BMJ Open

The reporting of adverse events associated with spinal manipulation in randomized clinical trials: an updated systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067526
Article Type:	Original research
Date Submitted by the Author:	17-Aug-2022
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Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS

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THE REPORTING OF ADVERSE EVENTS ASSOCIATED WITH SPINAL MANIPULATION IN RANDOMIZED CLINICAL TRIALS: AN UPDATED SYSTEMATIC REVIEW

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Sources of support

This project did not receive any funding.

Ethics approval statement

Ethics approval was not required for this systematic literature review.

Word count

Abstract: 296; Main text: 3598

Number of figures: 1

Number of tables: 2

Number of appendices: 3

ABSTRACT

Objectives

To describe if there has been a change in the reporting of adverse events associated with spinal manipulation in randomized controlled trials (RCTs) since 2016.

Design

Systematic literature review.

Data sources

Databases were searched from March 2016 to May 2022: MEDLINE (Ovid), Embase, CINAHL, ICL, PEDro and Cochrane Library. The following search terms and their derivatives were adapted for each platform: *spinal manipulation; chiropractic; osteopathy; physiotherapy; naprapathy; medical manipulation; clinical trial*.

Methods

Domains of interest (pertaining to adverse events) included: completeness and location of reporting; nomenclature and description; spinal location and practitioner delivering manipulation; methodological quality of the studies; and details of the publishing journal. Frequencies and proportions of studies reporting on each of these domains were calculated. Univariable and multivariable logistic regression models were fitted to examine the effect of potential predictors on the likelihood of studies reporting on adverse events.

Results

There were 5,399 records identified by the electronic searches, of which 154 (2.9%) were included in the analysis. Of these, ninety-four (61.0%) reported on adverse events with only 23.4% providing an explicit description of what constituted an adverse event. Reporting of adverse events in the abstract has increased (n= 29, 30.9%) while reporting in the results section has decreased (n= 83, 88.3%) over the past 6 years. Spinal manipulation was delivered to 7,518 participants in the included studies. No serious adverse events were reported in any of these studies.

Conclusions

While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased, the level is still unacceptable. Despite some improvement since our 2016 publication on the same topic, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is adequate reporting of both benefits and harms of spinal manipulation in RCTs.

ARTICLE SUMMARY

Strengths and limitations of this review

- This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (1)
- The current evidence on the reporting of adverse events associated with spinal manipulation across multiple professions is described
- Interestingly, there might be differences in the reporting of adverse events in RCTs depending on the type of practitioner delivering the intervention
- The inclusion of studies reporting on adverse events in all spinal regions allows for a more complete representation of adverse events that are associated with spinal manipulation
- The identification of factors which are related to the reporting of adverse events associated with spinal manipulation may bring awareness to researchers, journal editors and administrators of clinical trial registries regarding studies that are less likely to report such events

PROTOCOL

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=270543

FUNDING STATEMENT

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

WORD COUNT

3598

KEYWORDS

Adverse events; Harms; Literature review; Manipulation, spinal; Randomized controlled trials; Spinal manipulative therapy.

INTRODUCTION

The use of high-velocity, low-amplitude spinal manipulation to treat spinal pain and dysfunction is recommended in clinical and best practice guidelines (1–4) and is commonly used by several healthcare professions (5–7). Despite this, concerns remain surrounding adverse events following the intervention (8,9). Adverse events associated with spinal manipulation are typically benign, transient, and do not require further treatment (10). Indeed, some authors classify increased muscle soreness or stiffness in the treatment area as an 'expected outcome of treatment' rather than an adverse event (11). At the other end of the spectrum, catastrophic events, such as vertebral artery dissection, have been temporally associated with spinal manipulation (12). However, such events are rare, and as a result, are typically reported in individual case reports or case series with little to no information regarding the intervention that was delivered (13).

Randomized clinical trials (RCTs) are the gold standard study design for measuring effectiveness (benefit/s) of interventions for the treatment of spinal pain and dysfunction. However, as the risks of an intervention are also important to both patients and practitioners, RCTs should report on not only the efficacy of spinal manipulation, but also any adverse events associated with the intervention. The Consolidated Standards of Reporting Trials (CONSORT) statement, first published in 1996 with several updates since, provides the scientific community (specifically researchers and journal editors) with a scaffold to standardize and improve the quality of RCT reporting (14–16). The CONSORT statement acknowledges the importance of reporting adverse events alongside effectiveness data. The 2004 Harms extension document (17) provides specific recommendations for how and where this data should be included in scientific manuscripts. While there has been improvement in the reporting of adverse events since the publication of the 2004 extension, reporting remains insufficient (18), especially for RCTs that involve spinal manipulation (10). Thus, the objective of this review was to describe if there has been a change in the reporting of adverse events associated with spinal manipulation in randomized controlled trials (RCTs) since 2016.

METHODOLOGY

This systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (19).

Definitions

Spinal manipulation was defined as a manual procedure involving a high-velocity, low-amplitude (HVLA) thrust delivered to a spinal joint with the intention of moving the joint past its physiological range of motion but without exceeding the anatomic limit (20). For the purposes of this review, spinal manipulation delivered using drop-piece-table and mechanical implements were considered HVLA procedures (21).

An adverse event was defined as any unfavourable reaction with a temporal association to spinal manipulation that resulted in an alteration in a participant's activities of daily living (22,23), irrespective of the timing of onset, duration, or severity of the event (24).

To be classified as reporting on adverse events "directly", a study must have provided explicit description of their operational definition of an adverse event (e.g. "In the current study, an adverse event was defined as a sequelae of 1-week duration with any symptom perceived as distressing and unacceptable to the patient that required further treatment [63]." (25)), and/or how data on adverse events were measured (e.g. "Active and passive surveillance methods were used to collect information on adverse events." (26)), and/or provide a substantial description of adverse events observed during data collection (27,28). In contrast, all other studies reporting on adverse events "indirectly" did not explicitly provide such information.

Patient and public involvement

No patients were involved in this systematic literature review.

Ethics approval

Ethics approval was not required for this systematic literature review.

Eligibility criteria

Consistent with the 2016 review, RCTs reporting original data on spinal manipulation as either the sole intervention, or as the sole intervention in a comparator group, delivered by any regulated health professional, and published in English, were eligible for inclusion. Studies reporting on reviews, other trial designs, trial registrations, protocols, commentaries, editorials and conference proceedings were excluded. Further exclusion criteria included retracted articles, secondary analyses, studies in which the full text was not available in English, and studies where manipulation was only applied to an area other than the spine. Studies were also excluded if it was unclear if the intervention being delivered involved a HVLA thrust.

Search strategy

The following databases were searched from 1 March 2016 to 12 May 2022: MEDLINE (Ovid), Embase, CINAHL, ICL, PEDro and Cochrane Library. Reference lists of included studies were screened to insure all relevant literature was captured. The following search terms and derivatives were adapted for each platform: *spinal manipulation; chiropractic; osteopathy; physiotherapy; naprapathy; medical manipulation; clinical trial*. An example of the search strategy used in MEDLINE (Ovid) is provided in Appendix 1.

Study selection process

Records retrieved from the electronic searches were exported to the Rayyan online platform (29). Duplicate records were removed before title and abstract screening. Two authors (LG and BB) independently screened included studies in a step-wise process, beginning with review of each title and abstract. Full-texts of the studies remaining after this step were retrieved and further screened against the eligibility criteria (LG and RE). Any disagreements regarding inclusion were resolved by consensus and if consensus could not be reached, disagreements were resolved by a third author (BB).

Data extraction

Adverse events reporting data were extracted from the remaining studies by two authors (LG and RL). This data included descriptive information [i.e., title, author, year of publication, country where the data was collected, journal of publication, spinal region treated (e.g., cervical spine), type of practitioner delivering the spinal manipulation (e.g., chiropractor)], whether the study reported on

adverse events (i.e., reported/not and if reported; directly/indirectly), location of reporting within the article, classification of adverse events reported (e.g. mild, moderate, serious, severe etc), completeness of adverse events reporting (i.e., onset, duration, and number of events reported), number of participants in the spinal manipulation group/s, and descriptions of any definitions and/or classification systems used. Other data collated by the lead author (LG) included whether the study was published in a journal that follows the International Committee of Medical Journal Editors (ICMJE) guidelines via a search of the ICMJE website (30) on 29 May 2022. Additionally, the most recently published impact factor (year 2020) for each journal was manually extracted by the lead author (LG) from the Clarivate Journal Citations Reports website (31) on 29 May 2022.

Assessment of risk of bias using the Cochrane ROB 2 assessment tool (32) was performed by three authors working in pairs (LG and RE, LG and BB) for all included studies to assess the methodological quality of the publication. Disagreements were resolved by consensus and if consensus could not be reached, disagreements were resolved by a third author (RL).

Data analysis

Data were analysed using descriptive statistics. Frequencies and proportions of studies reporting on each of the specified domains above were calculated in Microsoft Excel (Version 2102, Microsoft Corporation, USA). Continuous variables with highly skewed distributions (i.e., journal impact factor and sample size of spinal manipulation group) were categorised into tertiles. Univariable and multivariable logistic regression models were fitted to examine the effect of potential predictors on the likelihood of studies reporting on adverse events. The multivariable logistic regression model was fitted using backward elimination, whereby the least significant potential predictors were sequentially eliminated from the multivariable model until only significant predictors remained. The observed effects from the univariable and multivariable logistic regression models were reported as odds ratios (OR) and adjusted odds ratios (aOR), respectively, with 95% confidence intervals (CI). All statistical analyses were performed using the statistical computing software R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

There were 5,399 records initially identified by the electronic searches (Figure 1). A total of 3,363 unique records remained after de-duplication (n=2,034) and the removal of records that had been withdrawn by the authors (n=2). After title and abstract screening, full texts of the 452 remaining studies were screened. Of these, 154 fulfilled the eligibility criteria and were included in the analysis (see Appendix 2). The most common reasons for exclusion were: the intervention did not consist of HVLA spinal manipulation (n=163) and/or the study related to a conference proceeding (n=49).

Insert around here: Figure 1: PRISMA flow-chart

Comprehensiveness of reporting of adverse events

Of the 154 included studies, 94 (61.0%) reported on adverse events. Of these 94 studies, 36 (38.3%) reported on adverse events directly. Indirect reporting occurred in 58 studies (61.7%). A description of what constituted an adverse event definition and/or the classification system used was provided in 22 studies (23.4%). However, most studies did not provide a description and instead used terms such as "adverse event" (n=70, 74.5%), "adverse effect" (n=22, 23.4%), "side effect" (n=19, 20.2%) and "harm" (n=11, 11.7%) without adequate explanation. When mentioned, terms pertaining to classification systems (predominantly severity) were (number of studies in which the term was used, %): "mild" (n=20, 21.3%), "moderate" (n=17, 18.1%), "serious" (n=27, 28.7%), and "severe" (n=14, 14.9%). The onset of an adverse event/s was unclear in 30 (31.9%) studies. Duration of adverse events were reported heterogeneously, with some studies providing a time from baseline or intervention, whereas others provided a temporal descriptor such as "short-term", "temporary" or, "transient". Of the 9 studies providing times, durations were as follows: <72hr (n=3, 3.2%), >72hr (n=2, 2.1%) or mixed duration (n=4, 4.3%). An evaluation tool was mentioned in 26 (27.7%) studies.

Number and location of adverse events reporting

No serious adverse events were reported in any of the 154 included studies, representing 7,518 participants who received spinal manipulation. Furthermore, of the 94 studies reporting on adverse events, 63 (67.0%) reported that no adverse events occurred. Adverse events were reported in the abstract of 29 (30.9%) and results section of 83 (88.3%) studies. Furthermore, adverse events were

mentioned in several locations throughout the included studies: the introduction (n=15, 16.0%), methods (n=56, 59.6%), discussion (n=30, 31.9%), conclusion (n=7, 7.4%), and supplementary materials (n=1, 1.1%).

Descriptors of studies reporting on adverse events

Descriptive statistics are provided in Table 1. Of the 94 studies reporting on adverse events, 55 (58.5%) were rated at a 'high risk of bias', 29 (30.9%) as 'some concerns' and 10 (10.6%) at a 'low risk of bias' (Appendix 3). Additionally, 33 (35.1%) were published in journals stating that they follow the ICMJE recommendations. For the remaining studies, the median of the most recently published (2020) impact factor was 2.5 (IQR: 2.1–4.2).

Insert around here: Table 1: Characteristics of included studies by reporting on adverse events

		Overall (n=154), n (%)	Reports on AE (n=94), n (%)	Does not report on AE (n=60), n (%)
ICMJE journal	Published in ICJME journal	53 (34.4)	33 (35.1)	20 (33.3)
Risk of bias	Low risk	13 (8.4)	10 (10.6)	3 (5.0)
	Some concerns	47 (30.5)	29 (30.9)	18 (30.0)
	High risk	94 (61.0)	55 (58.5)	39 (65.0)
Impact factor	Upper tertile	47 (30.5)	36 (38.3)	11 (18.3)
	Middle tertile	54 (35.1)	37 (39.4)	17 (28.3)
	Lower tertile	53 (34.4)	21 (22.3)	32 (53.3)
Spinal region	Cervical	24 (15.6)	17 (18.1)	7 (11.7)
	Thoracic	33 (21.4)	15 (16.0)	18 (30.0)
	Lumbopelvic	28 (18.2)	13 (13.8)	15 (25.0)
	Mixed/Unclear	69 (44.8)	49 (52.1)	20 (33.3)
Type of practitioner	Chiropractor	36 (23.4)	29 (30.9)	7 (11.7)
	Osteopath	15 (9.7)	6 (6.4)	9 (15.0)
	Physiotherapist	63 (40.9)	35 (37.2)	28 (46.7)
	Medical Practitioner	9 (5.8)	4 (4.3)	5 (8.3)
	Mixed/Other/Unclear	31 (20.1)	20 (21.2)	11 (18.3)
Sample size spinal manipulation group[1]	Upper tertile	51 (33.3)	40 (42.6)	11 (18.6)
	Middle tertile	50 (32.7)	28 (29.8)	22 (37.3)
	Lower tertile	52 (34.0)	26 (27.7)	26 (44.1)

[1] One study with unclear sample size excluded
AE; adverse event

Predictors for the reporting of adverse events

There was very strong evidence that studies with an impact factor in the upper (aOR: 5.72 [95% CI: 2.23-15.85]; p < 0.001) and middle (aOR: 3.52 [95% CI: 1.51-8.57]; p = 0.004) tertiles were more likely to report on adverse events than those in the lower tertile when the model was adjusted for risk of bias, impact factor, spinal region of manipulation, and number of participants receiving spinal manipulation (Table 2). There was also strong evidence that studies in which a chiropractor delivered the spinal manipulation were more likely to report on adverse events (aOR: 4.58 [95% CI: 1.14-20.24]; p = 0.036). Studies in which spinal manipulation was delivered to more than one region or, it was unclear which regions the manipulations were delivered, were also more likely to report on adverse events (aOR: 3.18 [95% CI: 1.16-9.05]; p = 0.027). While not achieving statistical significance, another factor of note included studies in which cervical spine manipulation was delivered (aOR: 3.04 [95% CI: 0.88-11.30]; p = 0.085).

Insert around here: Table 2: Univariable and multivariable logistic regression

Variable	OR	95%CI	p-value	aOR[1]	95%CI	p-value
ICMJE journal						
Yes	1.08	0.55-2.16	0.821	-	-	-
No[2]	-	-	-	-	-	-
Risk of bias						
Low risk	2.36	0.67-11.01	0.213	-	-	-
Some concerns	1.14	0.56-2.37	0.716	-	-	-
High risk[2]	-	-	-	-	-	-
Impact factor						
Upper tertile	4.99	2.14-12.32	<0.001	5.72	2.23-15.85	<0.001
Middle tertile	3.32	1.52-7.48	0.003	3.52	1.51-8.57	0.004
Lower tertile[2]	-	-	-	-	-	-
Spinal region						
Cervical	2.80	0.91-9.27	0.080	3.04	0.88-11.30	0.085
Thoracic	0.96	0.35-2.66	0.939	1.09	0.34-3.45	0.887
Lumbopelvic[2]	-	-	-	-	-	-
Mixed/Unclear	2.83	1.15-7.11	0.025	3.18	1.16-9.05	0.027
Type of practitioner						
Chiropractor	6.21	1.71-24.85	0.007	4.58	1.14-20.24	0.036
Osteopath[2]	-	-	-	-	-	-
Physiotherapist	1.88	0.60-6.19	0.282	1.35	0.37-5.18	0.648
Medical Practitioner	1.20	0.22-6.53	0.831	0.81	0.12-5.47	0.829
Mixed/Other/Unclear	2.72	0.78-10.17	0.121	2.26	0.57-9.64	0.253
Sample size spinal manipulation group[3]						
Upper tertile	3.64	1.57-8.87	0.003	-	-	-
Middle tertile	1.27	0.58-2.79	0.544	-	-	-

Lower tertile[2]	-	-	-	-	-	-

[1] The final model was adjusted for impact factor, spinal region of manipulation, and type of practitioner, while ICMJE journal status, risk of bias, and number of participants receiving spinal manipulation were omitted via backward elimination method.
[2] Reference group.
[3] One study with unclear sample size excluded.

DISCUSSION

This review highlights that the reporting of adverse events in RCTs involving spinal manipulation as an intervention remains inadequate. Specifically, of the 154 included studies, just over half (n= 94, 61.0%) reported on adverse events. Furthermore, of these 94 studies, less than half (38.3%) reported directly on adverse events, with only 23.4% providing an explicit description of what constituted an adverse event. Further complicating this issue is the vast heterogeneity of terms (i.e., "adverse effect", "side effect", "harm" etc) used to describe adverse events. This is disappointing given that there have been many calls in the literature for improvement of adverse events reporting in RCTs, and for the development and use of standardized definitions and classification systems (10,17,24,33–39).

In the absence of standardized definitions and classification systems for the reporting of adverse events associated with spinal manipulation, the 2004 CONSORT Harms extension provides a checklist of items to include when reporting on harms (adverse events) in RCTs (17). One important item on this checklist is that both benefits and harms should be stated in either the title and/or abstract of a manuscript. This point is salient as the abstract is the second-most read section of a scientific manuscript after the title (40). Encouragingly, the reporting of adverse events in the abstract has doubled (2016 – 15.7% vs. 2022 – 30.9%) when compared to our previous review of the literature (10). Despite this, the current reporting on adverse events in the title/abstract of RCTs utilizing spinal manipulation remains inadequate. This finding is congruent with the wider published literature discussing adverse events (41–44). Interestingly, adverse events reporting in the results section has decreased (93.6% vs 88.3%) over the past 6 years and remains lower than that in the wider published literature (42,45). It is unknown why there would be a decrease in the reporting on adverse events associated with spinal manipulation in the one section of a scientific manuscript that it could

reasonably be expected to be reported. Furthermore, the transparent reporting of both efficacy and adverse events data in RCTs is imperative as one source of evidence for the formulation of an informed risk-benefit analysis for the use of spinal manipulation as a treatment option by both clinician and patient (41,44).

Consistent with the literature (23,24,34,35,39), there was considerable heterogeneity of nomenclature used to describe adverse events associated with spinal manipulation. Similar terms were used to indicate an adverse event in the current (compared to 2016) review: "adverse event" (2016 – 73.0%; 2022 – 74.5% of studies), "adverse effect" (23.6%; 23.4%), "side effect" (21.3%; 20.2%) and "harm" (16.4%; 11.7%). Furthermore, while similar terms were used to describe classification systems previously reported (i.e., "serious", "mild", "moderate", and "severe"), these terms were rarely defined, which is consistent with the existing literature (10,44). Additionally, when present, the reporting of onset and duration of adverse events was inconsistent. Therefore, there is an urgent need for the development of a standardized definition and classification system for the reporting of adverse events (33). In addition to such definitions and classification systems, there is also a need for improved methodologies, reporting and statistical analyses for RCTs that include spinal manipulation as an intervention. Specifically, data on adverse events should be actively collected as it has been reported that passive surveillance leads to an under-reporting (18,46) and appropriate statistical analysis plans should be used to analyse the data (41,46,47). As a minimum standard, authors should explicitly state whether active or passive surveillance systems were used (38,41). Furthermore, the responsibility for improved reporting of adverse events falls not only to authors but also to journal editors and clinical trial registries to ensure that adverse events are adequately reported i.e., using the most recent CONSORT Harms extension guidelines (17), alongside efficacy/effectiveness data prior to publication (18,38,46). Encouragingly, it appears that an update to this guideline is emergent (18) and it is hoped that a dissemination strategy will ensure that authors and journal editors alike are both aware and implement the updated guidelines in the future.

Interestingly, RCTs published in journals with a higher impact factor, in which spinal manipulation was delivered by a chiropractor and to multiple/unclear regions, were more likely to report on adverse events. While it is perhaps intuitive that better designed studies, i.e., those at a lower risk of bias, could reasonably be published in higher impact journals, this does not appear to be the case as there was no influence of risk of bias level in the final model. This finding is congruent with a previous report where there were methodological weaknesses in 184 studies published in 2015-2016 by four of the top ranked general medical journals (BMJ, JAMA, Lancet, and NEJM) (46). Furthermore, while there is no obvious reason why studies in which spinal manipulation was delivered by a chiropractor would be more likely to report on adverse events, it is possible that this finding could be explained by a desire to 'prove' the safety of the intervention, specifically manipulation delivered to the cervical spine (48,49). This hypothesis is suggested by the data which shows that while not achieving statistical significance, studies in which cervical spine manipulation was delivered had approximately 3 times greater odds of reporting on adverse events. It is possible that this result did not achieve statistical significance due to the relatively small number of studies reporting on manipulation delivered only to the cervical spine. Regarding the increased likelihood of studies reporting on adverse events if spinal manipulation was delivered to multiple/unclear regions, it is possible that this finding is spurious as there was a larger number of studies (n=49) in this category compared to studies in which the intervention was delivered to a single region. This hypothesis is supported by our previous review which reported that the region treated was not a significant predictor for reporting on adverse events (50).

Our findings support the literature that serious adverse events are rarely associated with spinal manipulation (34,37,51,52). However, this finding was not surprising as the calculation of accurate incidence rates of such events is difficult due to their rarity. Additionally, RCTs are not the best research design for collecting this type of data as they often have strict inclusion criteria and may exclude participants who are at risk of experiencing a serious adverse event. Despite this, the consistent reporting of the number of spinal manipulations delivered to every participant in RCTs would allow for the calculation of accurate incidence rates for all classifications of adverse events

(serious included) and could eventually facilitate the pooling of data across multiple studies thus allowing for a better informed risk-benefit assessment of spinal manipulation (18,38). Indeed, the number of spinal manipulations delivered was only available in 75 (48.7%) of the included studies. Coupled with the implementation of standardized definitions and classification systems for adverse events associated with spinal manipulation, reporting on the number of spinal manipulations delivered in each study would allow for the inter-disciplinary calculation of incidence rates for all classifications across all healthcare professionals delivering the intervention. Such an outcome is extremely important in the context of obtaining informed consent to deliver spinal manipulation. Specifically, in many countries in which spinal manipulation is delivered, the process of obtaining informed consent requires the disclosure of all material information that a reasonable patient would require to make an informed decision about whether or not to receive that intervention (53). In the absence of accurate incidence rates for the different classifications of adverse events associated with spinal manipulation, this is a difficult task for the clinician to perform.

There are several differences between the current review and our 2016 review (10). Specifically, the current review included an improved search strategy, including both an expansion to the number of databases searched (i.e., MEDLINE (Ovid), Embase, CINAHL and ICL were added) in addition to the inclusion of several search terms that did not limit the search to spinal manipulation delivered by chiropractors and osteopaths (i.e., physiotherapists, naprapaths and medical manipulation were added). Additionally, the current review reports on analyses that we had previously reported separately in two manuscripts: the original review (10) and a secondary analysis (50). By reporting these analyses in a single manuscript, we hope it is clearer for readers to identify that the current level of reporting of adverse events associated with spinal manipulation in RCTs remains unacceptable, and understand the possible explanations for this observation. By streamlining the dissemination of this information, we hope to make it easier for readers to identify areas in which researchers may improve the reporting of adverse events in this field.

Limitations

There are several limitations to this literature review. Firstly, the decision to classify the reporting of adverse events as 'direct' (explicit description of operational definition of an adverse event provided and/or how data on adverse events were measured and/or a substantial description of adverse events observed during data collection provided) as opposed to 'indirect' (no explicit reporting of such information) was arbitrary. However, this classification did not influence whether the study reported on adverse events or not. As such, we do not feel this factor had any material influence on our results. Secondly, it was not possible to calculate an accurate incidence rate for any classification of adverse events due to the inadequate reporting of the number of manipulations delivered during individual studies. Thirdly, as outlined above, small differences in the methodology between the current and previous reviews (10,50) mean that it is not possible to directly compare all reported findings between the two reviews. However, as these differences occurred due to methodological improvements in the current review, we do not believe this affected the results and/or discussion in the current review.

CONCLUSION

The current level of reporting of adverse events associated with spinal manipulation in RCTs is unacceptable. While there has been some improvement since the publication of our 2016 review on the same topic, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is adequate reporting of both benefits and harms in RCTs that include spinal manipulation as an intervention. We strongly recommend that authors adhere to the most recent CONSORT Harms checklist when reporting their results and advocate for the creation of standardized definitions and classification systems relating to adverse events in manual therapy. This will facilitate the future pooling of adverse events data across all professions utilizing spinal manipulation and improve the ability to calculate incidence rates for the different levels of adverse events.

AUTHOR CONTRIBUTIONS

LG: conceptualization, screening, risk of bias assessment, data extraction and curation, formal analysis, methodology, project administration, visualization, writing – original draft, review & editing

RL: data extraction and curation, formal analysis, methodology, visualization, writing – original draft, review & editing

BB: screening, risk of bias assessment, writing – review & editing

RE: screening, risk of bias assessment, methodology, writing – review & editing

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr. Martina Gosteli for her assistance with the literature search.

DATA SHARING STATEMENT

Data are available from the corresponding author upon reasonable request.

REFERENCE STRENGTHS AND LIMITATIONS OF THE REVIEW

1. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

REFERENCES MANUSCRIPT

1. Whalen W, Farabaugh RJ, Hawk C, Minkalis AL, Lauretti W, Crivelli LS, et al. Best-practice recommendations for chiropractic management of patients with neck pain. J Manipulative Physiol Ther. 2019 Nov 1;42(9):635–50.

2. Bussieres AE, Stewart G, Al-Zoubi F, Decina P, Descarreaux M, Haskett D, et al. Spinal Manipulative Therapy and Other Conservative Treatments for Low Back Pain: A Guideline From the Canadian Chiropractic Guideline Initiative. J Manip Physiol Ther. 2018 Mar 29;

3. Bussieres AE, Stewart G, Al-Zoubi F, Decina P, Descarreaux M, Hayden J, et al. The treatment of neck pain-associated disorders and whiplash-associated disorders: a clinical practice guideline. J Manipulative Physiol Ther. 2016 Oct;39(8):523–64.

4. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CWC, Chenot JF, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. Eur Spine J. 2018 Nov 1;27(11):2791–803.

5. Beliveau PJH, Wong JJ, Sutton DA, Simon NB, Bussières AE, Mior SA, et al. The chiropractic profession: a scoping review of utilization rates, reasons for seeking care, patient profiles, and care provided. Chiropr Man Ther. 2017 Nov 22;25(35).

6. Lin I, Wiles L, Waller R, Goucke R, Nagree Y, Gibberd M, et al. What does best practice care for musculoskeletal pain look like? Eleven consistent recommendations from high-quality clinical practice guidelines: systematic review. Br J Sports Med. 2020 Jan 1;54(2):79.

7. National Institute for Health and Care Excellence (NICE). Low Back Pain and Sciatica in Over 16s: Assessment and Management. Natl Inst Health Care Excell NICE. 2016 Nov;

8. Puentedura EJ, March J, Anders J, Perez A, Landers MR, Wallmann HW, et al. Safety of cervical spine manipulation: are adverse events preventable and are manipulations being performed appropriately? A review of 134 case reports. J Man Manip Ther. 2012 May;20(2):66–74.

9. Biller J, Sacco RL, Albuquerque FC, Demaerschalk BM, Fayad P, Long PH, et al. Cervical arterial dissections and association with cervical manipulative therapy: a statement for healthcare professionals from the american heart association/american stroke association. Stroke J Cereb Circ. 2014 Oct;45(10):3155–74.

10. Gorrell LM, Engel RM, Brown B, Lystad RP. The reporting of adverse events following spinal manipulation in randomized clinical trials-a systematic review. Spine J. 2016 May 27;

11. Heneghan NR, Davies SE, Puentedura EJ, Rushton A. Knowledge and pre-thoracic spinal thrust manipulation examination: a survey of current practice in the UK. J Man Manip Ther. 2018 Oct 20;26(5):301–9.

12. Albuquerque FC, Hu YC, Dashti SR, Abla AA, Clark JC, Alkire B, et al. Craniocervical arterial dissections as sequelae of chiropractic manipulation: patterns of injury and management. J Neurosurg. 2011 Dec;115(6):1197–205.

13. Ernst E. Deaths after chiropractic: a review of published cases. Int J Clin Pract. 2010 Jul;64(8):1162–5.

14. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. JAMA. 1996;276.

15. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357.

16. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8.

17. Ioannidis JPA, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004;141.

18. Junqueira DR, Phillips R, Zorzela L, Golder S, Loke Y, Moher D, et al. Time to improve the reporting of harms in randomized controlled trials. J Clin Epidemiol. 2021 Aug 1;136:216–20.

19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

20. Herzog W. The biomechanics of spinal manipulation. J Bodyw Mov Ther. 2010 Jul;14(3):280–6.

21. Bergmann T. Chiropractic Technique Principles and Procedures. 3rd ed. Missouri: Elselvier Mosby, USA; 2011.

22. Pohlman KA, O'Beirne M, Thiel H, Cassidy JD, Mior S, Hurwitz EL, et al. Development and validation of providers' and patients' measurement instruments to evaluate adverse events after spinal manipulation therapy. Eur J Integr Med. 2014 Aug 1;6:451–66.

23. Walker BF, Hebert JJ, Stomski NJ, Clarke BR, Bowden RS, Losco B, et al. Outcomes of usual chiropractic. The OUCH randomized controlled trial of adverse events. Spine Phila Pa 1976. 2013 Sep 15;38:1723–9.

24. Carnes D, Mullinger B, Underwood M. Defining adverse events in manual therapies: a modified Delphi consensus study. Man Ther. 2010 Feb;15(1):2–6.

25. Dunning J, Butts R, Zacharko N, Fandry K, Young I, Wheeler K, et al. Spinal manipulation and perineural electrical dry needling in patients with cervicogenic headache: a multi-center randomized clinical trial. Spine J 2021 Feb212284-295. 2021;

26. Maiers M, Hartvigsen J, Evans R, Westrom K, Wang Q, Schulz C, et al. Short or long-term treatment of spinal disability in older adults with manipulation and exercise. Arthritis Care Res 2019 Nov71111516-1524. 2019;

27. Vining R, Long CR, Minkalis A, Gudavalli MR, Xia T, Walter J, et al. Effects of Chiropractic Care on Strength, Balance, and Endurance in Active-Duty U.S. Military Personnel with Low Back Pain: A Randomized Controlled Trial. J Altern Complement Med. 2020 Jul;26(7):592–601.

28. Schulz C, Evans R, Maiers M, Schulz K, Leininger B, Bronfort G. Spinal manipulative therapy and exercise for older adults with chronic low back pain: a randomized clinical trial. Chiropr Man Ther. 2019;27:21.

29. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016 Dec 5;5(1):210.

30. International Committeee of Medical Journal Editors (ICMJE). Journals following the ICMJE recommendations. 2016.

31. Clarivate Journal Citation Reports [Internet]. Clarivate Journal Citation Reports. [cited 2022 May 29]. Available from: https://clarivate.com/webofsciencegroup/solutions/journal-citation-reports/

32. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. In: Cochrane Handbook for Systematic Reviews of Interventions [Internet]. John Wiley & Sons, Ltd; 2019. p. 205–28. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119536604.ch8

33. Funabashi M, Pohlman KA, Gorrell LM, Salsbury SA, Bergna A, Heneghan NR. Expert consensus on a standardised definition and severity classification for adverse events associated with spinal and peripheral joint manipulation and mobilisation: protocol for an international e-Delphi study. BMJ Open. 2021 Nov 1;11(11):e050219.

34. Carnes D, Mars TS, Mullinger B, Froud R, Underwood M. Adverse events and manual therapy: a systematic review. Man Ther. 2010 Aug;15(4):355–63.

35. Carlesso L, Macdermid J, Santaguida P. Standardization of adverse event terminology and reporting in orthopaedic physical therapy: application to the cervical spine. J Orthop Sports Phys Ther. 2010 Aug;40:455–63.

36. Carlesso L, Cairney J, Dolovich L, Hoogenes J. Defining adverse events in manual therapy: an exploratory qualitative analysis of the patient perspective. Man Ther. 2011 Oct;16:440–6.

37. Carlesso L, Gross A, Santaguida P, Burnie S, Voth S, Sadi J. Adverse events associated with the use of cervical manipulation and mobilization for the treatment of neck pain in adults: a systematic review. Man Ther. 2010 Oct;15(5):434–44.

38. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ. 2016 Feb 1;352:i157.

39. Funabashi M, Gorrell LM, Pohlman KA, Bergna A, Heneghan NR. Definition and classification for adverse events following spinal and peripheral joint manipulation and mobilization: A scoping review. PLOS ONE. 2022 Jul 15;17(7):e0270671.

40. Pitkin RM. The importance of the abstract. Obstet Gynecol. 1987 Aug;70:267.

41. Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, et al. Quality of reporting in systematic reviews of adverse events: systematic review. BMJ. 2014;348:f7668.

42. Komorowski AS, MacKay HJ, Pezo RC. Quality of adverse event reporting in phase III randomized controlled trials of breast and colorectal cancer: A systematic review. Cancer Med. 2020 Jul 1;9(14):5035–50.

43. Berwanger O, Ribeiro RA, Finkelsztejn A, Watanabe M, Suzumura EA, Duncan BB, et al. The quality of reporting of trial abstracts is suboptimal: survey of major general medical journals. J Clin Epidemiol. 2009 Apr;62(4):387–92.

44. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Arch Intern Med. 2009 Oct 26;169:1756–61.

45. Nuovo J, Sather C. Reporting adverse events in randomized controlled trials. Pharmacoepidemiol Drug Saf. 2007 Mar;16(3):349–51.

46. Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open. 2019 Mar 1;9(2):e024537.

47. Phillips R, Sauzet O, Cornelius V. Statistical methods for the analysis of adverse event data in randomised controlled trials: a scoping review and taxonomy. BMC Med Res Methodol. 2020 Nov 30;20(1):288.

48. Gouveia LO, Castanho P, Ferreira JJ. Safety of chiropractic interventions: a systematic review. Spine Phila Pa 1976. 2009 May 15;34:E405-13.

49. Thiel HW, Bolton JE, Docherty S, Portlock JC. Safety of chiropractic manipulation of the cervical spine: a prospective national survey. Spine. 2007 Oct;32(21):2375–8; discussion 2379.

50. Gorrell LM, Brown B, Lystad RP, Engel RM. Predictive factors for reporting adverse events following spinal manipulation in randomized clinical trials – secondary analysis of a systematic review. Musculoskelet Sci Pract. 2017;30:34–41.

51. Cagnie B, Vinck E, Beernaert A, Cambier D. How common are side effects of spinal manipulation and can these side effects be predicted? Man Ther. 2004 Aug;9:151–6.

52. Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. BMJ. 2019 Mar 13;364:l689.

53. Winterbottom M, Boon H, Mior S, Facey M. Informed consent for chiropractic care: Comparing patients' perceptions to the legal perspective. Man Ther. 2015 Jun;20(3):463–8.

