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Efficacy and safety of Osteopathic Manipulative Treatment: an overview of systematic reviews

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Abstract

Objective: To summarize the best available clinical evidence on the efficacy and safety of osteopathic manipulative treatment (OMT) for different conditions.

Design: Overview of systematic reviews (SRs) and meta-analyses (MAs). PROSPERO CRD42020170983

Data sources: An electronics search was performed using four databases such as PubMed, EMBASE, CINAHL and Scopus, from their inception until 28th March 2021.

Eligibility criteria for selecting studies: SRs and MAs of randomized controlled trials evaluating the efficacy and safety of OMT for any condition were included.

Data extraction and synthesis: Data were independently extracted by two authors. The AMSTAR2 checklist was used to assess the methodological quality of the SRs and MAs. The overview was conducted and reported according to Reporting Items for Systematic Reviews and Meta-Analysis statement.

Results: The literature search revealed nine SRs conducted between 2013 and 2020 with 55 primary trials, involving 3740 participants. The SRs reported a wide range of conditions including low back pain (LBP, four SRs), chronic non-specific neck pain (one SR), chronic non-cancer pain (one SR), paediatric (one SR), neurological (one SR) and irritable bowel syndrome (IBS, one SR). According to AMSTAR2, the methodological quality of the included

SRs was low or critically low. There is encouraging evidence of OMT's efficacy in pain relief and functional status improvement in chronic non-specific low back pain patients and pregnant or postpartum women with LBP. The evidence is preliminary for headache and IBS and inconsistent for paediatric conditions. No adverse events were reported in most SRs.

Conclusion: Based on the currently available SRs, OMT appears to be clinically effective for the treatment of musculoskeletal disorders. Conflicting evidence supports the efficacy of OMT for other conditions. Further well-conducted SRs and clinical trials to confirm and extend the use of OMT in some conditions are needed. OMT is generally safe for clinical application.

Keywords osteopathic manipulative treatment, AMSTAR2, randomized controlled trial, low back pain, neck pain, paediatric, headache.

Strengths and limitations of this study

- ♦ We provide a comprehensive summary of the evidence for the efficacy and safety of osteopathic manipulative treatment in any conditions.
- ♦ A strength of this overview is the quality assessment of the included systematic reviews and meta-analyses using the AMSTAR2 tool.
- ♦ There is a lack of evidence to support the effectiveness of osteopathic manipulative treatment in the management of several condition including headaches, irritable bowel syndrome and paediatric conditions. However, encouraging evidence supports the use of osteopathic manipulative treatment for treating musculoskeletal disorders primarily in chronic non-specific low back pain patients and pregnant or postpartum women with low back pain.

Introduction

Osteopathic medicine is a manual therapy that is part of the Complementary and Alternative Medicine (CAM), developed by Andrew Taylor Still in the late 1800s in the Midwestern USA[1]. This therapy is based on the principle that the structure (anatomy) and function (physiology) of the individual's body are closely integrated and that a person's well-being depends on the balance of neurological, musculoskeletal and visceral structures [1].

Osteopathic medicine is provided on almost every continent and, in 2020, a survey estimated that 196,861 osteopathic practitioners provide osteopathic care worldwide in 46 countries [2].

Osteopathic medicine plays an important role primarily in the musculoskeletal healthcare. A

recent survey conducted in Switzerland [3] on a sample of 1.144 patients showed that over 80% of patients had requested an osteopathic consultation for musculoskeletal pain (mainly low back pain, neck pain and headache). Similar results are reported by a survey conducted in the United Kingdom [4] on a sample of approximately 1.600 patients with pain in the lumbar spine, cervical spine and pelvic region. Finally, a prospective study on 14.000 patients in Quebec – Canada [5] reported musculoskeletal pain, localized in the spine, thorax, pelvis and limbs as the most common reason for osteopathic consultations.

Osteopathic manipulative treatment (OMT) is defined in the Glossary of Osteopathic Terminology as "The therapeutic application of manually guided forces by an osteopathic practitioner to improve physiologic function and/or support homeostasis that has been altered by somatic dysfunction" [6]. OMT refers to a number of various types of approaches and techniques such as myofascial release, mobilization, osteopathy in cranial field (OCF) and visceral manipulation, in order to optimize the body's normal self-regulating mechanisms, with the aim to solve somatic dysfunction (ICD-10-CM Diagnosis Code M99.00-09) defined as the impaired or altered function of related components of the somatic system (skeletal, arthrodial and myofascial structures, and their related vascular, lymphatic and neural elements) [1].

In recent years, a number of systematic reviews and meta-analyses have been published to evaluate the clinical efficacy and safety of osteopathic medicine for any conditions such as low back pain, neck pain and migraine. However, due to differences in methodologies and quality of systematic reviews, no clear conclusions were achieved. The aim of this overview is to summarize the best available clinical evidence on the efficacy and safety of OMT for different conditions. This overview may be relevant to clinicians and policy makers to better understand in which conditions osteopathic medicine can be an effective and safety complementary therapy.

Methods

The overview was conducted according to the Cochrane Handbook for the Systematic Review of Interventions (Cochrane Book) and reported following the Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [7-9]. The protocol of the overview has been registered on PROSPERO (CRD42020170983).

Eligibility criteria

Type of review

This overview included only systematic reviews (SRs) and meta-analyses (MAs), published as a full paper, of randomised controlled trials (RCTs), which are well known to be the gold

standard for evaluating the efficacy of an intervention. SRs evaluating the inter-rater or intra-rater reliability for any type of osteopathic approach were excluded. SRs and MAs evaluating both RCTs and controlled clinical trials were excluded if a sub-analysis for RCTs was not performed. SRs not meeting all eligibility overview criteria were excluded. For SRs in which criteria were not understandable, the primary studies were analysed.

Participants/Population

Participants were human, of any gender, age and clinical condition undergoing OMT. Reviews including osteopathic manipulation on animal models as well as on healthy volunteers were excluded.

Intervention

The intervention consists of OMT performed by osteopaths, osteopathic physicians or osteopathic trainees, who used a black box method or a specific protocol without any restriction of approach and technique based on manual assessment, diagnosis, and treatment in accordance with the osteopathic principle [1,2]. SRs including primary studies on both OMT and other complementary manual interventions were excluded if a sub-analysis was not independently performed for each manual treatment. To verify that osteopathic treatment was performed by osteopaths, the primary clinical trials were analysed.

Comparison

In order to retrieve all clinical evidence currently reviewed in SRs and MAs, the comparison group included placebo, sham OMT, light touch therapy, no treatment, waiting list, conventional treatment, physiotherapy or other complementary medicine treatments.

Setting

SRs with trials performed in any health-related settings and/or health promotion centres were considered.

Main outcomes

The main outcomes were any clinically relevant endpoint measures, depending on the clinical condition reported in the SRs.

Any adverse events caused by OMT were considered. Other types of outcomes such as prevalence of somatic dysfunction, inter-rater or intra-rater reliability for any type of osteopathic approach were excluded.

Search Strategy

A systematic literature search was carried out independently by two reviewers (D.B. and D.R.) using the following electronic databases: MEDLINE (PubMed), EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Scopus, all from their inception until

28th March 2021. No language or date restrictions were applied. The search strategy was performed using the following search terms: osteopathic manipulative treatment, osteopathic medicine, osteopathic manipulation, review, systematic review and meta-analysis. The references list of the included SRs and MAs as well as narrative reviews were widely perused for the identification of additional articles. Full details of the search strategy for PubMed are provided in *Appendix*.

Data collection and analysis

Study selection

The selection was performed independently by two authors (D.B. and D.R.). All the retrieved articles were imported into the 1.19.8 Mendeley software version and the duplicate publications were excluded. Potential eligible SRs and MAs were read in abstract and full text and independently evaluated by the two authors for inclusion in the overview. SRs and MAs were excluded if they did not meet the inclusion criteria, firstly at the title and abstract level, and then at the full-text level. Disagreements were resolved through discussion and consensus between the two review authors; if no agreement was reached, the third member of the review team (F.B.) was then consulted.

Data extraction and management

Two authors (D.B. and F.B.) independently extracted data using an Excel spreadsheet. We collected the following information (where available) from SRs and MAs: first author, year of publication and country of the corresponding author, date assessed as up to date, condition treated, number of included studies and participants, gender distribution and age, osteopathic interventions and co-interventions description, and number of treatments, control description, outcome measures, time points reported, reporting adverse events, primary studies quality assessment included in each SRs and MAs, GRADE (Grading of Recommendations Assessment, Development and Evaluation) results (see "Strategy for data synthesis" section for more details), MAs data, if any, and SRs main results. We reported the mean difference (MD) or standard mean difference (SMD), 95% confidence intervals (CI) and results of any test of heterogeneity reported in the relevant meta-analysis. Mean and standard deviation (SD) for continuous variables as well as median, interquartile (IQR) and range for discrete variables were calculated.

Assessment of methodological quality of included SRs and MAs

The methodological quality of the included SRs and MAs was assessed using the AMSTAR-2 tool which is designed to generate an overall rating based on weaknesses of some critical domains (items 2,4,7,9,11,13,15) [10]. AMSTAR-2 classifies the overall confidence of the results

into four levels: high, no or one non-critical weakness; moderate, more than one non-critical weakness; low, one critical flaw with or without non-critical weaknesses; and critically low, more than one critical flaw or without non-critical weaknesses [10]. The quality assessment was evaluated independently by two authors (D.B. and F.B.), with any disagreements resolved through discussion with the third author (D.R.).

Overlapping systematic reviews

According to recent guidelines [11,12] we have decided to count the primary studies present in more than one SR only once. When more than one systematic review (which investigates the same research question and uses the same primary studies) was identified, only the latest one was selected if it used the most rigorous criteria to evaluate the methodological quality of the studies.

Strategy for data synthesis

Due to the overlap of studies and heterogeneity between reviews with regard to outcome measures, a critical synthesis of results was performed. The methodological quality of RCTs can be evaluated using several scores including the Jadad score, the PEDro scale and the Cochrane risk of bias tool for randomized trials (RoB). Different versions of RoB are available, which refer to different updates of the Cochrane Handbook for the systematic reviews of intervention [13 14]. Moreover, for musculoskeletal disorders, the Cochrane Back and Neck Review Group (CBN Group, before named CBRG) has developed a specific RoB guideline [also for this guideline some versions are available [15-17]]. Because of several versions that bring to different judgments, in our overview, when possible, we have reported results (judgments) according to the last version of the RoB tool [17,18]. In table 1 author's judgments are reported while our update judgments are reported in the text. Once, meta-analysis was performed we reported the data synthesis used in the meta-analysis: effect size (ES) and heterogeneity. Effect-size was reported according to Cohen [19]. Briefly, a small effect was defined as MD less than 10% of the scale and SMD less than 0.5%, a medium effect as MD from 10% to 20% of the scale and SMD from 0.50% to 0.80%, and a large effect was defined as MD greater than 20% of the scale and SMD scores greater than 0.80% [19]. Concerning heterogeneity, the following thresholds were considered for the interpretation of the reported I^2 statistic that assessed heterogeneity: i) 0%to 40%: might not be important, ii) 30% to 60% may represent moderate heterogeneity, iii) 50% to 90% may represent substantial heterogeneity, iv) 75% to 100% considerable heterogeneity [18]. We reported the GRADE results as rated by the SR's Authors. According to the GRADE approach the quality of evidence for each outcome (considering the RoB, imprecision, inconsistency of results, indirectness of evidence and publication bias) can

fall into four categories: high quality evidence (further research is very unlikely to change confidence in the estimated effect), moderate quality (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate) and very low quality (there is great uncertainty about the estimate) [20].

Results

Literature search results and study selection

The literature search yielded 1754 potentially relevant articles, after eliminating duplicate articles (631), 1123 articles were screened (see Fig.1). After reading the titles and abstracts 40 full texts were selected for eligibility of which 31 were excluded (see Supplementary Table 1) and nine SRs were considered relevant and included in this overview.

Description of included reviews

This overview included nine SRs published between 2013 and 2020. Eight articles were published in English and one in Portuguese.

Six SRs focused on musculoskeletal conditions [21-26], and one each on paediatric [27], neurological [28] and visceral conditions [29]. Detailed information on the included SRs/MAs is available in Table 1 and 2. The SRs included 71 primary studies with 5577 participants. Considering the overlapping of 16 trials and 1837 participants, the primary trials were 55 with 3740 participants (Supplementary Table 2 and 3).

Musculoskeletal conditions

Low back pain

Four reviews [21-24] with 34 RCTs (41 comparators) and 3369 participants assessed the efficacy of OMT on low back pain (LBP) including acute LBP (ALBP), chronic LBP (CLBP), LBP with sciatica, CLBP with menopause symptoms, LBP in obese, acute non-specific LBP (ANSLBP), chronic non-specific LBP (CNSLBP) and /or LBP and pelvic girdle pain in pregnancy and postpartum. Considering overlapping, the effective trials were 22 with a total of 2053 participants.

The SR performed by De Oliveira et al. [21] considered LBP in obese, CLBP, CLBP with sciatica and LBP in menopause or pregnancy. The review included five trials with 278 participants, three RCTs were also reported in other two systematic reviews (see Supplementary Table 2 and 3 for details). Conflicting results derived from the primary studies. In the inter-group analysis, OMT was not effective in reducing pain in the majority of the trials. Of note, in all

RCTs, the results of functional outcomes were not analyzed. According to the PEDro tool, the methodological quality of the five RTCs was classified from fair to excellent (PEDro range: from 5 to 9 out of 11 points). Adverse events were not analyzed.

The SR of Franke et al. included fifteen trials with 1502 participants with CNSLBP and ANSLBP [22]. Ten trials (1141 participants) and nine RCTs (1046 participants) investigated the effectiveness of OMT on pain and functional status, respectively. Nine RCTs were also reported in other systematic reviews (see Supplementary Table 2 and 3 for details). The meta-analysis revealed a medium and small effect in reducing pain and in improving functional status, respectively, and a moderate-quality of evidence (downgraded due to inconsistency). Moreover, a considerable (pain) and a moderate (functional status) heterogeneity were found. Similar meta-analysis results (effect and heterogeneity) have also been evidenced in a sub-analysis evaluating the effectiveness of OMT in CNSLBP patients. The GRADE revealed a moderate-quality of evidence for pain and high-quality evidence for the functional status.

Three trials (4 comparators) with 242 participants evaluated the effectiveness of OMT versus obstetric care, sham ultrasound, and untreated, for NSLBP in pregnant women. A large and a medium effect in reducing pain and in improving functional status was identified, respectively. Considerable (pain) and substantial (functional status) heterogeneity were found. GRADE evaluation reported a low quality of evidence for both outcomes.

Two RCTs with 119 participants evaluated the effectiveness of OMT for NSLBP in postpartum (PP) women. A large effect of OMT in reducing pain and in improving functional status was identified. No heterogeneity was found. However, a moderate quality of evidence for both outcomes was revealed.

The methodological quality of all RCTs, evaluated using the RoB from the Cochrane Back Review Group [16], reported a low and a high risk of bias for thirteen and two RCTs, respectively. However, considering the last version of the CBRG [17], all RCTs have to be rated as high risk of bias [domains at high RoB (% of RCTs): care provider (100%), patient blinding (67%), outcome assessor blinding (67%), groups similar at baseline (27%), lack of intention to treat analysis use (27%), free of selective outcome report (13%), dropouts described + acceptable (7%), similar timing outcome assessment (7%) and compliance acceptable (7%)].

Adverse events were evaluated only in four out of the fifteen primary studies. Two RCTs reported minor adverse events such as stiffness and tiredness, one no adverse event and the last one evidenced adverse event that, however, were not related to the treatment intervention.

In another SR, Franke et al. [23] identified eight RCTs with 850 participants evaluating the efficacy of OMT on NSLBP and pelvic girdle pain in pregnancy (five RCTs, seven

comparisons) and on NSLBP in postpartum women (three trials and three comparisons) (see Supplementary Table 2 and 3 for overlapping). The pooled analysis of five RCTs with 677 pregnancy participants reported the efficacy of OMT in reducing pain and improving functional status; however, a medium effect and a considerable heterogeneity were revealed. The GRADE indicated a moderate quality of evidence.

Similar results have been reported from the meta-analysis of three studies with 173 postpartum participants. Indeed, although a significant effect in favour of OMT in reducing pain and improving functional status was reported, the MA also evidenced a large effect and a substantial/considerable heterogeneity for both outcomes. The GRADE revealed a low quality of evidence.

The methodological quality of the included studies using the CBRG, Version 2009 [16] reported a low risk of bias for all RCTs. Considering the CBNG [17], all RCTs have to be rated at high risk of bias [domains at high RoB (% of RCTs): patient binding (100%), care provider binding (100%), outcome assessor blinding (100%), dropouts described + acceptable (25%), group similar at the baseline (25%), intention to treat analysis (25%), similar timing outcome assessment (25%) and compliance acceptable (12%)].

Concerning the adverse events, one study reported occasional tiredness after treatment in some patients, two studies (personal communications to Authors SR) did not find adverse events and the remaining five studies did not analyze adverse events.

The SR by Dal Farra and colleagues [24] evaluated the effectiveness of osteopathic interventions, performed by any type of manual therapists, in CNSLBP patients. A subgroup analysis evaluating the effectiveness of OMT performed only by osteopaths identified six trials (8 comparisons) with 739 participants; five trials also reported in other two SRs (see Supplementary Table 2 and 3 for more details).

A significant effect, clinically relevant according to the Cochrane back and neck group, of OMT in reducing pain (medium effect) and improving functional status (small effect) was revealed.

However, a substantial heterogeneity and a low quality of evidence (GRADE) were reported for both outcomes.

A further sub-analysis, including two trials (3 comparisons) with 548 participants, did not find evidence of OMT efficacy on functional status after a long-term treatment (12 weeks follow-up). Low quality of evidence and no heterogeneity were reported. The methodological quality of the primary studies, evaluated using the CBNG version 2015 [17], reported a high risk of bias for all RCTs [domains at high RoB (% of RCTs): high risk of bias for care provider (100%),

patient blinding (50%), outcome assessor blinding (17 %), participant allocation (33%) and reporting bias (17%)]. With regard to adverse events, a trial reported an increase of back muscle spasticity in a patient treated with OMT.

Neck pain

Franke and colleagues [25], evaluating three RCTs (three comparators) with 123 participants, provided evidence that OMT exerted beneficial effects on chronic non-specific neck pain (CNSNP). Specifically, a medium effect size in reducing pain and moderate quality of evidence on pain outcome were reported. A low level of heterogeneity was found. However, the meta-analysis did not evidence a significant effect on functional status. The methodological quality of all RCTs, evaluated using the CBRG [16], reported a low risk of bias for all RCTs. Considering the CBNG [17], all RCTs have to be rated at high risk of bias [domains at high RoB (% of RCTs): patient blinding (67%), care provider (100%), outcome assessor blinding (67%), dropouts described + acceptable (33%) and intention to treat analysis (100%)]. No adverse events, assessed by one RCT and reported as personal communications to SR authors by the other two RCTs, occurred.

Chronic non-cancer pain (CNCP)

The SR by Rehman and colleagues [26] evaluated the efficacy of osteopathic interventions, performed by manual therapists, in chronic non-cancer pain. In seven out of 16 retrieved RCTs, OMT was performed by osteopaths (see supplementary tables 2 and 3 for overlapping). A pooled analysis, including six RCTs with 728 participants (six comparators), found the efficacy of OMT vs standard care in reducing pain severity (small effect size, moderate quality of evidence and low level of heterogeneity). Moreover, another pooled analysis including two trials with 486 participants revealed the efficacy of OMT vs standard care in improving disability (large effect size, moderate quality of evidence and no heterogeneity). Similarly, the pooled analysis of the other two trials with 210 participants found that OMT vs standard care improved quality of life (a medium effect, moderate quality of evidence and no heterogeneity). The methodological quality of the included studies was performed using a modified version of the Handbook of Cochrane [30] where only six domains were considered (random sequence generation, allocation concealment, blinding of participants, healthcare provider, outcome assessors, and dropout rates). According to this modified version, the quality of the RCTs was reported to be at high risk of bias [domains at high RoB (% of RCTs): for patient blinding (100%), care provider (100%), outcome assessor blinding (57%), random sequence generation (29%), participant allocation concealment (29%), and dropout > 20% (43%)]. Adverse events were not considered by the SR authors.

Paediatric conditions

A SR by Posadzky and colleagues [27] evaluated the efficacy of OMT in paediatric conditions. This review included seventeen RCTs involving a total of 887 participants with different conditions: cerebral palsy evaluated in two clinical studies involving a total of 197 participants, respiratory conditions evaluated in four trials involving 186 patients [obstructive apnoea one RCT, asthma two RCTs (in one study not reported the number of patients), bronchiolitis one RCT], otitis media evaluated in three trial involving a total of 167 participants, musculoskeletal function evaluated in three trials with 80 patients (idiopathic scoliosis one RCT, mandibular kinematics one RCT, postural asymmetry one RCT) and attention-deficit/hyperactivity disorder (77 participants), prematurity (101 participants), infantile colic (28 participants), congenital nasolacrimal duct obstruction (30 patients) and functional voiding (21 participants) individually assessed by one RCT. The single trials provided evidence that OMT exerted beneficial effects on congenital nasolacrimal duct obstruction (post-treatment), daily weight gain and length of hospital stay, dysfunctional voiding, infantile colic and postural asymmetry. By contrast, no significant effects of OMT on idiopathic scoliosis, obstructive apnoea or temporomandibular disorders compared with various control interventions have been evidenced by the single RCTs. For conditions in which more than one RCT has been performed (asthma, otitis media and cerebral palsy), contradictory results are reported. From the SR emerges that low-quality RCTs favoured OMT, while moderate and high-quality RCTs failed to find an OMT effectiveness. The vast majority of the RCTs were reported to be at high risk of bias (15 RCTs) [domains at high RoB (% of RCTs): allocation concealment (67%) patient blinding (67%), care provider (100%), outcome assessor blinding (50%), addressing of incomplete data (33%), selective outcome reporting (33%), adequate sequence generation (28%)] with unclear or low risk of bias for the remaining two RCTs.

In 11 RCTs adverse events were not mentioned. No adverse events or serious adverse events occurred in five trials and no adverse events related to OMT in one RCT.

Neurological conditions

The SR of Cerritelli and colleagues [28], including five RCTs for a total of 235 participants, evaluated two different types of primary headache: migraine (two RCTs, 147 participants) and tension-type headache (three RCTs, 88 participants). Although the two RCTs evaluating the efficacy in the migraine reported positive results in favour of OMT (mainly in pain intensity reduction), inter-group analysis was performed only in one RCT. Similarly, evidence has been reported for the tension type headache only when a within group analysis was performed; inter-group analyses reported conflicting results. The RCTs were reported to be at high risk of bias

[domains at high RoB (% of RCTs): care provider blinding (100%), participant blinding (60%) and allocation concealment (20%)]. Due to a high heterogeneity (different types of primary headaches, different outcome measures and variable length of follow-up) a meta-analysis was not conducted by the Authors. Adverse events, evaluated in two RCTs, did not occur.

Visceral conditions

In a SR, Muller and colleagues [29], including five primary studies and involving 204 participants, evaluated the efficacy of OMT in the treatment of irritable bowel syndrome (IBS). Although more RCTs are needed due to the small sample size and high heterogeneity (in outcome measures and follow-up period), the results indicated that OMT was effective in IBS. The methodological quality of all RCTs, evaluated using the CBRG [16], reported a low risk of bias for all RCTs. Considering the CBNG [17], all RCTs have to be rated at high risk of bias [domains at high RoB (% of RCTs): care provider (100%), outcome assessor blinding (60%), randomized (20%), patient blinding (20%), groups similar at the baseline (20%) and intention to treat analysis (20%)]. No adverse events occurred in the patients from all RCTs.

