med.	1) ROM	1) NR
Han et al (2011) [34]	Korea (03/2011 – 07/2011)	RCT	Total: 58 Exp.: 29 Con.: 29	WAD	EA + HM	Sham EA + HM	1) pain VAS 2) NDI	1) 0.88, P=0.002 2) 0.57, P=0.03
Cameron et al (2011) [35]	Australia (03/2001 – 10/2004)	RCT	Total: 116 Exp.: 52 Con.: 64	WAD Ⅰ or Ⅱ (subacute or chronic WAD persisting more than 1 month)	EA	Sham EA	1) pain VAS 2) NDI	1) 0.21, P=0.25 2) -0.49, P=0.009

							1) pain VAS	1) 0.85, P<0.0001
							2) NDI	2) 0.29, P=0.15
							3) ROM	3)
Kim et al (2020) [36]	Korea (07/2019 – 09/2019)	RCT	Total: 97 Exp.: 48 Con.: 49	WAD (within 7 days)	MSAT + IKM	IKM (Atx. + pharm. + CMT + HM)	(1) Flex.	(1) 0.80, P=0.0001
							(2) Ext.	(2) 0.67, P=0.001
							(3) Rt. Rot. Flex.	(3) 1.01, P<0.001
							(4) Lt. Rot. Flex	(4) 0.88, P<0.001
							(5) Rt. Lat.	(5) 1.44, P<0.001
							(6) Lt. Lat.	(6) 1.43, P<0.001

CI: Confidence interval; RCT: Randomized controlled trial; Exp.: Experimental; Con.: Control; WAD: Whiplash-associated disorder; MSAT: Motion-style acupuncture treatment; IKM: Integrative Korean medicine treatment; Pharm.: Pharmacopuncture; CMT: Chuna manual therapy; HM: Herbal medicine; VAS: Visual analog scale; NDI: Neck disability index; ROM: Range of motion; Flex.: Flexion; Ext.: Extension; Rt.: Right; Rot.: Rotation; Lt.: Left; Lat.: Lateral; Atx.: Acupuncture therapy; UC: Usual care; PTx.: Physiotherapy; EA: Electroacupuncture; Med.: Medication

Standard for reporting acupuncture according to STRICTA

The eight studies were analyzed using STRICTA (online supplemental table S2). Regarding the type of acupuncture, five studies [16, 30-33] used general acupuncture, two used EA [34, 35], and one used MSAT [36]. Five studies [16, 31, 32, 34, 35] used specific acupoints, and three [30, 33, 36] used muscle trigger points instead of acupoints. The depth of needling was mentioned only in four studies [32, 34-36]. For stimulation response, two studies [31, 32] induced a *deqi* sensation, two [30, 33] used pecking, two [30, 32] used techniques such as twirling and rotation, and two [34, 35] used electrical stimulation. Regarding the total number of sessions, more than six sessions were performed in most studies [30, 32, 34-36], only one session was performed in one study [31], and two to six sessions were performed in one study depending on the degree of improvement in the symptoms [33]. The frequency of sessions was unreported in one study [16], whereas sessions were performed one to three times a week in the remaining seven studies. The number of weeks varied from one to six weeks, and the retention time varied from 15 to 60 min.

Risk of bias assessment

The eight selected studies were analyzed using the Cochrane RoB 2 tool. Six out of eight studies were identified as having low risk of bias with appropriate procedures for random sequence generation and allocation concealment [30-33, 35, 36]. Regarding deviations from the intended interventions, four studies were rated as having low risk of bias [30, 32, 35, 36], three as having some concerns [31, 33, 34], and one as having high risk of bias [16]. For missing outcome data, four studies were rated as having low risk of bias [31, 32, 34, 36]. In terms of bias in measurement of the outcome, except for one study that did not provide full text [16], all seven studies were identified as having low risk of bias. In terms of the selection of the reported result, studies that reported a pre-specified analysis plan were rated as having low risk of bias

[30-32, 36]. Overall, two studies showed low risk of bias in all five components [32, 36] (Figure 2, online supplemental figure S1).

Meta-analysis

A meta-analysis was performed with seven studies [30-36] according to the outcomes, after excluding one study [16] in which no comparison was made between the groups. The subgroups were divided into general acupuncture, EA, and MSAT according to the type of acupuncture treatment.

Pain VAS score

The result of the meta-analysis for the pain VAS score revealed that acupuncture was effective in treating patients with WAD (SMD: -0.57 [-0.86 to -0.28], p<0.001). The random-effects model was used for the analysis, as the heterogeneity (I^2) was 51%. Subgroup analysis revealed that general acupuncture and MSAT were effective in treating patients with WAD, whereas EA was ineffective (Figure 3).

ROM

Kwak et al. [32] and Kim et al. [36] recorded the ROM for all directions, whereas Sterling et al. [30] recorded the ROM for four directions: flexion, extension, right rotation, and left rotation. The results of the meta-analysis for ROM revealed that acupuncture was effective in improving extension in patients with WAD (SMD: 0.47 [0.05 to 0.89], p=0.03). The random-effects model was used for all directions of ROM, as the heterogeneity (I^2) was > 50%. Subgroup analysis showed that MSAT was effective in treating patients with WAD in all directions of ROM. However, general acupuncture was not effective for ROM in any direction

(Figure 4).

NDI

The results of the meta-analysis for NDI revealed that acupuncture was ineffective in improving the NDI. The random-effects model was used for the analysis as the heterogeneity (I^2) was > 50%. Subgroup analysis revealed that all treatments were ineffective in improving the NDI (online supplemental figure S2).

Adverse events

Five studies [30, 32, 33, 35, 36] reported adverse events (AEs), whereas three [16, 31, 34] did not. Except for one case of moderate AE, all reported AEs were mild. Pruritus of unknown cause was reported in the study by Kim et al. [36], necessitating the administration of antihistamines by injection, cream, and oral route. Other AEs caused by acupuncture included hives, dizziness, exacerbation of neck pain, bruising, fatigue, and somatic reactions (sweating and low blood pressure); however, these AEs were mild and were cured within a few days. AEs such as diarrhea, soft stools, nausea, heartburn, and vesicles were also reported; however, these were confirmed to be caused by interventions other than acupuncture.

Sensitivity analysis

A sensitivity analysis for the pain VAS score, ROM-flexion, ROM-extension, ROM-right rotation, ROM-left rotation, and NDI was performed, whereas ROM-right lateral flexion and ROM-left lateral flexion were excluded as they were included only in two studies (online supplemental table S3).

Pain VAS score

The results of the meta-analysis of the pain VAS score changed to moderate heterogeneity when the study by Tobbackx et al. [31] was removed (SMD: -0.65 [-0.96 to -0.35], p<0.001, I^2: 44%).

ROM

The result of the meta-analysis of ROM-extension was maintained when the study by Sterling et al. [30] was removed; however, the results were not maintained when the study by Kwak et al. [32] or Kim et al. [36] was removed. In particular, there was no heterogeneity when the study by Sterling et al. [30] was excluded. However, the results of the meta-analysis of ROM-flexion, ROM-right rotation, and ROM-left rotation were not significantly affected as the p-value was > 0.05 even after removing the included studies one by one.

NDI

The result of the meta-analysis of NDI changed to the p-value < 0.05 and no heterogeneity when the study by Cameron et al. [35] was removed (SMD: -0.29 [-0.51 to -0.08], p= 0.007, I^2: 0%).

Evidence quality

The quality of evidence of the outcomes was assessed using GradePro GDT (online supplemental table S4).

Pain VAS score

Six studies (n = 423) provided data regarding the pain VAS score. The risk of bias evaluation

revealed high bias in one study; however, the effect on the estimate was considered inconclusive, and the confidence level of the evidence was not lowered. For inconsistency, the pain VAS score was downgraded by one level as its heterogeneity (I^2) was 51%. Thus, the quality of evidence on the pain VAS score was graded as "moderate."

