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Systematic Review

Adverse Events After Cervical Spinal Manipulation – A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Background: Cervical manipulations are widely used by physiotherapists, chiropractors, osteopaths, and medical doctors for musculoskeletal dysfunctions like neck pain and cervicogenic headache. The use of cervical manipulation remains controversial, since it is often considered to pose a risk for not only benign adverse events (AEs), such as aggravation of pain or muscle soreness, but also severe AEs such as strokes in the vertebrobasilar or carotid artery following dissections. Studies finding an association between cervical manipulation and serious AEs such as artery dissections are mainly case control studies or case reports. These study designs are not appropriate for investigating incidences and therefore do not imply causal relationships. Randomized controlled trials (RCTs) are considered the gold standard study designs for assessing the unconfounded effects of benefits and harms, such as AEs, associated with therapies.

Objective: Due to the unclear risk level of AEs associated with high-velocity, low-amplitude (HVLA) cervical manipulation, the aim of this study was to extract available information from RCTs and thereby synthesize the comparative risk of AEs following cervical manipulation to that of various control interventions.

Study Design: Systematic review and meta-analysis.

Methods: A systematic literature search was conducted in the PubMed and Cochrane databases. This search included RCTs in which cervical HVLA manipulations were applied and AEs were reported. Two independent reviewers performed the study selection, the methodological quality assessment, and the GRADE approach. Incidence rate ratios (IRR) were calculated. The study quality was assessed by using the risk of bias 2 (RoB-2) tool, and the certainty of evidence was determined by using the GRADE approach.

Results: Fourteen articles were included in the systematic review and meta-analysis. The pooled IRR indicates no statistically significant differences between the manipulation and control groups. All the reported AEs were classified as mild, and none of the AEs reported were serious or moderate.

Limitations: The search strategy was limited to literature in English or German. Furthermore, selection bias may have occurred, since only PubMed and Cochrane were used as databases, and searching was done by hand. RCTs had to be excluded if the results did not indicate the group in which the AEs occurred. A mandatory criterion for inclusion in the meta-analysis was a quantitative reproduction of the frequencies of AEs that could be attributed to specific interventions.

Conclusion: In summary, HVLA manipulation does not impose an increased risk of mild or moderate AEs compared to various control interventions. However, these results must be interpreted with caution, since RCTs are not appropriate for detecting the rare serious AEs. In addition, future RCTs should follow a standardized protocol for reporting AEs in clinical trials.

Key words: Cervical manipulation, adverse events, randomized controlled trial, systematic review, meta-analysis

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Neck pain is a common condition that imposes a high global socioeconomic burden of disease. The point prevalence of neck pain comprises approximately 289 million cases worldwide and is nearly as frequent as osteoarthritis (approximately 303 million). Furthermore, about 65 million incident cases involving neck pain were estimated worldwide in 2017. The number of years lived with disease caused by neck pain represents one of the top causes of disability, and the condition has led to reduced quality of life, work disability, and high direct and indirect costs to health care systems and society (1-3).

Nonsurgical therapy strategies such as manual therapy are recommended treatment options in clinical practice guidelines, as are exercise therapy, injections, nonsteroidal anti-inflammatory drugs, psychological therapies, and multidisciplinary treatment modalities, depending on severity and chronicity (4).

Within manual therapy, cervical manipulations are widely used by physiotherapists, chiropractors, osteopaths, and medical doctors for musculoskeletal dysfunctions like neck pain and cervicogenic headache. Results of recent literature reviews highlight the efficacy of cervical manipulation to alter various factors such as pain, function, and quality of life (5-8).

However, the cervical manipulation technique remains controversial, since it is often considered to present a risk for not only benign adverse events (AEs) such as aggravation of pain, muscle soreness, or headache but also severe AEs such as post-dissection vertebrobasilar or carotid strokes, disc herniation, fractures, or spinal cord compression (9).

Swait and Finch (10) produced a scoping review concerning the risks manual therapy could present to the spine. Based on the synthesized literature, the review concluded that most observed AEs were benign and only a small proportion of the detected side effects were serious.

The evidence regarding the risk of AEs is contradictory (9,11-14). Studies that find an association between cervical manipulation and serious AEs such as artery dissections are mainly case control studies or case reports (9,15,16). These study designs are not appropriate for investigating incidences and thus do not imply causal relationships (17).

Randomized controlled trials (RCTs) are considered the gold standard study designs for assessing the unconfounded effects of various therapies' benefits and harms, such as AEs (18). Ideally, RCTs' results are synthesized in systematic reviews, including a meta-analysis that was conducted to evaluate the risk of spinal manipulation for low back pain (19), for example. Although RCTs that assess cervical manipulations exist, investigating what AEs may be associated with the procedure is a secondary research goal (20).

However, according to the authors´ knowledge, no up-to-date, RCT-based meta-analysis and/or systematic review has been conducted to assess the increase in the risk of AEs after cervical manipulation.

To fill the gaps in this knowledge, the aim of this meta-analysis was to extract available information from RCTs and use the data to synthesize the risk of AEs following cervical manipulation compared to various control interventions. Furthermore, we aimed to classify the AEs according to each event's severity and type (e.g., musculoskeletal AE or neurological AE).

Methods

The reporting of this systematic review and meta-analysis was based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (21). This systematic review and meta-analysis was registered in PROSPERO (CRD42021231403).

Study Selection

This systematic review and meta-analysis included studies of men and women of all ages with various musculoskeletal conditions such as headache, neck pain, neck-arm pain, and neck-related pain of both a specific and nonspecific nature and acute, subacute, and chronic status. Additionally, we considered other conditions in the orofacial area, such as those resulting from temporomandibular disorders.

The types of intervention applied consisted of any kind of manipulation of the cervical spine. The manipulation was defined as a high-velocity, low-amplitude (HVLA) manipulation applied to the upper, mid-, or lower cervical spine. HVLA spinal manipulation is defined as "a rapid use of force over a short duration, distance, and/or rotational area within the anatomical range of motion of a joint to engage the restrictive barrier in one or more planes of motion to elicit the release of restriction" (22). Studies in which manipulation is performed as an additional treatment have also been considered.

Nonthrust spinal manipulation consists of low-velocity and repeated joint movements of different amplitudes. All instances of nonthrust manipulation and manipulation in other spine areas were excluded.

For control interventions, we considered treatments such as sham manipulation, manipulation ap-

plied to a different spinal area (such as the thoracic spine), mobilization techniques (defined as low-velocity repeated joint movements with different amplitudes), soft tissue techniques (e.g., massage or trigger point therapy), active treatments like supervised exercises, home exercises, or rehabilitation programs, and any type of medication for pain relief.

In the systematic review and meta-analysis, only RCTs were included. All other study designs were excluded. To merit inclusion, the RCTs were required to contain exact information about the number and type of AEs that occurred and had to differentiate between the intervention group and the control group.