Methodological quality of included reviews

The summary of the finding of the AMSTAR-2 is provided in Table 1 and 3. According to the critical domain established in Shea et al. [10], seven [22-26 28,29] and two reviews [21,27]were rated as low and critically low quality, respectively.

Two of the nine SRs registered a protocol before beginning the study [24 26]. Eight SRs performed an appropriate literature search [22-29] and five SRs reported justification for the exclusion of primary studies [22,23,25,28,29]. All SRs [21-29] evaluated the risk of bias of the included studies and five SRs [22-26] carried out a meta-analysis and used appropriate methods for the statistical combination of findings. Eight SRs [22-29] accounted for the risk of bias when interpreting and discussing the results of the SR. Finally, domain 15 was rated as not applicable for all the SRs due to lack of a meta-analysis [21,27-29] or the inclusion in the meta-analysis of fewer than 10 trials [22-26].

Discussion

Osteopathic medicine, an alternative and complementary medicine (CAM), is a form of manual therapy used to normalize the structure-function relationship and to promote the body's own self-healing mechanism. In the last decade, CAM therapies have grown in use and popularity and, among these, many surveys have demonstrated an increasing interest in osteopathic medicine in patients with musculoskeletal disorders such as non-specific chronic low back pain and neck pain [31,32].

Recently, osteopathic medicine has been regulated in many countries including the USA, Australia, UK, Iceland, Denmark, Malta, Portugal, Switzerland, where it is a primary healthcare profession. In other countries, the regulation process has not yet been completed (i.e. Italy) or there is no legal recognition of the osteopathic profession [33]. In this context, we performed an overview to summarize the best available clinical evidence on the efficacy and safety of OMT. We identified nine SRs on the use of osteopathic care for the management of musculoskeletal, paediatric, visceral and neurological disorders with different effects and clinical relevance depending on the conditions.

From our overview emerge some relevant questionable problems related to the lack of appropriate guidelines for assessing the methodological quality of trials in manual therapy and problems due to inadequate reporting of trial methodology and results. In this regard, most of the trials included in the SRs reported a high or unclear risk of bias for blinding procedures: patient blinding, outcome assessor blinding and care provider blinding. In manual therapy, blinding is an issue as patients tend to be aware of the manual treatment and therapists cannot be blinded from the treatment intervention they deliver [34]. For participants-reported outcomes, for which the patient is the outcome assessor, such as for pain and functional status outcomes, blinding of patients is mandatory and therefore it is necessary to use, as control group, sham procedures (including light touch therapy) that simulate manipulation. These sham procedures should be reported in the RCTs; however, a lack of reporting placebo sham therapy procedures in both SRs and primary studies has been evidenced. It is important to note that although these findings have already been reported by Cerritelli et al. in 2016 [35], to date these suggestions have not been followed. More effort should be made to promote guidelines for designing the most reliable placebo for manual treatment to reduce the risk of bias for patient blinding.

Other issues that emerge from our overview is the lack of treatment description and timing of measuring outcomes (short and long-term) in the SRs as well as in primary trials. In osteopathic medicine, as in any other manual therapy, it is important to describe in adequate detail each phase of the intervention, including how and when they were administered, and when the outcomes are measured. Without a complete description of treatments, clinicians cannot reliably reproduce interventions that prove useful. Proper checklists for non-pharmacological treatments, such as the TIDieR checklist (Template for Intervention Description and Replication) and guide and the CONSORT (CONsolidated Standards of Reporting Trials) Statement for randomized non-pharmacological treatment studies, should be followed by clinical trial authors [36,37].

That said, our overview highlighted that evidence on the efficacy of OMT is: 1) limited and contradictory in the treatment of paediatric conditions (some conditions were evaluated by only one trial, some of which were of low methodological quality; contradictory results were obtained for conditions in which two RCTs were performed), 2) preliminary on headache and IBS and 3) encouraging in musculoskeletal disorders mainly in CNSLBP patients and LBP in pregnant or postpartum women.

The lack of solid evidence stems from a small sample size,[23,25-29] the presence of conflicting results [21,27,28] and a high heterogeneity [22-24,28,29]. Due to the different comparison interventions (i.e. physiotherapy, sham OMT, no treatment, usual obstetric care) population, type of intervention and outcome measures, a high heterogeneity was reported in the Mas [22-25]. Of note, reduced heterogeneity was found when the RCTs were pooled considering interventions and comparators [26].

According to AMSTAR-2, the methodological quality of the included SRs was rated low and critically low. Domain two was critical for 7 SRs. The lack of a written and registered protocol prior to conducting the review should ensure that review methods are transparent and reproducible, and adherence to this prespecified research plan [38]. These should help avoiding bias and unintended duplication of reviews.

Adverse events

Generally, manual therapies have been reported to be well tolerated and manual therapy-related adverse events are short-lived and mild or moderate in intensity [39]. In our overview, we have found that seven SRs [22-25,27-29] evaluated adverse events and from these SRs it emerges that no severe incident involving musculoskeletal, neurological, visceral and paediatric disorders occurs after OMT. The idea that manual therapies are safe should be demonstrated by adequately reporting any adverse events that arise during treatment. Specifically, adverse events should be assessed in each clinical trial and reported using an appropriate taxonomy and specific description to manual therapies [40,41].

Strengths and limitation

Numerous limitations can be found in our overview. First of all, considering our inclusion criteria, we may have missed some relevant SRs. Indeed, we included SRs by evaluating only RCTs (and not other study designs) in which OMT was performed by osteopathic physicians or osteopaths (and not by other manual therapists). Globally, two professional figures have emerged, largely due to different legal and regulatory systems around the world: osteopathic physicians, who are doctors with full and unlimited medical practice rights, and osteopaths who have obtained an academic and professional standards for diagnosing and practicing treatments

based on the principles of osteopathic philosophy. OMT is the core activity for both osteopathic physicians and osteopaths who follow the principles of osteopathic medicine by performing a personalized treatment according to the patient evaluation and subsequent tailoring [42]. Therefore, our decision to consider only osteopathic physicians or osteopaths arises from the premise of avoiding that the principles of osteopathic medicine are not followed. In this regard, we excluded six systematic reviews and, therefore, considering the overlapping, 12 RCTs were lost (see Supplementary Table 1 for details). According to our decision, a recent scoping review used more restrictive inclusion criteria considering only studies performed in the USA where OMT is practiced by osteopathic physicians [43]. Since RCTs are widely recognized as the best design for evaluating the efficacy of an intervention, we have also decided to include only SRs evaluating randomized controlled trials. In this regard, eight systematic reviews were excluded and considering the overlapping, 24 RCTs were lost (see Supplementary Table 1 for details).

Conclusion

In conclusion, this overview suggests that OMT could be effective in the management of musculoskeletal disorders, specifically with regards to CNSLBP patients and LBP in pregnant or postpartum women. By contrast, no conclusive evidence derived from SRs analyzing the OMT efficacy on other conditions (paediatric conditions, headache and IBS).

Although not all RCTs have investigated the safety of OMT, considering that not serious adverse events have been reported, OMT can be considered safe.

Nevertheless, our overview highlights the need to perform further well-conducted SRs as well as clinical trials (which have to follow the specific guidelines for non-pharmacological treatments) to confirm and extend the possible use of OMT in some conditions as well as its safety.

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Table 1. Characteristics of the included systematic reviews and meta-analyses.

First author, year, country of corresponding author, reference	Date assessed as up to date	Conditions	Trials number, participants number.	Gender distribution, Age (years)	Intervention (co-intervention): description. Number of treatments (SD).	Control or comparison description	Outcomes assessed	Time points reported	Main results	Adverse events	SR methodological quality
Musculoskeletal conditions: Low back pain											
De Oliveira Meirelles [21] 2013, Brazil,	NR	CLBP, CLBP in pregnancy, LBP with menopausal symptoms, LBP in obese, LBP with sciatica.	5 RCTs, 278 adults. 1 CLBP, 1 CLBP in pregnancy, 1 LBP with menopausal symptoms, 1 LBP in obese, 1 LBP with sciatica.	Gender:85% female,15% male. Mean age 40 (from 4 RCTs).	OMT (UOBC, SE): OCF, ART, HVLA, MRT, MET, range of motion technique. Treatments: median 10 (7-10)**	SUT, NT, SM, chemonucleolysis,	Pain: VAS, dichotomous pain, pain scale.	Treatment time: 2 weeks and 15 sessions (from 2 RCTs). Evaluation: 1 and 6 months (from 2 RCTs).	OMT improved LBP in comparison with no intervention (but not with SM).	NR	Critically low
Franke [22] 2014, Australia,	NR	ANSLBP, CNSLBP, NSLBP in pregnancy, NSLBP in PP	15 RCTs, 1502 adults. 10 NSLBP, 3 NSLBP in pregnancy, 2 NSLBP in PP.	Gender: NR. Mean age 36 (from 13 RCTs)	OMT (UC, heat &PT, UOBC, SE): NR. Treatments: median 4 (4-6)**	SUT, NT, SM, UC, PT, SWD.	Pain: VAS, NRS, MGPQ. Functional status: RMDQ, OPQ, ODI, LBP_DQ, Kinematic of thoracic/lumbar spine /pelvis during forward flexion, QBPDS.	Period: 2-9 weeks. 1- 3- 6 months.	OMT was effective in pain and functional status in ANSLBP, CNSLBP, NSLBP in pregnant and NSLBP in PP.	No serious AE (from 4 RCTs).	Low
Franke [23] 2017, Australia,	NR	ANSLBP, CNSLBP and /or pelvic pain during pregnancy and PP.	8 RCTs, 850 adults. 5 LBP in pregnancy, 3 LBP in PP.	Gender: 100% female, Mean age 29.5	OMT (UOBC): NR. Treatments: Pregnancy median 7 (5.5-7). Postpartum median 4 (4-4.5)**	SUT, NT, UC.	Pain: VAS, QVAS, FP. Functional status: RMDQ, QPP, QBPDS, PGPQ, OPQ.	Pregnancy: ranging from 3 to 9 weeks; follow-up 1 and 2 weeks. Postpartum: weeks. Follow-up 2 weeks	OMT significantly improved pain functional status in women with LBP during pregnancy and PP.	No serious AE (from 3 RCTs*)	Low
Dal Farra [24] 2020, Italy,	Inception to April 2020	CNSLBP	6 RCTs***** 739 adults	Gender: NPTC Mean age 46 (from 4 RCTs), median age 41 (29-51)**	OMT (SE, UC): HVLA, MET, CST, MFR, MVMA. Treatments: range 5-10 sessions, median 6 (5-8)**	SM, PT, SE	Pain: VAS. Functional status: RMDQ, ODI, SF-36, EQ-5D, BDI.	Ranging from 2 weeks to 6 months. Follow-up: from 1 month to 1 year.	OMT significantly improved pain and functional status in CNSLBP in the short-term (but not in the long-term).	No serious AE (from 5 RCTs). Increased back muscle spasticity in one occasion (from 1 RCT)	Low
Musculoskeletal conditions: Neck pain											
Franke [25] 2015, Australia,	NR	CNSNP	3 RCTs, 123 adults.	Gender: NR. Mean age 44.	OMT (SUT, UC): NR. Treatments: median 5 (5-6)**	SM, PT	Pain: VAS, NRS, NPPQ. Functional status: NDI, NQ.	Ranging from 1 to 12 weeks. Follow-up: 3 months (in 2 RCTs).	OMT significantly improved pain, but not functional status in CNSNP.	No serious AE (from 1 RCT).	Low
Musculoskeletal conditions: Chronic non-cancer pain											
Rehman [26] 2020, Canada,	Until July 2019	CNCP: Fibromyalgia, TMD, CNSLBP, CNSBP, CNSNP, CNP.	****** 7 RCTs, 759 adults. 1 Fibromyalgia, 1 TMD, 1 NSNP, 1 CNSBP, 2 CNSLBP, 1 CNSNP	Gender: 60% female, 40% male. Mean age 52 (from 5 RCTs), range 23-54 (from 2 RCTs).	OMT (non-steroidal medications, anti-inflammatory, analgesics and/or muscle relaxants, UC, SE, lumbar supports, physical therapies and CAM): MET, MFR, HVLA, BLT, CST, JA, MT, ST, FPR. Treatments: NR.	SUT, SE, PT, SC, use of an oral appliance, hot and/or cold packs, TENS, SM, LT, ROM activities, LTP.	Pain: VAS. Disability: RMDQ. SF-36, QOL	Duration of trial or follow-up period: ranging from 42 to 168 days (1-6 months).	OMT, in comparison to SC, was significantly effective in reducing pain and increasing disability as well as in improving QoL.	NR	Low

Paediatric conditions											
Posadzki [27] 2013, South Korea,	Inception to November 2012	Pediatric conditions: CP, respiratory conditions, OM, musculoskeletal function, ADHD, prematurity, IC, CNLDO, DV.	17 RCTs, 887 neonates/infants (from 16 RCTs). 2 CP, 4 respiratory conditions, 3 OM, 3 musculoskeletal function, 1 ADHD, 1 prematurity, 1 IC, 1 CNLDO, 1 DV	Gender: NR. Range from premature infants >28 weeks to 18 years.	OMT: VO, CST, OMT techniques (ART, BLT, BLM, CS, FPR, MET, MFR or rib-raising). Treatment: median 4 (3-5)**	UC, NT, SM, WL, SM+ placebo, SM+ Echinacea, postural drainage, bronchodilators.	Cerebral palsy: CHQ, GMFM-66, PEDI, WeeFIM. Respiratory: RR, EV, flow, MEP, PEF. Musculoskeletal: TM, SF, Kinesiographics (MO, MOV, MCV, OVA, CVA). Preterm infants: LOS, DWG. ADHD: Conners Scale. Infantile colic: MNHSCS. Otitis media: Antibiotic use, tympanograms, Audiometrics, SI, surgery -free months, reflectometer. CNLDO: FDT, MJT. Dysfunctional voiding: DV symptoms.	Cerebral Palsy: 6 months follow-up. Respiratory, Musculoskeletal, ADHD, congenital nasolacrimal duct obstruction, dysfunctional voiding: posttreatment. Prematurity: discharge from hospital.	No conclusive evidence on the efficacy of OMT for any pediatric condition due to i) low methodological quality of RCTs (when conditions were evaluated by individual RCTs) and ii) contradictory results for the conditions under which two RCTs were performed.	AE not reported in 11 RCTs. No AE (from 4 RCTs). Four patients had aggravation of vegetative symptoms after OMT (from 1 RCT).	Critically low
Neurological conditions											
Cerritelli [28] 2017, Italy,	Inception to April 2016	Primary headache: migraine, tension-type headache	5 RCTs, 235 adults. 2 migraine, 3 headache	Gender: 78 % female, 22% male (from 3 RCTs). Mean age 39.4 (from 3 RCTs)	OMT (UC, triptans, PMR): NBT (in 3 studies), use of protocols (in 2 studies). Treatment: median 4 (3-5)**	UC, SM, OE, PMR, rest	HIT-6 score, HF, WD, PI, DC.	Ranging from 1 to 6 months. Follow-up: 1, 3, 6 months.	OMT reduced pain intensity, frequency and disability in patients with headache.	No specific AE (from 2 RCTs)	Low
Visceral conditions											
Muller [29] 2014, Australia,	Inception to October 2013	Irritable bowel syndrome	5 RCTs. 204 adults.	Gender: 79% female, 21% male (from 3 RCTs). Mean age 47	OMT: applied to different body region, VO (approach on the abdomen and spine, abdomen and sacrum), NBT. Treatments: median 5 (3-5)**	UC, SM.	Pain: VAS. Constipation, diarrhea, AD, RS, CTT, meteorism. IBS severity score, FIS score, HAD, BDI, IBSQoL2000. FBDSI	Ranging from 1 week to 3 months. Follow-up: short-term (2, 4 weeks), long-term (3, 12 months)	OMT, in comparison to sham therapy or standard care, reduced the symptoms of IBS, such as abdominal pain, constipation, diarrhea, and improved general well-being.	No AE	Low

*In personal communications from authors of two RCTs, **median (Q1-Q3), ***The number is not reported for a RCT on asthma, ****Reported in methods but not performed, ***** subgroup analysis, ******13 RCTs only, 7 trials were used in our study.******* the outcomes measures are not reported in all studies. AD: abdominal distension, ADHD: attention deficit /hyperactivity disorder, AE: adverse events, ANSLBP: acute nonspecific low back pain, ART: articulatory treatment, BDI: Beck Depression Index, BLM: Balanced membranous tension, BLT: Balanced ligamentous tension, CHQ: child health questionnaire, CNLDO: congenital nasolacrimal duct obstruction, CNCP: chronic non-cancer pain, CNSBP: chronic non-specific body pain, CNLBP: chronic nonspecific low back pain, CNSNP: chronic nonspecific neck pain, CNP: chronic neck pain, CP: cerebral palsy, CS: counterstains, CST: cranial sacral therapy, CTT: colonic transit time, CVA: cranial vault asymmetry, CV4: a technique in cranial field, compression of the fourth ventricle, DV: dysfunctional voiding, DC: drug consumption, DWG: daily weight gain, EV: expiratory volume, FBDSI: functional bowel disorder severity Index, FDT: fluorescein disappearance test, FIS: fatigue impact scale, FP: frequency of pain, FPR: facilitated positional release, GMFM-66: gross motor function measure-66, HAD: hospital anxiety and depression, HF: headache frequency, HIT-6: headache impact test-6, HVLA: high velocity low amplitude thrust, IAT: immediately after treatment, IBS: irritable bowel syndrome, IBSQoL 2000: IBS quality of life, IC: infantile colic, JA: joint articulation, LBP-DQ: low back pain disability questionnaire, LBP: low back pain, LOS: length of stay, LT: light touch, LTP: laser therapy, MCV: maximal closing velocity, MEP: mid expiratory phase, MET: muscle energy treatment, MFR: myofascial release, MGPD: Mc Gill pain questionnaire, MNHSCS: modified numbers of hours spent crying and sleeping, MJT: modified jones test, MO: maximal mouth opening, MOV: maximal opening velocity, MRT: myofascial release treatment, MT: membranous tension, MVMA: medium velocity medium amplitude, NBT: need based treatment, NDI: Neck Disability Index, NP: not performed, NPPQ: Northwick park pain questionnaire, NPTC : not possible to calculate, NR: not reported, NRS: numeric rating scale, NQ: Nordic questionnaire, NSNP: non-specific neck pain, NT: no treatment, OCF: osteopathy in cranial field, ODI: oswestry disability Index, OE: osteopathic evaluation, OM: otitis media, OMT: osteopathic manipulative treatment, OPQ: oswestry pain questionnaire, Pedi: pediatric evaluation of disability inventory, PEF: peak expiratory flow, PGPQ: pelvic girdle pain questionnaire, PI: pain intensity, PMR: progressive muscular relaxation exercise, PP: postpartum, PT. physical therapy, QBPDS: Quebec back pain disability scale, QPP: questionnaire postpartum, QVAS: quadruple visual analogue scale, RMDQ: Roland Morris disability questionnaire, ROM: range of movement, RR: respiratory rate, RS: rectal sensitivity, SC: standard care, SD: standard deviation, SE: specific exercise, SF: spine flexibility, SI: surgical intervention, SM: sham manipulation, ST: Spencer technique, SUT: sham ultrasound treatment, SWD: short-wave diathermy, TENS: transcutaneous electrical nerve stimulation, TM: Trunk morphology, TMD: temporomandibular disorder, UC: usual care, UOBC: usual obstetrical care, VAS: visual analogic scale, VO: visceral osteopathy, WD: work disability, WL: waiting list, WeeFIM: functional independence measure for children

Table 2. Quality of the primary RCTs included in the systematic reviews/meta-analyses and meta-analyses quantitative results.

First author, year, country of corresponding author, reference	Primary studies quality. GRADE	Meta-analysis data
Musculoskeletal conditions: Low back pain		
De Oliveira Meirelles [21] 2013 Brazil,	Pedro score: 6 (2 RCTs), 9 (1 RCT), 7 (1 RCT), 5 (1 RCT).	NP
Franke [22] 2014 Australia,	Low RoB (13 RCTs, low risk of bias in at least 6 categories). High RoB (2 RCTs). **GRADE.** *1. ANSLBP and CNSLBP.* Pain and Functional status: MODERATE. *2. CNSLBP.* Pain: MODERATE, Functional status: HIGH. 3. *NSLBP in Pregnancy.* Pain: LOW, Functional status: LOW. *4.NSLBP in PP.* Pain: MODERATE, Functional status: MODERATE	*ANSLBP and CNSLBP:* Pain: [MD -12.91; 95% CI: -20.00, -5.82]. I^2=86%. Functional status: [SMD -0.36; 95% CI; -0.58, -0.14]. I^2=57% *CNSLBP:* Pain [MD -14.93; 95% CI; -25.18, -4.68]. I^2= 89%. Functional status [SMD -0.32; 95% CI: -0.58, -0.07]. I^2=49% *NSLBP in pregnant women:* Pain [MD -23.01; 95% CI: -44.13, -1.88]. I^2= 91% Functional status [SMD -0.80; 95% CI: -1.36, -0.23]. I^2=76% *NSLBP in PP women:* Pain [MD -41.85; 95% CI: -49.43, -34.27)]. I^2=0%. Functional status [SMD -1.78; 95% CI: -2.21, -1.35]. I^2=0%.
Franke [23] 2017 Australia,	Low RoB (all RCTs, low risk of bias in at least 6 categories). **GRADE:** *1. LBP in pregnancy:* Pain MODERATE; Functional status: MODERATE. *2. LBP in PP:* Pain: LOW, Functional status: LOW.	*LBP in pregnancy:* Pain: [MD -16.75; 95% CI: -31.79, -1.72]. I^2=94%. Functional status: [SMD -0.50; 95% CI: -0.93, -0.07]. I^2=84%. *LBP in PP:* Pain: [MD -38.00; 95% CI: 46.75, -29.24]. I^2=68%. Functional status: [SMD -2.12; 95% CI: -3.02, - 1.22]. I^2=81%.
Dal Farra [24] 2020, Italy,	High RoB (all RCTs). **GRADE.** *CNSLBP* Pain: LOW, Functional status: LOW. Functional status (12 weeks follow-up): LOW.	*CNSLBP* Pain [SMD -0.57; 95% CI: -0.90, -0.25]. I^2=72%. Functional status [SMD -0.34; 95% CI: - 0.65, -0.03]. I^2=71%. Functional status 12 weeks follow-up: [SMD -0.14; 95%CI: -0.31, 0.03]. I^2=0%.
Musculoskeletal conditions: Neck pain		
Franke [25] 2015, Australia,	Low RoB (all RCTs, low risk of bias in at least 6 categories). **GRADE:** *CNSNP* Pain: MODERATE, Functional status: MODERATE.	*CNSNP* Pain: [MD -13.04, 95% CI: -20.4, -5.44]. I^2=34%. Functional status [SMD: -0.38, 95%CI: -0.88, 0.11]. I^2=0%
Musculoskeletal conditions: Chronic non-cancer pain		
Rehman [26] 2020, Canada,	High RoB (all RCTs, based on a modified RoB with 6 domains). **GRADE:** *CNCP* Pain: MODERATE, Disability: MODERATE, Quality of life: MODERATE.	*CNCP* Pain (OMT vs SC) [SMD - 0.37; 95% CI: - 0.58, -0.17]. I^2=25%. Disability (OMT vs SC) [SMD -1.04; 95% CI: - 1.23, -0.85]. I^2= 0%. Quality of life (OMT vs SC) [SMD 0.67; 95% CI: 0.29, 1.05]. I^2=0%.
Pediatric conditions		
Posadzki [27] 2013, South Korea,	High risk (all RCTs).	NP
Neurology conditions		
Cerritelli [28] 2017, Italy,	JADAD NR*. The majority of RCTs have high or unclear RoB.	NP
Visceral conditions		
Muller [29] 2014, Australia,	Low RoB (all RCTs, low risk of bias in at least 6 categories).	NP

*Reported in methods but not performed. ANSLBP: acute non-specific low back pain, CNCP: chronic non-cancer pain, CNSBP: chronic non-specific body pain, CNSLBP: chronic non- specific low back pain, CNSNP: chronic non-specific neck pain, CNP: chronic neck pain, MD: mean difference, NP: not performed, NR: not reported, OMT: osteopathic manipulative treatment, PP: postpartum, RCT: randomized controlled trial, RoB: Risk of Bias, SC: standard care, SMD: standard mean difference.