ROM

Three studies (n = 216) provided data regarding ROM-flexion, ROM-extension, ROM-right rotation, and ROM-left rotation. Two studies (n = 137) provided data regarding ROM-right lateral flexion and ROM-left lateral flexion. The risk of bias evaluation revealed some concerns in one study; however, the effect on the estimate was considered inconclusive, and the confidence level of the evidence was not lowered. In the evaluation of consistency, ROM-extension and ROM-left lateral flexion were downgraded by one level as their heterogeneity (I^2) was higher than 50% but lower than 75%. Similarly, ROM-flexion, ROM-right lateral flexion, ROM-right rotation, and ROM-left rotation were downgraded by two levels as their heterogeneity (I^2) was > 75%. In the evaluation of imprecision, ROM-extension was downgraded by one level as the number of participants was less than 400. Similarly, ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation were degraded by two levels as the number of participants was less than 400 and their CI overlapped with no effect. Thus, ROM-extension was graded as "low," and ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation were graded as "very low."

NDI

Six studies (n = 462) reported data regarding the NDI. The risk of bias evaluation revealed high bias in one study; however, the effect on the estimate was considered inconclusive, and the

confidence level of the evidence was not lowered. For inconsistency, the NDI was downgraded by one level as its heterogeneity (I^2) was 69%. In the evaluation of imprecision, the NDI was downgraded by one level as the CI overlapped with no effect. Thus, the NDI was graded as "low."

Publication bias

Publication bias was evaluated using the funnel plot for the pain VAS score (online supplemental figure S3). The outcome was slightly asymmetric, meaning there was a little publication bias. However, as fewer than 10 studies were included, the power of the test is expected to be low.

DISCUSSION

This study revealed that acupuncture is effective in improving the pain VAS score and ROM-extension in patients with WAD. The analgesic effect of acupuncture is thought to relieve pain in patients with WAD. In addition, patients with WAD were able to effectively improve ROM-extension following acupuncture, as acupoints GB20, GB21, SI11, SI14, SI15, and TE15, which are used extensively in patients with WAD, are located in the posterior muscles of the cervical spine and upper thoracic spine. However, the NDI, ROM-flexion, ROM-right lateral flexion, ROM-left lateral flexion, ROM-right rotation, and ROM-left rotation did not show significant differences; thus, future studies are required to prove the effectiveness of acupuncture for these outcomes.

In the risk of bias assessment, except for one study published before 2010 [16], seven studies published after 2010 showed low bias in most domains [30-36]. In addition, although participant blinding is difficult owing to the nature of acupuncture [37], many studies have attempted to minimize this effect by utilizing placebo interventions. Moreover, four studies [30-32, 36] published after 2012 showed some concerns in only two domains and low bias in all other domains, indicating that recent studies on acupuncture interventions are consistently designed with high quality.

In the sensitivity analysis of the pain VAS score, a significant effect was maintained even when the included studies were removed one by one. In this context, acupuncture showed significant effects in patients with WAD, despite differences in design, participants, interventions, and comparisons among the studies. In addition, when the study by Tobbackx et al. [31] was removed, moderate heterogeneity was observed, meaning it was accountable for the substantial heterogeneity of the overall result. The crossover RCT design of Tobbackx et al. [31] is presumed to be the reason for the low effect size and high heterogeneity. For ROM-extension, there was no heterogeneity when the study by Sterling et al. [30] was removed; thus, it could

be assumed that the study was a potential source of heterogeneity. In the study by Sterling et al. [30], high-intensity ROM exercises, including craniocervical flexion training, neck extensor training, scapular training, posture re-education, and sensorimotor exercises, were performed for 1 h, which may have been the cause of heterogeneity. For the NDI, a significant effect appeared, and no heterogeneity was obtained when the study by Cameron et al. [35] was removed; therefore, the study was considered responsible for the between-study heterogeneity. It was presumed that the NDI SMD of the study favored the control group since it was > 0, affecting the overall effect size and heterogeneity.

A previous study [16] that analyzed the effectiveness of acupuncture in patients with WAD included studies published before 2014. This study differs from the previous study in the following ways. First, including two RCTs published after 2014, we analyzed a total of eight RCTs. Accordingly, this study provided more objective and quantitative evidence by synthesizing data on the efficacy of acupuncture for treating WAD. Second, the effect size of the pain VAS score, ROM, and NDI was verified by performing a meta-analysis. The directionality of the treatment effect and whether the CI of the individual studies overlapped were assessed using a forest plot. Third, a sensitivity analysis was performed to confirm the robustness of the results. The effect of individual studies on heterogeneity (I^2) and effect size was analyzed using the leave-one-out approach method. Fourth, a subgroup analysis was conducted according to the type of acupuncture treatment. The effect size of each type of acupuncture treatment was verified by dividing them into general acupuncture, EA, and MSAT subgroups. Fifth, the evidence quality of the pain VAS score, ROM, and NDI was assessed using the GRADE method. By presenting the certainty for each outcome, this study provided criteria that can be clinically referred to when using acupuncture for patients with WAD.

However, this study has some limitations. First, grey literature and other supplementary searches were not conducted, which may result in missing studies and the risk of publication

bias. However, we attempted to minimize publication bias by reviewing the references of a previously published SR. Second, the original text of one study could not be accessed. Third, except for ROM-extension, the efficacy of acupuncture in improving ROM in other directions was evaluated as being "very low." This is an area that needs to be verified through further studies.

CONCLUSION

The results of this study suggest that acupuncture may have clinical value in the treatment of patients with WAD. In the future, high-quality RCTs, based on the aforementioned data, must generate evidence of higher quality than that in the present study to confirm the efficacy of acupuncture in patients with WAD.

AUTHOR CONTRIBUTIONS

Conceptualization: Sang-Hyun Lee

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Funding acquisition: Sun-Young Park and Eui-Hyuoung Hwang

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Methodology: Sun-Young Park, In Heo, Eui-Hyuoung Hwang, and Byung-Cheul Shin

Project administration: Sun-Young Park, In Heo, Eui-Hyuoung Hwang and Man-Suk Hwang

Supervision: Byung-Cheul Shin and Man-Suk Hwang

Writing – original draft: Sang-Hyun Lee

Writing – review & editing: Sang-Hyun Lee, Eui-Hyuoung Hwang, Byung-Cheul Shin and Man-Suk Hwang

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DISCLAIMER

The funding source had no role in the design of the protocol, study search and selection, data extraction and management, data interpretation, report writing, or the decision to submit the report for publication.

COMPETING INTERESTS

None.

PATIENT CONSENT FOR PUBLICATION

Not required.

PROVENANCE AND PEER REVIEW

Not commissioned; extremally peer reviewed.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

AMENDMENT

In accordance with the reviewer's comment for revision, the RoB 2 tool and funnel plot were added to this review, unlike the proposed protocol. In addition, conference tracking was not

conducted.