Outcomes

The main outcomes measured were the number and type of any AE that followed cervical spine manipulation and a control intervention, such as aggravated pain, radiating symptoms, dizziness, local soreness, headache, back pain, neck pain, arm numbness, facial numbness, nausea, arm fatigue, tiredness, stiffness, pain in extremities, paresthesia, neck fatigue, and muscle twitching. AEs were classified as "musculoskeletal," "neurological," and "other." (The last category was used if no specific classification could be made, due to imprecise information in the study). Therefore, the incidence per person-time of the AEs in the manipulation and control groups and the incidence rate ratio (IRR) of the AEs between the manipulation groups and control groups were calculated. Furthermore, we differentiated among major, moderate, and mild AEs. According to a Delphi study conducted by Carnes et al in 2010, major and moderate AEs are defined as long-term persistent conditions of moderate or severe intensity that result in major impairment and usually require immediate medical attention. Mild AEs, on the other hand, present as reversible symptoms of short duration and do not require further treatment (23).

The authors of this review and meta-analysis (SN and NP) classified the AEs independently. In cases of inconsistency, a solution was found by discussion or consultation with the third author (NB).

Data Sources and Searches

All searches were conducted in MEDLINE and Cochrane between March 2020 and April 2020. An updated search was performed in May 2022. Key words, synonyms, and medical subject headings (MeSH) concerning spinal manipulation, AEs, and RCTs were identified prior to the search process. The identified search terms were combined using Boolean operators. The search was restricted to German- and English-language articles. No restrictions were made to the publication period of the articles being searched. This study's complete search strategy is availabe upon request.

Selection

Two independent authors screened the results (titles and abstracts) from the initial search and identified the full-text articles to be read. Full texts were read by two authors (NP and SN) independently. Any disagreements concerning appraisal of the inclusion criteria were resolved by discussion. In cases of unresolved disagreement, a third reviewer (NB) was consulted.

The following data were extracted from the included articles: rehabilitation area (profession: chiropractor, physical therapist, osteopath, etc.), specific rehabilitation area (musculoskeletal, neurological, etc.), specific condition or disease (asymptomatic, neck pain, or headache), object of the study, inclusion and exclusion criteria, intervention, type of randomization, blinding, recruitment, primary and secondary outcome, follow-up, localization of manipulation (unclear; upper, mid-, or lower cervical spine), number of manipulations, statistical analysis, number of participants, number of dropouts, mean age, gender, pre-existing diseases, reporting of AE (yes/no), type of AE, and severity of AE (major, moderate, or mild). The data were extracted independently by two authors (NP and SN) and entered in Microsoft Excel sheets.

Quality Assessment Tool 2

The Cochrane risk-of-bias (RoB 2) tool was used to evaluate the assessments' quality. Evaluations were conducted independently by NP and SN. In cases of disagreement, a solution was found by discussion. If consensus could not be reached, a third reviewer (NB) was consulted. During the evaluation process, the guidelines established by the Cochrane Collaboration to perform assessments for risk of bias (RoB) were followed.

Data Analysis and Synthesis

Data analysis was conducted using R and the meta and dmetar packages (24). Fixed effect models—or in case of heterogeneity, random effect models—and sensitivity analysis were applied. For the binary outcomes (AE: yes/no), the pooled effect size was IRR. The incidence rate (IR) was calculated by dividing the number of events per group by person-time per group. The person-time was determined as the observation period (intervention

and follow-up period). In studies with zero cell frequencies, continuity correction of 0.5 was used. The heterogeneity was evaluated statistically using the I^2 statistic. Additionally, a subgroup analysis was performed by grouping the studies into type of AE (musculoskeletal, neurological, other), profession of caregiver (chiropractor, physical therapist, mixed, unclear) and age groups of participants (18-40 years, 40-80 years). Publication bias was assessed by funnel plots.

Data synthesis was performed by 2 researchers independently. The quality of evidence and strength of recommendation were assessed using the GRADE approach (25).

Results

During the literature search, 5,711 potential articles were identified. Of those 5,711 publications, 301 articles were selected as relevant after screening the title and abstract. After the screening process, 43 full-text articles were considered relevant. Twenty-eight articles were excluded for not meeting the inclusion criteria. Ultimately, we included 14 articles. The detailed process of the literature research is depicted in Fig. 1. Details of the included articles are provided in Table 1.

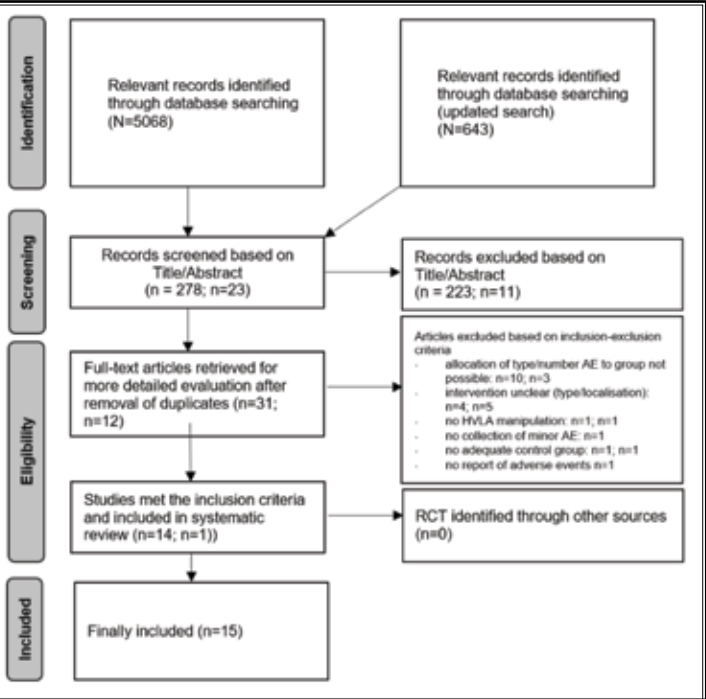

Fig. 1. *PRISMA flowchart of review.*

Methodological Quality Assessment (RoB 2)

The RoB results are graphically depicted in Fig. 2. Most of the studies were labeled high RoB or had some concerns in domain 2 ("bias due to deviations from intended interventions"). The questions concerning the blinding of the patients and the study staff were answered with "yes" or "probably yes," because of the nature of the applied intervention (26-32,35-39).

Two studies were rated as having some concerns in domain 1 ("Randomization Process") due to the lack of information about the randomization process (29,34).

In domain 4, 12 items were classified as "high risk" (26, 28-30, 32-29). Two articles could be classified as "low risk" because a sham manipulation was carried out (27,31). The analysis of the funnel plot (Fig. 3) indicates no evidence of publication bias for or against any kind of manipulation or control intervention.

