Spinal manipulation does not improve short-term pain and function in persons with painful shoulder : a systematic review with meta-analysis

Running head: Spinal manipulation in painful shoulder

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Authors by line: Fabrizio Brindisino, MSc; Fabiola Garzonio BSc; Giuseppe Giovannico, MSc; Francesco Isaia, BSc; Fabio Fiorentino, BSc; Claudia Cavaggion, MSc; Firas Mourad, PhD; Tiziano Innocenti, MSc

Authors Affiliations:

Fabrizio Brindisino PT, MSc, PhD student

Department of Medicine and Health Science "Vincenzo Tiberio", University of Molise c/o Cardarelli Hospital, C/da Tappino 86100 Campobasso, Italy.

ORCID: 0000-0001-8950-8203 e-mail: fabrizio.brindisino@unimol.it

Fabiola Garzonio PT, BSc

Department of Medicine and Health Science "Vincenzo Tiberio", University of Molise c/o Cardarelli Hospital, C/da Tappino 86100 Campobasso, Italy

ORCID: 0000-0001-7265-0692 e-mail: fabiola.garzonio@unimol.it

Giuseppe Giovannico PT, MSC, PhD student

Department of Medicine and Health Science "Vincenzo Tiberio", University of Molise c/o Cardarelli Hospital, C/da Tappino 86100 Campobasso, Italy

ORCID: 0000-0003-2385-6816 e-mail: giuseppe.giovannico@unimol.it

Francesco Isaia PT, BSc

Isaia physical therapy private practice, 91025 Marsala (TP), Italy

e-mail: isaia.fisioterapia@gmail.com

Fabio Fiorentino PT, BSc

Department of Medicine and Health Science "Vincenzo Tiberio", University of Molise c/o Cardarelli Hospital, C/da Tappino 86100 Campobasso, Italy

ORCID: 0000-0003-4112-8732 e-mail: fabio.fiorentino@unimol.it

Claudia Cavaggion PT, MSc, PhD student

Research Group MOVANT, Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium.

ORCID: 0000-0001-8215-342X e-mail: claudia.cavaggion@uantwerpen.be

Firas Mourad PT, MSc, PhD

Department of Physiotherapy, LUNEX International University of Health, Exercise and Sports, 4671 Differdange, Luxembourg.

Luxembourg Health & Sport Sciences Research Institute A.s.b.l., 50, Avenue du Parc des Sports, 4671 Differdange, Luxembourg.

ORCID: 0000-0002-8981-2085 e-mail: firas.mourad@me.com

Tiziano Innocenti PT, MSc, PhD student

Department of Health Sciences, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, The Netherlands

GIMBE Foundation, Via G. Amendola, Bologna, Italy

ORCID: 0000-0003-4696-6989 e-mail: t.innocenti@vu.nl

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Corresponding Author

Fabrizio Brindisino, PT, MSc, PhD student

Via della Libertà, 14, 73023 Lizzanello (Le) Italy

Phone: +39 3208311772

All correspondence should be addressed to Dr Brindisino: fabrizio.brindisino@unimol.it

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Author Contributions

Concept / idea: F. Brindisino, F. Garzonio

Research design: F. Brindisino, F. Garzonio, T. Innocenti

Writing: F. Brindisino, F. Garzonio, G. Giovannico, F. Isaia, F. Fiorentino, C. Cavaggion, F. Mourad, T. Innocenti

Data collection: F. Brindisino, F. Garzonio, G. Giovannico, F. Isaia, F. Fiorentino, C. Cavaggion

Data analysis: F. Brindisino, F. Garzonio, F. Isaia, C. Cavaggion T. Innocenti

Project management: F. Brindisino, F. Garzonio T. Innocenti

Consultation (including review of manuscript before submitting): F. Brindisino, F. Garzonio, G. Giovannico, F. Isaia, F. Fiorentino, C. Cavaggion, F. Mourad, T. Innocenti

Final approval of the Manuscript: F. Brindisino, F. Garzonio, G. Giovannico, F. Isaia, F. Fiorentino, C. Cavaggion, F. Mourad, T. Innocenti

LIST OF ABBREVIATION

CI; Confidence Interval

GRADE; Grading of Recommendations, Assessment, Development, and Evaluation

HVLAT; High-Velocity Low-Amplitude Thrust

MCID; Minimal Clinically Important Difference

NRS; Numeric Rating Scale

PICO; Population, Intervention, Comparison, Outcomes

RCT; Randomized Controlled Trial

RoB; Risk of Bias

SMD; Standardized mean Difference

TENS; Transcutaneous Electrical Nerve Stimulation

VAS; Visual Analogue Scale

ABSTRACT

Purpose: to investigate the benefit of spinal high velocity low amplitude thrust (HVLAT) in improving pain and disability in persons with painful shoulder as primary outcomes. Function, quality of life, persons (and clinicians) satisfaction, adverse events rate, and time for recovery were secondary outcomes.

Methods: A systematic review with meta-analysis was conducted and MEDLINE, CENTRAL, Embase and PEDro until 20th September 2023 were investigated. 2899 records were retrieved and 9 studies were included. Risk of Bias of included studies was assessed through the Revised Cochrane risk-of-bias tool. The certainty of evidence of the pooled results was graded with GRADE approach.

Results: The analysis included 9 studies (441 persons). The pooled results showed non-significant differences between HVLAT versus sham in pain at pre-post follow-up (MD -0.13, 95%CI -0.60; 0.35; p=0.61, I^2 =0%), and at <4 days follow-up (SMD 0.16, 95%CI -0.16; 0.48; p=0.34, I^2 =23%); in function at <4 days follow-up (SMD -0.29, 95%CI -0.69; 0.11; p=0.16, I^2 = 50%). The certainty of evidence ranged from low to very low.

Conclusion: HVLAT wasn't more effective than sham in improving pain and function at pre-post and at <4 days follow-up. When used as an "add-on technique", HVLAT didn't improve pain nor disability.

Keywords: Disability Evaluation, Physical Therapy Modalities, Shoulder Pain, Musculoskeletal Manipulations

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Implications for rehabilitation

- High velocity low amplitude thrust manipulation is no more effective than sham in improving shoulder pain at pre-post follow-up.
- Clinician should not be recommended to deliver high velocity low amplitude thrust manipulation in subjects with painful shoulder with the purpose of reducing pain intensity.
- However, high velocity low amplitude thrust manipulation should be considered within a multimodal approach to address function in painful shoulder subjects.

INTRODUCTION

Shoulder pain is common among musculoskeletal disorders, being the third most frequent reason for medical assistance in primary care [1] as it negatively affects night rest, daily activities, and sports performance [2]. Lifetime prevalence ranges from 5 to 47%, while annual prevalence from 7 to 67% [3]. Notably, shoulder pain increases with age and is often associated with incomplete resolution of symptoms, as about 40% of persons still reported complaints after 12 months [4]. Moreover, 50% of those who recover will experience a recurrence, often within 1 year, which may include persisting pain and limited range of motion [5]. Considering the high recurrence rate of shoulder pain and the increased life expectancy, it is essential to seek more adequate intervention strategies in the management of this condition.

Early physiotherapeutic conservative treatment is advocated as a first-line strategy to prevent chronic shoulder pain [6], and it is usually delivered in a multimodal package along with manual therapy, exercise, education, stretching, and medications [7, 8]. A multimodal approach has been shown to be useful in the reduction of pain and disability compared to other interventions [9-11].

Dysfunctions and reduced mobility of the thoracic, cervicothoracic and cervical spine have been suggested as predisposing factors, tripling the risk of developing shoulder pain, and being predictors of poor outcomes in shoulder disorders [5, 12]. Furthermore, spine and shoulder movements seem to be connected by the so-called regional interdependence [13, 14]; that is, apparently unrelated impairments in distant anatomical areas may have an influence on the primary symptoms, due to a complex interplay between biomechanical and neurophysiological responses [15, 16]. This concept led clinicians to explore treatments for painful shoulder which go beyond the glenohumeral joint and the subacromial space, namely the manipulation of cervicothoracic regions [13].

Spinal High-Velocity Low-Amplitude Thrust manipulation (HVLAT) is commonly administrated to persons with painful shoulder [17, 18]. It is defined as a rapid and short impulse to vertebral segments commonly accompanied by an audible popping sound, which induces

neurophysiological responses in both the central and the peripheral nervous system, resulting in optimal movement and function recovery and pain reduction [19-21]. From a biomechanical perspective, HVLAT has been observed to reduce short-term stiffness and increase shoulder mobility [22]; in addition, HVLAT has been observed to provide an innervation-related hypoalgesic effect by altering brain and spinal cord sensory processes, which in turn increase pressure pain threshold at sites remote from its application (e.g., thoracic spine manipulation and upper limb pressure pain threshold reduction) [23, 24]. Other studies reported supraspinal neurophysiological effects which were observed by activating specific neural areas implicated with pain, cognitive and affective modulation, related to symptoms reduction and motor performance [15, 21].

Findings regarding the effect of HVLAT manipulation in decreasing pain and disability in in persons with painful shoulder are contradicting[14, 25]. Two previous systematic reviews observed a moderate level of evidence supporting the effectiveness of manual and/or manipulative therapy in persons with painful shoulder. However, which technique and what location (on the spine and extremities) of manual therapy remain to be determined[1, 6]. To date, no studies investigated specifically HVLAT, and its effect is still under debate [10, 26]. In addition, to the best of the authors' knowledge, the two most recent systematic reviews, published in 2017 [17] and in 2018 [27], provided insufficient data to support or refute the contribution of HVLAT in improving shoulder pain and disability. Therefore, the primary purpose of our systematic review was to investigate if in persons with painful shoulder (*P, Population*) HVLAT directed to the thoracic or cervical spine (*I, Intervention*) compared with any other conservative intervention (*C, Comparators*) is effective in reducing pain and disability and in improving function and quality of life, persons (and clinicians) satisfaction, adverse events rate and time to recovery (*O, Outcome*) at short and long term (*T, Timing*), by including Randomized Controlled Trials (RCT) (*S, Study design*).

METHODS

This study is a systematic review with meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement was followed for a clear reporting [28], while the methodological guidance was represented by the Cochrane handbook for systematic review of intervention [29]. For improving clarity, transparency and reproducibility of results, the protocol of this study was prospectively registered on PROSPERO (CRD42022298774).

Searches

The research was conducted in four databases and two trial registers: MEDLINE, Cochrane Library (CENTRAL database), PEDro Database, Embase, and in study registers as Clinicaltrial.gov. In addition, other grey literature sources (e.g. Google Scholar, Conference abstracts) were investigated. The search was performed for studies published up to 1 December 2021, with no language restriction. To be sure that no more studies were published after December 2021, the search was updated to 20 September 2023.

Furthermore, a manual cross-referencing on the reference lists of included articles was performed and further manuscripts of interest were requested from experts in the field. The search used for MEDLINE database aiming to include all potentially eligible studies was reported in **Appendix A.**

Eligibility criteria for inclusion were described below using the PICOTS framework [30].

(P) Participants/population

Participants in the included studies had to meet the following criteria: ≥ 18 years old with painful shoulder, defined as any type of shoulder pain, unrelated to the cervical region, without any macro-instability and which flairs up with shoulder efforts. See detailed population's label description in **Appendix A.**

Exclusion criteria were represented by persons with shoulder fractures or shoulder dislocation (acute or recurrent) in the past year, frozen shoulder (primary and secondary), any previous

shoulder surgery procedure on the involved side (regardless of shoulder pathology), tumours, infections, any systemic disease (e.g. rheumatoid arthritis), history of extended use of corticosteroids and any contraindication to HVLAT.

(I) Intervention(s), exposure(s)

HVLAT directed to any part of cervical or thoracic region defined as “the application of rapid movement to vertebral segments producing joint surface separation, transient sensory afferent input, and reduction in perception of pain that result in intra-articular cavitation, which in turn, is commonly accompanied with an audible pop [31].

As HVLAT is often part of multimodal approach in painful shoulder persons management, it is relevant to include studies with multiple conservative therapies, in which HVLAT could be isolated as main contributor to the observed differences. Notably, studies in which HVLAT was delivered as an “add-on therapy”, only when HVLAT effect could be isolated as sole contributor to the observed differences, were also included. As an example, studies comparing HVLAT plus exercise with exercise alone would be included, whereas studies comparing HVLAT plus exercise with HVLAT alone would not.

(C) Comparator(s)/control

Any type of conservative strategies: any physiotherapy interventions such as manual therapy (manual techniques out of HVLAT such as non-thrust mobilization, massages, mobilization with movement), exercise therapy, education, stretching, physical agents (e.g diathermy, Transcutaneous Electrical Nerve Stimulation (TENS), laser therapy, shockwaves) or medications (oral intake and/or injections) and studies that compare thoracic versus cervical HVLAT techniques. Moreover, sham HVLAT, and no intervention groups were included as comparators. Studies that compared different HVLAT techniques in the same spinal region were excluded because did not fit the aim of this study.

(O) Outcomes

Primary outcomes: shoulder pain intensity and disability; secondary outcomes: function, quality of life, persons (and clinicians) satisfaction, adverse events, recovery time. Comparisons were analysed at short (< 1 month) and medium-long term follow-up (> 1 month).

(T) Timing

Any time of availability of results

(S) Study designs

RCTs considering HVLAT treatment (thoracic and cervical) alone, as “add-on” technique or compared with other conservative therapies were included.

Study selection

Studies retrieved from search strategies were exported to EndNote V.X9 (Clarivate Analytics, PA, USA). Duplicates were checked and removed. Records were moved to Ryyan QCRI online software [32] and two independent reviewers (FI and FG) selected potentially eligible trials according to inclusion/exclusion criteria 1) screening for title and abstract and 2) screening for full-text. Disagreements at any stage of the study selection process were resolved by a third author consultation (FB).

Data extraction

To sort out the included studies and extract data, two independent authors filled out a standardized Excel form (FI and GG); any disagreement was solved by either consensus or consultation with a third review author (FG). The following data were extracted: persons’ characteristics, selection criteria, description of intervention and comparison groups, follow-up periods, outcome measures and results (**Table 1**). To determine the reproducibility of interventions (i.e., the extent to which the intervention can be replicated in practice) we used the TIDieR checklist [33].

When additional data were required, the authors of the original included studies were contacted by mail to obtain the missing data. To prevent selective inclusion of data based on the results, authors used the pre-defined rules described in the protocol.

Risk of bias (quality) assessment

The Risk of Bias (RoB) of the individual studies assessment was performed for all the outcome of interest. Two authors independently assessed the RoB of the included studies by using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (FI and CC) [34]. Any disagreement over the assessment of RoB studies was resolved through discussion with a third author (FB); finally, RoB 2 graph was created through RobVis visualization tool [35].