Table 3. Quality of the included systematic reviews by the Amstar2 tool.

ID, Author, Year,	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9 RCT	Q9 NRSI	Q10	Q11 RCT	Q11 NRSI	Q12	Q13	Q14	Q15	Q16	Ranking of quality
Musculoskeletal conditions																			
De Oliveira Meirelles [21]	N	N	N	N	N	N	N	PY	Y	N/A	N	N/A	N/A	N/A	N	N	N/A		CRITICALLY LOW
Franke [22]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Franke [23]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Dal Farra[24]	Y	Y	Y	Y	Y	Y	N	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Franke [25]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Rehman [26]	Y	Y	N	Y	Y	Y	N	PY	Y		N	Y	N/A	Y	Y	Y	N/A		LOW
Pediatric conditions																			
Posadzki [27]	Y	N	N	PY	Y	Y	N	PY	Y	N/A	Y	N/A	N/A	N/A	Y	Y	N/A		CRITICALLY LOW
Neurology conditions																			
Cerritelli [28]	Y	N	N	Y	Y	Y	Y	Y	Y	N/A	Y	N/A	NA	N/A	Y	Y	N/A		LOW
Visceral conditions																			
Muller [29]	Y	N	N	PY	Y	Y	Y	PY	Y	N/A	N	N/A	N/A	N/A	Y	N	N/A		LOW

Y, yes; PY, partial yes; N, no; N/A, not applicable.

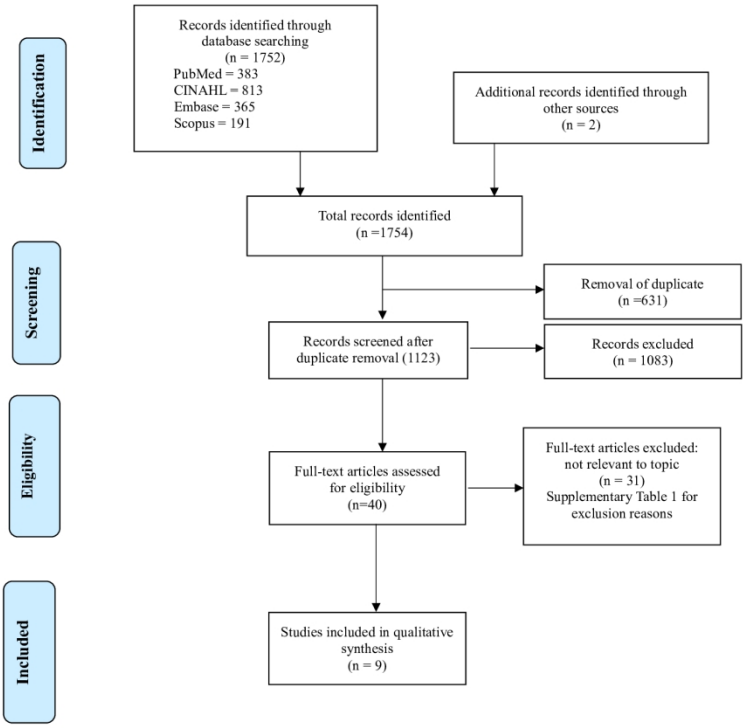

Figure 1: Flow diagram of screened articles.

209x297mm (200 x 200 DPI)

Appendix

Search Strategy: MEDLINE (PubMed)

01. osteopathic manipulative treatment ti.ab
02. osteopathic manipulation ti.ab.
03. osteopathic manipulative treatments ti.ab.
04. osteopathic medicine ti.ab.
05. osteopathic manipulative medicine ti.ab.
06. osteopathic manipulative medicine Mesh
07. osteopathic medicine Mesh
08. osteopathic manipulative treatment Mesh
09 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10. meta-analysis ti.ab.
11. metaanalysis ti.ab.
12 systematic review ti.ab.
13 review ti.ab.
14 10 OR 11 OR 12 OR 13
15 9 AND 14

Supplementary Table 1. Excluded systematic reviews.

Authors/Year	Title	Reason for exclusion
Spiegel et al., 2003 [1]	Osteopathic manipulative medicine in the treatment of hypertension: An alternative, conventional approach.	Narrative review.
Gamber et al., 2005 [2]	Cost-effective osteopathic manipulative medicine: a literature review of cost-effectiveness analyses for osteopathic manipulative treatment.	Evaluation of OMT cost-effectiveness.
Licciardone et al., 2005 [3]	Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials.	The SR included primary studies in which the intervention was not OMT.
Jäkel et al., 2011[4]	Therapeutic effects of cranial osteopathic manipulative medicine: a systematic review.	The SR included primary studies in healthy volunteers.
Posadzki et al., 2011 [5]	Osteopathy for musculoskeletal pain patients: A systematic review of randomized controlled trials.	The SR included primary studies in healthy volunteers and intervention was not OMT.
Orrock et al., 2013 [6]	Osteopathic intervention in chronic non-specific low back pain: a systematic review.	Overlap: 2 out of 2 studies. This SR was update by Franke 2014[22].
Cerritelli et al., 2015 [7]	Osteopathic manipulative treatment in neurological diseases: systematic review of the literature.	The SR included any study design.
Cicchitti et al., 2015 [8]	Chronic inflammatory disease and osteopathy: a systematic review.	The SR included study with an animal model and any type of study designs.
Majchrzycki et al., 2015 [9]	Application of osteopathic manipulative technique in the treatment of back pain during pregnancy.	The SR included primary studies in which the intervention was not OMT.
Vasconcelos et al., 2015 [10]	Effect of osteopathic maneuvers in the treatment of asthma: review of literature.	The SR included primary studies in which intervention was not OMT and any type of study design.
Guillard et al., 2016[11]	Reliability of diagnosis and clinical efficacy of cranial osteopathy: a systematic review.	The SR included primary study in which the intervention was not OMT.
Ruffini et al., 2016 [12]	Osteopathic manipulative treatment in gynecology and obstetrics: A systematic review.	The SR included any study designs.
Veloso et al., 2016 [13]	Osteopathic Manipulation Treatment on postural balance: a systematic review.	The SR included any study designs.
Raguckas et al.,2016 [14]	Osteopathic considerations in obstructive pulmonary disease: A systematic review of the evidence.	The SR included any study designs.
Do Vale et al., 2017 [15]	Effectiveness of the osteopathic treatment in intestinal constipation: A systematic review	Clinical outcomes are not reported.
Steel et al., 2017 [16]	Osteopathic manipulative treatment: A systematic review and critical appraisal of comparative effectiveness and health economics research.	The SR included any study designs.
Lanaro et al., 2017 [17]	Osteopathic manipulative treatment showed reduction of length of stay and costs in preterm infants.	The SR included RCTs and controlled clinical trials.
Guillaud et al., 2018 [18]	Reliability of diagnosis and clinical efficacy of visceral osteopathy: A systematic review.	The SR included primary study in which the intervention was not OMT.
Saracutu et al., 2018 [19]	The effects of osteopathic treatment on psychosocial factors in people with persistent pain: A systematic review.	The SR included primary studies in which the intervention was not OMT.
Sposato et al.2018 [20]	Osteopathic manipulative treatment in surgical care: short review of research publication in osteopathic Journals during the period 1990 to 2017.	The SR included any study designs.
Verhaeghe et al., 2018 [21]	Osteopathic care for spinal complaints: A systematic literature review.	The SR included primary studies in which the intervention was not OMT.
Verhaeghe et al., 2018 [22]	Osteopathic care for low back pain and neck pain. A cost-utility analysis.	Health economic evaluation of osteopathic care in low back pain and neck pain. Data about clinical outcomes were not completely reported.
Whalen et al., 2018 [23]	A Short Review of the Treatment of Headaches Using Osteopathic Manipulative Treatment.	The SR included primary studies in which the intervention was not OMT and any type of study design.
Rechberger et al, 2019 [24]	Effectiveness of an osteopathic treatment on the autonomic nervous system: a systematic review of the literature.	The SR included any type of study design, primary studies in healthy participants and intervention was not OMT.
Switters et al. 2019 [25]	Is visceral manipulation beneficial for patients with low back pain? A systematic review of the literature.	The SR included primary studies in which the intervention was not OMT.
Buscemi et al., 2020 [26]	Endocannabinoids release after osteopathic manipulative treatment. A brief review.	The SR included any study designs.

Santiago et al. 2020 [27]	Instrumentation used to assess pain in osteopathic interventions: A critical literature review.	Clinical outcomes are not reported.
Kiepe et al., 2020 [28]	Effects of osteopathic manipulative treatment on musicians: A systematic review.	The SR included any study designs.
Baroni et al., 2021 [29]	Osteopathic manipulative treatment and the Spanish flu: a historical literature review.	Historical review evaluating which OMT technique were administered in patients during the 1918 Spanish flu pandemic.
Tramontano et al., 2021 [30]	Vertigo and balance disorders- The role of osteopathic manipulative treatment: A systematic review.	The SR included any study designs and primary study in healthy participants.
De Marsh et al., 2021[31]	Pediatric osteopathic manipulative medicine: A scoping review.	The SR included any study designs.

OMT: osteopathic manipulative treatment, RCTs: randomized controlled trials.

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Supplementary Table 2. Summary of identified systematic reviews with overlapping.

Total SRs (n=9)	**Total**	**overlapping**	**Total**
Total trials	71	16	55
Total participants	5577	1837	3740
Musculoskeletal conditions (6 SRs) [21-26]			
Total trials	44	14	30
Total participants	4251	1837	2414
Trials low back pain	34	12	22
Participants low back pain	3369	1316	2053
Trials neck pain	3	0	3
Participants neck pain	123	0	123
Trials chronic non-cancer pain	7	2	5
Participants chronic non-cancer pain	759	521	238
Paediatric conditions (1 SR)[27]			
Trials pediatrics conditions	17	0	17
Participants pediatric conditions	887	0	887
Neurological conditions (1 SR) [28]			
Trials primary headache	5	0	5
Participants primary headache	235	0	235
Visceral conditions (1 SR) [29]			
Trials irritable bowel syndrome	5	0	5
Participants irritable bowel syndrome	204	0	204

SR: systematic review.

Supplementary Table 3. Identified SRs with studies overlapping.

Franke 2014 [22]		**De Oliveira 2013** [21]		**Dal Farra 2020** [24]		**Rehman 2020** [26]		**Franke 2017** [23]	
Primary studies	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**
Chown 2008	71			Chown 2008	131*	Albers 2018	48	Rohrich 2014	56
Gibson 1985	97					Cuccia 2010	50	Beltz 2014	41
Licciardone 2003	71	Licciardone 2003	71	Licciardone 2003	98**	Licciardone 2003	66	Schwerla 2015	30
Licciardone 2010	144	Licciardone 2010	144					Licciardone 2010	144
Licciardone 2013	455	Cleary 1994	12	Licciardone 2013	455	Licciardone 2013	455	Hensel 2015	45
Mandara 2008	94	Burton 2000	30	Mandara 2008	94	Papa 2012	72		
Peters 2006	57					Schwerla 2008	37	Peters 2006	57
Grundemann 2013	41					Stepnik 2018	31	Gundemann 2013	41
Recknagle 2007	39			De Oliveira 2019	38			Recknagle 2007	39
Vismara 2012	21	Vismara 2012	21	Vismara 2012	21				
Anderson 1999	155								
Adorjàn - Schaumann 1999	57								
Heinze 2006	60								
Cruser 2012	60								
Schwerla 2012	80								
Trials 15	**TP 1502**	**Trials 5**	**TP 278**	**Trials 6**	**TP 739**	**Trials 7**	**TP 759**	**Trials 8**	**TP 858**

TP, Total Participants. *OMT group counted twice and considered exercise group even if drop-out are >40%. **participants at 6 months, OMT counted twice.

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
Title			
	#1	Identify the report as an overview of systematic reviews.	1
Abstract			
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	3

Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	3
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	3-4
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, and date last searched.	4-5
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-5 Appendix
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the overview).	5
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	5
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	5
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	5-6. This is an overview therefore we used the AMSTAR2 tool.
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7

Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	6-7. Meta-analysis was not performed
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a This is an overview
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a. However, an overlapping analysis of the primary clinical trial was performed. 6
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1, Supplementary Table 1.
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	7-12 Table 1
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	This is an overview therefore we used the AMSTAR2 tool. 12 Table 3
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals.	Table 2
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	7-12 Meta- analysis was not performed
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a. This is an overview

Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplementary Table 2 and 3
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	12-14
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	15

BMJ Open

Efficacy and safety of osteopathic manipulative treatment: an overview of systematic reviews

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053468.R1
Article Type:	Original research
Date Submitted by the Author:	01-Dec-2021
Complete List of Authors:	Bagagiolo, Donatella; Scuola Superiore di Osteopatia Italiana, Research Department Rosa, Debora; Laboratory of Cardiovascular Neural and Metabolic Sciences Borrelli, Francesca; University of Naples Federico II, Department of Pharmacy
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Paediatrics, Neurology, Public health
Keywords:	COMPLEMENTARY MEDICINE, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Functional bowel disorders < GASTROENTEROLOGY, Migraine < NEUROLOGY

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Efficacy and safety of osteopathic manipulative treatment: an overview of systematic reviews

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Abstract

Objective: To summarize the available clinical evidence on the efficacy and safety of osteopathic manipulative treatment (OMT) for different conditions.

Design: Overview of systematic reviews (SRs) and meta-analyses (MAs). PROSPERO CRD42020170983

Data sources: Electronics search was performed using seven databases: PubMed, EMBASE, CINAHL, Scopus, JBI, Prospero and Cochrane Library, from their inception until 13th November 2021.

Eligibility criteria for selecting studies: SRs and MAs of randomized controlled trials evaluating the efficacy and safety of OMT for any condition were included.

Data extraction and synthesis: Data were independently extracted by two authors. The AMSTAR2 checklist was used to assess the methodological quality of the SRs and MAs. The overview was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Results: The literature search revealed nine SRs conducted between 2013 and 2020 with 55 primary trials, involving 3740 participants. The SRs reported a wide range of conditions including low back pain (LBP, four SRs), chronic non-specific neck pain (one SR), chronic non-cancer pain (one SR), paediatric (one SR), neurological (one SR) and irritable bowel syndrome (IBS, one SR). According to AMSTAR2, the methodological quality of the included

SRs was low or critically low. There is encouraging evidence of OMT's efficacy in pain relief and functional status improvement in chronic non-specific low back pain patients and pregnant or postpartum women with LBP. The evidence is preliminary for headache and IBS and inconsistent for paediatric conditions. No adverse events were reported in most SRs.

Conclusion: Based on the currently available SRs, OMT appears to be clinically effective for the treatment of musculoskeletal disorders. Conflicting evidence supports the efficacy of OMT for other conditions. Further well-conducted SRs and clinical trials to confirm and extend the use of OMT in some conditions as well as to corroborate its safety, are needed.

Keywords: low back pain, migraine disorders, neck pain, osteopathic manipulative treatment, paediatric, pregnancy, randomized controlled trial.

Strengths and limitations of this study

- ♦ This systematic overview included the comprehensive literature search for evidence on the efficacy and safety of osteopathic manipulative treatment.
- ♦ The present overview was conducted according to the Cochrane Handbook for the Systematic Review of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).
- ♦ The inclusion criteria were restricted to systematic reviews and meta-analyses of randomized controlled trials that included patients with any conditions.
- ♦ The quality of the evidence of the included systematic reviews and meta-analyses was assessed according to the AMSTAR-2 tool.

Introduction

Osteopathic medicine, depending on different legal and regulatory structures around the world, is a medical profession (USA), an allied health profession (e.g. UK) or a part of Complementary and Alternative Medicine (e.g. Italy or France). Developed by Andrew Taylor Still in the late 1800s in the Midwestern USA[1], this therapy is based on the principle that the structure (anatomy) and function (physiology) of the individual's body are closely integrated and that a person's well-being depends on the balance of neurological, musculoskeletal and visceral structures[1].

Osteopathic medicine is provided on almost every continent and, in 2020, a survey estimated that 196,861 osteopathic practitioners provide osteopathic care worldwide in 46 countries[2].

Osteopathic medicine plays an important role primarily in the musculoskeletal healthcare. A recent survey conducted in Switzerland[3] on a sample of 1.144 patients showed that over 80% of patients had requested an osteopathic consultation for musculoskeletal pain (mainly low back pain, neck pain and headache). Similar results are reported by a survey conducted in the United Kingdom[4] on a sample of approximately 1.600 patients with pain in the lumbar spine, cervical spine and pelvic region. Finally, a prospective study on 14.000 patients in Quebec – Canada[5] reported musculoskeletal pain, localized in the spine, thorax, pelvis and limbs as the most common reason for osteopathic consultations.

Osteopathic manipulative treatment (OMT) is defined in the Glossary of Osteopathic Terminology as "The therapeutic application of manually guided forces by an osteopathic practitioner to improve physiologic function and/or support homeostasis that has been altered by somatic dysfunction"[6]. OMT refers to a number of various types of approaches and techniques such as myofascial release, mobilization, osteopathy in cranial field (OCF) and visceral manipulation, in order to optimize the body's normal self-regulating mechanisms. The OMT aim is to solve somatic dysfunction (ICD-10-CM Diagnosis Code M99.00-09), although other care aspects have been proposed[1,7].

In recent years, a number of systematic reviews and meta-analyses have been published to evaluate the clinical efficacy and safety of osteopathic medicine for any conditions such as low back pain, neck pain and migraine. However, due to differences in methodologies and quality of systematic reviews, no clear conclusions were achieved. The aim of this overview is to summarize the available clinical evidence on the efficacy and safety of OMT for different conditions. This overview may be relevant to clinicians and policy makers to better understand in which conditions osteopathic medicine can be an effective and safety complementary therapy.

Methods

The overview was conducted according to the Cochrane Handbook for the Systematic Review of Interventions (Cochrane Book) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[8-10]. The protocol of the overview has been registered on PROSPERO (CRD42020170983).

Patient and public involvement statement. For this overview of systematic reviews and meta-analyses, patient or public were not involved.

Eligibility criteria

Type of review

This overview included only systematic reviews (SRs) and meta-analyses (MAs), published as a full paper, of randomised controlled trials (RCTs), which are well known to be the gold standard for evaluating the efficacy of an intervention[11]. SRs evaluating the inter-rater or intra-rater reliability for any type of osteopathic approach were excluded. SRs and MAs evaluating both RCTs and controlled clinical trials were excluded if a sub-analysis for RCTs was not performed. SRs not meeting all eligibility overview criteria were excluded. For SRs in which criteria were not understandable, the primary studies were analysed.

Participants/Population

Participants were human, of any gender, age and clinical condition undergoing OMT. Reviews including osteopathic manipulation on animal models as well as on healthy volunteers were excluded.

Intervention

The intervention consists of OMT performed by osteopaths, osteopathic physicians or osteopathic trainees, who used a black box method or a specific protocol without any restriction of approach and technique based on manual assessment, diagnosis, and treatment in accordance with the osteopathic principle[1,2]. SRs including primary studies on both OMT and other complementary manual interventions were excluded if a sub-analysis was not independently performed for each manual treatment. To verify that osteopathic treatment was performed by osteopaths, the primary clinical trials were analysed.

Comparison

In order to retrieve all clinical evidence currently reviewed in SRs and MAs, the comparison group included placebo, sham OMT, light touch therapy, no treatment, waiting list, conventional treatment, physiotherapy or other complementary medicine treatments.

Setting

SRs with trials performed in any health-related settings and/or health promotion centres were included.

Main outcomes

The main outcomes were any clinically relevant endpoint measures, depending on the clinical condition reported in the SRs.

Any adverse events caused by OMT were extracted. Other types of outcomes such as prevalence of somatic dysfunction, inter-rater or intra-rater reliability for any type of osteopathic approach were excluded.

Search Strategy

A systematic literature search was carried out independently by two reviewers (D.B. and D.R.) using the following electronic databases: MEDLINE (PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica database (EMBASE), Joanna Briggs Institute database of systematic reviews and implementation reports (JBI), Scopus, Prospero and Cochrane Library, all from their inception until 13th November 2021. No language or date restrictions were applied. The search strategy was performed using the following search terms: osteopathic treatment, osteopathic medicine, osteopathic manipulation, review, systematic review and meta-analysis. The references list of the included SRs and MAs as well as narrative reviews were widely perused for the identification of additional articles. Full details of the search strategy for PubMed are provided in *Appendix* (Supplementary materials).

Data collection and analysis

Study selection

The selection was performed independently by two authors (D.B. and D.R.). All the retrieved articles were imported into the 1.19.8 Mendeley software version and the duplicate publications were excluded. Potential eligible SRs and MAs were read in abstract and full text and independently evaluated by the two authors for inclusion in the overview. SRs and MAs were excluded if they did not meet the inclusion criteria, firstly at the title and abstract level, and then at the full-text level. Disagreements were resolved through discussion and consensus between the two review authors; if no agreement was reached, the third member of the review team (F.B.) was then consulted. Weighted kappa statistics were calculated to measure agreement between the authors.

Data extraction and management

Two authors (D.B. and F.B.) independently extracted data using an Excel spreadsheet. We collected the following information (where available) from SRs and MAs: first author, year of publication and country of the corresponding author, date assessed as up to date, condition treated, number of included studies and participants, gender distribution and age, osteopathic interventions and co-interventions description, and number of treatments, control description, outcome measures, time points reported, reporting adverse events, primary studies quality assessment included in each SRs and MAs, GRADE (Grading of Recommendations Assessment, Development and Evaluation) results (see "Strategy for data synthesis" section for more details), MAs data, if any, and SRs main results. We reported the mean difference (MD) or standard mean difference (SMD), 95% confidence intervals (CI) and results of any test of heterogeneity reported in the relevant meta-analysis. When not reported in the SRs,

mean and standard deviation (SD) for continuous variables as well as median, interquartile (IQR) and range for discrete variables were calculated (e.g. patient's age, gender).

Assessment of methodological quality of included SRs and MAs

The methodological quality of the included SRs and MAs was assessed using the AMSTAR-2 tool which is designed to generate an overall rating based on weaknesses of some critical domains (items 2,4,7,9,11,13,15)[10]. AMSTAR-2 classifies the overall confidence of the results into four levels: high, no or one non-critical weakness; moderate, more than one non-critical weakness; low, one critical flaw with or without non-critical weaknesses; and critically low, more than one critical flaw or without non-critical weaknesses[12]. The quality assessment was evaluated independently by two authors (D.B. and F.B.), with any disagreements resolved through discussion with the third author (D.R.). To provide a simple indication of the results for the reader, for each domain, we used a 'stop-light' indicator where green indicates "Yes", yellow "Partial Yes" and red "No". Weighted kappa statistics were calculated to measure agreement between the authors.

Overlapping systematic reviews

According to recent guidelines[13,14] we have decided to count the primary studies present in more than one SR only once. When more than one systematic review (which investigates the same research question and uses the same primary studies) was identified, only the latest one was selected if it used the most rigorous criteria to evaluate the methodological quality of the studies.