Level of Manipulation

In 4 publications, the manipulation was directed at the upper cervical spine (26,28,35,36). Three articles focused on manipulating the mid-cervical spine (27,30,38), and one article concerned the manipulation of the lower cervical spine (37). Five of the 14 studies included concerned clinical examinations to determine the most hypomobile cervical segments in need of manipulation (29,31-34).

Type of Comparator

Most studies used sham manipulation as a comparator on the same segment as the real manipulation (27,31,37,38). In addition, a mobilization of the cervical or upper thoracic spine was a common control intervention (33,34,39). Less frequently, a sustained pre-manipulative stretch was performed in the control group (28,36). Each of the following comparators was applied only once: lying supine for the duration of the intervention (26), home exercise, supervised exercises for the neck and upper back (29), HVLA manipulation of the upper thoracic spine (30), soft tissue massage or no intervention (35), and low-level-laser therapy (32).

Profession of Caregiver

In most cases, the treating professionals were physical therapists (26-28,30,35-38). In 4 of the articles, the subjects were manipulated by chiropractors (29,31-33). In a 1992

Table 1. *Characteristics of the included RCTs.*

	Author (Year)	Intervention	Profession	Sample	Measurement Time Points and Follow-up	Reported AE	Results/ Conclusion
1	Carrasco-Uribarren et al (2021) (26)	Intervention Group: 3 treatment sessions (11 minutes on alternating days), application of a traction-manipulation protocol; pre-manipulative section, traction manipulation in the resting position-section, post-manipulation section Total Number of Manipulations Per Person: 3 Control Group: The subjects lay supine for 11 minutes.	physiotherapist (with 10 years of experience)	Total: n = 40 Intervention Group: n = 20 Control Group: n = 20 Age/Gender (F/M): Intervention Group: 55.9 (SD 11.96); (16/4) person-time = 627 Control Group: 52.1 (SD 16.03); (16/4) person-time = 627 Condition: cervicogenic dizziness	T0: baseline T1: 48 h after the last intervention Follow-Up: one month	No AEs after treatment or follow-up were reported.	No patient experienced any AE after the application of the interventions.
2	García-Pérez- Juana et al (2018) (27)	Intervention Groups: 1) right cervical thrust group 2) left cervical thrust group Total Number of Manipulations Per Person: one Control Group: SM	physical therapist (12 years of clinical experience in treating patients with neck pain [certificate in SMT])	Total: n = 54 (n = 18 each group) Age/Gender (F/M): right thrust: 35 (SD 10); (14/4) left thrust: 38 (SD 7); (15/3) person-time = 288 Control Group: (SM) 39 (SD 7); (13/5) person-time = 144 Condition: chronic mechanical neck pain	T0: baseline T1: post-intervention Follow-Up: one week	No AE was reported by any patient.	No major AEs were reported in the 7-day follow-up.
3	Erhardt et al (2015) (28)	Intervention Group: high-velocity-thrust technique to atlanto-axial segments through posterior superior aspect of the right transverse process of C1 Total Number of Manipulations Per Person: one Control Group: static hold of pre-manipulative position for 3-5 seconds	physical therapist	Total: n = 23 Intervention Group: n = 11 Control Group: n = 12 Age/Gender (F/M): Intervention Group: 41.58 (SD 12.6); (9/3) person-time = 66 Control Group: 38.55 (SD 9); (5/6) person-time = 72 Condition: asymptomatic patients	T0: baseline T1: immediately after intervention Follow-Up: after 5 days	No AEs were reported.	In healthy patients, the HVLA technique used seems not to be associated with hemodynamic AEs.

Table 1 cont. *Characteristics of the included RCTs.*

	Author (Year)	Intervention	Profession	Sample	Measurement Time Points and Follow-up	Reported AE	Results/ Conclusion
4	Maiers et al (2015) (29)	Intervention Group: SMT (treated segments and number of treatments were individually determined; additionally, HE) Total Number of Manipulations Per Person: varied from individual to individual {AU: Please see that this edit retains your intended meaning.} (with a maximum of 20 visits) Control Groups: 1) HE (4x; 45-60 minutes; including pain education, postural information, practical demonstration of body mechanics for ADL, neck and back exercises (flexibility, balance and coordination) 2) SRE (20 exercise sessions, one hour, supervised by an exercise therapist, additional HE)	SMT: 11 different chiropractors (with a minimum of 5 years clinical practice) HE: chiropractor or exercise therapist SRE: exercise therapist	Total: n = 241 SMT Group: n = 80 HE Group: n = 79 SRE Group: n = 82 Age/Gender (F/M): Total: 72.3 (SD 5.4); (113/128) SMT: 71.7 (SD 5.2) (36/44) person-time = 6720 SRE: 72.6 (SD 5.6); (42/40), HE: 72.7 (SD 5.3); (35/44) person-time = 13524 Condition: mechanical neck pain	T0: baseline T1: after 12-week intervention phase	SMT/SRE/HE: aggravated neck pain (29/40/22); muscle soreness (10/26/5); lower extremity joint pain (5/22/5); back pain (6/16/3); upper extremity joint pain (7/13/0); stiffness (6/12/1); headache (8/6/2); dizziness (1/3/1); radiating symptoms (0/1/1); paraesthesia (2/0/0); fatigue (0/1/0)	No serious AEs; AEs were reported by 130 of 195 participants, SRE had 3 times more AEs than did HE, SMT had twice as many AEs as the HE group; majority of AEs were musculoskeletal
5	Martínez-Segura et al (2012) (30)	Intervention Groups: mid-cervical spine thrust manipulation (R or L side); level of the manipulated segment was determined individually Total Number of Manipulations Per Person: one-max. 2 attempts Control Group: HVLA anterior-posterior thrust to the upper Tx (no more than 2 attempts were performed)	one physical therapist (more than 10 years' experience; certificate in SMT)	Total: n = 90 Cx-Thrust R: n = 29 L: n = 28 Tx-Thrust: n = 33 Age/Gender (F/M): Cx-Thrust R: 35 (SD 8); (15/14) L: 36 (SD 9); (15/13) person-time = 456 Tx-Thrust: 38 (SD 7); (16/17) person-time = 264 Condition: bilateral chronic mechanical neck pain	T0: baseline T1: 10 minutes after intervention	Total Number of AEs: n = 2 Cx-Thrust R: increased neck pain Tx-Thrust: neck fatigue after treatment Both AEs resolved within 24 hours	No serious short-term AEs were reported after cervical spinal manipulation. Only one person reported symptoms after treatment, which were mild and became resolved within 24 hours.