Aiming to assess the certainty of evidence of pooled results, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach classified evidence as high, moderate, low, or very low quality based on considerations of RoB, consistency, directness, precision, and publication bias [36]. We used GRADEpro GDT to generate the GRADE summary of findings tables [37].

Strategy for data synthesis

A meta-analysis was conducted. We clustered the comparisons into three categories: HVLAT versus sham HVLAT, HVLAT versus exercise and HVLAT plus an intervention versus the same intervention alone (labelled as HVLAT as “add-on”). The statistical heterogeneity was evaluated using the I^2-test and an I^2 value greater than 60% was considered as substantial heterogeneity. When the heterogeneity was greater than 60% [38], we conducted sensitivity analyses (where indicated) to explore the possible sources of heterogeneity. Furthermore, aiming to investigate the variation of effect sizes, prediction intervals were calculated for each pooled result [39].
If the meta-analysis was not appropriate (e.g., unexplained heterogeneity of the included studies), a qualitative synthesis was provided with the information presented in the text and tables. Aiming to get a generalization of pooled results, authors in this paper choose for a random effect model accounting for different sources of variation among included studies with the mean differences as effect size measure for continuous outcomes. Standardized mean differences (SMD) were used if the same outcome was measured with different scales within the same meta-analysis. In particular, we used mean differences for pain pre-post, and SMD for pain and function <4 days and perceived

satisfaction at 2 days. Effectiveness was assessed based on statistical significance and clinical relevance. Statistical significance was based on whether the 95% CI of the between-group effect did not include the null value. Clinical relevance was judged differently depending on the minimal clinically important difference (MCID) of the outcomes measured. We used the threshold 1.5 for pain [40]; while for the other outcomes we used the effect size relating to the SMD [41]. The SMD could be considered as small, medium or large effect size if ranging between 0.2-0.5, 0.5-0.8 and if >0.8 [42], respectively.

We examined publication bias using funnel plots for outcomes for which data from 10 or more studies were available, as suggested by the Cochrane Handbook [43]. Publication bias was also assessed based on clinical trial register analysis, looking for those studies marked as “completed” but with no published results. In case the direction of the outcome scale was different within the same outcome area, this was adjusted accordingly in the forest plot. For example, in the Penn Shoulder Score (pain subscale) a higher score indicates a lower pain level, while in the Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS) for pain a higher score indicates a higher pain level. Therefore, the score of Penn was multiplied by -1.

Where multi-arm trials are reported in a single trial, we included only the arms which compared intervention of interest. For studies containing more than two intervention groups - allowing multiple pairwise comparisons among all possible pairs of intervention groups - we included the same group of participants in the meta-analysis only once. All analyses were performed using Review Manager Version 5.4 software (RevMan; The Cochrane Collaboration, London, UK; http://www.cochrane.org) for statistical analysis. No subgroup analysis was performed.

RESULTS

Two thousand eight hundred and ninety-nine records were retrieved from the search strategies. After removing 555 duplicates, the remaining 2344 records were independently screened for title and abstract by two authors, and 2320 records were excluded. The full text of the remaining 24 records was screened, and 15 papers were excluded (**Appendix B**). The search was updated on the 20th of September 2023 retrieving 219 reports. Of those, 7 full-text were screened (**Appendix B**, from number 16 to 22) but none was included. Nine studies were finally included in this review [25, 44-51]. The PRISMA flowchart details the selection process (**Figure 1**).

Data Extraction

Three RCTs authors [25, 44, 47] were contacted by mail in order to obtain additional information on the final values for the treatment and comparison arms.

Reporting of the performed interventions was summarised in **Appendix C** using the TIDieR checklist.

Risk of Bias assessment

All studies included were rated as high RoB in domain four (RoB in measurement of the outcome), while all but one [51] showed low RoB in domain three (RoB missing outcome data). Most of the included studies showed some concerns in domain five (RoB in the selection of the reported results) and low RoB in domain one (RoB due to randomization process); ratings ranged from low to high RoB in domain two (deviation from the intended intervention) for the included RCTs.

Figures from **2A** to **2D** showed the detailed RoB graphs and RoB plots for the primary outcomes investigated. Figures from **S1A** to **S1E** showed the detailed RoB graphs and RoB plots for the secondary outcomes (**Supplementary materials**).

Publication bias was not suspected since we found no study registration with no published results. Funnel plots were not performed since there were less than 10 studies in each meta-analysis.

Description of included studies

Overall, 441 persons were included, and the samples ranged from 61 [47] to 18 [51] persons. One RCT investigated the effect of cervical HVLAT manipulation versus exercise [44], and six RCTs investigated thoracic versus sham manipulation. Two RCTs [50, 51] included HVLAT in a multimodal approach: one study compared cervicothoracic and thoracic manipulation, shoulder mobilization and exercise versus exercise and shoulder mobilization [51], while the other RCT compared thoracic plus cervicothoracic junction manipulations and exercise versus home exercise [50].

One study administered cervical HVLAT [44], while four studies applied thoracic HVLAT [25, 45-47]. Moreover, two RCTs administered thoracic plus cervicothoracic HVLAT [48, 49] and two RCTs [50, 51] administered cervicothoracic HVLAT as an "add-on" technique with shoulder mobilization and/or exercise. One RCT [25] reported seated and supine manipulation groups. In the included studies, some authors used the DASH and Penn shoulder score for outcome measurement of function [25, 44, 46-50], while other studies used SPADI and SDQ for assessing disability [50, 51]. Authors choose to report data for both techniques in the evidence table **(Table 1)**, but decided to pool data only from the supine manipulation group because this position was also used in the other included studies. Moreover, no long-term data was retrieved and only very short term (< 1 week) was available. Thus, we subclassified short term in "pre-post" effect (e.g. immediate after the end of the treatment) and "<4 days".

HVLAT versus Sham HVLAT

Pain intensity

Five RCTs (271 persons) investigated shoulder pain differences between pre and post HVLAT [45-49]. One study used the VAS scale [45], while the others administered the NRS for pain intensity. Pooled results showed a non-significant difference between groups (mean difference -0.13, 95%CI -0.60; 0.35; p=0.61, I^2 =0%, **Figure 3A**). The certainty of evidence was very low (**Table 2**), and prediction intervals ranged from -0.903 to 0.650.

Four RCTs (201 persons) investigated differences between pre-manipulation and 4 days post HVLAT [25, 47-49]. One RCT uses the pain sub-score of the Penn Shoulder Score [25], while the other three administered the NRS for pain. The pooled results reported a non-significant difference between groups (SMD 0.16, 95%CI -0.16; 0.48; p=0.34, I^2 =23%, **Figure 3B**). The certainty of evidence was rated as very low (**Table 3**) and prediction intervals ranged from -0.857 to 1,180.

Function

No RCT investigated the pre- and post- HVLAT difference in function, while four RCTs investigated the change in function between pre-treatment and <4 days from HVLAT [25, 47-49]. One RCT administered the Disability of the Arm, Shoulder and Hand scale [47], while the other three studies used the Penn Shoulder Score. The pooled results showed a non-significant difference between groups (SMD -0.29, 95%CI -0.69; 0.11; p= 0.16, I^2 = 50%, **Figure 3C**). The certainty of evidence was rated as low (**Table 3**) and prediction intervals ranged from -1.860 to 1.270. Due to the high heterogeneity, a sensitivity analysis was performed (**Appendix D**).

Perceived Satisfaction

Three RCTs investigated persons perceived satisfaction at 48 hours after HVLAT [25, 48, 49]. One RCT used the satisfaction subscore of the Penn Shoulder Score [25], the other two used the GROC for perceived satisfaction. The pooled results showed significant differences in favour of the sham group (SMD -0.41, 95%CI -0.82; -0.01; p=0.05, I^2 =31%, **Figure 3D**). The certainty of evidence was rated as very low (**Table 3**), the effect size as small and prediction intervals ranged from -4.123 to 3.281.

Quality of Life

One RCT [47] with 61 persons assessed quality of life with Western Ontario Rotator Cuff scores between HVLAT and sham treatment and reported not differences between groups (between-

group difference in change score -3.2 95%CI -7.4; 1.1) after 2 days from the intervention, suggesting that HVLAT does not improve shoulder-related quality of life.

Adverse event rate

Three studies [25, 46, 47] investigated about adverse event rate. No adverse effects or worsening of shoulder symptoms following HVLAT or the sham intervention were reported by the participants.

No data for disability and time to recovery were retrieved.

HVLAT versus Exercise

Only one RCT [44] of 51 participants investigated about cervical spine HVLAT and compared it with home exercise and shoulder manipulation. The shoulder manipulation addressed the shoulder joint and not the spine and, as described in the protocol, this group was not of interest for this systematic review. However, Coronado et al. found no between-groups differences in clinical outcomes for both pain intensity ($F_{6,225}$= 1.83, p>0.05) and shoulder function ($F_{6,216}$= 1.372, p>0.05) at 12 weeks.

For this comparison, no data were retrieved for disability, quality of life, persons (and clinicians) satisfaction, adverse event rate and time for recovery.

HVLAT as "add-on" technique

Two RCTs investigated the efficacy of HVLAT as an "add on" technique in persons with painful shoulder [50, 51]. Vinuesa-Montoya et al. [50] compared cervicothoracic and thoracic HVLAT in association with home exercise programme versus home exercise programme-only in 41 persons at 5 weeks follow-up and reported that significant between-group differences were observed in function measured with Disability of Arm, Shoulder and Hand (Z = –2519, p=0.012) favoured manipulation group; however, no differences were achieved for shoulder disability measured by Shoulder Disability Questionnaire (Z = –1.874, p=0.061) or pain intensity (Z = –0.177, p=0.859).

Wrigth et al., [51] investigated the effect of thoracic and cervicothoracic HVLAT with shoulder mobilization and exercise versus shoulder mobilization and exercise at 2 and 4 weeks follow-up in 18 persons. No between-group differences were found at discharge for pain (NRS for Pain difference = -1.0 (95%CI -3.2; 1.2) and disability (Shoulder Pain and Disability Index difference = 2.8 95%CI -21.7; 27.4); moreover, no adverse events to any of the manual therapy procedures or treatment provided to any of the persons were reported.

No data were retrieved for persons (and clinicians) satisfaction and time to recovery.

For a detailed description of the results, please consult **Table 1**.

DISCUSSION

This systematic review with meta-analysis suggested very low to low evidence favouring spinal HVLAT in immediate or within 4 days after treatment pain and function improvement compared to sham. However, perceived satisfaction showed a small but significant effect favouring the sham treatment, but the certainty of evidence was very low. HVLAT compared to exercise or when administered as “add-on” intervention did not show greater improvement in pain or function. HVLAT did not improve quality of life compared to sham.

Only one RCT investigated quality of life and reported no improvement for HVLAT. For all the investigated outcomes, long-term follow-up data could not be collected nor analysed.

The certainty of evidence for pooled outcomes for pain, function and persons’ satisfaction at any follow-up ranged from low to very low due to RoB, limited sample size in the included studies, and heterogeneity.

Overall, a high RoB was found for the included RCTs, making it challenging to trust the evidence. Domain four is related to outcomes measurement and it has proven the most critical, followed by domain two, related to deviation from the intended intervention. In the authors’ opinions, the difficulty to blind the persons (especially when outcomes were collected from the patient-reported outcome measures and the persons were also evaluating their own pain and disability) and the careers (especially when physiotherapists could not be blinded in the treatment delivery) is likely to be the main cause, together with the failure to perform appropriate analysis to estimate the effect of assignment to intervention.

The TIDieR checklist has proven to be a valuable tool for assessing the completeness of intervention reporting in the RCTs. However, its use in the present systematic review highlighted certain areas that merit further discussion. Crucial information (i.e., materials, procedures description, timing, and dose of intervention) was well reported by all the RCTs included, while some data that were not fully reported (i.e., details such as the exact location of the intervention and the methods used to enhance and evaluate adherence rates) were considered less important.

This is because the intervention under review (HVLATs) typically did not involve home exercises or extensive collaboration or adherence from participants.

Notably, in the one study where participant collaboration in a home exercise program was a factor, compliance was encouraged during each intervention session but was not formally monitored. Taking these factors into consideration, it can be reasonably inferred that the interventions described in the majority of clinical trials included in the present study could be accurately reproduced in practice, and readers can rely on the information provided in the meta-analysis results. Additionally, incorporating prediction intervals into the analysis offers an extra layer of insight into the heterogeneity of the outcomes of the procedures.

Both sham and active thoracic thrust manipulation showed comparable improvement in persons-rated outcomes [17]; however, their mechanisms remain mainly speculative. Although sham thoracic HVLAT has been previously reported as believed active intervention [52], the results from RCTs on the efficacy of manual therapy for musculoskeletal disorders have been observed to have limited applicability in real practice [53]. One of the contributing factors could be that touch itself possesses a therapeutic value and specific action mechanisms which led to analgesic, affective and somato-perceptual effects [54]. In addition, RCTs are not able to determine the factors influence on clinical changes; as an example, placebo effects are one of the mechanisms behind HVLAT effectiveness [55] and it would contribute to explain the comparable efficacy observed between sham and active HVLAT [56-58]. That is, although certain HVLAT-related neurophysiological and pain modulation mechanisms appear to be independent from placebo effects [55], contextual factors (e.g., expectation and therapeutic alliance) have been shown to elicit placebo effects and play a role in influencing clinical outcomes [59-61]. More generally, all mediators related to the patient-reported outcome measure (e.g., satisfaction, preferences for HVLAT) are reinforced by rituals and contextual factors, which have the potential to influence overall therapeutic outcomes [54, 62, 63].

Other mechanisms supporting placebo effects in HVLAT procedure should be manual contact, interaction with a healthcare professional, positioning and movement of the persons through spinal range of motion and this is further confirmed by the significantly higher persons satisfaction in the

sham treatment group reported in the present meta-analysis, suggesting that either the sham was very well-delivered or that other factors might play an important role in persons satisfaction after HVLAT. However, since the level of certainty of persons satisfaction was very low, we cannot draw firm conclusions and we should interpret these results with caution.

Another reason could be the design of the available RCTs: the results mainly rely on a traditional construct of HVLAT intervention (e.g., specific technique for specific single target joint) and the tendency to average heterogeneous substrate (e.g., differences in execution and application between professions based on biomechanical rationales) [64]. In addition, HVLAT is typically delivered over several visits in a real clinical setting, which involve multiple thrust manipulations within and between sessions [65, 66]. The use of a single treatment session substantially limits the clinical interpretation of findings concerning the magnitude of effect of HVLAT in persons with painful shoulder.

In fact, the six studies included in the different meta-analyses delivered 1 or more manipulations in 1 or 2 sessions over 1 week period. However, the remaining three studies which were excluded from the data pooling included multiple HVLAT interventions – ranging from 2 to 12 weeks - and therefore they could have been more representative of routine HVLAT use. Therefore, we cannot make any long-term recommendations.

Provided all the above, the results of HVLAT RCTs should be considered with caution.

