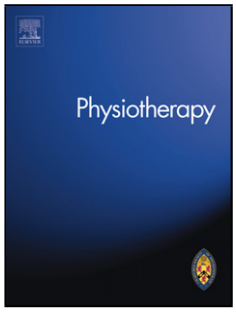

Title: Effects of joint mobilisation on clinical manifestations of sympathetic nervous system activity: a systematic review and meta-analysis

Authors: Marcos J. Navarro-Santana, Guido F. Gómez-Chiguano, Mihai D. Somkereki, César Fernández-de-las-Peñas, Joshua A. Cleland, Gustavo Plaza-Manzano

PII: S0031-9406(18)30148-2
DOI: https://doi.org/10.1016/j.physio.2019.07.001
Reference: PHYST 1121

To appear in: *Physiotherapy*

Please cite this article as: Navarro-Santana MJ, Gómez-Chiguano GF, Somkereki MD, Fernández-de-las-Peñas C, Cleland JA, Plaza-Manzano G, Effects of joint mobilisation on clinical manifestations of sympathetic nervous system activity: a systematic review and meta-analysis, *Physiotherapy* (2019), https://doi.org/10.1016/j.physio.2019.07.001

Effects of joint mobilisation on clinical manifestations of sympathetic nervous system activity: a systematic review and meta-analysis

Marcos J. Navarro-Santana[a], Guido F. Gómez-Chiguano[b], Mihai D. Somkereki[a], César Fernández-de-las-Peñas[c,*], Joshua A. Cleland[d,e,f], Gustavo Plaza-Manzano

[a]*Rehabilitación San Fernando, Madrid, Spain*

[b]*Podiatry Clinic, Faculty of Nursing, Physiotherapy and Podiatry, Universidad Complutense de Madrid, Madrid, Spain*

[c]*Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain*

[d]*Department of Physical Therapy, Franklin Pierce University, Manchester, NH, USA*

[e]*Rehabilitation Services, Concord Hospital, Concord, NH, USA*

[f]*Manual Therapy Fellowship Program, Regis University, Denver, CO, USA*

[g]*Department of Radiology, Rehabilitation and Physiotherapy, Universidad Complutense de Madrid, Madrid, Spain*

[h]*Instituto de Investigación Sanitaria del Hospital Clínico San Carlos, Madrid, Spain*

[*]Corresponding author. Address: Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Avenida de Atenas s/n, 28922 Alcorcón, Madrid, Spain. Tel.: + 34 91 488 88 84; fax: +34 91 488 89 57.

E-mail addresses: cesarfdlp@yahoo.es, cesar.fernandez@urjc.es (C. Fernández-de-las-Peñas).

Abstract

Background A potential mechanism of action of manual therapy is the activation of a sympathetic-excitatory response.

Objective To evaluate the effects of joint mobilisation on changes in clinical manifestations of sympathetic nervous system activity.

Data sources MEDLINE, EMBASE, AMED, CINAHL, EBSCO, PubMed, PEDro, Cochrane Collaboration Trials Register, Cochrane Database of Systematic Reviews and SCOPUS databases.

Study selection Randomised controlled trials that compared a mobilisation technique applied to the spine or the extremities with a control or placebo.

Data extraction and data synthesis Human studies collecting data on skin conductance or skin temperature were used. Data were extracted by two reviewers. Risk of bias was assessed using the Cochrane guidelines, and quality of evidence was assessed using the GRADE approach. Standardised mean differences (SMD) and random effects were calculated.

Results Eighteen studies were included in the review and 17 were included in the meta-analysis. The meta-analysis found a significant increase in skin conductance [SMD 1.21, 95% confidence interval (CI) 0.88 to 1.53, *n*=269] and a decrease in temperature (SMD 0.92, 95% CI -1.47 to -0.37, *n*=128) after mobilisation compared with the control group. An increase in skin conductance (SMD 0.73, 95% CI 0.51 to 0.96, *n*=293) and a decrease in temperature (SMD -0.50, 95% CI -0.82 to -0.18, *n*=134) were seen after mobilisation compared with placebo. The risk of bias was generally low, but the heterogenicity of the results downgraded the level of evidence.

Limitations Most trials (14/18) were conducted on asymptomatic healthy subjects.

Conclusion There is moderate evidence suggesting a sympatho-excitatory effect of joint mobilisation.

Systematic review registration number CRD42018089991.

Keywords: Mobilisation; Best evidence; Sympathetic nervous system; Skin conductance; Skin temperature

<A>Introduction

Manual joint mobilisation is commonly used by physical therapists to manage musculoskeletal pain [1,2], and is recommended as a useful therapeutic tool in clinical practice guidelines [3,4]. Joint mobilisation is defined as a low-velocity/high-amplitude intervention, as opposed to manipulation or a high-velocity/low-amplitude intervention. It has been shown that joint mobilisation techniques may have a pain-modulating effect by exerting hypoalgesic responses presenting as an increase in pressure pain threshold [5] or a decrease in pain [6]. However, the therapeutic mechanisms for inhibition of pain remain to be elucidated.

There are several potential therapeutic mechanisms that may contribute to the analgesic effects of manual therapies, including reduction of muscle activity, changes in neural mechanical sensitivity [7], and changes in endogenous substances or biomarkers (e.g. oxytocin, neurotensin or substance P) [8,9]. Additionally, there is evidence suggesting that manual therapies activate descending inhibitory pain responses from central nervous system areas, particularly the periaqueductal grey matter. This may be related to the fact that pain modulation associated with joint mobilisation may stimulate non-opioid central pathways [10].

Another potential mechanism explaining the therapeutic effect of joint mobilisation interventions is the impact on sympathetic nervous system activity [11]. Some authors proposed that the sympathetic nervous system is activated through central brain areas (e.g. periaqueductal grey matter), and therefore its activation can contribute to a central pain inhibition response during joint mobilisation. A study on an animal model found that electrical stimulation in the midbrain which originated from the periaqueductal grey matter resulted in an analgesic response accompanied by sympathetic nervous system activation [11,12]. This hypothesis is also supported by studies demonstrating that hypoalgesia induced with manual therapies occurs simultaneously with a sympathetic-excitatory change in humans [7,13]. Therefore, changes in sympathetic nervous system activity may be directly related to modulation responses during therapeutic interventions.

It has been suggested that stimulation of the sympathetic trunks can occur as a result of manual therapies applied to the spine [14,15]. Assessing the response of the sympathetic nervous system typically includes measures of skin conductance or skin temperature as clinical manifestations. In fact, several studies have shown increased skin conductance [7,13,15–20], respiratory rate and heart rate [21] and decreased skin temperature after the application of joint mobilisation targeting the spine [22,23], suggesting a sympathetic-excitatory effect. A meta-analysis examining the effects of joint mobilisation targeting the thoracic and cervical regions found a moderate to high effect on changes in skin conductance and skin temperature [24], indicating a potential response from the sympathetic nervous system with these interventions. These findings are supported by another recent systematic review that examined the mechanisms of spinal mobilisation [25]. However, previous reviews examined the changes associated with joint techniques directed at the spine, particularly the cervical and thoracic regions. To the

authors' knowledge, no meta-analysis to date has examined the effects of joint mobilisation targeting the extremities on activity of the sympathetic nervous system. Therefore, this systematic review and meta-analysis was undertaken to evaluate the effects of joint mobilisation targeting any anatomical region, spine or extremity, on changes in clinical manifestations (i.e. skin conductance or skin temperature) of sympathetic nervous system activity in individuals with and without pain.

A secondary objective was to examine the differences in changes in sympathetic nervous system activity in relation to the body region targeted by the mobilisation (spine vs extremities).

<A>Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [26], and was registered on PROSPERO (CRD42018089991).