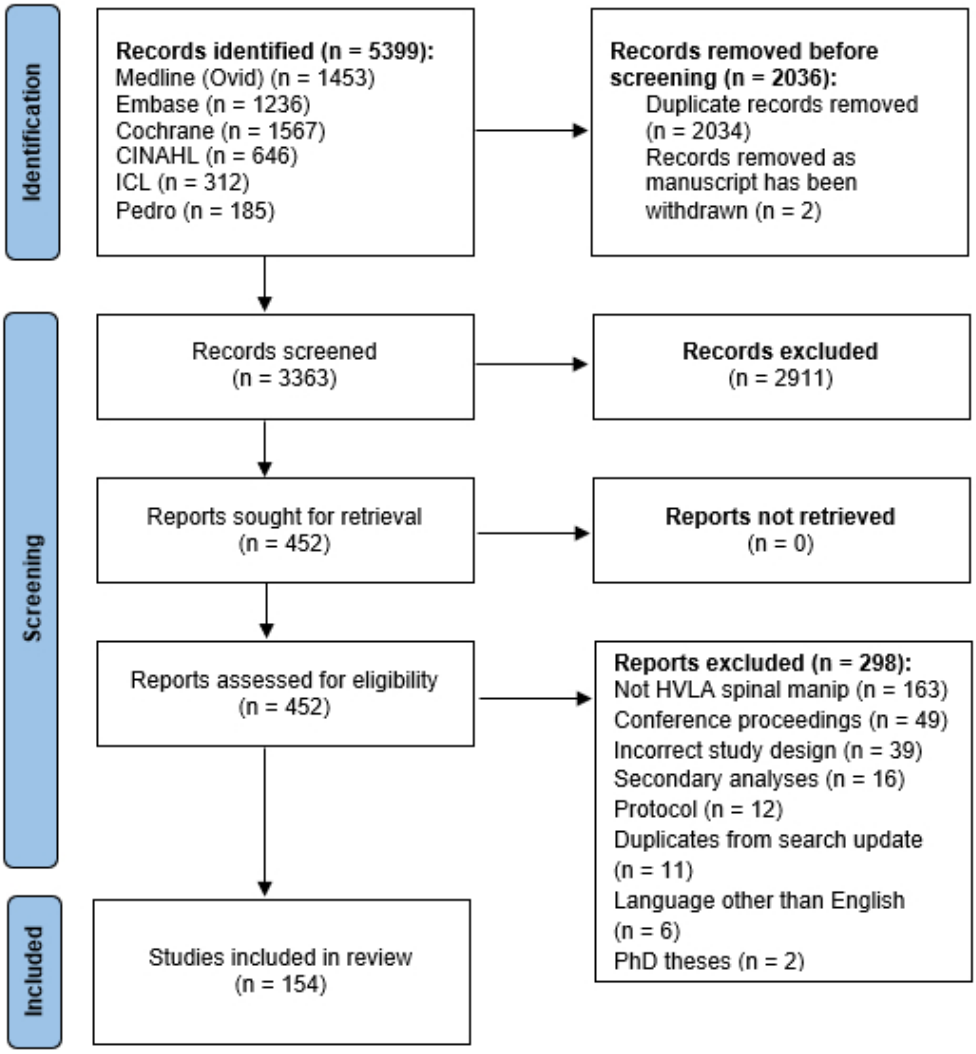

Figure 1: PRISMA flow-chart

351x381mm (38 x 38 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P6-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	------
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	------
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P8

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P8-9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P8
Study characteristics	17	Cite each included study and present its characteristics.	Appendix2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P9-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P9-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-------
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	------
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	------
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	------
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P12-16
	23b	Discuss any limitations of the evidence included in the review.	P12-16
	23c	Discuss any limitations of the review processes used.	P16
	23d	Discuss implications of the results for practice, policy, and future research.	P16-17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	P3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P3
Competing interests	26	Declare any competing interests of review authors.	P4
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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

Appendix 1: MEDLINE (Ovid) search strategy

#1 ((spine or spinal or medical) adj3 manip*).ti,ab,kw.

#2 (osteopath* or chiropract* or naprapath* or ((physiotherap* or (physical adj3 therap*)) and manip*)).ti,ab,kw.

#3 Manipulation, Chiropractic/ or Manipulation, Spinal/ or Musculoskeletal Manipulations/ or Manipulation, Osteopathic/

#4 1 or 2 or 3

#5 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)

#6 4 and 5

#7 limit 6 to yr="2016 -Current"

Appendix 2: Included studies reference list

1. Albers J, Jakel A, Wellmann K, von Hehn U, Schmidt T. Effectiveness of 2 Osteopathic Treatment Approaches on Pain, Pressure-Pain Threshold, and Disease Severity in Patients with Fibromyalgia: A Randomized Controlled Trial. Complement Med Res. 2018;25(2):122–8.

2. Alonso-Perez JL, Lopez-Lopez A, La Touche R, Lerma-Lara S, Suarez E, Rojas J, et al. Hypoalgesic effects of three different manual therapy techniques on cervical spine and psychological interaction: A randomized clinical trial. J Bodyw Mov Ther. 2017;21(4):798–803.

3. Alvarenga BAP, Fujikawa R, Joao F, Lara JPR, Veloso AP. The effects of a single session of lumbar spinal manipulative therapy in terms of physical performance test symmetry in asymptomatic athletes: a single-blinded, randomised controlled study. BMJ Open Sport Exerc Med. 2018;4(1):e000389.

4. Aspinall SL, Jacques A, Leboeuf-Yde C, Etherington SJ, Walker BF. No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: A randomised controlled trial in adults with low back pain. Musculoskelet Sci Pract. 2019;43:18–25.

5. Balbás-Álvarez L, Candelas-Fernández P, Del Corral T, La Touche R, López-de-Uralde-Villanueva I. Effect of manual therapy, motor control exercise, and inspiratory muscle training on maximum inspiratory pressure and postural measures in moderate smokers: A randomized controlled trial. J Manip Physiol Ther. 2018;41(5):372–82.

6. Bautista-Aguirre F, Oliva-Pascual-Vaca A, Heredia-Rizo AM, Bosca-Gandia JJ, Ricard F, Rodriguez-Blanco C. Effect of cervical vs. thoracic spinal manipulation on peripheral neural features and grip strength in subjects with chronic mechanical neck pain: a randomized controlled trial. Eur J Phys Rehabil Med. 2017;53(3):333–41.

7. Behrangrad S, Kamali F. Comparison of ischemic compression and lumbopelvic manipulation as trigger point therapy for patellofemoral pain syndrome in young adults: A double-blind randomized clinical trial. J Bodyw Mov Ther. 2017;21(3):554–64.

8. Bernal-Utrera C, Gonzalez-Gerez JJ, Anarte-Lazo E, Rodriguez-Blanco C. Manual therapy versus therapeutic exercise in non-specific chronic neck pain: a randomized controlled trial. Trials Electron Resour. 2020;21(1):682.

9. Boas Fernandes WV, Silveira Bicalho E, Capote AE, Ferretti Manffra E. Duration of the effects of spinal manipulation on pain intensity and electromyographic activity of paravertebral parts of individuals with chronic mechanical low back pain. Fisioter E Pesqui. 2016;23(2):155–62.

10. Boff TA, Pasinato F, Ben AJ, Bosmans JE, van Tulder M, Carregaro RL. Effectiveness of spinal manipulation and myofascial release compared with spinal manipulation alone on health-related outcomes in individuals with non-specific low back pain: randomized controlled trial. Physiother. 2020;10(7)71-80.

11. Bond BM, Kinslow CD, Yoder AW, Liu W. Effect of spinal manipulative therapy on mechanical pain sensitivity in patients with chronic nonspecific low back pain: a pilot randomized, controlled trial. J Man Manip Ther. 2020;28(1):15–27.

12. Bracht MA, Coan ACB, Yahya A, Dos Santos MJ. Effects of cervical manipulation on pain, grip force control, and upper extremity muscle activity: a randomized controlled trial. J Man Manip Ther. 2018;26(2):78–88.

13. Bronfort G, Maiers M, Schulz C, Leininger B, Westrom K, Angstman G, et al. Multidisciplinary integrative care versus chiropractic care for low back pain: a randomized clinical trial. Chiropr Man Ther. 2022;30(1):10.

14. Bruck K, Jacobi K, Schmidt T. Fascial treatment versus manual therapy (HVLA) in patients with chronic neck pain: A randomized controlled trial. J Back Musculoskelet Rehabil. 2021;04:04.

15. Cambron JA, Dexheimer JM, Duarte M, Freels S. Shoe Orthotics for the Treatment of Chronic Low Back Pain: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017;98(9):1752–62.

16. Carrasco-Martinez F, Ibanez-Vera AJ, Martinez-Amat A, Hita-Contreras F, Lomas-Vega R. Short-term effectiveness of the flexion-distraction technique in comparison with high-velocity vertebral manipulation in patients suffering from low-back pain. Complement Ther Med. 2019;44:61–7.

17. Carrasco-Uribarren A, Rodriguez-Sanz J, Lopez-de-Celis C, Perez-Guillen S, Tricas-Moreno JM, Cabanillas-Barea S. Short-term effects of the traction-manipulation protocol in dizziness intensity and disability in cervicogenic dizziness: a randomized controlled trial. Disabil Rehabil. 2021;20;1–9.

18. Castello Branco K, Moodley M. Chiropractic manipulative therapy of the thoracic spine in combination with stretch and strengthening exercises, in improving postural kyphosis in woman. Health SA Gesondheid. 2016;21(1):303–8.

19. Castro-Sanchez AM, Lara-Palomo IC, Mataran-Penarrocha GA, Fernandez-de-Las-Penas C, Saavedra-Hernandez M, Cleland J, et al. Short-term effectiveness of spinal manipulative therapy versus functional technique in patients with chronic nonspecific low back pain: a pragmatic randomized controlled trial. Spine J Off J North Am Spine Soc. 2016;16(3):302–12.

20. Castro-Sánchez AM, Gil-Martínez E, Fernández-Sánchez M, Lara-Palomo IC, Nastasia I, de los Ángeles Querol-Zaldívar M, et al. Manipulative therapy of sacral torsion versus myofascial release in patients clinically diagnosed posterior pelvic pain: A consort compliant randomized controlled trial. Spine J. 2021;21(11):1890-1899.

21. Chaibi A, Benth JS, Tuchin P, Russell MB. Chiropractic spinal manipulative therapy for migraine. A three-armed, single-blinded, placebo, randomized controlled trial. Eur J Neurol, 24: 143-153.

22. Cholewicki J, Popovich JM Jr, Reeves NP, DeStefano LA, Rowan JJ, Francisco TJ, et al. The effects of osteopathic manipulative treatment on pain and disability in patients with chronic neck pain: A single-blinded randomized controlled trial. PM&R: The Journal of Injury, Function and Rehabilitation. 2022; 1- 13. doi:10.1002/pmrj.12732.

23. Corum M, Aydin T, Medin Ceylan C, Kesiktas FN. The comparative effects of spinal manipulation, myofascial release and exercise in tension-type headache patients with neck pain: a randomized controlled trial. Complement Ther Clin Pract 2021; 43:10139.

24. Coste J, Medkour T, Maigne JY, Perez M, Laroche F, Perrot S. Osteopathic medicine for fibromyalgia: a sham-controlled randomized clinical trial. Ther Adv Musculoskelet Dis. 2021;13:1759720X211009017.

25. Crothers AL, French SD, Hebert JJ, Walker BF. Spinal manipulative therapy, Graston technique® and placebo for non-specific thoracic spine pain: A randomised controlled trial. Chiropr Man Ther. 2016;24:16. doi:10.1186/s12998-016-0096-9.

26. de Oliveira RF, Costa LOP, Nascimento LP, Rissato LL. Directed vertebral manipulation is not better than generic vertebral manipulation in patients with chronic low back pain: a randomised trial. J Physiother 2020; 66(3):174-179.

27. DeVocht JW, Vining R, Smith DL, Long C, Jones T, Goertz C. Effect of chiropractic manipulative therapy on reaction time in special operations forces military personnel: a randomized controlled trial. Trials Electron Resour. 2019;20(1):5.

28. Didehdar D, Kamali F, Yoosefinejad AK, Lotfi M. The effect of spinal manipulation on brain neurometabolites in chronic nonspecific low back pain patients: a randomized clinical trial. Ir J Med Sci. 2020;189(2):543–50.

29. Dishman JD, Burke JR, Dougherty P. Motor Neuron Excitability Attenuation as a Sequel to Lumbosacral Manipulation in Subacute Low Back Pain Patients and Asymptomatic Adults: A Cross-Sectional H-Reflex Study. J Manipulative Physiol Ther. 2018;41(5):363–71.

30. Dissing KB, Hartvigsen J, Wedderkopp N, Hestbaek L. Conservative care with or without manipulative therapy in the management of back and/or neck pain in Danish children aged 9 to 15: a randomised controlled trial nested in a school-based cohort. BMJ Open 2018;8(9):e021358.

31. Ditcharles S, Yiou E, Delafontaine A, Hamaoui A. Short-Term Effects of Thoracic Spine Manipulation on the Biomechanical Organisation of Gait Initiation: A Randomized Pilot Study. Front Hum Neurosci. 2017;11:343.

32. Dorron SL, Losco BE, Drummond PD, Walker BF. Effect of lumbar spinal manipulation on local and remote pressure pain threshold and pinprick sensitivity in asymptomatic individuals: a randomised trial. Chiropr Man Ther. 2016;24:47.

33. Dunning JR, Butts R, Mourad F, Young I, Fernandez-de-Las Peñas C, Hagins M, et al. Upper cervical and upper thoracic manipulation versus mobilization and exercise in patients with cervicogenic headache: a multi-center randomized clinical trial. BMC Musculoskelet Disord. 2016;17:64.

34. Dunning J, Butts R, Fernandez-de-Las-Penas C, Walsh S, Goult C, Gillett B, et al. Spinal manipulation and electrical dry needling in patients with subacromial pain syndrome: a multicenter randomized clinical trial. J Orthop Sports Phys Ther 2021;51(2):72-81.

35. Dunning J, Butts R, Zacharko N, Fandry K, Young I, Wheeler K, et al. Spinal manipulation and perineural electrical dry needling in patients with cervicogenic headache: a multi-center randomized clinical trial. Spine J. 2021;21(2):284-295.

36. Eklund A, Jensen I, Lohela-Karlsson M, Hagberg J, Leboeuf-Yde C, Kongsted A, et al. The nordic maintenance care program: Effectiveness of chiropractic maintenance care versus symptom-guided treatment for recurrent and persistent low back pain—a pragmatic randomized controlled trial. PLoS ONE. 2018;13(9):e0203029.

37. Engel RM, Gonski P, Beath K, Vemulpad S. Medium term effects of including manual therapy in a pulmonary rehabilitation program for chronic obstructive pulmonary disease (COPD): a randomized controlled pilot trial. J Man Manip Ther. 2016;24(2):80–9.

38. Erdem EU, Ünver B, Akbas E, Kinikli GI. Immediate effects of thoracic manipulation on cervical joint position sense in individuals with mechanical neck pain: A randomized controlled trial. J Back Musculoskelet Rehabil. 2021;34(5):735-742.

39. Espí-López GV, López-Bueno L, Vicente-Herrero MT, Martinez-Arnau FM, Monzani L. Efficacy of manual therapy on anxiety and depression in patients with tension-type headache. A randomized controlled clinical trial. Int J Osteopath Med. 2016;22:11–20.

40. Espi-Lopez GV, Lopez-Martinez S, Ingles M, Serra-Ano P, Aguilar-Rodriguez M. Effect of manual therapy versus proprioceptive neuromuscular facilitation in dynamic balance, mobility and flexibility in field hockey players. A randomized controlled trial. Phys Ther Sport. 2018;32:173–9.

41. Espi-Lopez GV, Rodriguez-Blanco C, Oliva-Pascual-Vaca A, Molina-Martinez F, Falla D. Do manual therapy techniques have a positive effect on quality of life in people with tension-type headache? A randomized controlled trial. Eur J Phys Rehabil Med. 2016;52(4):447–56.

42. Espi-Lopez GV, Zurriaga-Llorens R, Monzani L, Falla D. The effect of manipulation plus massage therapy versus massage therapy alone in people with tension-type headache. A randomized controlled clinical trial. Eur J Phys Rehabil Med. 2016;52(5):606–17.

43. Evans R, Haas M, Leininger B, Hanson L, Schulz C, Bronfort G. Spinal manipulation and exercise for low back pain in adolescents: a randomized trial. Glob Adv Health Med. 2018;7:200-201.

44. Fagundes Loss J, de Souza da Silva L, Ferreira Miranda I, Groisman S, Santiago Wagner Neto E, Souza C, et al. Immediate effects of a lumbar spine manipulation on pain sensitivity and postural control in individuals with nonspecific low back pain: a randomized controlled trial. Chiropr Man Ther. 2020;28(1):25.

45. Farazdaghi MR, Motealleh A, Abtahi F, Panjan A, Sarabon N, Ghaffarinejad F. Effect of sacroiliac manipulation on postural sway in quiet standing: a randomized controlled trial. Braz J Phys Ther 2018;22(2):120-126.

46. Fisher LR, Alvar BA, Maher SF, Cleland JA. Short-term Effects of Thoracic Spine Thrust Manipulation, Exercise, and Education in Individuals With Low Back Pain: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2020;50(1):24–32.

47. Ford JJ, Slater SL, Richards MC, Surkitt LD, Chan AYP, Taylor NF, et al. Individualised manual therapy plus guideline-based advice vs advice alone for people with clinical features of lumbar zygapophyseal joint pain: a randomised controlled trial. Physiotherapy. 2019;105(1):53–64.

48. Fosberg KK, Puentedura E, Schmitz B, Jain TK, Cleland JA. The Effects of Thrust Joint Manipulation on the Resting and Contraction Thickness of Transversus Abdominis in Patients With Low Back Pain: A Randomized Control Trial. J Manipulative Physiol Ther. 2020;43(4):339–55.

49. Fraix M, Badran S, Graham V, Redman-Bentley D, Hurwitz EL, Quan VL, et al. Osteopathic manipulative treatment in individuals with vertigo and somatic dysfunction: a randomized, controlled, comparative feasibility study. J Osteopath Med. 2021;121(1):71–83.

50. Fritz JM, Sharpe J, Greene T, Lane E, Hadizadeh M, McFadden M, et al. Optimization of Spinal Manipulative Therapy Protocols: A Factorial Randomized Trial Within a Multiphase Optimization Framework. J Pain. 2021;22(6):655–68.

51. Fritz JM, Lane E, McFadden M, Brennan G, Magel JS, Thackeray A, et al. Physical Therapy Referral From Primary Care for Acute Back Pain With Sciatica : a Randomized Controlled Trial. Ann Intern Med. 2021;174(1):8-17.

52. Galindez-Ibarbengoetxea X, Setuain I, Ramirez-Velez R, Andersen LL, Gonzalez-Izal M, Jauregi A, et al. Short-term effects of manipulative treatment versus a therapeutic home exercise protocol for chronic cervical pain: A randomized clinical trial. J Back Musculoskelet Rehabil. 2018;31(1):133–45.

53. Galindez-Ibarbengoetxea X, Setuain I, González-Izal M, Jauregi A, Ramírez-Velez R, Andersen LL, et al. Randomised controlled pilot trial of high-velocity, low-amplitude manipulation on cervical and upper thoracic spine levels in asymptomatic subjects. Int J Osteopath Med. 2017;25:6–14.

54. Galindez-Ibarbengoetxea X, Setuain I, Ramirez-Velez R, Andersen LL, Gonzalez-Izal M, Jauregi A, et al. Immediate Effects of Osteopathic Treatment Versus Therapeutic Exercise on Patients With Chronic Cervical Pain. Altern Ther Health Med. 2018;24(3):24–32.

55. Garcia-Perez-Juana D, Fernandez-de-las-Penas C, Arias-Buria JL, Cleland JA, Plaza-Manzano G, Ortega-Santiago R. Changes in cervicocephalic kinesthetic sensibility, widespread pressure pain sensitivity, and neck pain after cervical thrust manipulation in patients with chronic mechanical neck pain: a randomized clinical trial. J Manip Physiol Ther 2018;41(7):551-560.

56. Gattie E, Cleland JA, Pandya J, Snodgrass S. Dry Needling Adds No Benefit to the Treatment of Neck Pain: A Sham-Controlled Randomized Clinical Trial With 1-Year Follow-up. J Orthop Sports Phys Ther. 2021;51(1):37–45.

57. Gesslbauer C, Vavti N, Keilani M, Mickel M, Crevenna R. Effectiveness of osteopathic manipulative treatment versus osteopathy in the cranial field in temporomandibular disorders - a pilot study. Disabil Rehabil. 2018;40(6):631–6.

58. Ghasabmahaleh SH, Rezasoltani Z, Dadarkhah A, Hamidipanah S, Mofrad RK, Najafi S. Spinal manipulation for subacute and chronic lumbar radiculopathy: a randomized controlled trial. Am J Med 2021;134(1):135-141.

59. Goertz CM, Salsbury SA, Long CR, Vining RD, Andresen AA, Hondras MA, et al. Patient-centered professional practice models for managing low back pain in older adults: a pilot randomized controlled trial. BMC Geriatr. 2017;17(1):235.

60. Goertz CM, Salsbury SA, Vining RD, Long CR, Pohlman KA, Weeks WB, et al. Effect of spinal manipulation of upper cervical vertebrae on blood pressure: results of a pilot sham-controlled trial. J Manip Physiol Ther 2016;39(5):369-380.

61. Goertz CM, Xia T, Long CR, Vining RD, Pohlman KA, DeVocht JW, et al. Effects of spinal manipulation on sensorimotor function in low back pain patients--A randomised controlled trial. Man Ther. 2016;21:183–90.

62. Gomez F, Escriba P, Oliva-Pascual-Vaca J, Mendez-Sanchez R, Puente-Gonzalez AS. Immediate and short-term effects of upper cervical high-velocity, low-amplitude manipulation on standing postural control and cervical mobility in chronic nonspecific neck pain: a randomized controlled trial. J Clin Med 2020;9(8): 2580.

63. Gorrell LM, Beath K, Engel RM. Manual and instrument applied cervical manipulation for mechanical neck pain: a randomized controlled trial. J Manipulative Physiol Ther. 2016;39(5):319–29.

64. Grimes JK, Puentedura E, Cheng MS, Seitz AL. The comparative effects of upper thoracic spine thrust manipulation techniques in individuals with subacromial pain syndrome: a randomized clinical trial. J Orthop Sports Phys Ther 2019;49(10):716-724.

65. Griswold D, Learman K, Kolber MJ, O'Halloran B, Cleland JA. Pragmatically applied cervical and thoracic nonthrust manipulation versus thrust manipulation for patients with mechanical neck pain: a multicenter randomized clinical trial. J Orthop Sports Phys Ther 2018;48(3):137-145.

66. Groisman S, Malysz T, de Souza da Silva L, Rocha Ribeiro Sanches T, Camargo Bragante K, Locatelli F, et al. Osteopathic manipulative treatment combined with exercise improves pain and disability in individuals with non-specific chronic neck pain: a pragmatic randomized controlled trial. J Bodyw Mov Ther 2020; 24(2):189-195

67. Haas M, Bronfort G, Evans R, Schulz C, Vavrek D, Takaki L, et al. Dose-response and efficacy of spinal manipulation for care of cervicogenic headache: a dual-center randomized controlled trial. Spine J Off J North Am Spine Soc. 2018;18(10):1741–54.

68. Haider R, Bashir MS, Adeel M, Ijaz MJ, Ayub A. Comparison of conservative exercise therapy with and without Maitland Thoracic Manipulative therapy in patients with subacromial pain: Clinical trial. J Pak Med Assoc. 2018;68(3):381–7.

69. Haik MN, Alburquerque-Sendin F, Camargo PR. Short-Term Effects of Thoracic Spine Manipulation on Shoulder Impingement Syndrome: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017;98(8):1594–605.

70. Haleema B, Riaz H. Effects of thoracic spine manipulation on pressure pain sensitivity of rhomboid muscle active trigger points: A randomized controlled trial. J Pak Med Assoc. 2021;71(7):1720–4.

71. Hanney WJ, Puentedura EJ, Kolber MJ, Liu X, Pabian PS, Cheatham SW. The immediate effects of manual stretching and cervicothoracic junction manipulation on cervical range of motion and upper trapezius pressure pain thresholds. J Back Musculoskelet Rehabil. 2017;30(5):1005–13.

72. Hardas GM, Murrell GAC. Prospective, randomized, double-blind, placebo-controlled clinical trial assessing the effects of applying a force to C5 by a mechanically assisted instrument on referred pain to the shoulder. Spine 2018;43(7):461-466.

73. Harihara Prakash R, Mehta J, Patel D. Effect of thrust versus non-thrust mobilization directed at the thoracic spine in patients with mechanical neck pain: A randomized control trial. Natl J Physiol Pharm Pharmacol. 2020;10(10):878–83.

74. Hartstein AJ, Lievre AJ, Grimes JK, Hale SA. Immediate effects of thoracic spine thrust manipulation on neurodynamic mobility. J Manip Physiol Ther 2018;41(4):332-341.

75. Holt K, Niazi IK, Amjad I, Kumari N, Rashid U, Duehr J, et al. The Effects of 4 Weeks of Chiropractic Spinal Adjustments on Motor Function in People with Stroke: A Randomized Controlled Trial. Brain Sci. 2021;11(6):21.

76. Holt KR, Haavik H, Lee AC, Murphy B, Elley CR. Effectiveness of Chiropractic Care to Improve Sensorimotor Function Associated With Falls Risk in Older People: A Randomized Controlled Trial. J Manipulative Physiol Ther. 2016;39(4):267–78.

77. Javadov A, Ketenci A, Aksoy C. The efficiency of manual therapy and sacroiliac and lumbar exercises in patients with sacroiliac joint dysfunction syndrome. Pain Physician. 2021;24(3):223-233.

78. Joo S, Lee Y, Song CH. Immediate effects of thoracic spinal manipulation on pulmonary function in stroke patients: a preliminary study. J Manip Physiol Ther 2018;41(7):602-608.

79. Jordon MK, Beattie PF, D'Urso S, Scriven S. Spinal manipulation does not affect pressure pain thresholds in the absence of neuromodulators: a randomized controlled trial. J Man Manip Ther. 2017;25(4):172–81.

80. Joshi S, Balthillaya G, Neelapala YVR. Immediate effects of cervicothoracic junction mobilization versus thoracic manipulation on the range of motion and pain in mechanical neck pain with cervicothoracic junction dysfunction: a pilot randomized controlled trial. Chiropr Man Ther. 2020;28(1):38.

81. Kachmar O, Kushnir A, Matiushenko O, Hasiuk M. Influence of spinal manipulation on muscle spasticity and manual dexterity in participants with cerebral palsy: randomized controlled trial. J Chiropr Med 2018;17(3):141-150.

82. Kamali F, Zamanlou M, Ghanbari A, Alipour A, Bervis S. Comparison of manipulation and stabilization exercises in patients with sacroiliac joint dysfunction patients: A randomized clinical trial. J Bodyw Mov Ther. 2019;23(1):177–82.

83. Karas S, Olson Hunt MJ, Temes B, Thiel M, Swoverland T, Windsor B. The effect of direction specific thoracic spine manipulation on the cervical spine: a randomized controlled trial. J Man Manip Ther. 2018;26(1):3–10.

84. Kendall JC, French SD, Hartvigsen J, Azari MF. Chiropractic treatment including instrument-assisted manipulation for non-specific dizziness and neck pain in community-dwelling older people: a feasibility randomised sham-controlled trial. Chiropr Man Ther. 2018;26:14.

85. Laframboise MA, Vernon H, Srbely J. Effect of two consecutive spinal manipulations in a single session on myofascial pain pressure sensitivity: a randomized controlled trial. J Can Chiropr Assoc. 2016;60(2):137–45.

86. Langenfeld A, Humphreys BK, De Bie RA, Swanenburg J. Comparing manual and mechanically assisted manipulations of the thoracic spine in neck pain patients: A pilot study. F1000Research. 2018;7:156. doi.org/10.12688/f1000research.13780.

87. Lee KW, Kim WH. Effect of thoracic manipulation and deep craniocervical flexor training on pain, mobility, strength, and disability of the neck of patients with chronic nonspecific neck pain: a randomized clinical trial. J Phys Ther Sci 2016;28(1):175-180.

88. Lim KT, Hwang EH, Cho JH, Jung JY, Kim KW, Ha IH, et al. Comparative effectiveness of Chuna manual therapy versus conventional usual care for non-acute low back pain: a pilot randomized controlled trial. Trials Electron Resour. 2019;20(1):216.

89. Lisi AJ, Scheinowitz M, Saporito R, Onorato A. A Pulsed Electromagnetic Field Therapy Device for Non-Specific Low Back Pain: A Pilot Randomized Controlled Trial. Pain Ther. 2019;8(1):133–40.

90. Lohman EB, Pacheco GR, Gharibvand L, Daher N, Devore K, Bains G, et al. The immediate effects of cervical spine manipulation on pain and biochemical markers in females with acute non-specific mechanical neck pain: a randomized clinical trial. J Man Manip Ther. 2019;27(4):186–96.

91. Lopez-de-Uralde-Villanueva I, Beltran-Alacreu H, Fernandez-Carnero J, La Touche R. Pain management using a multimodal physiotherapy program including a biobehavioral approach for chronic nonspecific neck pain: a randomized controlled trial. Physiother Theory Pract. 2020;36(1):45–62.

92. Lopez-de-Uralde-Villanueva I, Candelas-Fernandez P, de-Diego-Cano B, Minguez-Calzada O, Del Corral T. The effectiveness of combining inspiratory muscle training with manual therapy and a therapeutic exercise program on maximum inspiratory pressure in adults with asthma: a randomized clinical trial. Clin Rehabil. 2018;32(6):752–65.

93. Lorenzo S, Nicotra CM, Mentreddy AR, Padia HJ, Stewart DO, Hussein MO, et al. Assessment of Pulmonary Function After Osteopathic Manipulative Treatment vs Standard Pulmonary Rehabilitation in a Healthy Population. J Am Osteopath Assoc. 2019; doi: 10.7556/jaoa.2019.026. Epub ahead of print. PMID: 30741314.

94. Luceno-Mardones A, Luceno-Rodriguez I, Rodriguez-Lopez ES, Oliva-Pascual-Vaca J, Rosety I, Oliva-Pascual-Vaca A. Effects of Osteopathic T9-T10 Vertebral Manipulation in Tonsillitis: A Randomized Clinical Trial. Healthcare. 2021;9(4):01.

95. Lynen A, Schömitz M, Vahle M, Jäkel A, Rütz M, Schwerla F. Osteopathic treatment in addition to standard care in patients with Gastroesophageal Reflux Disease (GERD) – A pragmatic randomized controlled trial. J Bodyw Mov Ther. 2022;29:223–31.

96. Lynge S, Dissing KB, Vach W, Christensen HW, Hestbaek L. Effectiveness of chiropractic manipulation versus sham manipulation for recurrent headaches in children aged 7–14 years - a randomised clinical trial. Chiropr Man Ther. 2021;29(1):1.

97. Maiers M, Hartvigsen J, Evans R, Westrom K, Wang Q, Schulz C, et al. Short or long-term treatment of spinal disability in older adults with manipulation and exercise. Arthritis Care Res 2019;71(11):1516-1524.

98. Marske C, Bernard N, Palacios A, Wheeler C, Preiss B, Brown M, et al. Fibromyalgia with Gabapentin and Osteopathic Manipulative Medicine: A Pilot Study. J Altern Complement Med. 2018;24(4):395–402.

99. McCarthy CJ, Potter L, Oldham JA. Comparing targeted thrust manipulation with general thrust manipulation in patients with low back pain. A general approach is as effective as a specific one. A randomised controlled trial. BMJ Open Sport Exerc Med 2019; 5(1):e000514.

100. Minarini G, Ford M, Esteves J. Immediate effect of T2, T5, T11 thoracic spine manipulation of asymptomatic patient on autonomic nervous system response: Single-blind, parallel-arm controlled-group experiment. Int J Osteopath Med. 2018;30:12–7.

101. Mintken PE, McDevitt AW, Cleland JA, Boyles RE, Beardslee AR, Burns SA, et al. Cervicothoracic Manual Therapy Plus Exercise Therapy Versus Exercise Therapy Alone in the Management of Individuals With Shoulder Pain: A Multicenter Randomized Controlled Trial. J Orthop Sports Phys Ther. 2016;46(8):617–28.

102. Moodley M, Craig M. The effect of sacroiliac chiropractic adjustments on innominate angles. Health SA Gesondheid. 2020;25:1398.

103. Motealleh A, Barzegar A, Abbasi L. The immediate effect of lumbopelvic manipulation on knee pain, knee position sense, and balance in patients with patellofemoral pain: A randomized controlled trial. J Bodyw Mov Ther. 2020;24(3):71–7.

104. Motealleh A, Gheysari E, Shokri E, Sobhani S. The immediate effect of lumbopelvic manipulation on EMG of vasti and gluteus medius in athletes with patellofemoral pain syndrome: A randomized controlled trial. Man Ther. 2016;22:16–21.

105. Moustafa IM, Diab AA, Taha S, Harrison DE. Addition of a Sagittal Cervical Posture Corrective Orthotic Device to a Multimodal Rehabilitation Program Improves Short- and Long-Term Outcomes in Patients With Discogenic Cervical Radiculopathy. Arch Phys Med Rehabil. 2016;97(12):2034–44.

106. Munoz-Gomez E, Ingles M, Serra-Ano P, Espi-Lopez GV. Effectiveness of a manual therapy protocol based on articulatory techniques in migraine patients. A randomized controlled trial. Musculoskelet Sci Pract. 2021;54:102386.

107. Nambi G, Kamal W, Es S, Joshi S, Trivedi P. Spinal manipulation plus laser therapy versus laser therapy alone in the treatment of chronic non-specific low back pain: a randomized controlled study. Eur J Phys Rehabil Med. 2018;54(6):880–9.

108. Nejati P, Safarcherati A, Karimi F. Effectiveness of Exercise Therapy and Manipulation on Sacroiliac Joint Dysfunction: A Randomized Controlled Trial. Pain Physician. 2019;22(1):53–61.

109. Nogueira N, Oliveira-Campelo N, Lopes Â, Torres R, Sousa ASP, Ribeiro F. The acute effects of manual and instrument-assisted cervical spine manipulation on pressure pain threshold, pressure pain perception, and muscle-related variables in symptomatic subjects: A randomized controlled trial. J Manip Physiol Ther. 2020;43(3):179–88.

110. Paanalahti K, Holm LW, Nordin M, Hoijer J, Lyander J, Asker M, et al. Three combinations of manual therapy techniques within naprapathy in the treatment of neck and/or back pain: a randomized controlled trial. BMC Musculoskelet Disord. 2016;23;17:176.

111. Page I, Descarreaux M. Effects of spinal manipulative therapy biomechanical parameters on clinical and biomechanical outcomes of participants with chronic thoracic pain: a randomized controlled experimental trial. BMC Musculoskelet Disord. 2019;18;20(1):29.

112. Papa L, Amodio A, Biffi F, Mandara A. Impact of osteopathic therapy on proprioceptive balance and quality of life in patients with dizziness. J Bodyw Mov Ther. 2017;21(4):866–72.

113. Paredes R, Crasto C, Magalhães B, Carvalho P. Short-Term Effects of Global Pelvic Manipulation on Knee Joint Position Sense in Asymptomatic Participants: A Double-Blind Randomized Controlled Trial. J Manipulative Physiol Ther. 2020;43(7):675–82.

114. Pascual-Vaca AO, Punzano-Rodríguez R, Escribá-Astaburuaga P, Fernández-Domínguez JC, Ricard F, Franco-Sierra MA, et al. Short-term changes in algometry, inclinometry, stabilometry, and urinary pH analysis after a thoracolumbar junction manipulation in patients with kidney stones. J Altern Complement Med. 2017;23(8):1–9.

115. Passmore SR, Johnson MG, Aloraini SM, Cooper S, Aziz M, Glazebrook CM. Impact of Spinal Manipulation on Lower Extremity Motor Control in Lumbar Spinal Stenosis Patients: A Small-Scale Assessor-Blind Randomized Clinical Trial. J Manipulative Physiol Ther. 2019;42(1):23–33.

116. Penza CW, Horn ME, George SZ, Bishop MD. Comparison of 2 Lumbar Manual Therapies on Temporal Summation of Pain in Healthy Volunteers. J Pain. 2017;18(11):1397–408.

117. Petrozzi MJ, Leaver A, Ferreira PH, Rubinstein SM, Jones MK, Mackey MG. Addition of MoodGYM to physical treatments for chronic low back pain: A randomized controlled trial. Chiropr Man Ther. 2019;27:54.

118. Qu L, Xing L, Norman W, Li M, Guo Y, Gao S, et al. Clinical effect of traditional Chinese spinal orthopedic manipulation in treatment of chondromalacia patellae. J Tradit Chin Med. 2016;36(6):718–23.

119. Qu LX, Xing LY, Wanda N, Chen H, Li MJ, Gao S, et al. A Clinical Observation of Functional Abdominal Pain Syndrome in Patients Treated by Traditional Chinese Spinal Orthopedic Manipulation. Chin J Integr Med. 2018;24(2):140–6.

120. Reynolds B, Puentedura EJ, Kolber MJ, Cleland JA. Effectiveness of cervical spine high velocity low amplitude thrust added to behavioral education, soft tissue mobilization, and exercise in individuals with temporomandibular disorder (TMD) with myalgia: a randomized clinical trial. J Orthop Sports Phys Ther 2020;50(8):455-465.

121. Rist PM, Bernstein C, Kowalski M, Osypiuk K, Connor JP, Vining R, et al. Multimodal chiropractic care for migraine: a pilot randomized controlled trial. Cephalalgia 2021;41(3):318-328.

122. Rodrigues PTV, Correa LA, Reis FJJ, Meziat-Filho NA, Silva BM, Nogueira LAC. One session of spinal manipulation improves the cardiac autonomic control in patients with musculoskeletal pain: a randomized placebo-controlled trial. Spine 2021;46(14):915-922.

123. Rodriguez-Sanz J, Malo-Urries M, Corral-de-Toro J, Lopez-de-Celis C, Lucha-Lopez MO, Tricas-Moreno JM, et al. Does the Addition of Manual Therapy Approach to a Cervical Exercise Program Improve Clinical Outcomes for Patients with Chronic Neck Pain in Short- and Mid-Term? A Randomized Controlled Trial. Int J Environ Res Public Health. 2020;17(18):10.