To the best of the authors' knowledge, this is the first systematic review with a meta-analysis focused only on RCTs which exclusively analyses spinal HVLATs in persons with painful shoulder. Evidence of moderate certainty supported therapeutic exercise as an effective treatment option for both pain and function outcomes in persons with painful shoulder [67], even if the optimal load, repetitions, speed, resistance, and timing were still to be defined. However, HVLAT has also been reported as an option for painful shoulder persons management [18]. Our results suggest that HVLAT versus exercise did not improve pain or function [44]; while when provided as "add-on" technique (e.g. with home exercise programme) function could be improved; however, no significant difference was found for disability or pain [50, 51]. Notably, only two studies investigated

this topic and their results were not pooled because differences in the follow-ups and in the delivered interventions (i.e., one study combined HVLAT with shoulder mobilization). These results could increase the adding value of the “real” HVLAT in a multimodal rehabilitation approach, and when function should be addressed, HVLAT could represent strategy to be considered.

The results of the present study are in line with previous reviews focusing on HVLATs directed at the shoulder and spine [17, 27] and chiropractic care [10, 68] that reported no evidences to support spinal HVLAT for painful shoulder. Our review addresses an unresolved knowledge gap and provide further evidence about the limited benefits of HVLAT in reducing pain and disability in persons suffering from shoulder disorders**.** Our results must be contextualized within the limit of available studies and the lack of knowledge of HVLAT effectiveness and mechanisms [69].

Strength and Limitation of this study

The strengths of this meta-analysis encompass a comprehensive search with no date or language restrictions, standardized methods for assessing the methodological quality of the included studies, appropriate statistical methods, and the GRADE approach. Moreover, prediction intervals were calculated for each outcome. Lastly, an a-priori registered protocol ensured transparency, clarity and reproducibility of this research and compliance with the PRISMA guidelines guaranteed a good reporting.

Even if search strategies were comprehensive and based on the PICOTS (Patients, Intervention, Comparison, Outcome, Time, Study design) approach, we may have skipped some studies of interest.

The high RoB weakens the internal validity of the RCTs included in our systematic review. Considering the low certainty of evidence, due mainly to the high RoB and the small size of the included studies, the conclusions of our systematic review should be interpreted with caution. However, these limitations were strictly attributable to the included studies and not to the present review, but, in turn, these could weaken the certainty of evidence of our results.

Future perspectives

RCTs with low risk of bias should be planned in the future, in order to strengthen the conclusions regarding HVLAT efficacy in persons with painful shoulder. In particular, future meta-research studies could focus about the reporting of intervention in RCT, aiming to assess the robustness of reporting itself and the applicability and repeatability of interventions.

Moreover, to improve the certainty of evidence, pragmatic RCTs should be designed with different HVLAT techniques (including peripherical manipulation) delivered in multiple sessions, reflecting common clinical practice [17]. Short-term effect could also be evaluated with more invasive interventions [1, 67]. Lastly, the additive or synergistic contribution of HVLAT should be evaluated within a multimodal approach.

To better understand the contribution of HVLAT in the conservative management of shoulder pain, future research should also determine the association between of all mediators related to HVLAT and patients-reported outcome measures. More research emphasizing effectiveness rather than efficacy is needed to improve the implementation in clinical practice [53].

Evidence suggests that persons with painful shoulder could improve in about three months; therefore, future research should focus on evaluating the effects in a long-term.

CONCLUSION

It is very uncertain that HVLAT improves pain and function compared to sham immediately after and within 4 days the treatment. Person satisfaction seems to be significantly higher with sham approach but the certainty of evidence is very low. Using HVLAT as an “add-on” to exercise intervention does not seem to add any benefit for pain and disability, but it could be beneficial for functional recovery. Moreover, HVLAT does not seem to improve quality of life compared with sham intervention nor increase adverse event.

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FIGURES

Figure 1: PRISMA flowchart

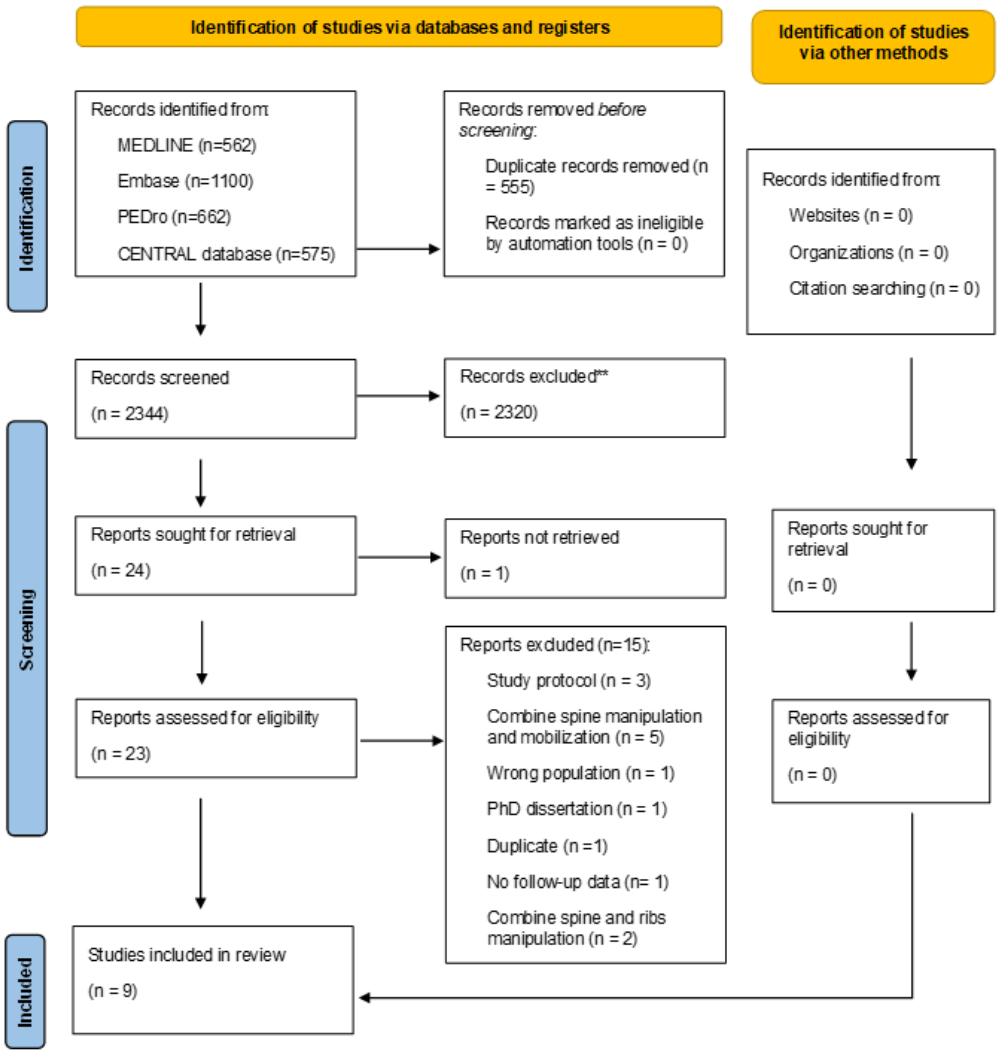
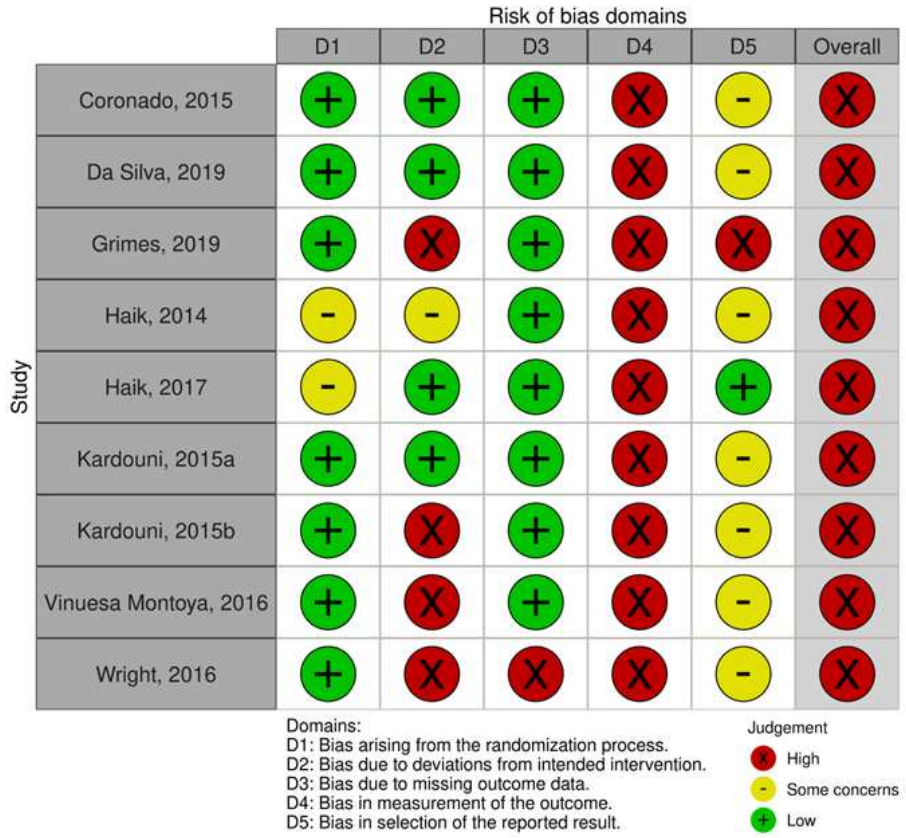
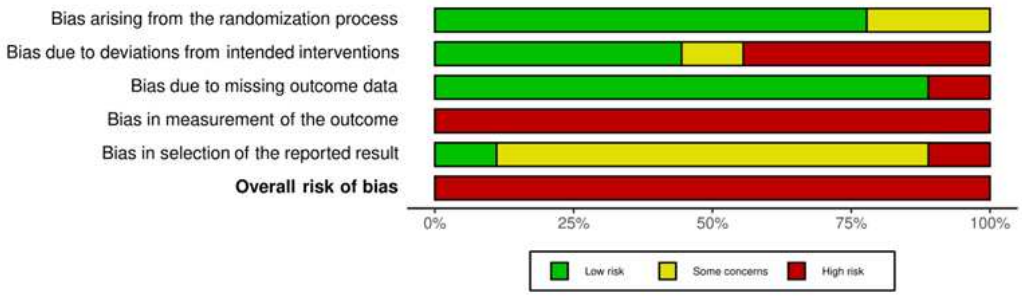


Figure 2: Risk of bias graphs(A), traffic light for pain; (B), RoB plot for pain; (C), traffic light for disability; (D), RoB plot for disability

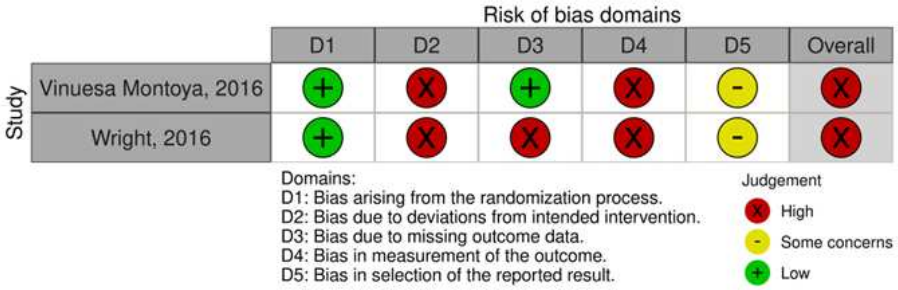
A)



B)



C)


Risk of bias domains
D1
D2
D3
D4
D5
Overall
Study
Vinuesa Montoya, 2016
Wright, 2016
Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.
Judgement
High
Some concerns
Low

D)

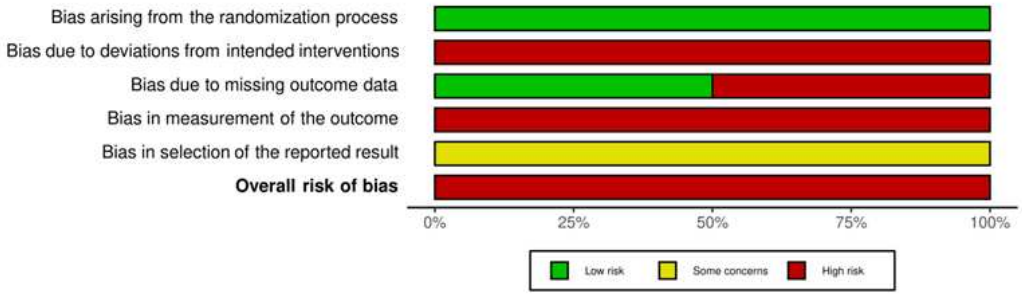
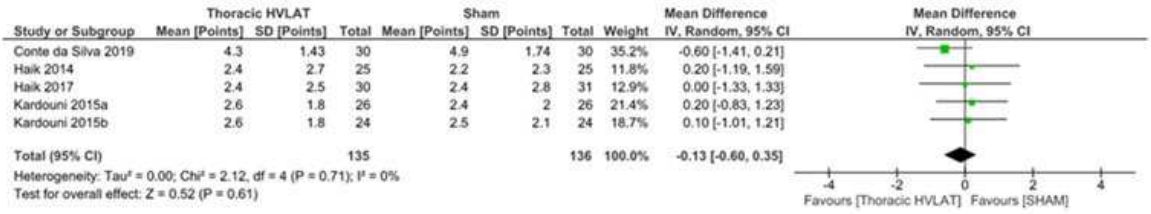

Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
Overall risk of bias
0%
25%
50%
75%
100%
Low risk
Some concerns
High risk

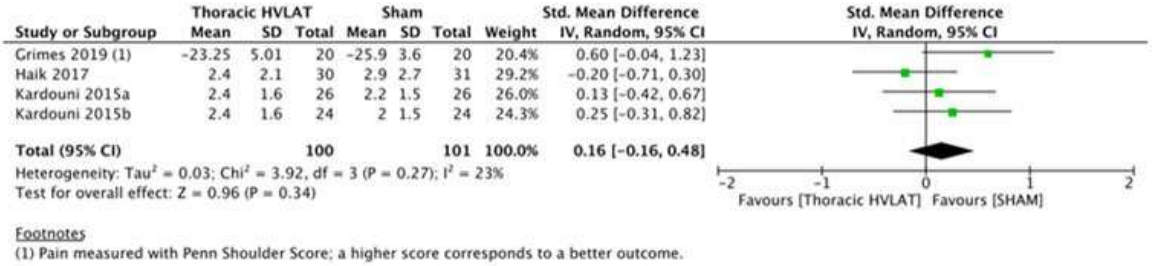
Figure 3: Forest Plots for: (A), pain pre-post; (B), pain <4 days; (C), function <4 days, and (D), perceived satisfaction at 2 days for persons with painful shoulder

Figure 3

A)



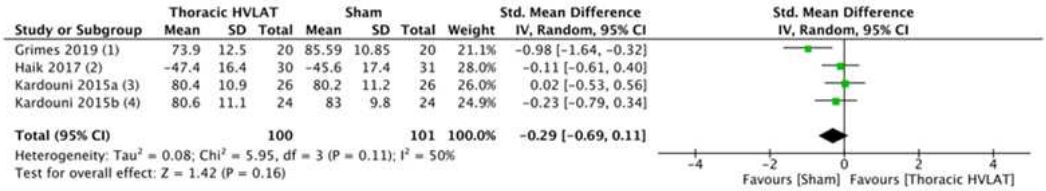
B)



Footnotes
(1) Pain measured with Penn Shoulder Score; a higher score corresponds to a better outcome.