<B>Literature database search

Electronic literature searches were conducted using MEDLINE, EMBASE, AMED, CINAHL, EBSCO, PubMed, PEDro, Cochrane Collaboration Trials Register and SCOPUS from their inception to 31 March 2018. When these databases allowed limits, searches were restricted to randomised clinical trials, including pilot studies. The reference lists of papers identified in the database searches were also screened.

<C>Population

Adults (aged ≥18 years) with or without pathology were included in this review. The search strategy had to include at least one of the following key words: healthy subjects OR healthy volunteers OR musculoskeletal pain.

<C>Intervention

Joint mobilisation (low frequency/high amplitude) was performed in isolation and manually (i.e. no instruments). The search strategy had to include one of the following key words: spinal mobilisation OR manual therapy OR musculoskeletal mobilisation OR peripheral mobilisation OR joint-biased manual therapy.

<C>Comparator

Acceptable comparators included any type of placebo, sham or no intervention. The search strategy had to include one of the following key words: sham OR placebo OR control OR no intervention.

<C>Outcomes

Any outcome evaluating the function of the sympathetic nervous system (i.e. skin conductance or skin temperature) was evaluated. An increase in skin conductance or a decrease in skin temperature is indicative of excitatory activation of the sympathetic nervous system. The search strategy had to include at least one of the following key words: skin conductance OR skin temperature OR galvanic skin response OR sympathetic nervous system.

The search strategy for each database is shown in Appendix 1.

<B>Inclusion criteria for article selection

For inclusion in this systematic review and meta-analysis, a study had to describe an experimental procedure (clinical trial) with a PEDro scale score ≥5 points that applied a non-thrust joint mobilisation. In this review, high-velocity/low-amplitude thrust manipulation interventions were excluded. No restriction was placed on the language of publication or the body area studied.

<B>Study selection

Articles identified through the database searches were reviewed independently by two authors. First, any duplicates were removed. Second, titles and abstracts were screened for eligibility. Next, the full text of the remaining studies was screened for eligibility criteria. The authors were required to achieve consensus on each included trial. In case of disagreement between the two authors, a third author decided whether the article should be included. The rate of agreement between the authors was 95%.

<B>Data extraction

Data from each trial were extracted independently by two authors. A standardised data extraction form containing data on sample size, participants, diagnosis, interventions, study design, results and outcomes was used. The authors were required to achieve consensus on each item on the data extraction form. In case of disagreement between the authors, a third author made the final decision.

<B>Assessment of risk of bias

Included trials were critically appraised for potential risk of bias (RoB) by two researchers using the Cochrane RoB assessment tool [27]. If blinding of the patient or therapist was impossible for technical reasons (as commonly happens in manual therapy

trials), it was rated as 'not applicable'. The domain 'incomplete outcome data' was considered to induce RoB if data were statistically analysed per protocol and losses to follow-up were ≥20% [28].

<B>Level of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence [29]. Evidence was classified as high, moderate, low or very low based on RoB of the trials. The quality of evidence was calculated based on the presence of study limitations (RoB), indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, and high probability of publication bias [30]. Two authors assessed the quality of evidence and RoB independently. In the case of controversy, a third author was consulted for the final decision.

<B>Statistical data analysis

Review Manager 5.3 was used for quantitative examination of the effects of joint mobilisation on skin conductance and temperature. Due to the methodological variability of the studies and the different variables used as outcomes, standardised mean differences (SMD) with their associated 95% confidence intervals (CI) were calculated using the random effects model. Differences between a joint mobilisation group and a control or placebo group were compared. Those variables that expressed changes in skin conductance or skin temperature during the intervention were selected. If these data were not provided, data reporting the effect over the total measurement period were used. To examine subgroup differences, effects on outcomes were compared by anatomical region

of joint mobilisation (spine vs extremities). SMD values of <0.5, 0.5 to 0.8 and >0.8 were considered small, moderate and large, respectively.

Heterogeneity of the studies was evaluated using the I^2 statistic. The Cochrane group has stated that I^2 of 0% to 40%, 30% to 60%, 50% to 90% and 75% to 100% may represent unimportant heterogeneity, moderate heterogeneity, substantial heterogeneity and considerable heterogeneity, respectively [31]. Asymmetry of data was evaluated using funnel plots with the Egger's test (when possible) to indicate the possible risk of publication bias of small trials with negative results (see online supplementary material).

<A>Results

<B>Literature search

The literature search of electronic databases identified 465 studies for review after the removal of duplicates. Four hundred and thirty-nine (*n*=439) studies did not fit the inclusion criteria, based on examination of titles/abstracts. Another eight trials were excluded for the following reasons: lack of a comparison group, not compared with control or placebo/sham groups [16,32,33], technique applied was a high-velocity/low-amplitude thrust manipulation [23,34,35], and several techniques were applied in the same session [36,37]. Finally,18 articles were included in the systematic review [7,13–15,17–20,22,38–46] and 17 trials were included in the meta-analysis [7,13–15,17–20,22,38–45] as one was excluded [46] due to lack of available data (Fig. 1). Another ongoing clinical study was identified in clinicaltrials.gov but was not included in the review (NCT02826590).

<insert Fig 1 near here>

<B>Included trials

A description of the studies included in the systematic review is given in Table 1. Seven studies used a randomisation procedure for group allocation [17–20,22,32,45], and the other 11 studies used cross-over designs where participants received all interventions in a random sequence [7,13,15,38–43,46]. Fourteen studies examined the effect of joint mobilisation in healthy people [14,15,17–20,39–46], and the other four studies included symptomatic populations: individuals with elbow pain [13,38], neck pain [7] or cervical–craniofacial pain [22].

<insert Table 1 near here>

Various joint mobilisation interventions were applied, including posterior–anterior joint mobilisation [7,14,18,40,41,44,45], unilateral lateral glides [38,39, 46], mobilisation with movement [13,15,17,20], sustained natural apophyseal glide (SNAG) mobilisation and anterior–posterior mobilisation [22,42]. In addition, various areas were targeted, including the cervical spine [7,14,22,38–41,43], thoracic spine [15,20,45,46], lumbar spine [17–19,44], elbow [13] and shoulder [42].

Every study comparing joint mobilisation with a control intervention (*n*=14) found a significant increase in skin conductance with joint mobilisation [7,13–15,17–19,38–44]. Of the 14 studies comparing joint mobilisation with a placebo group, 10 studies reported a significant increase in skin conductance [7,13–15,18,22,38,39,42,44] and four studies did not [19,20,43,45].

Five of the 10 studies [7,13–15,42] comparing joint mobilisation with a control group found a significant decrease in skin temperature with joint mobilisation. In

addition, two studies found a significant decrease in skin temperature with joint mobilisation compared with placebo [13,15].

<B>Risk of bias

Table 2 summarises the RoB assessment of the trials. None of the trials were able to blind the therapists, and seven studies were rated as 'unclear' for allocation concealment [15,39,40,42,43,45,46] as these data was not reported. In general, the RoB of the trials included in the meta-analysis was low or unclear.

<insert Table 2 near here>

<B>Changes in skin conductance

Comparisons between joint mobilisation groups (during the intervention period) and control groups for changes in skin conductance are shown in Fig. 2. The meta-analysis found a significant increase in skin conductance with a large effect size (SMD 1.21, 95% CI 0.88 to 1.53, n=269) but high heterogeneity (I^2=65%) after joint mobilisation compared with a control intervention. The subgroup analysis (spine vs extremity) found no differences (P=0.169) and moderate heterogeneity of the subgroups (I^2=42.7%). The funnel plot of comparison of skin conductance between treatment and control groups indicates possible publication bias (Suppl. Fig. 1, see online supplementary material).