124. Rodriguez-Sanz J, Malo-Urries M, Lucha-Lopez MO, Perez-Bellmunt A, Carrasco-Uribarren A, Fanlo-Mazas P, et al. Effects of the Manual Therapy Approach of Segments C0-1 and C2-3 in the Flexion-Rotation Test in Patients with Chronic Neck Pain: A Randomized Controlled Trial. Int J Environ Res Public Health. 2021;18(2):17.

125. Romero del Rey R, Saavedra Hernandez M, Rodriguez Blanco C, Palomeque del Cerro L, Alarcon Rodriguez R. Short-term effects of spinal thrust joint manipulation on postural sway in patients with chronic mechanical neck pain: a randomized controlled trial. Disabil Rehabil 2022;44(8):1227-1233.

126. Rose KA, Kizhakkeveettil A, Kadar GE, Losack M. Combining Spinal Manipulation With Standard Counseling for Tobacco Cessation: Results of a Feasibility Randomized Clinical Trial. J Chiropr Med. 2017;16(1):41–8.

127. Sampath KK, Botnmark E, Mani R, Cotter JD, Katare R, Munasinghe PE, et al. Neuroendocrine Response Following a Thoracic Spinal Manipulation in Healthy Men. J Orthop Sports Phys Ther. 2017;47(9):617–27.

128. Sarker KK, Sethi J, Mohanty U. Effect of spinal manipulation on pain sensitivity, postural sway, and health-related quality of life among patients with non-specific chronic low back pain: A randomised control trial. J Clin Diagn Res. 2019;13(2):YC01–5.

129. Schulz C, Evans R, Maiers M, Schulz K, Leininger B, Bronfort G. Spinal manipulative therapy and exercise for older adults with chronic low back pain: a randomized clinical trial. Chiropr Man Ther. 2019;27:21.

130. Shin DC, Lee YW. The immediate effects of spinal thoracic manipulation on respiratory functions. J Phys Ther Sci. 2016;28(9):2547–9.

131. Silva AC da, Santos GM, Marques CM de G, Marques JLB. Immediate Effects of Spinal Manipulation on Shoulder Motion Range and Pain in Individuals With Shoulder Pain: A Randomized Trial. J Chiropr Med. 2019;18(1):19–26.

132. Simoni G, Bozzolan M, Bonnini S, Grassi A, Zucchini A, Mazzanti C, et al. Effectiveness of standard cervical physiotherapy plus diaphragm manual therapy on pain in patients with chronic neck pain: a randomized controlled trial. J Bodyw Mov Ther. 2021;26:481-491.

133. Soal LJ, Bester CM, Shaw BS, Yelverton C. Changes in chronic neck pain following the introduction of a visco-elastic polyurethane foam pillow and/or chiropractic treatment. Health SA Gesondheid. 2019;24:1099.

134. Sparks CL, Liu WC, Cleland JA, Kelly JP, Dyer SJ, Szetela KM, et al. Functional magnetic resonance imaging of cerebral hemodynamic responses to pain following thoracic thrust manipulation in individuals with neck pain: a randomized trial. J Manip Physiol Ther 2017;40(9):625-634.

135. Stepnik J, Kedra A, Czaprowski D. Short-term effect of osteopathic manual techniques (OMT) on respiratory function in healthy individuals. PLoS ONE Electron Resour. 2020;15(6):e0235308.

136. Sueki D, Almaria S, Bender M, McConnell B. The immediate and 1-week effects of mid-thoracic thrust manipulation on lower extremity passive range of motion. Physiother Theory Pract. 2020;36(6):720–30.

137. Telles JD, Schiavon MAG, Costa ACDS, Rampazo ÉP, Liebano RE. Hypoalgesic Effects of Transcutaneous Electrical Nerve Stimulation Combined With Joint Manipulation: A Randomized Clinical Trial. J Manipulative Physiol Ther. 2021;44(3):244-254.

138. Thomas JS, Clark BC, Russ DW, France CR, Ploutz-Snyder R, Corcos DM, et al. Effect of spinal manipulative and mobilization therapies in young adults with mild to moderate chronic low back pain: a randomized clinical trial. JAMA Netw Open 2020;3(8):e2022589.

139. Vaden CD, Holder JM, McCoy M, Sayers J, Holder AM. P300 wave outcomes in subluxation based chiropractic in residential addiction treatment: A randomized controlled clinical trial. Ann Vert Sublux Res. 2020;178–92.

140. Valenzuela PL, Pancorbo S, Lucia A, Germain F. Spinal Manipulative Therapy Effects in Autonomic Regulation and Exercise Performance in Recreational Healthy Athletes: A Randomized Controlled Trial. Spine. 2019;44(9):609–14.

141. Valera-Calero A, Lluch Girbes E, Gallego-Izquierdo T, Malfliet A, Pecos-Martin D. Endocrine response after cervical manipulation and mobilization in people with chronic mechanical neck pain: a randomized controlled trial. Eur J Phys Rehabil Med. 2019;55(6):792–805.

142. Vilas Boas Fernandes W, Pizzol FD, Capote AE, de Andrade Melo S, Carvalho Schleder J. Immediate effects of spinal manipulation in pain and global joint mobility in patients with chronic nonspecific low back pain. Man Ther Posturology Rehabil J. 2016;14:1–5.

143. Vining R, Long CR, Minkalis A, Gudavalli MR, Xia T, Walter J, et al. Effects of Chiropractic Care on Strength, Balance, and Endurance in Active-Duty U.S. Military Personnel with Low Back Pain: A Randomized Controlled Trial. J Altern Complement Med. 2020;26(7):592–601.

144. Vinuesa-Montoya S, Aguilar-Ferrándiz ME, Matarán-Peñarrocha GA, Fernández-Sánchez M, Fernández-Espinar EM. A preliminary randomized clinical trial on the effect of cervicothoracic

manipulation plus supervised exercises vs a home exercise program for the treatment of shoulder impingement. J Chiropr Med. 2017;16(2):85–93.

145. Wang SQ, Chen M, Wei X, Gao XX, Zhao GD. Clinical research on lumbar oblique-pulling manipulation in combination with sling exercise therapy for patients with chronic nonspecific low back pain. Rev Assoc Med Bras. 2019;65(6):886–92.

146. Wang Y, Xu M, Shi Y. Efficacy of spinal chiropractic manipulative therapy for adjusting the relationship between cervical facet joints to treat headache caused by acute mountain sickness. J Int Med Res. 2020;48(1):0300060519898005.

147. Ward J, Tyer K, Pourmoghaddam A. Immediate influence of lumbar spine manipulation on pain, functional reach, static balance, and walking gait kinematics of individuals with acute low back pain. Chiropr J Aust. 2018;46(2):135–50.

148. Wright AA, Donaldson M, Wassinger CA, Emerson-Kavchak AJ. Subacute effects of cervicothoracic spinal thrust/non-thrust in addition to shoulder manual therapy plus exercise intervention in individuals with subacromial impingement syndrome: a prospective, randomized controlled clinical trial pilot study. J Man Manip Ther. 2017;25(4):190–200.

149. Xia T, Long CR, Gudavalli MR, Wilder DG, Vining RD, Rowell RM, et al. Similar Effects of Thrust and Nonthrust Spinal Manipulation Found in Adults With Subacute and Chronic Low Back Pain: A Controlled Trial With Adaptive Allocation. Spine. 2016;41(12):E702–9.

150. Yao SC, Zwibel H, Angelo N, Leder A, Mancini J. Effectiveness of Osteopathic Manipulative Medicine vs Concussion Education in Treating Student Athletes With Acute Concussion Symptoms. J Am Osteopath Assoc. 2020;07:07.

151. Younes M, Nowakowski K, Didier-Laurent B, Gombert M, Cottin F. Effect of spinal manipulative treatment on cardiovascular autonomic control in patients with acute low back pain. Chiropr Man Ther. 2017;25:33.

152. Young IA, Pozzi F, Dunning J, Linkonis R, Michener LA. Immediate and Short-term Effects of Thoracic Spine Manipulation in Patients With Cervical Radiculopathy: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2019;49(5):299–309.

153. Zafereo J, Wang-Price S, Roddey T, Brizzolara K. Regional manual therapy and motor control exercise for chronic low back pain: a randomized clinical trial. J Man Manip Ther. 2018;26(4):193–202.

154. Zago J, Amatuzzi F, Rondinel T, Matheus JP. Osteopathic Manipulative Treatment Versus Exercise Program in Runners With Patellofemoral Pain Syndrome: A Randomized Controlled Trial. J Sport Rehabil. 2021;30(4):609–18.

Appendix 3: Risk of bias assessment of included studies

Author, year (reference)	Overall risk of bias assessment
Albers et al, 2018 (1)	Some concerns
Alonso-Perez et al, 2017 (2)	Low risk
Alvarenga et al, 2018 (3)	Some concerns
Aspinall et al, 2019 (4)	Low risk
Balbás-Álvarez et al, 2018 (5)	Low risk
Bautista-Aguirre et al, 2017 (6)	Some concerns
Behrangrad & Kamali, 2017 (7)	High risk
Bernal-Utrera et al, 2020 (8)	High risk
Fernandes et al, 2016 (9)	High risk
Boff et al, 2020 (10)	High risk
Bond et al, 2020 (11)	High risk
Bracht et al, 2018 (12)	Some concerns
Bronfort et al, 2022 (13)	High risk
Brück et al, 2021 (14)	Some concerns
Cambron et al, 2017 (15)	High risk
Carrasco-Martínez et al, 2019 (16)	High risk
Carrasco-Uribarren et al, 2021(17)	High risk
Castello Branco & Moodley, 2016 (18)	High risk
Castro-Sanchez et al, 2016 (19)	Low risk
Castro-Sanchez et al, 2021 (20)	Low risk
Chaibi et al, 2017 (21)	High risk
Cholewicki et al, 2021 (22)	High risk
Corum et al, 2021 (23)	High risk
Coste et al, 2021 (24)	High risk
Crothers et al, 2016 (25)	High risk
de Oliveira et al, 2020 (26)	Some concerns
DeVocht et al, 2019 (27)	Low risk
Didehdar et al, 2020 (28)	High risk
Dishman et al, 2018 (29)	High risk
Dissing et al, 2018 (30)	Low risk
Ditcharles et al, 2017 (31)	Some concerns
Dorron et al, 2016 (32)	Some concerns
Dunning et al, 2016 (33)	Low risk
Dunning et al, 2021 (34)	Some concerns
Dunning et al, 2021 (35)	Some concerns
Eklund et al, 2018 (36)	Low risk
Engel et al, 2016 (37)	High risk

Erdem et al, 2021 [38]	Some concerns
Espi-López et al, 2016 [39]	High risk
Espi-López et al, 2018 [40]	High risk
Espi-López et al, 2016 [41]	Some concerns
Espi-López et al, 2016 [42]	High risk
Evans et al, 2018 [43]	High risk
Fagundes Loss et al, 2020 [44]	Some concerns
Farazdaghi et al, 2018 [45]	Low risk
Fisher et al, 2020 [46]	High risk
Ford et al, 2019 [47]	High risk
Fosberg et al, 2020 [48]	Low risk
Fraix et al, 2021 [49]	High risk
Fritz et al, 2021 [50]	High risk
Fritz et al, 2021 [51]	High risk
Galindez-Ibarbengoetxea et al, 2018 [52]	High risk
Galindez-Ibarbengoetxea et al, 2017 [53]	High risk
Galindez-Ibarbengoetxea et al, 2018 [54]	High risk
Garcia-Perez-Juana et al, 2018 [55]	High risk
Gattie et al, 2021 [56]	Some concerns
Gesslbauer et al, 2018 [57]	High risk
Ghasabmahaleh et al, 2021 [58]	High risk
Goertz et al, 2017 [59]	High risk
Goertz et al, 2016 [60]	High risk
Goertz et al, 2016 [61]	High risk
Gomez et al, 2020 [62]	Some concerns
Gorrell et al, 2016 [63]	Some concerns
Grimes et al, 2019 [64]	Some concerns
Griswold et al, 2018 [65]	Some concerns
Groisman et al, 2020 [66]	Some concerns
Haas et al, 2018 [67]	Some concerns
Haider et al, 2018 [68]	High risk
Haik et al, 2017 [69]	High risk
Haleema et al, 2021 [70]	High risk
Hanney et al, 2017 [71]	High risk
Hardas & Murrell, 2018 [72]	Some concerns
Harihara Prakash et al, 2020 [73]	High risk
Hartstein et al, 2018 [74]	High risk
Holt et al, 2021 [75]	High risk
Holt et al, 2016 [76]	High risk

Javadov et al, 2021 [77]	High risk
Joo et al, 2018 [78]	High risk
Jordon et al, 2017 [79]	High risk
Joshi et al, 2020 [80]	High risk
Kachmar et al, 2018 [81]	Some concerns
Kamali et al, 2019 [82]	Low risk
Karas et al, 2018 [83]	High risk
Kendall et al, 2018 [84]	High risk
Laframboise et al, 2016 [85]	High risk
Langenfeld et al, 2018 [86]	Some concerns
Lee & Kim, 2016 [87]	High risk
Lim et al, 2019 [88]	High risk
Lisi et al, 2019 [89]	High risk
Lohman et al, 2019 [90]	High risk
Lopez-de-Uralde-Villanueva et al, 2020 [91]	High risk
Lopez-de-Uralde-Villanueva et al, 2018 [92]	Some concerns
Lorenzo et al, 2019 [93]	High risk
Luceno-Mardones et al, 2021 [94]	High risk
Lynen et al, 2022 [95]	High risk
Lynge et al, 2021 [96]	Some concerns
Maiers et al, 2019 [97]	Some concerns
Marske et al, 2018 [98]	High risk
McCarthy et al, 2019 [99]	High risk
Minarini et al, 2018 [100]	High risk
Mintken et al, 2016 [101]	High risk
Moodley & Craig, 2020 [102]	High risk
Motealleh et al, 2020 [103]	High risk
Motealleh et al, 2016 [104]	High risk
Moustafa et al, 2016 [105]	High risk
Munoz-Gomez et al, 2021 [106]	Some concerns
Nambi et al, 2018 [107]	Some concerns
Nejati et al, 2019 [108]	Some concerns
Nogueira et al, 2020 [109]	Some concerns
Paanalahti et al, 2016 [110]	High risk
Page & Descarreaux, 2019 [111]	High risk
Papa et al, 2017 [112]	High risk
Paredes et al, 2020 [113]	High risk
Pascual-Vaca et al, 2017 [114]	High risk
Passmore et al, 2019 [115]	High risk

Penza et al, 2017 [116]	Some concerns
Petrozzi et al, 2019 [117]	Low risk
Qu et al, 2016 [118]	High risk
Qu et al, 2018 [119]	Some concerns
Reynolds et al, 2020 [120]	High risk
Rist et al, 2021 [121]	High risk
Rodrigues et al, 2021 [122]	High risk
Rodriguez-Sanz et al, 2020 [123]	High risk
Rodriguez-Sanz et al, 2021 [124]	Some concerns
Romero Del Rey et al, 2022 [125]	Some concerns
Rose et al, 2017 [126]	High risk
Sampath et al, 2017 [127]	High risk
Sarker et al, 2019 [128]	Some concerns
Schulz et al, 2019 [129]	Some concerns
Shin & Lee, 2016 [130]	Some concerns
Silva et al, 2019 [131]	Some concerns
Simoni et al, 2021 [132]	High risk
Soal et al, 2019 [133]	High risk
Sparks et al, 2017 [134]	Some concerns
Stepnik et al, 2020 [135]	High risk
Sueki et al, 2020 [136]	High risk
Telles et al, 2021 [137]	Some concerns
Thomas et al, 2020 [138]	High risk
Vaden et al, 2020 [139]	High risk
Valenzuela et al, 2019 [140]	Some concerns
Valera-Calero et al, 2019 [141]	Some concerns
Vilas Boas Fernandes et al, 2016 [142]	Some concerns
Vining et al, 2020 [143]	Some concerns
Vinuesa-Montoya et al, 2017 [144]	Some concerns
Wang et al, 2019 [145]	High risk
Wang et al, 2020 [146]	High risk
Ward et al, 2018 [147]	High risk
Wright et al, 2017 [148]	Some concerns
Xia et al, 2016 [149]	High risk
Yao et al, 2020 [150]	High risk
Younes et al, 2017 [151]	High risk
Young et al, 2019 [152]	High risk
Zafereo et al, 2018 [153]	Some concerns
Zago et al, 2021 [154]	High risk

BMJ Open

The reporting of adverse events associated with spinal manipulation in randomized clinical trials: an updated systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067526.R1
Article Type:	Original research
Date Submitted by the Author:	01-Mar-2023
Complete List of Authors:	Gorrell, Lindsay; Balgrist University Hospital, Integrative Spinal Research Group, Department of Chiropractic Medicine Brown, Benjamin T.; Macquarie Univ Engel, Roger; Macquarie University, Chiropractic Lystad, Reidar; Macquarie University, Australian Institute of Health Innovation
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS, REHABILITATION MEDICINE

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THE REPORTING OF ADVERSE EVENTS ASSOCIATED WITH SPINAL MANIPULATION IN RANDOMIZED CLINICAL TRIALS: AN UPDATED SYSTEMATIC REVIEW

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Sources of support

This project did not receive any funding.

Ethics approval statement

Ethics approval was not required for this systematic literature review.

Word count

Abstract: 300; Main text: 4399

Number of figures: 1

Number of tables: 3

Number of appendices: 3

ABSTRACT

Objectives

To describe if there has been a change in the reporting of adverse events associated with spinal manipulation in randomized controlled trials (RCTs) since 2016.

Design

Systematic literature review.

Data sources

Databases were searched from March 2016 to May 2022: MEDLINE (Ovid), Embase, CINAHL, ICL, PEDro and Cochrane Library. The following search terms and their derivatives were adapted for each platform: *spinal manipulation; chiropractic; osteopathy; physiotherapy; naprapathy; medical manipulation; clinical trial*.

Methods

Domains of interest (pertaining to adverse events) included: completeness and location of reporting; nomenclature and description; spinal location and practitioner delivering manipulation; methodological quality of the studies; and details of the publishing journal. Frequencies and proportions of studies reporting on each of these domains were calculated. Univariable and multivariable logistic regression models were fitted to examine the effect of potential predictors on the likelihood of studies reporting on adverse events.

Results

There were 5,399 records identified by the electronic searches, of which 154 (2.9%) were included in the analysis. Of these, ninety-four (61.0%) reported on adverse events with only 23.4% providing an explicit description of what constituted an adverse event. Reporting of adverse events in the abstract has increased (n= 29, 30.9%) while reporting in the results section has decreased (n= 83, 88.3%) over the past 6 years. Spinal manipulation was delivered to 7,518 participants in the included studies. No serious adverse events were reported in any of these studies.

Conclusions

While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased since our 2016 publication on the same topic, the level remains low and inconsistent with established standards. As such, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is more balanced reporting of both benefits and harms in RCTs involving spinal manipulation.

ARTICLE SUMMARY

Strengths and limitations of this review

- This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (1)
- The search strategy was inclusive of professions that deliver spinal manipulation
- The search included several databases relevant to manual therapy
- Due to heterogeneity of reporting of adverse events, only descriptive statistics were used to describe domains of interest

PROTOCOL

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=270543

FUNDING STATEMENT

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

WORD COUNT

4399

KEYWORDS

Adverse events; Harms; Literature review; Manipulation, spinal; Randomized controlled trials; Spinal manipulative therapy.

INTRODUCTION

The use of high-velocity, low-amplitude spinal manipulation to treat spinal pain and dysfunction is recommended in clinical and best practice guidelines (1–4) and is commonly used by several healthcare professions (5–7). Despite this, concerns remain surrounding adverse events following the intervention (8,9). Adverse events associated with spinal manipulation are typically benign, transient, and do not require further treatment (10). Indeed, some authors classify increased muscle soreness or stiffness in the treatment area as an 'expected outcome of treatment' rather than an adverse event (11). At the other end of the spectrum, catastrophic events, such as vertebral artery dissection, have been temporally associated with spinal manipulation (12). However, such events are rare, and as a result, are typically reported in individual case reports or case series with little to no information regarding the intervention that was delivered (13). Indeed, synthesis of the current literature suggests that there is no evidence for cervical spine manipulation causing cervical artery dissection (14). Additionally, several large population-based studies have reported that there is no difference in risk of cervical artery dissection following visits to a chiropractor compared to those occurring following a visit to a primary care provider (15,16) or, in those who received cervical spinal manipulation compared to matched controls (17,18). Furthermore, recent biomechanical studies report that head angular displacements and vertebral artery length changes are small during cervical spine manipulation thrusts (19) and that the vertebral artery does not experience longitudinal force during cervical spine manipulation (20). Despite this literature, the serious nature of such events that are temporally associated with cervical spine manipulation makes it imperative that the circumstances surrounding such events are reported transparently.

Randomized clinical trials (RCTs) are the gold standard study design for measuring effectiveness (benefit/s) of interventions for the treatment of spinal pain and dysfunction. However, as the risks of an intervention are also important to both patients and practitioners, RCTs should report on not only the efficacy of spinal manipulation, but also any adverse events associated with the intervention. The Consolidated Standards of Reporting Trials (CONSORT) statement, first published in 1996 with several updates since, provides the scientific community (specifically researchers and journal editors)

with a scaffold to standardize and improve the quality of RCT reporting (21–23). The CONSORT statement acknowledges the importance of reporting adverse events alongside effectiveness data. The 2004 Harms extension document (24) provides specific recommendations for how and where this data should be included in scientific manuscripts. While there has been improvement in the reporting of adverse events since the publication of the 2004 extension, reporting remains insufficient (25), especially for RCTs that involve spinal manipulation (26). Thus, the objective of this review was to describe if there has been a change in the reporting of adverse events associated with spinal manipulation in RCTs since 2016.

METHODOLOGY

This systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (27).

Definitions

Spinal manipulation was defined as a manual procedure involving a high-velocity, low-amplitude (HVLA) thrust delivered to a spinal joint with the intention of moving the joint past its physiological range of motion but without exceeding the anatomic limit (28). For the purposes of this review, spinal manipulation delivered using drop-piece-table and mechanical implements (e.g. Activator instrument) were considered HVLA procedures (29).

An adverse event was defined as any unfavourable reaction with a temporal association to spinal manipulation that resulted in an alteration in a participant's activities of daily living (30,31), irrespective of the timing of onset, duration, or severity of the event (32).

A serious adverse event was defined as any unfavourable sign, symptom, or disease temporally associated with the treatment, whether or not caused by the treatment that results in death or is life-threatening or results in inpatient hospitalization or prolongation of existing hospitalization for more than 24 hours with a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (30).

To be classified as reporting on adverse events "directly", a study must have provided explicit description of their operational definition of an adverse event (e.g. "In the current study, an adverse

event was defined as a sequelae of 1-week duration with any symptom perceived as distressing and unacceptable to the patient that required further treatment [excerpt from reference 63]." (33)), and/or how data on adverse events were measured (e.g. "Active and passive surveillance methods were used to collect information on adverse events." (34)), and/or provide a substantial description of adverse events observed during data collection (35,36). In contrast, all other studies reporting on adverse events "indirectly" did not explicitly provide such information.

Patient and public involvement

No patients were involved in this systematic literature review.

Ethics approval

Ethics approval was not required for this systematic literature review.

Eligibility criteria

Consistent with the 2016 review (26), RCTs reporting original data on spinal manipulation as either the sole intervention, or as the sole intervention in a comparator group, delivered by any regulated health professional, and published in English, were eligible for inclusion. Studies reporting on reviews, other trial designs, trial registrations, protocols, commentaries, editorials and conference proceedings were excluded. Further exclusion criteria included retracted articles, secondary analyses, studies in which the full text was not available in English, and studies where manipulation was only applied to an area other than the spine. Studies were also excluded if it was unclear if the intervention being delivered involved an HVLA manipulation.

Search strategy

The following databases were searched from 1 March 2016 to 12 May 2022: MEDLINE (Ovid), Embase, CINAHL, ICL, PEDro and Cochrane Library. Reference lists of included studies were screened to insure all relevant literature was captured. The following search terms and derivatives were adapted for each platform: *spinal manipulation; chiropractic; osteopathy; physiotherapy; naprapathy; medical manipulation; clinical trial*. An example of each search strategy is provided in Appendix 1.

Study selection process

Records retrieved from the electronic searches were exported to the Rayyan online platform (37). Duplicate records, and records included in the 2016 review were removed before title and abstract screening. Two authors (LG and BB) independently screened included studies in a step-wise process, beginning with review of each title and abstract. Full-texts of the studies remaining after this step were retrieved and further screened against the eligibility criteria (LG and RE). Any disagreements regarding inclusion were resolved by consensus and if consensus could not be reached, disagreements were resolved by a third author (BB).

Data extraction

Adverse events reporting data were extracted from the remaining studies by two authors (LG and RL). This data included descriptive information [i.e., title, author, year of publication, country where the data was collected, journal of publication, spinal region treated (e.g., cervical spine), type of practitioner delivering the spinal manipulation (e.g., chiropractor)], whether the study reported on adverse events (i.e., reported/not and if reported; directly/indirectly), location of reporting within the article, classification of adverse events reported (e.g., mild, moderate, serious, severe), completeness of adverse events reporting (i.e., onset, duration, and number of events reported), number of participants in the spinal manipulation group/s, and descriptions of any definitions and/or classification systems used. Other data collated by the lead author (LG) included whether the study was published in a journal that follows the International Committee of Medical Journal Editors (ICMJE) guidelines via a search of the ICMJE website (38) on 29 May 2022. Additionally, the most recently published impact factor (year 2020) for each journal was manually extracted by the lead author (LG) from the Clarivate Journal Citations Reports website (39) on 29 May 2022.

Assessment of risk of bias using the Cochrane ROB 2 assessment tool (40) was performed by three authors working in pairs (LG and RE, LG and BB) for all included studies to assess the methodological quality of the publication. Disagreements were resolved by consensus and if consensus could not be reached, disagreements were resolved by a third author (RL).

Data analysis

Data were analysed using descriptive statistics. Frequencies and proportions of studies reporting on each of the specified domains above were calculated in Microsoft Excel (Version 2102, Microsoft Corporation, USA). Continuous variables with highly skewed distributions (i.e., journal impact factor and sample size of spinal manipulation group) were categorised into tertiles. Univariable and multivariable logistic regression models were fitted to examine the effect of potential predictors on the likelihood of studies reporting on adverse events. The multivariable logistic regression model was fitted using backward elimination, whereby the least significant potential predictors were sequentially eliminated from the multivariable model until only significant predictors remained. The observed effects from the univariable and multivariable logistic regression models were reported as odds ratios (OR) and adjusted odds ratios (aOR) respectively, with 95% confidence intervals (CI). All statistical analyses were performed using the statistical computing software R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

There were 5,399 records initially identified by the electronic searches (Figure 1). A total of 3,363 unique records remained after de-duplication (n=2,034) and the removal of retracted articles (n=2). After title and abstract screening, full texts of the 452 remaining studies were screened. Of these, 154 fulfilled the eligibility criteria and were included in the analysis (see Appendix 2). The most common reasons for exclusion were: the intervention did not consist of HVLA spinal manipulation (n=163) and/or the study related to a conference proceeding (n=49).

Insert around here: Figure 1: PRISMA flow diagram.

Comprehensiveness of reporting of adverse events

Of the 154 included studies, 94 (61.0%) reported on adverse events. Of these 94 studies, 36 (38.3%) directly reported on adverse events, with studies in which spinal manipulation was delivered by a chiropractor most frequently reporting this data (n=17; 47.2%, Table 1). Indirect reporting occurred in 58 studies (61.7%), with studies in which spinal manipulation was delivered by a physiotherapist being the most frequent (n=29; 50.0%, Table 1). Of the 60 studies (39.0%) that did not report on adverse events, studies in which spinal manipulation was delivered by a physiotherapist were the most

frequent (n=28; 46.7%, Table 1). A description of what constituted an adverse event definition and/or the classification system used was provided in 22 studies (23.4%). However, most studies did not provide a description and instead used terms such as "adverse event" (n=70, 74.5%), "adverse effect" (n=22, 23.4%), "side effect" (n=19, 20.2%) and "harm" (n=11, 11.7%) without adequate explanation. When mentioned, terms pertaining to classification systems (predominantly severity) were (number of studies in which the term was used, %): "mild" (n=20, 21.3%), "moderate" (n=17, 18.1%), "serious" (n=27, 28.7%), and "severe" (n=14, 14.9%). The onset of an adverse event/s was unclear in 30 (31.9%) studies. Duration of adverse events were reported heterogeneously, with some studies providing a time from either baseline or the start of intervention, whereas others provided a temporal descriptor such as "short-term", "temporary" or, "transient". Of the 9 studies providing times, durations were as follows: <72hr (n=3, 3.2%), >72hr (n=2, 2.1%) or mixed duration (n=4, 4.3%). An evaluation tool was mentioned in 26 (27.7%) studies.

Insert around here: Table 1: Comprehensiveness of reporting of adverse events by provider delivering the intervention

	Directly reports on AE (n=36), n (%)	Indirectly reports on AE (n=58), n (%)	Does not report on AE (n=60), n (%)
Chiropractor	17 (47.2)	12 (20.7)	7 (11.7)
Medical Practitioner	1 (2.8)	4 (6.9)	5 (8.3)
Mixed	7 (19.4)	7 (12.1)	7 (11.7)
Naprapath	0 (0.0)	0 (0.0)	1 (1.7)
Osteopath	4 (11.1)	2 (3.4)	9 (15.0)
Physiotherapist	6 (16.7)	29 (50.0)	28 (46.7)
Unclear	1 (2.8)	4 (6.9)	3 (5.0)

AE; adverse event

Number and location of adverse events reporting

No serious adverse events were reported in any of the 154 included studies, representing 7,518 participants who received spinal manipulation. Furthermore, of the 94 studies reporting on adverse events, 63 (67.0%) reported that no adverse events occurred. Adverse events were reported in the abstract of 29 (30.9%) and results section of 83 (88.3%) studies. Furthermore, adverse events were mentioned in several locations throughout the included studies: the introduction (n=15, 16.0%),

methods (n=56, 59.6%), discussion (n=30, 31.9%), conclusion (n=7, 7.4%), and supplementary materials (n=1, 1.1%).

Descriptors of studies reporting on adverse events

Descriptive statistics are provided in Table 2. Of the 94 studies reporting on adverse events, 55 (58.5%) were rated at a 'high risk of bias', 29 (30.9%) as 'some concerns' and 10 (10.6%) at a 'low risk of bias' (Appendix 3). Additionally, 33 (35.1%) were published in journals stating that they follow the ICMJE recommendations. For the remaining studies, the median of the most recently published (2020) impact factor was 2.5 (IQR: 2.1–4.2).

Insert around here: Table 2: Characteristics of included studies by reporting on adverse events

		Overall (n=154), n (%)	Reports on AE (n=94), n (%)	Does not report on AE (n=60), n (%)
ICMJE journal	Published in ICJME journal	53 (34.4)	33 (35.1)	20 (33.3)
Risk of bias	Low risk	13 (8.4)	10 (10.6)	3 (5.0)
	Some concerns	47 (30.5)	29 (30.9)	18 (30.0)
	High risk	94 (61.0)	55 (58.5)	39 (65.0)
Impact factor	Upper tertile	47 (30.5)	36 (38.3)	11 (18.3)
	Middle tertile	54 (35.1)	37 (39.4)	17 (28.3)
	Lower tertile	53 (34.4)	21 (22.3)	32 (53.3)
Spinal region	Cervical	24 (15.6)	17 (18.1)	7 (11.7)
	Thoracic	33 (21.4)	15 (16.0)	18 (30.0)
	Lumbopelvic	28 (18.2)	13 (13.8)	15 (25.0)
	Mixed/Unclear	69 (44.8)	49 (52.1)	20 (33.3)
Type of practitioner	Chiropractor	36 (23.4)	29 (30.9)	7 (11.7)
	Osteopath	15 (9.7)	6 (6.4)	9 (15.0)
	Physiotherapist	63 (40.9)	35 (37.2)	28 (46.7)
	Medical Practitioner	9 (5.8)	4 (4.3)	5 (8.3)
	Mixed/Other/Unclear	31 (20.1)	20 (21.2)	11 (18.3)
Sample size spinal manipulation group[1]	Upper tertile	51 (33.3)	40 (42.6)	11 (18.6)
	Middle tertile	50 (32.7)	28 (29.8)	22 (37.3)
	Lower tertile	52 (34.0)	26 (27.7)	26 (44.1)

[1] One study with unclear sample size excluded
AE; adverse event

Predictors for the reporting of adverse events

There was very strong evidence that studies with an impact factor in the upper (aOR: 5.72 [95% CI: 2.23-15.85]; $p < 0.001$) and middle (aOR: 3.52 [95% CI: 1.51-8.57]; $p = 0.004$) tertiles were more

likely to report on adverse events than those in the lower tertile when the model was adjusted for risk of bias, impact factor, spinal region of manipulation, and number of participants receiving spinal manipulation (Table 3). There was also strong evidence that studies in which a chiropractor delivered the spinal manipulation were more likely to report on adverse events (aOR: 4.58 [95% CI: 1.14-20.24]; p = 0.036). Studies in which spinal manipulation was delivered to more than one region or, it was unclear which regions the manipulations were delivered, were also more likely to report on adverse events (aOR: 3.18 [95% CI: 1.16-9.05]; p = 0.027). While not achieving statistical significance, another factor of note included studies in which cervical spine manipulation was delivered (aOR: 3.04 [95% CI: 0.88-11.30]; p = 0.085).

Insert around here: Table 3: Univariable and multivariable logistic regression

Variable	OR	95%CI	p-value	aOR[1]	95%CI	p-value
ICMJE journal						
Yes	1.08	0.55-2.16	0.821	-	-	-
No[2]	-	-	-	-	-	-
Risk of bias						
Low risk	2.36	0.67-11.01	0.213	-	-	-
Some concerns	1.14	0.56-2.37	0.716	-	-	-
High risk[2]	-	-	-	-	-	-
Impact factor						
Upper tertile	4.99	2.14-12.32	<0.001	5.72	2.23-15.85	<0.001
Middle tertile	3.32	1.52-7.48	0.003	3.52	1.51-8.57	0.004
Lower tertile[2]	-	-	-	-	-	-
Spinal region						
Cervical	2.80	0.91-9.27	0.080	3.04	0.88-11.30	0.085
Thoracic	0.96	0.35-2.66	0.939	1.09	0.34-3.45	0.887
Lumbopelvic[2]	-	-	-	-	-	-
Mixed/Unclear	2.83	1.15-7.11	0.025	3.18	1.16-9.05	0.027
Type of practitioner						
Chiropractor	6.21	1.71-24.85	0.007	4.58	1.14-20.24	0.036
Osteopath[2]	-	-	-	-	-	-
Physiotherapist	1.88	0.60-6.19	0.282	1.35	0.37-5.18	0.648
Medical Practitioner	1.20	0.22-6.53	0.831	0.81	0.12-5.47	0.829
Mixed/Other/Unclear	2.72	0.78-10.17	0.121	2.26	0.57-9.64	0.253
Sample size spinal manipulation group[3]						
Upper tertile	3.64	1.57-8.87	0.003	-	-	-
Middle tertile	1.27	0.58-2.79	0.544	-	-	-
Lower tertile[2]	-	-	-	-	-	-

[1] The final model was adjusted for impact factor, spinal region of manipulation, and type of practitioner, while ICMJE journal status, risk of bias, and number of participants receiving spinal manipulation were omitted via backward elimination method.
[2] Reference group.
[3] One study with unclear sample size excluded.

DISCUSSION

There has been a change in the reporting of adverse events associated with spinal manipulation in RCTs since 2016. Specifically, the percentage of included studies reporting adverse events has increased from 38.0% (2016 study (26)) to 61.0% (current study). However, the current review highlights that the reporting of adverse events in RCTs involving spinal manipulation as an intervention remains poor and is not consistent with established standards. Specifically, of the 154 included studies, just over half (n= 94, 61.0%) reported on adverse events. Furthermore, of these 94 studies, less than half (38.3%) reported directly on adverse events, with only 23.4% providing an explicit description of what constituted an adverse event. Further complicating this issue is the vast heterogeneity of terms (i.e., "adverse effect", "side effect", "harm" etc) used to describe adverse events. This is disappointing given that there have been many calls in the literature for the improvement of adverse events reporting in RCTs, and for the development and use of standardized definitions and classification systems (24,26,32,41–46).

A recent scoping review explores the complexity of the current literature reporting on adverse events associated with spinal and peripheral joint manipulation and mobilisation (47). Specifically, the authors report that conflicting opinions regarding facets of adverse event definition and classification such as: symptom severity and duration, relatedness to the intervention (e.g., time to onset, treatment provided), action taken to treat the symptoms, expectedness, which profession delivered the intervention and geographical location (with possible medico-legal constraints and/or different expectations of reporting/not reporting) are all factors to reflect on when considering adverse events associated with joint manipulation and mobilisation. In an attempt to address the lack of standardized definitions and classification systems across professions that deliver spinal manipulation, the same authors have conducted an international Delphi study (manuscript in preparation; protocol paper (41)) to determine, by expert consensus, a standardised definition and severity classification for adverse events associated with spinal and peripheral joint manipulation and mobilisation. The development

and use of such guidelines would constitute an important step toward uniform reporting of adverse events associated with spinal manipulation across all stakeholder professions and geographical locations.