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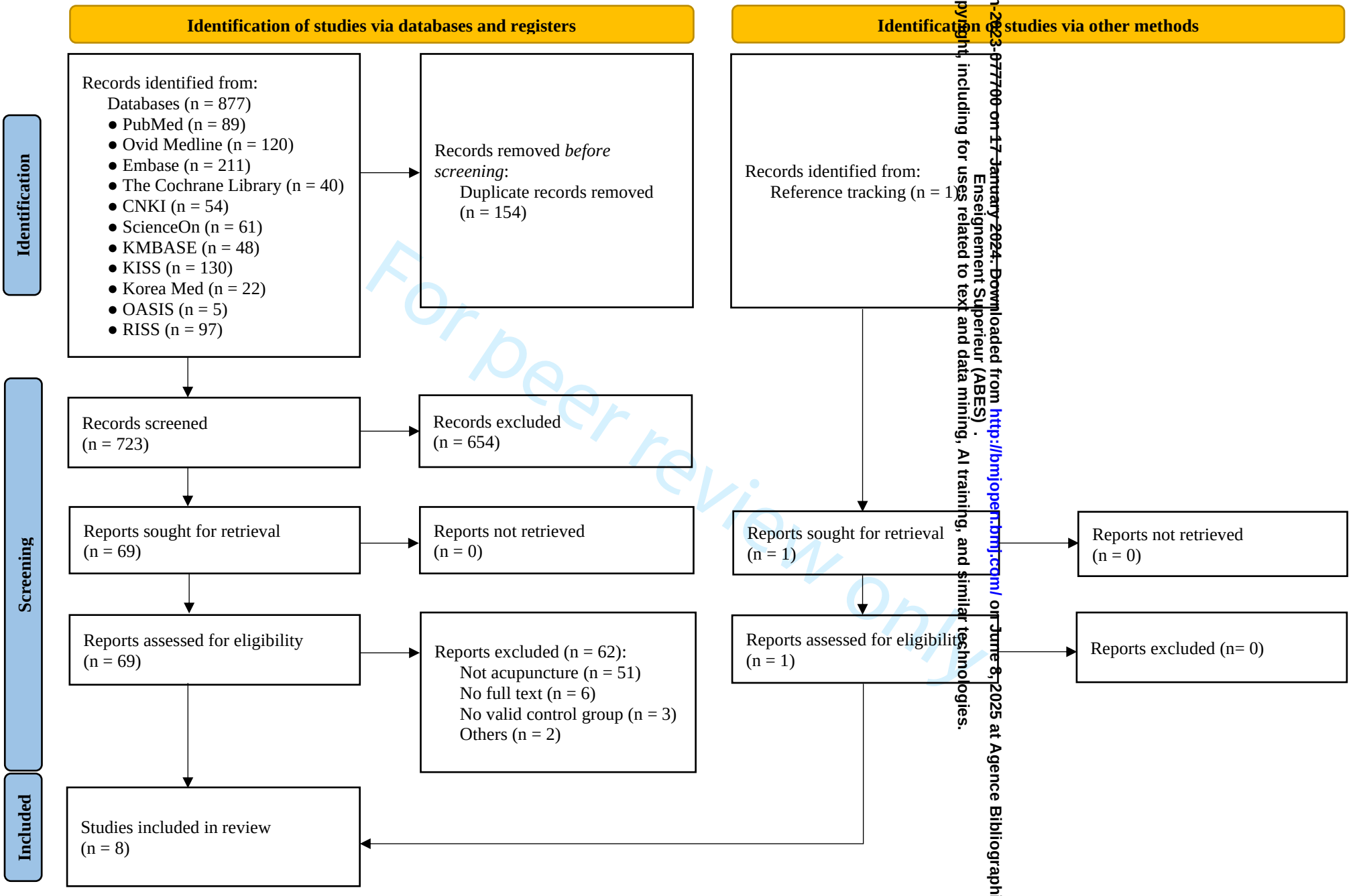
FIGURE LEGENDS

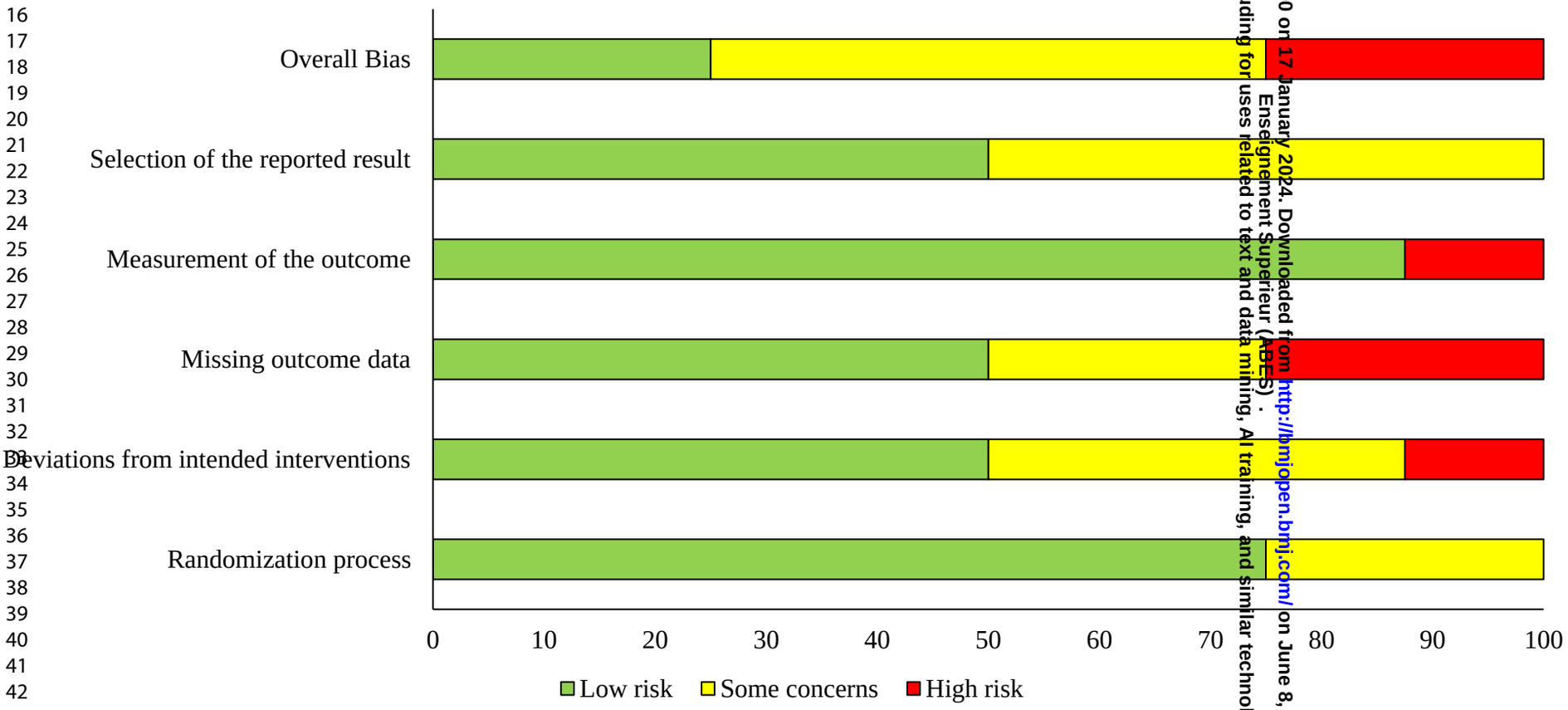
Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart of the included studies

Figure 2. Summary in risk of bias 2

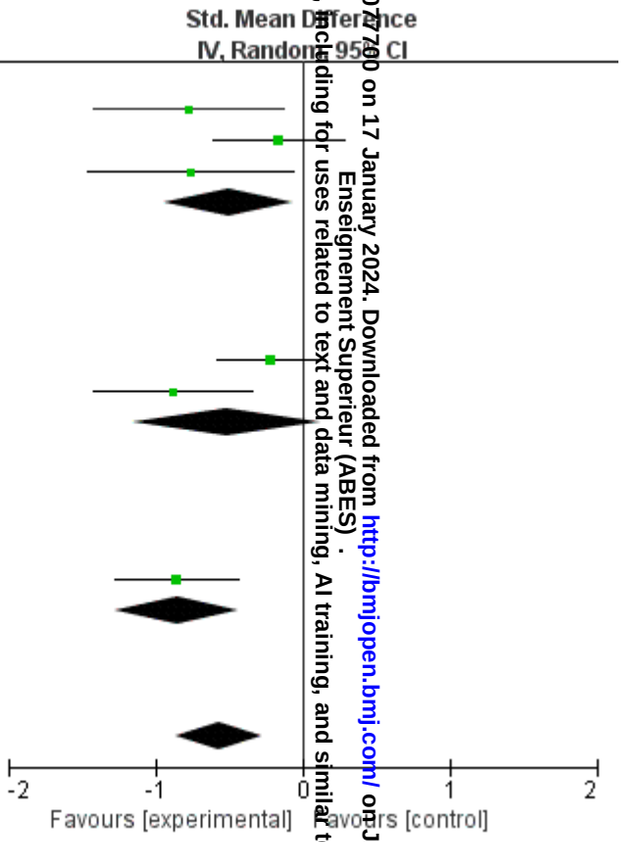
Figure 3. Forest plot of the meta-analysis for the pain visual analog scale score