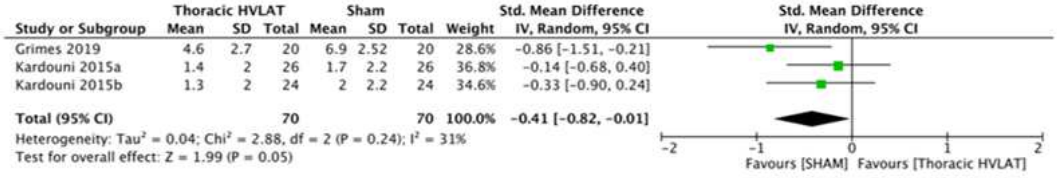
Figure 3

C)



Footnotes
(1) Function measured with Penn Shoulder Score (Functional subscale); a higher score corresponds to a better outcome.
(2) Function measured with DASH Score; a lower score corresponds to a better outcome.
(3) Function measured with Penn Shoulder Score (Functional subscale); a higher score corresponds to a better outcome.
(4) Function measured with Penn Shoulder Score (Functional subscale); a higher score corresponds to a better outcome.

D)



TABLES

Table 1: Table for data extraction

AUTHOR, YEAR, JOURNAL, STUDY DESIGN	PARTICIPANTS (N) INCLUSION/EXCLUSION CRITERIA	INTERVENTION GROUP (IG)	COMPARISON/CONTROL GROUP (CG)	OUTCOME MEASURES, FOLLOW-UP	MAIN RESULTS	FINAL STUDY'S CONCLUSION
Coronado et al, 2015, Journal of orthopaedic and sport physical therapy, Single blind randomized trial [44]	N = 51 *Inclusion criteria* • adult, age 18 - 65 years old • English speaking • primary complaint of unilateral shoulder pain • current episode of shoulder pain < 6 months • current pain ≥ 4/10 NPRS • no traumatic tears *Exclusion criteria* • currently treated in physical therapy for shoulder pain • current complaint of neck pain • history of surgery for shoulder or neck • shoulder pain as a result of traumatic injury • fracture • shoulder instability • frozen shoulder • serious medical condition • signs of cervical nerve root involvement • contraindications for manipulation	N = 26 Cervical thrust manipulation (The person was positioned supine, with the head in a side-flexed and contralateral rotated position. The provider's hands cradled the head, with the hand in contact with the mid cervical region. The technique was performed as a high-velocity, low-amplitude force in a rotation direction on the side of shoulder pain)	N = 25 Home exercise program targeting shoulder region (standard range-of-motion and isometric strengthening exercises designed to address general flexibility and strength impairments of the painful shoulder region)	*Shoulder pain* BPI (baseline, 4, 8, 12 weeks) *Shoulder Function* Penn - function subscale (baseline, 4, 8, 12 weeks)	**BPI** *Cervical Thrust Manipulation. Mean (SD)* Baseline 4.87 (1.89) 4 weeks 3.22 (2.82) 8 weeks 2.62 (2.71) 12 weeks 3.08 (2.75) *Home Exercise Program. Mean (SD)* Baseline 4.16 (2.09) 4 weeks 2.87 (1.99) 8 weeks 3.08 (2.14) 12 weeks 3.32 (2.33) **Penn Shoulder Score** *Cervical Thrust Manipulation. Mean (SD)* Baseline 43.75 (8.13) 4 weeks 47.39 (9.94) 8 weeks 49.55 (9.95) 12 weeks 48.20 (10.93) *Home Exercise Program. Mean (SD)* Baseline 42.21 (9.34) 4 weeks 46.02 (8.34) 8 weeks 44.26 (10.13) 12 weeks 43.96 (12.31)	A time effect was observed for shoulder pain intensity (F3,225 = 41.382, p<0.05): compared to baseline. Similarly, a time effect was observed for shoulder function (F3,216 = 10.43, p<0.05): compared to baseline,
Conte da Silva et al, 2019, Journal of Chiropractic Medicine, Randomized controlled trial quasi-experimental study [45]	N = 60 *Inclusion criteria* • men and women • adult, age 20 - 70 • shoulder pain ≥ 6 months • positive results in 3 of 5 clinical tests indicating signs of rotator cuff tear • agreeing to kinetic-functional evaluation or presenting a medical diagnosis or imaging of the rotator cuff injury • to not take medication containing beta-blockers or anti-inflammatories for at least 1 month • not being in physical therapy treatment • pain ≥ 3 on VAS.	N = 30 Upper thoracic manipulation (Spinal manipulation was performed on the upper thoracic spine, between the fourth and fifth thoracic vertebrae segments. The proposed technique for manipulation is designated prone position)	N = 30 Placebo manipulation (The persons were positioned prone and the hands of the physiotherapist contacted the upper posterior thoracic spinous process. However, at the end of the expiration no thrust on the vertebrae was performed; instead, the therapist maintained physical contact with minimum pressure)	Shoulder pain VAS (pre-intervention, post intervention)	**VAS** *Pre-intervention. Mean (SD)* Upper thoracic manipulation group = 4.90 (1.56) Placebo manipulation group = 5.27 (1.73) Main effect of time = 5.08 (0.21) *Post intervention. Mean (SD)* Upper thoracic manipulation group = 4.30 (1.43) Placebo manipulation group = 4,90 (1.74) Main effect of time = 4.63 (0.20) *Mean Difference (95%CI)* Upper thoracic manipulation group = -0.53 (-1.2; 0.4) Placebo manipulation group = -0.37(-0.48; 1.2) Main effect of time = -0.45 (0.26; 0.64) *p-values* Upper thoracic manipulation group pre/post = 0.38 Placebo manipulation group pre/post = 0.38	There was a main effect of time (p<0.01; F = 23.02) with a statistically significant reduction in shoulder pain in both groups after the intervention (mean difference of 0.53 cm and effect size = 0.36 for manipulation group; mean difference of 0.37 cm and effect size = 0.14 for placebo manipulation group)

	Exclusion criteria • Clinical signs of complete rotator cuff tear (drop arm test positive) • history of shoulder surgery • any absolute contraindication to manipulation indicated by red flags • spinal pain complaints (thoracic region) • heart transplant, pacemaker • history of surgery or trauma to the spine • pregnant women • neurological disease • visual or hearing impairment				Main effect of time pre/post <0.01	
Grimes et al, 2019, Journal of orthopaedic and sport physical therapy, Randomized clinical trial [25]	N = 60 *Inclusion Criteria* • adults, age 18 - 65 years old • shoulder pain ≤ 6 months • have ≥ 3 of the following findings: pain localized to the proximal anterolateral shoulder region, positive Neer or Hawkins-Kennedy test, pain with active shoulder elevation, AROM shoulder abduction ≥ 90°, PROM shoulder external rotation ≥ 45°, pain with isometric resisted abduction or external rotation *Exclusion Criteria* • complete rotator cuff tear • significant loss of glenohumeral motion • acute inflammation • cervical spine-related symptoms • signs of central nervous system, cervical nerve root or cervical radiculopathy involvement • previous neck or shoulder surgery • shoulder instability • history of shoulder fracture • history of nerve injury affecting upper extremity function • contraindication for thrust manipulation • fear or unwillingness to undergo to spinal manipulation	N = 40 Thoracic spine thrust manipulation N = 20 manipulation with person supine (The person lie down supine and the physiotherapist used his body to push down through the participant's upper arms to provide a high-velocity, low-amplitude thrust in the anterior-to-posterior direction) N = 20 manipulation with person seated (The person was seated anf the physiotherapist applied a high-velocity, low-amplitude distraction thrust in a cephalad direction)	N = 20 Sham manipulation group (The sham technique was performed in the same manner as the seated manipulation, moving the participant through the same motion but delivering no manipulative thrust)	Self-reported pain, satisfaction and function by Penn Shoulder Score (baseline and 48 hours after intervention)	**Penn Shoulder Score** **Pain category** *Supine manipulation group (n = 20). Mean (SD)* baseline 18.70 (4.37) 48 hours post intervention 23.25 (5.01) change 4.55 (3.38) *Seated manipulation group (n = 20). Mean (SD)* baseline 19.70 (4.88) 48 hours post intervention 23.85 (6.07) change 4.15 (4.43) *Sham manipulation group (n = 20). Mean (SD)* baseline 20.40 (3.91) 48 hours post intervention 25.90 (3.60) change 5.50 (3.41) **Function category** *Supine manipulation group (n = 20). Mean (SD)* baseline 43.84 (7.47) 48 hours post intervention 46.10 (7.46) change 2.26 (3.15) *Seated manipulation group (n = 20). Mean (SD)* baseline 44.66 (8.62) 48 hours post intervention 48.64 (10.24) change 3.98 (7.97) *Sham manipulation group (n = 20). Mean (SD)* baseline 48.42 (6.47) 48 hours post intervention 52.84 (5.71) change 4.42 (5.41) **Satisfaction category** *Supine manipulation group (n = 20). Mean (SD)* baseline 3.70 (2.72) 48 hours post intervention 4.55 (2.72) change 0.85 (2.03) *Seated manipulation group (n = 20). Mean (SD)* baseline 4.80 (2.19) 48 hours post intervention 5.85 (3.31) change 1.05 (2.91) *Sham manipulation group (n = 20). Mean (SD)* baseline 4.65 (2.82) 48 hours post intervention 6.85 (2.52) change 2.20 (2.82)	Seated vs supine manipulation for individuals with shoulder pain did not have a superior effect on self-reported pain, function, and satisfaction or on changes in impairments in scapular motion, shoulder isometric muscle force production, or pectoralis minor muscle length when compared to a sham manipulation treatment.

					Total score *Supine manipulation group (n = 20). Mean (SD)* baseline 66.24 (11.62) 48 hours post intervention 73.90 (12.50) change 7.66 (6.87) *Seated manipulation group (n = 20). Mean (SD)* baseline 69.16 (12.40) 48 hours post intervention 78.34 (17.56) change 9.18 (12.64) *Sham manipulation group (n = 20). Mean (SD)* Baseline 73.47 (10.48) 48 hours post intervention 85.59 (10.85) change 12.12 (8.98) No significant differences were reached between groups	
Haik et al, 2014, Journal of orthopaedic and sport physical therapy, Randomized controlled trial with immediate follow-up [46]	N = 50 <u>*Inclusion Criteria SIS*</u> persons with ≥ 3 of the following findings: • positive Neer test • positive Hawkins test • positive Jobe test • pain with passive or isometric resisted shoulder external rotation • pain with active shoulder elevation • pain with palpation of rotator cuff tendons • pain in the C5 or C6 dermatome region • persons had to be able to reach to at least 150° of arm elevation, as determined by visual observation <u>*Exclusion Criteria (for all groups)*</u> • red flags • pregnancy • systemic illnesses • physical therapy or manual therapy treatment within 6 months prior to the evaluation • signs of complete rotator cuff tear • acute inflammation • cervicothoracic spine–related symptoms • scoliosis • glenohumeral instability • previous upper extremity fracture • previous shoulder surgery • asymptomatic persons positive for shoulder impingement tests	N = 25 Thoracic manipulation (The person assumed a seated position and the therapist performed a thrust technique. If no cavitation was detected with the manipulation, the thrust was repeated up to 3 times)	N = 25 Sham manipulation (The person assumed the same seated position and the therapist held the person in the same position as that of the thrust manipulation intervention. The therapist applied the same forces as those of a thrust manipulation, while holding the position for a few seconds, without actually performing a thrust manipulation)	Pain NPRS (before and 3 minutes after the intervention) Function DASH and WORC (baseline)	**NPRS** **Pre-intervention.** Mean *(SD)* Manipulation = 3.3 (2.6) Sham = 2.4 (2.4) Main effect of time 2.9 (2.5) **Post intervention.** Mean *(SD)* Manipulation = 2.4 (2.7) Sham = 2.2 (2.3) Main effect of time = 2.3 (2.5) **Mean Difference.** (95%CI) Manipulation = –0.8 (–1.2; –0.5) Sham = –0.2 (–0.6; 0.1) Main effect of time = –0.6 (–0.9; –0.2) ***p*-value** Manipulation/ Sham= 0.11 Main effect of time= 0.004 (Main effect of time was significant within impingement group for the NPRS scores) **Pooled SD** Manipulation = 2.7 Sham = 2.3 Main effect of time = 2.5 **Effect Size Cohen *d*** Manipulation = –0.31 Sham = –0.10 Main effect of time = –0.22 The main effect of time showed a significant decrease (0.6 points) in pain score at post intervention, independent of the intervention applied (F = 8.96, *p*= 0.004). **DASH** **baseline** Mean *(SD)* Manipulation = 26.9 (12.7) Sham = 23.3 (16.5) **WORC** **baseline** Mean *(SD)* Manipulation = 786.4 (397.2) Sham = 731.9 (504.5)	Shoulder pain during elevation and lowering of the arm decreases immediately after a single session of manipulation or sham manipulation directed to the midthoracic spine in persons with shoulder pain. Although a few changes were also observed in scapular kinematics after the manipulation, these were not considered to be clinically relevant. Self-reported shoulder pain in the symptomatic individuals seemed to decrease independently of the intervention applied (manipulation or sham).
Haik et al, 2017,	N = 61 <u>*Inclusion criteria*</u>	N = 30 Thoracic manipulation	N = 31 Sham Thoracic manipulation	Pain NPRS (baseline, pre-intervention, post-intervention, follow up)	**NPRS** *Thoracic manipulation group. Mean (SD)* Baseline = 3.3 (2.4) Pre-intervention = 2.5 (2.4)	Thoracic manipulation does not seem to produce important changes in self-reported shoulder pain during arm