Table 1 cont. *Characteristics of the included RCTs.*

	Author (Year)	Intervention	Profession	Sample	Measurement Time Points and Follow-up	Reported AE	Results/ Conclusion
6	Vernon et al (2012) (31)	Intervention Group: RM, which consisted of one RM on the side of the lesion and one SM on the opposite side (60-second rest between the 2 manipulations). Manipulation position: mild flexion, rotation away from side of lesion, head rests on therapist's forearm; local joint preload was applied by pressure over the target joint. Total Number of Manipulations Per Person: one Control Group: SM, which consisted of one SM on the side of the lesion and one SM on the opposite side (procedure like the RM without preload thrust—therefore, a rapid movement was created by a drop action of the headpiece cam mechanism with an associated sharp sound)	chiropractor with 35 years of experience	Total: n = 67 RM: n = 33 SM: n = 34 Age/Gender (F/M): RM: 38.3 (SD 9.9); (14/18) person-time = 66 SM: 38.8 (SD 11.3); (20/12) person-time = 68 Condition: mechanical neck pain	T0: baseline T1: 5 and 15 minutes after intervention	RM: n = one; mild pain (resolved within 24 hours)	Only one AE occurred in the RM group. The event was a mild post- treatment pain reaction lasting < 24 hours
7	Saayman et al (2011) (32)	Intervention Groups: 1) cervical HVLA techniques were used; no more than 3 joints were treated per session 2) manipulative therapy + LLLT Total Number of Manipulations Per Person: between 6 and 18 Control Group: LLLT	chiropractor	Total: n = 60 (n = 20 each group) Age/Gender (F/M): Intervention Groups: HVLA: 31 (SD 7.6) HVLA + LLLT: 28 (SD 6.2) person-time = 253.33 Control Group: LLLT: 29 (SD 6.7) person-time = 1026.66 Condition: cervical facet joint pain	T0: baseline T1: post-intervention (2 and 3 weeks) Follow-Up: 4 weeks	No serious AEs were reported in any of the groups.	During the 4-week follow-up, no serious AEs were reported.

Table 1 cont. *Characteristics of the included RCTs.*

	Author (Year)	Intervention	Profession	Sample	Measurement Time Points and Follow-up	Reported AE	Results/ Conclusion
8	Gemmel and Miller (2010) (33)	Level of manipulation or mobilization was individually determined by clinical examination. Intervention Group: HVLA Manipulation: one-2 thrusts at the Cx or the upper Tx Total Number of Manipulations Per Person: between 6 and 12 AI: one setting for the Atlas and 2 settings for the Cx and Tx (HVLA) Total Number of Manipulations Per Person: 18 Control Group: mobilization (low-grade passive movements with different amplitudes applied to one or more restricted segments in the Cx and Tx)	2 chiropractors (first one with 30 years of experience and second one with 15 years of experience)	Total: n = 57 HVLA Manipulation Group: n = 16 AI Group: n = 16 Mobilization Group: n = 15 Age/Gender (F/M): HVLA Manipulation Group: 46.9 (SD 9.1); (13/3) AI Group: 46.8 (SD 11.8); (11/5) person-time = 12,320 Mobilization Group: 42.8 (SD 13); (13/15) person-time = 5,775 Condition: subacute nonspecific neck pain	T0: baseline T1: post-intervention (3 weeks) Follow-Up: 3, 6, and 12 months	15 subjects reported minor AEs after manual therapy (resolved one-3 days after treatment) AEs: (AI/ HVLA manipulation/ mobilization) mildly increased neck pain (7/4/2); mildly radiating pain (5/2/1); mild arm weakness (1/0/0); mild arm numbness (1/0/0); mild headache (3/3/4); mild fatigue (3/3/0); mild dizziness (1/1/1); mild muscle twitching (0/1/0)	Low risk of AEs after chiropractic treatment. All AEs were minor and resolved after one-3 days following treatment. The events arose equally often in the 3 different groups.
9	Leaver et al (2010) (34)	Level and type of manipulation and mobilization were individually determined by clinical examination. Intervention Group: HVLA neck manipulation Control Group: neck mobilization by manual low-velocity oscillating passive movements	Chiropractors, physiotherapists, and osteopaths (minimum of 2 years' experience; postgraduate qualification)	Total: n = 182 (n = 91 in each group) Age/Gender (F/M): HVLA Neck Manipulation Group: 38 (SD 10.3); (52/39) person-time = 9,555 Control Group (Neck Mobilization): 39.7 (SD 11.1); (66/25) person-time = 9,555 Condition: recent onset of nonspecific neck pain	T0: baseline T1: post-intervention (2 weeks) Follow-Up: 3 months	There were no serious AEs reported by the participants after the 3-month follow-up. Mobilization Group: 2 serious AEs that were unrelated to the treatment (cardiac surgery and severe arm pain and weakness) Minor AEs (Manipulation/ Mobilization): neck pain (28/24); headache (22/17); dizziness/vertigo (7/6); nausea (4/7); paresthesia (8/5); other (7/3)	There were no major AEs after the treatment and the follow-up. Minor AEs were often reported.

Table 1 cont. *Characteristics of the included RCTs.*

	Author (Year)	Intervention	Profession	Sample	Measurement Time Points and Follow-up	Reported AE	Results/ Conclusion
10	Oliveira-Campelo et al (2010) (35)	Intervention Group: manipulation group (atlanto-occipital joint thrust) Total Number of Manipulations Per Person: a maximum of 2 manipulations Control Groups: 1) soft tissue group (inhibition technique over suboccipital muscles) 2) control (no intervention)	6 years of postgraduate training in SMT and more than 7 years of clinical experience in the management of spinal disorders.	Total: n = 122 Manipulation Group: n = 41 Soft Tissue Group: n = 41 Control (Wait and See): n = 40 Age/Gender (F/M): Manipulation Group: 21 (SD 2); (30/10) person-time = 41 Soft Tissue Group: 21 (SD 3); (32/9) Control Group: 20 (SD 2); (29/12) person-time = 81 Condition: latent trigger points in the masseter muscle	T0: baseline T1: 2 minutes after intervention	No AEs were reported by any participant after the manipulation procedure.	No AEs were reported in the manipulation group immediately after the treatment.
11	Mansilla-Ferragut et al (2009) (36)	Intervention Group: Manipulation Group: bilateral thrust manipulation of the atlanto-occipital joint Total Number of Manipulations Per Person: 2 Control Group: The Cx was held {AU: Edited to avoid redundancy.} in the manipulation position for 30 seconds (no thrust, just holding). This procedure was repeated on both sides.	Manual/physical therapist (6 years of postgraduate training in SMT; more than 7 years of clinical experience in the management of spinal disorders)	Total: n = 37 Manipulation Group: n = 18 Control Group: n = 19 Age/Gender (F/M): Manipulation Group: 36 (SD 7); person-time = 18 Control Group: 34 (SD 8); person-time = 19 Condition: mechanical neck pain	T0: baseline T1: post-intervention	No AEs were reported by any participant after the manipulation procedure.	No AEs were reported in the manipulation group immediately after the treatment.
12	Fernandez de las Penas et al (2008) (37)	Intervention Groups: HVLA cervicothoracic junction manipulation (C7-Th1) 1) dominant side 2) nondominant side Total Number of Manipulations Per Person: a maximum of 2 attempts Control Group: 3) placebo intervention: simulation of the manipulation without thrust or tissue tension	physical therapist (6-year postgraduate background in SMT; 7 years' experience in the management of spinal disorders)	Total: n = 30 (n = 10 in each group) Age/Gender (F/M): Manipulation Groups: Dominant Side: 25 (SD 5); (6/4) Nondominant Side: 27 (SD 6); (5/5) person-time = 20 Control Group: 25 (SD 4.5); (6/4) person-time = 10 Condition: asymptomatic subjects	T0: baseline T1: post-intervention (after 5 minutes)	No patients reported any AEs after the manipulations.	