<insert Fig 2 near here>

Comparisons between joint mobilisation groups (during the intervention period) and placebo groups for skin conductance are shown in Fig. 3. The meta-analysis found an increase in skin conductance with a moderate effect size (SMD 0.73, 95% CI 0.51 to 0.96, *n*=293) and moderate heterogeneity (I^2=39%) after joint mobilisation compared with a placebo intervention. The subgroup analysis revealed no significant differences (*P*=0.15) and moderate heterogeneity of the subgroups (I^2=42.8%). The funnel plot comparing the effect of joint mobilisation with a placebo intervention for skin conductance indicates no publication bias (Suppl. Fig. 2, see online supplementary material).

<insert Fig 3 near here>

<B>Changes in skin temperature

Fig. 4 summarises the comparison between the joint mobilisation groups (during the intervention period) and the control groups for skin temperature. The results showed a decrease in skin temperature with a large effect size (SMD -0.92, 95% CI -1.47 to -0.37, *n*=128) but high heterogeneity (I^2=76%) after joint mobilisation compared with the control intervention. Subgroup analysis (spine vs extremity) revealed no significant differences (*P*=0.89) and was homogeneous (I^2=0%). The funnel plot comparing the effect of joint mobilisation with a control intervention for skin temperature indicates no risk of publication bias (Suppl. Fig. 3, see online supplementary material).

<insert Fig 4 near here>

Fig. 5 summarises the comparison between the joint mobilisation groups (during the intervention period) with the placebo groups for skin temperature. When comparing the joint mobilisation group with the placebo group, there was a small to moderate effect size (SMD -0.50, 95% CI -0.82 to -0.18, *n*=134) and low heterogeneity (I^2=0%) reporting a decrease in skin temperature after joint mobilisation. Subgroup analysis (spine vs extremities) revealed no significant differences (*P*=0.38) and was homogeneous (I^2=0%). The funnel plot comparing the effects of joint mobilisation with a placebo intervention for skin temperature indicates low risk of publication bias (Suppl. Fig. 4, see online supplementary material).

<insert Fig 5 near here>

<B>Quality of evidence (GRADE)

The details of GRADE assessment of the included trials are displayed in Table 3. Most of the trials included in this meta-analysis had low or unclear RoB. Although significant differences were found, the evidence was downgraded, particularly for level of heterogeneity (inconsistency).

<insert Table 3 near here>

<A>Discussion

The main objective of this systematic review and meta-analysis was to evaluate changes in clinical manifestations (i.e. skin conductance and/or skin temperature) of sympathetic nervous system activity in subjects with and without pain. This study also examined if changes were different if mobilisation was applied to the spine or the

extremities. This meta-analysis found evidence suggesting that joint mobilisation is able to produce a sympathetic-excitatory effect as all changes were excitatory in nature (i.e. an increase in skin conductance and a decrease in skin temperature) compared with control or placebo interventions, indicating sympathetic upregulation in individuals with and without pain. Additionally, no significant differences were found between joint mobilisation applied to the spine and joint mobilisation applied to the extremities.

Current findings support a sympathetic-excitatory effect of joint mobilisation, and that this effect is not related to the region of application. These results are similar to the meta-analysis conducted by Chu *et al.* [24], which found an increase in skin conductance (large effect) and a decrease in skin temperature (moderate effect) after the application of spinal manipulation or mobilisation. The fact that no differences existed between area of application supports the results of the systematic review by Kingston *et al.* [11], which found similar sympathetic-excitatory activation independent from the spine region where the mobilisation was applied. Nevertheless, the present meta-analysis is the first to investigate the effects of joint mobilisation applied to the peripheral joints (extremities) on sympathetic nervous system activity.

An interesting finding of this meta-analysis was a reduction in effect size, from large to moderate, for skin conductance or skin temperature when joint mobilisation was compared with placebo rather than a control condition, which would support a small effect of placebo on the sympathetic nervous system. Future studies should investigate the effect of placebo on activation of the sympathetic nervous system.

Different theories can potentially explain the effect of joint mobilisation on sympathetic nervous system activity. First, several studies have observed changes in the sympathetic nervous system concomitant with an hypoalgesic effect supporting activation of the periaqueductal grey matter [7,10–12,43,47]. In fact, these responses are similar to

those found in mice receiving electrical stimulation of the midbrain, associated with a typical dangerous response. Therefore, this may be the result of a stress response from activation of the dorsal periaqueductal grey matter. Findings from this meta-analysis are consistent with the hypothesis that a sympathetic-excitatory response may be related to a stress response. In agreement with this, Plaza-Manzano *et al.* [8] observed an increase in neurotensin, a neurotransmitter involved in the stress response and serotoninergic descending pathways, after application of a thoracic manipulation. Another hypothesis explaining the sympathetic-excitatory effect may be stimulation of the ganglia at the respective vertebral level [11]. Some studies observed greater effects on the ipsilateral side of joint mobilisation, suggesting activation of sympathetic fibres through spinal mobilisation [15,17,44,45]. However, others found bilateral responses after spinal mobilisation [7,20,32,39,43]. It is possible that the sympathetic-excitatory response after joint mobilisation is not related to a single mechanism, and both mechanisms may act simultaneously. In fact, as no difference was found in the sympathetic-excitatory response between joint mobilisation targeting the spine or upper extremities, it is possible that the mechanisms underlying the sympathetic nervous system effect of joint mobilisation may involve central mechanisms, suggesting that it might not matter which joint is mobilised. It is also plausible that different sympathetic nervous system activation mechanisms may be induced according to the mobilisation technique: glide technique vs SNAG, unilateral techniques or high-frequency mobilisation [17,45]. In fact, some trials showed that when oscillatory techniques were not performed, no differences in skin conductance were found compared with the placebo group [17,19,20,43]. Therefore, the oscillatory characteristic of joint mobilisation seems to be of particular relevance for this effect. In fact, several authors found that frequencies of 2 Hz in the cervical region and 3 Hz in the lumbar region resulted in greater activation of the sympathetic nervous system [18,40]. However, others

did not find significant differences when using an oscillatory mobilisation technique at a frequency of 0.5 Hz [45]. These results support the hypothesis that different mechanisms of action may occur with varying frequencies of oscillation, but further studies should be conducted.

The sympathetic-excitatory effect has also been related to an increase in pressure pain threshold and a decrease in pain intensity in individuals with pain, suggesting that this effect was associated with benefits for pain and function; however, no previous study has investigated whether changes in sympathetic nervous system activity were associated with treatment benefits [7,13,22,38]. Therefore, it is not yet known if the observed changes in sympathetic nervous system activity are clinically relevant or can only be used to explain the underlying mechanisms of manual therapies. Significant differences in sympathetic nervous system activity were not observed between asymptomatic and symptomatic populations, in agreement with previous reviews [11,24]. Therefore, current findings suggest that joint mobilisation is able to modulate sympathetic nervous system activity independently of the presence or the absence of symptoms.

Some potential limitations to this meta-analysis should be recognised. First, many of the trials included were conducted on asymptomatic subjects; nevertheless, differences were not noted between trials including healthy individuals and trials including a patient population (although their number was small). Therefore, extrapolation of these results to pain conditions should be considered with caution. Further, the heterogeneity of the included studies was moderate to high, and a risk of publication bias exists. Usually, asymmetry of funnel plots is related to publication bias, but other reasons, such as high heterogeneity or a small number of trials, could justify this finding. These factors probably resulted in a downgraded level of evidence (see Table 3). Finally, further studies are necessary to examine changes in sympathetic nervous system activity associated with

the use of manual therapies by controlling the type (mobilisation or manipulation), the rate of oscillations, and their association with treatment benefits in pain conditions.

<A>Conclusions

This meta-analysis found moderate to high evidence suggesting that application of joint mobilisation techniques to the spine or the upper extremities produces a sympathetic-excitatory effect, expressed as an increase in skin conductance and a decrease in skin temperature, compared with a control or placebo intervention. However, this finding should be interpreted with caution due to heterogeneity of the data and the extrapolation to pain population samples.

Conflict of interest

None declared.