Strategy for data synthesis

Due to the overlap of studies and heterogeneity between reviews with regard to outcome measures, a critical synthesis of results was performed. The methodological quality of RCTs can be evaluated using several scores including the Jadad score, the PEDro scale and the Cochrane risk of bias tool for randomized trials (RoB). Different versions of RoB are available, which refer to different updates of the Cochrane Handbook for the systematic reviews of intervention[15,16]. Moreover, for musculoskeletal disorders, the Cochrane Back and Neck Review Group (CBN Group, before named CBRG) has developed a specific RoB guideline [also for this guideline some versions are available[17-19]]. Because of several versions that bring to different judgments, in our overview, when possible, we have reported results (judgments) according to the last version of the RoB tool[19,20]. In table 1 authors' judgments are reported while our update judgments are reported in the text. Once, meta-analysis was performed we reported the data synthesis used in the meta-analysis: effect size (ES) and heterogeneity. Effect-size was reported according to Cohen[21]. Briefly, a small effect was defined as MD less than 10%

of the scale and SMD less than 0.5%, a medium effect as MD from 10% to 20% of the scale and SMD from 0.50% to 0.80%, and a large effect was defined as MD greater than 20% of the scale and SMD scores greater than 0.80%[19] Concerning heterogeneity, the following thresholds were considered for the interpretation of the reported I^2 statistic that assessed heterogeneity: i) 0%to 40%: might not be important, ii) 30% to 60% may represent moderate heterogeneity, iii) 50% to 90% may represent substantial heterogeneity, iv) 75% to 100% considerable heterogeneity[20]. We reported the GRADE results as rated by the SR's Authors. According to the GRADE approach the quality of evidence for each outcome (considering the RoB, imprecision, inconsistency of results, indirectness of evidence and publication bias) can fall into four categories: high quality evidence (further research is very unlikely to change confidence in the estimated effect), moderate quality (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate) and very low quality (there is great uncertainty about the estimate)[22]. To provide a simple indication of the results for the reader, we used a 'stop-light' indicator, where green indicates high quality of evidence, yellow denotes moderate evidence and red indicates low quality of evidence.

Results

Literature search results and study selection

The literature search yielded 13128 potentially relevant articles and, after eliminating duplicate articles (4778), 8350 articles were screened (see Fig.1). After reading the titles and abstracts, 44 full texts were selected for eligibility of which 35 were excluded (see Supplementary Table 1) and nine SRs were considered relevant and included in this overview. A review that agreed with the outcomes of the current review was identified in Prospero (CRD42021280994). The Authors were contacted and replied that the results were not yet available. The agreement on the included studies eligibility, performed by the two authors (D.B. and D.R.), resulted in a 0.78 kappa value[23].

Description of included reviews

This overview included nine SRs published between 2013 and 2020. Eight articles were published in English and one in Portuguese.

Six SRs focused on musculoskeletal conditions[24-29], and one each on paediatric[30], neurological[31] and visceral conditions[32]. Detailed information on the included SRs/MAs is available in Table 1 and 2. The SRs included 71 primary studies with 5577 participants.

Considering the overlapping of 16 trials and 1837 participants, the primary trials were 55 with 3740 participants (Supplementary Table 2 and 3).

Musculoskeletal conditions

Low back pain

Four reviews[24-27] with 34 RCTs (41 comparators) and 3369 participants assessed the efficacy of OMT on low back pain (LBP) including acute LBP (ALBP), chronic LBP (CLBP), LBP with sciatica, CLBP with menopause symptoms, LBP in obese, acute non-specific LBP (ANSLBP), chronic non-specific LBP (CNSLBP) and /or LBP and pelvic girdle pain in pregnancy and postpartum. Considering overlapping, the effective trials were 22 with a total of 2053 participants.

The SR performed by De Oliveira and colleagues considered LBP in obese, CLBP, CLBP with sciatica and LBP in menopause or pregnancy[24]. The review included five trials with 278 participants, three RCTs were also reported in other two systematic reviews (see Supplementary Table 2 and 3 for details). Conflicting results derived from the primary studies. In the inter-group analysis, OMT was not effective in reducing pain in the majority of the trials. Of note, in all RCTs, the results of functional outcomes were not analyzed. Using the PEDro tool, the methodological quality of the five RCTs was classified by the Authors as fair to excellent (PEDro range: from 5 to 9 out of 11 points). Adverse events were not analyzed.

The SR of Franke and colleagues included fifteen trials with 1502CNSLBP or ANSLBP participants[25]. Ten trials (1141 participants) and nine RCTs (1046 participants) investigated the effectiveness of OMT on pain and functional status, respectively. Nine RCTs were also reported in other systematic reviews (see Supplementary Table 2 and 3 for details). The meta-analysis revealed a medium and small effect in reducing pain and in improving functional status, respectively, and a moderate quality of evidence (downgraded due to inconsistency). Moreover, a considerable (pain) and a moderate (functional status) heterogeneity were found. Similar meta-analysis results (effect and heterogeneity) have also been evidenced in a sub-analysis evaluating the effectiveness of OMT in CNSLBP patients. The GRADE performed by the Authors revealed both a moderate quality of evidence for pain and a high-quality of evidence for the functional status.

Three trials (4 comparators) with 242 participants evaluated the effectiveness of OMT versus obstetric care, sham ultrasound, and untreated, for NSLBP in pregnant women. A large and a medium effect in reducing pain and in improving functional status was identified, respectively. Considerable (pain) and substantial (functional status) heterogeneity were found. GRADE evaluation by the Authors reported a low quality of evidence for both outcomes.

Two RCTs with 119 participants evaluated the effectiveness of OMT for NSLBP in postpartum (PP) women. A large effect of OMT in reducing pain and in improving functional status was identified. No heterogeneity was found. However, a moderate quality of evidence for both outcomes was revealed. The methodological quality of all RCTs, evaluated by the Authors using the RoB from the Cochrane Back Review Group[18], reported a low and a high risk of bias for thirteen and two RCTs, respectively. However, considering the last version of the CBRG[19], we rated all RCTs at high risk of bias [domains at high RoB (% of RCTs): care provider (100%), patient blinding (67%), outcome assessor blinding (67%), groups similar at baseline (27%), lack of intention to treat analysis use (27%), free of selective outcome report (13%), dropouts described + acceptable (7%), similar timing outcome assessment (7%) and compliance acceptable (7%)].

Adverse events were evaluated only in four out of the fifteen primary studies. Two RCTs reported minor adverse events such as stiffness and tiredness, one no adverse event and the last one evidenced adverse event that, however, were not related to the treatment intervention.

In another SR, Franke and colleagues[26] identified eight RCTs with 850 participants evaluating the efficacy of OMT on NSLBP and pelvic girdle pain in pregnancy (five RCTs, seven comparisons) and on NSLBP in postpartum women (three trials and three comparisons) (see Supplementary Table 2 and 3 for overlapping). The pooled analysis of five RCTs with 677 pregnancy participants reported the efficacy of OMT in reducing pain and improving functional status; however, a medium effect and a considerable heterogeneity were revealed. The GRADE performed by the Authors indicated a moderate quality of evidence.

The meta-analysis including three studies with 173 postpartum participants revealed a significant effect in favour of OMT in reducing pain and improving functional status, although a large effect and a substantial/considerable heterogeneity for both outcomes was reported. The GRADE performed by the Authors also found a low quality of evidence.

The methodological quality of the included studies evaluated by the Authors using the CBRG, Version 2009[18] identified a low risk of bias for all RCTs. Considering the CBNG[19], we rated all RCTs as at high risk of bias [domains at high RoB (% of RCTs): patient binding (100%), care provider binding (100%), outcome assessor blinding (100%), dropouts described + acceptable (25%), group similar at the baseline (25%), intention to treat analysis (25%), similar timing outcome assessment (25%) and compliance acceptable (12%)].

Concerning the adverse events, one study reported occasional tiredness in some patients after OMT, two studies (personal communications to Authors SR) did not find adverse events and the remaining five studies did not analyse adverse events.

The SR by Dal Farra and colleagues[27] evaluated the effectiveness of osteopathic interventions, performed by any type of manual therapists, in CNSLBP patients. A subgroup analysis evaluating the effectiveness of OMT performed only by osteopaths identified six trials (8 comparisons) with 739 participants; five trials also reported in other two SRs (see Supplementary Table 2 and 3 for more details).

The Authors revealed a significant effect, clinically relevant according to the Cochrane Back and Neck Group, of OMT in reducing pain (medium effect) and improving functional status (small effect). However, a substantial heterogeneity and a low quality of evidence (GRADE) were reported for both outcomes.

A further sub-analysis, including two trials (3 comparisons) with 548 participants, did not find evidence of OMT efficacy on functional status after a long-term treatment (12 weeks follow-up). Low quality of evidence and no heterogeneity were reported. The methodological quality of the primary studies, evaluated by the Authors using the CBNG version 2015[19], reported a high risk of bias for all RCTs [domains at high RoB (% of RCTs): high risk of bias for care provider (100%), patient blinding (50%), outcome assessor blinding (17%), participant allocation (33%) and reporting bias (17%)]. With regard to adverse events, a trial reported an increase of back muscle spasticity in a patient treated with OMT.

Neck pain

Franke and colleagues[28], evaluating three RCTs (three comparators) with 123 participants, provided evidence that OMT exerted beneficial effects on chronic non-specific neck pain (CNSNP). Specifically, a medium effect size in reducing pain and moderate quality of evidence on pain outcome was reported. A low level of heterogeneity was found. However, the meta-analysis did not evidence a significant effect on functional status. The methodological quality of all RCTs, evaluated by the Authors using the CBRG [18], reported a low risk of bias for all RCTs. Considering the CBNG version 2015[19], we rated all RCTs at high risk of bias [domains at high RoB (% of RCTs): patient blinding (67%), care provider (100%), outcome assessor blinding (67%), dropouts described + acceptable (33%) and intention to treat analysis (100%)]. No serious adverse events occurred in all RCTs (data reported in a RCT and as personal communications to SR Authors in the other two studies).

Chronic non-cancer pain (CNCP)

The SR by Rehman and colleagues[29] evaluated the efficacy of osteopathic interventions, performed by manual therapists, in chronic non-cancer pain. In seven out of 16 retrieved RCTs, OMT was performed by osteopaths (see supplementary tables 2 and 3 for overlapping). A pooled analysis, including six RCTs with 728 participants (six comparators), found the efficacy

of OMT *vs* standard care in reducing pain severity (small effect size, moderate quality of evidence and low level of heterogeneity). Moreover, another pooled analysis including two trials with 486 participants revealed the efficacy of OMT *vs* standard care in improving disability (large effect size, moderate quality of evidence and no heterogeneity). Similarly, the pooled analysis of the other two trials with 210 participants found that OMT *vs* standard care improved the quality of life (medium effect, moderate quality of evidence and no heterogeneity).

The methodological quality of the included studies was performed by the Authors using a modified version of the Handbook of Cochrane[33] where only six domains were considered (random sequence generation, allocation concealment, blinding of participants, healthcare provider, outcome assessors, and dropout rates). According to this modified version, the quality of the RCTs was reported by the Authors to be at high risk of bias [domains at high RoB (% of RCTs): for patient blinding (100%), care provider (100%), outcome assessor blinding (57%), random sequence generation (29%), participant allocation concealment (29%), and dropout > 20% (43%)]. Adverse events were not considered by the SR authors.

Paediatric conditions

A SR by Posadzky and colleagues[30] evaluated the efficacy of OMT in paediatric conditions. This review included seventeen RCTs involving a total of 887 participants with different conditions: cerebral palsy evaluated in two clinical studies involving a total of 197 participants, respiratory conditions evaluated in four trials involving 186 patients [obstructive apnoea one RCT, asthma two RCTs (in one study not reported the number of patients), bronchiolitis one RCT], otitis media evaluated in three trial involving a total of 167 participants, musculoskeletal function evaluated in three trials with 80 patients (idiopathic scoliosis one RCT, mandibular kinematics one RCT, postural asymmetry one RCT) and attention-deficit/hyperactivity disorder (77 participants), prematurity (101 participants), infantile colic (28 participants), congenital nasolacrimal duct obstruction (30 patients) and functional voiding (21 participants) individually assessed by one RCT. The single trials provided evidence that OMT exerted beneficial effects on congenital nasolacrimal duct obstruction (post-treatment), daily weight gain and length of hospital stay, dysfunctional voiding, infantile colic and postural asymmetry. By contrast, no significant effects of OMT on idiopathic scoliosis, obstructive apnoea or temporomandibular disorders compared with various control interventions have been evidenced by the single RCTs. For conditions in which more than one RCT has been performed (asthma, otitis media and cerebral palsy), contradictory results are reported. From the SR emerges that low-quality RCTs favoured OMT, while moderate and high-quality RCTs failed

to find an OMT effectiveness. The vast majority of the RCTs were reported by the Authors to be at high risk of bias (15 RCTs) [domains at high RoB (% of RCTs): allocation concealment (67%) patient blinding (67%), care provider (100%), outcome assessor blinding (50%), addressing of incomplete data (33%), selective outcome reporting (33%), adequate sequence generation (28%)] with unclear or low risk of bias for the remaining two RCTs.

In 11 RCTs adverse events were not analyzed. No adverse events or serious adverse events following OMT were reported in four trials. Adverse events occurred in one RCT but they were not related to OMT. One trial reported aggravation of vegetative symptoms in four patients.

Neurological conditions

The SR of Cerritelli and colleagues[31], including five RCTs for a total of 235 participants, evaluated two different types of primary headache: migraine (two RCTs, 147 participants) and tension-type headache (three RCTs, 88 participants). Although the two RCTs evaluating the efficacy in the migraine reported positive results in favour of OMT (mainly in pain intensity reduction), inter-group analysis was performed only in one RCT. Similarly, evidence has been reported for the tension type headache only when a within group analysis was performed; inter-group analyses reported conflicting results. The RCTs were reported by the Authors to be at high risk of bias [domains at high RoB (% of RCTs): care provider blinding (100%), participant blinding (60%) and allocation concealment (20%)]. Due to high heterogeneity (different types of primary headaches, different outcome measures and variable length of follow-up) a meta-analysis was not conducted by the Authors. Adverse events, evaluated in two RCTs, did not occur.

Visceral conditions

In a SR, Muller and colleagues[32], including five primary studies and involving 204 participants, evaluated the efficacy of OMT in the treatment of irritable bowel syndrome (IBS). Although a high heterogeneity (in outcome measures and follow-up period) was evidenced, the results indicated that OMT was effective in IBS. The methodological quality of all RCTs, evaluated by the Authors using the CBRG[18], reported a low risk of bias for all RCTs. Considering the CBNG[19], we rated all RCTs at high risk of bias [domains at high RoB (% of RCTs): care provider (100%), outcome assessor blinding (60%), randomized (20%), patient blinding (20%), groups similar at the baseline (20%) and intention to treat analysis (20%)]. No adverse events occurred in the patients from all RCTs.

Methodological quality of included reviews

The summary of the finding of the AMSTAR-2 is provided in Table 1 and 3. The inter-rater agreement between the two overview authors (D.B. and F.B.) on the ranking of quality, achieved a 0.89 kappa value[23].

According to the critical domain established in Shea et al.[12], seven[25-29 31,32] and two systematic reviews[24,30]were rated as low and critically low quality, respectively.

Two of the nine SRs registered a protocol before beginning the study[27,29]. Eight SRs performed an appropriate literature search [25-32] and five SRs reported justification for the exclusion of primary studies[25,26,28,31,32]. All SRs[24-32] evaluated the risk of bias of the included studies and five SRs[25-29] carried out a meta-analysis and used appropriate methods for the statistical combination of findings. Eight SRs [25-32] accounted for the risk of bias when interpreting and discussing the results of the SR. Finally, domain 15 (publication bias assessment) was rated as not applicable for all the SRs due to lack of a meta-analysis [24,30-32] or the inclusion in the meta-analysis of fewer than 10 trials [25-29].

Discussion

Osteopathic medicine, an alternative and complementary medicine (CAM), is a form of manual therapy used to normalize the structure-function relationship and to promote the body's own self-healing mechanism. In the last decade, CAM therapies have grown in use and popularity and, among these, many surveys have demonstrated an increasing interest in osteopathic medicine in patients with musculoskeletal disorders such as non-specific chronic low back pain and neck pain[34,35].

Recently, osteopathic medicine has been regulated in many countries including the USA, Australia, UK, Iceland, Denmark, Malta, Portugal, Switzerland, where it is a primary healthcare profession. In other countries, the regulation process has not yet been completed (i.e. Italy) or there is no legal recognition of the osteopathic profession[36]. In this context, we performed an overview to summarize the best available clinical evidence on the efficacy and safety of OMT. We identified nine SRs on the use of osteopathic care for the management of musculoskeletal, paediatric, visceral and neurological disorders with different effects and clinical relevance depending on the conditions.

From our overview emerge some relevant questionable problems related to the lack of appropriate guidelines for assessing the methodological quality of trials in manual therapy and problems due to inadequate reporting of trial methodology and results. In this regard, most of the trials included in the SRs reported a high or unclear risk of bias for blinding procedures: patient, outcome assessor and care provider blinding. In manual therapy, blinding is an issue

as patients tend to be aware of the manual treatment and therapists cannot be blinded from the treatment intervention they deliver[37]. For participants-reported outcomes, for which the patient is the outcome assessor, such as for pain and functional status outcomes, blinding of patients is mandatory and therefore it is necessary to use, as control group, sham procedures (including light touch therapy) that simulate manipulation. These sham procedures should be reported in the RCTs; however, a lack of reporting placebo sham therapy procedures in both SRs and primary studies has been evidenced. It is important to note that although these findings have already been reported by Cerritelli and colleagues in 2016[38], to date these suggestions have not been followed. More effort should be made to promote guidelines for designing the most reliable placebo for manual treatment to reduce the risk of bias for patient blinding. However, interesting a recent meta-epidemiological study found no evidence that lack of patients' blinding had an impact on estimate effects[39].

Other issues that emerge from our overview is the lack of treatment description and timing of measuring outcomes (short and long-term) in the SRs as well as in primary trials. In osteopathic medicine, as in any other manual therapy, it is important to describe in adequate detail each phase of the intervention, including how and when they were administered, and when the outcomes are measured. Without a complete description of treatments, clinicians cannot reliably reproduce useful interventions. Proper checklists for non-pharmacological treatments, such as the TIDieR (Template for Intervention Description and Replication) guide/checklist and the CONSORT (CONsolidated Standards of Reporting Trials) statement for randomized non-pharmacological treatment studies, should be followed by clinical trial authors[40,41].

That said, our overview highlightes that evidence on the efficacy of OMT is: 1) limited and contradictory in the treatment of paediatric conditions (some conditions were evaluated by only one trial, some of which were of low methodological quality; contradictory results were obtained for conditions in which two RCTs were performed), 2) preliminary on headache and IBS and 3) encouraging in musculoskeletal disorders mainly in CNSLBP patients and LBP in pregnant or postpartum women.

The lack of solid evidence stems from a small sample size,[26,28-32] the presence of conflicting results[24,30,31] and a high heterogeneity in participants[25,31], outcomes measures[31,32], interventions[25-27,31] and comparison interventions[25-27,32]. Of note, reduced heterogeneity was found when the RCTs were pooled considering interventions and comparators[29].

According to AMSTAR-2, the methodological quality of the included SRs was rated low and critically low. Domain two (registered protocol) was critical for 7 SRs. The lack of a written and registered protocol prior to conducting the review should ensure that review methods are

transparent and reproducible, and adherence to this prespecified research plan[42]. These should help avoiding bias and unintended duplication of reviews.

Adverse events

Generally, manual therapies have been reported to be well tolerated and manual therapy-related adverse events are short-lived and mild or moderate in intensity[43]. In our overview, we find that seven SRs[25-28,30-32] evaluated adverse events and from these SRs it emerges that no severe incident involving musculoskeletal, neurological, visceral and paediatric disorders occurs after OMT. However, should be noted that among these seven SRs only two of them reported the definition used to measure adverse events. The idea that manual therapies are safe could be only demonstrated if adverse events are defined and assessed in each clinical trial. Specifically, the Authors should adequately report in details the approach used to measure adverse events which need to be defined using an appropriate taxonomy[44,45].

Strengths and limitation

Numerous limitations can be found in our overview. First of all, considering our inclusion criteria, we may have missed some relevant SRs. Indeed, we included SRs by evaluating only RCTs (and not other study designs) in which OMT was performed by osteopathic physicians or osteopaths (and not by other manual therapists). Globally, two professional figures have emerged, largely due to different legal and regulatory systems around the world: osteopathic physicians, who are doctors with full and unlimited medical practice rights, and osteopaths who have obtained academic and professional standards for diagnosing and practicing treatments based on the principles of osteopathic philosophy. OMT is the core activity for both osteopathic physicians and osteopaths who follow the principles of osteopathic medicine by performing a personalized treatment according to the patient evaluation and subsequent tailoring [46]. Therefore, our decision to consider only osteopathic physicians or osteopaths arises from the premise of avoiding that the principles of osteopathic medicine are not followed. In this regard, we excluded seven systematic reviews and, therefore, considering the overlapping, 5 RCTs were lost (see Supplementary Table 1 for details). According to our decision, a recent scoping review used more restrictive inclusion criteria considering only studies performed in the USA where OMT is practiced by osteopathic physicians[47]. Considering that in most countries osteopathy is often delivered in the private sector (e.g. UK, France and Italy) the participants included in the primary studies might not be generalizable to the population.

Since RCTs are widely recognized as the best design for evaluating the efficacy of an intervention, we have also decided to include only SRs evaluating randomized controlled trials. In this regard, eleven systematic reviews were excluded and considering the overlapping, 17

RCTs were lost (see Supplementary Table 1 for details).

Conclusion

In conclusion, this overview suggests that OMT could be effective in the management of musculoskeletal disorders, specifically with regards to CNSLBP patients and LBP in pregnant or postpartum women. By contrast, no conclusive evidence derived from SRs analyzing the OMT efficacy on other conditions (paediatric conditions, headache and IBS).

Although not all RCTs have investigated the safety of OMT, considering that not serious adverse events have been reported, OMT can be considered safe.

Nevertheless, based on the low number of studies some of which of moderate quality, our overview highlights the need to perform further well-conducted SRs as well as clinical trials (which have to follow the specific guidelines for non-pharmacological treatments) to confirm and extend the possible use of OMT in some conditions as well as its safety.

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Table 1. Characteristics of the included systematic reviews and meta-analyses.