Table 1 cont. *Characteristics of the included RCTs.*

	Author (Year)	Intervention	Profession	Sample	Measurement Time Points and Follow-up	Reported AE	Results/ Conclusion
13	Ruiz-Sáez et al (2007) (38)	Intervention Group: HVLA manipulation to C3-4. (The side chosen for manipulation was based on the joint dysfunctions and detected myofascial trigger points.) Total Number of Manipulations Per Person: a maximum of 2 attempts Control Group: SM	physical therapist (6-year postgraduate background in SMT; 7 years' experience in the management of spinal disorders)	Total: n = 72 (n = 36 in each group) Age/Gender (F/M): HVLA Manipulation: 31 (SD 7); (22/14) person-time = 36 SM Group: 32 (SD 11); (24/12) person-time = 36 Condition: asymptomatic subjects	T0: baseline T1: post-intervention (immediately and after 5-10 minutes)	No patients reported any AEs after the manipulations.	
14	Cassidy et al (1992) (39)	Both treatments were applied once at the symptomatic side. Intervention Group: manipulation (HVLA) Total Number of Manipulations Per Person: one Control Group: mobilization	experienced clinician	Total: n = 100 Manipulation Group: n = 52 Mobilization Group: n = 48 Age/Gender (F/M): Manipulation Group: 34.5 (SD 13); person-time = 52 Mobilization Group: 37.7 (12.5) {AU: Do you mean "SD 12.5"?}; person-time = 48 Condition: unilateral neck pain with referral to the trapezius muscle	T0: baseline T1: post-intervention (5 minutes after treatment)	There were no complications reported after both treatments {AU: Do you mean "either treatment"?}.	

n: number of participants; f: female; m: male; R: right; L: left; SD: standard deviation; T0: pre-interventional assessment; T1: post-interventional assessment; C: cervical vertebrae; Th: thoracic vertebrae; Cx: cervical spine; Tx: thoracic spine; SMT: spinal manipulative therapy; HE: home exercises; SRE: supervised rehabilitation exercise; ADL: activities of daily living; RM: real manipulation; SM: sham manipulation; LLLT: low-level laser therapy; AI: activator instrument.

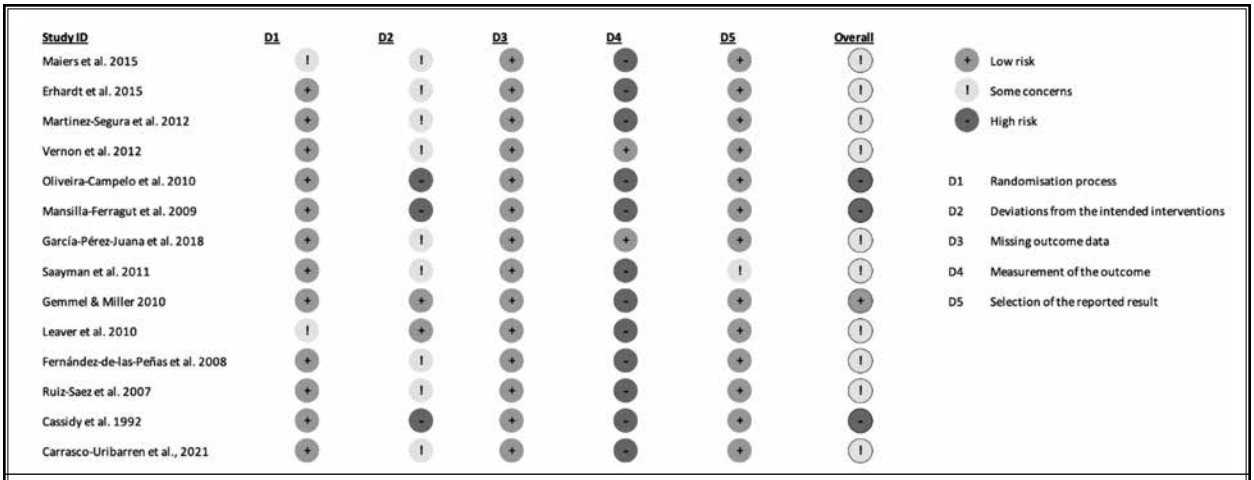

Fig. 2. *RoB of studies investigating AEs after HVLA cervical spinal manipulation.*

study by Cassidy et al (39), the caregiver was described as an experienced clinician. In a 2010 study by Leaver et al (34), the group of treating therapists consisted of chiropractors, physiotherapists, and osteopaths. In most of the studies, the authors stated that the treating therapists had considerable clinical experience (26,27,29-31,33-39).

Patients

The patients' ages in most studies ranged from 30 to 50 (26-28,30-39). Patients' musculoskeletal conditions were mostly different types of neck pain (27,29-34,36,39). One study population consisted of patients with myofascial TMD (35), whereas another comprised patients with dizziness and neck pain (26). Three studies included healthy volunteers (28,37,38).

AEs After Cervical HVLA Manipulation

The reporting of side effects was not the primary goal of the studies apart from one conducted by Maiers et al (29). In the manipulation group, 187 AEs occurred during 31,691 person-days, corresponding to an IR of 0.0059. In the control group, 251 AEs were observed during 30,623 person-days, giving an IR of 0.0082. None of the AEs that occurred were serious or moderate. The pooled IRR indicates no statistically significant group difference (IRR = 1.03; 95% CI [0.84,1.26]) (Fig. 4). The certainty of evidence is moderate.

Subgroup Analysis

Subgroup analysis of patients' age, profession, and type of AE found that the risk of an AE after cervical manipulation did not differ significantly in association with any of those factors. Results are shown in the online supplement.