<A>References

[1] Carlesso LC, MacDermid JC, Gross AR, Walton DM, Santaguida PL. Treatment preferences amongst physical therapists and chiropractors for the management of neck pain: results of an international survey. Chiropr Man Therap 2014;22:11.

[2] Jull G. Use of high and low velocity cervical manipulative therapy procedures by Australian manipulative physiotherapists. Aust J Physiother 2002;48:189–93.

[3] Bier JD, Scholten-Peeters WGM, Staal JB, Pool J, van Tulder MW, Beekman E, *et al.* Clinical practice guideline for physical therapy assessment and treatment in patients with nonspecific neck pain. Phys Ther 2018;98:162–71.

[4] Delitto A, George SZ, Dillen L Van, Whitman JM, Sowa G, Shekelle P, *et al.* Low back pain. J Orthop Sport Phys Ther 2012;42:A1–57.

[5] Voogt L, de Vries J, Meeus M, Struyf F, Meuffels D, Nijs J. Analgesic effects of manual therapy in patients with musculoskeletal pain: a systematic review. Man Ther 2015;20:250–6.

[6] Young JL, Walker D, Snyder S, Daly K. Thoracic manipulation versus mobilization in patients with mechanical neck pain: a systematic review. J Man Manip Ther 2014;22:141–53.

[7] Sterling MM, Jull GG, Wright A. Cervical mobilisation: concurrent effects on pain, sympathetic nervous system activity and motor activity. Man Ther 2001;6:72–81.

[8] Plaza-Manzano G, Molina-Ortega F, Lomas-Vega R, Martínez-Amat A, Achalandabaso A, Hita-Contreras F. Changes in biochemical markers of pain perception and stress response after spinal manipulation. J Orthop Sport Phys Ther 2014;44:231–9.

[9] Molina-Ortega F, Lomas-Vega R, Hita-Contreras F, Plaza Manzano G, Achalandabaso A, Ramos-Morcillo AJ, *et al.* Immediate effects of spinal manipulation on nitric oxide, substance P and pain perception. Man Ther 2014;19:411–7.

[10] Paungmali A, Souvlis T, Vicenzino B. Naloxone fails to antagonize initial hypoalgesic effect of a manual therapy treatment for lateral epicondylalgia. J Manip Physiol Ther 2003;27:180–5.

[11] Kingston L, Claydon L, Tumilty S. The effects of spinal mobilizations on the sympathetic nervous system: a systematic review. Man Ther 2014;19:281–7.

[12] Lovick TA. Interactions between descending pathways from the dorsal and ventrolateral periaqueductal gray matter in the rat. In: Depaulis A, Bandler R, editors. The midbrain periaqueductal gray matter. NATO ASI Series (Series A: Life Sciences), Vol. 213. Boston, MA: Springer; 1991.

[13] Paungmali A, O'Leary S, Souvlis T, Vicenzino B. Hypoalgesic and sympatho-excitatory effects of mobilization with movement for lateral epicondylalgia. Phys Ther 2003;83:374–83.

[14] Petersen N, Vicenzino B, Wright W, Wright A. The effects of a cervical mobilisation technique on sympathetic outflow to the upper limb in normal subjects. Physiother Theory Pract 1993;9:149–56.

[15] Slater H, Vicenzino B, Wright A. 'Sympathetic slump': the effects of a novel manual therapy technique on peripheral sympathetic nervous system function. J Man Manip Ther 1994;2:156–62.

[16] Perry J, Green A, Singh S, Watson P. A randomised, independent groups study investigating the sympathetic nervous system responses to two manual therapy treatments in patients with LBP. Man Ther 2015;20:861–7.

[17] Tsirakis V, Perry J. The effects of a modified spinal mobilisation with leg movement (SMWLM) technique on sympathetic outflow to the lower limbs. Man Ther 2015;20:103–8.

[18] Piekarz V, Perry J. An investigation into the effects of applying a lumbar Maitland mobilisation at different frequencies on sympathetic nervous system activity levels in the lower limb. Man Ther 2016;23:83–9.

[19] Moutzouri M, Perry J, Billis E. Investigation of the effects of a centrally applied lumbar sustained natural apophyseal glide mobilization on lower limb sympathetic nervous system activity in asymptomatic subjects. J Manipulative Physiol Ther 2012;35:286–94.

[20] Cleland J, Durall C, Scott SA. Effects of slump long sitting on peripheral sudomotor and vasomotor function: a pilot study. J Man Manip Ther 2002;10:67–75.

[21] Vicenzino B, Cartwright T, Collins D, Wright A. Cardiovascular and respiratory changes produced by lateral glide mobilization of the cervical spine. Man Ther 1998;3:67–71.

[22] La Touche R, París-Alemany A, Mannheimer JS, Angulo-Díaz-Parreño S, Bishop MD, Lopéz-Valverde-Centeno A, *et al.* Does mobilization of the upper cervical spine affect pain sensitivity and autonomic nervous system function in patients with cervico-craniofacial pain? A randomized-controlled trial. Clin J Pain 2013;29:205–15.

[23] Roy RA, Boucher JP, Comtois A. Paraspinal cutaneous temperature modification after spinal manipulation at L5. J Manip Physiol Ther 2010;33:308–14.

[24] Chu J, Allen DD, Pawlowsky S, Smoot B. Peripheral response to cervical or thoracic spinal manual therapy: an evidence-based review with meta-analysis. J Man Manip Ther 2014;22:220–9.

[25] Lascurain-Aguirrebena I, Newham D, Critchley DJ. Mechanism of action of spinal mobilizations: a systematic review. Spine 2016;41:159–72.

[26] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[27] Higgins JPT, Douglas A. Assessing risk of bias in included studies. In: Cochrane handbook for systematic reviews of interventions. Wiley Online Books; 2008. Available at: https://doi.org/10.1002/9780470712184.ch8

[28] Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, *et al.* How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child 2008;93:458–61.

[29] Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Bossuyt P, Chang S, *et al.* GRADE: assessing the quality of evidence for diagnostic recommendations. Evid Based Med 2008;13:162–3.

[30] Austin TM, Richter RR, Sebelski CA. Introduction to the GRADE approach for guideline development: considerations for physical therapist practice. Phys Ther 2014;94:1652–9.

[31] Deeks JJ, Higgins JPT, Altman DG, editors. Chapter 9: Analyzing data and undertaking metanalyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS, editors. Cochrane handbook for systematic reviews of interventions Version 5.2.0 Oxford: Cochrane; 2017. Available at: www.training.cochrane.org/handbook.

[32] Perry J, Green A, Singh S, Watson P. A preliminary investigation into the magnitude of effect of lumbar extension exercises and a segmental rotatory manipulation on sympathetic nervous system activity. Man Ther 2011;16:190–5.

[33] Yu IY, Jung IG, Kang MH, Lee DK, Oh JS. Immediate effects of an end-range mobilization technique on shoulder range of motion and skin temperature in individuals with posterior shoulder tightness. J Phys Ther Sci 2015;27:1723–5.

[34] Roy RA, Boucher JP, Comtois AS. Effects of a manually assisted mechanical force on cutaneous temperature. J Manipulative Physiol Ther. 2008; 31: 230-6.

[35] Packer AC, Dibai-filho AV, Cláudia A, Costa DS, Macedo AB, Bortolazzo GL, *et al.* Immediate effects of upper thoracic manipulation on the skin surface temperature of the vertebral region in healthy women. Fisioter Pesqui 2015;22:54–60.

[36] Dibai-Filho AV, de Oliveira AK, Girasol CE, Dias FRC, Guirro RR. Additional effect of static ultrasound and diadynamic currents on myofascial trigger points in a manual therapy program for patients with chronic neck pain. Am J Phys Med Rehabil 2017;96:243–52.

[37] Ellestad SM, Nagle R V, Boesler DR, Kilmore MA. Electromyographic and skin resistance responses to osteopathic manipulative treatment for low-back pain. J Am Osteopat Assoc 1988;88:991–7.