However, until this work is published, the 2004 CONSORT Harms extension provides a checklist of items to include and specific examples of good reporting (Appendix 2) when reporting on harms (adverse events) in RCTs (24). Furthermore, it appears that an update to this guideline is emergent (25). It is hoped that these updated guidelines will ensure that authors and journal editors alike are both aware of and implement better harms reporting in the future. We strongly encourage researchers and journal editors alike to read and use the most recent CONSORT Harms checklist during all phases of study development, data collection, manuscript preparation, submission and during the review process. One important item on this checklist is that both benefits and harms should be stated in either the title and/or abstract of a manuscript. This point is salient as the abstract is the second-most read section of a scientific manuscript after the title (48). Encouragingly, the reporting of adverse events in the abstract has doubled (15.7-30.9%, 2016 to current) when compared to our previous review of the literature (26). Despite this, the current reporting on adverse events in the title/abstract of RCTs utilizing spinal manipulation remains poor, a finding that is also present in the wider published medical literature discussing adverse events (49–52). Despite an overall increase in the number of studies reporting on adverse events in RCTs involving spinal manipulation (38.0-61.0%, 2016 (26) to current), adverse events reporting in the results section has decreased (93.6% vs 88.3%) over the past 6 years and remains lower than that in the wider published literature (50,53). It is unknown why there would be a decrease in the reporting on adverse events associated with spinal manipulation in the one section of a scientific manuscript that it could reasonably be expected to be reported. Furthermore, an important source of information for the formulation of a considered evidence-based risk-benefit analysis for the use of spinal manipulation as a treatment option by both clinician and patient (49,52) is transparent data reporting on both the efficacy and adverse events occurring in RCTs involving spinal manipulation.

Consistent with the literature (31,32,42,43,47), there was considerable heterogeneity of nomenclature used to describe adverse events associated with spinal manipulation. Similar terms were used to indicate an adverse event in the current (compared to 2016) review: "adverse event" (2016 – 73.0%; 2022 – 74.5% of studies), "adverse effect" (23.6%; 23.4%), "side effect" (21.3%; 20.2%) and "harm" (16.4%; 11.7%). Additionally, while similar terms were used to describe classification systems previously reported (i.e., "serious", "mild", "moderate", and "severe"), these terms were rarely defined, which is consistent with the existing literature (26,52). Additionally, when present, the reporting of onset and duration of adverse events was inconsistent, again highlighting that there is an urgent need for the development of a standardized definition and classification system for the reporting of adverse events (41). Furthermore, the responsibility for improved reporting of adverse events falls not only to authors but also to custodians of clinical trial registries and journal editors to ensure that there are provisions in study protocols for the adequate capture of adverse events and also that these events are adequately reported i.e., using the most recent CONSORT Harms extension guidelines (24), alongside efficacy/effectiveness data (25,46,54).

Manuscript reviewers and journal editors must be aware of the current best-practices for the reporting of harms (24) and enforce these guidelines during peer review processes of both protocol and end-of-study results papers. However, this may not be as straight-forward as it appears. Despite this, there is a need for improved reporting of adverse events in RCTs that include spinal manipulation as an intervention and a first step would be for journals to incorporate clear instructions on harms reporting in their guidelines and instructions to authors. As a second step, journal editors may facilitate this process by limiting publication to only those studies that adhere to the current guidelines for the reporting of harms in RCTs that include spinal manipulation as an intervention. Indeed, if this was to occur, authors would need to 'step-up', to use expanded methodologies, reporting and statistical analyses that allow for the capture and reporting of adverse events data in RCTs that include spinal manipulation as an intervention. Specifically, data on adverse events should be actively collected as it has been reported that passive surveillance leads to an under-reporting (25,54) and appropriate

statistical analysis plans should be used to analyse the data (49,54,55). As a minimum standard, authors should explicitly state whether active or passive surveillance systems were used (46,49).

RCTs published in journals with a higher impact factor, in which spinal manipulation was delivered by a chiropractor and to multiple/unclear regions, were more likely to report on adverse events. While it is perhaps intuitive that better designed studies, i.e., those at a lower risk of bias, could reasonably be published in higher impact journals, this does not appear to be the case as there was no influence of risk of bias level in the final model. This disconnect between the publication of studies with better methodological quality in higher impact journals is also seen in the medical literature. Specifically, a previous study reported that there were methodological weaknesses in 184 studies published in 2015-2016 by four of the top ranked general medical journals (BMJ, JAMA, Lancet, and NEJM) (54). Furthermore, while there is no obvious reason why studies in which spinal manipulation was delivered by a chiropractor would be more likely to report on adverse events, it is possible that this finding could be explained by a desire to provide evidence to refute critics of the intervention who claim that spinal manipulation, specifically when delivered to the cervical spine, is unsafe (56,57). This hypothesis is suggested by the data which shows that while not achieving statistical significance, studies in which cervical spine manipulation was delivered had approximately 3 times greater odds of reporting on adverse events. It is possible that this result did not achieve statistical significance due to the relatively small number of studies reporting on manipulation delivered only to the cervical spine. Regarding the increased likelihood of studies reporting on adverse events if spinal manipulation was delivered to multiple/unclear regions, it is possible that this finding is spurious as there was a larger number of studies (n=49) in this category compared to studies in which the intervention was delivered to a single region. This hypothesis is supported by a secondary analysis of our previous review which reported that the region treated was not a significant predictor for reporting on adverse events (58).

Due to the methodological design of the review, we are unable to comment on the incidence of adverse events associated with spinal manipulation. Furthermore, RCTs are not necessarily the best research design for collecting data on serious adverse events as they often have strict inclusion criteria

and may exclude participants who are at risk of experiencing such events. Additionally, RCTs are powered to detect intervention effects and thus are likely to be underpowered for estimating the risk of serious adverse events. Despite this, the consistent reporting of the number of spinal manipulations delivered to every participant in RCTs would allow for the calculation of accurate incidence rates for all classifications of adverse events (serious included) and could eventually facilitate the pooling of data across multiple studies thus allowing for a better informed risk-benefit assessment of spinal manipulation (25,46). Indeed, the number of spinal manipulations delivered was only available in 75 (48.7%) of the included studies. Coupled with the implementation of standardized definitions and classification systems for adverse events associated with spinal manipulation, reporting on the number of spinal manipulations delivered in each study would allow for the inter-disciplinary calculation of incidence rates for all classifications across all healthcare professionals delivering the intervention. Such an outcome is extremely important in the context of obtaining informed consent to deliver spinal manipulation. Specifically, in many countries in which spinal manipulation is delivered, the process of obtaining informed consent requires the disclosure of all material information that a reasonable patient would require to make an informed decision about whether or not to receive that intervention (59). In the absence of accurate incidence rates for the different classifications of adverse events associated with spinal manipulation, this is a difficult task for the clinician to perform.

There are several differences between the current review and our 2016 review (26). Specifically, the current review included an improved search strategy, including both an expansion to the number of databases searched (i.e., MEDLINE (Ovid), Embase, CINAHL and ICL were added) in addition to the inclusion of several search terms that did not limit the search to spinal manipulation delivered by chiropractors and osteopaths (i.e., physiotherapists, naprapaths and medical manipulation were added). Additionally, the current review reports on analyses that we had previously reported separately in two manuscripts: the original review (26) and a secondary analysis (58). By reporting these analyses in a single manuscript, we hope it is clearer for readers to identify that the current level of reporting of adverse events associated with spinal manipulation in RCTs is both poor and not consistent with established standards, and understand the possible explanations for this observation.

By streamlining the dissemination of this information, we hope to make it easier for readers to identify areas in which researchers may improve the reporting of adverse events in this field.

Limitations

There are several limitations to this literature review. Firstly, the decision to classify the reporting of adverse events as 'direct' (explicit description of operational definition of an adverse event provided and/or how data on adverse events were measured and/or a substantial description of adverse events observed during data collection provided) as opposed to 'indirect' (no explicit reporting of such information) was arbitrary. However, this classification did not influence whether the study reported on adverse events or not. As such, we do not feel this factor had any material influence on our results. Secondly, as outlined above, small differences in the methodology between the current and previous reviews (26,58) mean that it is not possible to directly compare all reported findings between the two reviews. However, as these differences occurred due to methodological improvements in the current review, we do not believe this affected the results and/or discussion in the current review.

CONCLUSION

While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased since our 2016 publication on the same topic, the level remains low and inconsistent with established standards. As such, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is more balanced reporting of both benefits and harms of spinal manipulation in RCTs. We strongly recommend that authors adhere to the most recent CONSORT Harms checklist when reporting their results and advocate for the creation of standardized definitions and classification systems relating to adverse events in manual therapy. This will facilitate the future pooling of adverse events data across all professions utilizing spinal manipulation and improve the ability to calculate incidence rates for the different levels of adverse events.

AUTHOR CONTRIBUTIONS

LG: conceptualization, screening, risk of bias assessment, data extraction and curation, formal analysis, methodology, project administration, visualization, writing – original draft, review & editing

RL: data extraction and curation, formal analysis, methodology, visualization, writing – original draft, review & editing

BB: screening, risk of bias assessment, writing – review & editing

RE: screening, risk of bias assessment, methodology, writing – review & editing

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr. Martina Gosteli for her assistance with the literature search.

DATA SHARING STATEMENT

Data are available from the corresponding author upon reasonable request.

REFERENCE STRENGTHS AND LIMITATIONS OF THE REVIEW

1. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

REFERENCES MANUSCRIPT

1. Whalen W, Farabaugh RJ, Hawk C, Minkalis AL, Lauretti W, Crivelli LS, et al. Best-practice recommendations for chiropractic management of patients with neck pain. J Manipulative Physiol Ther. 2019 Nov 1;42(9):635–50.

2. Bussieres AE, Stewart G, Al-Zoubi F, Decina P, Descarreaux M, Haskett D, et al. Spinal Manipulative Therapy and Other Conservative Treatments for Low Back Pain: A Guideline From the Canadian Chiropractic Guideline Initiative. J Manip Physiol Ther. 2018 Mar 29;

3. Bussieres AE, Stewart G, Al-Zoubi F, Decina P, Descarreaux M, Hayden J, et al. The treatment of neck pain-associated disorders and whiplash-associated disorders: a clinical practice guideline. J Manipulative Physiol Ther. 2016 Oct;39(8):523–64.

4. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CWC, Chenot JF, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. Eur Spine J. 2018 Nov 1;27(11):2791–803.

5. Beliveau PJH, Wong JJ, Sutton DA, Simon NB, Bussières AE, Mior SA, et al. The chiropractic profession: a scoping review of utilization rates, reasons for seeking care, patient profiles, and care provided. Chiropr Man Ther. 2017 Nov 22;25(35).

6. Lin I, Wiles L, Waller R, Goucke R, Nagree Y, Gibberd M, et al. What does best practice care for musculoskeletal pain look like? Eleven consistent recommendations from high-quality clinical practice guidelines: systematic review. Br J Sports Med. 2020 Jan 1;54(2):79.

7. National Institute for Health and Care Excellence (NICE). Low Back Pain and Sciatica in Over 16s: Assessment and Management. Natl Inst Health Care Excell NICE. 2016 Nov;

8. Puentedura EJ, March J, Anders J, Perez A, Landers MR, Wallmann HW, et al. Safety of cervical spine manipulation: are adverse events preventable and are manipulations being performed appropriately? A review of 134 case reports. J Man Manip Ther. 2012 May;20(2):66–74.

9. Biller J, Sacco RL, Albuquerque FC, Demaerschalk BM, Fayad P, Long PH, et al. Cervical arterial dissections and association with cervical manipulative therapy: a statement for healthcare professionals from the american heart association/american stroke association. Stroke J Cereb Circ. 2014 Oct;45(10):3155–74.

10. Funabashi M, Pohlman KA, Goldsworthy R, Lee A, Tibbles A, Mior S, et al. Beliefs, perceptions and practices of chiropractors and patients about mitigation strategies for benign adverse events after spinal manipulation therapy. Chiropr Man Ther. 2020;28(1):46.

11. Heneghan NR, Davies SE, Puentedura EJ, Rushton A. Knowledge and pre-thoracic spinal thrust manipulation examination: a survey of current practice in the UK. J Man Manip Ther. 2018 Oct 20;26(5):301–9.

12. Albuquerque FC, Hu YC, Dashti SR, Abla AA, Clark JC, Alkire B, et al. Craniocervical arterial dissections as sequelae of chiropractic manipulation: patterns of injury and management. J Neurosurg. 2011 Dec;115(6):1197–205.

13. Ernst E. Deaths after chiropractic: a review of published cases. Int J Clin Pract. 2010 Jul;64(8):1162–5.

14. Church EW, Sieg EP, Zalatimo O, Hussain NS, Glantz M, Harbaugh RE. Systematic Review and Meta-analysis of Chiropractic Care and Cervical Artery Dissection: No Evidence for Causation. Cureus [Internet]. [cited 2019 Jul 26];8(2). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4794386/

15. Cassidy JD, Boyle E, Côté P, He Y, Hogg-Johnson S, Silver FL, et al. Risk of vertebrobasilar stroke and chiropractic care: results of a population-based case-control and case-crossover study. Eur Spine J. 2008 29;17(1):176–83.

16. Whedon JM, Song Y, Mackenzie TA, Phillips RB, Lukovits TG, Lurie JD. Risk of stroke after chiropractic spinal manipulation in medicare B beneficiaries aged 66 to 99 years with neck pain. J Manipulative Physiol Ther. 2015 Feb;38(2):93–101.

17. Cassidy JD, Boyle E, Côté P, Hogg-Johnson S, Bondy SJ, Haldeman S. Risk of Carotid Stroke after Chiropractic Care: A Population-Based Case-Crossover Study. J Stroke Cerebrovasc Dis. 2017;26(4):842–50.

18. Whedon JM, Petersen CL, Li Z, Schoelkopf WJ, Haldeman S, MacKenzie TA, et al. Association between cervical artery dissection and spinal manipulative therapy –a medicare claims analysis. BMC Geriatr. 2022 Nov 29;22(1):917.

19. Gorrell LM, Kuntze G, Ronsky JL, Carter R, Symons B, Triano JJ, et al. Kinematics of the head and associated vertebral artery length changes during high-velocity, low-amplitude cervical spine manipulation. Chiropr Man Ther. 06 01;30(1):28.

20. Gorrell LM, Sawatsky A, Edwards WB, Herzog W. Vertebral arteries do not experience tensile force during manual cervical spine manipulation applied to human cadavers. J Man Manip Ther. 2022 Nov 15;1–9.

21. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. JAMA. 1996;276.

22. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357.

23. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8.

24. Ioannidis JPA, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004;141.

25. Junqueira DR, Phillips R, Zorzela L, Golder S, Loke Y, Moher D, et al. Time to improve the reporting of harms in randomized controlled trials. J Clin Epidemiol. 2021 Aug 1;136:216–20.

26. Gorrell LM, Engel RM, Brown B, Lystad RP. The reporting of adverse events following spinal manipulation in randomized clinical trials-a systematic review. Spine J. 2016 May 27;

27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

28. Herzog W. The biomechanics of spinal manipulation. J Bodyw Mov Ther. 2010 Jul;14(3):280–6.

29. Bergmann T. Chiropractic Technique Principles and Procedures. 3rd ed. Missouri: Elselvier Mosby, USA; 2011.

30. Pohlman KA, O'Beirne M, Thiel H, Cassidy JD, Mior S, Hurwitz EL, et al. Development and validation of providers' and patients' measurement instruments to evaluate adverse events after spinal manipulation therapy. Eur J Integr Med. 2014 Aug 1;6:451–66.

31. Walker BF, Hebert JJ, Stomski NJ, Clarke BR, Bowden RS, Losco B, et al. Outcomes of usual chiropractic. The OUCH randomized controlled trial of adverse events. Spine Phila Pa 1976. 2013 Sep 15;38:1723–9.

32. Carnes D, Mullinger B, Underwood M. Defining adverse events in manual therapies: a modified Delphi consensus study. Man Ther. 2010 Feb;15(1):2–6.

33. Dunning J, Butts R, Zacharko N, Fandry K, Young I, Wheeler K, et al. Spinal manipulation and perineural electrical dry needling in patients with cervicogenic headache: a multi-center randomized clinical trial. Spine J 2021 Feb212284-295. 2021;

34. Maiers M, Hartvigsen J, Evans R, Westrom K, Wang Q, Schulz C, et al. Short or long-term treatment of spinal disability in older adults with manipulation and exercise. Arthritis Care Res 2019 Nov71111516-1524. 2019;

35. Vining R, Long CR, Minkalis A, Gudavalli MR, Xia T, Walter J, et al. Effects of Chiropractic Care on Strength, Balance, and Endurance in Active-Duty U.S. Military Personnel with Low Back Pain: A Randomized Controlled Trial. J Altern Complement Med. 2020 Jul;26(7):592–601.

36. Schulz C, Evans R, Maiers M, Schulz K, Leininger B, Bronfort G. Spinal manipulative therapy and exercise for older adults with chronic low back pain: a randomized clinical trial. Chiropr Man Ther. 2019;27:21.

37. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016 Dec 5;5(1):210.

38. International Committeee of Medical Journal Editors (ICMJE). Journals following the ICMJE recommendations. 2016.

39. Clarivate Journal Citation Reports [Internet]. Clarivate Journal Citation Reports. [cited 2022 May 29]. Available from: https://clarivate.com/webofsciencegroup/solutions/journal-citation-reports/

40. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. In: Cochrane Handbook for Systematic Reviews of Interventions [Internet]. John Wiley & Sons, Ltd; 2019. p. 205–28. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119536604.ch8

41. Funabashi M, Pohlman KA, Gorrell LM, Salsbury SA, Bergna A, Heneghan NR. Expert consensus on a standardised definition and severity classification for adverse events associated with spinal and peripheral joint manipulation and mobilisation: protocol for an international e-Delphi study. BMJ Open. 2021 Nov 1;11(11):e050219.

42. Carnes D, Mars TS, Mullinger B, Froud R, Underwood M. Adverse events and manual therapy: a systematic review. Man Ther. 2010 Aug;15(4):355–63.

43. Carlesso L, Macdermid J, Santaguida P. Standardization of adverse event terminology and reporting in orthopaedic physical therapy: application to the cervical spine. J Orthop Sports Phys Ther. 2010 Aug;40:455–63.

44. Carlesso L, Cairney J, Dolovich L, Hoogenes J. Defining adverse events in manual therapy: an exploratory qualitative analysis of the patient perspective. Man Ther. 2011 Oct;16:440–6.

45. Carlesso L, Gross A, Santaguida P, Burnie S, Voth S, Sadi J. Adverse events associated with the use of cervical manipulation and mobilization for the treatment of neck pain in adults: a systematic review. Man Ther. 2010 Oct;15(5):434–44.

46. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ. 2016 Feb 1;352:i157.

47. Funabashi M, Gorrell LM, Pohlman KA, Bergna A, Heneghan NR. Definition and classification for adverse events following spinal and peripheral joint manipulation and mobilization: A scoping review. PLOS ONE. 2022 Jul 15;17(7):e0270671.

48. Pitkin RM. The importance of the abstract. Obstet Gynecol. 1987 Aug;70:267.

49. Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, et al. Quality of reporting in systematic reviews of adverse events: systematic review. BMJ. 2014;348:f7668.

50. Komorowski AS, MacKay HJ, Pezo RC. Quality of adverse event reporting in phase III randomized controlled trials of breast and colorectal cancer: A systematic review. Cancer Med. 2020 Jul 1;9(14):5035–50.

51. Berwanger O, Ribeiro RA, Finkelsztejn A, Watanabe M, Suzumura EA, Duncan BB, et al. The quality of reporting of trial abstracts is suboptimal: survey of major general medical journals. J Clin Epidemiol. 2009 Apr;62(4):387–92.

52. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Arch Intern Med. 2009 Oct 26;169:1756–61.

53. Nuovo J, Sather C. Reporting adverse events in randomized controlled trials. Pharmacoepidemiol Drug Saf. 2007 Mar;16(3):349–51.

54. Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open. 2019 Mar 1;9(2):e024537.

55. Phillips R, Sauzet O, Cornelius V. Statistical methods for the analysis of adverse event data in randomised controlled trials: a scoping review and taxonomy. BMC Med Res Methodol. 2020 Nov 30;20(1):288.

56. Gouveia LO, Castanho P, Ferreira JJ. Safety of chiropractic interventions: a systematic review. Spine Phila Pa 1976. 2009 May 15;34:E405-13.

57. Thiel HW, Bolton JE, Docherty S, Portlock JC. Safety of chiropractic manipulation of the cervical spine: a prospective national survey. Spine. 2007 Oct;32(21):2375–8; discussion 2379.

58. Gorrell LM, Brown B, Lystad RP, Engel RM. Predictive factors for reporting adverse events following spinal manipulation in randomized clinical trials – secondary analysis of a systematic review. Musculoskelet Sci Pract. 2017;30:34–41.

59. Winterbottom M, Boon H, Mior S, Facey M. Informed consent for chiropractic care: Comparing patients' perceptions to the legal perspective. Man Ther. 2015 Jun;20(3):463–8.

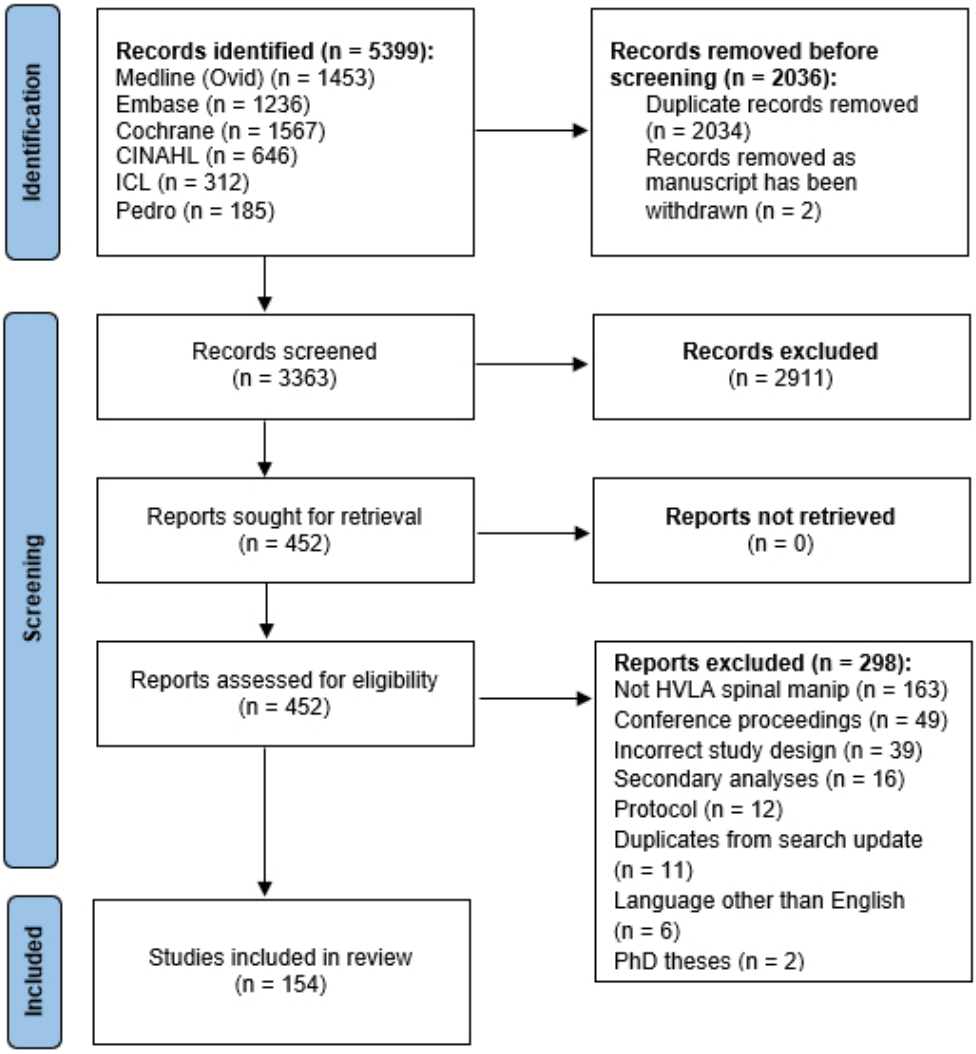

Figure 1: PRISMA flow-chart

351x381mm (38 x 38 DPI)

Appendix 1:

MEDLINE (Ovid) search strategy

	Searches
#1	((spine or spinal or medical) adj3 manip*).ti,ab,kw.
#2	(osteopath* or chiropract* or naprapath* or ((physiotherap* or (physical adj3 therap*)) and manip*)).ti,ab,kw.
#3	Manipulation, Chiropractic/ or Manipulation, Spinal/ or Musculoskeletal Manipulations/ or Manipulation, Osteopathic/
#4	1 or 2 or 3
#5	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
#6	4 and 5
#7	limit 6 to yr="2016 -Current"

CINAHL search strategy

	Query	Limiters/expanders
1	TI ((spine OR spinal OR medical) N3 manip*) OR AB ((spine OR spinal OR medical) N3 manip*)	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S2	TI (osteopath* OR chiropract* OR naprapath*) OR AB (osteopath* OR chiropract* OR naprapath*) OR TI (((physiotherap* OR (physical N3 therap*)) AND manip*) OR AB (((physiotherap* OR (physical N3 therap*)) AND manip*)	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S3	(MH "Manipulation, Chiropractic") OR (MH "Manipulation, Osteopathic")	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S4	S1 OR S2 OR S3	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S5	(MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample OR TI (randomised OR randomized) OR AB (random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR AB (control W5 group) OR MH (crossover design) OR MH (comparative studies) OR AB (cluster W3 RCT)) NOT ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human))	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S6	S4 AND S5	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S7	S4 AND S5	Limiters - Published Date: 20160101- Expanders - Apply equivalent subjects Search modes - Find all my search terms

Cochrane Library search strategy

	Advanced search	Limits
#1	((spine OR spinal OR medical) NEAR/3 manip*):ti,ab,kw	
#2	MeSH descriptor: [Musculoskeletal Manipulations] this term only	
#3	MeSH descriptor: [Manipulation, Spinal] explode all trees	
#4	MeSH descriptor: [Manipulation, Chiropractic] explode all trees	
#5	MeSH descriptor: [Manipulation, Osteopathic] explode all trees	
#6	osteopath*:ti,ab,kw	
#7	chiropract*:ti,ab,kw Limits 1160 − +	
#8	physiotherap*:ti,ab,kw OR (physical NEAR/3 therap*):ti,ab,kw) AND manip*:ti,ab,kw	
#9	naprapath*:ti,ab,kw	
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	in Trials
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	with Publication Year from 2016 to 2022, in Trials

Embase search strategy

	Query
#1	((spine OR spinal OR medical) NEAR/3 manip*):ti,ab,kw
#2	osteopath*:ti,ab,kw OR chiropract*:ti,ab,kw OR naprapath*:ti,ab,kw OR ((physiotherap*:ti,ab,kw OR ((physical NEAR/3 therap*):ti,ab,kw)) AND manip*:ti,ab,kw
#3	'chiropractic manipulation'/de OR 'musculoskeletal manipulation'/de OR 'spine manipulation'/de OR 'osteopathic manipulation'/de
#4	#1 OR #2 OR #3
#5	('randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab OR compare:ti OR compared:ti OR comparison:ti OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR ((open NEAR/1 label):ti,ab) OR (((double OR single OR doubly OR singly) NEAR/1 (blind OR blinded OR blindly)):ti,ab) OR 'double blind procedure'/de OR 'parallel group*':ti,ab OR crossover:ti,ab OR 'cross over':ti,ab OR (((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group* OR intervention* OR patient* OR subject* OR participant$)):ti,ab) OR assigned:ti,ab OR allocated:ti,ab OR ((controlled NEAR/7 (study OR design OR trial)):ti,ab) OR volunteer:ti,ab OR volunteers:ti,ab OR 'human experiment'/de OR trial:ti) NOT ((((random* NEAR/1 sampl* NEAR/7 ('cross section*' OR questionnaire$ OR survey* OR database$)):ti,ab) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomized controlled':ti,ab OR 'randomised controlled':ti,ab OR 'randomly assigned':ti,ab) OR ('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'randomized controlled':ti,ab OR 'randomised controlled':ti,ab OR "control group$":ti,ab)) OR ((case NEAR/1 control*) AND random*)) NOT ('randomized controlled':ti,ab OR 'randomised controlled':ti,ab) OR ('systematic review':ti NOT (trial:ti OR study:ti)) OR (nonrandom*:ti,ab NOT random*:ti,ab) OR 'random field*':ti,ab OR (('random cluster' NEAR/3 sampl*):ti,ab) OR (review:ab AND 'review':it NOT trial:ti) OR ('we searched':ab AND (review:ti OR 'review':it)) OR 'update review':ab OR ((databases NEAR/4 searched):ab) OR ((rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset$:ti) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de)))
#6	#4 AND #5
#7	#4 AND #5 AND [conference abstract]/lim
#8	#4 AND #5 NOT [conference abstract]/lim
#9	#4 AND #5 NOT [conference abstract]/lim AND [2016-2022]/py

ICL search strategy

	Query
S1	Subject:\"Manipulation, Chiropractic\" OR Subject:\"Manipulation, Spinal\" OR Subject:\"Manipulation, Osteopathic\"
S2	All Fields:spine OR All Fields:spinal OR All Fields:physiotherap*
S3	All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal
S4	All Fields:manip*
S5	All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal
S6	All Fields:manip* AND All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal
S7	All Fields:osteopath* OR All Fields:chiropract* OR All Fields:naprapath*
S8	Subject:\"Manipulation, Chiropractic\" OR Subject:\"Manipulation, Spinal\" OR Subject:\"Manipulation, Osteopathic\" OR All Fields:manip* AND All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal OR All Fields:osteopath* OR All Fields:chiropract* OR All Fields:naprapath*
S9	All Fields:random* OR All Fields:placebo OR All Fields:trial OR All Fields:groups OR All Fields:rct
S10	Subject:\"Manipulation, Chiropractic\" OR Subject:\"Manipulation, Spinal\" OR Subject:\"Manipulation, Osteopathic\" OR All Fields:manip* AND All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal OR All Fields:osteopath* OR All Fields:chiropract* OR All Fields:naprapath* AND All Fields:random* OR All Fields:placebo OR All Fields:trial OR All Fields:groups OR All Fields:rct
S11	, Year: from 2016 to 2022
S12	Subject:\"Manipulation, Chiropractic\" OR Subject:\"Manipulation, Spinal\" OR Subject:\"Manipulation, Osteopathic\" OR All Fields:manip* AND All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal OR All Fields:osteopath* OR All Fields:chiropract* OR All Fields:naprapath* AND All Fields:random* OR All Fields:placebo OR All Fields:trial OR All Fields:groups OR All Fields:rct AND , Year: from 2016 to 2022

PEDro search strategy

	Search records added since 01/01/2016
S1	spin* AND manip* AND RCT
S2	spin* AND manip* AND trial
S3	spin* AND manip* AND random*
S4	totally selected

Appendix 2: Included studies reference list

1. Albers J, Jakel A, Wellmann K, von Hehn U, Schmidt T. Effectiveness of 2 Osteopathic Treatment Approaches on Pain, Pressure-Pain Threshold, and Disease Severity in Patients with Fibromyalgia: A Randomized Controlled Trial. Complement Med Res. 2018;25(2):122–8.

2. Alonso-Perez JL, Lopez-Lopez A, La Touche R, Lerma-Lara S, Suarez E, Rojas J, et al. Hypoalgesic effects of three different manual therapy techniques on cervical spine and psychological interaction: A randomized clinical trial. J Bodyw Mov Ther. 2017;21(4):798–803.

3. Alvarenga BAP, Fujikawa R, Joao F, Lara JPR, Veloso AP. The effects of a single session of lumbar spinal manipulative therapy in terms of physical performance test symmetry in asymptomatic athletes: a single-blinded, randomised controlled study. BMJ Open Sport Exerc Med. 2018;4(1):e000389.

4. Aspinall SL, Jacques A, Leboeuf-Yde C, Etherington SJ, Walker BF. No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: A randomised controlled trial in adults with low back pain. Musculoskelet Sci Pract. 2019;43:18–25.

5. Balbás-Álvarez L, Candelas-Fernández P, Del Corral T, La Touche R, López-de-Uralde-Villanueva I. Effect of manual therapy, motor control exercise, and inspiratory muscle training on maximum inspiratory pressure and postural measures in moderate smokers: A randomized controlled trial. J Manip Physiol Ther. 2018;41(5):372–82.

6. Bautista-Aguirre F, Oliva-Pascual-Vaca A, Heredia-Rizo AM, Bosca-Gandia JJ, Ricard F, Rodriguez-Blanco C. Effect of cervical vs. thoracic spinal manipulation on peripheral neural features and grip strength in subjects with chronic mechanical neck pain: a randomized controlled trial. Eur J Phys Rehabil Med. 2017;53(3):333–41.

7. Behrangrad S, Kamali F. Comparison of ischemic compression and lumbopelvic manipulation as trigger point therapy for patellofemoral pain syndrome in young adults: A double-blind randomized clinical trial. J Bodyw Mov Ther. 2017;21(3):554–64.

8. Bernal-Utrera C, Gonzalez-Gerez JJ, Anarte-Lazo E, Rodriguez-Blanco C. Manual therapy versus therapeutic exercise in non-specific chronic neck pain: a randomized controlled trial. Trials Electron Resour. 2020;21(1):682.

9. Boas Fernandes WV, Silveira Bicalho E, Capote AE, Ferretti Manffra E. Duration of the effects of spinal manipulation on pain intensity and electromyographic activity of paravertebral parts of individuals with chronic mechanical low back pain. Fisioter E Pesqui. 2016;23(2):155–62.

10. Boff TA, Pasinato F, Ben AJ, Bosmans JE, van Tulder M, Carregaro RL. Effectiveness of spinal manipulation and myofascial release compared with spinal manipulation alone on health-related outcomes in individuals with non-specific low back pain: randomized controlled trial. Physiother. 2020;10(7)71-80.

11. Bond BM, Kinslow CD, Yoder AW, Liu W. Effect of spinal manipulative therapy on mechanical pain sensitivity in patients with chronic nonspecific low back pain: a pilot randomized, controlled trial. J Man Manip Ther. 2020;28(1):15–27.

12. Bracht MA, Coan ACB, Yahya A, Dos Santos MJ. Effects of cervical manipulation on pain, grip force control, and upper extremity muscle activity: a randomized controlled trial. J Man Manip Ther. 2018;26(2):78–88.

13. Bronfort G, Maiers M, Schulz C, Leininger B, Westrom K, Angstman G, et al. Multidisciplinary integrative care versus chiropractic care for low back pain: a randomized clinical trial. Chiropr Man Ther. 2022;30(1):10.

14. Bruck K, Jacobi K, Schmidt T. Fascial treatment versus manual therapy (HVLA) in patients with chronic neck pain: A randomized controlled trial. J Back Musculoskelet Rehabil. 2021;04:04.

15. Cambron JA, Dexheimer JM, Duarte M, Freels S. Shoe Orthotics for the Treatment of Chronic Low Back Pain: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017;98(9):1752–62.

16. Carrasco-Martinez F, Ibanez-Vera AJ, Martinez-Amat A, Hita-Contreras F, Lomas-Vega R. Short-term effectiveness of the flexion-distraction technique in comparison with high-velocity vertebral manipulation in patients suffering from low-back pain. Complement Ther Med. 2019;44:61–7.

17. Carrasco-Uribarren A, Rodriguez-Sanz J, Lopez-de-Celis C, Perez-Guillen S, Tricas-Moreno JM, Cabanillas-Barea S. Short-term effects of the traction-manipulation protocol in dizziness intensity and disability in cervicogenic dizziness: a randomized controlled trial. Disabil Rehabil. 2021;20;1–9.

18. Castello Branco K, Moodley M. Chiropractic manipulative therapy of the thoracic spine in combination with stretch and strengthening exercises, in improving postural kyphosis in woman. Health SA Gesondheid. 2016;21(1):303–8.

19. Castro-Sanchez AM, Lara-Palomo IC, Mataran-Penarrocha GA, Fernandez-de-Las-Penas C, Saavedra-Hernandez M, Cleland J, et al. Short-term effectiveness of spinal manipulative therapy versus functional technique in patients with chronic nonspecific low back pain: a pragmatic randomized controlled trial. Spine J Off J North Am Spine Soc. 2016;16(3):302–12.

20. Castro-Sánchez AM, Gil-Martínez E, Fernández-Sánchez M, Lara-Palomo IC, Nastasia I, de los Ángeles Querol-Zaldívar M, et al. Manipulative therapy of sacral torsion versus myofascial release in patients clinically diagnosed posterior pelvic pain: A consort compliant randomized controlled trial. Spine J. 2021;21(11):1890-1899.

21. Chaibi A, Benth JS, Tuchin P, Russell MB. Chiropractic spinal manipulative therapy for migraine. A three-armed, single-blinded, placebo, randomized controlled trial. Eur J Neurol, 24: 143-153.