First author, year, country of corresponding author, reference	Date assessed as up to date	Conditions	Trials number, participants number.	Gender distribution, Age (years)	Intervention (co-intervention): description. Number of treatments (SD).	Control or comparison description	Outcomes assessed	Time points reported	Main results	Definition used to measure AEs§. Reported AEs	AMSTAR-2
Musculoskeletal conditions: Low back pain											
De Oliveira Meirelies[24] 2013, Brazil,	NR	CLBP, CLBP in pregnancy, LBP with menopausal symptoms, LBP in obese, LBP with sciatica.	5 RCTs, 278 adults. 1 CLBP, 1 CLBP in pregnancy, 1 LBP with menopausal symptoms, 1 LBP in obese, 1 LBP with sciatica.	Gender:85% female,15% male. Mean age 40 (from 4 RCTs).	OMT (UOBC, SE): OCF, ART, HVLA, MRT, MET, range of motion technique. Treatments: median 10 (7-10)**	SUT, NT, SM, chemonucleolysis,	Pain: VAS, dichotomous pain, pain scale.	Treatment time: 2 weeks and 15 years (from 2 RCTs). Evaluation: 1 week, 12 months (from 2 RCTs).	OMT improved LBP in comparison with no intervention (but not with SM).	NR	Critically low
Franke [25] 2014, Australia,	NR	ANSLBP, CNSLBP, NSLBP in pregnancy, NSLBP in PP	15 RCTs, 1502 adults. 10 NSLBP, 3 NSLBP in pregnancy, 2 NSLBP in PP.	Gender: NR. Mean age 36 (from 13 RCTs)	OMT (UC, heat &PT, UOBC, SE): NR. Treatments: median 4 (4-6)**	SUT, NT, SM, UC, PT, SWD.	Pain: VAS, NRS, MGPQ. Functional status: RMDQ, OPQ, ODI, LBP_DQ, Kinematic of thoracic/lumbar spine /pelvis during forward flexion, QBPDS.	Period: 2-9 weeks, 1- 3- 6 months.	OMT was effective in pain and functional status in ANSLBP, CNSLBP, NSLBP in pregnant and NSLBP in PP.	NR Only 4 RCTs reported AEs. 2 RCTs reported minor AEs such as stiffness and tiredness; 1 RCT reported that 6% of patients had AEs (but not serious). 1 RCT reported that no AEs occurred.	Low
Franke[26] 2017, Australia,	NR	ANSLBP, CNSLBP and /or pelvic pain during pregnancy and PP.	8 RCTs, 850 adults. 5 LBP in pregnancy, 3 LBP in PP.	Gender: 100% female, Mean age 29.5	OMT (UOBC): NR. Treatments: Pregnancy median 7 (5.5-7). Postpartum median 4 (4-4.5)**	SUT, NT, UC.	Pain: VAS, QVAS, FP. Functional status: RMDQ, QPP, QBPDS, PGPQ, OPQ.	Pregnancy: ranging from 3 to 9 weeks; follow-up 1 and 2 weeks. Postpartum: 2 weeks. Follow-up 2 weeks	OMT significantly improved pain functional status in women with LBP during pregnancy and PP.	NR No serious AEs (from 3 RCTs*). 1 RCT reported occasional tiredness in some patients.	Low
Dal Farra[27] 2020, Italy,	Inception to April 2020	CNSLBP	6 RCTs***** 739 adults	Gender: NPTC Mean age 46 (from 4 RCTs), median age 41 (29-51)**	OMT (SE, UC): HVLA, MET, CST, MFR, MVMA. Treatments: range 5-10 sessions, median 6 (5-8)**	SM, PT, SE	Pain: VAS. Functional status: RMDQ, ODI, SF-36, EQ-5D, BDI.	Ranging from 2 weeks to 6 months. Follow-up: from 1 month to 1 year.	OMT significantly improved pain and functional status in CNSLBP in the short-term (but not in the long-term).	Frequency of adverse events and/or relative study withdrawals, and self-reported scales and questionnaires including quality of life and psychological function (e.g. fear avoidance beliefs, catastrophizing, pain-related fear); additional indicators considered were frequency of analgesic and/or NSAIDs use, economic impact or cost reduction and patient's care satisfaction. No AEs (from 5 RCTs). 1 RCT reported increased back muscle spasticity in a patient.	Low

Musculoskeletal conditions: Neck pain											
Franke[28] 2015, Australia,	NR	CNSNP	3 RCTs, 123 adults.	Gender: NR. Mean age 44.	OMT (SUT, UC): NR. Treatments: median 5 (5-6)**	SM, PT	Pain: VAS, NRS, NPPQ. Functional status: NDI, NQ.	Ranging from 1 to 11 weeks. Follow-up: 3 months (in 2 RCTs).	OMT significantly improved pain, but not functional status in CNSNP.	NR Only 1 RCT reported not serious AEs, such as tiredness on the day of treatment and short-term aggravation of symptoms in other 'familiar' regions, were noted.	Low
Musculoskeletal conditions: Chronic non-cancer pain											
Rehman[29] 2020, Canada,	NR starting date. Until July 2019	CNCP: Fibromyalgia, TMD, CNSLBP, CNSBP, CNSNP, CNP.	****** 7 RCTs, 759 adults. 1 Fibromyalgia, 1 TMD, 1 NSNP, 1 CNSBP, 2 CNSLBP, 1 CNSNP	Gender: 60% female, 40% male. Mean age 52 (from 5 RCTs), range 23-54 (from 2 RCTs).	OMT (non-steroidal medications, anti-inflammatory, analgesics and/or muscle relaxants, UC, SE, lumbar supports, physical therapies and CAM): MET, MFR, HVLA, BLT, CST, JA, MT, ST, FPR. Treatments: NR.	SUT, SE, PT, SC, use of an oral appliance, hot and/or cold packs, TENS, SM, LT, ROM activities, LTP.	Pain: VAS. Disability: RMDQ. SF-36, QOL	Duration of treatment/follow-up period: ranging from 1-42 to 168 days (1-6 months).	OMT, in comparison to SC, was significantly effective in reducing pain and increasing disability as well as in improving QoL.	NR	Low
Paediatric conditions											
Posadzki[30] 2013, South Korea,	Inception to November 2012	Pediatric conditions: CP, respiratory conditions, OM, musculoskeletal function, ADHD, prematurity, IC, CNLDO, DV.	17 RCTs, 887 neonates/infants (from 16 RCTs). 2 CP, 4 respiratory conditions, 3 OM, 3 musculoskeletal function, 1 ADHD, 1 prematurity, 1 IC, 1 CNLDO, 1 DV	Gender: NR. Range from premature infants >28 weeks to 18 years.	OMT: VO, CST, OMT techniques (ART, BLT, BLM, CS, FPR, MET, MFR or rib-raising). Treatment: median 4 (3-5)**	UC, NT, SM, WL, SM+ placebo, SM+ Echinacea, postural drainage, bronchodilators.	Cerebral palsy: CHQ, GMFM-66, PEDI, WeeFIM. Respiratory: RR, EV, flow, MEP, PEF. Musculoskeletal: TM, SF, Kinesiographics (MO, MOV, MCV, OVA, CVA). Preterm infants: LOS, DWG. ADHD: Conners Scale. Infantile colic: MNHSCS. Otitis media: Antibiotic use, tympanograms, Audiometrics, SI, surgery -free months, reflectometer. CNLDO: FDT, MJT. Dysfunctional voiding: DV symptoms.	Cerebral Palsy: 6 months follow-up. Respiratory, Musculoskeletal, ADHD, congenital nasolacrimal duct obstruction, dysfunctional voiding: posttreatment. Prematurity: discharge from hospital.	No conclusive evidence on the efficacy of OMT for any pediatric condition due to i) low methodological quality of RCTs (when conditions were evaluated by individual RCTs) and ii) contradictory results for the conditions under which two RCTs were performed.	NR AEs not evaluated in 11 RCTs. No AEs occurred in 4 RCTs. 1 RCT reported patients (4) aggravation of vegetative symptoms after OMT. 1 RCT reported AEs not related to OMT.	Critically low
Neurological conditions											
Cerritelli[31] 2017, Italy,	Inception to April 2016	Primary headache: migraine, tension-type headache	5 RCTs, 235 adults. 2 migraine, 3 headache	Gender: 78 % female, 22% male (from 3 RCTs). Mean age 39.4 (from 3 RCTs)	OMT (UC, triptans, PMR): NBT (in 3 studies), use of protocols (in 2 studies). Treatment: median 4 (3-5)**	UC, SM, OE, PMR, rest	HIT-6 score, HF, WD, PI, DC.	Ranging from IAT to 6 months. Follow-up: 1, 3 months.	OMT reduced pain intensity, frequency and disability in patients with headache.	Number and types of AEs. AEs not evaluated in 3 RCTs, 2 RCTs reported none AEs.	Low

Visceral conditions											
Muller[32] 2014, Australia,	Inception to October 2013	Irritable bowel syndrome	5 RCTs. 204 adults.	Gender: 79% female, 21% male (from 3 RCTs). Mean age 47	OMT: applied to different body region, VO (approach on the abdomen and spine, abdomen and sacrum), NBT. Treatments: median 5 (3-5)**	UC, SM.	Pain: VAS. Constipation, diarrhea, AD, RS, CTT, meteorism. IBS severity score, FIS score, HAD, BDI, IBSQoL2000. FBDSI	Ranging from 1 week to 3 months. Follow-up: short-term (2, 4 weeks), long-term (3, 12 months)	OMT, in comparison to sham therapy or standard care, reduced the symptoms of IBS, such as abdominal pain, constipation, diarrhea, and improved general well-being.	NR All RCTs reported that no serious or statistically significant AEs occured.	Low

§ Reported by the Authors of the SRs. *In personal communications from authors of two RCTs, **median (Q1-Q3), ***The number is not reported for a RCT on asthma, ****Reported in methods but not performed, *****group analysis, ******13 RCTs, only 7 trials were used in our study, *******the outcomes measures are not reported in all studies. AD: abdominal distension, ADHD: attention deficit /hyperactivity disorder, AE: adverse events, ANSLBP: acute nonspecific low back pain, ART: articular treatment, BDI: Beck Depression Index, BLM: Balanced membranous tension, BLM: Balanced membranous tension, BLT: Balanced ligamentous tension, CHQ: child health questionnaire, CNLDO: congenital nasolacrimal duct obstruction, CNCP: chronic non-cancer pain, CNSBP: chronic non-specific body pain, CNSLBP: chronic nonspecific low back pain, CNSNP: chronic nonspecific neck pain, CNP: chronic neck pain, CP: cerebral palsy, CS: counterstains, CST: cranial sacral therapy, CTT: colonic transit time, CVA: cranial vault asymmetry, CV4: a technique in cranial field, compression of fourth ventricle, DV: dysfunctional voiding, DC: drug consumption, DWG: daily weight gain, EV: expiratory volume, FBDSI: functional bowel disorder severity Index, FDT: fluorescein disappearance test, FIS: fatigue impact scale, FP: frequency of pain, FPR: facilitated positional release, GMFM-66: gross motor function measure-66, HAD: hospital anxiety and depression, HF: headache frequency, HIT-6: headache impact test-6, HVLA: high velocity low amplitude thrust, IAT: immediately after treatment, IBS: irritable bowel syndrome, IBSQoL 2000: IBS quality of life, IC: infantile colic, IJA: joint articulation, LBP-DQ: low back pain disability questionnaire, LBP: low back pain, LOS: length of stay, LT: light touch, LTP: laser therapy, MCV: maximal closing velocity, MEP: mid expiratory phase, MET: muscle energy treatment, MFR: myofascial release, MGPD: Mc Gill pain questionnaire, MNHSCS: mean numbers of hours spent crying and sleeping, MJT: modified jones test, MO: maximal mouth opening, MOV: maximal opening velocity, MRT: myofascial release treatment, MT: membranous tension, MVMA: medium velocity medium amplitude, NBT: need based treatment, NDI: Neck Disability Index, NP: not performed, NPPQ: Northwick park pain questionnaire, NPTC : not possible to calculate, NR: not reported, NRS: numeric rating scale, NQ: Nordic questionnaire, NSNP: non-specific neck pain, NT: no treatment, OCF: osteopathy in cranial field, ODI: oswestry disability index, OE: osteopathic evaluation, OM: otitis media, OMT: osteopathic manipulative treatment, OPQ: oswestry pain questionnaire, Pedi: pediatric evaluation of disability inventory, PEF: peak expiratory flow, PGPQ: pelvic girdle pain questionnaire, PI: pain intensity, PMR: progressive muscular relaxation exercise, PP: postpartum, PT. physical therapy, QBPDS: Quebec back pain disability scale, QPP: questionnaire postpartum, QVAS: quadruple visual analogue scale, RMDQ: Roland Morris disability questionnaire, ROM: range of movement, RR: respiratory rate, RS: rectal sensitivity, SC: standard care, SD: standard deviation, SE: specific exercise, SF: spine flexibility, SI: surgical intervention, SM: sham manipulation, ST: Spencer technique, SUT: sham ultrasound treatment, SWD: short-wave diathermy, TENS: transcutaneous electrical nerve stimulation, TM: Trunk morphology, TMD: temporomandibular disorder, UC: usual care, UOBC: usual obstetrical care, VAS: visual analogic scale, VO: visceral osteopathy, WD: work disability, WL: waiting list, WeeFIM: functional independence measure for children

Table 2. Quality of the primary RCTs included in the systematic reviews/meta-analyses and meta-analyses quantitative results.

First author, year, country of corrisponding author, reference	Primary studies quality. GRADE	Summary of evidence	Meta-analysis data
Musculoskeletal conditions: Low back pain			
De Oliveira Meirelles[24] 2013 Brazil	Pedro score: 6 (2 RCTs), 9 (1 RCT), 7 (1 RCT), 5 (1 RCT).		NP
Franke[25] 2014 Australia	Low RoB (13 RCTs, low risk of bias in at least 6 categories). High RoB (2 RCTs).		
	GRADE		
	ANSLBP and CNSLBP		
	Pain: MODERATE		Pain: [MD -12.91; 95% CI: -20.00, -5.82]. I^2=86%.
	Functional status: MODERATE		Functional status: [SMD -0.36; 95% CI; -0.58, -0.14]. I^2=57%.
	CNSLBP		
	Pain: MODERATE		Pain [MD -14.93; 95% CI; -25.18, -4.68]. I^2= 89%.
	Functional status: HIGH		Functional status [SMD -0.32; 95% CI: -0.58, -0.07]. I^2=49%.
	NSLBP in Pregnancy		
	Pain: LOW		Pain [MD -23.01; 95% CI: -44.13, -1.88]. I^2= 91%.
	Functional status: LOW		Functional status [SMD -0.80; 95% CI: -1.36, -0.23]. I^2=76%.
	NSLBP in PP		
	Pain: MODERATE		Pain [MD -41.85; 95% CI: -49.43, -34.27)]. I^2=0%.
	Functional status: MODERATE		Functional status [SMD -1.78; 95% CI: -2.21, -1.35]. I^2=0%.
Franke[26] 2017 Australia,	Low RoB (all RCTs, low risk of bias in at least 6 categories).		
	GRADE		
	LBP in pregnancy		
	Pain: MODERATE		Pain: [MD -16.75; 95% CI: -31.79, -1.72]. I^2=94%.
	Functional status: MODERATE		Functional status: [SMD -0.50; 95% CI: -0.93, -0.07]. I^2=84%.
	LBP in PP		
	Pain: LOW		Pain: [MD -38.00; 95% CI: 46.75, -29.24]. I^2=68%.
	Functional status: LOW		Functional status: [SMD -2.12; 95% CI: -3.02, - 1.22]. I^2=81%.
Dal Farra[27] 2020, Italy	High RoB (all RCTs).		
	GRADE		
	CNSLBP		
	Pain: LOW		Pain [SMD -0.57; 95% CI: -0.90, -0.25]. I^2=72%.
	Functional status: LOW		Functional status [SMD -0.34; 95% CI: - 0.65, -0.03]. I^2=71%.
	Functional status (12 weeks follow-up): LOW.		Functional status 12 weeks follow-up: [SMD -0.14; 95%CI: -0.31, 0.03]. I^2=0%.
Musculoskeletal conditions: Neck pain			
Franke[28] 2015, Australia	Low RoB (all RCTs, low risk of bias in at least 6 categories).		
	GRADE		
	CNSNP		
	Pain: MODERATE		Pain: [MD -13.04, 95% CI: -20.4, -5.44]. I^2=34%.
	Functional status: MODERATE		Functional status [SMD: -0.38, 95%CI: -0.88, 0.11]. I^2=0%.
Musculoskeletal conditions: Chronic non-cancer pain			
Rehman[29] 2020, Canada	High RoB (all RCTs, based on a modified RoB with 6 domains).		
	GRADE		
	CNCP		
	Pain: MODERATE		Pain (OMT vs SC) [SMD - 0.37; 95% CI: - 0.58, -0.17]. I^2=25%.
	Disability: MODERATE		Disability (OMT vs SC) [SMD -1.04; 95% CI: - 1.23, -0.85]. I^2= 0%.
	Quality of life: MODERATE		Quality of life (OMT vs SC) [SMD 0.67; 95% CI: 0.29, 1.05]. I^2=0%.
Pediatric conditions			
Posadzki[30] 2013, South Korea	High risk (all RCTs).		NP
Neurology conditions			
Cerritelli[31] 2017, Italy	JADAD NR*. The majority of RCTs have high or unclear RoB.		NP
Visceral conditions			
Muller[32] 2014, Australia	Low RoB (all RCTs, low risk of bias in at least 6 categories).		NP

*Reported in methods but not performed. ANSLBP: acute non-specific low back pain, CNCP: chronic non-cancer pain, CNSBP: chronic non-specific body pain, CNSLBP: chronic non- specific low back pain, CNSNP: chronic non-specific neck pain, CNP: chronic neck pain, MD: mean difference, NP: not performed, NR: not reported, OMT: osteopathic manipulative treatment, PP: postpartum, RCT: randomized controlled trial, RoB: Risk of Bias, SC: standard care, SMD: standard mean difference.

Table 3. Quality of the included systematic reviews by the Amstar-2 tool.

ID, Author, Year,	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9 RCT	Q9 NRSI	Q10	Q11 RCT	Q11 NRSI	Q12	Q13	Q14	Q15	Q16	Ranking of quality
Musculoskeletal conditions																			
De Oliveira Meirelles[24]	N	N	N	N	N	N	N	PY	Y	N/A	N	N/A	N/A	N/A	N	N	N/A		CRITICALLY LOW
Franke[25]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Franke[26]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Dal Farra[27]	Y	Y	Y	Y	Y	Y	N	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Franke[28]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Rehman[29]	Y	Y	N	Y	Y	Y	N	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Pediatric conditions																			
Posadzki[30]	Y	N	N	PY	Y	Y	N	PY	Y	N/A	Y	N/A	N/A	N/A	Y	Y	N/A		CRITICALLY LOW
Neurology conditions																			
Cerritelli[31]	Y	N	N	Y	Y	Y	Y	Y	Y	N/A	Y	N/A	N/A	N/A	Y	Y	N/A		LOW
Visceral conditions																			
Muller[32]	Y	N	N	PY	Y	Y	Y	PY	Y	N/A	N	N/A	N/A	N/A	Y	N	N/A		LOW

Y, yes; PY, partial yes; N, no; N/A, not applicable. In grey are reported the critical domains.

Figure 1: Flow diagram of screened articles.

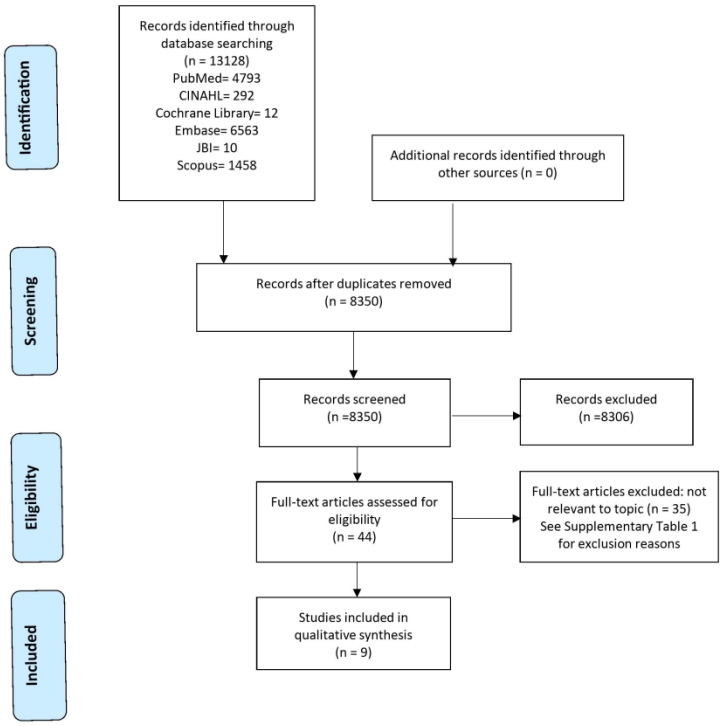

Figure 1: Flow diagram of screened articles.

Figure 1: Flow diagram of screened articles

209x297mm (300 x 300 DPI)

Appendix

Search Strategy: MEDLINE (PubMed)

01. osteopath* AND medicine
02. osteopath* AND treatment
03. osteopath* AND manipulat*
04. Manipulation, Osteopathic [Mesh]
05. Osteopathic Medicine [Mesh]

06. 01 OR 02 OR 03 OR 04 OR 05

07. meta-analysis
08. meta-analysis
09. metaanalysis
10. systematic review
11. review
12. Review Literature as Topic [Mesh]
13. Review" [Publication Type]
14. Meta-Analysis [Publication Type]
15. Meta-Analysis as Topic"[Mesh]

16. 07 OR 08 OR 09 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15

17. 06 AND 16

Supplementary Table 1. Excluded systematic reviews.

Authors/Year	Title	Reason for exclusion
Schwerla et al., 1999[1]	[Evaluation and critical review published in the European literature on osteopathic studies in the clinical field and in the area of fundamental research]	The SR included any type of study design.
Spiegel et al., 2003[2]	Osteopathic manipulative medicine in the treatment of hypertension: An alternative, conventional approach.	Narrative review.
Gamber et al., 2005[3]	Cost-effective osteopathic manipulative medicine: a literature review of cost-effectiveness analyses for osteopathic manipulative treatment.	Evaluation of OMT cost-effectiveness.
Licciardone et al., 2005[4]	Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Jäkel et al., 2011[5]	Therapeutic effects of cranial osteopathic manipulative medicine: a systematic review.	The SR included primary studies in healthy volunteers.
Posadzki et al., 2011[6]	Osteopathy for musculoskeletal pain patients: A systematic review of randomized controlled trials.	The SR included primary studies in healthy volunteers and intervention was not performed by osteopathic physicians or osteopaths.
Orrock et al., 2013[7]	Osteopathic intervention in chronic non-specific low back pain: a systematic review.	Overlap: 2 out of 2 studies. This SR was update by Franke 2014[10].
Cerritelli et al., 2015[8]	Osteopathic manipulative treatment in neurological diseases: systematic review of the literature.	The SR included any type of study design.
Cicchitti et al., 2015[9]	Chronic inflammatory disease and osteopathy: a systematic review.	The SR included study with an animal model and any type of study designs.
Majchrzycki et al., 2015[10]	Application of osteopathic manipulative technique in the treatment of back pain during pregnancy.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Vasconcelos et al., 2015[11]	Effect of osteopathic maneuvers in the treatment of asthma: review of literature.	The SR included any type of study design, and the intervention was not performed by osteopathic physicians or osteopaths.
Guillard et al., 2016[12]	Reliability of diagnosis and clinical efficacy of cranial osteopathy: a systematic review.	The SR included primary study in which the intervention was not performed by osteopathic physicians or osteopaths.
Kruger S., 2016[13]	Osteopathic treatment of irritable bowel syndrome - A review	Overlap:4 out 4 studies. Most rigorous criteria were used in Muller' s SR[9].
Ruffini et al., 2016[14]	Osteopathic manipulative treatment in gynecology and obstetrics: A systematic review.	The SR included any type of study designs.
Veloso et al., 2016[15]	Osteopathic Manipulation Treatment on postural balance: a systematic review.	The SR included any type of study designs.
Raguckas et al.,2016[16]	Osteopathic considerations in obstructive pulmonary disease: A systematic review of the evidence.	The SR included any type of study designs.
Ahmad R., 2017[17]	Current Clinical Status of Osteopathy: Study Based on Retrospective Evidences of Six Years, A Systemic Review	The SR included any type of study design, and the intervention was not performed by osteopathic physicians or osteopaths.
Do Vale et al., 2017[18]	Effectiveness of the osteopathic treatment in intestinal constipation: A systematic review	Clinical outcomes are not reported.
Steel et al., 2017[19]	Osteopathic manipulative treatment: A systematic review and critical appraisal of comparative effectiveness and health economics research.	The SR included any study designs.
Lanaro et al., 2017[20]	Osteopathic manipulative treatment showed reduction of length of stay and costs in preterm infants.	The SR included RCTs and controlled clinical trials.
Guillaud et al., 2018[21]	Reliability of diagnosis and clinical efficacy of visceral osteopathy: A systematic review.	The SR included primary study in which the intervention was not performed by osteopathic physicians or osteopaths.
Potekhina et al., 2018[22]	Osteopathy is a new medical specialty. Assessment of clinical effectiveness of osteopathic manipulative therapy in various diseases.	The SR included any type of study design, and the intervention was not performed by osteopathic physicians or osteopaths.
Saracutu et al., 2018[23]	The effects of osteopathic treatment on psychosocial factors in people with persistent pain: A systematic review.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Sposato et al.2018[24]	Osteopathic manipulative treatment in surgical care: short review of research publication in osteopathic Journals during the period 1990 to 2017.	The SR included any study designs.
Verhaeghe et al., 2018[25]	Osteopathic care for spinal complaints: A systematic literature review.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.