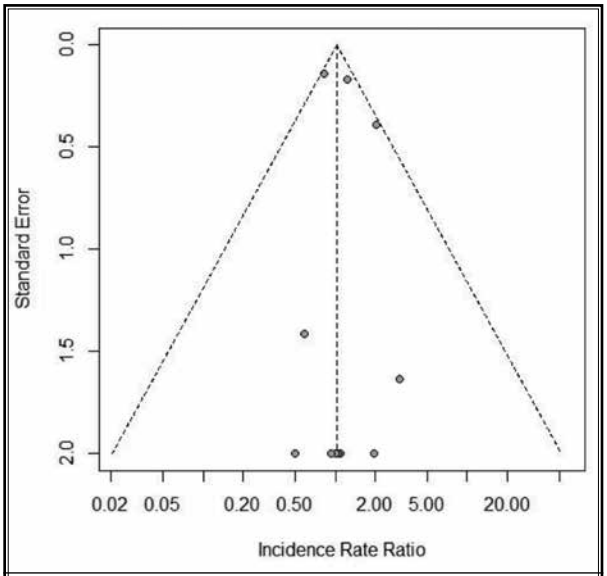

Fig. 3. *Publication bias (funnel plot).*

Discussion

The aim of this systematic review and meta-analysis was to extract available information from RCTs and thereby compare the risk of AEs following cervical manipulation to those posed by various control interventions. According to the authors' knowledge, this study is the only current meta-analysis of this topic.

The review includes 14 RCTs. None of the reported AEs were serious. The present meta-analysis could not

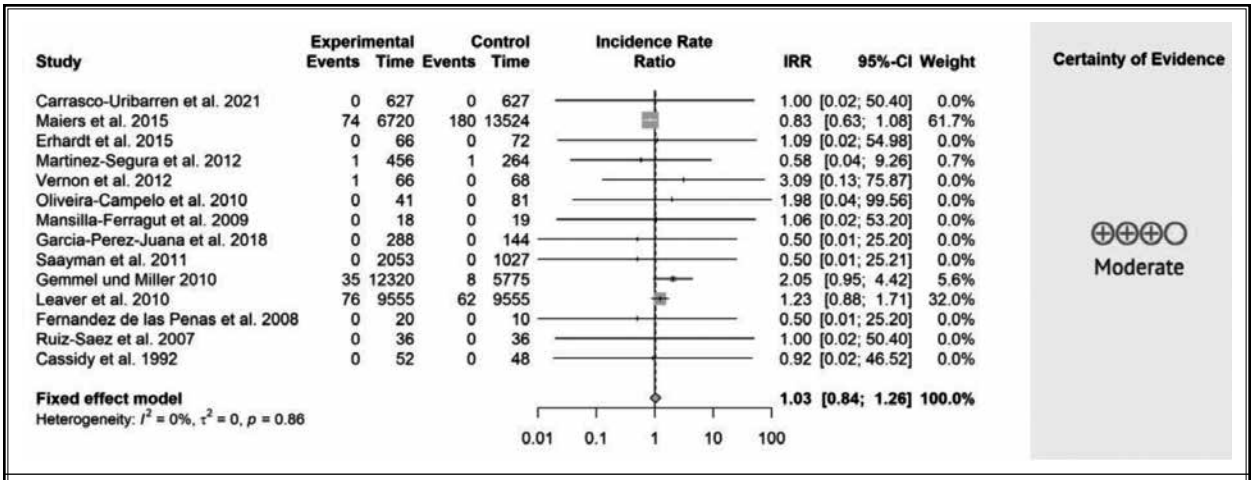

Fig. 4. *Occurrence of AEs related to manipulation or control intervention, calculated by incidence rate ratio (IRR). CI: confidence interval.*

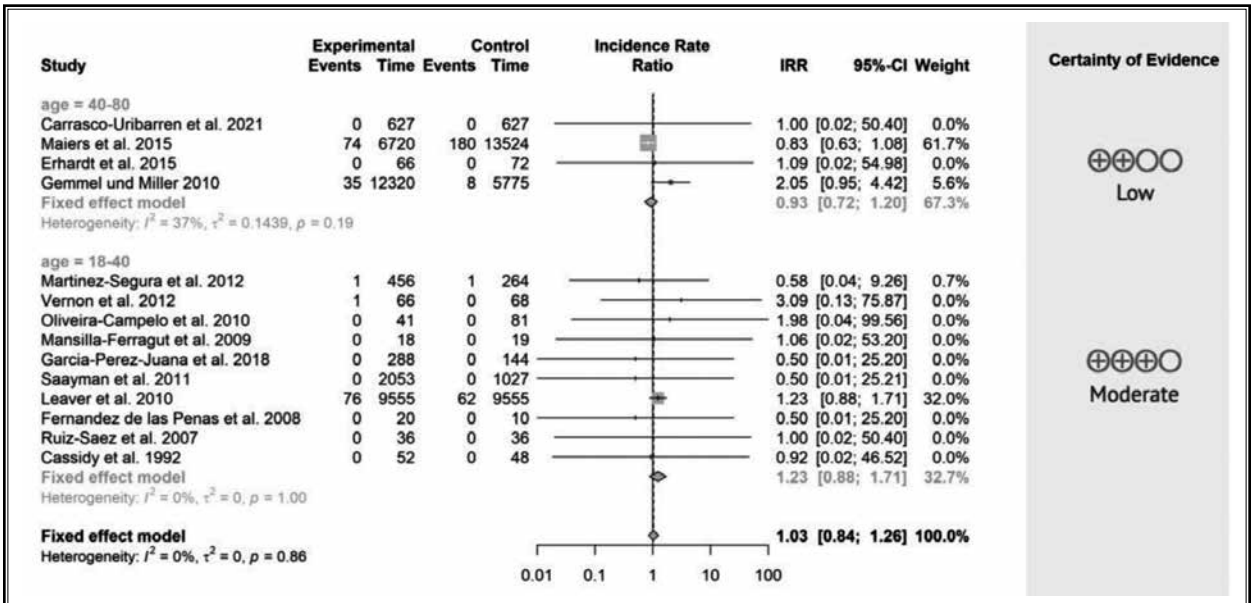

Fig. 5. *Occurrence of AEs subgrouped by age related to manipulation or control intervention, calculated by incidence rate ratio (IRR). CI: confidence interval.*

identify statistically significant differences between the intervention groups, who received cervical HVLA manipulations, and the control groups. The certainty of the evidence is rated as moderate for the overall analysis. Furthermore, when subgroup analysis was performed (age level, type of AE, and profession), no significant differences between the intervention and control groups were found.

These results are consistent with the findings of the review by Carlesso et al (2010), in that the AEs reported are mild and transitory (20). However, Carlesso et al's meta-analysis included only 2 RCTs. Additionally, unlike the present review, the 2010 meta-analysis included patients who had only neck pain and considered only studies that used mobilization treatment as a control intervention (20).