22. Cholewicki J, Popovich JM Jr, Reeves NP, DeStefano LA, Rowan JJ, Francisco TJ, et al. The effects of osteopathic manipulative treatment on pain and disability in patients with chronic neck pain: A single-blinded randomized controlled trial. PM&R: The Journal of Injury, Function and Rehabilitation. 2022; 1- 13. doi:10.1002/pmrj.12732.

23. Corum M, Aydin T, Medin Ceylan C, Kesiktas FN. The comparative effects of spinal manipulation, myofascial release and exercise in tension-type headache patients with neck pain: a randomized controlled trial. Complement Ther Clin Pract 2021; 43:10139.

24. Coste J, Medkour T, Maigne JY, Perez M, Laroche F, Perrot S. Osteopathic medicine for fibromyalgia: a sham-controlled randomized clinical trial. Ther Adv Musculoskelet Dis. 2021;13:1759720X211009017.

25. Crothers AL, French SD, Hebert JJ, Walker BF. Spinal manipulative therapy, Graston technique® and placebo for non-specific thoracic spine pain: A randomised controlled trial. Chiropr Man Ther. 2016;24:16. doi:10.1186/s12998-016-0096-9.

26. de Oliveira RF, Costa LOP, Nascimento LP, Rissato LL. Directed vertebral manipulation is not better than generic vertebral manipulation in patients with chronic low back pain: a randomised trial. J Physiother 2020; 66(3):174-179.

27. DeVocht JW, Vining R, Smith DL, Long C, Jones T, Goertz C. Effect of chiropractic manipulative therapy on reaction time in special operations forces military personnel: a randomized controlled trial. Trials Electron Resour. 2019;20(1):5.

28. Didehdar D, Kamali F, Yoosefinejad AK, Lotfi M. The effect of spinal manipulation on brain neurometabolites in chronic nonspecific low back pain patients: a randomized clinical trial. Ir J Med Sci. 2020;189(2):543–50.

29. Dishman JD, Burke JR, Dougherty P. Motor Neuron Excitability Attenuation as a Sequel to Lumbosacral Manipulation in Subacute Low Back Pain Patients and Asymptomatic Adults: A Cross-Sectional H-Reflex Study. J Manipulative Physiol Ther. 2018;41(5):363–71.

30. Dissing KB, Hartvigsen J, Wedderkopp N, Hestbaek L. Conservative care with or without manipulative therapy in the management of back and/or neck pain in Danish children aged 9 to 15: a randomised controlled trial nested in a school-based cohort. BMJ Open 2018;8(9):e021358.

31. Ditcharles S, Yiou E, Delafontaine A, Hamaoui A. Short-Term Effects of Thoracic Spine Manipulation on the Biomechanical Organisation of Gait Initiation: A Randomized Pilot Study. Front Hum Neurosci. 2017;11:343.

32. Dorron SL, Losco BE, Drummond PD, Walker BF. Effect of lumbar spinal manipulation on local and remote pressure pain threshold and pinprick sensitivity in asymptomatic individuals: a randomised trial. Chiropr Man Ther. 2016;24:47.

33. Dunning JR, Butts R, Mourad F, Young I, Fernandez-de-Las Peñas C, Hagins M, et al. Upper cervical and upper thoracic manipulation versus mobilization and exercise in patients with cervicogenic headache: a multi-center randomized clinical trial. BMC Musculoskelet Disord. 2016;17:64.

34. Dunning J, Butts R, Fernandez-de-Las-Penas C, Walsh S, Goult C, Gillett B, et al. Spinal manipulation and electrical dry needling in patients with subacromial pain syndrome: a multicenter randomized clinical trial. J Orthop Sports Phys Ther 2021;51(2):72-81.

35. Dunning J, Butts R, Zacharko N, Fandry K, Young I, Wheeler K, et al. Spinal manipulation and perineural electrical dry needling in patients with cervicogenic headache: a multi-center randomized clinical trial. Spine J. 2021;21(2):284-295.

36. Eklund A, Jensen I, Lohela-Karlsson M, Hagberg J, Leboeuf-Yde C, Kongsted A, et al. The nordic maintenance care program: Effectiveness of chiropractic maintenance care versus symptom-guided treatment for recurrent and persistent low back pain—a pragmatic randomized controlled trial. PLoS ONE. 2018;13(9):e0203029.

37. Engel RM, Gonski P, Beath K, Vemulpad S. Medium term effects of including manual therapy in a pulmonary rehabilitation program for chronic obstructive pulmonary disease (COPD): a randomized controlled pilot trial. J Man Manip Ther. 2016;24(2):80–9.

38. Erdem EU, Ünver B, Akbas E, Kinikli GI. Immediate effects of thoracic manipulation on cervical joint position sense in individuals with mechanical neck pain: A randomized controlled trial. J Back Musculoskelet Rehabil. 2021;34(5):735-742.

39. Espí-López GV, López-Bueno L, Vicente-Herrero MT, Martinez-Arnau FM, Monzani L. Efficacy of manual therapy on anxiety and depression in patients with tension-type headache. A randomized controlled clinical trial. Int J Osteopath Med. 2016;22:11–20.

40. Espi-Lopez GV, Lopez-Martinez S, Ingles M, Serra-Ano P, Aguilar-Rodriguez M. Effect of manual therapy versus proprioceptive neuromuscular facilitation in dynamic balance, mobility and flexibility in field hockey players. A randomized controlled trial. Phys Ther Sport. 2018;32:173–9.

41. Espi-Lopez GV, Rodriguez-Blanco C, Oliva-Pascual-Vaca A, Molina-Martinez F, Falla D. Do manual therapy techniques have a positive effect on quality of life in people with tension-type headache? A randomized controlled trial. Eur J Phys Rehabil Med. 2016;52(4):447–56.

42. Espi-Lopez GV, Zurriaga-Llorens R, Monzani L, Falla D. The effect of manipulation plus massage therapy versus massage therapy alone in people with tension-type headache. A randomized controlled clinical trial. Eur J Phys Rehabil Med. 2016;52(5):606–17.

43. Evans R, Haas M, Leininger B, Hanson L, Schulz C, Bronfort G. Spinal manipulation and exercise for low back pain in adolescents: a randomized trial. Glob Adv Health Med. 2018;7:200-201.

44. Fagundes Loss J, de Souza da Silva L, Ferreira Miranda I, Groisman S, Santiago Wagner Neto E, Souza C, et al. Immediate effects of a lumbar spine manipulation on pain sensitivity and postural control in individuals with nonspecific low back pain: a randomized controlled trial. Chiropr Man Ther. 2020;28(1):25.

45. Farazdaghi MR, Motealleh A, Abtahi F, Panjan A, Sarabon N, Ghaffarinejad F. Effect of sacroiliac manipulation on postural sway in quiet standing: a randomized controlled trial. Braz J Phys Ther 2018;22(2):120-126.

46. Fisher LR, Alvar BA, Maher SF, Cleland JA. Short-term Effects of Thoracic Spine Thrust Manipulation, Exercise, and Education in Individuals With Low Back Pain: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2020;50(1):24–32.

47. Ford JJ, Slater SL, Richards MC, Surkitt LD, Chan AYP, Taylor NF, et al. Individualised manual therapy plus guideline-based advice vs advice alone for people with clinical features of lumbar zygapophyseal joint pain: a randomised controlled trial. Physiotherapy. 2019;105(1):53–64.

48. Fosberg KK, Puentedura E, Schmitz B, Jain TK, Cleland JA. The Effects of Thrust Joint Manipulation on the Resting and Contraction Thickness of Transversus Abdominis in Patients With Low Back Pain: A Randomized Control Trial. J Manipulative Physiol Ther. 2020;43(4):339–55.

49. Fraix M, Badran S, Graham V, Redman-Bentley D, Hurwitz EL, Quan VL, et al. Osteopathic manipulative treatment in individuals with vertigo and somatic dysfunction: a randomized, controlled, comparative feasibility study. J Osteopath Med. 2021;121(1):71–83.

50. Fritz JM, Sharpe J, Greene T, Lane E, Hadizadeh M, McFadden M, et al. Optimization of Spinal Manipulative Therapy Protocols: A Factorial Randomized Trial Within a Multiphase Optimization Framework. J Pain. 2021;22(6):655–68.

51. Fritz JM, Lane E, McFadden M, Brennan G, Magel JS, Thackeray A, et al. Physical Therapy Referral From Primary Care for Acute Back Pain With Sciatica : a Randomized Controlled Trial. Ann Intern Med. 2021;174(1):8-17.

52. Galindez-Ibarbengoetxea X, Setuain I, Ramirez-Velez R, Andersen LL, Gonzalez-Izal M, Jauregi A, et al. Short-term effects of manipulative treatment versus a therapeutic home exercise protocol for chronic cervical pain: A randomized clinical trial. J Back Musculoskelet Rehabil. 2018;31(1):133–45.

53. Galindez-Ibarbengoetxea X, Setuain I, González-Izal M, Jauregi A, Ramírez-Velez R, Andersen LL, et al. Randomised controlled pilot trial of high-velocity, low-amplitude manipulation on cervical and upper thoracic spine levels in asymptomatic subjects. Int J Osteopath Med. 2017;25:6–14.

54. Galindez-Ibarbengoetxea X, Setuain I, Ramirez-Velez R, Andersen LL, Gonzalez-Izal M, Jauregi A, et al. Immediate Effects of Osteopathic Treatment Versus Therapeutic Exercise on Patients With Chronic Cervical Pain. Altern Ther Health Med. 2018;24(3):24–32.

55. Garcia-Perez-Juana D, Fernandez-de-las-Penas C, Arias-Buria JL, Cleland JA, Plaza-Manzano G, Ortega-Santiago R. Changes in cervicocephalic kinesthetic sensibility, widespread pressure pain sensitivity, and neck pain after cervical thrust manipulation in patients with chronic mechanical neck pain: a randomized clinical trial. J Manip Physiol Ther 2018;41(7):551-560.

56. Gattie E, Cleland JA, Pandya J, Snodgrass S. Dry Needling Adds No Benefit to the Treatment of Neck Pain: A Sham-Controlled Randomized Clinical Trial With 1-Year Follow-up. J Orthop Sports Phys Ther. 2021;51(1):37–45.

57. Gesslbauer C, Vavti N, Keilani M, Mickel M, Crevenna R. Effectiveness of osteopathic manipulative treatment versus osteopathy in the cranial field in temporomandibular disorders - a pilot study. Disabil Rehabil. 2018;40(6):631–6.

58. Ghasabmahaleh SH, Rezasoltani Z, Dadarkhah A, Hamidipanah S, Mofrad RK, Najafi S. Spinal manipulation for subacute and chronic lumbar radiculopathy: a randomized controlled trial. Am J Med 2021;134(1):135-141.

59. Goertz CM, Salsbury SA, Long CR, Vining RD, Andresen AA, Hondras MA, et al. Patient-centered professional practice models for managing low back pain in older adults: a pilot randomized controlled trial. BMC Geriatr. 2017;17(1):235.

60. Goertz CM, Salsbury SA, Vining RD, Long CR, Pohlman KA, Weeks WB, et al. Effect of spinal manipulation of upper cervical vertebrae on blood pressure: results of a pilot sham-controlled trial. J Manip Physiol Ther 2016;39(5):369-380.

61. Goertz CM, Xia T, Long CR, Vining RD, Pohlman KA, DeVocht JW, et al. Effects of spinal manipulation on sensorimotor function in low back pain patients--A randomised controlled trial. Man Ther. 2016;21:183–90.

62. Gomez F, Escriba P, Oliva-Pascual-Vaca J, Mendez-Sanchez R, Puente-Gonzalez AS. Immediate and short-term effects of upper cervical high-velocity, low-amplitude manipulation on standing postural control and cervical mobility in chronic nonspecific neck pain: a randomized controlled trial. J Clin Med 2020;9(8): 2580.

63. Gorrell LM, Beath K, Engel RM. Manual and instrument applied cervical manipulation for mechanical neck pain: a randomized controlled trial. J Manipulative Physiol Ther. 2016;39(5):319–29.

64. Grimes JK, Puentedura E, Cheng MS, Seitz AL. The comparative effects of upper thoracic spine thrust manipulation techniques in individuals with subacromial pain syndrome: a randomized clinical trial. J Orthop Sports Phys Ther 2019;49(10):716-724.

65. Griswold D, Learman K, Kolber MJ, O'Halloran B, Cleland JA. Pragmatically applied cervical and thoracic nonthrust manipulation versus thrust manipulation for patients with mechanical neck pain: a multicenter randomized clinical trial. J Orthop Sports Phys Ther 2018;48(3):137-145.

66. Groisman S, Malysz T, de Souza da Silva L, Rocha Ribeiro Sanches T, Camargo Bragante K, Locatelli F, et al. Osteopathic manipulative treatment combined with exercise improves pain and disability in individuals with non-specific chronic neck pain: a pragmatic randomized controlled trial. J Bodyw Mov Ther 2020; 24(2):189-195

67. Haas M, Bronfort G, Evans R, Schulz C, Vavrek D, Takaki L, et al. Dose-response and efficacy of spinal manipulation for care of cervicogenic headache: a dual-center randomized controlled trial. Spine J Off J North Am Spine Soc. 2018;18(10):1741–54.

68. Haider R, Bashir MS, Adeel M, Ijaz MJ, Ayub A. Comparison of conservative exercise therapy with and without Maitland Thoracic Manipulative therapy in patients with subacromial pain: Clinical trial. J Pak Med Assoc. 2018;68(3):381–7.

69. Haik MN, Alburquerque-Sendin F, Camargo PR. Short-Term Effects of Thoracic Spine Manipulation on Shoulder Impingement Syndrome: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017;98(8):1594–605.

70. Haleema B, Riaz H. Effects of thoracic spine manipulation on pressure pain sensitivity of rhomboid muscle active trigger points: A randomized controlled trial. J Pak Med Assoc. 2021;71(7):1720–4.

71. Hanney WJ, Puentedura EJ, Kolber MJ, Liu X, Pabian PS, Cheatham SW. The immediate effects of manual stretching and cervicothoracic junction manipulation on cervical range of motion and upper trapezius pressure pain thresholds. J Back Musculoskelet Rehabil. 2017;30(5):1005–13.

72. Hardas GM, Murrell GAC. Prospective, randomized, double-blind, placebo-controlled clinical trial assessing the effects of applying a force to C5 by a mechanically assisted instrument on referred pain to the shoulder. Spine 2018;43(7):461-466.

73. Harihara Prakash R, Mehta J, Patel D. Effect of thrust versus non-thrust mobilization directed at the thoracic spine in patients with mechanical neck pain: A randomized control trial. Natl J Physiol Pharm Pharmacol. 2020;10(10):878–83.

74. Hartstein AJ, Lievre AJ, Grimes JK, Hale SA. Immediate effects of thoracic spine thrust manipulation on neurodynamic mobility. J Manip Physiol Ther 2018;41(4):332-341.

75. Holt K, Niazi IK, Amjad I, Kumari N, Rashid U, Duehr J, et al. The Effects of 4 Weeks of Chiropractic Spinal Adjustments on Motor Function in People with Stroke: A Randomized Controlled Trial. Brain Sci. 2021;11(6):21.

76. Holt KR, Haavik H, Lee AC, Murphy B, Elley CR. Effectiveness of Chiropractic Care to Improve Sensorimotor Function Associated With Falls Risk in Older People: A Randomized Controlled Trial. J Manipulative Physiol Ther. 2016;39(4):267–78.

77. Javadov A, Ketenci A, Aksoy C. The efficiency of manual therapy and sacroiliac and lumbar exercises in patients with sacroiliac joint dysfunction syndrome. Pain Physician. 2021;24(3):223-233.

78. Joo S, Lee Y, Song CH. Immediate effects of thoracic spinal manipulation on pulmonary function in stroke patients: a preliminary study. J Manip Physiol Ther 2018;41(7):602-608.

79. Jordon MK, Beattie PF, D'Urso S, Scriven S. Spinal manipulation does not affect pressure pain thresholds in the absence of neuromodulators: a randomized controlled trial. J Man Manip Ther. 2017;25(4):172–81.

80. Joshi S, Balthillaya G, Neelapala YVR. Immediate effects of cervicothoracic junction mobilization versus thoracic manipulation on the range of motion and pain in mechanical neck pain with cervicothoracic junction dysfunction: a pilot randomized controlled trial. Chiropr Man Ther. 2020;28(1):38.

81. Kachmar O, Kushnir A, Matiushenko O, Hasiuk M. Influence of spinal manipulation on muscle spasticity and manual dexterity in participants with cerebral palsy: randomized controlled trial. J Chiropr Med 2018;17(3):141-150.

82. Kamali F, Zamanlou M, Ghanbari A, Alipour A, Bervis S. Comparison of manipulation and stabilization exercises in patients with sacroiliac joint dysfunction patients: A randomized clinical trial. J Bodyw Mov Ther. 2019;23(1):177–82.

83. Karas S, Olson Hunt MJ, Temes B, Thiel M, Swoverland T, Windsor B. The effect of direction specific thoracic spine manipulation on the cervical spine: a randomized controlled trial. J Man Manip Ther. 2018;26(1):3–10.

84. Kendall JC, French SD, Hartvigsen J, Azari MF. Chiropractic treatment including instrument-assisted manipulation for non-specific dizziness and neck pain in community-dwelling older people: a feasibility randomised sham-controlled trial. Chiropr Man Ther. 2018;26:14.

85. Laframboise MA, Vernon H, Srbely J. Effect of two consecutive spinal manipulations in a single session on myofascial pain pressure sensitivity: a randomized controlled trial. J Can Chiropr Assoc. 2016;60(2):137–45.

86. Langenfeld A, Humphreys BK, De Bie RA, Swanenburg J. Comparing manual and mechanically assisted manipulations of the thoracic spine in neck pain patients: A pilot study. F1000Research. 2018;7:156. doi.org/10.12688/f1000research.13780.

87. Lee KW, Kim WH. Effect of thoracic manipulation and deep craniocervical flexor training on pain, mobility, strength, and disability of the neck of patients with chronic nonspecific neck pain: a randomized clinical trial. J Phys Ther Sci 2016;28(1):175-180.

88. Lim KT, Hwang EH, Cho JH, Jung JY, Kim KW, Ha IH, et al. Comparative effectiveness of Chuna manual therapy versus conventional usual care for non-acute low back pain: a pilot randomized controlled trial. Trials Electron Resour. 2019;20(1):216.

89. Lisi AJ, Scheinowitz M, Saporito R, Onorato A. A Pulsed Electromagnetic Field Therapy Device for Non-Specific Low Back Pain: A Pilot Randomized Controlled Trial. Pain Ther. 2019;8(1):133–40.

90. Lohman EB, Pacheco GR, Gharibvand L, Daher N, Devore K, Bains G, et al. The immediate effects of cervical spine manipulation on pain and biochemical markers in females with acute non-specific mechanical neck pain: a randomized clinical trial. J Man Manip Ther. 2019;27(4):186–96.

91. Lopez-de-Uralde-Villanueva I, Beltran-Alacreu H, Fernandez-Carnero J, La Touche R. Pain management using a multimodal physiotherapy program including a biobehavioral approach for chronic nonspecific neck pain: a randomized controlled trial. Physiother Theory Pract. 2020;36(1):45–62.

92. Lopez-de-Uralde-Villanueva I, Candelas-Fernandez P, de-Diego-Cano B, Minguez-Calzada O, Del Corral T. The effectiveness of combining inspiratory muscle training with manual therapy and a therapeutic exercise program on maximum inspiratory pressure in adults with asthma: a randomized clinical trial. Clin Rehabil. 2018;32(6):752–65.

93. Lorenzo S, Nicotra CM, Mentreddy AR, Padia HJ, Stewart DO, Hussein MO, et al. Assessment of Pulmonary Function After Osteopathic Manipulative Treatment vs Standard Pulmonary Rehabilitation in a Healthy Population. J Am Osteopath Assoc. 2019; doi: 10.7556/jaoa.2019.026. Epub ahead of print. PMID: 30741314.

94. Luceno-Mardones A, Luceno-Rodriguez I, Rodriguez-Lopez ES, Oliva-Pascual-Vaca J, Rosety I, Oliva-Pascual-Vaca A. Effects of Osteopathic T9-T10 Vertebral Manipulation in Tonsillitis: A Randomized Clinical Trial. Healthcare. 2021;9(4):01.

95. Lynen A, Schömitz M, Vahle M, Jäkel A, Rütz M, Schwerla F. Osteopathic treatment in addition to standard care in patients with Gastroesophageal Reflux Disease (GERD) – A pragmatic randomized controlled trial. J Bodyw Mov Ther. 2022;29:223–31.

96. Lynge S, Dissing KB, Vach W, Christensen HW, Hestbaek L. Effectiveness of chiropractic manipulation versus sham manipulation for recurrent headaches in children aged 7–14 years - a randomised clinical trial. Chiropr Man Ther. 2021;29(1):1.

97. Maiers M, Hartvigsen J, Evans R, Westrom K, Wang Q, Schulz C, et al. Short or long-term treatment of spinal disability in older adults with manipulation and exercise. Arthritis Care Res 2019;71(11):1516-1524.

98. Marske C, Bernard N, Palacios A, Wheeler C, Preiss B, Brown M, et al. Fibromyalgia with Gabapentin and Osteopathic Manipulative Medicine: A Pilot Study. J Altern Complement Med. 2018;24(4):395–402.

99. McCarthy CJ, Potter L, Oldham JA. Comparing targeted thrust manipulation with general thrust manipulation in patients with low back pain. A general approach is as effective as a specific one. A randomised controlled trial. BMJ Open Sport Exerc Med 2019; 5(1):e000514.

100. Minarini G, Ford M, Esteves J. Immediate effect of T2, T5, T11 thoracic spine manipulation of asymptomatic patient on autonomic nervous system response: Single-blind, parallel-arm controlled-group experiment. Int J Osteopath Med. 2018;30:12–7.

101. Mintken PE, McDevitt AW, Cleland JA, Boyles RE, Beardslee AR, Burns SA, et al. Cervicothoracic Manual Therapy Plus Exercise Therapy Versus Exercise Therapy Alone in the Management of Individuals With Shoulder Pain: A Multicenter Randomized Controlled Trial. J Orthop Sports Phys Ther. 2016;46(8):617–28.

102. Moodley M, Craig M. The effect of sacroiliac chiropractic adjustments on innominate angles. Health SA Gesondheid. 2020;25:1398.

103. Motealleh A, Barzegar A, Abbasi L. The immediate effect of lumbopelvic manipulation on knee pain, knee position sense, and balance in patients with patellofemoral pain: A randomized controlled trial. J Bodyw Mov Ther. 2020;24(3):71–7.

104. Motealleh A, Gheysari E, Shokri E, Sobhani S. The immediate effect of lumbopelvic manipulation on EMG of vasti and gluteus medius in athletes with patellofemoral pain syndrome: A randomized controlled trial. Man Ther. 2016;22:16–21.

105. Moustafa IM, Diab AA, Taha S, Harrison DE. Addition of a Sagittal Cervical Posture Corrective Orthotic Device to a Multimodal Rehabilitation Program Improves Short- and Long-Term Outcomes in Patients With Discogenic Cervical Radiculopathy. Arch Phys Med Rehabil. 2016;97(12):2034–44.

106. Munoz-Gomez E, Ingles M, Serra-Ano P, Espi-Lopez GV. Effectiveness of a manual therapy protocol based on articulatory techniques in migraine patients. A randomized controlled trial. Musculoskelet Sci Pract. 2021;54:102386.

107. Nambi G, Kamal W, Es S, Joshi S, Trivedi P. Spinal manipulation plus laser therapy versus laser therapy alone in the treatment of chronic non-specific low back pain: a randomized controlled study. Eur J Phys Rehabil Med. 2018;54(6):880–9.

108. Nejati P, Safarcherati A, Karimi F. Effectiveness of Exercise Therapy and Manipulation on Sacroiliac Joint Dysfunction: A Randomized Controlled Trial. Pain Physician. 2019;22(1):53–61.

109. Nogueira N, Oliveira-Campelo N, Lopes Â, Torres R, Sousa ASP, Ribeiro F. The acute effects of manual and instrument-assisted cervical spine manipulation on pressure pain threshold, pressure pain perception, and muscle-related variables in symptomatic subjects: A randomized controlled trial. J Manip Physiol Ther. 2020;43(3):179–88.

110. Paanalahti K, Holm LW, Nordin M, Hoijer J, Lyander J, Asker M, et al. Three combinations of manual therapy techniques within naprapathy in the treatment of neck and/or back pain: a randomized controlled trial. BMC Musculoskelet Disord. 2016;23;17:176.

111. Page I, Descarreaux M. Effects of spinal manipulative therapy biomechanical parameters on clinical and biomechanical outcomes of participants with chronic thoracic pain: a randomized controlled experimental trial. BMC Musculoskelet Disord. 2019;18;20(1):29.

112. Papa L, Amodio A, Biffi F, Mandara A. Impact of osteopathic therapy on proprioceptive balance and quality of life in patients with dizziness. J Bodyw Mov Ther. 2017;21(4):866–72.

113. Paredes R, Crasto C, Magalhães B, Carvalho P. Short-Term Effects of Global Pelvic Manipulation on Knee Joint Position Sense in Asymptomatic Participants: A Double-Blind Randomized Controlled Trial. J Manipulative Physiol Ther. 2020;43(7):675–82.

114. Pascual-Vaca AO, Punzano-Rodríguez R, Escribá-Astaburuaga P, Fernández-Domínguez JC, Ricard F, Franco-Sierra MA, et al. Short-term changes in algometry, inclinometry, stabilometry, and urinary pH analysis after a thoracolumbar junction manipulation in patients with kidney stones. J Altern Complement Med. 2017;23(8):1–9.

115. Passmore SR, Johnson MG, Aloraini SM, Cooper S, Aziz M, Glazebrook CM. Impact of Spinal Manipulation on Lower Extremity Motor Control in Lumbar Spinal Stenosis Patients: A Small-Scale Assessor-Blind Randomized Clinical Trial. J Manipulative Physiol Ther. 2019;42(1):23–33.

116. Penza CW, Horn ME, George SZ, Bishop MD. Comparison of 2 Lumbar Manual Therapies on Temporal Summation of Pain in Healthy Volunteers. J Pain. 2017;18(11):1397–408.

117. Petrozzi MJ, Leaver A, Ferreira PH, Rubinstein SM, Jones MK, Mackey MG. Addition of MoodGYM to physical treatments for chronic low back pain: A randomized controlled trial. Chiropr Man Ther. 2019;27:54.

118. Qu L, Xing L, Norman W, Li M, Guo Y, Gao S, et al. Clinical effect of traditional Chinese spinal orthopedic manipulation in treatment of chondromalacia patellae. J Tradit Chin Med. 2016;36(6):718–23.

119. Qu LX, Xing LY, Wanda N, Chen H, Li MJ, Gao S, et al. A Clinical Observation of Functional Abdominal Pain Syndrome in Patients Treated by Traditional Chinese Spinal Orthopedic Manipulation. Chin J Integr Med. 2018;24(2):140–6.

120. Reynolds B, Puentedura EJ, Kolber MJ, Cleland JA. Effectiveness of cervical spine high velocity low amplitude thrust added to behavioral education, soft tissue mobilization, and exercise in individuals with temporomandibular disorder (TMD) with myalgia: a randomized clinical trial. J Orthop Sports Phys Ther 2020;50(8):455-465.

121. Rist PM, Bernstein C, Kowalski M, Osypiuk K, Connor JP, Vining R, et al. Multimodal chiropractic care for migraine: a pilot randomized controlled trial. Cephalalgia 2021;41(3):318-328.

122. Rodrigues PTV, Correa LA, Reis FJJ, Meziat-Filho NA, Silva BM, Nogueira LAC. One session of spinal manipulation improves the cardiac autonomic control in patients with musculoskeletal pain: a randomized placebo-controlled trial. Spine 2021;46(14):915-922.

123. Rodriguez-Sanz J, Malo-Urries M, Corral-de-Toro J, Lopez-de-Celis C, Lucha-Lopez MO, Tricas-Moreno JM, et al. Does the Addition of Manual Therapy Approach to a Cervical Exercise Program Improve Clinical Outcomes for Patients with Chronic Neck Pain in Short- and Mid-Term? A Randomized Controlled Trial. Int J Environ Res Public Health. 2020;17(18):10.

124. Rodriguez-Sanz J, Malo-Urries M, Lucha-Lopez MO, Perez-Bellmunt A, Carrasco-Uribarren A, Fanlo-Mazas P, et al. Effects of the Manual Therapy Approach of Segments C0-1 and C2-3 in the Flexion-Rotation Test in Patients with Chronic Neck Pain: A Randomized Controlled Trial. Int J Environ Res Public Health. 2021;18(2):17.

125. Romero del Rey R, Saavedra Hernandez M, Rodriguez Blanco C, Palomeque del Cerro L, Alarcon Rodriguez R. Short-term effects of spinal thrust joint manipulation on postural sway in patients with chronic mechanical neck pain: a randomized controlled trial. Disabil Rehabil 2022;44(8):1227-1233.

126. Rose KA, Kizhakkeveettil A, Kadar GE, Losack M. Combining Spinal Manipulation With Standard Counseling for Tobacco Cessation: Results of a Feasibility Randomized Clinical Trial. J Chiropr Med. 2017;16(1):41–8.

127. Sampath KK, Botnmark E, Mani R, Cotter JD, Katare R, Munasinghe PE, et al. Neuroendocrine Response Following a Thoracic Spinal Manipulation in Healthy Men. J Orthop Sports Phys Ther. 2017;47(9):617–27.

128. Sarker KK, Sethi J, Mohanty U. Effect of spinal manipulation on pain sensitivity, postural sway, and health-related quality of life among patients with non-specific chronic low back pain: A randomised control trial. J Clin Diagn Res. 2019;13(2):YC01–5.

129. Schulz C, Evans R, Maiers M, Schulz K, Leininger B, Bronfort G. Spinal manipulative therapy and exercise for older adults with chronic low back pain: a randomized clinical trial. Chiropr Man Ther. 2019;27:21.

130. Shin DC, Lee YW. The immediate effects of spinal thoracic manipulation on respiratory functions. J Phys Ther Sci. 2016;28(9):2547–9.

131. Silva AC da, Santos GM, Marques CM de G, Marques JLB. Immediate Effects of Spinal Manipulation on Shoulder Motion Range and Pain in Individuals With Shoulder Pain: A Randomized Trial. J Chiropr Med. 2019;18(1):19–26.

132. Simoni G, Bozzolan M, Bonnini S, Grassi A, Zucchini A, Mazzanti C, et al. Effectiveness of standard cervical physiotherapy plus diaphragm manual therapy on pain in patients with chronic neck pain: a randomized controlled trial. J Bodyw Mov Ther. 2021;26:481-491.

133. Soal LJ, Bester CM, Shaw BS, Yelverton C. Changes in chronic neck pain following the introduction of a visco-elastic polyurethane foam pillow and/or chiropractic treatment. Health SA Gesondheid. 2019;24:1099.

134. Sparks CL, Liu WC, Cleland JA, Kelly JP, Dyer SJ, Szetela KM, et al. Functional magnetic resonance imaging of cerebral hemodynamic responses to pain following thoracic thrust manipulation in individuals with neck pain: a randomized trial. J Manip Physiol Ther 2017;40(9):625-634.

135. Stepnik J, Kedra A, Czaprowski D. Short-term effect of osteopathic manual techniques (OMT) on respiratory function in healthy individuals. PLoS ONE Electron Resour. 2020;15(6):e0235308.

136. Sueki D, Almaria S, Bender M, McConnell B. The immediate and 1-week effects of mid-thoracic thrust manipulation on lower extremity passive range of motion. Physiother Theory Pract. 2020;36(6):720–30.

137. Telles JD, Schiavon MAG, Costa ACDS, Rampazo ÉP, Liebano RE. Hypoalgesic Effects of Transcutaneous Electrical Nerve Stimulation Combined With Joint Manipulation: A Randomized Clinical Trial. J Manipulative Physiol Ther. 2021;44(3):244-254.

138. Thomas JS, Clark BC, Russ DW, France CR, Ploutz-Snyder R, Corcos DM, et al. Effect of spinal manipulative and mobilization therapies in young adults with mild to moderate chronic low back pain: a randomized clinical trial. JAMA Netw Open 2020;3(8):e2022589.

139. Vaden CD, Holder JM, McCoy M, Sayers J, Holder AM. P300 wave outcomes in subluxation based chiropractic in residential addiction treatment: A randomized controlled clinical trial. Ann Vert Sublux Res. 2020;178–92.

140. Valenzuela PL, Pancorbo S, Lucia A, Germain F. Spinal Manipulative Therapy Effects in Autonomic Regulation and Exercise Performance in Recreational Healthy Athletes: A Randomized Controlled Trial. Spine. 2019;44(9):609–14.

141. Valera-Calero A, Lluch Girbes E, Gallego-Izquierdo T, Malfliet A, Pecos-Martin D. Endocrine response after cervical manipulation and mobilization in people with chronic mechanical neck pain: a randomized controlled trial. Eur J Phys Rehabil Med. 2019;55(6):792–805.

142. Vilas Boas Fernandes W, Pizzol FD, Capote AE, de Andrade Melo S, Carvalho Schleder J. Immediate effects of spinal manipulation in pain and global joint mobility in patients with chronic nonspecific low back pain. Man Ther Posturology Rehabil J. 2016;14:1–5.

143. Vining R, Long CR, Minkalis A, Gudavalli MR, Xia T, Walter J, et al. Effects of Chiropractic Care on Strength, Balance, and Endurance in Active-Duty U.S. Military Personnel with Low Back Pain: A Randomized Controlled Trial. J Altern Complement Med. 2020;26(7):592–601.

144. Vinuesa-Montoya S, Aguilar-Ferrándiz ME, Matarán-Peñarrocha GA, Fernández-Sánchez M, Fernández-Espinar EM. A preliminary randomized clinical trial on the effect of cervicothoracic

manipulation plus supervised exercises vs a home exercise program for the treatment of shoulder impingement. J Chiropr Med. 2017;16(2):85–93.

145. Wang SQ, Chen M, Wei X, Gao XX, Zhao GD. Clinical research on lumbar oblique-pulling manipulation in combination with sling exercise therapy for patients with chronic nonspecific low back pain. Rev Assoc Med Bras. 2019;65(6):886–92.

146. Wang Y, Xu M, Shi Y. Efficacy of spinal chiropractic manipulative therapy for adjusting the relationship between cervical facet joints to treat headache caused by acute mountain sickness. J Int Med Res. 2020;48(1):0300060519898005.

147. Ward J, Tyer K, Pourmoghaddam A. Immediate influence of lumbar spine manipulation on pain, functional reach, static balance, and walking gait kinematics of individuals with acute low back pain. Chiropr J Aust. 2018;46(2):135–50.

148. Wright AA, Donaldson M, Wassinger CA, Emerson-Kavchak AJ. Subacute effects of cervicothoracic spinal thrust/non-thrust in addition to shoulder manual therapy plus exercise intervention in individuals with subacromial impingement syndrome: a prospective, randomized controlled clinical trial pilot study. J Man Manip Ther. 2017;25(4):190–200.

149. Xia T, Long CR, Gudavalli MR, Wilder DG, Vining RD, Rowell RM, et al. Similar Effects of Thrust and Nonthrust Spinal Manipulation Found in Adults With Subacute and Chronic Low Back Pain: A Controlled Trial With Adaptive Allocation. Spine. 2016;41(12):E702–9.

150. Yao SC, Zwibel H, Angelo N, Leder A, Mancini J. Effectiveness of Osteopathic Manipulative Medicine vs Concussion Education in Treating Student Athletes With Acute Concussion Symptoms. J Am Osteopath Assoc. 2020;07:07.

151. Younes M, Nowakowski K, Didier-Laurent B, Gombert M, Cottin F. Effect of spinal manipulative treatment on cardiovascular autonomic control in patients with acute low back pain. Chiropr Man Ther. 2017;25:33.

152. Young IA, Pozzi F, Dunning J, Linkonis R, Michener LA. Immediate and Short-term Effects of Thoracic Spine Manipulation in Patients With Cervical Radiculopathy: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2019;49(5):299–309.

153. Zafereo J, Wang-Price S, Roddey T, Brizzolara K. Regional manual therapy and motor control exercise for chronic low back pain: a randomized clinical trial. J Man Manip Ther. 2018;26(4):193–202.

154. Zago J, Amatuzzi F, Rondinel T, Matheus JP. Osteopathic Manipulative Treatment Versus Exercise Program in Runners With Patellofemoral Pain Syndrome: A Randomized Controlled Trial. J Sport Rehabil. 2021;30(4):609–18.