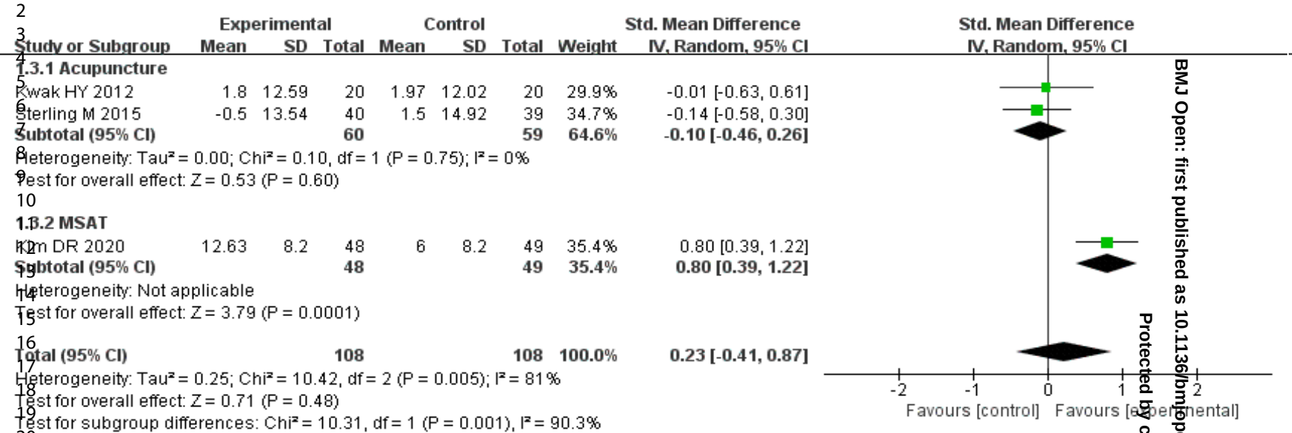
Figure 4. Forest plot of the meta-analysis for the range of motion



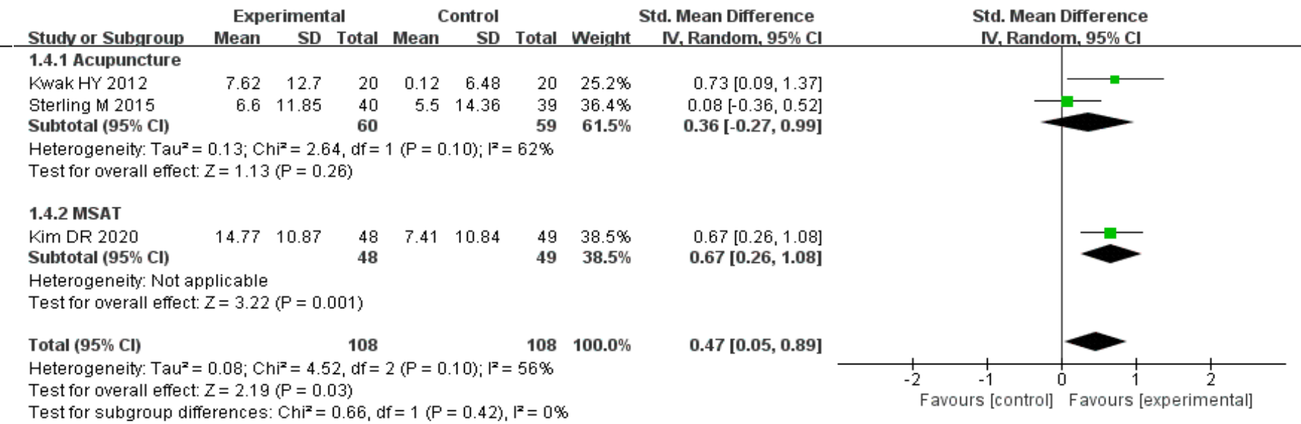


Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Acupuncture								
Kwak HY 2012	-1.85	1.88	20	-0.4	1.78	20	12.6%	-0.78 [-1.42, -0.13]
Tobbackx Y 2012	-7	21.24	39	-3.6	20.15	39	18.8%	-0.16 [-0.61, 0.28]
Tough EA 2010	-3.2	1.49	17	-1.8	2.08	17	11.4%	-0.76 [-1.45, -0.06]
Subtotal (95% CI)			**76**			**76**	**42.8%**	**-0.50 [-0.93, -0.06]**
Heterogeneity: Tau² = 0.06; Chi² = 3.32, df = 2 (P = 0.19); I² = 40%								
Test for overall effect: Z = 2.25 (P = 0.02)								
1.1.2 Electroacupuncture								
Cameron ID 2011	-1.6	1.88	64	-1.2	1.84	52	21.8%	-0.21 [-0.58, 0.15]
Han SY 2011	-4.9	1.05	29	-3.72	1.56	29	15.5%	-0.88 [-1.42, -0.33]
Subtotal (95% CI)			**93**			**81**	**37.3%**	**-0.51 [-1.16, 0.13]**
Heterogeneity: Tau² = 0.16; Chi² = 3.95, df = 1 (P = 0.05); I² = 75%								
Test for overall effect: Z = 1.56 (P = 0.12)								
1.1.3 MSAT								
Kim DR 2020	-2.03	1.34	48	-0.88	1.34	49	19.8%	-0.85 [-1.27, -0.44]
Subtotal (95% CI)			**48**			**49**	**19.8%**	**-0.85 [-1.27, -0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.01 (P < 0.0001)								
Total (95% CI)			**217**			**206**	**100.0%**	**-0.57 [-0.86, -0.28]**
Heterogeneity: Tau² = 0.07; Chi² = 10.30, df = 5 (P = 0.07); I² = 51%								
Test for overall effect: Z = 3.81 (P = 0.0001)								
Test for subgroup differences: Chi² = 1.53, df = 2 (P = 0.46), I² = 0%								