[38] Vicenzino B, Collins D, Benson H, Wright A. An investigation of the interrelationship between manipulative therapy-induced hypoalgesia and sympatho-excitation. J Manip Physiol Ther 1998;21:448–53.

[39] Vicenzino B, Collins D, Wright T. Sudomotor changes induced by neural mobilisation techniques in asymptomatic subjects. J Man Manip Ther 1994;2:66–74.

[40] Chiu TWW, Wright A. To compare the effects of different rates of application of a cervical mobilisation technique on sympathetic outflow to the upper limb in normal subjects. Man Ther 1996;1:198–203.

[41] Chiu TWW, Wright A. Comparing the effects of two cervical mobilisation techniques on sympathetic outflow to the upper limb in normal subjects. Hong Kong Physiother J 1998;16:13–8.

[42] Simon R, Vicenzino B, Wright A. The influence of an anteroposterior accessory glide of the glenohumeral join on measures of peripheral sympathetic nervous system function in the upper limb. Man Ther 1997;2:18–23.

[43] Moulson A, Watson T. A preliminary investigation into the relationship between cervical snags and sympathetic nervous system activity in the upper limbs of an asymptomatic population. Man Ther 2006;11:214–24.

[44] Perry J, Green A. An investigation into the effects of a unilaterally applied lumbar mobilisation technique on peripheral sympathetic nervous system activity in the lower limbs. Man Ther 2008;13:492–9.

[45] Jowsey P, Perry J. Sympathetic nervous system effects in the hands following a grade III postero-anterior rotatory mobilisation technique applied to T4: a randomised, placebo-controlled trial. Man Ther 2010;15:248–53.

[46] Zegarra-Parodi R, Pazdernik VK, Roustit M, Park PYS, Degenhardt BF. Effects of pressure applied during standardized spinal mobilizations on peripheral skin blood flow: a randomised cross-over study. Man Ther 2016;21:220–6.

[47] Schmid A, Brunner F, Wright A, Bachmann LM. Paradigm shift in manual therapy? Evidence for a central nervous system component in the response to passive cervical joint mobilisation. Man Ther 2008;13:387–96.

Figure 1. Study search concerning skin conductance and skin temperature with the application of joint mobilisations.

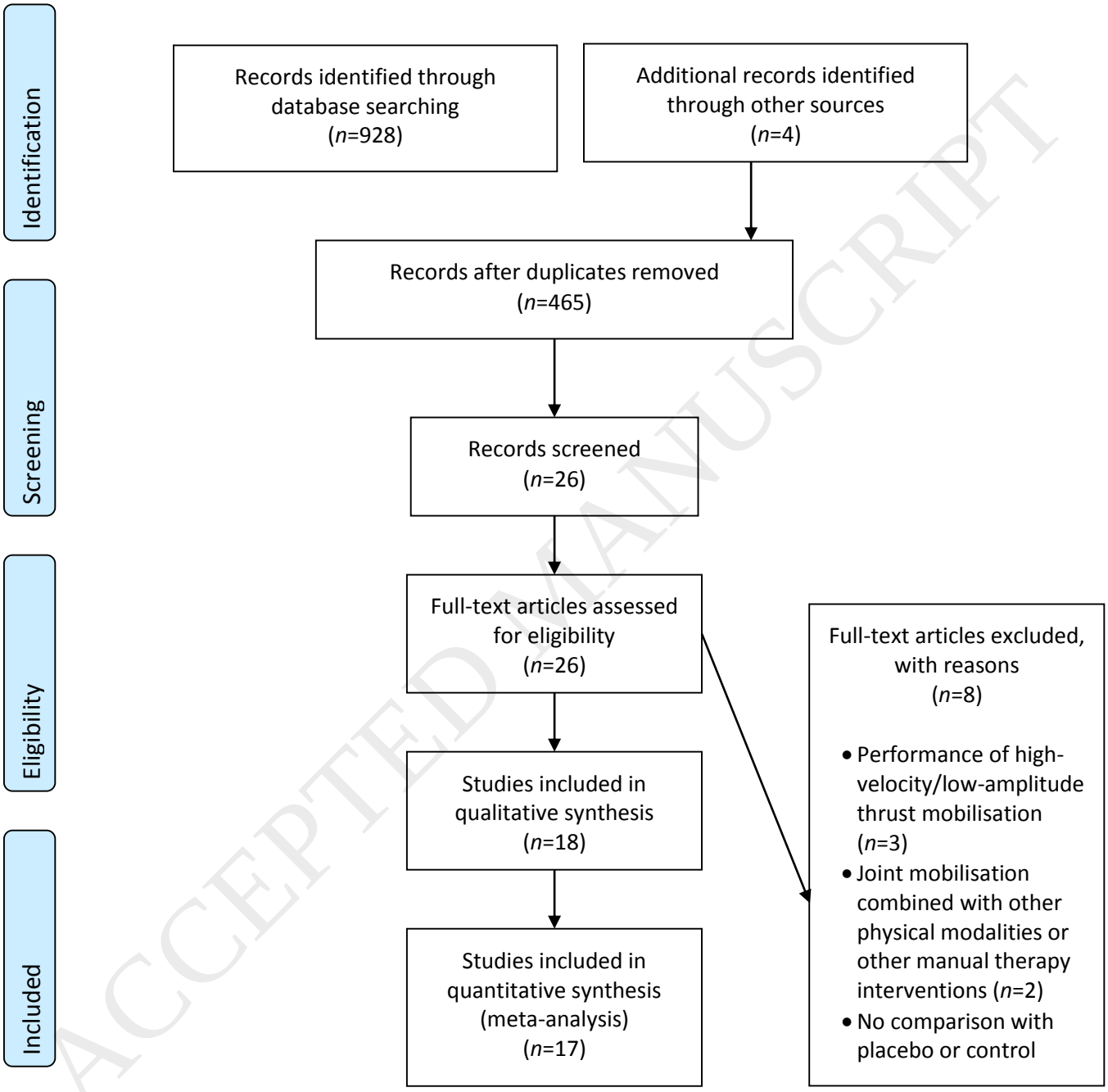

Figure 2. Comparison between the effects of joint mobilisation and control condition on skin conductance during the intervention period.

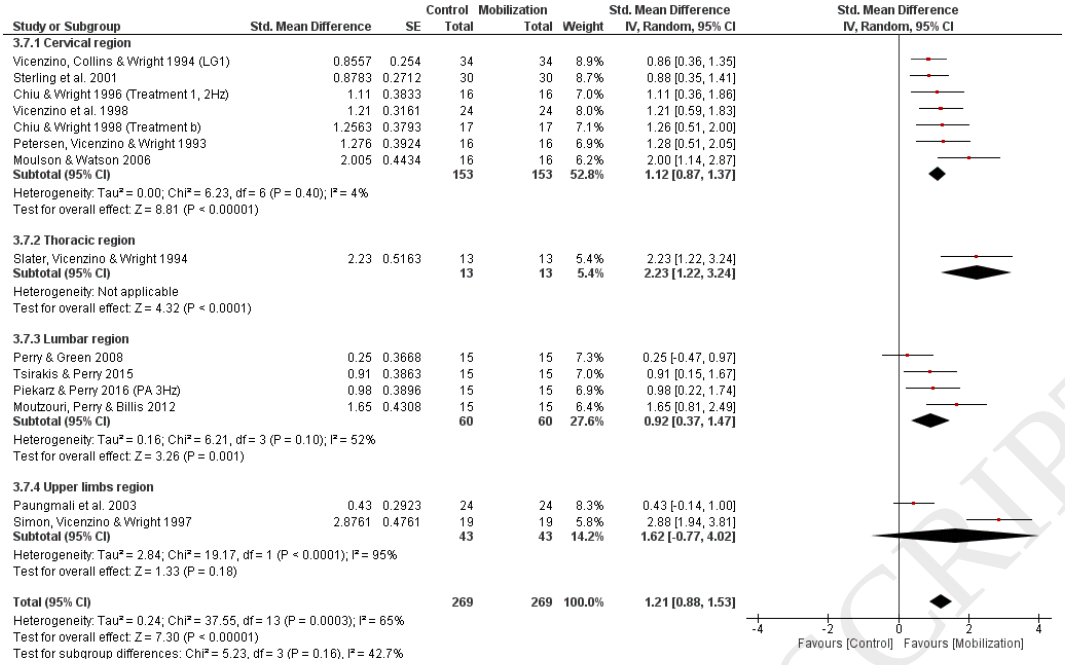

Figure 3. Comparison between the effects of joint mobilisation and placebo condition on skin conductance during the intervention period.