Appendix 3: Risk of bias assessment of included studies

Author, year (reference)	Overall risk of bias assessment
Albers et al, 2018 (1)	Some concerns
Alonso-Perez et al, 2017 (2)	Low risk
Alvarenga et al, 2018 (3)	Some concerns
Aspinall et al, 2019 (4)	Low risk
Balbás-Álvarez et al, 2018 (5)	Low risk
Bautista-Aguirre et al, 2017 (6)	Some concerns
Behrangrad & Kamali, 2017 (7)	High risk
Bernal-Utrera et al, 2020 (8)	High risk
Fernandes et al, 2016 (9)	High risk
Boff et al, 2020 (10)	High risk
Bond et al, 2020 (11)	High risk
Bracht et al, 2018 (12)	Some concerns
Bronfort et al, 2022 (13)	High risk
Brück et al, 2021 (14)	Some concerns
Cambron et al, 2017 (15)	High risk
Carrasco-Martínez et al, 2019 (16)	High risk
Carrasco-Uribarren et al, 2021(17)	High risk
Castello Branco & Moodley, 2016 (18)	High risk
Castro-Sanchez et al, 2016 (19)	Low risk
Castro-Sanchez et al, 2021 (20)	Low risk
Chaibi et al, 2017 (21)	High risk
Cholewicki et al, 2021 (22)	High risk
Corum et al, 2021 (23)	High risk
Coste et al, 2021 (24)	High risk
Crothers et al, 2016 (25)	High risk
de Oliveira et al, 2020 (26)	Some concerns
DeVocht et al, 2019 (27)	Low risk
Didehdar et al, 2020 (28)	High risk
Dishman et al, 2018 (29)	High risk
Dissing et al, 2018 (30)	Low risk
Ditcharles et al, 2017 (31)	Some concerns
Dorron et al, 2016 (32)	Some concerns
Dunning et al, 2016 (33)	Low risk
Dunning et al, 2021 (34)	Some concerns
Dunning et al, 2021 (35)	Some concerns
Eklund et al, 2018 (36)	Low risk
Engel et al, 2016 (37)	High risk

Erdem et al, 2021 [38]	Some concerns
Espi-López et al, 2016 [39]	High risk
Espi-López et al, 2018 [40]	High risk
Espi-López et al, 2016 [41]	Some concerns
Espi-López et al, 2016 [42]	High risk
Evans et al, 2018 [43]	High risk
Fagundes Loss et al, 2020 [44]	Some concerns
Farazdaghi et al, 2018 [45]	Low risk
Fisher et al, 2020 [46]	High risk
Ford et al, 2019 [47]	High risk
Fosberg et al, 2020 [48]	Low risk
Fraix et al, 2021 [49]	High risk
Fritz et al, 2021 [50]	High risk
Fritz et al, 2021 [51]	High risk
Galindez-Ibarbengoetxea et al, 2018 [52]	High risk
Galindez-Ibarbengoetxea et al, 2017 [53]	High risk
Galindez-Ibarbengoetxea et al, 2018 [54]	High risk
Garcia-Perez-Juana et al, 2018 [55]	High risk
Gattie et al, 2021 [56]	Some concerns
Gesslbauer et al, 2018 [57]	High risk
Ghasabmahaleh et al, 2021 [58]	High risk
Goertz et al, 2017 [59]	High risk
Goertz et al, 2016 [60]	High risk
Goertz et al, 2016 [61]	High risk
Gomez et al, 2020 [62]	Some concerns
Gorrell et al, 2016 [63]	Some concerns
Grimes et al, 2019 [64]	Some concerns
Griswold et al, 2018 [65]	Some concerns
Groisman et al, 2020 [66]	Some concerns
Haas et al, 2018 [67]	Some concerns
Haider et al, 2018 [68]	High risk
Haik et al, 2017 [69]	High risk
Haleema et al, 2021 [70]	High risk
Hanney et al, 2017 [71]	High risk
Hardas & Murrell, 2018 [72]	Some concerns
Harihara Prakash et al, 2020 [73]	High risk
Hartstein et al, 2018 [74]	High risk
Holt et al, 2021 [75]	High risk
Holt et al, 2016 [76]	High risk

Javadov et al, 2021 [77]	High risk
Joo et al, 2018 [78]	High risk
Jordon et al, 2017 [79]	High risk
Joshi et al, 2020 [80]	High risk
Kachmar et al, 2018 [81]	Some concerns
Kamali et al, 2019 [82]	Low risk
Karas et al, 2018 [83]	High risk
Kendall et al, 2018 [84]	High risk
Laframboise et al, 2016 [85]	High risk
Langenfeld et al, 2018 [86]	Some concerns
Lee & Kim, 2016 [87]	High risk
Lim et al, 2019 [88]	High risk
Lisi et al, 2019 [89]	High risk
Lohman et al, 2019 [90]	High risk
Lopez-de-Uralde-Villanueva et al, 2020 [91]	High risk
Lopez-de-Uralde-Villanueva et al, 2018 [92]	Some concerns
Lorenzo et al, 2019 [93]	High risk
Luceno-Mardones et al, 2021 [94]	High risk
Lynen et al, 2022 [95]	High risk
Lynge et al, 2021 [96]	Some concerns
Maiers et al, 2019 [97]	Some concerns
Marske et al, 2018 [98]	High risk
McCarthy et al, 2019 [99]	High risk
Minarini et al, 2018 [100]	High risk
Mintken et al, 2016 [101]	High risk
Moodley & Craig, 2020 [102]	High risk
Motealleh et al, 2020 [103]	High risk
Motealleh et al, 2016 [104]	High risk
Moustafa et al, 2016 [105]	High risk
Munoz-Gomez et al, 2021 [106]	Some concerns
Nambi et al, 2018 [107]	Some concerns
Nejati et al, 2019 [108]	Some concerns
Nogueira et al, 2020 [109]	Some concerns
Paanalahti et al, 2016 [110]	High risk
Page & Descarreaux, 2019 [111]	High risk
Papa et al, 2017 [112]	High risk
Paredes et al, 2020 [113]	High risk
Pascual-Vaca et al, 2017 [114]	High risk
Passmore et al, 2019 [115]	High risk

Penza et al, 2017 [116]	Some concerns
Petrozzi et al, 2019 [117]	Low risk
Qu et al, 2016 [118]	High risk
Qu et al, 2018 [119]	Some concerns
Reynolds et al, 2020 [120]	High risk
Rist et al, 2021 [121]	High risk
Rodrigues et al, 2021 [122]	High risk
Rodriguez-Sanz et al, 2020 [123]	High risk
Rodriguez-Sanz et al, 2021 [124]	Some concerns
Romero Del Rey et al, 2022 [125]	Some concerns
Rose et al, 2017 [126]	High risk
Sampath et al, 2017 [127]	High risk
Sarker et al, 2019 [128]	Some concerns
Schulz et al, 2019 [129]	Some concerns
Shin & Lee, 2016 [130]	Some concerns
Silva et al, 2019 [131]	Some concerns
Simoni et al, 2021 [132]	High risk
Soal et al, 2019 [133]	High risk
Sparks et al, 2017 [134]	Some concerns
Stepnik et al, 2020 [135]	High risk
Sueki et al, 2020 [136]	High risk
Telles et al, 2021 [137]	Some concerns
Thomas et al, 2020 [138]	High risk
Vaden et al, 2020 [139]	High risk
Valenzuela et al, 2019 [140]	Some concerns
Valera-Calero et al, 2019 [141]	Some concerns
Vilas Boas Fernandes et al, 2016 [142]	Some concerns
Vining et al, 2020 [143]	Some concerns
Vinuesa-Montoya et al, 2017 [144]	Some concerns
Wang et al, 2019 [145]	High risk
Wang et al, 2020 [146]	High risk
Ward et al, 2018 [147]	High risk
Wright et al, 2017 [148]	Some concerns
Xia et al, 2016 [149]	High risk
Yao et al, 2020 [150]	High risk
Younes et al, 2017 [151]	High risk
Young et al, 2019 [152]	High risk
Zafereo et al, 2018 [153]	Some concerns
Zago et al, 2021 [154]	High risk

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P6-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	------
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	------
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P8

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P8-9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P8
Study characteristics	17	Cite each included study and present its characteristics.	Appendix2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P9-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P9-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-------
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	------
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	------
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	------
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P12-16
	23b	Discuss any limitations of the evidence included in the review.	P12-16
	23c	Discuss any limitations of the review processes used.	P16
	23d	Discuss implications of the results for practice, policy, and future research.	P16-17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	P3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P3
Competing interests	26	Declare any competing interests of review authors.	P4
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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

BMJ Open

The reporting of adverse events associated with spinal manipulation in randomized clinical trials: an updated systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067526.R2
Article Type:	Original research
Date Submitted by the Author:	03-Apr-2023
Complete List of Authors:	Gorrell, Lindsay; Balgrist University Hospital, Integrative Spinal Research Group, Department of Chiropractic Medicine Brown, Benjamin T.; Macquarie University, Department of Chiropractic Engel, Roger; Macquarie University, Department of Chiropractic Lystad, Reidar; Macquarie University, Australian Institute of Health Innovation
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS, REHABILITATION MEDICINE

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THE REPORTING OF ADVERSE EVENTS ASSOCIATED WITH SPINAL MANIPULATION IN RANDOMIZED CLINICAL TRIALS: AN UPDATED SYSTEMATIC REVIEW

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Sources of support

This project did not receive any funding.

Ethics approval statement

Ethics approval was not required for this systematic literature review.

Word count

Abstract: 300; Main text: 4454

Number of figures: 1

Number of tables: 3

Number of appendices: 3

ABSTRACT

Objectives

To describe if there has been a change in the reporting of adverse events associated with spinal manipulation in randomized controlled trials (RCTs) since 2016.

Design

Systematic literature review.

Data sources

Databases were searched from March 2016 to May 2022: MEDLINE (Ovid), Embase, CINAHL, ICL, PEDro and Cochrane Library. The following search terms and their derivatives were adapted for each platform: *spinal manipulation; chiropractic; osteopathy; physiotherapy; naprapathy; medical manipulation; clinical trial*.

Methods

Domains of interest (pertaining to adverse events) included: completeness and location of reporting; nomenclature and description; spinal location and practitioner delivering manipulation; methodological quality of the studies; and details of the publishing journal. Frequencies and proportions of studies reporting on each of these domains were calculated. Univariable and multivariable logistic regression models were fitted to examine the effect of potential predictors on the likelihood of studies reporting on adverse events.

Results

There were 5,399 records identified by the electronic searches, of which 154 (2.9%) were included in the analysis. Of these, ninety-four (61.0%) reported on adverse events with only 23.4% providing an explicit description of what constituted an adverse event. Reporting of adverse events in the abstract has increased (n= 29, 30.9%) while reporting in the results section has decreased (n= 83, 88.3%) over the past 6 years. Spinal manipulation was delivered to 7,518 participants in the included studies. No serious adverse events were reported in any of these studies.

Conclusions

While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased since our 2016 publication on the same topic, the level remains low and inconsistent with established standards. As such, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is more balanced reporting of both benefits and harms in RCTs involving spinal manipulation.

ARTICLE SUMMARY

Strengths and limitations of this review

- This systematic review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (1)
- The search strategy was inclusive of professions that deliver spinal manipulation
- The search included several databases relevant to manual therapy
- Due to heterogeneity of reporting of adverse events, only descriptive statistics were used to describe domains of interest

PROTOCOL

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=270543

FUNDING STATEMENT

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

WORD COUNT

4454

KEYWORDS

Adverse events; Harms; Literature review; Manipulation, spinal; Randomized controlled trials; Spinal manipulative therapy.

INTRODUCTION

The use of high-velocity, low-amplitude spinal manipulation to treat spinal pain and dysfunction is recommended in clinical and best practice guidelines (1–4) and is commonly used by several healthcare professions (5–7). Despite this, concerns remain surrounding adverse events following the intervention (8,9). Adverse events associated with spinal manipulation are typically benign, transient, and do not require further treatment (10). Indeed, some authors classify increased muscle soreness or stiffness in the treatment area as an 'expected outcome of treatment' rather than an adverse event (11). At the other end of the spectrum, catastrophic events, such as vertebral artery dissection, have been temporally associated with spinal manipulation (12). However, such events are rare, and as a result, are typically reported in individual case reports or case series with little to no information regarding the intervention that was delivered (13). Indeed, synthesis of the current literature suggests that there is no evidence for cervical spine manipulation causing cervical artery dissection (14). Additionally, several large population-based studies have reported that there is no difference in risk of cervical artery dissection following visits to a chiropractor compared to those occurring following a visit to a primary care provider (15,16) or, in those who received cervical spinal manipulation compared to matched controls (17,18). Furthermore, recent biomechanical studies report that head angular displacements and vertebral artery length changes are small during cervical spine manipulation thrusts (19) and that the vertebral artery does not experience longitudinal force during cervical spine manipulation (20). Despite this literature, the serious nature of such events that are temporally associated with cervical spine manipulation makes it imperative that the circumstances surrounding such events are reported transparently.

Randomized clinical trials (RCTs) are the gold standard study design for measuring effectiveness (benefit/s) of interventions for the treatment of spinal pain and dysfunction. However, as the risks of an intervention are also important to both patients and practitioners, RCTs should report on not only the efficacy of spinal manipulation, but also any adverse events associated with the intervention. The Consolidated Standards of Reporting Trials (CONSORT) statement, first published in 1996 with several updates since, provides the scientific community (specifically researchers and journal editors)

with a scaffold to standardize and improve the quality of RCT reporting (21–23). The CONSORT statement acknowledges the importance of reporting adverse events alongside effectiveness data. The 2004 Harms extension document (24) provides specific recommendations for how and where these data should be included in scientific manuscripts. However, reporting of adverse events in RCTs in the wider medical literature remains insufficient since the publication of the 2004 extension (25), a finding that is also evident in RCTs that involve spinal manipulation (26). Thus, the objective of this review was to describe if there has been a change in the reporting of adverse events associated with spinal manipulation in RCTs since 2016.

METHODOLOGY

This systematic literature review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (27).

Definitions

Spinal manipulation was defined as a manual procedure involving a high-velocity, low-amplitude (HVLA) thrust delivered to a spinal joint with the intention of moving the joint past its physiological range of motion but without exceeding the anatomic limit (28). For the purposes of this review, spinal manipulation delivered using drop-piece-table and mechanical implements (e.g. Activator instrument) were considered HVLA procedures (29).

An adverse event was defined as any unfavourable reaction with a temporal association to spinal manipulation that resulted in an alteration in a participant's activities of daily living (30,31), irrespective of the timing of onset, duration, or severity of the event (32).

A serious adverse event was defined as any unfavourable sign, symptom, or disease temporally associated with the treatment, whether or not caused by the treatment that results in death or is life-threatening or results in inpatient hospitalization or prolongation of existing hospitalization for more than 24 hours with a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (30).

To be classified as reporting on adverse events "directly", a study must have provided explicit description of their operational definition of an adverse event (e.g. "In the current study, an adverse

event was defined as a sequelae of 1-week duration with any symptom perceived as distressing and unacceptable to the patient that required further treatment [excerpt from reference 63]." (33)), and/or how data on adverse events were measured (e.g. "Active and passive surveillance methods were used to collect information on adverse events." (34)), and/or provide a substantial description of adverse events observed during data collection (35,36). In contrast, all other studies reporting on adverse events "indirectly" did not explicitly provide such information.

Patient and public involvement

No patients were involved in this systematic literature review.

Ethics approval

Ethics approval was not required for this systematic literature review.

Eligibility criteria

Consistent with the 2016 review (26), RCTs reporting original data on spinal manipulation as either the sole intervention, or as the sole intervention in a comparator group, delivered by any regulated health professional, and published in English, were eligible for inclusion. Studies reporting on reviews, other trial designs, trial registrations, protocols, commentaries, editorials and conference proceedings were excluded. Further exclusion criteria included retracted articles, secondary analyses, studies in which the full text was not available in English, and studies where manipulation was only applied to an area other than the spine. Studies were also excluded if it was unclear if the intervention being delivered involved an HVLA manipulation.

Search strategy

The following databases were searched from 1 March 2016 to 12 May 2022: MEDLINE (Ovid), Embase, CINAHL, ICL, PEDro and Cochrane Library. Reference lists of included studies were screened to insure all relevant literature was captured. The following search terms and derivatives were adapted for each platform: *spinal manipulation; chiropractic; osteopathy; physiotherapy; naprapathy; medical manipulation; clinical trial*. An example of each search strategy is provided in Appendix 1.

Study selection process

Records retrieved from the electronic searches were exported to the Rayyan online platform (37). Duplicate records, and records included in the 2016 review were removed before title and abstract screening. Two authors (LG and BB) independently screened included studies in a step-wise process, beginning with review of each title and abstract. Full-texts of the studies remaining after this step were retrieved and further screened against the eligibility criteria (LG and RE). Any disagreements regarding inclusion were resolved by consensus and if consensus could not be reached, disagreements were resolved by a third author (BB).

Data extraction

Adverse events reporting data were extracted from the remaining studies by two authors (LG and RL). These data included descriptive information [i.e., title, author, year of publication, country where the data was collected, journal of publication, spinal region treated (e.g., cervical spine), type of practitioner delivering the spinal manipulation (e.g., chiropractor)], whether the study reported on adverse events (i.e., reported/not and if reported; directly/indirectly), location of reporting within the article, classification of adverse events reported (e.g., mild, moderate, serious, severe), completeness of adverse events reporting (i.e., onset, duration, and number of events reported), number of participants in the spinal manipulation group/s, and descriptions of any definitions and/or classification systems used. Other data collated by the lead author (LG) included whether the study was published in a journal that follows the International Committee of Medical Journal Editors (ICMJE) guidelines via a search of the ICMJE website (38) on 29 May 2022. Additionally, the most recently published impact factor (year 2020) for each journal was manually extracted by the lead author (LG) from the Clarivate Journal Citations Reports website (39) on 29 May 2022.

Assessment of risk of bias using the Cochrane ROB 2 assessment tool (40) was performed by three authors working in pairs (LG and RE, LG and BB) for all included studies to assess the methodological quality of the publication. Disagreements were resolved by consensus and if consensus could not be reached, disagreements were resolved by a third author (RL).

Data analysis

Data were analysed using descriptive statistics. Frequencies and proportions of studies reporting on each of the specified domains above were calculated in Microsoft Excel (Version 2102, Microsoft Corporation, USA). Continuous variables with highly skewed distributions (i.e., journal impact factor and sample size of spinal manipulation group) were categorised into tertiles. Univariable and multivariable logistic regression models were fitted to examine the effect of potential predictors on the likelihood of studies reporting on adverse events. The multivariable logistic regression model was fitted using backward elimination, whereby the least significant potential predictors were sequentially eliminated from the multivariable model until only significant predictors remained. The observed effects from the univariable and multivariable logistic regression models were reported as odds ratios (OR) and adjusted odds ratios (aOR) respectively, with 95% confidence intervals (CI). All statistical analyses were performed using the statistical computing software R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

There were 5,399 records initially identified by the electronic searches (Figure 1). A total of 3,363 unique records remained after de-duplication (n=2,034) and the removal of retracted articles (n=2). After title and abstract screening, full texts of the 452 remaining studies were screened. Of these, 154 fulfilled the eligibility criteria and were included in the analysis (see Appendix 2). The most common reasons for exclusion were: the intervention did not consist of HVLA spinal manipulation (n=163) and/or the study related to a conference proceeding (n=49).

Insert around here: Figure 1: PRISMA flow diagram.

Comprehensiveness of reporting of adverse events

Of the 154 included studies, 94 (61.0%) reported on adverse events. Of these 94 studies, 36 (38.3%) directly reported on adverse events, with studies in which spinal manipulation was delivered by a chiropractor most frequently reporting these data (n=17; 47.2%, Table 1). Indirect reporting occurred in 58 studies (61.7%), with studies in which spinal manipulation was delivered by a physiotherapist being the most frequent (n=29; 50.0%, Table 1). Of the 60 studies (39.0%) that did not report on adverse events, studies in which spinal manipulation was delivered by a physiotherapist were the most

frequent (n=28; 46.7%, Table 1). A description of what constituted an adverse event definition and/or the classification system used was provided in 22 studies (23.4%). However, most studies did not provide a description and instead used terms such as "adverse event" (n=70, 74.5%), "adverse effect" (n=22, 23.4%), "side effect" (n=19, 20.2%) and "harm" (n=11, 11.7%) without adequate explanation. When mentioned, terms pertaining to classification systems (predominantly severity) were (number of studies in which the term was used, %): "mild" (n=20, 21.3%), "moderate" (n=17, 18.1%), "serious" (n=27, 28.7%), and "severe" (n=14, 14.9%). The onset of an adverse event/s was unclear in 30 (31.9%) studies. Duration of adverse events were reported heterogeneously, with some studies providing a time from either baseline or the start of intervention, whereas others provided a temporal descriptor such as "short-term", "temporary" or, "transient". Of the 9 studies providing times, durations were as follows: <72hr (n=3, 3.2%), >72hr (n=2, 2.1%) or mixed duration (n=4, 4.3%). An evaluation tool was mentioned in 26 (27.7%) studies.

Insert around here: Table 1: Comprehensiveness of reporting of adverse events by provider delivering the intervention

	Directly reports on AE (n=36), n (%)	Indirectly reports on AE (n=58), n (%)	Does not report on AE (n=60), n (%)
Chiropractor	17 (47.2)	12 (20.7)	7 (11.7)
Medical Practitioner	1 (2.8)	4 (6.9)	5 (8.3)
Mixed	7 (19.4)	7 (12.1)	7 (11.7)
Naprapath	0 (0.0)	0 (0.0)	1 (1.7)
Osteopath	4 (11.1)	2 (3.4)	9 (15.0)
Physiotherapist	6 (16.7)	29 (50.0)	28 (46.7)
Unclear	1 (2.8)	4 (6.9)	3 (5.0)

AE; adverse event

Number and location of adverse events reporting

No serious adverse events were reported in any of the 154 included studies, representing 7,518 participants who received spinal manipulation. Furthermore, of the 94 studies reporting on adverse events, 63 (67.0%) reported that no adverse events occurred. Adverse events were reported in the abstract of 29 (30.9%) and results section of 83 (88.3%) studies. Furthermore, adverse events were mentioned in several locations throughout the included studies: the introduction (n=15, 16.0%),

methods (n=56, 59.6%), discussion (n=30, 31.9%), conclusion (n=7, 7.4%), and supplementary materials (n=1, 1.1%).

Descriptors of studies reporting on adverse events

Descriptive statistics are provided in Table 2. Of the 94 studies reporting on adverse events, 55 (58.5%) were rated at a 'high risk of bias', 29 (30.9%) as 'some concerns' and 10 (10.6%) at a 'low risk of bias' (Appendix 3). Additionally, 33 (35.1%) were published in journals stating that they follow the ICMJE recommendations. For the remaining studies, the median of the most recently published (2020) impact factor was 2.5 (IQR: 2.1–4.2).

Insert around here: Table 2: Characteristics of included studies by reporting on adverse events

		Overall (n=154), n (%)	Reports on AE (n=94), n (%)	Does not report on AE (n=60), n (%)
ICMJE journal	Published in ICJME journal	53 (34.4)	33 (35.1)	20 (33.3)
Risk of bias	Low risk	13 (8.4)	10 (10.6)	3 (5.0)
	Some concerns	47 (30.5)	29 (30.9)	18 (30.0)
	High risk	94 (61.0)	55 (58.5)	39 (65.0)
Impact factor	Upper tertile	47 (30.5)	36 (38.3)	11 (18.3)
	Middle tertile	54 (35.1)	37 (39.4)	17 (28.3)
	Lower tertile	53 (34.4)	21 (22.3)	32 (53.3)
Spinal region	Cervical	24 (15.6)	17 (18.1)	7 (11.7)
	Thoracic	33 (21.4)	15 (16.0)	18 (30.0)
	Lumbopelvic	28 (18.2)	13 (13.8)	15 (25.0)
	Mixed/Unclear	69 (44.8)	49 (52.1)	20 (33.3)
Type of practitioner	Chiropractor	36 (23.4)	29 (30.9)	7 (11.7)
	Osteopath	15 (9.7)	6 (6.4)	9 (15.0)
	Physiotherapist	63 (40.9)	35 (37.2)	28 (46.7)
	Medical Practitioner	9 (5.8)	4 (4.3)	5 (8.3)
	Mixed/Other/Unclear	31 (20.1)	20 (21.2)	11 (18.3)
Sample size spinal manipulation group[1]	Upper tertile	51 (33.3)	40 (42.6)	11 (18.6)
	Middle tertile	50 (32.7)	28 (29.8)	22 (37.3)
	Lower tertile	52 (34.0)	26 (27.7)	26 (44.1)

[1] One study with unclear sample size excluded
AE; adverse event

Predictors for the reporting of adverse events

There was very strong evidence that studies with an impact factor in the upper (aOR: 5.72 [95% CI: 2.23-15.85]; $p < 0.001$) and middle (aOR: 3.52 [95% CI: 1.51-8.57]; $p = 0.004$) tertiles were more

likely to report on adverse events than those in the lower tertile when the model was adjusted for risk of bias, impact factor, spinal region of manipulation, and number of participants receiving spinal manipulation (Table 3). There was also strong evidence that studies in which a chiropractor delivered the spinal manipulation were more likely to report on adverse events (aOR: 4.58 [95% CI: 1.14-20.24]; p = 0.036). Studies in which spinal manipulation was delivered to more than one region or, it was unclear which regions the manipulations were delivered, were also more likely to report on adverse events (aOR: 3.18 [95% CI: 1.16-9.05]; p = 0.027). While not achieving statistical significance, another factor of note included studies in which cervical spine manipulation was delivered (aOR: 3.04 [95% CI: 0.88-11.30]; p = 0.085).

Insert around here: Table 3: Univariable and multivariable logistic regression

Variable	OR	95%CI	p-value	aOR[1]	95%CI	p-value
ICMJE journal						
Yes	1.08	0.55-2.16	0.821	-	-	-
No[2]	-	-	-	-	-	-
Risk of bias						
Low risk	2.36	0.67-11.01	0.213	-	-	-
Some concerns	1.14	0.56-2.37	0.716	-	-	-
High risk[2]	-	-	-	-	-	-
Impact factor						
Upper tertile	4.99	2.14-12.32	<0.001	5.72	2.23-15.85	<0.001
Middle tertile	3.32	1.52-7.48	0.003	3.52	1.51-8.57	0.004
Lower tertile[2]	-	-	-	-	-	-
Spinal region						
Cervical	2.80	0.91-9.27	0.080	3.04	0.88-11.30	0.085
Thoracic	0.96	0.35-2.66	0.939	1.09	0.34-3.45	0.887
Lumbopelvic[2]	-	-	-	-	-	-
Mixed/Unclear	2.83	1.15-7.11	0.025	3.18	1.16-9.05	0.027
Type of practitioner						
Chiropractor	6.21	1.71-24.85	0.007	4.58	1.14-20.24	0.036
Osteopath[2]	-	-	-	-	-	-
Physiotherapist	1.88	0.60-6.19	0.282	1.35	0.37-5.18	0.648
Medical Practitioner	1.20	0.22-6.53	0.831	0.81	0.12-5.47	0.829
Mixed/Other/Unclear	2.72	0.78-10.17	0.121	2.26	0.57-9.64	0.253
Sample size spinal manipulation group[3]						
Upper tertile	3.64	1.57-8.87	0.003	-	-	-
Middle tertile	1.27	0.58-2.79	0.544	-	-	-
Lower tertile[2]	-	-	-	-	-	-

[1] The final model was adjusted for impact factor, spinal region of manipulation, and type of practitioner, while ICMJE journal status, risk of bias, and number of participants receiving spinal manipulation were omitted via backward elimination method.
[2] Reference group.
[3] One study with unclear sample size excluded.

DISCUSSION

There has been a change in the reporting of adverse events associated with spinal manipulation in RCTs since 2016. Specifically, the percentage of included studies reporting adverse events has increased from 38.0% (2016 study (26)) to 61.0% (current study). However, the current review highlights that the reporting of adverse events in RCTs involving spinal manipulation as an intervention remains poor and is not consistent with established standards. Specifically, of the 154 included studies, just over half (n= 94, 61.0%) reported on adverse events. Furthermore, of these 94 studies, less than half (38.3%) reported directly on adverse events, with only 23.4% providing an explicit description of what constituted an adverse event. Further complicating this issue is the vast heterogeneity of terms (i.e., "adverse effect", "side effect", "harm" etc) used to describe adverse events. This is disappointing given that there have been many calls in the literature for the improvement of adverse events reporting in RCTs, and for the development and use of standardized definitions and classification systems (24,26,32,41–46).

A recent scoping review explores the complexity of the current literature reporting on adverse events associated with spinal and peripheral joint manipulation and mobilisation (47). Specifically, the authors report that conflicting opinions regarding facets of adverse event definition and classification such as: symptom severity and duration, relatedness to the intervention (e.g., time to onset, treatment provided), action taken to treat the symptoms, expectedness, which profession delivered the intervention and geographical location (with possible medico-legal constraints and/or different expectations of reporting/not reporting) are all factors to reflect on when considering adverse events associated with joint manipulation and mobilisation. In an attempt to address the lack of standardized definitions and classification systems across professions that deliver spinal manipulation, the same authors have conducted an international Delphi study (manuscript in preparation; protocol paper (41)) to determine, by expert consensus, a standardised definition and severity classification for adverse events associated with spinal and peripheral joint manipulation and mobilisation. The development

and use of such guidelines would constitute an important step toward uniform reporting of adverse events associated with spinal manipulation across all stakeholder professions and geographical locations.

However, until this work is published, Appendix 2 of the 2004 CONSORT Harms extension (24) provides a checklist of items to include and specific examples of good reporting when reporting on harms (adverse events) in RCTs. Furthermore, it appears that an update to this guideline is emergent (25). It is hoped that these updated guidelines will ensure that authors and journal editors alike are both aware of and implement better harms reporting in the future. We strongly encourage researchers and journal editors alike to read and use the most recent CONSORT Harms checklist during all phases of study development, data collection, manuscript preparation, submission and during the review process. One important item on this checklist is that both benefits and harms should be stated in either the title and/or abstract of a manuscript. This point is salient as the abstract is the second-most read section of a scientific manuscript after the title (48). Encouragingly, the reporting of adverse events in the abstract has doubled (15.7-30.9%, 2016 to current) when compared to our previous review of the literature (26). Despite this, the current reporting on adverse events in the title/abstract of RCTs utilizing spinal manipulation remains poor, a finding that is also present in the wider published medical literature discussing adverse events (49–52). Despite an overall increase in the number of studies reporting on adverse events in RCTs involving spinal manipulation (38.0-61.0%, 2016 (26) to current), adverse events reporting in the results section has decreased (93.6% vs 88.3%) over the past 6 years and remains lower than that in the wider published literature (50,53). It is unknown why there would be a decrease in the reporting on adverse events associated with spinal manipulation in the one section of a scientific manuscript that it could reasonably be expected to be reported. Furthermore, an important source of information for the formulation of a considered evidence-based risk-benefit analysis for the use of spinal manipulation as a treatment option by both clinician and patient (49,52) is transparent data reporting on both the efficacy and adverse events occurring in RCTs involving spinal manipulation.

Consistent with the literature (31,32,42,43,47), there was considerable heterogeneity of nomenclature used to describe adverse events associated with spinal manipulation. Similar terms were used to indicate an adverse event in the current (compared to 2016) review: "adverse event" (2016 – 73.0%; 2022 – 74.5% of studies), "adverse effect" (23.6%; 23.4%), "side effect" (21.3%; 20.2%) and "harm" (16.4%; 11.7%). Additionally, while similar terms were used to describe classification systems previously reported (i.e., "serious", "mild", "moderate", and "severe"), these terms were rarely defined, which is consistent with the existing literature (26,52). Additionally, when present, the reporting of onset and duration of adverse events was inconsistent, again highlighting that there is an urgent need for the development of a standardized definition and classification system for the reporting of adverse events (41). Furthermore, the responsibility for improved reporting of adverse events falls not only to authors but also to custodians of clinical trial registries and journal editors to ensure that there are provisions in study protocols for the adequate capture of adverse events and also that these events are adequately reported i.e., using the most recent CONSORT Harms extension guidelines (24), alongside efficacy/effectiveness data (25,46,54).

Manuscript reviewers and journal editors must be aware of the current best-practices for the reporting of harms (24) and enforce these guidelines during peer review processes of both protocol and end-of-study results papers. However, this may not be as straight-forward as it appears. Despite this, there is a need for improved reporting of adverse events in RCTs that include spinal manipulation as an intervention and a first step would be for journals to incorporate clear instructions on harms reporting in their guidelines and instructions to authors. As a second step, journal editors may facilitate this process by limiting publication to only those studies that adhere to the current guidelines for the reporting of harms in RCTs that include spinal manipulation as an intervention. Indeed, if this was to occur, authors would need to 'step-up', to use expanded methodologies, reporting and statistical analyses that allow for the capture and reporting of adverse events data in RCTs that include spinal manipulation as an intervention. Specifically, data on adverse events should be actively collected as it has been reported that passive surveillance leads to an under-reporting (25,54) and appropriate

statistical analysis plans should be used to analyse the data (49,54,55). As a minimum standard, authors should explicitly state whether active or passive surveillance systems were used (46,49).

RCTs published in journals with a higher impact factor, in which spinal manipulation was delivered by a chiropractor and to multiple/unclear regions, were more likely to report on adverse events. While it is perhaps intuitive that better designed studies, i.e., those at a lower risk of bias, could reasonably be published in higher impact journals, this does not appear to be the case as there was no influence of risk of bias level in the final model. This disconnect between the publication of studies with better methodological quality in higher impact journals is also seen in the medical literature. Specifically, a previous study reported that there were methodological weaknesses in 184 studies published in 2015-2016 by four of the top ranked general medical journals (BMJ, JAMA, Lancet, and NEJM) (54). Furthermore, while there is no obvious reason why studies in which spinal manipulation was delivered by a chiropractor would be more likely to report on adverse events, possible reasons for this finding could include that chiropractors are more likely to deliver cervical spine manipulation in general and/or that due to perceived 'risks' of cervical spine manipulation, other professions choose not to conduct trials investigating this intervention. This hypothesis is suggested by the data which shows that while not achieving statistical significance, studies in which cervical spine manipulation was delivered had approximately 3 times greater odds of reporting on adverse events. It is possible that this result did not achieve statistical significance due to the relatively small number of studies reporting on manipulation delivered only to the cervical spine. Regarding the increased likelihood of studies reporting on adverse events if spinal manipulation was delivered to multiple/unclear regions, it is possible that this finding is spurious as there was a larger number of studies (n=49) in this category compared to studies in which the intervention was delivered to a single region. This hypothesis is supported by a secondary analysis of our previous review which reported that the region treated was not a significant predictor for reporting on adverse events (56).

Due to the methodological design of the review, we are unable to comment on the incidence of adverse events associated with spinal manipulation. Furthermore, RCTs are not necessarily the best

research design for collecting data on serious adverse events as they often have strict inclusion criteria and may exclude participants who are at risk of experiencing such events. Additionally, RCTs are powered to detect intervention effects and thus are likely to be underpowered for estimating the risk of serious adverse events. Despite this, the consistent reporting of the number of spinal manipulations delivered to every participant in RCTs could allow for the calculation of accurate incidence rates for all classifications of adverse events (serious included) and could eventually facilitate the pooling of data across multiple studies thus allowing for a better informed risk-benefit assessment of spinal manipulation (25,46). We acknowledge that the calculation of accurate incidence rates is not straight-forward. Indeed, factors such as the use of different spinal manipulation techniques, how to parse out adverse events attributable to different interventions (e.g. orthopaedic testing, soft tissue treatment or exercise) and how to amalgamate reports on different cohorts (e.g. neck vs. low back pain) must all be considered. While this task seems insurmountable, consistent reporting of the number of spinal manipulations delivered to every participant in RCTs is the first step towards this goal. To this end, the number of spinal manipulations delivered was only available in 75 (48.7%) of the included studies. Coupled with the implementation of standardized definitions and classification systems for adverse events associated with spinal manipulation, reporting on the number of spinal manipulations delivered in each study could allow for the inter-disciplinary calculation of incidence rates for all classifications across all healthcare professionals delivering the intervention. Such an outcome is extremely important in the context of obtaining informed consent to deliver spinal manipulation. Specifically, in many countries in which spinal manipulation is delivered, the process of obtaining informed consent requires the disclosure of all material information that a reasonable patient would require to make an informed decision about whether or not to receive that intervention (57). In the absence of accurate incidence rates for the different classifications of adverse events associated with spinal manipulation, this is a difficult task for the clinician to perform.

There are several differences between the current review and our 2016 review (26). Specifically, the current review included an improved search strategy, including both an expansion to the number of databases searched (i.e., MEDLINE (Ovid), Embase, CINAHL and ICL were added) in addition to the

inclusion of several search terms that did not limit the search to spinal manipulation delivered by chiropractors and osteopaths (i.e., physiotherapists, naprapaths and medical manipulation were added). Additionally, the current review reports on analyses that we had previously reported separately in two manuscripts: the original review (26) and a secondary analysis (56). By reporting these analyses in a single manuscript, we hope it is clearer for readers to identify that the current level of reporting of adverse events associated with spinal manipulation in RCTs is both poor and not consistent with established standards, and understand the possible explanations for this observation. By streamlining the dissemination of this information, we hope to make it easier for readers to identify areas in which researchers may improve the reporting of adverse events in this field.