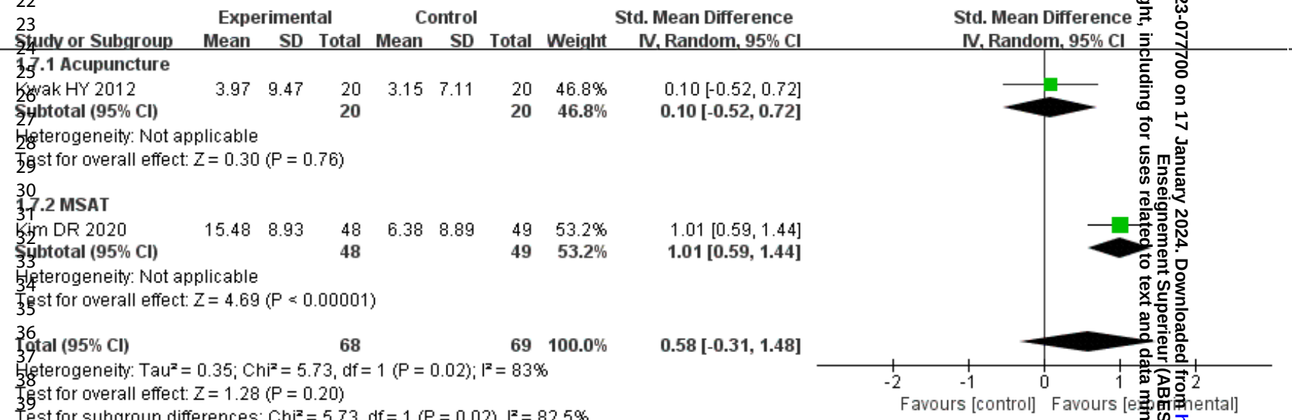




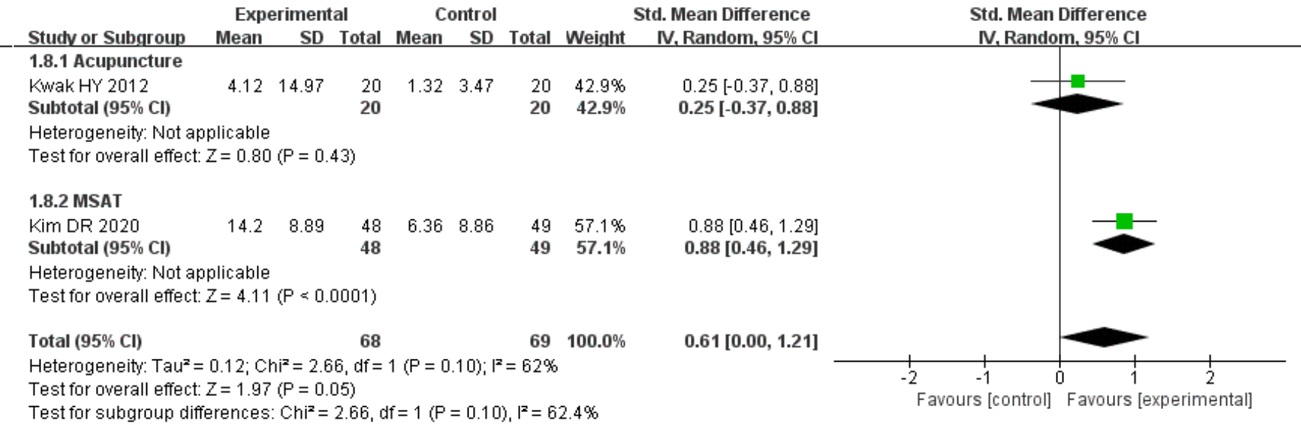
(A) Flexion



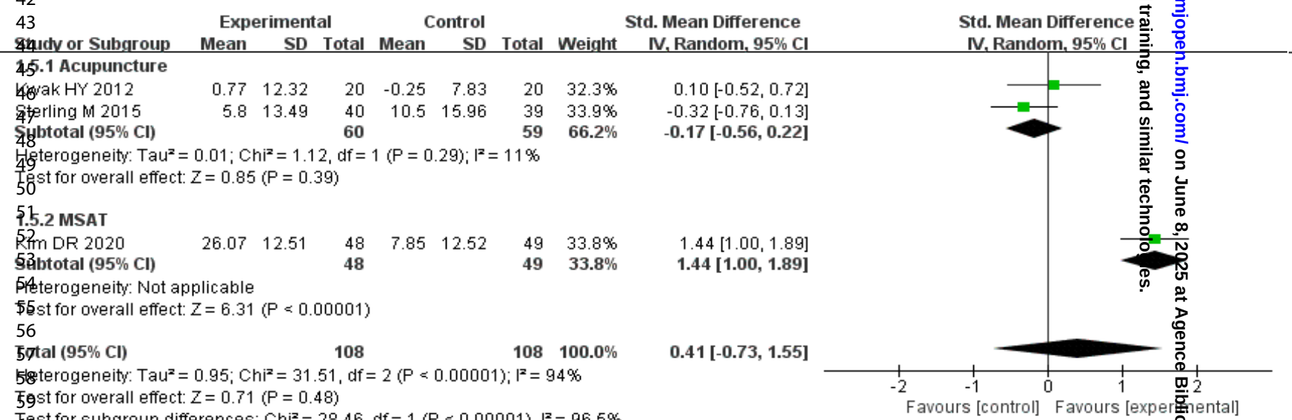
(B) Extension



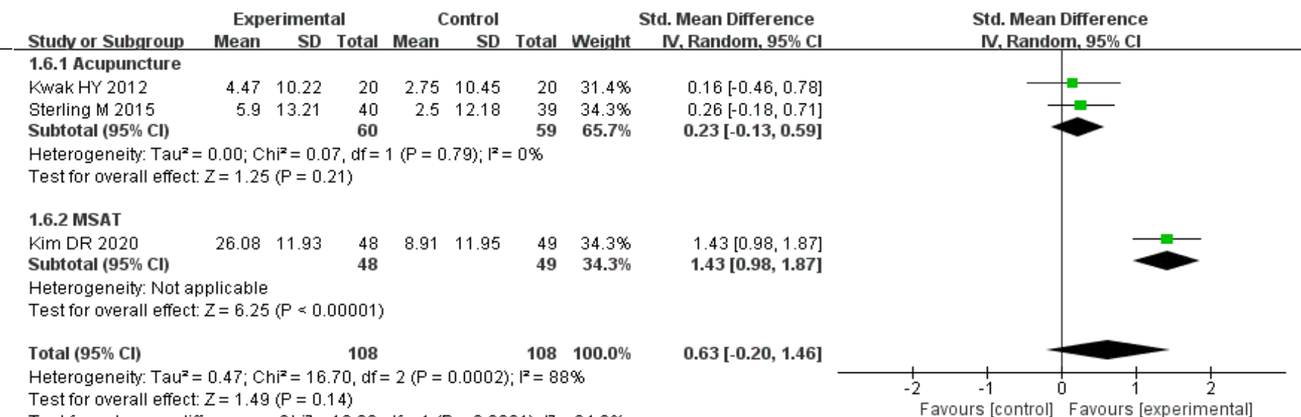
(C) Right lateral flexion



(D) Left lateral flexion



(E) Right rotation



(F) Left rotation

Supplemental table S1. Search strategy and terms used

Database: PubMed (pubmed.ncbi.nlm.nih.gov; 1946-2023)		
No.	Search strategy	Results
#1	whiplash OR acute whiplash injury* OR acute whiplash associated disorder* OR acute WAD OR acute whiplash associated disorder* II OR acute WAD II OR whiplash associated disorder* OR WAD OR whiplash associated disorder* II OR WAD II, OR whiplash OR whiplash injury* OR whiplash patient* OR whiplash syndrome* OR cervical spine disorder* OR cervical spine injury* OR "Accidents, Traffic" [Mesh] OR (("Motor Vehicles"[Mesh:NoExp] OR "Automobiles"[Mesh] OR "Motorcycles"[Mesh] OR traffic[tiab] OR vehicle[tiab] OR vehicular[tiab] OR car[tiab] OR cars[tiab] OR automobile[tiab] OR automobiles[tiab] OR motorcycle[tiab] OR motorcycles[tiab] OR taxi[tiab] OR cab[tiab] OR road[tiab] OR pedestrian[tiab] OR pedestrians[tiab]) AND (accident[tiab] OR accidents[tiab] OR injury[tiab] OR injuries[tiab] OR crash[tiab] OR crashes[tiab] OR "Wounds and Injuries"[Mesh] OR "injuries"[Subheading])) AND (cervic* OR thoracic* OR lumba*)	24,250
#2	acupuncture	42,653
#3	electroacupuncture	7,448
#4	acupressure	1,832
#5	((((((((((((((((((((((meridian) OR acupoint) OR acupuncture [mh]) OR acupuncture Analgesia [mh]) OR acupuncture Therapy [mh]) OR acupuncture points [mh]) OR acupuncture, ear [mh]) OR acupuncture [Text Word]) OR acupressure [Text Word]) OR electroacupuncture) OR electro acupuncture) OR electro-acupuncture) OR meridian* [Text Word]) OR needling [Text Word]) OR acu-point*) OR acu point* [Text Word]) OR acupoint* [Text Word]) OR Acupuncture [mh]) OR electroacupuncture [mh]) OR acupuncture* [Text Word]) OR elctroacupuncture* [Text Word]) OR (acupuncture AND th[sh])) OR acupuncture[tiab]) OR acupuncture[mh]) OR acupuncture/th[mh]	51,277
#6	#2 or #3 or #4 or #5	54,150
#7	#1 and #6	89
Database: Ovid Medline (ovidsp.ovid.com; 1946-2023)		
1	exp Whiplash Injuries/	3,423
2	whiplash.tw.	3,292
3	acute whiplash injury*.tw.	75
4	acute whiplash associated disorder*.tw.	71
5	acute WAD.tw.	66
6	WAD.tw.	1,038

7	whiplash patient*.tw.	201
8	whiplash syndrome*.tw.	183
9	cervical spine disorder*.tw.	228
10	cervical spine injury*.tw.	1,571
11	exp Accidents, Traffic/	48,509
12	exp Motor Vehicles/	24,289
13	exp Automobiles/	7,798
14	exp Motorcycles/	2,900
15	traffic.tw.	58,851
16	vehicle.tw.	134,582
17	vehicular.tw.	4,046
18	car.tw.	36,938
19	cars.tw.	9,562
20	automobile.tw.	6,526
21	automobiles.tw.	1,392
22	motorcycle.tw.	3,814
23	motorcycles.tw.	931
24	taxi.tw.	1,261
25	cab.tw.	3,755
26	road.tw.	48,507
27	pedestrian.tw.	5,278
28	pedestrians.tw.	3,859
29	accident.tw.	53,887
30	accidents.tw.	48,861
31	injury.tw.	801,932
32	injuries.tw.	254,612
33	crash.tw.	11,757
34	crashes.tw.	9,905
35	exp "Wounds and Injuries"/	1,014,422
36	or/29-35	1,675,831
37	or/11-28	298,607
38	or/1-10	6,385