The investigation of serious AEs after cervical manipulation is very challenging due to the population's

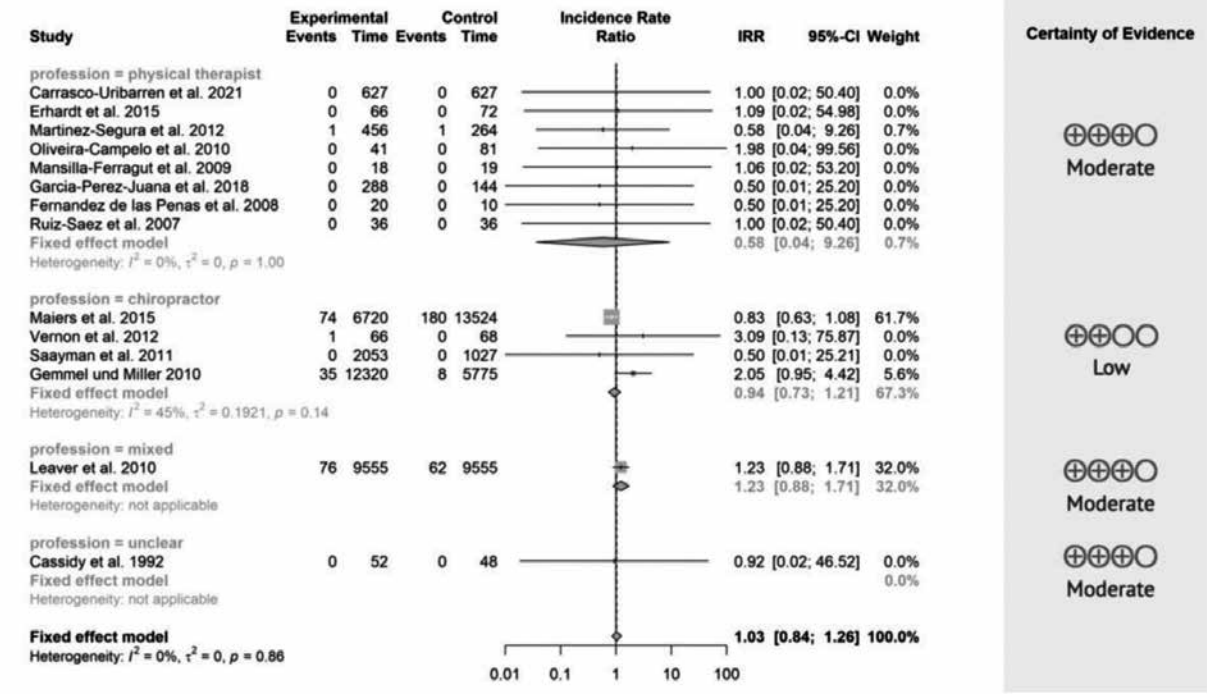

Fig. 6. *Occurrence of AEs subgrouped by caregiver related to manipulation or control intervention, calculated by incidence rate ratio (IRR). CI: confidence interval.*

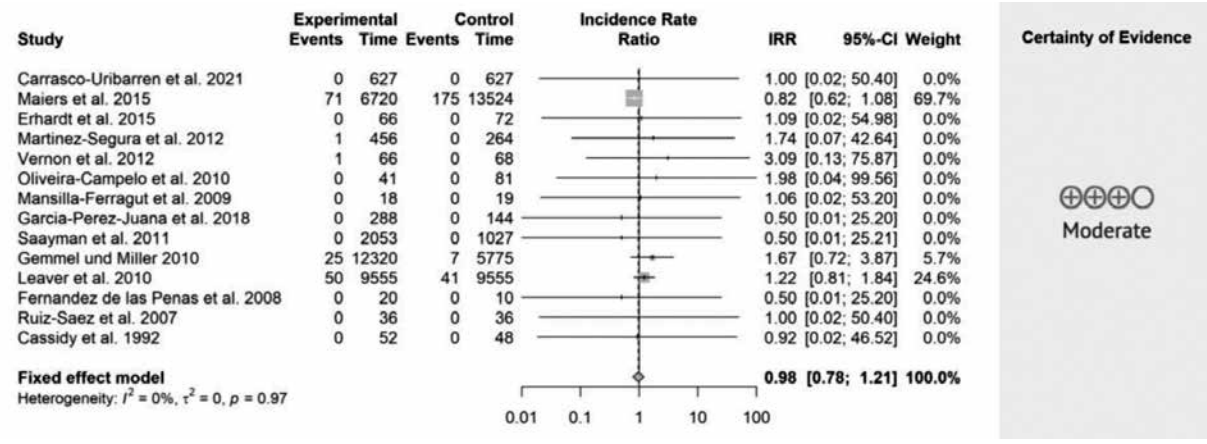

Fig. 7. *Occurrence of musculoskeletal AEs related to manipulation or control intervention, calculated by incidence rate ratio (IRR). CI: confidence interval.*

very low occurrence of serious events such as arterial disruptions (10). For instance, the annual incidence of internal carotid artery dissection is estimated at 1.72 per 100,000 members of a population (41). To prospectively identify (either by RCT or cohort studies) a sufficient number of cases for a valid comparison, enormous sample sizes would be required. Performing studies on the AEs that follow an intervention involves a comparatively short observation period and low sample sizes. Consequently, prospective studies such as RCTs are not suitable for detecting the rare serious AEs of an intervention. Various attempts to investigate these

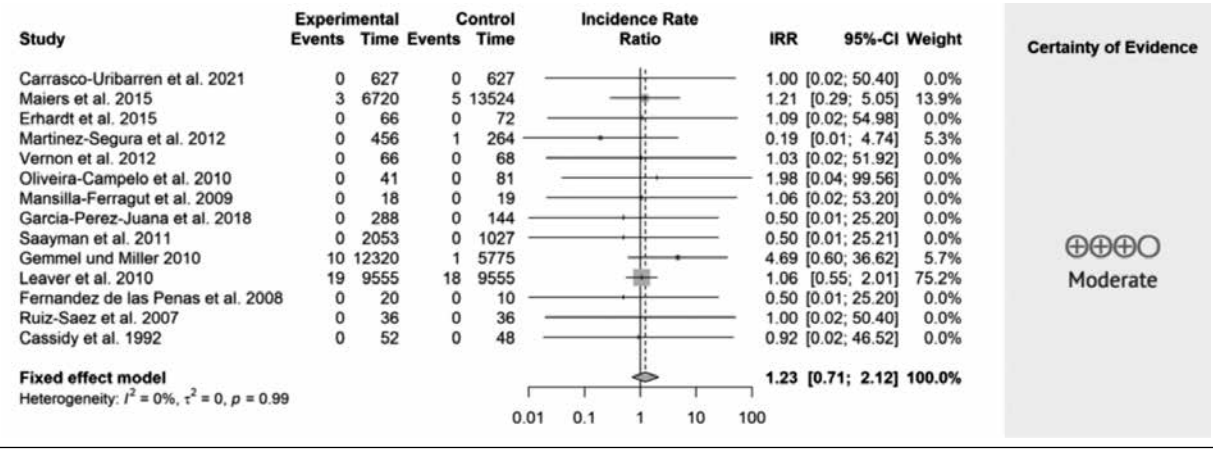

Fig. 8. *Occurrence of neurological AEs related to manipulation or control intervention, calculated by incidence rate ratio (IRR). CI: confidence interval.*