Archives of Physical Medicine and Rehabilitation, Randomized controlled trial [47]	• shoulder pain in the C5 or C6 dermatome region • adults, age 18 - 60 years old • person have ≥ 3 of the following clinical signs for SIS: Neer; Hawkins; Jobe; pain during active elevation in the scapular or sagittal plane and pain or weakness with resisted shoulder external rotation • all individuals had to reach 150° of arm elevation as determined by visual observation <u>*Exclusion criteria*</u> • red flags for spina manipulation • history of shoulder or cervicothoracic spine fracture • history of shoulder or cervicothoracic spine surgery • signs of cervical nerve root or central nervous system involvement • clinical signs of complete rotator cuff tear • adhesive capsulitis • glenohumeral instability • physical therapy treatment within 6 months before the evaluation • analgesic pills within 1 month before the intervention • systemic illness • scoliosis • pregnancy	(Thoracic manipulation was applied in the middle thoracic spine, with the person seated with arms crossed over the chest. The therapist located behind the person and performed a thrust technique with arms and chest around the thoracic region of the persons)	(The positions of the person and therapist were the same and the therapist held the position for few seconds, without performing the thrust)	Function DASH (baseline, pre-intervention, post-interventon, follow up) Quality of life related to the rotator cuff WORC (baseline, pre-intervention, post-intervention, follow up) Follow up explanation: Follow up: baseline; before the first intervention), day 2 preintervention (3e4days after day 1), day 2 postintervention (immediately after the second intervention), and day 3 (follow-up at 3e4days after the second intervention)	Post intervention = 2.4 (2.5) Follow up = 2.4 (2.1) *Sham manipulation group. Mean (SD)* Baseline = 2.7 (2.5) Pre-intervention = 2.4 (2.7) Post intervention = 2.4 (2.8) Follow up = 2.9 (2.7) **Within-group change from baseline (95%CI)/within-group ES (95%CI)** *Thoracic manipulation group* Pre-intervention = -0.7 (-1.3; -0.1)/-0.33 (-0.8; 0.2); p< 0.05 Post-intervention = -0.9 (-1.5; -0.3)/-0.37 (-0.9; 0.1); p< 0.05 Follow up = -0.9 (-1.5; -0.2)/-0.39 (-0.9; 0.1) *Sham manipulation group* Pre-intervention = -0.3 (-0.8; 0.2)/-0.12 (-0.6; 0.4) Post-intervention = -0.3 (-0.8; 0.2)/-0.11 (-0.6; 0.4) Follow up = 0.2 (-0.4; 0.8)/-0.08 (-0.4; 0.6) **Between-group difference in change score (95%CI)/between-group ES (95%CI)** Pre-intervention = -0.4 (-1.0; 0.1)/-0.3 (-0.8; 0.2) Post-intervention = -0.6 (-1.1; 0.0)/-0.4 (-0.9; 0.1) Follow up = -1.1 (-1.7; -0.5) /-0.6 (-1.1; -0.1) **DASH** **Within-group difference from baseline (95%CI)/within-group ES (95%CI)** *Thoracic manipulation group* Pre-intervention = -3.9 (-6.3; -1.6)/-0.3 (0.8; -0.2) Follow up = -4.6 (-7.2; -2.0)/-0.3 (-0.8; 0.2) *Sham manipulation group* Pre-intervention = -1.0 (0.8; -2.9)/-0.05 (-0.5; 0.4) Follow up = -4.7 (-2.1; -7.4)/-0.3 (-0.8; 0.2) **DASH** **Between-group difference in change score (95%CI)/between-group ES (95%CI)** Pre-intervention = -2.9 (-5.1; -0.8)/-0.5 (-1.0; 0.03) Follow up = 0.1 (-2.5; 2.8) /0.01 (-0.5; 0.5) **DASH** **follow up** Mean *(SD)* Manipulation = 47.44 (16.35) Sham = 45.59 (17.40) **Total WORC** **Within-group difference from baseline (95%CI)/within-group ES (95%CI)** *Thoracic manipulation group* Pre-intervention = -4.1 (-8.8; 0.6)/-0.2 (-0.7; 0.3) Follow up = -7.7 (-2.6; -12.8)/-0.4 (-0.9; 0.1) *Sham manipulation group* Pre-intervention = -0.9 (-4.4; 2.5)/0.0 (-0.5; 0.5) Follow up = -2.7 (-6.9; -1.5)/ 0.1 (-0.6; 0.4) **Total WORC** **Between-group difference in change score (95%CI)/between-group ES (95%CI)** Pre-intervention = -3.2 (-7.4; 1.1)/-0.3 (-0.8; 0.2) Follow up = -5.0 (-9.7; - 0.3) /-0.5 (-1.0; 0.0) **WORC** **follow up** Mean *(SD)* Manipulation= 644.17 (493.08)	movement. Improvements in function were observed for both groups. Despite the moderate effect size, DASH questionnaire and WORC scores were not different between groups suggesting that manipulation does not improve shoulder function.

					Sham= 695.37 (569.81)	
Kardouni et al, 2015, (A) Journal of orthopaedic and sport physical therapy, Randomized controlled trial [48]	N = 52 *Inclusion criteria* • pain duration of ≥ 6 weeks • pain intensity ≥ 2/10 NPRS • adults, 18 - 60 years old • Have ≥ 3 of the following 5 clinical signs of subacromial impingement syndrome: positive Hawkins test, positive Neer test, pain during active arm elevation of greater than 60° in the scapular or sagittal plane, positive Jobe/Empty Can test for pain or weakness and pain or weakness with resisted shoulder external rotation with the arm at the side *Exclusion Criteria* • history of shoulder or spine surgery • primary complaint of neck • thoracic signs of central nervous system involvement • signs of cervical nerve root involvement • cervical radiculopathy • contraindications to manipulative therapy • frozen shoulder • primary instability of the shoulder • reproduction of shoulder or arm pain with cervical rotation, axial compression, or Spurling test	N = 26 Thoracic + cervicothoracic manipulation (The thoracic manipulation interventions were applied to the lower, middle, and upper -cervicothoracic junction- thoracic spine. Each technique was applied twice, for a total of 6 thoracic manipulation or sham manipulation applications. During thoracic manipulation, a high-velocity, low-amplitude thrust was applied at the end of the available spinal motion. For the middle and lower thoracic manipulation, the participants were prone, and the thrust was directed in the posterior to anterior direction. For the cervicothoracic junction manipulation, the participants were seated, and the thrust was provided as an axial (cephalad) distraction).	N = 26 Thoracic + cervicothoracic sham manipulation (The sham-manipulation was performed with identical body positioning of both the participant and therapist. The therapist applied minimal pressure to maintain physical contact and “skin lock” with the participant. The therapist followed the participant through the same range of motion, but no manipulative thrust was delivered).	Pain NPRS (baseline, post-intervention, follow up) Function Penn Shoulder Score (baseline, follow up) Self-perceived improvement GROC (follow up) Follow up at 24-48 hours.	**NPRS** *Thoracic manipulation group. Mean (SD)* Pre-treatment = 3.5 (1.4) Post-treatment = 2.6 (1.8) Follow up = 2.4 (1.6) *Sham manipulation group. Mean (SD)* Pre-treatment = 3.6 (1.4) Post-treatment = 2.4 (2.0) Follow up = 2.2 (1.5) **Penn Shoulder Score** *Thoracic manipulation group. Mean (SD)* Pre-treatment = 71.8 (11.1) Follow up = 80.4 (10.9) *Sham manipulation group. Mean (SD)* Pre-treatment = 70.9 (12.5) Follow up = 80.2 (11.2) Scores on the NPRS and the Penn were significantly different in both treatment groups following treatment (p<0.001); but there was no difference in clinical improvement between the groups (NPRS, p=0.735; Penn, p=0.886). **GROC** Thoracic manipulation group. Mean *(SD)* Follow up = 1.4 (2.0) Sham manipulation group. Mean *(SD)* Follow up = 1.7 (2.2)	There were no differences between treatment groups in NPRS or Penn Shoulder Score, with both groups improving in both outcomes following treatment. A *t* test revealed no statistically significant difference in the GROC between the 2 treatment groups (t_{49} = 0.57, *p*= 0.574), with the means in both groups (thoracic SMT, 1.4; sham SMT, 1.7) showing small improvements
Kardouni et al, 2015, (B) Manual Therapy, Randomized controlled study [49]	N = 48 *Inclusion criteria* • pain duration ≥ 6 weeks • pain intensity ≥ 2/10 NPRS • adults 18 - 60 years old • have ≥ 3 of 5 clinical signs of subacromial impingement syndrome: 1) positive Hawkin's Test, 2) positive Neer Test, 3) pain during active elevation >60 in the scapular or sagittal plane, 4) positive Jobe/Empty Can test for pain or weakness, 5) pain or weakness with resisted shoulder external rotation with the arm at the side *Exclusion criteria* • shoulder or cervical or thoracic spine surgery • primary complaint of neck or thoracic pain • signs of central nervous system involvement	N = 24 Thoracic manipulation + cervicothoracic manipulation (The manipulation interventions were applied to the lower thoracic spine, mid thoracic spine, and cervicothoracic junction. Each technique was applied 2 times at each of the 3 regions, for a total of 6 thoracic manipulation or sham thoracic manipulation maneuvers. During administration of the thoracic manipulation, a high velocity, low-amplitude thrust was applied at the end of available spinal motion after the person exhaled. For the mid and lower thoracic manipulation, the participants were prone, and the thrust was directed	N = 24 Sham thoracic + cervicothoracic manipulation (The sham thoracic manipulation was performed with identical body positioning of both the person and therapist. During the sham thoracic manipulation, the therapist maintained manual contact through the range of motion during exhalation, but no manipulative thrust was delivered).	Pain NPRS (baseline, post manipulation, follow up) Function Penn Shoulder Score (baseline, post, follow up) Change in quality of life following treatment GROC (follow up) Follow up 24 – 48 hours post manipulation	**NPRS** *Thoracic manipulation Mean (SD)* Baseline 3.5 (1.4) Post 2.6 (1.8) Follow up 2.4 (1.6) *Sham manipulation Mean (SD)* Baseline 4.0 (1.4) Post 2.5 (2.1) Follow up 2.0 (1.5) NPRS decreased across the groups 1.1 95%CI (0.6; 1.6) points from pre-treatment to post-treatment measures and 1.5 95%CI (0.9; 2.0) points from pre-treatment to the follow up (F=0.0; p-value group = 0.984). There was a main effect for Time for the NPRS (F=15,8; p<0.001), indicating that score improved in both groups from pre-to post-treatment There were no differences between the two groups in pre-treatment to post-treatment changes (Group*time F= 1,3; p=0.278). **Function/disability** **Penn Shoulder Score** *Thoracic manipulation, Mean (SD)* Baseline 71.4 (11.2) Follow up 80.6 (11.1)	Both groups had improved persons rated outcomes following treatment. Since both the sham thoracic manipulation and the thoracic manipulation groups showed improvement in person-rated outcomes, the mechanisms of improvement from manual therapy to the thoracic spine may be independent of the use of a manipulative thrust.

	• signs of cervical nerve root involvement • contraindications to manipulative therapy • adhesive capsulitis • shoulder instability • shoulder or arm pain • with cervical rotation to the ipsilateral side, axial compression, or Spurling's Test.	in the posterior to anterior direction. For the cervicothoracic junction manipulation, participants were seated, and the thrust was an axial (cephalad) distraction).			*Sham manipulation Mean (SD)* Baseline 72.0 (12.1) Follow up 83.0 (9.8) Penn scores improved across the groups 10.1, 95%CI (7.3,12.9) points from pre-treatment to the follow up (F= 0.2; p-value group = 0.627) There was a main effect for Time for the Penn Shoulder Score (F=53.5; p< 0.001), indicating that scores improved in both groups from pre-to post-treatment There were no differences between the two groups in pre-treatment to post-treatments changes, (Group*time F= 0.4, p=0.518). **Change in quality of life following treatment** **GROC** *Thoracic manipulation Mean (SD)* Follow up 1.3 (2.0) *Sham manipulation Mean (SD)* Follow up 2.0 (2.2) no statistically significant difference in the GROC between the two treatment groups, ($t_{(43)}$ = 1.2, p=0.235).	
Vinuesa-Montoya et al, 2017, Journal of Chiropractic Medicine, Randomized clinical trial [50]	N = 41 <u>*Inclusion Criteria*</u> • pain/dysfunction during overhead activities or during active shoulder movements • painful arc of the arm from 60° to 120° of flexion • baseline pain level ≥ 2/11 VAS • unilateral shoulder pain • positive Neer/Hawkins-Kennedy test • recent onset within the last 12 months • non-traumatic onset <u>*Exclusion Criteria*</u> • red flags • frozen shoulder • disorders of the acromioclavicular joint • degenerative arthritis of the glenohumeral joint • calcifying tendonitis (identified by radiograph) • shoulder instability • post traumatic disorders • shoulder surgery • elbow, hand, wrist and cervical primary disorders	N = 21 Cervicothoracic/thoracic manipulation + Home exercise program (A treatment package of manipulation was applied to the lower, middle, and upper cervicothoracic spine. The persons received 5 manipulation techniques on the thoracic spine: technique lift with impulse, high velocity, and low amplitude applied to the midthoracic area, consisting of a manipulation of axial distraction with fulcrum on the thoracic area; dog technique manipulation in flexion applied to (a) the upper thoracic spine (T1-T4), (b) the midthoracic spine (T5-T8), and (c) the low thoracic spine (T9-T12); + home exercise programme)	N = 20 Home exercise program (The protocol of exercises was the following: flexion and extension exercises with arms in front of a wall, shoulder flexion 90°, and pose with hand on healthy shoulder; counter-resistance exercises with elbow flexion 90° and an elastic band; counter-resistance exercises with shoulder flexion 90° and an elastic band; shoulder flexion with elbow extension holding a bar (1-4 kg); shoulder flexed to 90° and elbow extended holding a bar (1-4 kg); body lift from a seated position with elbows extended; exercises for flexion, extension, rotation, and head tilt; and exercises with shoulder circles; for 5 weeks)	Pain VAS (baseline, after the 5 weeks treatment) Function DASH (baseline, after the 5 weeks treatment) Disability SDQ (baseline, after the 5 weeks treatment)	**Pain** **VAS** *Manipulation + exercise group Mean (SD)* Baseline 5.57 (1.46) Post-treatment 4.65 (2.32) p within group = 0.039 within group change score = 0.95 (95%CI 0.02; 1.88) *Home exercise group Mean (SD)* Baseline 5.53 (1.38) Post-treatment 4.56 (2.22) p within group = 0.054 within group change score = 0.81 (95%CI 0.01; 1.62) *Between group change score* = -0.09 (95%CI -1.64; 1.46) After 5 weeks of treatment, no significant between-group differences observed in VAS (Z = -0.177, p= 0.859). Only manipulation + exercise group had a significant improvement in pain intensity. **Function/disability** ***DASH*** *Manipulation + exercise group Mean (SD)* Baseline 61.48 (18.32) Post-treatment 50.55 (18.16) p within group = 0.001 within group change score = 10.70 (95%CI 6.85; 14.54) *Home exercise group Mean (SD)* Baseline 78.21 (17.10) Post-treatment 68.81 (20.48) p within group = 0.036 within group change score =8.75 (95%CI 1.27; 16.22) between group change score = 18.26 (95%CI 5.15; 31.36) **SDQ** *Manipulation + exercise group Mean (SD)* Baseline 62.50 (17.00) Post-treatment 47.19 (17.38) p within group = 0.001	This study suggests that thoracic manipulative treatment + exercise therapy improve intensity of pain compared with home exercise alone; however, the between group change score is not significant.