39	36 and 37	79,754
40	38 or 39	84,652
41	acupuncture.mp.	34,547
42	electroacupuncture.mp.	7,050
43	acupressure.mp.	1,813
44	meridian.mp.	4,833
45	acupoint.mp.	4,164
46	exp acupuncture/	2,043
47	acupuncture.tw.	27,126
48	acupressure.tw.	1,523
49	electro acupuncture.mp.	951
50	meridian*.tw.	6,456
51	needling.tw.	3,936
52	acu-point*.mp.	33
53	acu point*.tw.	33
54	acupoint*.tw.	7,040
55	elctroacupuncture*.tw.	1
56	(acupuncture and th).mp.	79
57	or/41-56	44,775
58	40 and 57	120
Database: Embase (embase.com; 1947-2023)		
1	'automobiles'/exp	11,661
2	'motor vehicle'/exp	28,069
3	'accident, traffic'/exp	75,665
4	'motorcycle'/exp	3,664
5	vehicle:ta,ab,de	203,388
6	traffic:ta,ab,de	153,433
7	vehicular:ta,ab,de	4,909
8	car:ta,ab,de	77,435
9	cars:ta,ab,de	12,857
10	automobile:ta,ab,de	7,368
11	automobiles:ta,ab,de	1,524

12	motorcycle:ta,ab,de	5,934
13	motorcycles:ta,ab,de	1,104
14	taxi:ta,ab,de	1,535
15	cab:ta,ab,de	5,070
16	road:ta,ab,de	48,308
17	pedestrian:ta,ab,de	7,726
18	pedestrians:ta,ab,de	4,183
19	accident:ta,ab,de	593,740
20	accidents:ta,ab,de	56,438
21	injury:ta,ab,de	1,928,938
22	injuries:ta,ab,de	280,812
23	crash:ta,ab,de	12,698
24	crashes:ta,ab,de	10,253
25	'wounds and injuries'/exp	2,824,750
26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	3,658,250
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	427,543
28	#26 AND #27	136,545
29	acupuncture	65,725
30	electroacupuncture	10,710
31	acupressure	3,180
32	acupoint	6,816
33	acupoint:ta,ab,de	6,154
34	'acupuncture analgesia'	2,374
35	'acupuncture therapy'	2,500
36	'acupuncture points'	2,351
37	'acupuncture, ear'	42
38	acupuncture:ta,ab,de	56,629
39	acupressure:ta,ab,de	3,077
40	electroacupuncture	10,710
41	'electro acupuncture'	1,442
42	meridian*:ta,ab,de	9,056

43	needling:ta,ab,de	5,115
44	'acu point*'	50
45	acu AND point*:ta,ab,de	968
46	acupoint*:ta,ab,de	9,351
47	'acupuncture'/exp	57,828
48	'electroacupuncture'/exp	9,355
49	acupuncture*:ta,ab,de	56,660
50	electroacupuncture*:ta,ab,de	10,236
51	acupuncture.:ta,ab,de	56,629
52	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	77,464
53	#28 AND #52	211
Database: The Cochrane Library (thecochranelibrary.com; -2023)		
#1	whiplash	589
#2	acute whiplash injury*	139
#3	acute whiplash associated disorder*	97
#4	acute WAD	113
#5	acute whiplash associated disorder* II	37
#6	acute WAD II	44
#7	whiplash associated disorder*	297
#8	WAD	382
#9	whiplash associated disorder* II	69
#10	WAD II	76
#11	whiplash patient*	426
#12	whiplash syndrome*	98
#13	cervical spine disorder*	605
#14	cervical spine injury*	623
#15	MeSH descriptor: [Accidents, Traffic] explode all trees	547
#16	MeSH descriptor: [Motor Vehicles] explde all trees	361
#17	MeSH descriptor: [Automobiles] this term only	77
#18	MeSH descriptor: [Motorcycles] this term only	35
#19	traffic:ti,ab,kw	2,624

#20	vehicle:ti,ab,kw	8,257
#21	vehicular:ti,ab,kw	56
#22	car:ti,ab,kw	4,202
#23	cars:ti,ab,kw	463
#24	automobile:ti,ab,kw	1,157
#25	automobiles:ti,ab,kw	95
#26	motor cycle*:ti,ab,kw	1,169
#27	taxi*:ti,ab,kw	260
#28	cab*:ti,ab,kw	11,113
#29	road*:ti,ab,kw	2,087
#30	pedestrian*:ti,ab,kw	231
#31	accident*:ti,ab,kw	25,630
#32	injur*:ti,ab,kw	76,691
#33	crash*:ti,ab,kw	773
#34	MeSH descriptor: [Wounds and Injuries] explode all trees	35,004
#35	Any MeSH descriptor in all MeSH products and with qualifier(s): [injuries - IN]	3,961
#36	cervic$ or thoracic$ or lumba$	33,603
#37	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	1,770
#38	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30	28,521
#39	#31 or #32 or #33 or #34 or #35	112,456
#40	#38 and #39	4,739
#41	#37 or #40	6,352
#42	#41 and #36	429
#43	acupuncture	21,079
#44	electroacupuncture	3,539
#45	acupressure	2,174
#46	meridian	1,465
#47	acupoint	3,749
#48	MeSH descriptor: [acupuncture] explode all trees	713
#49	MeSH descriptor: [acupuncture Analgesia] explode all trees	339
#50	MeSH descriptor: [acupuncture Therapy] explode all trees	6,467

#51	MeSH descriptor: [acupuncture points] explode all trees	2,520
#52	MeSH descriptor: [acupuncture, ear] explode all trees	244
#53	acupuncture:ti,ab,kw	19,015
#54	acupressure:ti,ab,kw	2,062
#55	electro acupuncture	1,023
#56	electro-acupuncture	783
#57	meridian*:ti,ab,kw	1,399
#58	needling:ti,ab,kw	3,062
#59	acu-point*	43
#60	acu point*:ti,ab,kw	257
#61	acupoint*:ti,ab,kw	5,508
#62	MeSH descriptor: [electroacupuncture] explode all trees	1,161
#63	elctroacupuncture*:ti,ab,kw	4
#64	acupuncture AND th	1,248
#65	#43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64	26,713
#66	#42 and #65	40
Database: China National Knowledge Infrastructure (CNKI) (cnki.net; 1993-2023)		
1	(SU='traffic accident' OR SU='交通事故' OR SU='whiplash injury' OR SU='颈椎屈伸损伤' OR SU='whiplash associated disorder' OR SU='挥鞭样损伤' OR SU='cervical spine disorder' OR SU='颈椎功能紊乱' OR SU='cervical spine injury' OR SU='颈椎损伤') AND (SU='acupuncture' OR SU='針' or SU='electro acupuncture' OR SU='电針' OR SU='meridian' OR SU='经穴' or SU='acupoint' or SU='acupuncture-ear' OR SU='耳针')	54
Database: ScienceOn (scienceon.kisti.re.kr; 2001-2023)		
1	전체=(교통사고 | 편타성 손상 | 채찍질 손상 | 경항통 | 경추부 염좌) AND 전체=(침 | 전침 | 경혈 | 이침)	61
Database: KMBASE (kmbase.medric.or.kr; 1985-2023)		
1	[ALL=교통사고]	864

2	[ALL=편타성 손상]	25
3	[ALL=채찍질 손상]	0
4	[ALL=경항통]	89
5	[ALL=경추부 염좌]	4
6	[ALL=침]	14,195
7	[ALL=전침]	377
8	[ALL=이침]	80
9	[ALL=경혈]	326
10	(((([ALL=교통사고] OR [ALL=편타성 손상]) OR [ALL=채찍질 손상]) OR [ALL=경항통]) OR [ALL=경추부 염좌])	946
11	((([ALL=침] OR [ALL=전침]) OR [ALL=이침]) OR [ALL=경혈])	14,801
12	(((([ALL=교통사고] OR [ALL=편타성 손상]) OR [ALL=채찍질 손상]) OR [ALL=경항통]) OR [ALL=경항통]) AND ((([ALL=침] OR [ALL=전침]) OR [ALL=이침]) OR [ALL=경혈]))	48
Database: Korean Studies Information Service System (KISS) (kiss.kstudy.com; 1993-2023)		
1	교통사고 and 침	126
2	교통사고 and 전침	4
3	교통사고 and 이침	0
4	교통사고 and 경혈	0
Database: Korea Med (koreamed.org; 1992-2023)		
1	((((("traffic"[ALL])) OR ("automobile"[ALL])) OR ("whiplash injury"[ALL])) OR ("whiplash associated disorder"[ALL])) OR ("cervical spine disorder"[ALL])) OR ("cervical spine injury"[ALL])	1,706
2	((("acupuncture"[ALL])) OR ("electroacupuncture"[ALL])) OR ("meridian"[ALL])) OR ("acupoint"[ALL])	553
3	#1 AND #2	22