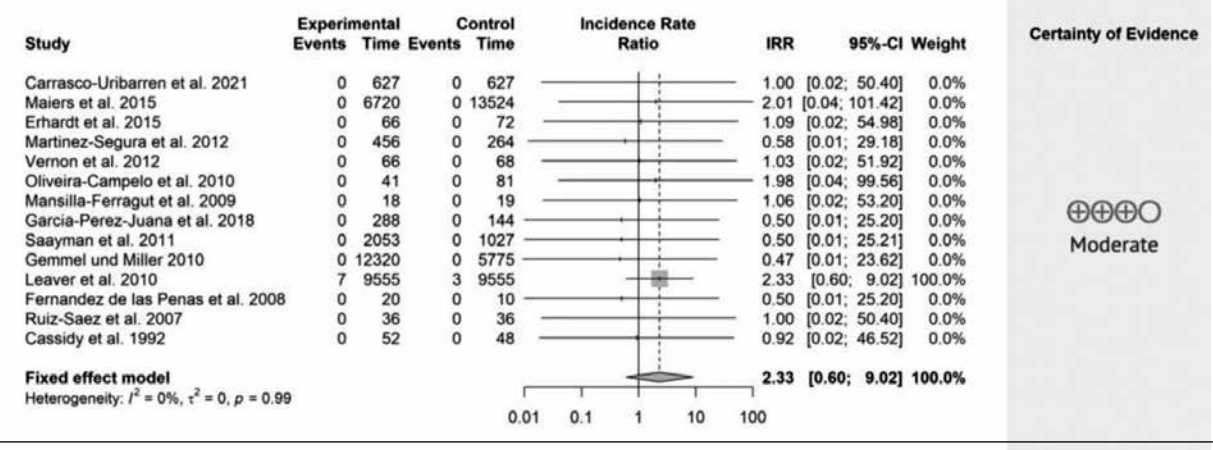

Fig. 9. *Occurrence of other AEs related to manipulation or control intervention calculated by incidence rate ratio (IRR). CI: confidence interval.*

associations have been made. Ernst and Kranenburg et al conducted retrospective case reports, case series, and reviews of case reports that found that arterial dissection was the most common serious complication after the application of cervical manipulation (11,12,42). However, due to their lack of methodology (e.g., a missing control group or a study's retrospective nature), these study designs do not allow any conclusion about the causal relationship between cervical manipulations and serious AEs. Studies designed to include control groups, such as case-control studies, showed significant associations. However, these results are suspected to come from protopathic bias. "Protopathic bias" arises when an exposure is initiated in response to a clinical sign of an initially undiagnosed illness and may lead to the erroneous interpretation of a harmful association between exposure and disease (13,43,44). This phenomenon is called reversed causation. For example, patients could be seeking care in the form of cervical manipulation due to head and neck pain, which are also pre-symptoms of dissection-related stroke. Hence, manipulation is erroneously associated with subsequent dissection-related stroke. Studies that tried to overcome protopathic bias by applying population-based case-crossover designs (13,14) compared the risk of serious AEs, such as vertebrobasilar stroke, associated with cervical manipulations to the risk associated with visits to primary care physicians. The results showed that no

difference of risks could be detected. In summary, the study results are in conflict with one another due to the underlying biases of the study designs, and a conclusion regarding the association of cervical manipulation and serious AEs cannot be drawn. Therefore, causality can be neither confirmed nor refuted.

Another aspect to be considered when interpreting the results is the heterogenous way of reporting AEs. There is no standardized, transparent AE-reporting procedure (45). In some studies, AEs are not discussed at all; in others, AEs are mentioned incidentally in the presentation of results. Other studies, however, present all AEs in tabular form and as absolute or percentage frequencies. A clear assignment of AEs to the intervention administered is possible in some cases. Consistent reporting that includes a standardized protocol for AE reporting is necessary for comparable and robust statements regarding the occurrence of AEs (10,15,45).

Clinical Implications

Headache and neck pain are typical symptoms of CAD. Often, they may be the only symptoms of CAD and masquerade as musculoskeletal in origin. In such cases, it is difficult to distinguish between serious pathology and purely musculoskeletal symptoms. If headache and neck pain are misclassified as musculoskeletal symptoms and treatment such as manipulation is initiated, there may be potentially harmful consequences for the patient and/or legal consequences for the clinician. In clinical practice, there are no sufficiently valid tests that exclude or confirm serious pathologies. Although clinical screening is recommended, it remains unclear to what extent clinical screening tests possess a predictive value in identifying patients at risk for serious AEs (46).

Risk of Bias

The RoB 2 tool was used to determine the risk of bias. In domain 4, it was assessed whether the outcome measurement contained a risk of bias because the investigators were not blinded. In this case, the occurrence of AE was assessed by the patients themselves in the form of self-reports. Thus, the patients were considered investigators, and since blinding was not possible in most cases due to the nature of the intervention, this study had to be rated as containing a high risk of bias.

Limitations and Strengths

The search strategy was limited to English and German literature because the authors were unable to translate articles in other languages. Furthermore, selection bias may have occurred, since only PubMed and Cochrane were used as databases, as well as articles found through a hand search.

RCTs had to be excluded if the results did not indicate the group in which the AEs occurred. A mandatory criterion for inclusion in the meta-analysis was a quantitative reproduction of the frequency of AEs that could be attributed to specific interventions. The strength of this meta-analysis lies in its extensiveness. In contrast to other reviews, this study's authors included a variety of control interventions and performed subgroup analysis, providing a detailed picture of the risk of AEs after cervical manipulation. Furthermore, our results are substantiated by the evaluation of the certainty of evidence using the GRADE approach.

Conclusion

In conclusion, HVLA manipulations do not pose a greater risk of mild or moderate AEs than do various control interventions such as mobilizations, sham manipulations, or exercises. No serious AEs were detected following HVLA manipulations in the studies this meta-analysis used. However, it must be remembered that RCTs are not an appropriate study design for detecting rare, serious AEs, and thus no conclusion can be drawn about the causal association between cervical manipulation and serious AEs. In the future, RCTs should report AEs following a standardized protocol, which will track AEs routinely in a systematic and valid way, to disentangle what role HVLA manipulations may or may not play in the occurrence of serious AEs.

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