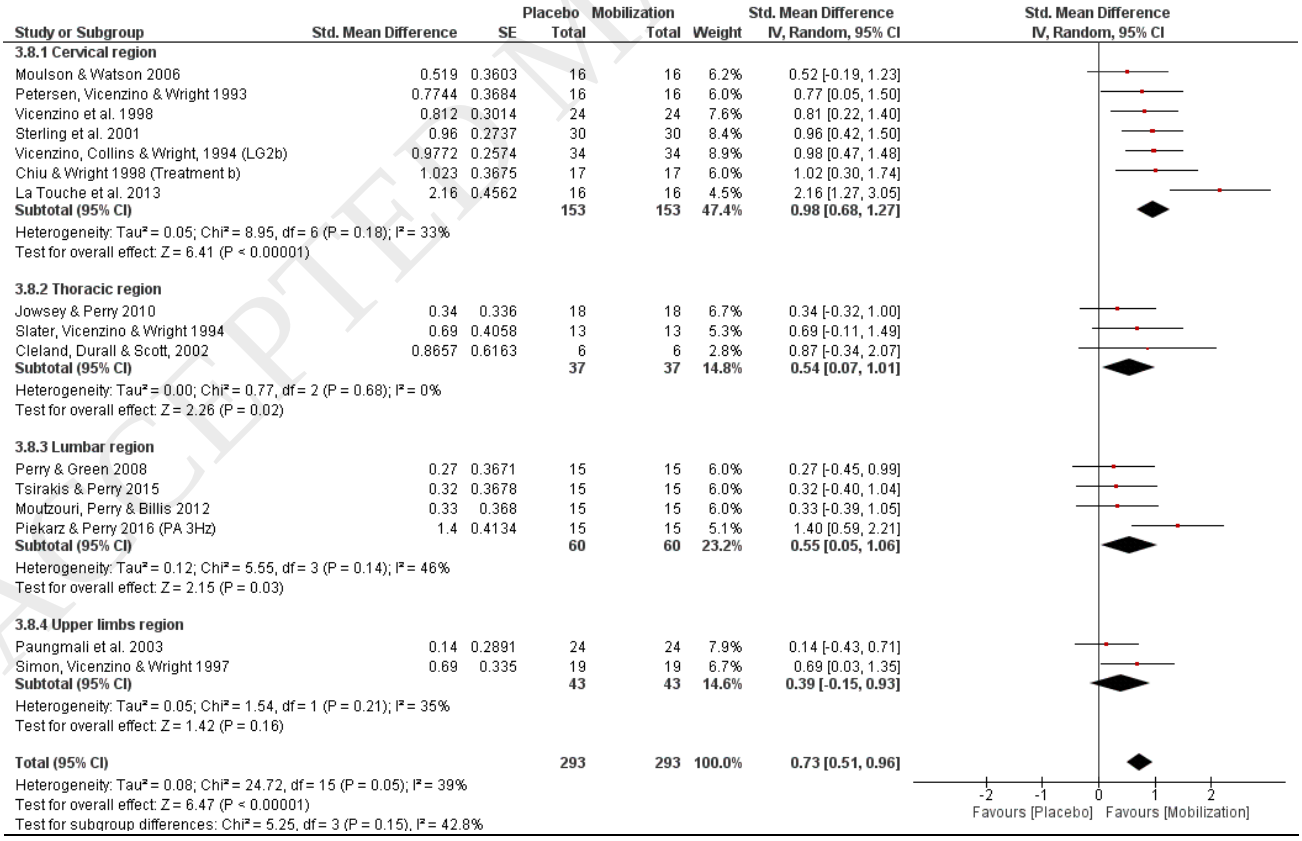

Figure 4. Comparison between the effects of joint mobilisation and control condition on skin temperature during the intervention period.

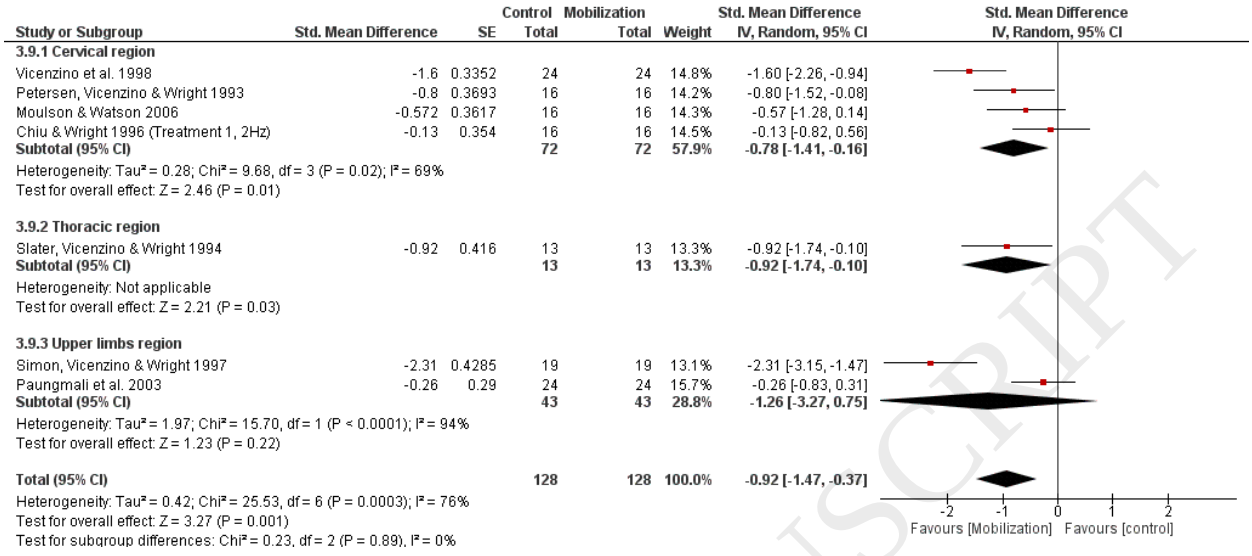

Figure 5. Comparison between the effects of joint mobilisation and placebo condition on skin temperature during the intervention period.