Database: Oriental Medicine Advanced Searching Integrated System (OASIS) (oasis.kiom.re.kr; 1963-2023)		
1	교통사고 침	1
2	교통사고 전침	4
3	교통사고 이침	0
4	교통사고 경혈	0
Database: Research Information Sharing Service (RISS) (riss.kr; 1988-2023)		
1	전체 : 교통사고 <AND> 전체 : 침	92
2	전체 : 교통사고 <AND> 전체 : 전침	4
3	전체 : 교통사고 <AND> 전체 : 이침	0
4	전체 : 교통사고 <AND> 전체 : 경혈	1

Supplemental table S2. Appraisal of acupuncture procedure based on the revised SRICTA criteria (2010)

First author (year)	Type of acupuncture	Acupoints	Depth of needling	Stimulation response	Total sessions	Frequency and Retention
Sterling et al (2015)	General acupuncture	Posterior muscles of the cervical spine and upper thoracic spine	NR	Pecking, Twirling	6	Frequency: 2 times/week X 3 weeks Retention: 30 minute
Tobbackx et al (2012)	General acupuncture	Choose from GV14, C1-C7, GB20, SI11, GB21, TE15, SI14, BL17, SP10, SI3, BL64, TE5, GB41, Shiqizhuixia, Ear Zero point, Ear Jerome point, Ear C0.	NR	Deqi sensation	1	Frequency: 1 time/week X 1 week Retention: 20 minute
Kwak et al (2012)	General acupuncture	SI2, SI3, SI5, SI7, SI14, SI15, LI11, BL10, BL12, BL13, BL14, BL60, BL62, BL66,	1.0-2.0 cm	Deqi sensation, Rotating	6	Frequency: 3 times/week X 2 weeks Retention: 15 minute

		GB20, GB21, GB40, GB41, TE5, TE15				
Tough et al (2010)	General acupuncture	Myofascial trigger points in muscles in and around the neck	NR	Pecking (6-7 times/s)	2-6	Frequency: 1 time/week X 2-6 times Retention: NR
Aigner et al (1998)	General acupuncture	TB5, SI6 bilaterally	NR	NR	NR	NR
Han et al (2011)	Electroacupuncture	ST25, GB20, GB21, SI11, SI14, SI15, Ashi points	1.0-2.0 cm	Electrical frequency: 300 Hz	8	Frequency: 2 times/week X 4 weeks Retention: 15 minute
Cameron et al (2011)	Electroacupuncture	GB39, GB20, LI14, SI6 bilaterally	1.0-1.5 cm	Electrical frequency: 2-5 Hz Electrical intensity: 1.5 volts	12	Frequency: 2 times/week X 6 weeks Retention: 20 – 60 minutes
Kim et al (2020)	MSAT	3 points at trapezius muscle	0.5-1.0 cm	NR	6	Frequency: 2 times/day X 3 days Retention: 15 minute

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture; MSAT: Motion-style acupuncture treatment; NR: Not reported

Supplemental table S3. The "leave-one-out" approach for sensitivity analysis of whiplash-associated disorder

Study omitted	Pooled estimate	95% Confidence interval		p-value	I^2(%)
		Lower	Upper		
Pain VAS score					
Kwak HY 2012	-0.54	-0.87	-0.21	0.001	59
Tobbackx Y 2012	-0.65	-0.96	-0.35	<0.0001	44
Tough EA 2010	-0.55	-0.87	-0.22	0.001	59
Cameron ID 2011	-0.65	-1.01	-0.29	0.0005	53
Han SY 2011	-0.47	-0.84	-0.11	0.01	61
Kim DR 2020	-0.45	-0.81	-0.10	0.01	53
ROM – flexion					
Kwak HY 2012	0.33	-0.59	1.26	0.48	89
Sterling M 2015	0.43	-0.37	1.22	0.29	78
Kim DR 2020	-0.10	-0.46	0.26	0.60	0
ROM – extension					
Kwak HY 2012	0.38	-0.19	0.96	0.19	73
Sterling M 2015	0.69	0.34	1.03	<0.0001	0
Kim DR 2020	0.36	-0.27	0.99	0.26	62
ROM – right rotation					
Kwak HY 2012	0.56	-1.16	2.29	0.52	97
Sterling M 2015	0.79	-0.53	2.11	0.24	92
Kim DR 2020	-0.17	-0.56	0.22	0.39	11
ROM – left rotation					
Kwak HY 2012	0.85	-0.29	1.98	0.15	92
Sterling M 2015	0.81	-0.42	2.05	0.20	90
Kim DR 2020	0.23	-0.13	0.59	0.21	0
NDI					
Sterling M 2015	-0.19	-0.61	0.23	0.37	75

Tobbackx Y 2012	-0.18	-0.59	0.24	0.40	75
Tough EA 2010	-0.11	-0.46	0.25	0.56	71
Cameron ID 2011	-0.29	-0.51	-0.08	0.007	0
Han SY 2011	-0.09	-0.45	0.26	0.61	68
Kim DR 2020	-0.15	-0.56	0.26	0.48	73

VAS: Visual analog scale; ROM: Range of motion; NDI: Neck disability index

Supplemental table S4. Evidence quality assessment according to GRADE

Certainty assessment							No. of patients		Effect	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Experimental	Control	Absolute (95% CI)	Certainty
Pain VAS score										
6	RCT	Not serious	Serious*	Not serious	Not serious	None	217	206	SMD 0.57 lower (1.02 lower to 0.28 lower)	⊕⊕⊕○ Moderate
ROM-flexion										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	108	SMD 0.23 higher (0.41 lower to 0.87 higher)	⊕○○○ Very low
ROM-extension										
3	RCT	Not serious	Serious*	Not serious	Serious‡	None	108	108	SMD 0.47 higher (0.05 higher to 0.89 higher)	⊕⊕○○ Low
ROM-right lateral flexion										

2	RCT	Not serious	Very serious§	Not serious	Very serious†	None	68	69	SMD 0.58 higher (0.3 lower to 1.48 higher)	⊕○○○ Very low
ROM-left lateral flexion										
2	RCT	Not serious	Serious*	Not serious	Very serious†	None	68	69	SMD 0.61 higher (0.01 lower to 1.21 higher)	⊕○○○ Very low
ROM-right rotation										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	108	SMD 0.41 higher (0.73 lower to 1.55 higher)	⊕○○○ Very low
ROM-left rotation										
3	RCT	Not serious	Very serious§	Not serious	Very serious†	None	108	108	SMD 0.63 higher (0.2 lower to 1.46 higher)	⊕○○○ Very low
NDI										
6	RCT	Not serious	Serious*	Not serious	Serious¶	None	237	225	SMD 0.17 lower (0.5 lower to 0.17 higher)	⊕⊕○○ Low

*: Downgraded one level due to inconsistency (I^2, 50–75%)