Limitations

There are several limitations to this literature review. Firstly, the decision to classify the reporting of adverse events as 'direct' (explicit description of operational definition of an adverse event provided and/or how data on adverse events were measured and/or a substantial description of adverse events observed during data collection provided) as opposed to 'indirect' (no explicit reporting of such information) was arbitrary. However, this classification did not influence whether the study reported on adverse events or not. As such, we do not feel this factor had any material influence on our results. Secondly, as outlined above, small differences in the methodology between the current and previous reviews (26,56) mean that it is not possible to directly compare all reported findings between the two reviews. However, as these differences occurred due to methodological improvements in the current review, we do not believe this affected the results and/or discussion in the current review.

CONCLUSION

While the current level of reporting of adverse events associated with spinal manipulation in RCTs has increased since our 2016 publication on the same topic, the level remains low and inconsistent with established standards. As such, it is imperative for authors, journal editors and administrators of clinical trial registries to ensure there is more balanced reporting of both benefits and harms of spinal manipulation in RCTs. We strongly recommend that authors adhere to the most recent CONSORT

Harms checklist when reporting their results and advocate for the creation of standardized definitions and classification systems relating to adverse events in manual therapy. This will facilitate the future pooling of adverse events data across all professions utilizing spinal manipulation and improve the ability to calculate incidence rates for the different levels of adverse events.

AUTHOR CONTRIBUTIONS

LG: conceptualization, screening, risk of bias assessment, data extraction and curation, formal analysis, methodology, project administration, visualization, writing – original draft, review & editing

RL: data extraction and curation, formal analysis, methodology, visualization, writing – original draft, review & editing

BB: screening, risk of bias assessment, writing – review & editing

RE: screening, risk of bias assessment, methodology, writing – review & editing

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr. Martina Gosteli for her assistance with the literature search.

DATA SHARING STATEMENT

Data are available from the corresponding author upon reasonable request.

REFERENCE STRENGTHS AND LIMITATIONS OF THE REVIEW

1. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

REFERENCES MANUSCRIPT

1. Whalen W, Farabaugh RJ, Hawk C, Minkalis AL, Lauretti W, Crivelli LS, et al. Best-practice recommendations for chiropractic management of patients with neck pain. J Manipulative Physiol Ther. 2019 Nov 1;42(9):635–50.

2. Bussieres AE, Stewart G, Al-Zoubi F, Decina P, Descarreaux M, Haskett D, et al. Spinal Manipulative Therapy and Other Conservative Treatments for Low Back Pain: A Guideline From the Canadian Chiropractic Guideline Initiative. J Manip Physiol Ther. 2018 Mar 29;

3. Bussieres AE, Stewart G, Al-Zoubi F, Decina P, Descarreaux M, Hayden J, et al. The treatment of neck pain-associated disorders and whiplash-associated disorders: a clinical practice guideline. J Manipulative Physiol Ther. 2016 Oct;39(8):523–64.

4. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CWC, Chenot JF, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. Eur Spine J. 2018 Nov 1;27(11):2791–803.

5. Beliveau PJH, Wong JJ, Sutton DA, Simon NB, Bussières AE, Mior SA, et al. The chiropractic profession: a scoping review of utilization rates, reasons for seeking care, patient profiles, and care provided. Chiropr Man Ther. 2017 Nov 22;25(35).

6. Lin I, Wiles L, Waller R, Goucke R, Nagree Y, Gibberd M, et al. What does best practice care for musculoskeletal pain look like? Eleven consistent recommendations from high-quality clinical practice guidelines: systematic review. Br J Sports Med. 2020 Jan 1;54(2):79.

7. National Institute for Health and Care Excellence (NICE). Low Back Pain and Sciatica in Over 16s: Assessment and Management. Natl Inst Health Care Excell NICE. 2016 Nov;

8. Puentedura EJ, March J, Anders J, Perez A, Landers MR, Wallmann HW, et al. Safety of cervical spine manipulation: are adverse events preventable and are manipulations being performed appropriately? A review of 134 case reports. J Man Manip Ther. 2012 May;20(2):66–74.

9. Biller J, Sacco RL, Albuquerque FC, Demaerschalk BM, Fayad P, Long PH, et al. Cervical arterial dissections and association with cervical manipulative therapy: a statement for healthcare professionals from the american heart association/american stroke association. Stroke J Cereb Circ. 2014 Oct;45(10):3155–74.

10. Funabashi M, Pohlman KA, Goldsworthy R, Lee A, Tibbles A, Mior S, et al. Beliefs, perceptions and practices of chiropractors and patients about mitigation strategies for benign adverse events after spinal manipulation therapy. Chiropr Man Ther. 2020;28(1):46.

11. Heneghan NR, Davies SE, Puentedura EJ, Rushton A. Knowledge and pre-thoracic spinal thrust manipulation examination: a survey of current practice in the UK. J Man Manip Ther. 2018 Oct 20;26(5):301–9.

12. Albuquerque FC, Hu YC, Dashti SR, Abla AA, Clark JC, Alkire B, et al. Craniocervical arterial dissections as sequelae of chiropractic manipulation: patterns of injury and management. J Neurosurg. 2011 Dec;115(6):1197–205.

13. Ernst E. Deaths after chiropractic: a review of published cases. Int J Clin Pract. 2010 Jul;64(8):1162–5.

14. Church EW, Sieg EP, Zalatimo O, Hussain NS, Glantz M, Harbaugh RE. Systematic Review and Meta-analysis of Chiropractic Care and Cervical Artery Dissection: No Evidence for Causation. Cureus [Internet]. [cited 2019 Jul 26];8(2). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4794386/

15. Cassidy JD, Boyle E, Côté P, He Y, Hogg-Johnson S, Silver FL, et al. Risk of vertebrobasilar stroke and chiropractic care: results of a population-based case-control and case-crossover study. Eur Spine J. 2008 29;17(1):176–83.

16. Whedon JM, Song Y, Mackenzie TA, Phillips RB, Lukovits TG, Lurie JD. Risk of stroke after chiropractic spinal manipulation in medicare B beneficiaries aged 66 to 99 years with neck pain. J Manipulative Physiol Ther. 2015 Feb;38(2):93–101.

17. Cassidy JD, Boyle E, Côté P, Hogg-Johnson S, Bondy SJ, Haldeman S. Risk of Carotid Stroke after Chiropractic Care: A Population-Based Case-Crossover Study. J Stroke Cerebrovasc Dis. 2017;26(4):842–50.

18. Whedon JM, Petersen CL, Li Z, Schoelkopf WJ, Haldeman S, MacKenzie TA, et al. Association between cervical artery dissection and spinal manipulative therapy –a medicare claims analysis. BMC Geriatr. 2022 Nov 29;22(1):917.

19. Gorrell LM, Kuntze G, Ronsky JL, Carter R, Symons B, Triano JJ, et al. Kinematics of the head and associated vertebral artery length changes during high-velocity, low-amplitude cervical spine manipulation. Chiropr Man Ther. 06 01;30(1):28.

20. Gorrell LM, Sawatsky A, Edwards WB, Herzog W. Vertebral arteries do not experience tensile force during manual cervical spine manipulation applied to human cadavers. J Man Manip Ther. 2022 Nov 15;1–9.

21. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. JAMA. 1996;276.

22. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357.

23. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8.

24. Ioannidis JPA, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004;141.

25. Junqueira DR, Phillips R, Zorzela L, Golder S, Loke Y, Moher D, et al. Time to improve the reporting of harms in randomized controlled trials. J Clin Epidemiol. 2021 Aug 1;136:216–20.

26. Gorrell LM, Engel RM, Brown B, Lystad RP. The reporting of adverse events following spinal manipulation in randomized clinical trials-a systematic review. Spine J. 2016 May 27;

27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

28. Herzog W. The biomechanics of spinal manipulation. J Bodyw Mov Ther. 2010 Jul;14(3):280–6.

29. Bergmann T. Chiropractic Technique Principles and Procedures. 3rd ed. Missouri: Elselvier Mosby, USA; 2011.

30. Pohlman KA, O'Beirne M, Thiel H, Cassidy JD, Mior S, Hurwitz EL, et al. Development and validation of providers' and patients' measurement instruments to evaluate adverse events after spinal manipulation therapy. Eur J Integr Med. 2014 Aug 1;6:451–66.

31. Walker BF, Hebert JJ, Stomski NJ, Clarke BR, Bowden RS, Losco B, et al. Outcomes of usual chiropractic. The OUCH randomized controlled trial of adverse events. Spine Phila Pa 1976. 2013 Sep 15;38:1723–9.

32. Carnes D, Mullinger B, Underwood M. Defining adverse events in manual therapies: a modified Delphi consensus study. Man Ther. 2010 Feb;15(1):2–6.

33. Dunning J, Butts R, Zacharko N, Fandry K, Young I, Wheeler K, et al. Spinal manipulation and perineural electrical dry needling in patients with cervicogenic headache: a multi-center randomized clinical trial. Spine J 2021 Feb212284-295. 2021;

34. Maiers M, Hartvigsen J, Evans R, Westrom K, Wang Q, Schulz C, et al. Short or long-term treatment of spinal disability in older adults with manipulation and exercise. Arthritis Care Res 2019 Nov71111516-1524. 2019;

35. Vining R, Long CR, Minkalis A, Gudavalli MR, Xia T, Walter J, et al. Effects of Chiropractic Care on Strength, Balance, and Endurance in Active-Duty U.S. Military Personnel with Low Back Pain: A Randomized Controlled Trial. J Altern Complement Med. 2020 Jul;26(7):592–601.

36. Schulz C, Evans R, Maiers M, Schulz K, Leininger B, Bronfort G. Spinal manipulative therapy and exercise for older adults with chronic low back pain: a randomized clinical trial. Chiropr Man Ther. 2019;27:21.

37. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016 Dec 5;5(1):210.

38. International Committeee of Medical Journal Editors (ICMJE). Journals following the ICMJE recommendations. 2016.

39. Clarivate Journal Citation Reports [Internet]. Clarivate Journal Citation Reports. [cited 2022 May 29]. Available from: https://clarivate.com/webofsciencegroup/solutions/journal-citation-reports/

40. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. In: Cochrane Handbook for Systematic Reviews of Interventions [Internet]. John Wiley & Sons, Ltd; 2019. p. 205–28. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119536604.ch8

41. Funabashi M, Pohlman KA, Gorrell LM, Salsbury SA, Bergna A, Heneghan NR. Expert consensus on a standardised definition and severity classification for adverse events associated with spinal and peripheral joint manipulation and mobilisation: protocol for an international e-Delphi study. BMJ Open. 2021 Nov 1;11(11):e050219.

42. Carnes D, Mars TS, Mullinger B, Froud R, Underwood M. Adverse events and manual therapy: a systematic review. Man Ther. 2010 Aug;15(4):355–63.

43. Carlesso L, Macdermid J, Santaguida P. Standardization of adverse event terminology and reporting in orthopaedic physical therapy: application to the cervical spine. J Orthop Sports Phys Ther. 2010 Aug;40:455–63.

44. Carlesso L, Cairney J, Dolovich L, Hoogenes J. Defining adverse events in manual therapy: an exploratory qualitative analysis of the patient perspective. Man Ther. 2011 Oct;16:440–6.

45. Carlesso L, Gross A, Santaguida P, Burnie S, Voth S, Sadi J. Adverse events associated with the use of cervical manipulation and mobilization for the treatment of neck pain in adults: a systematic review. Man Ther. 2010 Oct;15(5):434–44.

46. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ. 2016 Feb 1;352:i157.

47. Funabashi M, Gorrell LM, Pohlman KA, Bergna A, Heneghan NR. Definition and classification for adverse events following spinal and peripheral joint manipulation and mobilization: A scoping review. PLOS ONE. 2022 Jul 15;17(7):e0270671.

48. Pitkin RM. The importance of the abstract. Obstet Gynecol. 1987 Aug;70:267.

49. Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, et al. Quality of reporting in systematic reviews of adverse events: systematic review. BMJ. 2014;348:f7668.

50. Komorowski AS, MacKay HJ, Pezo RC. Quality of adverse event reporting in phase III randomized controlled trials of breast and colorectal cancer: A systematic review. Cancer Med. 2020 Jul 1;9(14):5035–50.

51. Berwanger O, Ribeiro RA, Finkelsztejn A, Watanabe M, Suzumura EA, Duncan BB, et al. The quality of reporting of trial abstracts is suboptimal: survey of major general medical journals. J Clin Epidemiol. 2009 Apr;62(4):387–92.

52. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Arch Intern Med. 2009 Oct 26;169:1756–61.

53. Nuovo J, Sather C. Reporting adverse events in randomized controlled trials. Pharmacoepidemiol Drug Saf. 2007 Mar;16(3):349–51.

54. Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open. 2019 Mar 1;9(2):e024537.

55. Phillips R, Sauzet O, Cornelius V. Statistical methods for the analysis of adverse event data in randomised controlled trials: a scoping review and taxonomy. BMC Med Res Methodol. 2020 Nov 30;20(1):288.

56. Gorrell LM, Brown B, Lystad RP, Engel RM. Predictive factors for reporting adverse events following spinal manipulation in randomized clinical trials – secondary analysis of a systematic review. Musculoskelet Sci Pract. 2017;30:34–41.

57. Winterbottom M, Boon H, Mior S, Facey M. Informed consent for chiropractic care: Comparing patients' perceptions to the legal perspective. Man Ther. 2015 Jun;20(3):463–8.

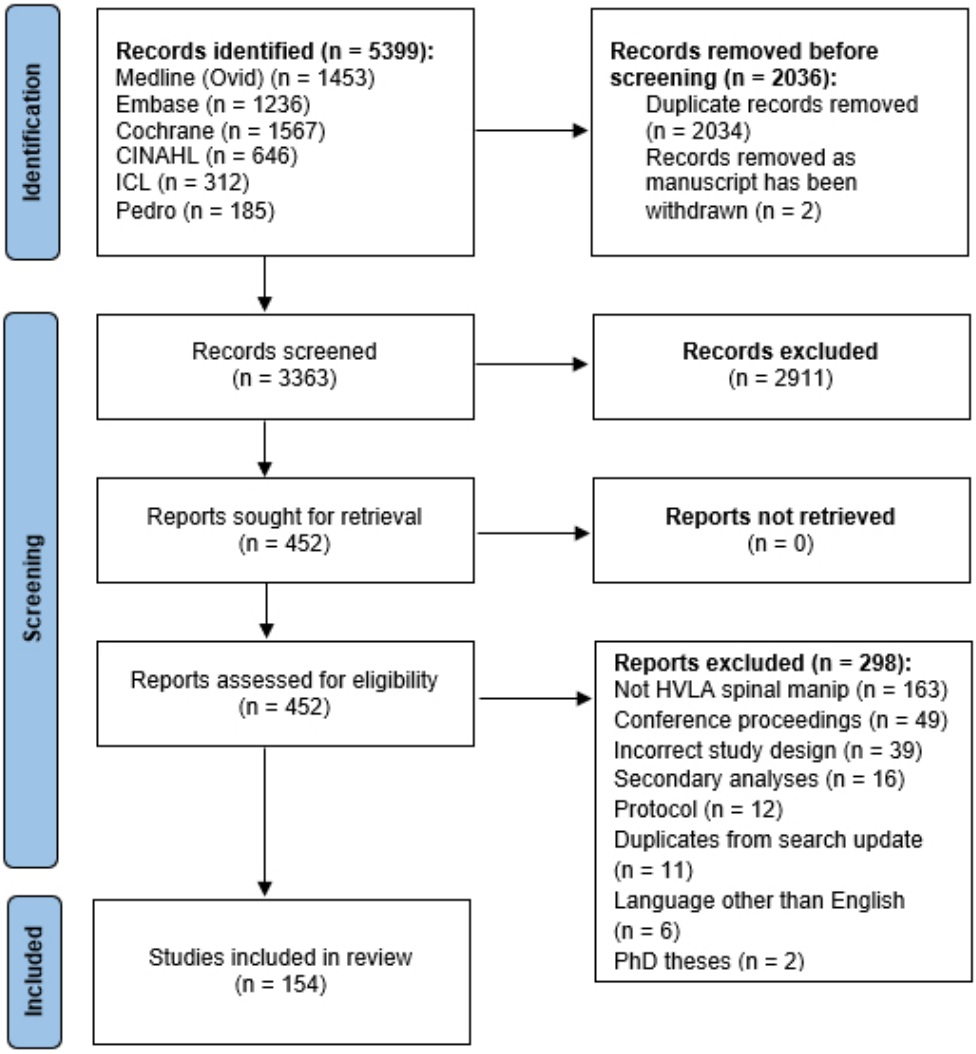

Figure 1: PRISMA flow-chart

351x381mm (38 x 38 DPI)

Appendix 1:

MEDLINE (Ovid) search strategy

	Searches
#1	((spine or spinal or medical) adj3 manip*).ti,ab,kw.
#2	(osteopath* or chiropract* or naprapath* or ((physiotherap* or (physical adj3 therap*)) and manip*)).ti,ab,kw.
#3	Manipulation, Chiropractic/ or Manipulation, Spinal/ or Musculoskeletal Manipulations/ or Manipulation, Osteopathic/
#4	1 or 2 or 3
#5	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
#6	4 and 5
#7	limit 6 to yr="2016 -Current"

CINAHL search strategy

	Query	Limiters/expanders
1	TI ((spine OR spinal OR medical) N3 manip*) OR AB ((spine OR spinal OR medical) N3 manip*)	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S2	TI (osteopath* OR chiropract* OR naprapath*) OR AB (osteopath* OR chiropract* OR naprapath*) OR TI (((physiotherap* OR (physical N3 therap*)) AND manip*) OR AB (((physiotherap* OR (physical N3 therap*)) AND manip*)	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S3	(MH "Manipulation, Chiropractic") OR (MH "Manipulation, Osteopathic")	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S4	S1 OR S2 OR S3	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S5	(MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample OR TI (randomised OR randomized) OR AB (random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR AB (control W5 group) OR MH (crossover design) OR MH (comparative studies) OR AB (cluster W3 RCT)) NOT ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human))	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S6	S4 AND S5	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S7	S4 AND S5	Limiters - Published Date: 20160101- Expanders - Apply equivalent subjects Search modes - Find all my search terms

Cochrane Library search strategy

	Advanced search	Limits
#1	((spine OR spinal OR medical) NEAR/3 manip*):ti,ab,kw	
#2	MeSH descriptor: [Musculoskeletal Manipulations] this term only	
#3	MeSH descriptor: [Manipulation, Spinal] explode all trees	
#4	MeSH descriptor: [Manipulation, Chiropractic] explode all trees	
#5	MeSH descriptor: [Manipulation, Osteopathic] explode all trees	
#6	osteopath*:ti,ab,kw	
#7	chiropract*:ti,ab,kw Limits 1160 − +	
#8	physiotherap*:ti,ab,kw OR (physical NEAR/3 therap*):ti,ab,kw) AND manip*:ti,ab,kw	
#9	naprapath*:ti,ab,kw	
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	in Trials
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	with Publication Year from 2016 to 2022, in Trials

Embase search strategy

	Query
#1	((spine OR spinal OR medical) NEAR/3 manip*):ti,ab,kw
#2	osteopath*:ti,ab,kw OR chiropract*:ti,ab,kw OR naprapath*:ti,ab,kw OR ((physiotherap*:ti,ab,kw OR ((physical NEAR/3 therap*):ti,ab,kw)) AND manip*:ti,ab,kw
#3	'chiropractic manipulation'/de OR 'musculoskeletal manipulation'/de OR 'spine manipulation'/de OR 'osteopathic manipulation'/de
#4	#1 OR #2 OR #3
#5	('randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab OR compare:ti OR compared:ti OR comparison:ti OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR ((open NEAR/1 label):ti,ab) OR (((double OR single OR doubly OR singly) NEAR/1 (blind OR blinded OR blindly)):ti,ab) OR 'double blind procedure'/de OR 'parallel group*':ti,ab OR crossover:ti,ab OR 'cross over':ti,ab OR (((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group* OR intervention* OR patient* OR subject* OR participant$)):ti,ab) OR assigned:ti,ab OR allocated:ti,ab OR ((controlled NEAR/7 (study OR design OR trial)):ti,ab) OR volunteer:ti,ab OR volunteers:ti,ab OR 'human experiment'/de OR trial:ti) NOT ((((random* NEAR/1 sampl* NEAR/7 ('cross section*' OR questionnaire$ OR survey* OR database$)):ti,ab) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomized controlled':ti,ab OR 'randomised controlled':ti,ab OR 'randomly assigned':ti,ab) OR ('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'randomized controlled':ti,ab OR 'randomised controlled':ti,ab OR "control group$":ti,ab)) OR ((case NEAR/1 control*) AND random*)) NOT ('randomized controlled':ti,ab OR 'randomised controlled':ti,ab) OR ('systematic review':ti NOT (trial:ti OR study:ti)) OR (nonrandom*:ti,ab NOT random*:ti,ab) OR 'random field*':ti,ab OR (('random cluster' NEAR/3 sampl*):ti,ab) OR (review:ab AND 'review':it NOT trial:ti) OR ('we searched':ab AND (review:ti OR 'review':it)) OR 'update review':ab OR ((databases NEAR/4 searched):ab) OR ((rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset$:ti) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de)))
#6	#4 AND #5
#7	#4 AND #5 AND [conference abstract]/lim
#8	#4 AND #5 NOT [conference abstract]/lim
#9	#4 AND #5 NOT [conference abstract]/lim AND [2016-2022]/py

ICL search strategy

	Query
S1	Subject:\"Manipulation, Chiropractic\" OR Subject:\"Manipulation, Spinal\" OR Subject:\"Manipulation, Osteopathic\"
S2	All Fields:spine OR All Fields:spinal OR All Fields:physiotherap*
S3	All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal
S4	All Fields:manip*
S5	All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal
S6	All Fields:manip* AND All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal
S7	All Fields:osteopath* OR All Fields:chiropract* OR All Fields:naprapath*
S8	Subject:\"Manipulation, Chiropractic\" OR Subject:\"Manipulation, Spinal\" OR Subject:\"Manipulation, Osteopathic\" OR All Fields:manip* AND All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal OR All Fields:osteopath* OR All Fields:chiropract* OR All Fields:naprapath*
S9	All Fields:random* OR All Fields:placebo OR All Fields:trial OR All Fields:groups OR All Fields:rct
S10	Subject:\"Manipulation, Chiropractic\" OR Subject:\"Manipulation, Spinal\" OR Subject:\"Manipulation, Osteopathic\" OR All Fields:manip* AND All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal OR All Fields:osteopath* OR All Fields:chiropract* OR All Fields:naprapath* AND All Fields:random* OR All Fields:placebo OR All Fields:trial OR All Fields:groups OR All Fields:rct
S11	, Year: from 2016 to 2022
S12	Subject:\"Manipulation, Chiropractic\" OR Subject:\"Manipulation, Spinal\" OR Subject:\"Manipulation, Osteopathic\" OR All Fields:manip* AND All Fields:spine OR All Fields:spinal OR All Fields:physiotherap* OR All Fields:\"physical therapy\" OR All Fields:\"physical therapist\" OR All Fields:\"physical therapists\" OR All Fields:spine OR All Fields:spinal OR All Fields:osteopath* OR All Fields:chiropract* OR All Fields:naprapath* AND All Fields:random* OR All Fields:placebo OR All Fields:trial OR All Fields:groups OR All Fields:rct AND , Year: from 2016 to 2022

PEDro search strategy

	Search records added since 01/01/2016
S1	spin* AND manip* AND RCT
S2	spin* AND manip* AND trial
S3	spin* AND manip* AND random*
S4	totally selected

Appendix 2: Included studies reference list

1. Albers J, Jakel A, Wellmann K, von Hehn U, Schmidt T. Effectiveness of 2 Osteopathic Treatment Approaches on Pain, Pressure-Pain Threshold, and Disease Severity in Patients with Fibromyalgia: A Randomized Controlled Trial. Complement Med Res. 2018;25(2):122–8.

2. Alonso-Perez JL, Lopez-Lopez A, La Touche R, Lerma-Lara S, Suarez E, Rojas J, et al. Hypoalgesic effects of three different manual therapy techniques on cervical spine and psychological interaction: A randomized clinical trial. J Bodyw Mov Ther. 2017;21(4):798–803.

3. Alvarenga BAP, Fujikawa R, Joao F, Lara JPR, Veloso AP. The effects of a single session of lumbar spinal manipulative therapy in terms of physical performance test symmetry in asymptomatic athletes: a single-blinded, randomised controlled study. BMJ Open Sport Exerc Med. 2018;4(1):e000389.

4. Aspinall SL, Jacques A, Leboeuf-Yde C, Etherington SJ, Walker BF. No difference in pressure pain threshold and temporal summation after lumbar spinal manipulation compared to sham: A randomised controlled trial in adults with low back pain. Musculoskelet Sci Pract. 2019;43:18–25.

5. Balbás-Álvarez L, Candelas-Fernández P, Del Corral T, La Touche R, López-de-Uralde-Villanueva I. Effect of manual therapy, motor control exercise, and inspiratory muscle training on maximum inspiratory pressure and postural measures in moderate smokers: A randomized controlled trial. J Manip Physiol Ther. 2018;41(5):372–82.

6. Bautista-Aguirre F, Oliva-Pascual-Vaca A, Heredia-Rizo AM, Bosca-Gandia JJ, Ricard F, Rodriguez-Blanco C. Effect of cervical vs. thoracic spinal manipulation on peripheral neural features and grip strength in subjects with chronic mechanical neck pain: a randomized controlled trial. Eur J Phys Rehabil Med. 2017;53(3):333–41.

7. Behrangrad S, Kamali F. Comparison of ischemic compression and lumbopelvic manipulation as trigger point therapy for patellofemoral pain syndrome in young adults: A double-blind randomized clinical trial. J Bodyw Mov Ther. 2017;21(3):554–64.

8. Bernal-Utrera C, Gonzalez-Gerez JJ, Anarte-Lazo E, Rodriguez-Blanco C. Manual therapy versus therapeutic exercise in non-specific chronic neck pain: a randomized controlled trial. Trials Electron Resour. 2020;21(1):682.

9. Boas Fernandes WV, Silveira Bicalho E, Capote AE, Ferretti Manffra E. Duration of the effects of spinal manipulation on pain intensity and electromyographic activity of paravertebral parts of individuals with chronic mechanical low back pain. Fisioter E Pesqui. 2016;23(2):155–62.

10. Boff TA, Pasinato F, Ben AJ, Bosmans JE, van Tulder M, Carregaro RL. Effectiveness of spinal manipulation and myofascial release compared with spinal manipulation alone on health-related outcomes in individuals with non-specific low back pain: randomized controlled trial. Physiother. 2020;10(7)71-80.

11. Bond BM, Kinslow CD, Yoder AW, Liu W. Effect of spinal manipulative therapy on mechanical pain sensitivity in patients with chronic nonspecific low back pain: a pilot randomized, controlled trial. J Man Manip Ther. 2020;28(1):15–27.

12. Bracht MA, Coan ACB, Yahya A, Dos Santos MJ. Effects of cervical manipulation on pain, grip force control, and upper extremity muscle activity: a randomized controlled trial. J Man Manip Ther. 2018;26(2):78–88.

13. Bronfort G, Maiers M, Schulz C, Leininger B, Westrom K, Angstman G, et al. Multidisciplinary integrative care versus chiropractic care for low back pain: a randomized clinical trial. Chiropr Man Ther. 2022;30(1):10.

14. Bruck K, Jacobi K, Schmidt T. Fascial treatment versus manual therapy (HVLA) in patients with chronic neck pain: A randomized controlled trial. J Back Musculoskelet Rehabil. 2021;04:04.

15. Cambron JA, Dexheimer JM, Duarte M, Freels S. Shoe Orthotics for the Treatment of Chronic Low Back Pain: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017;98(9):1752–62.

16. Carrasco-Martinez F, Ibanez-Vera AJ, Martinez-Amat A, Hita-Contreras F, Lomas-Vega R. Short-term effectiveness of the flexion-distraction technique in comparison with high-velocity vertebral manipulation in patients suffering from low-back pain. Complement Ther Med. 2019;44:61–7.

17. Carrasco-Uribarren A, Rodriguez-Sanz J, Lopez-de-Celis C, Perez-Guillen S, Tricas-Moreno JM, Cabanillas-Barea S. Short-term effects of the traction-manipulation protocol in dizziness intensity and disability in cervicogenic dizziness: a randomized controlled trial. Disabil Rehabil. 2021;20;1–9.

18. Castello Branco K, Moodley M. Chiropractic manipulative therapy of the thoracic spine in combination with stretch and strengthening exercises, in improving postural kyphosis in woman. Health SA Gesondheid. 2016;21(1):303–8.

19. Castro-Sanchez AM, Lara-Palomo IC, Mataran-Penarrocha GA, Fernandez-de-Las-Penas C, Saavedra-Hernandez M, Cleland J, et al. Short-term effectiveness of spinal manipulative therapy versus functional technique in patients with chronic nonspecific low back pain: a pragmatic randomized controlled trial. Spine J Off J North Am Spine Soc. 2016;16(3):302–12.

20. Castro-Sánchez AM, Gil-Martínez E, Fernández-Sánchez M, Lara-Palomo IC, Nastasia I, de los Ángeles Querol-Zaldívar M, et al. Manipulative therapy of sacral torsion versus myofascial release in patients clinically diagnosed posterior pelvic pain: A consort compliant randomized controlled trial. Spine J. 2021;21(11):1890-1899.

21. Chaibi A, Benth JS, Tuchin P, Russell MB. Chiropractic spinal manipulative therapy for migraine. A three-armed, single-blinded, placebo, randomized controlled trial. Eur J Neurol, 24: 143-153.

22. Cholewicki J, Popovich JM Jr, Reeves NP, DeStefano LA, Rowan JJ, Francisco TJ, et al. The effects of osteopathic manipulative treatment on pain and disability in patients with chronic neck pain: A single-blinded randomized controlled trial. PM&R: The Journal of Injury, Function and Rehabilitation. 2022; 1- 13. doi:10.1002/pmrj.12732.

23. Corum M, Aydin T, Medin Ceylan C, Kesiktas FN. The comparative effects of spinal manipulation, myofascial release and exercise in tension-type headache patients with neck pain: a randomized controlled trial. Complement Ther Clin Pract 2021; 43:10139.

24. Coste J, Medkour T, Maigne JY, Perez M, Laroche F, Perrot S. Osteopathic medicine for fibromyalgia: a sham-controlled randomized clinical trial. Ther Adv Musculoskelet Dis. 2021;13:1759720X211009017.

25. Crothers AL, French SD, Hebert JJ, Walker BF. Spinal manipulative therapy, Graston technique® and placebo for non-specific thoracic spine pain: A randomised controlled trial. Chiropr Man Ther. 2016;24:16. doi:10.1186/s12998-016-0096-9.

26. de Oliveira RF, Costa LOP, Nascimento LP, Rissato LL. Directed vertebral manipulation is not better than generic vertebral manipulation in patients with chronic low back pain: a randomised trial. J Physiother 2020; 66(3):174-179.

27. DeVocht JW, Vining R, Smith DL, Long C, Jones T, Goertz C. Effect of chiropractic manipulative therapy on reaction time in special operations forces military personnel: a randomized controlled trial. Trials Electron Resour. 2019;20(1):5.

28. Didehdar D, Kamali F, Yoosefinejad AK, Lotfi M. The effect of spinal manipulation on brain neurometabolites in chronic nonspecific low back pain patients: a randomized clinical trial. Ir J Med Sci. 2020;189(2):543–50.

29. Dishman JD, Burke JR, Dougherty P. Motor Neuron Excitability Attenuation as a Sequel to Lumbosacral Manipulation in Subacute Low Back Pain Patients and Asymptomatic Adults: A Cross-Sectional H-Reflex Study. J Manipulative Physiol Ther. 2018;41(5):363–71.

30. Dissing KB, Hartvigsen J, Wedderkopp N, Hestbaek L. Conservative care with or without manipulative therapy in the management of back and/or neck pain in Danish children aged 9 to 15: a randomised controlled trial nested in a school-based cohort. BMJ Open 2018;8(9):e021358.

31. Ditcharles S, Yiou E, Delafontaine A, Hamaoui A. Short-Term Effects of Thoracic Spine Manipulation on the Biomechanical Organisation of Gait Initiation: A Randomized Pilot Study. Front Hum Neurosci. 2017;11:343.

32. Dorron SL, Losco BE, Drummond PD, Walker BF. Effect of lumbar spinal manipulation on local and remote pressure pain threshold and pinprick sensitivity in asymptomatic individuals: a randomised trial. Chiropr Man Ther. 2016;24:47.

33. Dunning JR, Butts R, Mourad F, Young I, Fernandez-de-Las Peñas C, Hagins M, et al. Upper cervical and upper thoracic manipulation versus mobilization and exercise in patients with cervicogenic headache: a multi-center randomized clinical trial. BMC Musculoskelet Disord. 2016;17:64.

34. Dunning J, Butts R, Fernandez-de-Las-Penas C, Walsh S, Goult C, Gillett B, et al. Spinal manipulation and electrical dry needling in patients with subacromial pain syndrome: a multicenter randomized clinical trial. J Orthop Sports Phys Ther 2021;51(2):72-81.

35. Dunning J, Butts R, Zacharko N, Fandry K, Young I, Wheeler K, et al. Spinal manipulation and perineural electrical dry needling in patients with cervicogenic headache: a multi-center randomized clinical trial. Spine J. 2021;21(2):284-295.

36. Eklund A, Jensen I, Lohela-Karlsson M, Hagberg J, Leboeuf-Yde C, Kongsted A, et al. The nordic maintenance care program: Effectiveness of chiropractic maintenance care versus symptom-guided treatment for recurrent and persistent low back pain—a pragmatic randomized controlled trial. PLoS ONE. 2018;13(9):e0203029.

37. Engel RM, Gonski P, Beath K, Vemulpad S. Medium term effects of including manual therapy in a pulmonary rehabilitation program for chronic obstructive pulmonary disease (COPD): a randomized controlled pilot trial. J Man Manip Ther. 2016;24(2):80–9.

38. Erdem EU, Ünver B, Akbas E, Kinikli GI. Immediate effects of thoracic manipulation on cervical joint position sense in individuals with mechanical neck pain: A randomized controlled trial. J Back Musculoskelet Rehabil. 2021;34(5):735-742.

39. Espí-López GV, López-Bueno L, Vicente-Herrero MT, Martinez-Arnau FM, Monzani L. Efficacy of manual therapy on anxiety and depression in patients with tension-type headache. A randomized controlled clinical trial. Int J Osteopath Med. 2016;22:11–20.

40. Espi-Lopez GV, Lopez-Martinez S, Ingles M, Serra-Ano P, Aguilar-Rodriguez M. Effect of manual therapy versus proprioceptive neuromuscular facilitation in dynamic balance, mobility and flexibility in field hockey players. A randomized controlled trial. Phys Ther Sport. 2018;32:173–9.

41. Espi-Lopez GV, Rodriguez-Blanco C, Oliva-Pascual-Vaca A, Molina-Martinez F, Falla D. Do manual therapy techniques have a positive effect on quality of life in people with tension-type headache? A randomized controlled trial. Eur J Phys Rehabil Med. 2016;52(4):447–56.

42. Espi-Lopez GV, Zurriaga-Llorens R, Monzani L, Falla D. The effect of manipulation plus massage therapy versus massage therapy alone in people with tension-type headache. A randomized controlled clinical trial. Eur J Phys Rehabil Med. 2016;52(5):606–17.

43. Evans R, Haas M, Leininger B, Hanson L, Schulz C, Bronfort G. Spinal manipulation and exercise for low back pain in adolescents: a randomized trial. Glob Adv Health Med. 2018;7:200-201.

44. Fagundes Loss J, de Souza da Silva L, Ferreira Miranda I, Groisman S, Santiago Wagner Neto E, Souza C, et al. Immediate effects of a lumbar spine manipulation on pain sensitivity and postural control in individuals with nonspecific low back pain: a randomized controlled trial. Chiropr Man Ther. 2020;28(1):25.

45. Farazdaghi MR, Motealleh A, Abtahi F, Panjan A, Sarabon N, Ghaffarinejad F. Effect of sacroiliac manipulation on postural sway in quiet standing: a randomized controlled trial. Braz J Phys Ther 2018;22(2):120-126.

46. Fisher LR, Alvar BA, Maher SF, Cleland JA. Short-term Effects of Thoracic Spine Thrust Manipulation, Exercise, and Education in Individuals With Low Back Pain: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2020;50(1):24–32.

47. Ford JJ, Slater SL, Richards MC, Surkitt LD, Chan AYP, Taylor NF, et al. Individualised manual therapy plus guideline-based advice vs advice alone for people with clinical features of lumbar zygapophyseal joint pain: a randomised controlled trial. Physiotherapy. 2019;105(1):53–64.

48. Fosberg KK, Puentedura E, Schmitz B, Jain TK, Cleland JA. The Effects of Thrust Joint Manipulation on the Resting and Contraction Thickness of Transversus Abdominis in Patients With Low Back Pain: A Randomized Control Trial. J Manipulative Physiol Ther. 2020;43(4):339–55.

49. Fraix M, Badran S, Graham V, Redman-Bentley D, Hurwitz EL, Quan VL, et al. Osteopathic manipulative treatment in individuals with vertigo and somatic dysfunction: a randomized, controlled, comparative feasibility study. J Osteopath Med. 2021;121(1):71–83.