Verhaeghe et al., 2018[26]	Osteopathic care for low back pain and neck pain. A cost-utility analysis.	Health economic evaluation of osteopathic care in low back pain and neck pain. Data about clinical outcomes were not completely reported.
Whalen et al., 2018[27]	A Short Review of the Treatment of Headaches Using Osteopathic Manipulative Treatment.	The SR included any type of study design, and the intervention was not performed by osteopathic physicians or osteopaths
Rechberger et al, 2019[28]	Effectiveness of an osteopathic treatment on the autonomic nervous system: a systematic review of the literature.	The SR included any type of study design, primary studies in healthy participants and intervention was not performed by osteopathic physicians or osteopaths.
Switters et al. 2019[29]	Is visceral manipulation beneficial for patients with low back pain? A systematic review of the literature.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Buscemi et al., 2020[30]	Endocannabinoids release after osteopathic manipulative treatment. A brief review.	The SR included any type of study designs.
Santiago et al. 2020[31]	Instrumentation used to assess pain in osteopathic interventions: A critical literature review.	Clinical outcomes are not reported.
Kiepe et al., 2020[32]	Effects of osteopathic manipulative treatment on musicians: A systematic review.	The SR included any type of study designs.
Baroni et al., 2021[33]	Osteopathic manipulative treatment and the Spanish flu: a historical literature review.	Historical review evaluating which OMT technique were administered in patients during the 1918 Spanish flu pandemic.
Tramontano et al., 2021[34]	Vertigo and balance disorders- The role of osteopathic manipulative treatment: A systematic review.	The SR included any type of study designs and primary study in healthy participants.
De Marsh et al., 2021[35]	Pediatric osteopathic manipulative medicine: A scoping review.	The SR included any type of study designs.

OMT: osteopathic manipulative treatment, RCTs: randomized controlled trials, SR. systematic review

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Supplementary Table 2. Summary of identified systematic reviews with overlapping.

Total SRs (n=9)	**Total**	**overlapping**	**Total**
Total trials	71	16	55
Total participants	5577	1837	3740
Musculoskeletal conditions (6 SRs)[24-29]			
Total trials	44	14	30
Total participants	4251	1837	2414
Trials low back pain	34	12	22
Participants low back pain	3369	1316	2053
Trials neck pain	3	0	3
Participants neck pain	123	0	123
Trials chronic non-cancer pain	7	2	5
Participants chronic non-cancer pain	759	521	238
Paediatric conditions (1 SR)[30]			
Trials pediatrics conditions	17	0	17
Participants pediatric conditions	887	0	887
Neurological conditions (1 SR)[31]			
Trials primary headache	5	0	5
Participants primary headache	235	0	235
Visceral conditions (1 SR)[32]			
Trials irritable bowel syndrome	5	0	5
Participants irritable bowel syndrome	204	0	204

SR: systematic review.

Supplementary Table 3. Identified SRs with studies overlapping.

Franke 2014[25]		De Oliveira 2013[24]		Dal Farra 2020[27]		Rehman 2020[29]		Franke 2017[26]	
Primary studies	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**
Chown 2008	71			Chown 2008	131*	Albers 2018	48	Rohrich 2014	56
Gibson 1985	97					Cuccia 2010	50	Beltz 2014	41
Licciardone 2003	71	Licciardone 2003	71	Licciardone 2003	98**	Licciardone 2003	66	Schwerla 2015	30
Licciardone 2010	144	Licciardone 2010	144					Licciardone 2010	144
Licciardone 2013	455	Cleary 1994	12	Licciardone 2013	455	Licciardone 2013	455	Hensel 2015	52
Mandara 2008	94	Burton 2000	30	Mandara 2008	94	Papa 2012	72		
Peters 2006	57					Schwerla 2008	37	Peters 2006	57
Grundemann 2013	41					Stepnik 2018	31	Gundemann 2013	41
Recknagle 2007	39			De Oliveira 2019	38			Recknagle 2007	39
Vismara 2012	21	Vismara 2012	21	Vismara 2012	21				
Anderson 1999	155								
Adorjàn - Schaumann 1999	57								
Heinze 2006	60								
Cruser 2012	60								
Schwerla 2012	80								
Trials 15	**TP 1502**	**Trials 5**	**TP 278**	**Trials 6**	**TP 739**	**Trials 7**	**TP 759**	**Trials 8**	**TP 858**

TP, Total Participants. *OMT group counted twice and considered exercise group even if drop-out are >40%. **participants at 6 months, OMT counted twice.

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
Title			
	#1	Identify the report as an overview of systematic reviews.	1
Abstract			
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	3

Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	4
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	4-5
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, and date last searched.	5
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 Appendix
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the overview).	5
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	5-6
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	6. This is an overview therefore we used the AMSTAR-2 tool.
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7

Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	6-7. Meta-analysis was not performed
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a This is an overview
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a. However, an overlapping analysis of the primary clinical trial was performed. 6
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1, Supplementary Table 1.
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	8-13 Table 1
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	This is an overview therefore we used the AMSTAR-2 tool. 13 Table 3
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals.	Table 2
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	7-13 Meta- analysis was not performed
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a. This is an overview

Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplementary Table 2 and 3
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	13-15
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	14-16
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	16

BMJ Open

Efficacy and safety of osteopathic manipulative treatment: an overview of systematic reviews

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Paediatrics, Neurology, Public health
Keywords:	COMPLEMENTARY MEDICINE, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Functional bowel disorders < GASTROENTEROLOGY, Migraine < NEUROLOGY

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Efficacy and safety of osteopathic manipulative treatment: an overview of systematic reviews

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Abstract

Objective: To summarize the available clinical evidence on the efficacy and safety of osteopathic manipulative treatment (OMT) for different conditions.

Design: Overview of systematic reviews (SRs) and meta-analyses (MAs). PROSPERO CRD42020170983

Data sources: An electronic search was performed using seven databases: PubMed, EMBASE, CINAHL, Scopus, JBI, Prospero and Cochrane Library, from their inception until November 2021.

Eligibility criteria for selecting studies: SRs and MAs of randomized controlled trials evaluating the efficacy and safety of OMT for any condition were included.

Data extraction and synthesis: The data were independently extracted by two authors. The AMSTAR-2 checklist was used to assess the methodological quality of the SRs and MAs. The overview was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Results: The literature search revealed 9 SRs or MAs conducted between 2013 and 2020 with 55 primary trials involving 3740 participants. The SRs reported a wide range of conditions including acute and chronic non-specific low back pain (NSLBP, four SRs), chronic non-specific neck pain (CNSNP, one SR), chronic non-cancer pain (CNCP, one SR), paediatric

(one SR), neurological (primary headache, one SR) and irritable bowel syndrome (IBS, one SR). Although with a different effect size and quality of evidence, MAs reported that OMT is more effective than comparators in reducing pain and improving functional status in acute/chronic NSLBP, CNSNP and CNCP. Due to small sample size, presence of conflicting results and high heterogeneity, questionable evidence existed on OMT efficacy for paediatric conditions, primary headache and IBS.

No adverse events were reported in most SRs. According to AMSTAR-2, the methodological quality of the included SRs was rated low or critically low.

Conclusion: Based on the currently available SRs and MAs, promising evidence suggests the possible effectiveness of OMT for musculoskeletal disorders. Limited and inconclusive evidence occurs for paediatric conditions, primary headache and IBS. Further well-conducted SRs and MAs are needed to confirm and extend the efficacy and safety of OMT.

Keywords: low back pain, migraine disorders, neck pain, osteopathic manipulative treatment, paediatric, pregnancy, randomized controlled trial.

Strengths and limitations of this study

- ♦ This systematic overview included a comprehensive literature search for evidence on the efficacy and safety of osteopathic manipulative treatment for any condition.
- ♦ The present overview was conducted according to the Cochrane Handbook for the Systematic Review of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).
- ♦ The inclusion criteria were restricted to systematic reviews and meta-analyses of randomized controlled trials that included patients with any conditions.
- ♦ Since only randomized controlled trials in which OMT was performed by osteopathic physicians or osteopaths were included, some relevant systematic reviews could have been missed.
- ♦ The quality of the evidence from the included systematic reviews and meta-analyses was assessed according to the AMSTAR-2 tool.

Introduction

Osteopathic medicine, depending on different legal and regulatory structures around the world, is a medical profession (e.g. USA), an allied health profession (e.g. UK) or a part of complementary and alternative medicine (e.g. Italy or France). Developed by Andrew Taylor Still in the late 1800s in the Midwestern USA,[1]thistherapy is based on the principle that the structure (anatomy) and function (physiology) of the individual's body are closely integrated and that a person's well-being depends on the balance of neurological, musculoskeletal and visceral structures.[1]

Osteopathic medicine is provided on almost every continent, and in 2020, a survey estimated that 196,861 osteopathic practitioners provide osteopathic care worldwide in 46 countries.[2]

Osteopathic medicine plays an important role primarily in musculoskeletal healthcare. A recent survey conducted in Switzerland[3] on a sample of 1144 patients showed that over 80% of patients had requested an osteopathic consultation for musculoskeletal pain (mainly low back pain, neck pain and headaches). Similar results were reported by a survey conducted in the United Kingdom[4] on a sample of approximately 1600 patients with pain in the lumbar spine, cervical spine and pelvic region. Finally, a prospective study on 14000 patients in Quebec, Canada[5] reported musculoskeletal pain, localized in the spine, thorax, pelvis and limbs as the most common reason for osteopathic consultations.

Osteopathic manipulative treatment (OMT) is defined in the Glossary of Osteopathic Terminology as "the therapeutic application of manually guided forces by an osteopathic practitioner to improve physiologic function and/or support homeostasis that has been altered by somatic dysfunction".[6] OMT refers to a number of various types of approaches and techniques such as myofascial release, mobilization, osteopathy in cranial field (OCF) and visceral manipulation, in order to optimize the body's normal self-regulating mechanisms. The aim of OMT is to solve somatic dysfunction (ICD-10-CM diagnosis code M99.00-09), although other care aspects have been proposed.[1,7]

In recent years, a number of systematic reviews and meta-analyses have been published to evaluate the clinical efficacy and safety of osteopathic medicine for conditions such as low back pain, neck pain and migraine. However, due to differences in methodologies and the quality of systematic reviews, no clear conclusions were achieved. The aim of this overview is to summarize the available clinical evidence on the efficacy and safety of OMT for different conditions. This overview may be relevant to clinicians and policy makers to better understand in which conditions osteopathic medicine can be an effective and safe complementary therapy.

Methods

The overview was conducted according to the Cochrane Handbook for the Systematic Review of Interventions (Cochrane Book) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[8-10] The protocol of the overview has been registered on PROSPERO (CRD42020170983).

Patient and public involvement statement

For this overview of systematic reviews and meta-analyses, patients or the public were not involved.

Eligibility criteria

Type of review

This overview included only systematic reviews (SRs) and meta-analyses (MAs), published as a full paper, of randomised controlled trials (RCTs), which are well known to be the gold standard for evaluating the efficacy of an intervention.[11] SRs evaluating the inter-rater or intra-rater reliability for any type of osteopathic approach were excluded. SRs and MAs evaluating both RCTs and controlled clinical trials were excluded if a sub-analysis for RCTs was not performed. SRs that did not meet all eligibility overview criteria were excluded. For SRs in which criteria were not understandable, the primary studies were analysed.

Participants/population

Participants were human, of any gender, age or clinical condition undergoing OMT. Reviews including osteopathic manipulation on animal models as well as on healthy volunteers were excluded.

Intervention

The intervention consists of OMT performed by osteopaths, osteopathic physicians or osteopathic trainees who used a black box method or a specific protocol without any restriction of approach and technique based on manual assessment, diagnosis, and treatment in accordance with the osteopathic principle.[1,2] SRs including primary studies on both OMT and other complementary manual interventions were excluded if a sub-analysis was not independently performed for each manual treatment. To verify that osteopathic treatment was performed by osteopaths, the primary clinical trials were analysed.

Comparison

In order to retrieve all clinical evidence currently reviewed in SRs and MAs, the comparison group included placebo, sham OMT, light touch therapy, no treatment, waiting list, conventional treatment, physiotherapy or other complementary medicine treatments.

Setting

SRs with trials performed in any health-related settings and/or health promotion centres were included.

Main outcomes

The main outcomes were any clinically relevant endpoint measures, depending on the clinical condition reported in the SRs.

Any adverse events caused by OMT were extracted. Other types of outcomes such as prevalence of somatic dysfunction and inter-rater or intra-rater reliability for any type of osteopathic approach were excluded.

Search strategy

A systematic literature search was carried out independently by two reviewers (D.B. and D.R.) using the following electronic databases: MEDLINE (PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica database (EMBASE), Joanna Briggs Institute database of systematic reviews and implementation reports (JBI), Scopus, Prospero and Cochrane Library, all from their inception until 13th November 2021. No language or date restrictions were applied. The search strategy was performed using the following search terms: osteopathic treatment, osteopathic medicine, osteopathic manipulation, review, systematic review and meta-analysis. The references list of the included SRs and MAs, as well as narrative reviews, were widely perused for the identification of additional articles. Full details of the search strategy for PubMed are provided in the *Appendix* (supplementary materials).

Data collection and analysis

Study selection

The selection was performed independently by two authors (D.B. and D.R.). All the retrieved articles were imported into version 1.19.8 of the Mendeley software, and duplicate publications were excluded. Potential eligible SRs and MAs were read in the abstract and full text and independently evaluated by the two authors for inclusion in the overview. SRs and MAs were excluded if they did not meet the inclusion criteria, first at the title and abstract level, and then at the full-text level. Disagreements were resolved through discussion and consensus between the two review authors; if no agreement was reached, the third member of the review team (F.B.) was then consulted. Weighted kappa statistics were calculated to measure agreement between the authors.

Data extraction and management

Two authors (D.B. and F.B.) independently extracted data using an Excel spreadsheet. We collected the following information (where available) from SRs and MAs: first author, year of publication and country of the corresponding author, date assessed as up to date, condition

treated, number of included studies and participants, gender distribution and age, osteopathic interventions and co-interventions description, and number of treatments, control description, outcome measures, time points reported, reporting adverse events, primary studies quality assessment included in each SRs and MAs, GRADE (Grading of Recommendations Assessment, Development and Evaluation) results (see "Strategy for data synthesis" section for more details), MAs data, if any, and SRs main results. We reported the mean difference (MD) or standard mean difference (SMD), 95% confidence intervals (CI) and results of any test of heterogeneity reported in the relevant meta-analysis. When not reported in the SRs, mean and standard deviation (SD) for continuous variables as well as median, interquartile (IQR) and range for discrete variables were calculated (e.g. patient's age, gender).

Assessment of the methodological quality of included SRs and MAs

The methodological quality of the included SRs and MAs was assessed using the AMSTAR-2 tool, which is designed to generate an overall rating based on weaknesses of some critical domains (items 2,4,7,9,11,13 and 15).[10] AMSTAR-2 classifies the overall confidence of the results into four levels: high (no or one non-critical weakness), moderate (more than one non-critical weakness), low (one critical flaw with or without non-critical weaknesses) and critically low (more than one critical flaw or without non-critical weaknesses).[12] The quality assessment was evaluated independently by two authors (D.B. and F.B.), with any disagreements resolved through discussion with the third author (D.R.). To provide a simple indication of the results for the reader, for each domain we used a "stop-light" indicator where green indicates "Yes", yellow indicates "Partial Yes" and red indicates "No". Weighted kappa statistics were calculated to measure agreement between the authors.

Overlapping systematic reviews

In accordance with recent guidelines,[13,14] we decided to count the primary studies present in more than one SR only once. When more than one systematic review (which investigated the same research question and used the same primary studies) was identified, only the latest one was selected if it used the most rigorous criteria (e.g. followed the PRISMA criteria, used the more recent SR/MA guidelines) to evaluate the methodological quality of the studies.

Strategy for data synthesis

Due to the overlap of studies and heterogeneity between reviews with regard to outcome measures, a critical synthesis of the results was performed. The methodological quality of RCTs can be evaluated using several scores, including the Jadad score, the PEDro scale and the Cochrane risk of bias tool for randomized trials (RoB). Different versions of RoB are available, which refer to different updates of the Cochrane Handbook for systematic reviews

of intervention.[15,16] Moreover, for musculoskeletal disorders, the Cochrane Back and Neck Review Group (CBN Group, previously named CBRG) has developed a specific RoB guideline [also for this guideline, different versions are available[17-19]]. Considering different judgements in our overview, when possible we have reported results (judgements) according to the last version of the RoB tool.[19,20] In table 1, authors' judgements are reported, while our update judgements are reported in the text. Once meta-analysis was performed, we reported the data synthesis used in the meta-analysis: effect size (ES) and heterogeneity. Effect size was reported according to Cohen.[21] Briefly, a small effect was defined as MD less than 10% of the scale and SMD less than 0.50%, a medium effect as MD from 10% to 20% of the scale and SMD from 0.50% to 0.80%, and a large effect was defined as MD greater than 20% of the scale and SMD scores greater than 0.80%.[19] Concerning heterogeneity, the following thresholds were considered for the interpretation of the reported I^2 statistic index: i) 0% to 40% might not be important, ii) 30% to 60% may represent moderate heterogeneity, iii) 50% to 90% may represent substantial heterogeneity, iv) 75% to 100% considerable heterogeneity.[20] We reported the GRADE results as rated by the SR's authors. According to the GRADE approach, the quality of evidence for each outcome (considering the RoB, imprecision, inconsistency of results, indirectness of evidence and publication bias) can fall into four categories: high quality evidence (further research is very unlikely to change confidence in the estimated effect), moderate quality (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate) and very low quality (there is great uncertainty about the estimate).[22] To provide a simple indication of the results for the readers, we developed a "Traffic Light Evidence" (TLE) derived from the SR or/and MA evidence. The colour of the TLE is explained in supplementary materials. Moreover, we created an "Overall Traffic Light Evidence" (OTLE) resulting from: Green light, high-quality evidence from MAs indicates intervention effectiveness; Yellow light, promising evidence suggests possible effectiveness, but more research would increase our confidence in the estimate of the effect; Red light, limited or inconclusive evidence.

Results

Literature search results and study selection

The literature search yielded 13128 potentially relevant articles, and after eliminating duplicate articles (4778), 8350 articles were screened (see figure 1). After reading the titles and abstracts, 44 full texts were selected for eligibility of which 35 were excluded (see supplementary table

1) and 9 SRs were considered relevant and included in this overview. A review that agreed with the outcomes of the current review was identified in Prospero (CRD42021280994). The authors were contacted and replied that the results were not yet available. The agreement on the eligibility of the included studies, performed by the two authors (D.B. and D.R.), resulted in a 0.78 kappa value.[23]

Description of included reviews

This overview included nine SRs published between 2013 and 2020. Eight articles were published in English and one in Portuguese.

Six SRs focused on musculoskeletal conditions[24-29] and one each on paediatric,[30] neurological[31] and visceral conditions.[32] Detailed information on the included SRs/MAs is available in tables 1 and 2. The SRs included 71 primary studies with 5577 participants. Considering the overlapping of 16 trials and 1837 participants, the primary trials were 55 with 3740 participants (supplementary tables 2 and 3). The TLE is reported in supplementary table 4, and the OTLE is presented in table 3 and supplementary table 4.

Musculoskeletal conditions

Low back pain

Four reviews[24-27] with 34 RCTs (41 comparators) and 3369 participants assessed the efficacy of OMT on low back pain (LBP), including acute LBP (ALBP), chronic LBP (CLBP), LBP with sciatica, CLBP with menopause symptoms, LBP in obese patients, acute non-specific LBP (ANSLBP), chronic non-specific LBP (CNSLBP) and/or LBP and pelvic girdle pain in pregnancy and postpartum. Taking into account overlapping, there were 22 effective trials with a total of 2053 participants.

The SR performed by De Oliveira and colleagues considered LBP in obese patients, CLBP, CLBP with sciatica and LBP in menopause or pregnancy.[24] The review included 5 trials with 278 participants, and 3 RCTs were also reported in 2 more systematic reviews (see supplementary tables 2 and 3 for details). Conflicting results derived from the primary studies. In the inter-group analysis, OMT was not effective in reducing pain in the majority of the trials. Notably, in all RCTs, the results of functional outcomes were not analysed. Using the PEDro tool, the methodological quality of the 5 RCTs was classified by the authors as fair to excellent (PEDro range: from 5 to 9 out of 11 points). The OTLE for OMT efficacy in reducing pain in LBP with sciatica and LBP with menopausal symptoms was assessed to be red. Adverse events were not analysed.

The SR of Franke and colleagues included 15 trials with 1502 CNSLBP or ANSLBP participants.[25] Ten trials (1141 participants) and 9 RCTs (1046 participants) investigated the

effectiveness of OMT on pain and functional status, respectively. Nine RCTs were also reported in other systematic reviews (see supplementary tables 2 and 3 for details). The meta-analysis revealed a medium and small effect in reducing pain and improving functional status, respectively, and a moderate quality of evidence (downgraded due to inconsistency). Moreover, considerable (pain) and moderate (functional status) heterogeneity were found. Similar meta-analysis results (effect and heterogeneity) have also been found in a sub-analysis evaluating the effectiveness of OMT in CNSLBP patients (6 trials, 771 participants). The GRADE performed by the authors revealed both a moderate quality of evidence for pain and a high quality of evidence for functional status.

Three trials (4 comparators) with 242 participants evaluated the effectiveness of OMT versus obstetric care, sham ultrasound and untreated, for NSLBP in pregnant women. A large and a medium effect in reducing pain and improving functional status, respectively, were identified. Considerable (pain) and substantial (functional status) heterogeneity were found. GRADE evaluation by the authors reported a low quality of evidence for both outcomes.

Two RCTs with 119 participants evaluated the effectiveness of OMT for NSLBP in postpartum (PP) women. A large effect of OMT in reducing pain and improving functional status was identified. No heterogeneity was found. However, a moderate quality of evidence for both outcomes was revealed. The methodological quality of all RCTs, evaluated by the authors using the RoB from the Cochrane Back Review Group,[18] reported a low and a high risk of bias for 13 and 2 RCTs, respectively. However, considering the last version of the CBRG[19], we rated all RCTs at high risk of bias [domains at high RoB (% of RCTs): care provider (100%), patient blinding (67%), outcome assessor blinding (67%), groups similar at baseline (27%), lack of intention to treat analysis use (27%), free of selective outcome report (13%), dropouts described + acceptable (7%), similar timing outcome assessment (7%) and compliance acceptable (7%)]. The OTLE for the outcomes of each condition was assessed to be yellow.

Adverse events were evaluated in only 4 out of the 15 primary studies. Two RCTs reported minor adverse events such as stiffness and tiredness, one no adverse event and the last one evidenced adverse events not related to the treatment intervention.

In another SR, Franke and colleagues[26] identified 8 RCTs with 850 participants evaluating the efficacy of OMT on NSLBP and pelvic girdle pain in pregnancy (5 RCTs, 7 comparisons) and on NSLBP in postpartum women (3 trials and 3 comparisons) (see supplementary tables 2 and 3 for overlapping). The pooled analysis of 5 RCTs with 677 pregnancy participants reported the efficacy of OMT in reducing pain and improving functional status; however, a medium

effect and a considerable heterogeneity were revealed. The GRADE performed by the authors indicated a moderate quality of evidence.

The meta-analysis including 3 studies with 173 postpartum participants, revealed a significant effect in favour of OMT in reducing pain and improving functional status, although a large effect and substantial/considerable heterogeneity for both outcomes were reported. The GRADE performed by the authors also found a low quality of evidence.