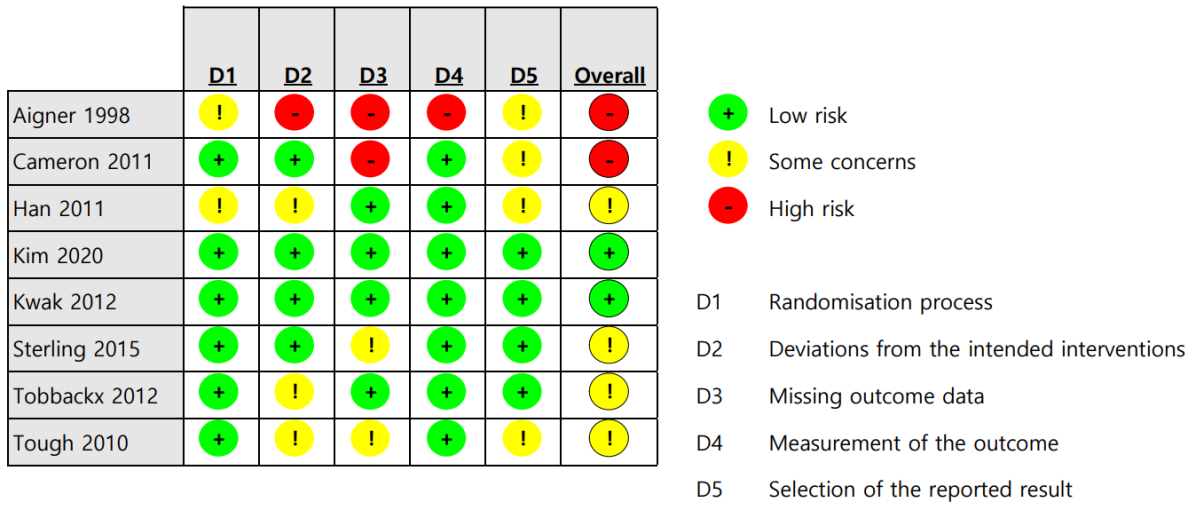
†: Downgraded two levels due to imprecision (fewer than 400 participants and CI overlaps with no effect)

‡: Downgraded one level due to imprecision (fewer than 400 participants)

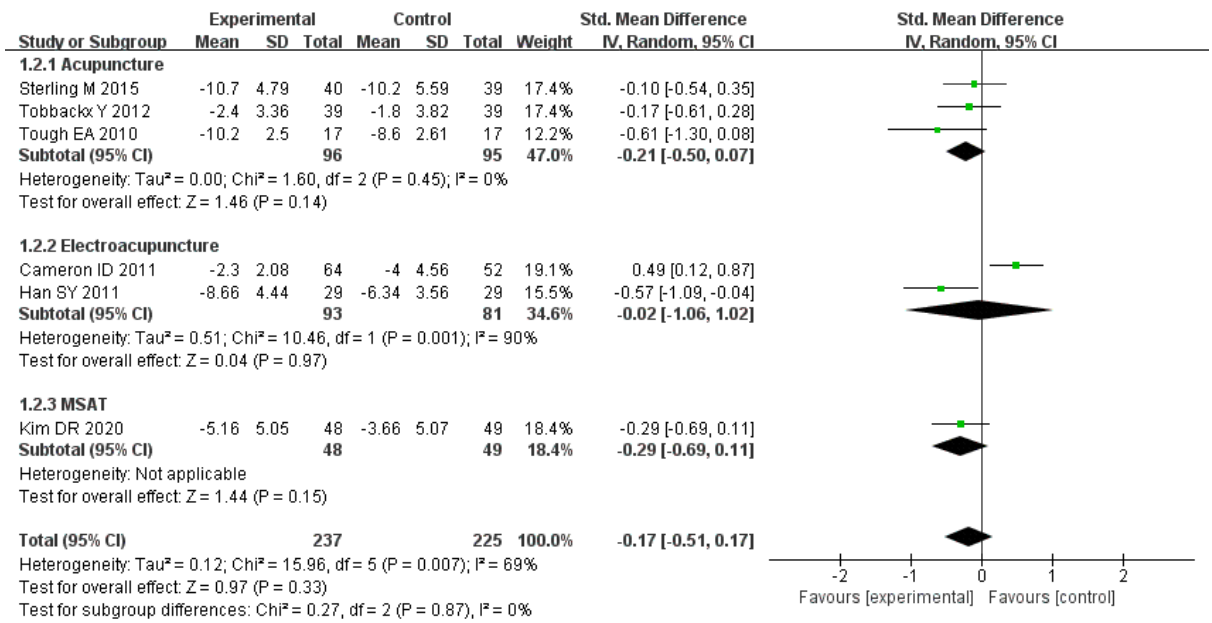
§: Downgraded two levels due to inconsistency (I^2>75%)

¶: Downgraded one level due to imprecision (CI overlaps with no effect)

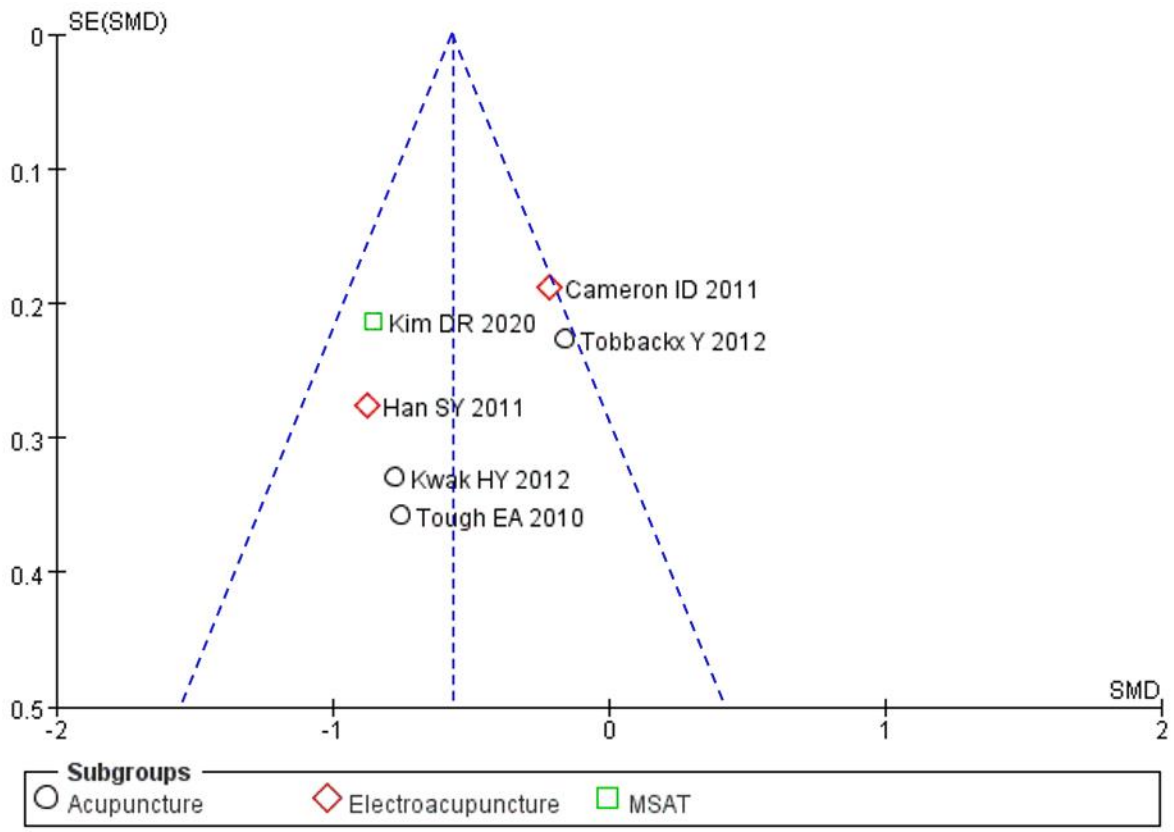
CI: Confidence interval; SMD: Standard mean difference; VAS: Visual analog scale; ROM: Range of motion; NDI: Neck disability index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation



Supplemental figure S1. Individual data of RoB 2



Supplemental figure S2. Forest plot of the meta-analysis for the neck disability index



Supplemental figure S3. Funnel plot for the pain visual analog scale score

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4-5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6 Supple table 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 Supple table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8-9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8-9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8-9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10 Figure 1.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	10 Figure 1.
Study characteristics	17	Cite each included study and present its characteristics.	10 Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	14-15 Figure 2. Supple figure 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	15-16 Figure 3,4. Supple figure 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	15-17 Figure 2,3,4. Supple figure 1,2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	15-16 Figure 3,4. Supple figure 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	16-17 Supple table 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	16-17 Supple table 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	19 Supple figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	17-19 Supple table 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	20-21
	23b	Discuss any limitations of the evidence included in the review.	21-22
	23c	Discuss any limitations of the review processes used.	21-22
	23d	Discuss implications of the results for practice, policy, and future research.	20-22

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	23
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	22-23
Competing interests	26	Declare any competing interests of review authors.	23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	23

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/