					within group change score = 15.00 (95%CI 8.61; 21.39) *Home exercise group Mean (SD)* Baseline 72.04 (16.84) Post-treatment 57.81 (27.90) p within group = 0.022 within group change score = 14.06 (95%CI 3.22; 24.91) between group change score = 10.63 (95%CI - 4.80; 26.05) After 5 weeks of treatment, significant between-group differences observed in DASH (Z = -2.519, p=0.012); however, no differences were achieved for SDQ (Z = -1.874, p=0.061)	
Wright et al, 2016, Journal of Manual & Manipulative Therapy, Prospective, randomized controlled clinical trial - pilot study [51]	N = 18 <u>*Inclusion criteria*</u> • have ≥ 2 of 3 positive tests for the diagnosis of SIS: Hawkins–Kennedy test; painful arc sign; weakness in external rotation with the arm at the side <u>*Exclusion criteria*</u> • red flags • previous shoulder surgery • fracture • current oral steroid use • analgesic injection in the past 3 months • cervicothoracic neurological symptoms and/or sinister pathology • shoulder pain related to cervical spine primary disorders	N = 10 Thoracic and Cervico-thoracic manipulation + shoulder mobilization + exercise • Cervico-thoracic manipulation techniques: • Distraction manipulation of the upper thoracic segments • Sitting thoracic distraction manipulation • Supine upper/middle thoracic spine thrust manipulation technique/"Pistol" Manipulation • Thoracic thrust in prone/"Screw" Manipulation	N = 8 Shoulder mobilization + Exercise (The exercise component consisted of a multimodal, supervised program of muscle strengthening, muscle stretch, and neuromuscular/motor control exercise intended to normalize shoulder movement, improve muscle force-generating capacity, decrease pain, and improve functional ability)	Pain NPRS (baseline, 2 weeks, 4 weeks and person discharge) disability SPADI (baseline, at 2 weeks, 4 weeks and person discharge)	**NPRS** *Thoracic manipulation + shoulder mobilization group Mean (SD)* Baseline 4.5 (2.3) 2 weeks 1.8 (1.0) 4 weeks 1.0 (1.2) Discharge 1.0 (1.0) *Shoulder mobilization group Mean (SD)* Baseline 4.0 (1.5) 2 weeks 2.7 (1.9) 4 weeks 2.3 (1.7) Discharge 1.5 (1.6) **Change within groups** *Thoracic manipulation + shoulder mobilization group Mean (95%CI)* 2 weeks -2.7 (-4.0; -1.4) 4 weeks -3.6 (-5.5; -1.6) discharge -3.5 (-5.3; -1.8) *Shoulder mobilization group Mean (95%CI)* 2 weeks -1.3 (-2.5; -0.2) 4 weeks -1.7 (-2.7; -0.6) discharge -2.5 (-4.0; -1.0) **Difference in change between groups**. (Change in cervicothoracic group - change in shoulder group; negative difference in change between groups favors manipulation group). Mean (95%CI) 2 weeks -1.4 (-3.0; 0.3) ES: -0.86 4 weeks -1.9 (-4.1; 0.4) ES: -0.93 discharge -1.0 (-3.2; 1.2) ES: -0.46 No statistically significant between-group differences for pain using NPRS. Both groups showed statistically significant improvements in pain over the course of treatment. These within group improvements met criteria for clinical significance for pain (MCID: 1.1). In general, improvements in pain tended to favor the thoracic manipulation + shoulder mobilization group with ES ranging from 0.46 to 0.93, although not statistically significant. **Function/disability** **SPADI** *Thoracic manipulation + shoulder mobilization group Mean (SD)* Baseline 47.3 (20.3) 2 weeks 19.3 (12.5) 4 weeks 11.5 (6.5) Discharge 11.3 (11.2) *Shoulder mobilization group Mean (SD)* Baseline 48.9 (28.4) 2 weeks 24.4 (20.3)	The addition of thoracic spinal thrust to shoulder treatment did not significantly improve in pain or function in persons with subacromial pathology. Both approaches appeared to provide an equally notable benefit. Both groups improved in all outcomes and met the criteria for clinical relevance for both pain and function.

4 weeks 15.2 (13.8)
Discharge 10.0 (13.8)

Change within groups
Thoracic manipulation + shoulder mobilization group Mean (95%CI)
2 weeks -28.0 (-42.3; -13.7)
4 weeks -35.7 (-51.8; -19.6)
discharge -36.0 (-52.0; -20.0)

Shoulder mobilization group Mean (95%CI)
2 weeks -24.4 (-48.2; -0.7)
4 weeks -36.5 (-64.6; -8.4)
discharge -38.9 (-61.3; -16.4)

Difference in change between groups. (Change in cervicothoracic group - change in shoulder group; negative difference in change between groups favors manipulation group) Mean (95%CI)
2 weeks -3.6 (-27.7; 20.6) ES: -0.15
4 weeks 0.8 (-26.7; 28.2) ES: 0.03
discharge 2.8 (-21.7; 27.4) ES: 0.12

No statistically significant between-group differences for physical function using SPADI. Both groups showed statistically significant improvements in function over the course of treatment. These within group improvements met criteria for clinical significance for function (MCID: range 8-13).

Acronyms

AROM active range of motion, *BPI* Brief pain inventory, *BW* body weight, *CI* confidence interval, *CG* control group, *DASH* Disability of the arm, shoulder and hand questionnaire, *ES* effect size, *GRCS* Global rating of change scale, *GROC* Global rating of change, *HPT* Heat pain threshold, *IG* intervention group, *MD* mean difference, *MDC* minimal detectable change, *MG* manipulation group, *NPRS* numeric pain rating scale, *PENN* Pennsylvania shoulder score, *PG* placebo group, *PPT* pressure pain threshold, *PROM* passive range of motion, *SD* standard deviation, *SDQ* Shoulder disability questionnaire, *SIS* shoulder impingement syndrome, *SMT* spinal manipulation therapy, *SPADI* Shoulder pain and disability index, *TSTM* thoracic spine thrust manipulation, *VAS* visual analogue scale, *WORC* Western Ontario rotator cuff index

Table 2: Thoracic HVLAT compared to Sham (Pre-post) for Painful Shoulder

Certainty assessment							№ of patients		Effect		Certainty	Comments
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thoracic HVLAT	Sham (Pre-post)	Relative (95% CI)	Absolute (95% CI)		
Pain												
5	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	135	136	-	MD **0.13 Points lower** (0.6 lower to 0.35 higher)	⨁◯◯◯ Very low	Thoracic HVLAT may reduce/have little to no effect on pain but the evidence is very uncertain

CI: confidence interval; **MD:** mean difference; **HVLAT**:High Velocity Low Amplitude Thrust

Explanations

a. Downgrade by one level due to high risk of bias in domain 4 (please see the detailed description reported in risk of bias paragraph)

b. Downgrade by two levels due to the small number of participants enrolled (wide confidence intervals).

Table 3: Thoracic HVLAT compared to Sham for persons with painful shoulder (<4 days)

Certainty assessment							№ of patients		Effect		Certainty	Comments
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thoracic HVLAT	Sham (<4d)	Relative (95% CI)	Absolute (95% CI)		
Pain												
4	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	100	101	-	SMD **0.16 higher** (0.16 lower to 0.48 higher)	⨁◯◯◯ Very low	Thoracic HVLAT may reduce/have little to no effect on pain but the evidence is very uncertain.
Function												
4	randomised trials	serious[a]	not serious	not serious	serious[c]	none	100	101	-	SMD **0.24 lower** (0.68 lower to 0.21 higher)	⨁⨁◯◯ Low	Thoracic HVLAT may reduce/have little to no effect on function but the evidence is uncertain
Patient Satisfaction assessed at 2 days												
3	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	70	70	-	SMD **0.41 lower** (0.82 lower to 0.01 lower)	⨁◯◯◯ Very low	Thoracic HVLAT may reduce person Satisfaction but the evidence is very uncertain

CI: confidence interval; **SMD:** standardised mean difference; **HVLAT**: High Velocity Low Amplitude Thrust

Explanations

a. Downgrade by one level due to high risk of bias in domain 4 (please see the detailed description reported in risk of bias paragraph)

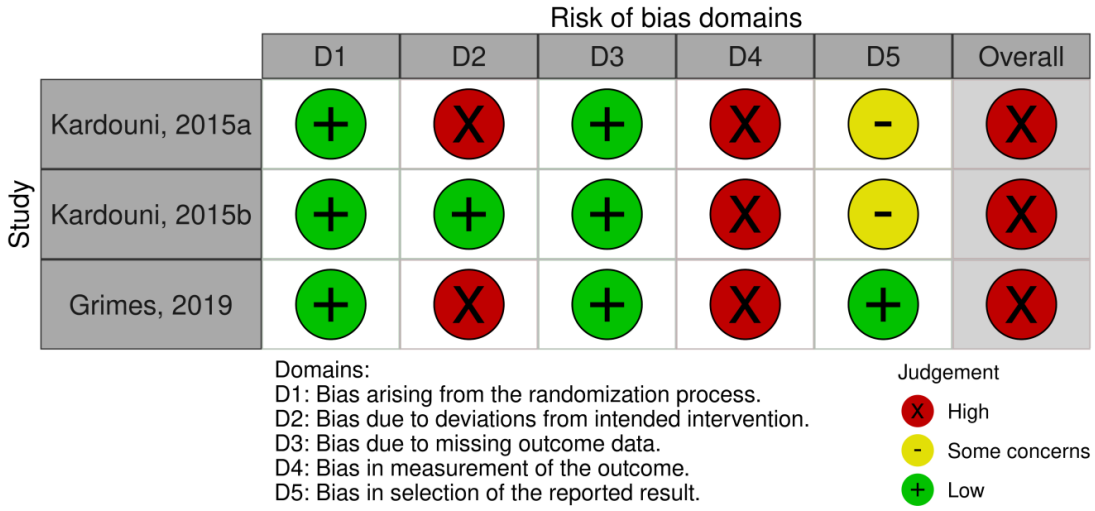
b. Downgrade by two levels due to the small number of participants enrolled and wide confidence intervals