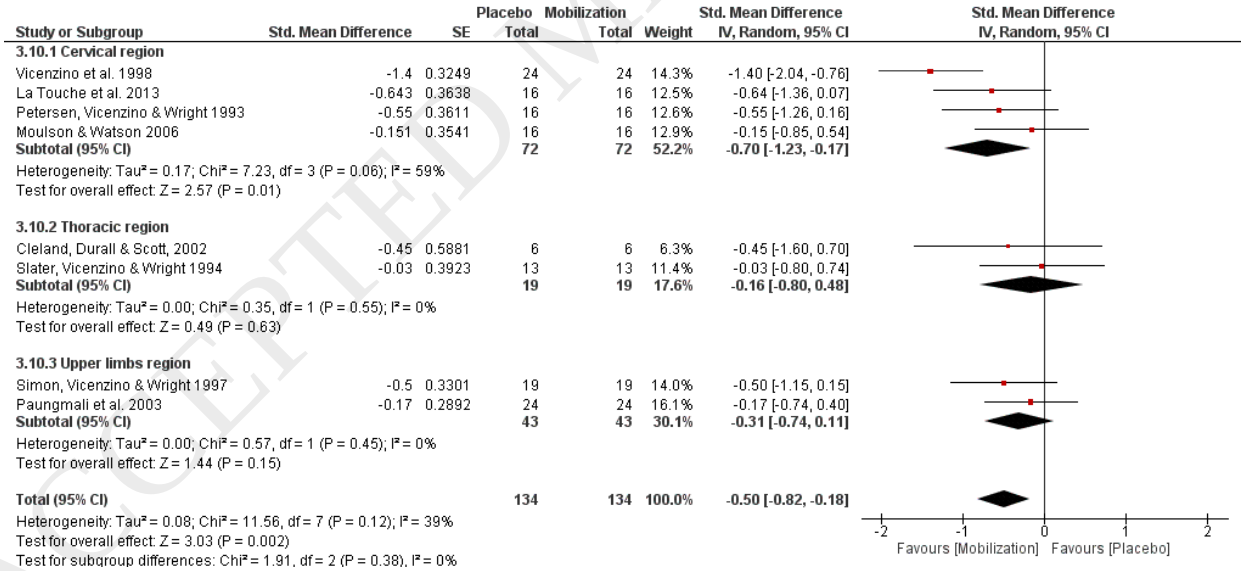

Table 1 Description of the studies included in the systematic review and meta-analysis (year of publication)

Authors	Subjects	Groups	Results
Petersen *et al.* [14]	16 healthy subjects received all conditions	I: PA Grade III central mobilisation on C5. Three series of 1 minute each. P: Soft touch with the thumbs over the spinous process of C5. The position was maintained without movement. Three series of 1 minute each. C: No contact with the researcher.	I produced a significant reduction in skin temperature and a significant increase in skin conductance compared with P or C. No differences between P and C were found.
Slater *et al.* [15]	22 healthy subjects received all conditions	I: 'Sympathetic slump' over the right sympathetic trunk in sitting position with left lateral flexion of the trunk. In this position, PA unilateral mobilisation is performed (Grade IV) over the T6 costovertebral joint. P: Same position as experimental position but with soft touch at the T6 level. C: Supine position without manual contact.	I produced a significant increase in skin conductance and a significant reduction in skin temperature during the treatment compared with P or C. No differences between P and I were found.
Vicenzino *et al.* [39]	34 healthy subjects received all conditions	I: Grade III left lateral glide of C5/C6 with the upper limb in the tension test 1 position. I2: Grade III left lateral glide of C5/C6 with the upper limb in the tension test 2b position. P: Manual contact but no position was performed in the application of tests 1 and 2b. C: Therapist next to the head of the subject without establishing any manual contact.	I and I2 produced a significant reduction in skin temperature and a significant increase in skin conductance compared with P and C. No differences between I and I2 or between P and C were found.
Chiu and Wright [40]	16 healthy subjects received all conditions	I: Grade III central PA over C5 at 2 Hz. I2: Grade III central PA over C5 at 0.5 Hz. C: Control.	I produced a significant increase in skin conductance compared with I2 and C. No significant differences in skin temperature were found between C and I and I2.
Vicenzino *et al.* [38]	24 subjects with unilateral epicondylalgia. All subjects received all conditions.	I: Grade III left lateral glide of C5/C6 with motion segment directed contralaterally to the affected upper limb. P: Manual contact but no oscillatory movement. C: Subject was positioned for the above conditions without any manual contact.	I produced a significant increase in skin conductance and a significant reduction in skin temperature compared with P and C.
Simon *et al.* [42]	19 healthy subjects received all conditions	I: Grade III AP over the glenohumeral joint. P: Arm and shoulder in a 90º position. C: Same position during the measurements.	I produced increase in skin conductance compared with P and C. No differences in reduction of skin temperature between I and P were found. Significant differences in reduction in skin temperature were found between I and C.

Chiu and Wright [41]	17 healthy subjects received all conditions	I1: Grade III unilateral PA over right posterior surface C5 articular. I2: C5 transverse vertebral pressure Grade II mobilisation. P: Grade III central PA over C5 at 0.5 Hz. C: Control.	I2 produced a significant increase in skin conductance compared with C, P and I1. I1 did not produce a significant increase in skin conductance compared with P or C. No differences were found in skin temperature between all groups.
Sterling *et al.* [7]	30 patients with cervical pain for >3 months and C5/6 dysfunction. All subjects participated in all conditions	I: Grade III unilateral PA oscillatory technique over the symptomatic side over the C5/C6. Three series of 1 minute. P: Manual contact on the symptomatic side over the C5/C6 joint without any movement. C: No physical contact between the subject and the researcher.	I produced a significant increase in skin conductance compared with P and C, and a significant reduction in skin temperature compared with C but similar changes to P. Minimum skin temperature was greater for I compared with P and C.
Cleland *et al.* [20]	12 healthy subjects, six per group	I: 'Sympathetic slump' (Grade IV) over the T6 costovertebral joint. P: Sitting position with the hand applying soft touch at the T6 level.	Non-significant changes in skin conductance and skin temperature between P and I.
Paungmali *et al.* [13]	24 patients with lateral epicondylalgia received all conditions	I: Lateral elbow glide. P: Manual contact was applied, and the patient was performing the grip without pain. C: Without manual contact, and the patient was performing the grip without pain.	Lateral elbow glide produced a significant increase in skin conductance and a significant reduction in skin temperature compared with P and C.
Moulson and Watson [43]	16 asymptomatic subjects received all conditions	I: Cervical SNAG performed at C5/6 at the same time as the subject turned their head to the right (three times). P: The researcher performed the same contact over the vertebrae but did not apply the accessory glide of the SNAG. The subject turned their head to the right and to the neutral position while the therapist maintained contact over C5/C6 with their thumbs (three times). C: No contact with the patient. Neutral position of the head.	I did not produce a significant reduction in skin temperature during the intervention and post-intervention period compared with P and C. I produced a significant increase in skin conductance compared with P and C in the intervention and post-intervention period.
Perry and Green [44]	45 healthy subjects (males), 15 per group	I: Grade III unilateral oscillatory mobilisation over the left zygapophyseal joint of L4/L5 at 2 Hz. P: Same hand position of the therapist on the area but applying a very soft touch and without the application of oscillatory movement. C: Same patient position but without any manual contact or movement.	I produced a significant increase in skin conductance compared with P or C during treatment.
Jowsey and Perry [45]	36 healthy subjects, 18 per group	I: Grade III PA rotational mobilisation over T4 at 0.5 Hz. P: Same position as real technique.	I produced a significant increase in skin conductance in the right extremity during the post-treatment period compared with P. No differences in skin conductance were observed between I and P.

Moutzouri and Perry [19]	45 healthy participants, 15 per group	I: SNAG mobilisation to the spinous process of L4. P: The researcher placed their hands in the same location over the column but did not apply glide with the lumbar movement. C: Participant was sitting with the therapist behind them without any manual contact and without performing any movement.	I produced a significant increase in skin conductance compared with C, but similar changes as P. No differences in skin conductance were found between P and C.
La Touche *et al.* [22]	32 patients with craniofacial chronic pain, 16 per group	I: AP(QP) mobilisation (C0 to C3) at 0.5 Hz. P: Hands on the occipital region. Same as before, but without mobilisation.	I produced an increase in skin conductance over time and sessions compared with P. No differences in skin temperature were observed between I and P.
Tsirakis and Perry [17]	45 healthy men, 15 per group	I: Medial glide of the fourth lumbar vertebrae with leg movement in extended position (hip flexion). P: Performed in the same way as the real technique but the hand on the spinous process does not perform the medial accessory glide on the vertebral segment. Same pressure is applied. C: The participant stayed in the left lateral decubitus position and did move their leg or receive manual contact.	I produced a significant increase in skin conductance in the right leg during the intervention period compared with C. A non-significant increase in the left leg was found during the intervention and post-intervention period compared with C and P.
Piekarz and Perry [18]	60 healthy participants, 15 per group	I1: PA mobilisation with 94 to 109 N force at 3 Hz. Three series of 1 minute each. I2: PA mobilisation with 94 to 109 N force at 2 Hz. Three series of 1 minute each. P: Same hand position but statically applied pressure over L4 during three periods of 1 minute each with a force of 101 N. C: Patient lying but without receiving any manual contact for 5 minutes.	I1 produced a significant increase in skin conductance compared with P and C during the intervention period. I1 produced a significant increase in skin conductance compared with C during the post-intervention period. I2 did not produce a significant increase in skin conductance compared with C, P or I1.
Zegarra-Parodi *et al.* [46]	32 healthy participants received all conditions	I1: Lateral glide on T1 at 40% of PPT for low-pressure mobilisation. I2: Lateral glide of T1 at 80% of PPT for high-pressure mobilisation. C: Control (without touching).	No significant changes in skin temperature were observed among the three groups.