The methodological quality of the included studies evaluated by the authors using the CBRG, Version 2009[18] identified a low risk of bias for all RCTs. Considering the CBNG,[19] we rated all RCTs as at high risk of bias [domains at high RoB (% of RCTs): patient binding (100%), care provider binding (100%), outcome assessor blinding (100%), dropouts described + acceptable (25%), group similar at the baseline (25%), intention to treat analysis (25%), similar timing outcome assessment (25%) and compliance acceptable (12%)].The OTLE for outcomes of each condition was assessed to be yellow.

Concerning the adverse events, one study reported occasional tiredness in some patients after OMT, two studies (personal communications to authors SR) did not find adverse events and the remaining 5 studies did not analyse adverse events.

The SR by Dal Farra and colleagues[27] evaluated the effectiveness of osteopathic interventions, performed by any type of manual therapist in CNSLBP patients. A subgroup analysis evaluating the effectiveness of OMT performed only by osteopaths identified 6 trials (8 comparisons) with 739 participants; 5 trials were also reported in other 2 further SRs (see supplementary tables 2 and 3 for more details).

The authors revealed a significant effect, clinically relevant according to the Cochrane Back and Neck Group, of OMT in reducing pain (medium effect) and improving functional status (small effect). However, substantial heterogeneity and a low quality of evidence (GRADE) were reported for both outcomes.

A further sub-analysis, including 2 trials (3 comparisons) with 548 participants, did not find evidence of OMT efficacy on functional status after a long-term treatment (12 weeks follow-up). Low quality of evidence and no heterogeneity were reported. The methodological quality of the primary studies, evaluated by the authors using the CBNG version 2015,[19] reported a high risk of bias for all RCTs [domains at high RoB (% of RCTs): high risk of bias for care provider (100%), patient blinding (50%), outcome assessor blinding (17%), participant allocation (33%) and reporting bias (17%)]. The OTLE for outcomes was assessed to be yellow.

With regard to adverse events, a trial reported an increase in back muscle spasticity in one patient treated with OMT.

Neck pain

Franke and colleagues,[28] evaluating 3 RCTs (3 comparators) with 123 participants, provided evidence that OMT exerted beneficial effects on chronic non-specific neck pain (CNSNP). Specifically, a medium effect size in reducing pain and a moderate quality of evidence on pain outcome were reported. A low level of heterogeneity was found. However, the meta-analysis did not show a significant effect on functional status. The methodological quality of all RCTs, evaluated by the authors using the CBRG,[18] reported a low risk of bias for all RCTs. Considering the CBNG version 2015,[19] we rated all RCTs at high risk of bias [domains at high RoB (% of RCTs): patient blinding (67%), care provider (100%), outcome assessor blinding (67%), dropouts described + acceptable (33%) and intention to treat analysis (100%)]. The OTLE for outcomes was assessed to be yellow.

No serious adverse events occurred in any RCTs (data reported in an RCT and as personal communications to SR authors in the other two studies).

Chronic non-cancer pain (CNCP)

The SR by Rehman and colleagues[29] evaluated the efficacy of osteopathic interventions performed by manual therapists in chronic non-cancer pain. In 7 out of 16 retrieved RCTs, OMT was performed by osteopaths (see supplementary tables 2 and 3 for overlapping). A pooled analysis, including 6 RCTs with 728 participants (6 comparators), found the efficacy of OMT *vs* standard care in reducing pain severity (small effect size, moderate quality of evidence and low level of heterogeneity). Moreover, another pooled analysis including two trials with 486 participants revealed the efficacy of OMT *vs* standard care in improving disability (large effect size, moderate quality of evidence and no heterogeneity). Similarly, the pooled analysis of the other 2 trials with 210 participants found that OMT *vs* standard care improved the quality of life (medium effect, moderate quality of evidence and no heterogeneity).

The methodological quality of the included studies was performed by the authors using a modified version of the Handbook of Cochrane[33] where only six domains were considered (random sequence generation, allocation concealment, blinding of participants, healthcare provider, outcome assessors and dropout rates). According to this modified version, the quality of the RCTs was reported by the authors to be at high risk of bias [domains at high RoB (% of RCTs): for patient blinding (100%), care provider blinding (100%), outcome assessor blinding (57%), random sequence generation (29%), participant allocation concealment (29%), and

dropout > 20% (43%)]. The OTLE for the outcomes of each condition was assessed to be yellow.

Adverse events were not considered by the SR authors.

Paediatric conditions

The SR by Posadzky and colleagues[30] evaluated the efficacy of OMT in paediatric conditions. This review included 17 RCTs involving a total of 887 participants with different conditions: cerebral palsy evaluated in 2 clinical studies involving a total of 197 participants, respiratory conditions evaluated in 4 trials involving 186 patients [obstructive apnoea 1 RCT, asthma 2 RCTs (in 1 study not reported the number of patients), bronchiolitis 1 RCT], otitis media evaluated in 3 trial involving a total of 167 participants, musculoskeletal function evaluated in 3 trials with 80 patients (idiopathic scoliosis 1 RCT, mandibular kinematics 1 RCT, postural asymmetry 1 RCT) and attention-deficit/hyperactivity disorder (77 participants), prematurity (101 participants), infantile colic (28 participants), congenital nasolacrimal duct obstruction (30 patients) and functional voiding (21 participants) individually assessed by 1 RCT. The single trials provided evidence that OMT exerted beneficial effects on congenital nasolacrimal duct obstruction (post-treatment), daily weight gain and length of hospital stay, dysfunctional voiding, infantile colic and postural asymmetry. By contrast, no significant effects of OMT on idiopathic scoliosis, obstructive apnoea or temporomandibular disorders compared with various control interventions have been evidenced by the single RCTs. For conditions in which more than one RCT has been performed (asthma, otitis media and cerebral palsy), contradictory results are reported. From the SR it emerges that low-quality RCTs favoured OMT, while moderate and high-quality RCTs failed to find OMT effectiveness. The vast majority of the RCTs were reported by the authors to be at high risk of bias (15 RCTs) [domains at high RoB (% of RCTs): allocation concealment (67%), patient blinding (67%), care provider blinding (100%), outcome assessor blinding (50%), addressing of incomplete data (33%), selective outcome reporting (33%), adequate sequence generation (28%)] with unclear or low risk of bias for the remaining two RCTs. The OTLE for outcomes of each condition was assessed to be red.

In 11 RCTs, adverse events were not analysed. No adverse events or serious adverse events following OMT were reported in 4 trials. Adverse events occurred in 1 RCT, but they were not related to OMT. One trial reported the aggravation of vegetative symptoms in 4 patients.

Neurological conditions

The SR of Cerritelli and colleagues,[31] including 5 RCTs with a total of 235 participants, evaluated 2 different types of primary headache: migraine (2 RCTs, 147 participants) and

tension-type headache (3 RCTs, 88 participants). Although the two RCTs evaluating efficacy in migraine reported positive results in favour of OMT (mainly in pain intensity reduction), inter-group analysis was performed only in 1 RCT. Similarly, evidence has been reported for the tension-type headache only when within-group analysis was performed; inter-group analyses reported conflicting results. The RCTs were reported by the authors to be at high risk of bias [domains at high RoB (% of RCTs): care provider blinding (100%), participant blinding (60%) and allocation concealment (20%)]. Due to high heterogeneity (different types of primary headaches, different outcome measures and variable length of follow-up), a meta-analysis was not conducted by the authors. The OTLE for the outcomes of each condition was assessed to be red.

Adverse events, evaluated in 2 RCTs, did not occur.

Visceral conditions

In a SR, Muller and colleagues,[32] including 5 primary studies and involving 204 participants, evaluated the efficacy of OMT in the treatment of irritable bowel syndrome (IBS). Although high heterogeneity (in outcome measures and follow-up period) was evidenced, the results indicated that OMT was effective in IBS. The methodological quality of all RCTs, evaluated by the authors using the CBRG,[18] reported a low risk of bias for all RCTs. Considering the CBNG,[19] we rated all RCTs at high risk of bias [domains at high RoB (% of RCTs): care provider blinding (100%), outcome assessor blinding (60%), randomization (20%), patient blinding (20%), groups similar at the baseline (20%) and intention to treat analysis (20%)]. The OTLE for the outcomes of each condition was assessed to be red.

No adverse events occurred in the patients from any of the RCTs.

Methodological quality of included reviews

A summary of the findings of the AMSTAR-2 is provided in tables 1 and 4. Inter-rater agreement between the two overview authors (D.B. and F.B.) on the ranking of quality achieved a 0.89 kappa value.[23]

According to the critical domain established in Shea et al.,[12] seven[25-29 31,32] and two systematic reviews[24,30]were rated as low and critically low quality, respectively.

Two of the nine SRs registered a protocol before beginning the study.[27,29] Eight SRs performed an appropriate literature search,[25-32] and five SRs reported justification for the exclusion of primary studies.[25,26,28,31,32] All SRs[24-32] evaluated the risk of bias of the included studies and five SRs[25-29] carried out a meta-analysis and used appropriate methods for the statistical combination of findings. Eight SRs[25-32] accounted for the risk of bias when interpreting and discussing the results of the SR. Finally, domain 15 (publication bias assessment) was rated as

not applicable for all the SRs due to lack of a meta-analysis[24,30-32] or the inclusion in the meta-analysis of fewer than 10 trials. [25-29]

Discussion

Osteopathic medicine, a form of complementary and alternative medicine (CAM), is a type of manual therapy used to normalize the structure-function relationship and to promote the body's own self-healing mechanism. In the last decade, CAM therapies have grown in use and popularity, and among these, many surveys have demonstrated an increasing interest in osteopathic medicine in patients with musculoskeletal disorders such as non-specific chronic low back pain and neck pain.[34,35]

Recently, osteopathic medicine has been regulated in many countries including the USA, Australia, the UK, Iceland, Denmark, Malta, Portugal and Switzerland, where it is a primary healthcare profession. In other countries, the regulation process has not yet been completed (i.e. Italy), or there is no legal recognition of the osteopathic profession.[36] In this context, we performed an overview to summarize the best available clinical evidence on the efficacy and safety of OMT. We identified nine SRs on the use of osteopathic care for the management of musculoskeletal, paediatric, visceral and neurological disorders with different effects and clinical relevance depending on the conditions.

From our overview, some relevant questionable problems emerge related to the lack of appropriate guidelines for assessing the methodological quality of trials in manual therapy and problems due to inadequate reporting of trial methodology and results. In this regard, most of the trials included in the SRs reported a high or unclear risk of bias for blinding procedures: patient, outcome assessor and care provider blinding. In manual therapy, blinding is an issue, as patients tend to be aware of the manual treatment and therapists cannot be blinded to the treatment intervention they deliver.[37] For participant-reported outcomes, for which the patient is the outcome assessor, such as for pain and functional status outcomes, blinding of patients is mandatory, and therefore, it is necessary to use, as a control group, sham procedures (including light touch therapy) that simulate manipulation. These sham procedures should be reported in RCTs; however, a lack of reporting placebo sham therapy procedures in both SRs and primary studies has been evidenced. It is important to note that, although these findings have already been reported by Cerritelli and colleagues in 2016,[38] to date, these suggestions have not been followed. More effort should be made to promote guidelines for designing the most reliable placebo for manual treatment to reduce the risk of bias in patient blinding.

However, a recent meta-epidemiological study found no evidence that lack of patients' blinding had an impact on estimate effects.[39]

Other issues that emerge from our overview are the lack of treatment description and timing of measuring outcomes (short- and long-term) in the SRs as well as in primary trials. In osteopathic medicine, as in any other manual therapy, it is important to describe in adequate detail each phase of the intervention, including how and when they were administered, and when the outcomes are measured. Without a complete description of treatments, clinicians cannot reliably reproduce useful interventions. Proper checklists for non-pharmacological treatments, such as the TIDieR (Template for Intervention Description and Replication) guide/checklist and the CONSORT (CONsolidated Standards of Reporting Trials) statement for randomized non-pharmacological treatment studies, should be followed by clinical trial authors.[40,41]

That said, our overview highlights that evidence on the efficacy of OMT is: 1) promising in musculoskeletal disorders, mainly in reducing pain and improving functional status in acute and chronic NSLBP patients, NSLBP in pregnancy or postpartum (OTLE: yellow), 2) limited and contradictory in the treatment of paediatric conditions (some conditions were evaluated by only one trial, some of which were of low methodological quality, and contradictory results were obtained for conditions in which two RCTs were performed, OTLE: red) and 3) limited on primary headache and IBS (OTLE: red).

The lack of solid evidence stems from a small sample size,[26,28-32] the presence of conflicting results[24,30,31] and a high heterogeneity in participants,[25,31] outcomes measures,[31,32] interventions[25-27,31] and comparison interventions.[25-27,32] Notably reduced heterogeneity was found when the RCTs were pooled considering interventions and comparators.[29]

According to AMSTAR-2, the methodological quality of the included SRs was rated low and critically low. Domain two (registered protocol) was critical for 7 SRs. The presence of a written and registered protocol prior to conducting the review should ensure that review methods are transparent and reproducible, and adhere to this prespecified research plan.[42] These should help avoid bias and unintended duplication of reviews.

Adverse events

Generally, manual therapies have been reported to be well tolerated, and manual therapy-related adverse events are short-lived and mild or moderate in intensity.[43] In our overview, we found that seven SRs[25-28,30-32] evaluated adverse events, and from these SRs it emerges that no severe incident involving musculoskeletal, neurological, visceral or paediatric disorders occurred after OMT. However, it should be noted that among these seven SRs, only two

reported the definition used to measure adverse events. The idea that manual therapies are safe could only be demonstrated if adverse events are defined and assessed in each clinical trial. Specifically, the authors should adequately report in detail the approach used to measure adverse events, which need to be defined using an appropriate taxonomy.[44,45]

Strengths and limitations

Numerous limitations can be found in our overview. First, considering our inclusion criteria, we may have missed some relevant SRs. Indeed, we included SRs by evaluating only RCTs (and not other study designs) in which OMT was performed by osteopathic physicians or osteopaths (and not by other manual therapists). Globally, two professional figures have emerged, largely due to different legal and regulatory systems around the world: osteopathic physicians, who are doctors with full and unlimited medical practice rights, and osteopaths who have obtained academic and professional standards for diagnosing and practicing treatments based on the principles of osteopathic philosophy. OMT is the core activity for both osteopathic physicians and osteopaths who follow the principles of osteopathic medicine by performing a personalized treatment according to the patient evaluation and subsequent tailoring. [46] Therefore, our decision to consider only osteopathic physicians or osteopaths arises from the premise of avoiding the fact that the principles of osteopathic medicine are not followed. In this regard, we excluded seven systematic reviews, and therefore, considering the overlapping, five RCTs were lost (see supplementary table 1 for details). According to our decision, a recent scoping review used more restrictive inclusion criteria, considering only studies performed in the USA where OMT is practiced by osteopathic physicians.[47] Considering that in most countries osteopathy is often conducted in the private sector (e.g. the UK, France and Italy), the participants included in the primary studies might not be generalizable to the population.

Since RCTs are widely recognized as the best design for evaluating the efficacy of an intervention, we also decided to include only SRs evaluating randomized controlled trials. In this regard, eleven systematic reviews were excluded and, considering the overlapping, 17 RCTs were lost (see supplementary table 1 for details).

Conclusion

This overview suggests that OMT could be effective in the management of musculoskeletal disorders, specifically with regard to CNSLBP patients and LBP in pregnant or postpartum women. In contrast, inconclusive evidence was derived from SRs analysing the OMT efficacy on paediatric conditions, primary headache and IBS. Although not all RCTs have investigated

the safety of OMT, considering that no serious adverse events have been reported, OMT can be considered safe.

Nevertheless, based on the low number of studies, some of which are of moderate quality, our overview highlights the need to perform further well-conducted SRs as well as clinical trials (which have to follow the specific guidelines for non-pharmacological treatments) to confirm and extend the possible use of OMT in some conditions as well as its safety.

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Table 1. Characteristics of the included systematic reviews and meta-analyses.

First author, year, country	Date assessed as up to date	Conditions	Trials number, participants number.	Gender distribution, Age (years)	Intervention (co-intervention): description. Number of treatments (SD).	Control or comparison description	Outcomes assessed	Time points reported	Main results	Definition used to measure AEs§. Reported AEs	AMSTAR-2
Musculoskeletal conditions: Low back pain											
De Oliveira Meirelles, 2013[24], Brazil	NR	CLBP, CLBP in pregnancy, LBP with menopausal symptoms, LBP in obese, LBP with sciatica.	5 RCTs, 278 adults. 1 CLBP, 1 CLBP in pregnancy, 1 LBP with menopausal symptoms, 1 LBP in obese, 1 LBP with sciatica.	Gender:85% female,15% male. Mean age 40 (from 4 RCTs).	OMT (UOBC, SE): OCF, ART, HVLA, MRT, MET, range of motion technique. Treatments: median 10 (7-10)**	SUT, NT, SM, chemonucleolysis,	Pain: VAS, dichotomous pain, pain scale.	Treatment time: 1 weeks and 15 weeks (from 2 RCTs). Evaluation: 1, 3 and 6 months (from 1 RCT)	OMT improved LBP in comparison with no intervention (but not with SM).	NR	Critically low
Franke, 2014[25], Australia	NR	ANSLBP, CNSLBP, NSLBP in pregnancy, NSLBP in PP	15 RCTs, 1502 adults. 10 NSLBP, 3 NSLBP in pregnancy, 2 NSLBP in PP.	Gender: NR. Mean age 36 (from 13 RCTs)	OMT (UC, heat &PT, UOBC, SE): NR. Treatments: median 4 (4-6)**	SUT, NT, SM, UC, PT, SWD.	Pain: VAS, NRS, MGPQ. Functional status: RMDQ, OPQ, ODI, LBP_DQ, Kinematic of thoracic/lumbar spine /pelvis during forward flexion, QBPDS.	Period: 2-9 weeks 1- 3- 6 months	OMT was effective in pain and functional status in ANSLBP, CNSLBP, NSLBP in pregnant and NSLBP in PP.	NR Only 4 RCTs reported AEs. 2 RCTs reported minor AEs such as stiffness and tiredness; 1 RCT reported that 6% of patients had AEs (but not serious). 1 RCT reported that no AEs occurred.	Low
Franke, 2017[26], Australia	NR	ANSLBP, CNSLBP and /or pelvic pain during pregnancy and PP.	8 RCTs, 850 adults. 5 LBP in pregnancy, 3 LBP in PP.	Gender: 100% female, Mean age 29.5	OMT (UOBC): NR. Treatments: Pregnancy median 7 (5.5-7). Postpartum median 4 (4-4.5)**	SUT, NT, UC.	Pain: VAS, QVAS, FP. Functional status: RMDQ, QPP, QBPDS, PGPQ, OPQ.	Pregnancy: ranged from 3 to 9 weeks, follow-up 1 and 2 weeks. Postpartum: 6 weeks. Follow-up: 2 weeks	OMT significantly improved pain and functional status in women with LBP during pregnancy and PP.	NR No serious AEs (from 3 RCTs*). 1 RCT reported occasional tiredness in some patients.	Low
Dal Farra 2020[27], Italy	Inception to April 2020	CNSLBP	6 RCTs***** 739 adults	Gender: NPTC Mean age 46 (from 4 RCTs), median age 41 (29-51)**	OMT (SE, UC): HVLA, MET, CST, MFR, MVMA. Treatments: range 5-10 sessions, median 6 (5-8)**	SM, PT, SE	Pain: VAS. Functional status: RMDQ, ODI, SF-36, EQ-5D, BDI.	Ranging from 2 weeks to 6 months. Follow-up: from 1 month to 1 year.	OMT significantly improved pain and functional status in CNSLBP in the short-term (but not in the long-term).	Frequency of adverse events and/or relative study withdrawals, and self-reported scales and questionnaires including quality of life and psychological function (e.g. fear avoidance beliefs, catastrophizing, pain-related fear); additional indicators considered were frequency of analgesic and/or NSAIDs use, economic impact or cost reduction and patient's care satisfaction. No AEs (from 5 RCTs). 1 RCT reported increased back muscle spasticity in a patient.	Low
Musculoskeletal conditions: Neck pain											
Franke, 2015[28], Australia	NR	CNSNP	3 RCTs, 123 adults.	Gender: NR. Mean age 44.	OMT (SUT, UC): NR. Treatments: median 5 (5-6)**	SM, PT	Pain: VAS, NRS, NPPQ. Functional status: NDI, NQ.	Ranging from 6 to 11 weeks. Follow-up: 3 months (in 2 RCTs).	OMT significantly improved pain, but not functional status in CNSNP.	NR Only 1 RCT reported not serious AEs, such as tiredness on the day of treatment and short-term aggravation of symptoms in other 'familiar' regions, were noted.	Low
Musculoskeletal conditions: Chronic non-cancer pain											

Rehman, 2020[29], Canada	NR starting date. Until July 2019	CNCP: Fibromyalgia, TMD, CNSLBP, CNSBP, CNSNP, CNP.	****** 7 RCTs, 759 adults. 1 Fibromyalgia, 1 TMD, 1 NSNP, 1 CNSBP, 2 CNSLBP, 1 CNSNP	Gender: 60% female, 40% male. Mean age 52 (from 5 RCTs), range 23-54 (from 2 RCTs).	OMT (non-steroidal medications, anti-inflammatory, analgesics and/or muscle relaxants, UC, SE, lumbar supports, physical therapies and CAM): MET, MFR, HVLA, BLT, CST, JA, MT, ST, FPR. Treatments: NR.	SUT, SE, PT, SC, use of an oral appliance, hot and/or cold packs, TENS, SM, LT, ROM activities, LTP.	Pain: VAS. Disability: RMDQ. SF-36, QOL	Duration of trial or follow-up period ranging from 42 to 168 days (1-6 months).	OMT, in comparison to [illegible] was significantly effective in reducing pain and increasing mobility as well as in improving QoL.	NR	Low
Paediatric conditions											
Posadzki, 2013[30], South Korea	Inception to November 2012	Pediatric conditions: CP, respiratory conditions, OM, musculoskeletal function, ADHD, prematurity, IC, CNLDO, DV.	17 RCTs, 887 neonates/infants (from 16 RCTs). 2 CP, 4 respiratory conditions, 3 OM, 3 musculoskeletal function, 1 ADHD, 1 prematurity, 1 IC, 1 CNLDO, 1 DV	Gender: NR. Range from premature infants >28 weeks to 18 years.	OMT: VO, CST, OMT techniques (ART, BLT, BLM, CS, FPR, MET, MFR or rib-raising). Treatment: median 4 (3-5)**	UC, NT, SM, WL, SM+ placebo, SM+ Echinacea, postural drainage, bronchodilators.	Cerebral palsy: CHQ, GMFM-66, PEDI, WeeFIM. Respiratory: RR, EV, flow, MEP, PEF. Musculoskeletal: TM, SF, Kinesiographics (MO, MOV, MCV, OVA, CVA). Preterm infants: LOS, DWG. ADHD: Conners Scale. Infantile colic: MNHSCS. Otitis media: Antibiotic use, tympanograms, Audiometrics, SI, surgery -free months, reflectometer. CNLDO: FDT, MJT. Dysfunctional voiding: DV symptoms.	Cerebral Palsy: 6 months follow-up. Respiratory, Musculoskeletal, ADHD, congenital nasolacrimal duct obstruction, dysfunctional voiding: posttreatment. Prematurity: discharge from hospital.	[illegible] conclusive evidence on the efficacy of OMT for any pediatric condition due to i) low methodological quality of RCTs (when conditions were evaluated by individual RCTs) and ii) contradictory results for the conditions under which two RCTs were performed.	NR AEs not evaluated in 11 RCTs. No AEs occurred in 4 RCTs. 1 RCT reported patients (4) aggravation of vegetative symptoms after OMT. 1 RCT reported AEs not related to OMT.	Critically low
Neurological conditions											
Cerritelli, 2017[31], Italy	Inception to April 2016	Primary headache: migraine, tension-type headache	5 RCTs, 235 adults. 2 migraine, 3 tension-type headache	Gender: 78 % female, 22% male (from 3 RCTs). Mean age 39.4 (from 3 RCTs)	OMT (UC, triptans, PMR): NBT (in 3 studies), use of protocols (in 2 studies). Treatment: median 4 (3-5)**	UC, SM, OE, PMR, rest	HIT-6 score, HF, WD, PI, DC.	Ranging from IAT to 6 months. Follow-up: 1, 3 months.	OMT reduced pain intensity, frequency and disability in patients with headache.	Number and types of AEs. AEs not evaluated in 3 RCTs, 2 RCTs reported no AEs.	Low
Visceral conditions											
Muller, 2014[32], Australia	Inception to October 2013	Irritable bowel syndrome	5 RCTs. 204 adults.	Gender: 79% female, 21% male (from 3 RCTs). Mean age 47	OMT: applied to different body region, VO (approach on the abdomen and spine, abdomen and sacrum), NBT. Treatments: median 5 (3-5)**	UC, SM.	Pain: VAS. Constipation, diarrhea, AD, RS, CTT, meteorism. IBS severity score, FIS score, HAD, BDI, IBSQoL2000. FBDSI	Ranging from 1 week to 3 months. Follow-up: short-term (2, 4 weeks), long-term (3, 12 months)	OMT, in comparison to sham therapy or standard care, reduced the symptoms of IBS, such as abdominal pain, constipation, diarrhea, and improved general well-being.	NR All RCTs reported that no serious or statistically significant AEs occurred.	Low