c. Downgrade by one level due to the small number of participants enrolled

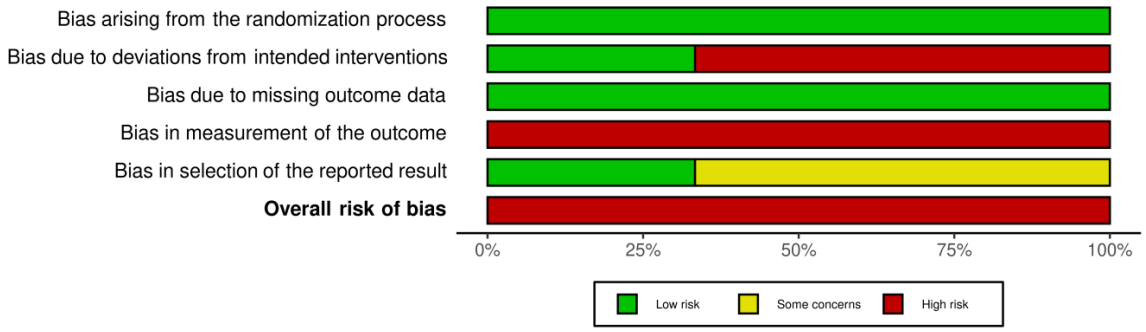
SUPPLEMENTARY MATERIALS

Supplementary material 1

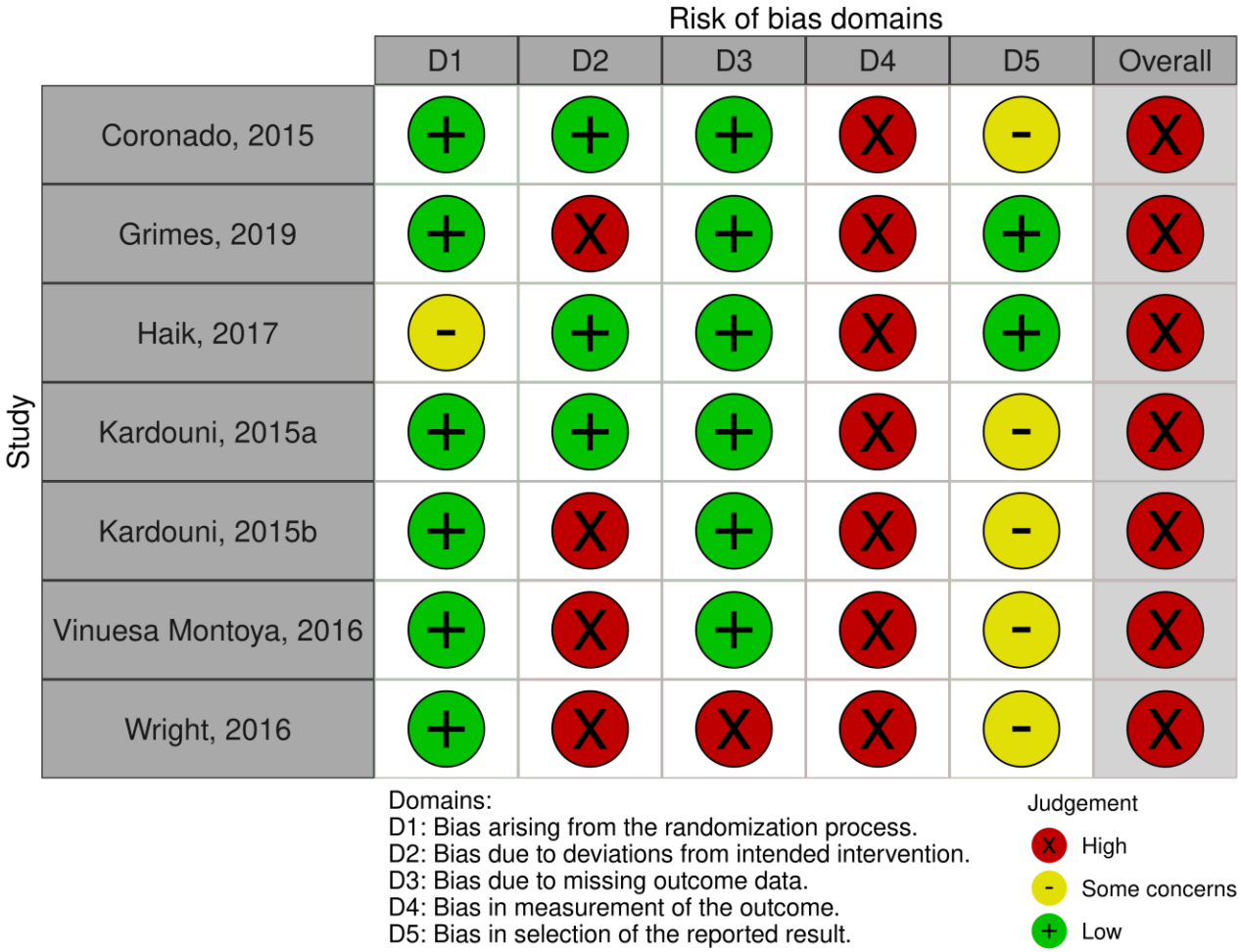
S1A) traffic light for perceived effect



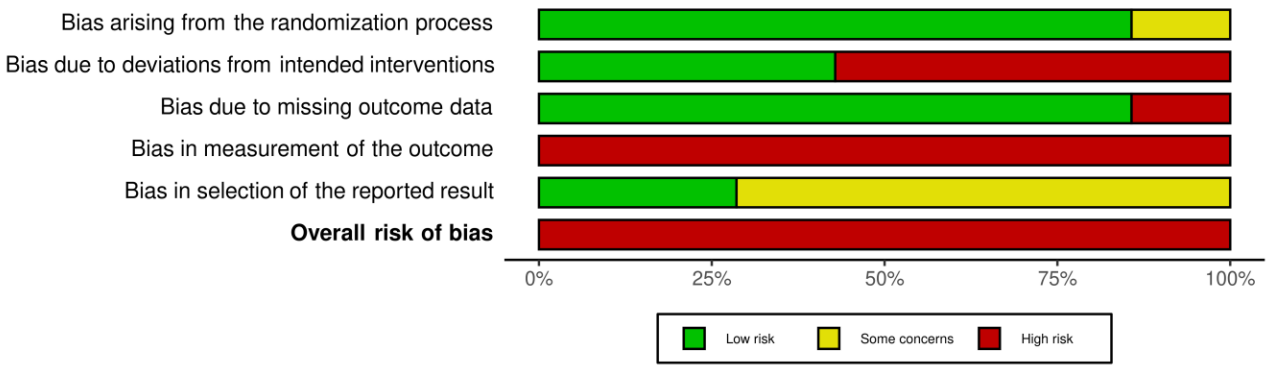
S1B) RoB plot for perceived effect



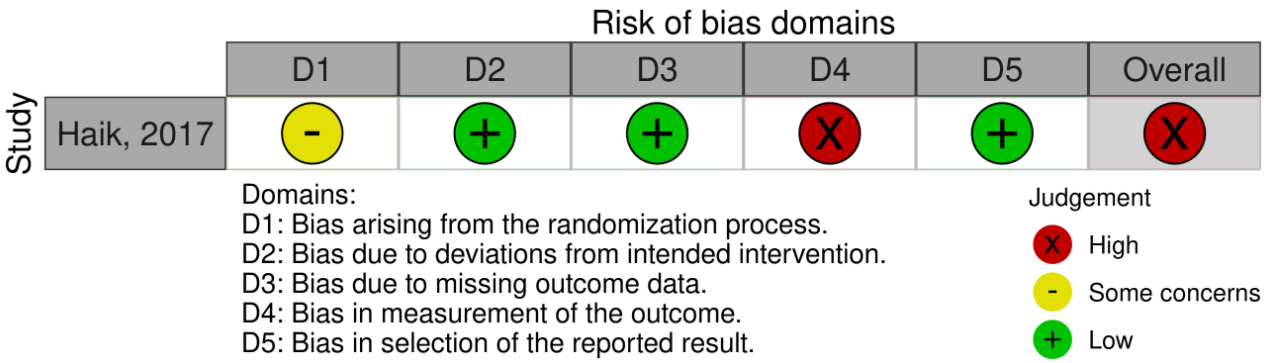
S1C) traffic light for function



S1D) RoB plot for function



S1E) traffic light for quality of life


Risk of bias domains
D1
D2
D3
D4
D5
Overall
Study
Haik, 2017
Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.
Judgement
High
Some concerns
Low

SUPPLEMENATARY MATERIALS 2

APPENDIX A. Medline research string

APPENDIX B. Reports excluded, with reason

APPENDIX C. TIDieR Checklist to report the intervention performed in the included studies

APPENDIX D. Sensitivity analysis

APPENDIX A

P = persons with painful shoulder	1. ("shoulder*"[All Fields] 2. “Shoulder pain” [MeSH] 3. "shoulder impingement syndrome*"[All Fields] 4. “shoulder Impingement Syndrome” [MeSH] 5. “Rotator Cuff Impingement” [All fields] 6. “Shoulder Impingement” [all fields] 7. “Shoulder Impingement” [all fields] 8. “Rotator Cuff Impingement Syndrome” [all fields] 9. “painful shoulder” [all fields] 10. “subacromial impingement syndrome” [all fields] 11. “subacromial impingement” [all fields] 12. “subacromial pain” [all fields] 13. “subacromial pain syndrome” [all fields] 14. "shoulder joint"[All Fields] 15. “Rotator cuff related shoulder pain” [all fields] 16. 1/15 OR
E = thoracic, cervical and cervicothoracic HVLAT	17. “musculoskeletal manipulation [MeSH] 18. “manipulation spinal” [MeSH] 19. “Manipulation, Osteopathic” [MeSH] 20. “Manipulation, Chiropractic” [MeSH] 21. "manipulability"[All Fields] 22. "manipulable"[All Fields] 23. "manipulate"[All Fields] 24. "manipulated"[All Fields] 25. "manipulates"[All Fields] 26. "manipulating"[All Fields] 27. "manipulation"[All Fields] 28. "manipulations"[All Fields] 29. "manipulator"[All Fields] 30. "manipulators"[All Fields] 31. "manipulators"[All Fields] 32. "manipul*"[All Fields] 33. "manipulation therapy"[All Fields] 34. "spinal manipulation"[All Fields] 35. "thrust"[All Fields] 36. "thrusting"[All Fields] 37. "thrusts"[All Fields] 38. "high velocity low amplitude thrust"[All Fields] 39. "hvlat"[All Fields] 40. "thoracic manipulation"[All Fields] 41. "cervical manipulation"[All Fields] 42. "cervicothoracic manipulation"[All Fields] 43. “manipulative therapy” [all fields”] 44. 17/43 OR

Acronyms: *E*, exposition; *HVLAT*, High Velocity Low Amplitude Thrust; *P*, population

APPENDIX B

	Author	Title	Year of publication	Reasons for exclusion
1	Mintken et al	Examination of a clinical prediction rule to identify subjects with shoulder pain likely to benefit from cervicothoracic manipulation: A multicenter randomized clinical trial	2017	Combined spine manipulation and mobilization
2	Mintken et al	Cervicothoracic Manual Therapy Plus Exercise Therapy Versus Exercise Therapy Alone in the Management of Individuals with Shoulder Pain: a Multicenter Randomized Controlled Trial	2016	Combined spine manipulation and mobilization
3	Winters et al	Treatment of shoulder complaints in general practice: long term results of a randomized, single blind study comparing physiotherapy, manipulation, and corticosteroid injection	1999	Combined spine manipulation and mobilization
4	Bergman et al	Manipulative Therapy added on Usual Medical Care in subjects with shoulder pain and dysfunction: a randomized controlled trial	2004	Combined spine manipulation and ribs manipulation
5	Dunning et al	Spinal manipulation and electrical dry needling in subjects with 2 subacromial pain syndrome: a multi-center randomized clinical trial	2021	Combined spine manipulation and ribs manipulation
6	Michener et al	Validation of a sham comparator for thoracic spinal manipulation in subjects with shoulder pain	2015	No follow up data on pain and function were provided
7	Da Silva et al	Immediate Effects of Spinal Manipulation on Shoulder Motion Range and Pain in Individuals with Shoulder Pain: a Randomized Trial	2019	duplicate
8	Grimes	The immediate effects of a seated versus supine upper thoracic spine thrust manipulation compared to sham manipulation in individuals with Subacromial Pain Syndrome: a randomized controlled trial	2017	Phd dissertation
9	Haider et al	Comparison of conservative exercise therapy with and without Maitland thoracic manipulative therapy in subjects with subacromial pain: clinical trial	2018	Combined spine manipulation and mobilization
10	Michener et al	Development of a sham comparator for thoracic spinal manipulative therapy for use with shoulder disorders	2013	Wrong population (Healthy subject)

11	Winters et al	Comparison of physiotherapy, manipulation, and corticosteroid injection for treating shoulder complaints in general practice: randomised, single blind study	1997	Combined spine manipulation and mobilization
12		Effectiveness of Cervicothoracic Manipulative Treatment in Unilateral Shoulder Impingement Syndrome: a Randomized Controlled Trial		Study protocol
13		Short-term Effects of Thoracic Manipulation in Shoulder Impingement		Study protocol
14		Thoracic Spine Thrust Manipulation Compared to Sham Manipulation in Individuals with Subacromial Pain Syndrome		Study protocol
15		Clinical effect of manipulation maneuver in treatment of subacromial impingement syndrome		Full text not found
16	Hunter DJ et al	Thoracic Manual Therapy Improves Pain and Disability in Individuals With Shoulder Impingement Syndrome Compared With Placebo: A Randomized Controlled Trial With 1-Year Follow-up.	2022	No high velocity low amplitude thrust were provided
17	Thoomes E et al	Effectiveness of thoracic spine manipulation for upper quadrant musculoskeletal disorders: protocol for a systematic review.	2023	Study protocol
18	Gutiérrez-Espinoza H et al	Effectiveness of scapular mobilization in people with subacromial impingement syndrome: A randomized controlled trial.	2023	No high velocity low amplitude thrust were provided
19	Liu S et al	Efficacy of five-step shoulder manipulation for rotator cuff-related shoulder pain: protocol for a multicenter randomized controlled trial.	2023	Study protocol
20	Azin Z et al	Comparison of Manual Therapy Technique to Therapeutic Exercise in the Treatment of Patients With Subacromial Impingement Syndrome: A Randomized Clinical Trial.	2023	No high velocity low amplitude thrust were provided
21	Karasuno H Et al	Adduction Manipulation of the Glenohumeral Joint versus Physiotherapy for Atraumatic Rotator Cuff Tears: A Randomized Controlled Trial.	2023	No spine high velocity low amplitude thrust were provided
22	Naranjo-Cinto F et al	Real versus Sham Manual Therapy in Addition to Therapeutic Exercise in the	2022	No high velocity low amplitude

		Treatment of Non-Specific Shoulder Pain: A Randomized Controlled Trial.		thrust were provided

APPENDIX C

	Coronado et al, 2015 [44]	Conte da Silva et al, 2019 [45]	Grimes et al, 2019 [25]	Haik et al, 2014 [46]	Haik et al, 2017 [47]	Kardouni et al, 2015, (A) [48]	Kardouni et al, 2015, (B) [49]	Vinuesa-Montoya et al, 2017 [50]	Wright et al, 2016 [51]
1. BRIEF NAME	YES Cervical manipulation *vs* shoulder thrust manipulation *vs* shoulder home exercise program	YES Thoracic manipulation *vs* placebo manipulation.	YES Upper thoracic manipulation supine *vs* seated *vs* sham manipulation.	YES Thoracic manipulation in individuals with shoulder symptoms *vs* healthy subjects.	YES Thoracic manipulation *vs* sham manipulation.	YES Thoracic manipulation *vs* sham manipulation.	YES Thoracic manipulation *vs* sham manipulation.	YES Cervicothoracic manipulation plus supervised exercises *vs* home exercise program.	YES Cervicothoracic spinal thrust/ non-thrust plus shoulder manual therapy plus exercise intervention.
2. WHY	YES Primary aim: to advance the current mechanistic evidence on manipulation by investigating the	YES Primary aim: to investigate the influence of spinal manipulation on shoulder range of motion in	YES Primary aim: to compare the immediate and short-term effects (48 hours later) of 2 distinct manipulati	YES Primary aim: based on regional interdependence and the neurophysiological effects of spinal manipulation, to evaluate the immediate	YES Primary aim: to investigate the short-term effects of 2 sessions of manipulation on pain, function, scapular kinematics,	YES Primary aim: to determine if thoracic spinal manipulation alters thoracic kinematics, thoracic excursion, and scapular kinematics compared to a	YES Primary aim: based on the assumption that thoracic manipulation could improve symptoms in patients with subacromial	YES Primary aim: to investigate changes in pain, disability, and range of movement after 10 sessions of cervicothora	YES Primary aim: to investigate whether treatment directed at the cervicothoracic spine and shoulder is more beneficial

	effects of the location of manipulation on pain sensitivity. Secondary aim: to explore the association of changes in pain sensitivity with clinical outcome. The hypothesis of the study was that participants with shoulder pain would show enhanced pain sensitivity both in local and remote areas. Significant relationships between	individuals with shoulder pain. Secondary aim: to investigate the influence of manipulation on shoulder pain. The hypothesis of the study was that manipulation would cause an increase in shoulder range of motion and a decrease in shoulder pain.	ons and a sham technique in individuals with shoulder pain. Primary outcomes: pain, function, satisfaction, and the immediate effects on the secondary outcome of scapular impairment.	effects of manipulation on shoulder pain and on scapular kinematics in individuals with shoulder symptoms. Secondary purpose: to evaluate the immediate effects of manipulation on scapular kinematics during elevation and lowering of the arm in subjects without symptoms. The hypothesis of the study was that manipulation would reduce pain in subjects with shoulder impingement syndrome and it would cause changes in scapular	and scapular muscle activity in individuals with shoulder pain. Secondary aim: to investigated within- and between-group effects of manipulation and sham manipulation on shoulder outcomes. The hypothesis of the study was that individuals who received manipulation compared to sham would show decreased shoulder pain; increased shoulder function;	sham manipulation in individuals with subacromial impingement syndrome. Second aim: to compare changes in patient-reported outcomes between two treatment groups. The hypothesis of the study was that individuals who received thoracic manipulation compared to the sham manipulation would show (1) increased thoracic spinal extension during arm elevation, (2) increased thoracic spinal excursion, (3)	impingement syndrome, to assess the immediate pain response in patients with shoulder pain following thoracic spinal manipulative therapy using pressure pain threshold. Second aim of the study: to assess the relationship of change in pain sensitivity to patient-rated outcomes of pain and function following treatment.	cic manipulative treatment plus exercise therapy compared with a home exercise program in patients with unilateral shoulder impingement.	than treatment directed solely at the shoulder for patients with subacromial impingement syndrome. The hypothesis of the study was that patients receiving spinal manual therapy in addition to shoulder-specific treatments would exhibit greater improvements than shoulder interventions alone.

	changes in pain sensitivity and clinical outcomes would support pain sensitivity as a potential treatment target and mechanism by which manual therapy interventions could inhibit pain.			kinematics in subjects with and without impingement symptoms.	changes in scapular kinematics; and changes in the activity of scapular muscles.	alterations in scapular kinematics, and (4) improved patient-reported pain and function/disability.			
3. WHAT - Materials	YES Handheld pressure algometer, 30x30-mm thermode connected to a pathway model ATS, Contact thermode with 2.5-	YES Colored paper (30 orange and 30 blue), VAS and a ruler, Carci universal goniometer,	YES Penn Shoulder Score: self-reported pain, satisfaction, and function. Goniometer: active shoulder elevation assessed in	YES DASH, WORC, NPRS, 3-D measurements, data capture and analysis were completed using Flock of Birds hardware	YES 2000Hz/channel using Bagnoli-8 EMG System, 3-D measurements, data capture and analysis were completed using Flock	YES Penn Shoulder Score, NPRS, GROC, 3-D kinematics of the scapula and humerus were measured with a 6-degree-of-	YES FABQ, NPRS, Penn Shoulder Score, GROC, Mechanical pressure algometer for assessing	YES VAS, DASH, SDQ.	YES NPRS, SPADI, FABQ, Opaque folder.

	cm^2 surface areas connected to a pathway model CHEPS, Brief Pain Inventory, Penn Shoulder Score: function, Handout for home exercise program.		the scapular plane, with the participant standing. Modified digital inclinometer: measurements of scapular upward rotation, posterior tilt, active and passive ROM. Handheld dynamometer: middle trapezius, lower trapezius, and serratus anterior. Opaque folder.	(miniBIRD; Ascension Technology Corporation, Shelburne, VT) integrated with Motion Monitor software (Innovative Sports Training, Inc, Chicago, IL).	of Birds hardware (miniBIRD; Ascension Technology Corporation, Shelburne, VT) integrated with Motion Monitor software, DASH, WORC, NPRS.	freedom electromagnetic tracking apparatus (3SPACE FASTRAK; Polhemus, Colchester, VT) integrated with MotionMonitor software (Innovative Sports Training, Inc, Chicago, IL).	pressure pain threshold.		