50. Fritz JM, Sharpe J, Greene T, Lane E, Hadizadeh M, McFadden M, et al. Optimization of Spinal Manipulative Therapy Protocols: A Factorial Randomized Trial Within a Multiphase Optimization Framework. J Pain. 2021;22(6):655–68.

51. Fritz JM, Lane E, McFadden M, Brennan G, Magel JS, Thackeray A, et al. Physical Therapy Referral From Primary Care for Acute Back Pain With Sciatica : a Randomized Controlled Trial. Ann Intern Med. 2021;174(1):8-17.

52. Galindez-Ibarbengoetxea X, Setuain I, Ramirez-Velez R, Andersen LL, Gonzalez-Izal M, Jauregi A, et al. Short-term effects of manipulative treatment versus a therapeutic home exercise protocol for chronic cervical pain: A randomized clinical trial. J Back Musculoskelet Rehabil. 2018;31(1):133–45.

53. Galindez-Ibarbengoetxea X, Setuain I, González-Izal M, Jauregi A, Ramírez-Velez R, Andersen LL, et al. Randomised controlled pilot trial of high-velocity, low-amplitude manipulation on cervical and upper thoracic spine levels in asymptomatic subjects. Int J Osteopath Med. 2017;25:6–14.

54. Galindez-Ibarbengoetxea X, Setuain I, Ramirez-Velez R, Andersen LL, Gonzalez-Izal M, Jauregi A, et al. Immediate Effects of Osteopathic Treatment Versus Therapeutic Exercise on Patients With Chronic Cervical Pain. Altern Ther Health Med. 2018;24(3):24–32.

55. Garcia-Perez-Juana D, Fernandez-de-las-Penas C, Arias-Buria JL, Cleland JA, Plaza-Manzano G, Ortega-Santiago R. Changes in cervicocephalic kinesthetic sensibility, widespread pressure pain sensitivity, and neck pain after cervical thrust manipulation in patients with chronic mechanical neck pain: a randomized clinical trial. J Manip Physiol Ther 2018;41(7):551-560.

56. Gattie E, Cleland JA, Pandya J, Snodgrass S. Dry Needling Adds No Benefit to the Treatment of Neck Pain: A Sham-Controlled Randomized Clinical Trial With 1-Year Follow-up. J Orthop Sports Phys Ther. 2021;51(1):37–45.

57. Gesslbauer C, Vavti N, Keilani M, Mickel M, Crevenna R. Effectiveness of osteopathic manipulative treatment versus osteopathy in the cranial field in temporomandibular disorders - a pilot study. Disabil Rehabil. 2018;40(6):631–6.

58. Ghasabmahaleh SH, Rezasoltani Z, Dadarkhah A, Hamidipanah S, Mofrad RK, Najafi S. Spinal manipulation for subacute and chronic lumbar radiculopathy: a randomized controlled trial. Am J Med 2021;134(1):135-141.

59. Goertz CM, Salsbury SA, Long CR, Vining RD, Andresen AA, Hondras MA, et al. Patient-centered professional practice models for managing low back pain in older adults: a pilot randomized controlled trial. BMC Geriatr. 2017;17(1):235.

60. Goertz CM, Salsbury SA, Vining RD, Long CR, Pohlman KA, Weeks WB, et al. Effect of spinal manipulation of upper cervical vertebrae on blood pressure: results of a pilot sham-controlled trial. J Manip Physiol Ther 2016;39(5):369-380.

61. Goertz CM, Xia T, Long CR, Vining RD, Pohlman KA, DeVocht JW, et al. Effects of spinal manipulation on sensorimotor function in low back pain patients--A randomised controlled trial. Man Ther. 2016;21:183–90.

62. Gomez F, Escriba P, Oliva-Pascual-Vaca J, Mendez-Sanchez R, Puente-Gonzalez AS. Immediate and short-term effects of upper cervical high-velocity, low-amplitude manipulation on standing postural control and cervical mobility in chronic nonspecific neck pain: a randomized controlled trial. J Clin Med 2020;9(8): 2580.

63. Gorrell LM, Beath K, Engel RM. Manual and instrument applied cervical manipulation for mechanical neck pain: a randomized controlled trial. J Manipulative Physiol Ther. 2016;39(5):319–29.

64. Grimes JK, Puentedura E, Cheng MS, Seitz AL. The comparative effects of upper thoracic spine thrust manipulation techniques in individuals with subacromial pain syndrome: a randomized clinical trial. J Orthop Sports Phys Ther 2019;49(10):716-724.

65. Griswold D, Learman K, Kolber MJ, O'Halloran B, Cleland JA. Pragmatically applied cervical and thoracic nonthrust manipulation versus thrust manipulation for patients with mechanical neck pain: a multicenter randomized clinical trial. J Orthop Sports Phys Ther 2018;48(3):137-145.

66. Groisman S, Malysz T, de Souza da Silva L, Rocha Ribeiro Sanches T, Camargo Bragante K, Locatelli F, et al. Osteopathic manipulative treatment combined with exercise improves pain and disability in individuals with non-specific chronic neck pain: a pragmatic randomized controlled trial. J Bodyw Mov Ther 2020; 24(2):189-195

67. Haas M, Bronfort G, Evans R, Schulz C, Vavrek D, Takaki L, et al. Dose-response and efficacy of spinal manipulation for care of cervicogenic headache: a dual-center randomized controlled trial. Spine J Off J North Am Spine Soc. 2018;18(10):1741–54.

68. Haider R, Bashir MS, Adeel M, Ijaz MJ, Ayub A. Comparison of conservative exercise therapy with and without Maitland Thoracic Manipulative therapy in patients with subacromial pain: Clinical trial. J Pak Med Assoc. 2018;68(3):381–7.

69. Haik MN, Alburquerque-Sendin F, Camargo PR. Short-Term Effects of Thoracic Spine Manipulation on Shoulder Impingement Syndrome: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017;98(8):1594–605.

70. Haleema B, Riaz H. Effects of thoracic spine manipulation on pressure pain sensitivity of rhomboid muscle active trigger points: A randomized controlled trial. J Pak Med Assoc. 2021;71(7):1720–4.

71. Hanney WJ, Puentedura EJ, Kolber MJ, Liu X, Pabian PS, Cheatham SW. The immediate effects of manual stretching and cervicothoracic junction manipulation on cervical range of motion and upper trapezius pressure pain thresholds. J Back Musculoskelet Rehabil. 2017;30(5):1005–13.

72. Hardas GM, Murrell GAC. Prospective, randomized, double-blind, placebo-controlled clinical trial assessing the effects of applying a force to C5 by a mechanically assisted instrument on referred pain to the shoulder. Spine 2018;43(7):461-466.

73. Harihara Prakash R, Mehta J, Patel D. Effect of thrust versus non-thrust mobilization directed at the thoracic spine in patients with mechanical neck pain: A randomized control trial. Natl J Physiol Pharm Pharmacol. 2020;10(10):878–83.

74. Hartstein AJ, Lievre AJ, Grimes JK, Hale SA. Immediate effects of thoracic spine thrust manipulation on neurodynamic mobility. J Manip Physiol Ther 2018;41(4):332-341.

75. Holt K, Niazi IK, Amjad I, Kumari N, Rashid U, Duehr J, et al. The Effects of 4 Weeks of Chiropractic Spinal Adjustments on Motor Function in People with Stroke: A Randomized Controlled Trial. Brain Sci. 2021;11(6):21.

76. Holt KR, Haavik H, Lee AC, Murphy B, Elley CR. Effectiveness of Chiropractic Care to Improve Sensorimotor Function Associated With Falls Risk in Older People: A Randomized Controlled Trial. J Manipulative Physiol Ther. 2016;39(4):267–78.

77. Javadov A, Ketenci A, Aksoy C. The efficiency of manual therapy and sacroiliac and lumbar exercises in patients with sacroiliac joint dysfunction syndrome. Pain Physician. 2021;24(3):223-233.

78. Joo S, Lee Y, Song CH. Immediate effects of thoracic spinal manipulation on pulmonary function in stroke patients: a preliminary study. J Manip Physiol Ther 2018;41(7):602-608.

79. Jordon MK, Beattie PF, D'Urso S, Scriven S. Spinal manipulation does not affect pressure pain thresholds in the absence of neuromodulators: a randomized controlled trial. J Man Manip Ther. 2017;25(4):172–81.

80. Joshi S, Balthillaya G, Neelapala YVR. Immediate effects of cervicothoracic junction mobilization versus thoracic manipulation on the range of motion and pain in mechanical neck pain with cervicothoracic junction dysfunction: a pilot randomized controlled trial. Chiropr Man Ther. 2020;28(1):38.

81. Kachmar O, Kushnir A, Matiushenko O, Hasiuk M. Influence of spinal manipulation on muscle spasticity and manual dexterity in participants with cerebral palsy: randomized controlled trial. J Chiropr Med 2018;17(3):141-150.

82. Kamali F, Zamanlou M, Ghanbari A, Alipour A, Bervis S. Comparison of manipulation and stabilization exercises in patients with sacroiliac joint dysfunction patients: A randomized clinical trial. J Bodyw Mov Ther. 2019;23(1):177–82.

83. Karas S, Olson Hunt MJ, Temes B, Thiel M, Swoverland T, Windsor B. The effect of direction specific thoracic spine manipulation on the cervical spine: a randomized controlled trial. J Man Manip Ther. 2018;26(1):3–10.

84. Kendall JC, French SD, Hartvigsen J, Azari MF. Chiropractic treatment including instrument-assisted manipulation for non-specific dizziness and neck pain in community-dwelling older people: a feasibility randomised sham-controlled trial. Chiropr Man Ther. 2018;26:14.

85. Laframboise MA, Vernon H, Srbely J. Effect of two consecutive spinal manipulations in a single session on myofascial pain pressure sensitivity: a randomized controlled trial. J Can Chiropr Assoc. 2016;60(2):137–45.

86. Langenfeld A, Humphreys BK, De Bie RA, Swanenburg J. Comparing manual and mechanically assisted manipulations of the thoracic spine in neck pain patients: A pilot study. F1000Research. 2018;7:156. doi.org/10.12688/f1000research.13780.

87. Lee KW, Kim WH. Effect of thoracic manipulation and deep craniocervical flexor training on pain, mobility, strength, and disability of the neck of patients with chronic nonspecific neck pain: a randomized clinical trial. J Phys Ther Sci 2016;28(1):175-180.

88. Lim KT, Hwang EH, Cho JH, Jung JY, Kim KW, Ha IH, et al. Comparative effectiveness of Chuna manual therapy versus conventional usual care for non-acute low back pain: a pilot randomized controlled trial. Trials Electron Resour. 2019;20(1):216.

89. Lisi AJ, Scheinowitz M, Saporito R, Onorato A. A Pulsed Electromagnetic Field Therapy Device for Non-Specific Low Back Pain: A Pilot Randomized Controlled Trial. Pain Ther. 2019;8(1):133–40.

90. Lohman EB, Pacheco GR, Gharibvand L, Daher N, Devore K, Bains G, et al. The immediate effects of cervical spine manipulation on pain and biochemical markers in females with acute non-specific mechanical neck pain: a randomized clinical trial. J Man Manip Ther. 2019;27(4):186–96.

91. Lopez-de-Uralde-Villanueva I, Beltran-Alacreu H, Fernandez-Carnero J, La Touche R. Pain management using a multimodal physiotherapy program including a biobehavioral approach for chronic nonspecific neck pain: a randomized controlled trial. Physiother Theory Pract. 2020;36(1):45–62.

92. Lopez-de-Uralde-Villanueva I, Candelas-Fernandez P, de-Diego-Cano B, Minguez-Calzada O, Del Corral T. The effectiveness of combining inspiratory muscle training with manual therapy and a therapeutic exercise program on maximum inspiratory pressure in adults with asthma: a randomized clinical trial. Clin Rehabil. 2018;32(6):752–65.

93. Lorenzo S, Nicotra CM, Mentreddy AR, Padia HJ, Stewart DO, Hussein MO, et al. Assessment of Pulmonary Function After Osteopathic Manipulative Treatment vs Standard Pulmonary Rehabilitation in a Healthy Population. J Am Osteopath Assoc. 2019; doi: 10.7556/jaoa.2019.026. Epub ahead of print. PMID: 30741314.

94. Luceno-Mardones A, Luceno-Rodriguez I, Rodriguez-Lopez ES, Oliva-Pascual-Vaca J, Rosety I, Oliva-Pascual-Vaca A. Effects of Osteopathic T9-T10 Vertebral Manipulation in Tonsillitis: A Randomized Clinical Trial. Healthcare. 2021;9(4):01.

95. Lynen A, Schömitz M, Vahle M, Jäkel A, Rütz M, Schwerla F. Osteopathic treatment in addition to standard care in patients with Gastroesophageal Reflux Disease (GERD) – A pragmatic randomized controlled trial. J Bodyw Mov Ther. 2022;29:223–31.

96. Lynge S, Dissing KB, Vach W, Christensen HW, Hestbaek L. Effectiveness of chiropractic manipulation versus sham manipulation for recurrent headaches in children aged 7–14 years - a randomised clinical trial. Chiropr Man Ther. 2021;29(1):1.

97. Maiers M, Hartvigsen J, Evans R, Westrom K, Wang Q, Schulz C, et al. Short or long-term treatment of spinal disability in older adults with manipulation and exercise. Arthritis Care Res 2019;71(11):1516-1524.

98. Marske C, Bernard N, Palacios A, Wheeler C, Preiss B, Brown M, et al. Fibromyalgia with Gabapentin and Osteopathic Manipulative Medicine: A Pilot Study. J Altern Complement Med. 2018;24(4):395–402.

99. McCarthy CJ, Potter L, Oldham JA. Comparing targeted thrust manipulation with general thrust manipulation in patients with low back pain. A general approach is as effective as a specific one. A randomised controlled trial. BMJ Open Sport Exerc Med 2019; 5(1):e000514.

100. Minarini G, Ford M, Esteves J. Immediate effect of T2, T5, T11 thoracic spine manipulation of asymptomatic patient on autonomic nervous system response: Single-blind, parallel-arm controlled-group experiment. Int J Osteopath Med. 2018;30:12–7.

101. Mintken PE, McDevitt AW, Cleland JA, Boyles RE, Beardslee AR, Burns SA, et al. Cervicothoracic Manual Therapy Plus Exercise Therapy Versus Exercise Therapy Alone in the Management of Individuals With Shoulder Pain: A Multicenter Randomized Controlled Trial. J Orthop Sports Phys Ther. 2016;46(8):617–28.

102. Moodley M, Craig M. The effect of sacroiliac chiropractic adjustments on innominate angles. Health SA Gesondheid. 2020;25:1398.

103. Motealleh A, Barzegar A, Abbasi L. The immediate effect of lumbopelvic manipulation on knee pain, knee position sense, and balance in patients with patellofemoral pain: A randomized controlled trial. J Bodyw Mov Ther. 2020;24(3):71–7.

104. Motealleh A, Gheysari E, Shokri E, Sobhani S. The immediate effect of lumbopelvic manipulation on EMG of vasti and gluteus medius in athletes with patellofemoral pain syndrome: A randomized controlled trial. Man Ther. 2016;22:16–21.

105. Moustafa IM, Diab AA, Taha S, Harrison DE. Addition of a Sagittal Cervical Posture Corrective Orthotic Device to a Multimodal Rehabilitation Program Improves Short- and Long-Term Outcomes in Patients With Discogenic Cervical Radiculopathy. Arch Phys Med Rehabil. 2016;97(12):2034–44.

106. Munoz-Gomez E, Ingles M, Serra-Ano P, Espi-Lopez GV. Effectiveness of a manual therapy protocol based on articulatory techniques in migraine patients. A randomized controlled trial. Musculoskelet Sci Pract. 2021;54:102386.

107. Nambi G, Kamal W, Es S, Joshi S, Trivedi P. Spinal manipulation plus laser therapy versus laser therapy alone in the treatment of chronic non-specific low back pain: a randomized controlled study. Eur J Phys Rehabil Med. 2018;54(6):880–9.

108. Nejati P, Safarcherati A, Karimi F. Effectiveness of Exercise Therapy and Manipulation on Sacroiliac Joint Dysfunction: A Randomized Controlled Trial. Pain Physician. 2019;22(1):53–61.

109. Nogueira N, Oliveira-Campelo N, Lopes Â, Torres R, Sousa ASP, Ribeiro F. The acute effects of manual and instrument-assisted cervical spine manipulation on pressure pain threshold, pressure pain perception, and muscle-related variables in symptomatic subjects: A randomized controlled trial. J Manip Physiol Ther. 2020;43(3):179–88.

110. Paanalahti K, Holm LW, Nordin M, Hoijer J, Lyander J, Asker M, et al. Three combinations of manual therapy techniques within naprapathy in the treatment of neck and/or back pain: a randomized controlled trial. BMC Musculoskelet Disord. 2016;23;17:176.

111. Page I, Descarreaux M. Effects of spinal manipulative therapy biomechanical parameters on clinical and biomechanical outcomes of participants with chronic thoracic pain: a randomized controlled experimental trial. BMC Musculoskelet Disord. 2019;18;20(1):29.

112. Papa L, Amodio A, Biffi F, Mandara A. Impact of osteopathic therapy on proprioceptive balance and quality of life in patients with dizziness. J Bodyw Mov Ther. 2017;21(4):866–72.

113. Paredes R, Crasto C, Magalhães B, Carvalho P. Short-Term Effects of Global Pelvic Manipulation on Knee Joint Position Sense in Asymptomatic Participants: A Double-Blind Randomized Controlled Trial. J Manipulative Physiol Ther. 2020;43(7):675–82.

114. Pascual-Vaca AO, Punzano-Rodríguez R, Escribá-Astaburuaga P, Fernández-Domínguez JC, Ricard F, Franco-Sierra MA, et al. Short-term changes in algometry, inclinometry, stabilometry, and urinary pH analysis after a thoracolumbar junction manipulation in patients with kidney stones. J Altern Complement Med. 2017;23(8):1–9.

115. Passmore SR, Johnson MG, Aloraini SM, Cooper S, Aziz M, Glazebrook CM. Impact of Spinal Manipulation on Lower Extremity Motor Control in Lumbar Spinal Stenosis Patients: A Small-Scale Assessor-Blind Randomized Clinical Trial. J Manipulative Physiol Ther. 2019;42(1):23–33.

116. Penza CW, Horn ME, George SZ, Bishop MD. Comparison of 2 Lumbar Manual Therapies on Temporal Summation of Pain in Healthy Volunteers. J Pain. 2017;18(11):1397–408.

117. Petrozzi MJ, Leaver A, Ferreira PH, Rubinstein SM, Jones MK, Mackey MG. Addition of MoodGYM to physical treatments for chronic low back pain: A randomized controlled trial. Chiropr Man Ther. 2019;27:54.

118. Qu L, Xing L, Norman W, Li M, Guo Y, Gao S, et al. Clinical effect of traditional Chinese spinal orthopedic manipulation in treatment of chondromalacia patellae. J Tradit Chin Med. 2016;36(6):718–23.

119. Qu LX, Xing LY, Wanda N, Chen H, Li MJ, Gao S, et al. A Clinical Observation of Functional Abdominal Pain Syndrome in Patients Treated by Traditional Chinese Spinal Orthopedic Manipulation. Chin J Integr Med. 2018;24(2):140–6.

120. Reynolds B, Puentedura EJ, Kolber MJ, Cleland JA. Effectiveness of cervical spine high velocity low amplitude thrust added to behavioral education, soft tissue mobilization, and exercise in individuals with temporomandibular disorder (TMD) with myalgia: a randomized clinical trial. J Orthop Sports Phys Ther 2020;50(8):455-465.

121. Rist PM, Bernstein C, Kowalski M, Osypiuk K, Connor JP, Vining R, et al. Multimodal chiropractic care for migraine: a pilot randomized controlled trial. Cephalalgia 2021;41(3):318-328.

122. Rodrigues PTV, Correa LA, Reis FJJ, Meziat-Filho NA, Silva BM, Nogueira LAC. One session of spinal manipulation improves the cardiac autonomic control in patients with musculoskeletal pain: a randomized placebo-controlled trial. Spine 2021;46(14):915-922.

123. Rodriguez-Sanz J, Malo-Urries M, Corral-de-Toro J, Lopez-de-Celis C, Lucha-Lopez MO, Tricas-Moreno JM, et al. Does the Addition of Manual Therapy Approach to a Cervical Exercise Program Improve Clinical Outcomes for Patients with Chronic Neck Pain in Short- and Mid-Term? A Randomized Controlled Trial. Int J Environ Res Public Health. 2020;17(18):10.

124. Rodriguez-Sanz J, Malo-Urries M, Lucha-Lopez MO, Perez-Bellmunt A, Carrasco-Uribarren A, Fanlo-Mazas P, et al. Effects of the Manual Therapy Approach of Segments C0-1 and C2-3 in the Flexion-Rotation Test in Patients with Chronic Neck Pain: A Randomized Controlled Trial. Int J Environ Res Public Health. 2021;18(2):17.

125. Romero del Rey R, Saavedra Hernandez M, Rodriguez Blanco C, Palomeque del Cerro L, Alarcon Rodriguez R. Short-term effects of spinal thrust joint manipulation on postural sway in patients with chronic mechanical neck pain: a randomized controlled trial. Disabil Rehabil 2022;44(8):1227-1233.

126. Rose KA, Kizhakkeveettil A, Kadar GE, Losack M. Combining Spinal Manipulation With Standard Counseling for Tobacco Cessation: Results of a Feasibility Randomized Clinical Trial. J Chiropr Med. 2017;16(1):41–8.

127. Sampath KK, Botnmark E, Mani R, Cotter JD, Katare R, Munasinghe PE, et al. Neuroendocrine Response Following a Thoracic Spinal Manipulation in Healthy Men. J Orthop Sports Phys Ther. 2017;47(9):617–27.

128. Sarker KK, Sethi J, Mohanty U. Effect of spinal manipulation on pain sensitivity, postural sway, and health-related quality of life among patients with non-specific chronic low back pain: A randomised control trial. J Clin Diagn Res. 2019;13(2):YC01–5.

129. Schulz C, Evans R, Maiers M, Schulz K, Leininger B, Bronfort G. Spinal manipulative therapy and exercise for older adults with chronic low back pain: a randomized clinical trial. Chiropr Man Ther. 2019;27:21.

130. Shin DC, Lee YW. The immediate effects of spinal thoracic manipulation on respiratory functions. J Phys Ther Sci. 2016;28(9):2547–9.

131. Silva AC da, Santos GM, Marques CM de G, Marques JLB. Immediate Effects of Spinal Manipulation on Shoulder Motion Range and Pain in Individuals With Shoulder Pain: A Randomized Trial. J Chiropr Med. 2019;18(1):19–26.

132. Simoni G, Bozzolan M, Bonnini S, Grassi A, Zucchini A, Mazzanti C, et al. Effectiveness of standard cervical physiotherapy plus diaphragm manual therapy on pain in patients with chronic neck pain: a randomized controlled trial. J Bodyw Mov Ther. 2021;26:481-491.

133. Soal LJ, Bester CM, Shaw BS, Yelverton C. Changes in chronic neck pain following the introduction of a visco-elastic polyurethane foam pillow and/or chiropractic treatment. Health SA Gesondheid. 2019;24:1099.

134. Sparks CL, Liu WC, Cleland JA, Kelly JP, Dyer SJ, Szetela KM, et al. Functional magnetic resonance imaging of cerebral hemodynamic responses to pain following thoracic thrust manipulation in individuals with neck pain: a randomized trial. J Manip Physiol Ther 2017;40(9):625-634.

135. Stepnik J, Kedra A, Czaprowski D. Short-term effect of osteopathic manual techniques (OMT) on respiratory function in healthy individuals. PLoS ONE Electron Resour. 2020;15(6):e0235308.

136. Sueki D, Almaria S, Bender M, McConnell B. The immediate and 1-week effects of mid-thoracic thrust manipulation on lower extremity passive range of motion. Physiother Theory Pract. 2020;36(6):720–30.

137. Telles JD, Schiavon MAG, Costa ACDS, Rampazo ÉP, Liebano RE. Hypoalgesic Effects of Transcutaneous Electrical Nerve Stimulation Combined With Joint Manipulation: A Randomized Clinical Trial. J Manipulative Physiol Ther. 2021;44(3):244-254.

138. Thomas JS, Clark BC, Russ DW, France CR, Ploutz-Snyder R, Corcos DM, et al. Effect of spinal manipulative and mobilization therapies in young adults with mild to moderate chronic low back pain: a randomized clinical trial. JAMA Netw Open 2020;3(8):e2022589.

139. Vaden CD, Holder JM, McCoy M, Sayers J, Holder AM. P300 wave outcomes in subluxation based chiropractic in residential addiction treatment: A randomized controlled clinical trial. Ann Vert Sublux Res. 2020;178–92.

140. Valenzuela PL, Pancorbo S, Lucia A, Germain F. Spinal Manipulative Therapy Effects in Autonomic Regulation and Exercise Performance in Recreational Healthy Athletes: A Randomized Controlled Trial. Spine. 2019;44(9):609–14.

141. Valera-Calero A, Lluch Girbes E, Gallego-Izquierdo T, Malfliet A, Pecos-Martin D. Endocrine response after cervical manipulation and mobilization in people with chronic mechanical neck pain: a randomized controlled trial. Eur J Phys Rehabil Med. 2019;55(6):792–805.

142. Vilas Boas Fernandes W, Pizzol FD, Capote AE, de Andrade Melo S, Carvalho Schleder J. Immediate effects of spinal manipulation in pain and global joint mobility in patients with chronic nonspecific low back pain. Man Ther Posturology Rehabil J. 2016;14:1–5.

143. Vining R, Long CR, Minkalis A, Gudavalli MR, Xia T, Walter J, et al. Effects of Chiropractic Care on Strength, Balance, and Endurance in Active-Duty U.S. Military Personnel with Low Back Pain: A Randomized Controlled Trial. J Altern Complement Med. 2020;26(7):592–601.

144. Vinuesa-Montoya S, Aguilar-Ferrándiz ME, Matarán-Peñarrocha GA, Fernández-Sánchez M, Fernández-Espinar EM. A preliminary randomized clinical trial on the effect of cervicothoracic

manipulation plus supervised exercises vs a home exercise program for the treatment of shoulder impingement. J Chiropr Med. 2017;16(2):85–93.

145. Wang SQ, Chen M, Wei X, Gao XX, Zhao GD. Clinical research on lumbar oblique-pulling manipulation in combination with sling exercise therapy for patients with chronic nonspecific low back pain. Rev Assoc Med Bras. 2019;65(6):886–92.

146. Wang Y, Xu M, Shi Y. Efficacy of spinal chiropractic manipulative therapy for adjusting the relationship between cervical facet joints to treat headache caused by acute mountain sickness. J Int Med Res. 2020;48(1):0300060519898005.

147. Ward J, Tyer K, Pourmoghaddam A. Immediate influence of lumbar spine manipulation on pain, functional reach, static balance, and walking gait kinematics of individuals with acute low back pain. Chiropr J Aust. 2018;46(2):135–50.

148. Wright AA, Donaldson M, Wassinger CA, Emerson-Kavchak AJ. Subacute effects of cervicothoracic spinal thrust/non-thrust in addition to shoulder manual therapy plus exercise intervention in individuals with subacromial impingement syndrome: a prospective, randomized controlled clinical trial pilot study. J Man Manip Ther. 2017;25(4):190–200.

149. Xia T, Long CR, Gudavalli MR, Wilder DG, Vining RD, Rowell RM, et al. Similar Effects of Thrust and Nonthrust Spinal Manipulation Found in Adults With Subacute and Chronic Low Back Pain: A Controlled Trial With Adaptive Allocation. Spine. 2016;41(12):E702–9.

150. Yao SC, Zwibel H, Angelo N, Leder A, Mancini J. Effectiveness of Osteopathic Manipulative Medicine vs Concussion Education in Treating Student Athletes With Acute Concussion Symptoms. J Am Osteopath Assoc. 2020;07:07.

151. Younes M, Nowakowski K, Didier-Laurent B, Gombert M, Cottin F. Effect of spinal manipulative treatment on cardiovascular autonomic control in patients with acute low back pain. Chiropr Man Ther. 2017;25:33.

152. Young IA, Pozzi F, Dunning J, Linkonis R, Michener LA. Immediate and Short-term Effects of Thoracic Spine Manipulation in Patients With Cervical Radiculopathy: A Randomized Controlled Trial. J Orthop Sports Phys Ther. 2019;49(5):299–309.

153. Zafereo J, Wang-Price S, Roddey T, Brizzolara K. Regional manual therapy and motor control exercise for chronic low back pain: a randomized clinical trial. J Man Manip Ther. 2018;26(4):193–202.

154. Zago J, Amatuzzi F, Rondinel T, Matheus JP. Osteopathic Manipulative Treatment Versus Exercise Program in Runners With Patellofemoral Pain Syndrome: A Randomized Controlled Trial. J Sport Rehabil. 2021;30(4):609–18.

Appendix 3: Risk of bias assessment of included studies

Author, year (reference)	Overall risk of bias assessment
Albers et al, 2018 (1)	Some concerns
Alonso-Perez et al, 2017 (2)	Low risk
Alvarenga et al, 2018 (3)	Some concerns
Aspinall et al, 2019 (4)	Low risk
Balbás-Álvarez et al, 2018 (5)	Low risk
Bautista-Aguirre et al, 2017 (6)	Some concerns
Behrangrad & Kamali, 2017 (7)	High risk
Bernal-Utrera et al, 2020 (8)	High risk
Fernandes et al, 2016 (9)	High risk
Boff et al, 2020 (10)	High risk
Bond et al, 2020 (11)	High risk
Bracht et al, 2018 (12)	Some concerns
Bronfort et al, 2022 (13)	High risk
Brück et al, 2021 (14)	Some concerns
Cambron et al, 2017 (15)	High risk
Carrasco-Martínez et al, 2019 (16)	High risk
Carrasco-Uribarren et al, 2021(17)	High risk
Castello Branco & Moodley, 2016 (18)	High risk
Castro-Sanchez et al, 2016 (19)	Low risk
Castro-Sanchez et al, 2021 (20)	Low risk
Chaibi et al, 2017 (21)	High risk
Cholewicki et al, 2021 (22)	High risk
Corum et al, 2021 (23)	High risk
Coste et al, 2021 (24)	High risk
Crothers et al, 2016 (25)	High risk
de Oliveira et al, 2020 (26)	Some concerns
DeVocht et al, 2019 (27)	Low risk
Didehdar et al, 2020 (28)	High risk
Dishman et al, 2018 (29)	High risk
Dissing et al, 2018 (30)	Low risk
Ditcharles et al, 2017 (31)	Some concerns
Dorron et al, 2016 (32)	Some concerns
Dunning et al, 2016 (33)	Low risk
Dunning et al, 2021 (34)	Some concerns
Dunning et al, 2021 (35)	Some concerns
Eklund et al, 2018 (36)	Low risk
Engel et al, 2016 (37)	High risk

Erdem et al, 2021 [38]	Some concerns
Espi-López et al, 2016 [39]	High risk
Espi-López et al, 2018 [40]	High risk
Espi-López et al, 2016 [41]	Some concerns
Espi-López et al, 2016 [42]	High risk
Evans et al, 2018 [43]	High risk
Fagundes Loss et al, 2020 [44]	Some concerns
Farazdaghi et al, 2018 [45]	Low risk
Fisher et al, 2020 [46]	High risk
Ford et al, 2019 [47]	High risk
Fosberg et al, 2020 [48]	Low risk
Fraix et al, 2021 [49]	High risk
Fritz et al, 2021 [50]	High risk
Fritz et al, 2021 [51]	High risk
Galindez-Ibarbengoetxea et al, 2018 [52]	High risk
Galindez-Ibarbengoetxea et al, 2017 [53]	High risk
Galindez-Ibarbengoetxea et al, 2018 [54]	High risk
Garcia-Perez-Juana et al, 2018 [55]	High risk
Gattie et al, 2021 [56]	Some concerns
Gesslbauer et al, 2018 [57]	High risk
Ghasabmahaleh et al, 2021 [58]	High risk
Goertz et al, 2017 [59]	High risk
Goertz et al, 2016 [60]	High risk
Goertz et al, 2016 [61]	High risk
Gomez et al, 2020 [62]	Some concerns
Gorrell et al, 2016 [63]	Some concerns
Grimes et al, 2019 [64]	Some concerns
Griswold et al, 2018 [65]	Some concerns
Groisman et al, 2020 [66]	Some concerns
Haas et al, 2018 [67]	Some concerns
Haider et al, 2018 [68]	High risk
Haik et al, 2017 [69]	High risk
Haleema et al, 2021 [70]	High risk
Hanney et al, 2017 [71]	High risk
Hardas & Murrell, 2018 [72]	Some concerns
Harihara Prakash et al, 2020 [73]	High risk
Hartstein et al, 2018 [74]	High risk
Holt et al, 2021 [75]	High risk
Holt et al, 2016 [76]	High risk

Javadov et al, 2021 [77]	High risk
Joo et al, 2018 [78]	High risk
Jordon et al, 2017 [79]	High risk
Joshi et al, 2020 [80]	High risk
Kachmar et al, 2018 [81]	Some concerns
Kamali et al, 2019 [82]	Low risk
Karas et al, 2018 [83]	High risk
Kendall et al, 2018 [84]	High risk
Laframboise et al, 2016 [85]	High risk
Langenfeld et al, 2018 [86]	Some concerns
Lee & Kim, 2016 [87]	High risk
Lim et al, 2019 [88]	High risk
Lisi et al, 2019 [89]	High risk
Lohman et al, 2019 [90]	High risk
Lopez-de-Uralde-Villanueva et al, 2020 [91]	High risk
Lopez-de-Uralde-Villanueva et al, 2018 [92]	Some concerns
Lorenzo et al, 2019 [93]	High risk
Luceno-Mardones et al, 2021 [94]	High risk
Lynen et al, 2022 [95]	High risk
Lynge et al, 2021 [96]	Some concerns
Maiers et al, 2019 [97]	Some concerns
Marske et al, 2018 [98]	High risk
McCarthy et al, 2019 [99]	High risk
Minarini et al, 2018 [100]	High risk
Mintken et al, 2016 [101]	High risk
Moodley & Craig, 2020 [102]	High risk
Motealleh et al, 2020 [103]	High risk
Motealleh et al, 2016 [104]	High risk
Moustafa et al, 2016 [105]	High risk
Munoz-Gomez et al, 2021 [106]	Some concerns
Nambi et al, 2018 [107]	Some concerns
Nejati et al, 2019 [108]	Some concerns
Nogueira et al, 2020 [109]	Some concerns
Paanalahti et al, 2016 [110]	High risk
Page & Descarreaux, 2019 [111]	High risk
Papa et al, 2017 [112]	High risk
Paredes et al, 2020 [113]	High risk
Pascual-Vaca et al, 2017 [114]	High risk
Passmore et al, 2019 [115]	High risk

Penza et al, 2017 [116]	Some concerns
Petrozzi et al, 2019 [117]	Low risk
Qu et al, 2016 [118]	High risk
Qu et al, 2018 [119]	Some concerns
Reynolds et al, 2020 [120]	High risk
Rist et al, 2021 [121]	High risk
Rodrigues et al, 2021 [122]	High risk
Rodriguez-Sanz et al, 2020 [123]	High risk
Rodriguez-Sanz et al, 2021 [124]	Some concerns
Romero Del Rey et al, 2022 [125]	Some concerns
Rose et al, 2017 [126]	High risk
Sampath et al, 2017 [127]	High risk
Sarker et al, 2019 [128]	Some concerns
Schulz et al, 2019 [129]	Some concerns
Shin & Lee, 2016 [130]	Some concerns
Silva et al, 2019 [131]	Some concerns
Simoni et al, 2021 [132]	High risk
Soal et al, 2019 [133]	High risk
Sparks et al, 2017 [134]	Some concerns
Stepnik et al, 2020 [135]	High risk
Sueki et al, 2020 [136]	High risk
Telles et al, 2021 [137]	Some concerns
Thomas et al, 2020 [138]	High risk
Vaden et al, 2020 [139]	High risk
Valenzuela et al, 2019 [140]	Some concerns
Valera-Calero et al, 2019 [141]	Some concerns
Vilas Boas Fernandes et al, 2016 [142]	Some concerns
Vining et al, 2020 [143]	Some concerns
Vinuesa-Montoya et al, 2017 [144]	Some concerns
Wang et al, 2019 [145]	High risk
Wang et al, 2020 [146]	High risk
Ward et al, 2018 [147]	High risk
Wright et al, 2017 [148]	Some concerns
Xia et al, 2016 [149]	High risk
Yao et al, 2020 [150]	High risk
Younes et al, 2017 [151]	High risk
Young et al, 2019 [152]	High risk
Zafereo et al, 2018 [153]	Some concerns
Zago et al, 2021 [154]	High risk

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P6-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	------
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	------
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P8

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P8-9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P8
Study characteristics	17	Cite each included study and present its characteristics.	Appendix2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P9-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P9-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-------
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	------
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	------
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	------
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P12-16
	23b	Discuss any limitations of the evidence included in the review.	P12-16
	23c	Discuss any limitations of the review processes used.	P16
	23d	Discuss implications of the results for practice, policy, and future research.	P16-17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	P3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P3
Competing interests	26	Declare any competing interests of review authors.	P4
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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