I, intervention; C, control; P, placebo; PA, postero-anterior; AP, antero-posterior; PPT, pain pressure threshold; SNAG, sustained natural apophyseal glide.

Table 2. Risk of bias of randomised clinical trials included in the systematic review and meta-analysis

Study	1	2	3	4	5	6	7	8
Petersen *et al.* [14]	+	+	+	NA	+	+	+	-
Slater *et al.* [15]	?	?	+	NA	+	+	+	-
Vicenzino *et al.* [39]	?	?	+	NA	+	+	+	-
Chiu and Wright [40]	?	?	+	NA	+	+	+	-
Simon *et al.* [42]	?	?	?	NA	+	+	+	-
Chiu and Wright [41]	+	+	?	NA	+	+	+	-
Vicenzino *et al.* [38]	+	+	?	NA	+	+	+	?
Sterling *et al.* [7]	+	+	+	NA	+	+	+	-
Cleland *et al.* [20]	?	-	?	NA	+	+	+	+
Paungmali *et al.* [13]	+	+	-	NA	+	+	+	-
Moulson and Watson [43]	?	?	+	NA	?	+	+	-
Perry and Green [44]	+	+	+	NA	+	+	+	+
Jowsey and Perry [45]	?	?	+	NA	+	+	+	+
Moutzouri and Perry [19]	+	-	+	NA	?	+	+	+
La Touche *et al.* [22]	+	-	+	NA	+	+	+	+
Tsirakis and Perry [17]	+	+	+	NA	+	+	+	+
Zegarra-Parodi *et al.* [46]	+	?	-	NA	-	+	+	-
Piekarz and Perry [18]	+	+	+	NA	+	+	+	+

1, sequence generation; 2, allocation concealment; 3, participant blinding; 4, therapist blinding; 5, assessor blinding; 6, incomplete outcome data; 7, selective reporting; 8, other risks of bias; +, low risk of bias; –, high risk of bias; ?, unclear risk of bias; NA, not applicable.

Table 3. GRADE evidence profile for mobilisation interventions in the sympathetic nervous system

Quality assessment								Summary of findings			
								Number of participants			
Comparison	Outcome	Number of trials (design)	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	Subjects in intervention group	Subjects in control group	Estimate SMD (95% CI)	Quality
Mobilisation interventions vs control	Skin conductance	Fourteen RCTs	Low	Serious. High heterogeneity (I^2=65%)	Serious	Not serious	Strongly suspected	269	269	1.21 (0.88 to 1.53)	Very low
Mobilisation interventions vs control (cervical region)	Skin conductance	Seven RCTs	Low	Not serious. Low heterogeneity (I^2=4%)	Serious	Not serious	Undetected	153	153	1.12 (0.87 to 1.37)	Moderate
Mobilisation interventions vs control (thoracic region)	Skin conductance	One RCTs	Low	NA	Not serious	Serious	NA	13	13	2.23 (1.22 to 3.24)	Moderate
Mobilisation interventions vs control (lumbar region)	Skin conductance	Four RCTs	Low	Serious. Moderate heterogeneity (I^2=52%)	Not serious	Serious	Undetected	60	60	0.85 (0.4 to 1.3)	Low
Mobilisation interventions vs control (upper limbs region)	Skin conductance	Two RCTs	High	Very serious. High heterogeneity (I^2=95%)	Serious	Serious	NA	43	43	1.62 (-0.77 to 4.01)	Very low
Mobilisation interventions vs control	Skin temperature	Seven RCTs	Low	Serious. High heterogeneity (I^2=71%)	Serious	Serious	Undetected	128	128	-0.92 (-1.47 to -0.37)	Very low

Mobilisation interventions vs control (cervical region)	Skin temperature	Four RCTs	Low	Serious. High heterogeneity (I^2=69%)	Not serious	Serious	NA	72	72	-0.78 (-1.41 to -0.16)	Low
Mobilisation interventions vs control (thoracic region)	Skin temperature	One RCT	Low	NA	Not serious	Serious	NA	13	13	-0.92 (-1.74 to -0.10)	Moderate
Mobilisation interventions vs control (upper limbs region)	Skin temperature	Two RCTs	High	Very serious. High heterogeneity (I^2=94%)	Serious	Serious	NA	43	43	-1.26 (-3.27 to 0.75)	Very low
Mobilisation interventions vs placebo	Skin conductance	Sixteen RCTs	Low	Not serious. Low heterogeneity (I^2=39%)	Serious	Not serious	No	293	293	0.73 (0.51 to 0.96)	Moderate
Mobilisation interventions vs placebo (cervical region)	Skin conductance	Seven RCTs	Low	Not serious. Low heterogeneity (I^2=33%)	Serious	Not serious	No	153	153	0.98 (0.68 to 1.27)	Moderate
Mobilisation interventions vs placebo (thoracic region)	Skin conductance	Three RCTs	Low	Not serious. Homogeneous (I^2=0%)	Not serious	Serious	NA	37	37	0.54 (0.07 to 1.01)	Moderate
Mobilisation interventions vs placebo (lumbar region)	Skin conductance	Four RCTs	Low	Serious. Moderate heterogeneity (I^2=46%)	Not serious	Serious	NA	60	60	0.55 (0.05 to 1.06)	Low
Mobilisation interventions vs placebo (upper limbs region)	Skin conductance	Two RCTs	High	Not serious. Moderate heterogeneity (I^2=35%)	Serious	Serious	NA	43	43	0.39 (-0.15 to 0.93)	Low

Mobilisation interventions vs placebo	Skin temperature	Eight RCTs	Low	Not serious. Low heterogeneity (I^2=39%)	Serious	Serious	Undetected	134	134	-0.50 (-0.82 to -0.18)	Low
Mobilisation interventions vs placebo (cervical region)	Skin temperature	Four RCTs	Low	Serious. Moderate heterogeneity (I^2=59%)	Serious	Serious	NA	72	72	-0.70 (-1.23 to -0.17)	Very low
Mobilisation interventions vs placebo (thoracic region)	Skin temperature	Two RCTs	Low	Not serious. Homogeneous (I^2=0%)	Not serious	Serious	NA	19	19	-0.16 (-0.80 to 0.48)	Moderate
Mobilisation interventions vs placebo (upper limbs region)	Skin temperature	Two RCTs	Low	Not serious. Homogeneous (I^2=0%)	Serious	Serious	NA	43	43	-0.31 (-0.74 to 0.11)	Low

RCT, randomised controlled trial; SMD, standardised mean difference; NA, not applicable.

[a]No risk of bias was found in any study.

[b]I^2>40%: serious; I^2>80%: very serious.

[c]No indirectness of evidence was found in any study.

[d]n<300, serious; n<300 and estimated effect little or absent, very serious.

[e]Based on funnel plot analysis.