4. WHAT - Procedures	YES Cervical manipulation: participant supine. The intervention provider prepositioned the participant's head in a side-flexed and contralateral rotated position. The provider's hands cradled the head, with the hands in contact with the mid cervical region. The manipulation was performed in rotation on the side of shoulder pain.	YES Spinal manipulation group: participants were lying in a prone position on a low stretcher. The therapist positioned the hypothenar eminence of his hands on the transverse processes of the thoracic vertebrae. The therapist then requested the patient to inhale completely and exhale completely. The therapist followed the patient through the	YES The upper thoracic supine manipulation: the examiner used his body to push down through the participant's upper arms to provide a high-velocity, low-amplitude thrust in the anterior-to-posterior direction. The upper thoracic seated manipulation: The examiner applied a high-velocity, low-amplitude	YES Data were collected with the subjects in a relaxed standing position in front of the transmitter. Kinematic motion analysis was based on scapular orientation data measured at the humerothoracic angles of 30°, 60°, 90° and 120° during arm elevation and lowering. Manipulation intervention: the subject assumed a seated position and the therapist performed a thrust technique. Sham technique:	YES Manipulation in the middle thoracic spine: patient seated with arms crossed over the chest. The therapist located behind the patient and performed a thrust technique with arms and chest around the thoracic region of the subject. Sham-Manipulation: the positions of the patient and therapist were the same and the therapist held the position for few seconds,	YES Manipulations were applied to lower, middle, and upper thoracic spine. During thoracic manipulation, a high-velocity, low-amplitude thrust was applied at the end of the available spinal motion. For the middle and lower thoracic manipulation, participants were prone, and the thrust was directed in the posterior-to-anterior direction. For the cervicothoracic junction manipulation, participants were seated, and the thrust was provided	YES Manipulations were applied to lower, middle, and upper thoracic spine. During thoracic manipulation, a high-velocity, low-amplitude thrust was applied at the end of the available spinal motion. For the middle and lower thoracic manipulation, participants were prone, and the thrust was directed in the posterior-to-anterior direction.	YES Spinal manipulation and exercise therapy: a treatment package of manipulations was applied to the lower, middle, and upper cervicothoracic spine shoulder pain, specifically high velocity, low-amplitude thrusts applied at the end of the joint motion. In this study, the patients received repetitive lateral translation from both sides at the	NO – not sufficiently reported. At least one manual therapy technique and one exercise technique was required at each visit for a minimum of 15 min. This included both a spinal and shoulder manual therapy technique for cervicothoracic spinal thrust/non-thrust group and at least one shoulder manual therapy technique for the shoulder treatment-only group.

	Shoulder manipulation: this technique is a variant of the common distraction mobilization for the shoulder region. The shoulder manipulation was performed with the participant supine and the shoulder placed approximately 90° of flexion with internal rotation. The Home Exercise Program: the range-of-motion exercises included self-	exhalation and applied downward pressure to remove the slack from the soft tissue. At the end of expiration, the therapist applied a low-amplitude, high-velocity thrust to achieve manipulation. Placebo manipulation group: the same position was adopted, although at the end of the expiration no thrust on the vertebrae was performed;	distraction thrust in a cephalic direction. Sham technique: performed in the same manner as the seated manipulation, moving the participant through the same motion but delivering no manipulative thrust.	the therapist applied the same forces as those of a thrust manipulation, while holding the position for a few seconds, without performing a thrust manipulation.	without performing the thrust.	as an axial distraction. The sham manipulation was performed with identical body positioning of both the participant and therapist. The therapist applied minimal pressure to maintain physical contact with the participant. The therapist followed the participant through the same range of motion, but no manipulative thrust was delivered.	For the cervicothoracic junction manipulation, participants were seated, and the thrust was provided as an axial distraction. The sham manipulation was performed with identical body positioning of both the participant and therapist. The therapist maintained manual contact through the range of motion during exhalation, but no manipulative	beginning of the treatment. After this technique, the patients received 5 thoracic manipulations. Home Exercise Program: in this program, patients performed stretching and muscle strengthening exercises targeting the shoulder girdle for 5 weeks.	

	generated movements for shoulder flexion, abduction, and internal and external rotation. Each range-of-motion exercise was held for 30 seconds and performed twice within each exercise bout.	the therapist maintained the physical contact with minimum pressure.					thrust was delivered.		
5. WHO PROVIDED	YES All interventions were administered by licensed physical therapists with special	YES The evaluation and the spinal manipulation were performed by a physiotherapist who	YES All participants were examined and treated by a physical therapist who was board certi-	YES A physiotherapist with 4 years of experience in manual therapy administered the manipulation or sham intervention,	YES Interventions were performed by a physical therapist with 4 years of experience in manual therapy.	YES Both real manipulation and sham manipulation were administered by a licensed physical therapist with 11 years of	YES Both the thoracic manipulation and sham thoracic manipulation were administered by a licensed	YES Every group was treated by a physical therapist with more than 15 years of experience in	NO Physiotherapist (unspecified)

	training in manual therapy or a licensed chiropractor.	had 6 years of clinical experience in the area.	fied in orthopedics and had 14 years of clinical experience.	targeting the midthoracic spine of the subjects.		orthopaedic physical therapy experience.	physical therapist with 11 years of orthopedic physical therapy experience.	the management of individuals with shoulder pain.	
6. HOW	YES Face-to-face interventions and home not supervised program.	YES Face-to-face.	YES Face-to-face.	YES Face-to-face.	YES Face-to-face.	YES Face-to-face.	YES Face-to-face.	YES Face-to-face interventions and home not supervised program.	YES Face-to-face.
7. WHERE	YES University of Florida	NO Clinical School of Physiotherapy of a university and a private clinic.	YES All participants were examined and treated in a university clinical setting.	NO	YES All measurement and interventions were conducted at the Laboratory of Analysis and Intervention of the Shoulder Complex at the Federal University of Sao Carlos.	YES Testing and treatment occurred in a research lab in the Department of Physical Therapy at Virginia Commonwealth University.	YES This study took place in a research laboratory in the Physical Therapy Department at Virginia Commonwealth University.	YES Interventions were provided at three separate sites (University of Illinois Hospital & Health Sciences System, Walsh University Department of Physical Therapy, and Carolina	YES Interventions were provided at 3 separate sites in the USA: University of Illinois Hospital & Health Sciences System, Walsh University Department of Physical Therapy, and Carolina

								Physical Therapy Specialists) in the USA. Patients' home.	Physical Therapy Specialists.
8. WHEN and HOW MUCH	YES The interventio n portion of the randomized trial was conducted over 2 weeks. A total of 3 treatment sessions within 2-week period were completed for the primary purpose of assessing the effects on mechanisti c outcome. Pre and post interventio	YES Intervention delivered once.	YES Interventio n delivered once.	YES Intervention delivered once. Manipulation intervention: if no cavitation was detected with the manipulation, the thrust was repeated up to 3 times.	YES Two intervention sessions over a 1-week period. The technique was applied twice in a period of 3 to 4 days apart.	YES Each technique was applied twice, for a total of 6 thoracic manipulation or sham applications.	YES Each technique was applied 2 times at each of the 3 regions, for a total of 6 thoracic manipulatio ns or sham thoracic manipulatio ns.	YES Ten sessions for 5 weeks (2 sessions/wee k. Patients performed a home exercise program for 30 minutes twice a day.	YES Patients were typically scheduled for 45 min sessions, 2 times per week, progressed as tolerated, until discharge. Patient discharge, treatment length, and frequency of treatment were determined by the physiotherapi sts, although some patients terminated treatment themselves.

	n pain sensitivity assessments were conducted at baseline, 1 week, and 2 weeks. Clinical assessments were conducted at 4, 8, and 12 weeks. The Home Exercise Group received formal training and supervision of the exercise program during the initial intervention session and a handout with details of the program for								

	performance at home twice a day.								
9. TAILORING	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	YES Treatment selection and dosage of the interventions was specific to the examination findings.
10. MODIFICATIONS	NO Not relevant.	NO Not relevant.	NO Not relevant.	NO Not relevant.	NO Not relevant.	NO Not relevant.	NO Not relevant.	NO Not relevant.	NO Not relevant.
11. HOW WELL	NO Home exercise program compliance was encouraged during each intervention session but not formally monitored.	NO	NO	NO	NO	NO	NO	NO	NO

12. HOW WELL - Actual:	NO Home exercise program compliance was encouraged during each intervention session but not formally monitored.	NO	NO	NO	NO	NO	NO	NO	NO

N/A = not applicable; NO = information about the element is not reported/not sufficiently reported; YES = information about the element is sufficiently reported

DASH = Disabilities of the Arm, Shoulder, and Hand questionnaire; FABQ = Fear Avoidance Beliefs Questionnaire; GROC = global rating of change; NPRS = Numeric Pain Rating Scale; SDQ = Shoulder Disability Questionnaire; SPADI = Shoulder Pain and Disability Index; VAS = Visual Analogue Scale; WORC = Western Ontario Rotator Cuff index.

From: Hoffmann TC, Glasziou PP, Boutron I et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348: g1687

APPENDIX D

Sensitivity analysis

Function between pre-treatment and <4 days

Due to the small number of studies included, we did not find a subgroup variable to investigate; therefore, the high rate of heterogeneity was explored through a sensitivity analysis.

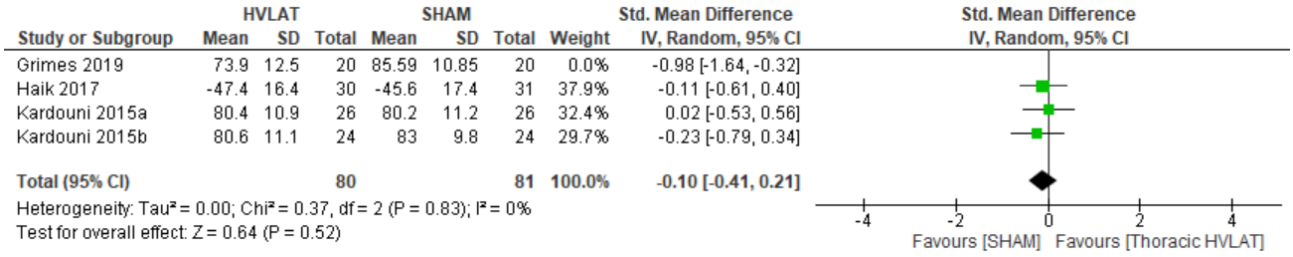
Extraction data process revealed differences between the study from Grimes et al, 2019, and the other studies included in the pooled analysis.

In particular, the sample involved was relevantly different: in Grimes et al., 2019, subjects were involved if they complained pain < 6 months; while in Haik et al., 2017, mean duration of symptoms was 41 months, and in Kardouni et al, 2015 A and B, subjects were included if they complained symptoms > 6 weeks. Notably, in subjects with shoulder pain, longer duration of symptoms was associated with an unfavorable outcome [1,2]

Moreover, in Grimes et al., 2015 subjects were included if they complained pain, while weakness was not mentioned. On the contrary, the other three studies included subjects that complained pain and/or weakness when tested for resisted shoulder external rotation at arm by side. Noteworthy, weakness could higher the index of suspicion of rotator cuff disorders [3]. With this in mind, the samples of Haik et al 2017, Kardouni et al 2015 A and B could also include subjects with disorders of rotator cuff, while Grimes et al 2019 probably included subjects with non-specific shoulder pain.

These differences suggest removing the study by Grimes et al. 2019. Consequently, the heterogeneity decreased to 0% and resulted non-significant function improvement in favor of sham intervention (SMD= -0.10, 95% IC -0.41, 0.21, p= 0.52, I^2= 0%, figure below).

However, these results should be interpreted with caution due to the presence of only three studies (161 subjects) in this last meta-analysis.



[1] Littlewood C, May S, Walters S. Epidemiology of Rotator Cuff Tendinopathy: A Systematic Review. Shoulder & Elbow. 2013;5(4):256-265. doi:10.1111/sae.12028

[2] Major DH, Røe Y, Småstuen MC, van der Windt D, Sandbakk TB, Jæger M, Grotle M. Fear of movement and emotional distress as prognostic factors for disability in patients with shoulder pain: a prospective cohort study. BMC Musculoskelet Disord. 2022 Feb 26;23(1):183. doi: 10.1186/s12891-022-05139-6. PMID: 35219313; PMCID: PMC8882288.

[3] Sgroi M, Loitsch T, Reichel H, Kappe T. Diagnostic Value of Clinical Tests for Infraspinatus Tendon Tears. Arthroscopy. 2019 May;35(5):1339-1347. doi: 10.1016/j.arthro.2018.12.003. Epub 2019 Feb 13. PMID: 30770251.