§ Reported by the Authors of the SRs. *In personal communications from authors of two RCTs, **median (Q1-Q3), ***The number is not reported for a RCT on asthma, ****Reported in methods but not performed, ***** subgroup analysis, ******13 RCTs, only 7 trials were used in our study, *******the outcomes measures are not reported in all studies. AD: abdominal distension, ADHD: attention deficit /hyperactivity disorder, AE: adverse events, ANSLBP: acute non-specific low back pain, ART: articulatory treatment, BDI: Beck Depression Index, BLM: Balanced membranous tension, BLM: Balanced membranous tension, BLT: Balanced ligamentous tension, CHQ: child health questionnaire, CNLDO: congenital nasolacrimal duct obstruction, CNCP: chronic non-cancer pain, CNSBP: chronic non-specific body pain, CNSLBP: chronic nonspecific low back pain, CNSNP: chronic nonspecific neck pain, CNP: chronic neck pain, CP: cerebral palsy, CS: counterstains, CST: cranial sacral therapy, CTT: colonic transit time, CVA: cranial vault asymmetry, CV4: a technique in cranial field, compression of the fourth ventricle, DV: dysfunctional voiding, DC: drug consumption, DWG: daily weight gain, EV: expiratory volume, FBDSI: functional bowel disorder severity Index, FDT: fluorescein disappearance test, FIS: fatigue impact scale, FP: frequency of pain, FPR: facilitated positional release, GMFM-66: gross motor function measure-66, HAD: hospital anxiety and depression, HF: headache frequency, HIT-6: headache impact test-6, HVLA: high velocity low amplitude thrust, IAT: immediately after treatment, IBS: irritable bowel syndrome, IBSQoL 2000: IBS quality of life, IC: infantile colic, JA: joint articulation, LBP-DQ: low back pain disability questionnaire, LBP: low back pain, LOS: length of stay, LT: light touch, LTP: laser therapy, MCV: maximal closing velocity, MEP: mid expiratory phase, MET: muscle energy treatment, MFR: myofascial release, MGPD: Mc Gill pain questionnaire, MNHSCS: mean numbers of hours spent crying and sleeping, MJT: modified jones test, MO: maximal mouth opening, MOV: maximal opening velocity, MRT: myofascial release treatment, MT: membranous tension, MVMA: medium velocity medium amplitude, NBT: need based treatment, NDI: Neck Disability Index, NP: not performed, NPPQ: Northwick park pain questionnaire, NPTC : not possible to calculate, NR: not reported, NRS: numeric rating scale, NQ: Nordic questionnaire, NSNP: non-specific neck pain, NT: no treatment, OCF: osteopathy in cranial field, ODI: oswestry disability Index, OE: osteopathic evaluation, OM: otitis media, OMT: osteopathic manipulative treatment, OPQ: oswestry pain questionnaire, Pedi: pediatric evaluation of disability inventory, PEF: peak expiratory flow, PGPQ: pelvic girdle pain questionnaire, PI: pain intensity, PMR: progressive muscular relaxation exercise, PP: postpartum, PT. physical therapy, QBPDS: Quebec back pain disability scale, QPP: questionnaire postpartum, QVAS: quadruple visual analogue scale, RMDQ: Roland Morris disability questionnaire, ROM: range of movement, RR: respiratory rate, RS: rectal sensitivity, SC: standard care, SD: standard deviation, SE: specific exercise, SF: spine flexibility, SI: surgical intervention, SM: sham manipulation, ST: Spencer technique, SUT: sham ultrasound treatment, SWD: short-wave diathermy, TENS: transcutaneous electrical nerve stimulation, TM: Trunk morphology, TMD: temporomandibular disorder, UC: usual care, UOBC: usual obstetrical care, VAS: visual analogic scale, VO: visceral osteopathy, WD: work disability, WL: waiting list, WeeFIM: functional independence measure for children

Table 2. Quality of the primary RCTs included in the systematic reviews/meta-analyses and meta-analyses quantitative results.

First author, year, country	Primary studies quality. GRADE	Meta-analysis data
Musculoskeletal conditions: Low back pain		
De Oliveira Meirelles, 2013[24], Brazil	Pedro score: 6 (2 RCTs), 9 (1 RCT), 7 (1 RCT), 5 (1 RCT).	NP
Franke, 2014[25], Australia	Low RoB (13 RCTs, low risk of bias in at least 6 categories). High RoB (2 RCTs).	
	GRADE	
	ANSLBP and CNSLBP	
	Pain: MODERATE	Pain: [MD -12.91; 95% CI: -20.00, -5.82]. I^2=86%.
	Functional status: MODERATE	Functional status: [SMD -0.36; 95% CI; -0.58, -0.14]. I^2=57%.
	CNSLBP	
	Pain: MODERATE	Pain [MD -14.93; 95% CI; -25.18, -4.68]. I^2= 89%.
	Functional status: HIGH	Functional status [SMD -0.32; 95% CI: -0.58, -0.07]. I^2=49%.
	NSLBP in Pregnancy	
	Pain: LOW	Pain [MD -23.01; 95% CI: -44.13, -1.88]. I^2= 91%.
	Functional status: LOW	Functional status [SMD -0.80; 95% CI: -1.36, -0.23]. I^2=76%.
	NSLBP in PP	
	Pain: MODERATE	Pain [MD -41.85; 95% CI: -49.43, -34.27)]. I^2=0%.
	Functional status: MODERATE	Functional status [SMD -1.78; 95% CI: -2.21, -1.35]. I^2=0%.
Franke, 2017[26], Australia	Low RoB (all RCTs, low risk of bias in at least 6 categories).	
	GRADE	
	NSLBP in pregnancy	
	Pain: MODERATE	Pain: [MD -16.75; 95% CI: -31.79, -1.72]. I^2=94%.
	Functional status: MODERATE	Functional status: [SMD -0.50; 95% CI: -0.93, -0.07]. I^2=84%.
	LBP in PP	
	Pain: LOW	Pain: [MD -38.00; 95% CI: 46.75, -29.24]. I^2=68%.
	Functional status: LOW	Functional status: [SMD -2.12; 95% CI: -3.02, - 1.22]. I^2=81%.
Dal Farra, 2020[27], Italy	High RoB (all RCTs).	
	GRADE	
	CNSLBP	
	Pain: LOW	Pain [SMD -0.57; 95% CI: -0.90, -0.25]. I^2=72%.
	Functional status: LOW	Functional status [SMD -0.34; 95% CI: - 0.65, -0.03]. I^2=71%.
	Functional status (12 weeks follow-up): LOW.	Functional status 12 weeks follow-up: [SMD -0.14; 95%CI: -0.31, 0.03]. I^2=0%.
Musculoskeletal conditions: Neck pain		
Franke, 2015[28], Australia	Low RoB (all RCTs, low risk of bias in at least 6 categories).	
	GRADE	
	CNSNP	
	Pain: MODERATE	Pain: [MD -13.04, 95% CI: -20.4, -5.44]. I^2=34%.
	Functional status: MODERATE	Functional status [SMD: -0.38, 95%CI: -0.88, 0.11]. I^2=0%.
Musculoskeletal conditions: Chronic non-cancer pain		
Rehman, 2020[29], Canada	High RoB (all RCTs, based on a modified RoB with 6 domains).	
	GRADE	
	CNCP	
	Pain: MODERATE	Pain (OMT vs SC) [SMD - 0.37; 95% CI: - 0.58, -0.17]. I^2=25%.
	Disability: MODERATE	Disability (OMT vs SC) [SMD -1.04; 95% CI: - 1.23, -0.85]. I^2= 0%.
	Quality of life: MODERATE	Quality of life (OMT vs SC) [SMD 0.67; 95% CI: 0.29, 1.05]. I^2=0%.
Pediatric conditions		
Posadzki, 2013[30], South Korea	High risk (all RCTs).	NP
Neurology conditions		
Cerritelli, 2017[31], Italy	JADAD NR*. The majority of RCTs have high or unclear RoB.	NP
Visceral conditions		
Muller, 2014[32], Australia	Low RoB (all RCTs, low risk of bias in at least 6 categories).	NP

*Reported in methods but not performed. ANSLBP: acute non-specific low back pain, CNCP: chronic non-cancer pain, CNSBP: chronic non-specific body pain, CNSLBP: chronic non-specific low back pain, CNSNP: chronic non-specific neck pain, CNP: chronic neck pain, MD: mean difference, NP: not performed, NR: not reported, OMT: osteopathic manipulative treatment, PP: postpartum, RCT: randomized controlled trial, RoB: Risk of Bias, SC: standard care, SMD: standard mean difference.

Table 3. Overall traffic light evidence for OMT efficacy.

Musculoskeletal conditions	First author, year	Overall traffic light evidence
1. ANSLBP/CNSLBP		
Pain	Franke, 2014[25]	
	Dal Farra, 2020[27]	
Functional status	Franke, 2014[25]	
	Dal Farra, 2020[27]	
2. CNSLBP		
Pain	Franke, 2014[25]	
	Dal Farra, 2020[27]	
Functional status	Franke, 2014[25]	
	Dal Farra, 2020[27]	
3. NSLBP in Pregnancy		
Pain	Franke, 2014[25]	
	Franke, 2017[26]	
Functional status	Franke, 2014[25]	
	Franke, 2017[26]	
4. NSLBP in PP		
Pain	Franke, 2014[25]	
	Franke, 2017[26]	
Functional status	Franke, 2014[25]	
	Franke, 2017[26]	
5. LBP WITH SCIATICA		
Pain	De Oliveira Meirelles, 2013[24]	
6. LBP with MENOPAUSAL SYMPTOMS		
Pain	De Oliveira, 2013[24]	
7. CNSNP		
Pain	Franke, 2015[28]	
Functional status	Franke, 2015[28]	
8. CNCP		
Pain	Rehman, 2020[29]	
Disability	Rehman, 2020[29]	
Quality of life	Rehman, 2020[29]	
PAEDIATRIC CONDITIONS		
Outcomes for different conditions *	Posadzky, 2013[30]	
NEUROLOGICAL CONDITIONS		
*Outcomes for migraine and tension-type headache***	Cerritelli, 2017[31]	
VISCERAL CONDITION		
*Outcomes for IBS****	Muller, 2014[32]	

Overall traffic light evidence:Yellow light, promising evidence suggests possible effectiveness, but more research would increase our confidence in the estimate of the effect; **Red light**, limited or inconclusive evidence.
ANSLBP: acute non-specific low back pain, CNCP: chronic non-cancer pain, CNSLBP: chronic non- specific low back pain, CNSNP: chronic non-specific neck pain, IBS: irritable bowel syndrome, LBP: low back pain, NSLBP: non-specific low back pain, PP: postpartum.
*Different conditions were considered. It's not possible to evaluate the single outcome for each condition,**pain, work disability, headache frequency, quality of life,***pain, constipation, quality of life.

Table 4. Quality of the included systematic reviews by the Amstar-2 tool.

First author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9 RCT	Q9 NRSI	Q10	Q11 RCT	Q11 NRSI	Q12	Q13	Q14	Q15	Q16	Ranking of quality
Musculoskeletal conditions																			
De Oliveira Meirelles, 2013[24]	N	N	N	N	N	N	N	PY	Y	N/A	N	N/A	N/A	N/A	N	N	N/A		CRITICALLY LOW
Franke, 2014[25]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Franke, 2017[26]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Dal Farra, 2020[27]	Y	Y	Y	Y	Y	Y	N	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Franke, 2015[28]	Y	N	N	Y	Y	Y	Y	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Rehman, 2020[29]	Y	Y	N	Y	Y	Y	N	PY	Y	N/A	N	Y	N/A	Y	Y	Y	N/A		LOW
Pediatric conditions																			
Posadzki, 2013[30]	Y	N	N	PY	Y	Y	N	PY	Y	N/A	Y	N/A	N/A	N/A	Y	Y	N/A		CRITICALLY LOW
Neurology conditions																			
Cerritelli, 2017[31]	Y	N	N	Y	Y	Y	Y	Y	Y	N/A	Y	N/A	N/A	N/A	Y	Y	N/A		LOW
Visceral conditions																			
Muller, 2014[32]	Y	N	N	PY	Y	Y	Y	PY	Y	N/A	N	N/A	N/A	N/A	Y	N	N/A		LOW

Y, yes; PY, partial yes; N, no; N/A, not applicable. In grey are reported the critical domains.

Figure 1: Flow diagram of screened articles.

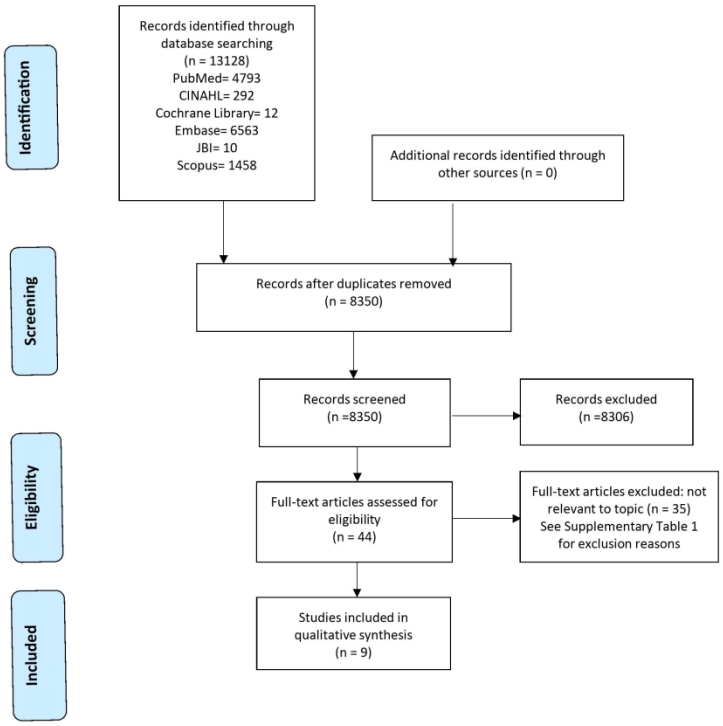

Figure 1: Flow diagram of screened articles.

Figure 1: Flow diagram of screened articles

209x297mm (300 x 300 DPI)

Appendix

Search Strategy: MEDLINE (PubMed)

01. osteopath* AND medicine
02. osteopath* AND treatment
03. osteopath* AND manipulat*
04. Manipulation, Osteopathic [Mesh]
05. Osteopathic Medicine [Mesh]

06. 01 OR 02 OR 03 OR 04 OR 05

07. meta-analysis
08. meta-analysis
09. metaanalysis
10. systematic review
11. review
12. Review Literature as Topic [Mesh]
13. Review" [Publication Type]
14. Meta-Analysis [Publication Type]
15. Meta-Analysis as Topic"[Mesh]

16. 07 OR 08 OR 09 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15

17. 06 AND 16

Supplementary Table 1. Excluded systematic reviews.

First author, year	Title	Reason for exclusion
Schwerla, 1999[1]	[Evaluation and critical review published in the European literature on osteopathic studies in the clinical field and in the area of fundamental research]	The SR included any type of study design.
Spiegel, 2003[2]	Osteopathic manipulative medicine in the treatment of hypertension: An alternative, conventional approach.	Narrative review.
Gamber, 2005[3]	Cost-effective osteopathic manipulative medicine: a literature review of cost-effectiveness analyses for osteopathic manipulative treatment.	Evaluation of OMT cost-effectiveness.
Licciardone, 2005[4]	Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Jäkel, 2011[5]	Therapeutic effects of cranial osteopathic manipulative medicine: a systematic review.	The SR included primary studies in healthy volunteers.
Posadzki, 2011[6]	Osteopathy for musculoskeletal pain patients: A systematic review of randomized controlled trials.	The SR included primary studies in healthy volunteers and intervention was not performed by osteopathic physicians or osteopaths.
Orrock, 2013[7]	Osteopathic intervention in chronic non-specific low back pain: a systematic review.	Overlap: 2 out of 2 studies. This SR was update by Franke 2014[25].
Cerritelli, 2015[8]	Osteopathic manipulative treatment in neurological diseases: systematic review of the literature.	The SR included any type of study design.
Cicchitti, 2015[9]	Chronic inflammatory disease and osteopathy: a systematic review.	The SR included study with an animal model and any type of study designs.
Majchrzycki, 2015[10]	Application of osteopathic manipulative technique in the treatment of back pain during pregnancy.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Vasconcelos, 2015[11]	Effect of osteopathic maneuvers in the treatment of asthma: review of literature.	The SR included any type of study design, and the intervention was not performed by osteopathic physicians or osteopaths.
Guillard, 2016[12]	Reliability of diagnosis and clinical efficacy of cranial osteopathy: a systematic review.	The SR included primary study in which the intervention was not performed by osteopathic physicians or osteopaths.
Kruger, 2016[13]	Osteopathic treatment of irritable bowel syndrome - A review	Overlap:4 out 4 studies. Most rigorous criteria were used in Muller' s SR[32].
Ruffini, 2016[14]	Osteopathic manipulative treatment in gynecology and obstetrics: A systematic review.	The SR included any type of study designs.
Veloso, 2016[15]	Osteopathic Manipulation Treatment on postural balance: a systematic review.	The SR included any type of study designs.
Raguckas, 2016[16]	Osteopathic considerations in obstructive pulmonary disease: A systematic review of the evidence.	The SR included any type of study designs.
Ahmad, 2017[17]	Current Clinical Status of Osteopathy: Study Based on Retrospective Evidences of Six Years, A Systemic Review	The SR included any type of study design, and the intervention was not performed by osteopathic physicians or osteopaths.
Do Vale, 2017[18]	Effectiveness of the osteopathic treatment in intestinal constipation: A systematic review	Clinical outcomes are not reported.
Steel, 2017[19]	Osteopathic manipulative treatment: A systematic review and critical appraisal of comparative effectiveness and health economics research.	The SR included any study designs.
Lanaro, 2017[20]	Osteopathic manipulative treatment showed reduction of length of stay and costs in preterm infants.	The SR included RCTs and controlled clinical trials.
Guillaud, 2018[21]	Reliability of diagnosis and clinical efficacy of visceral osteopathy: A systematic review.	The SR included primary study in which the intervention was not performed by osteopathic physicians or osteopaths.
Potekhina, 2018[22]	Osteopathy is a new medical specialty. Assessment of clinical effectiveness of osteopathic manipulative therapy in various diseases.	The SR included any type of study design, and the intervention was not performed by osteopathic physicians or osteopaths.
Saracutu, 2018[23]	The effects of osteopathic treatment on psychosocial factors in people with persistent pain: A systematic review.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Sposato, 2018[24]	Osteopathic manipulative treatment in surgical care: short review of research publication in osteopathic Journals during the period 1990 to 2017.	The SR included any study designs.
Verhaeghe, 2018[25]	Osteopathic care for spinal complaints: A systematic literature review.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Verhaeghe, 2018[26]	Osteopathic care for low back pain and neck pain. A cost-utility analysis.	Health economic evaluation of osteopathic care in low back pain and neck pain. Data about clinical outcomes were not completely reported.

Whalen, 2018[27]	A Short Review of the Treatment of Headaches Using Osteopathic Manipulative Treatment.	The SR included any type of study design, and the intervention was not performed by osteopathic physicians or osteopaths
Rechberger, 2019[28]	Effectiveness of an osteopathic treatment on the autonomic nervous system: a systematic review of the literature.	The SR included any type of study design, primary studies in healthy participants and intervention was not performed by osteopathic physicians or osteopaths.
Switters, 2019[29]	Is visceral manipulation beneficial for patients with low back pain? A systematic review of the literature.	The SR included primary studies in which the intervention was not performed by osteopathic physicians or osteopaths.
Buscemi, 2020[30]	Endocannabinoids release after osteopathic manipulative treatment. A brief review.	The SR included any type of study designs.
Santiago, 2020[31]	Instrumentation used to assess pain in osteopathic interventions: A critical literature review.	Clinical outcomes are not reported.
Kiepe, 2020[32]	Effects of osteopathic manipulative treatment on musicians: A systematic review.	The SR included any type of study designs.
Baroni, 2021[33]	Osteopathic manipulative treatment and the Spanish flu: a historical literature review.	Historical review evaluating which OMT technique were administered in patients during the 1918 Spanish flu pandemic.
Tramontano, 2021[34]	Vertigo and balance disorders- The role of osteopathic manipulative treatment: A systematic review.	The SR included any type of study designs and primary study in healthy participants.
De Marsh, 2021[35]	Pediatric osteopathic manipulative medicine: A scoping review.	The SR included any type of study designs.

OMT: osteopathic manipulative treatment, RCTs: randomized controlled trials, SR: systematic review.

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Supplementary Table 2. Summary of identified systematic reviews with overlapping.

Total SRs (n=9)	**Total**	**overlapping**	**Total**
Total trials	71	16	55
Total participants	5577	1837	3740
Musculoskeletal conditions (6 SRs)[24-29]			
Total trials	44	14	30
Total participants	4251	1837	2414
Trials low back pain	34	12	22
Participants low back pain	3369	1316	2053
Trials neck pain	3	0	3
Participants neck pain	123	0	123
Trials chronic non-cancer pain	7	2	5
Participants chronic non-cancer pain	759	521	238
Paediatric conditions (1 SR)[30]			
Trials pediatrics conditions	17	0	17
Participants pediatric conditions	887	0	887
Neurological conditions (1 SR)[31]			
Trials primary headache	5	0	5
Participants primary headache	235	0	235
Visceral conditions (1 SR)[32]			
Trials irritable bowel syndrome	5	0	5
Participants irritable bowel syndrome	204	0	204

SR: systematic review.

Supplementary Table 3. Identified SRs with studies overlapping.

Franke, 2014[25]		De Oliveira Meirelles, 2013[24]		Dal Farra, 2020[27]		Rehman, 2020[29]		Franke, 2017[26]	
Primary studies	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**	**Primary studies**	**Participants**
Chown 2008	71			Chown 2008	131*	Albers 2018	48	Rohrich 2014	56
Gibson 1985	97					Cuccia 2010	50	Beltz 2014	41
Licciardone 2003	71	Licciardone 2003	71	Licciardone 2003	98**	Licciardone 2003	66	Schwerla 2015	30
Licciardone 2010	144	Licciardone 2010	144					Licciardone 2010	144
Licciardone 2013	455	Cleary 1994	12	Licciardone 2013	455	Licciardone 2013	455	Hensel 2015	52
Mandara 2008	94	Burton 2000	30	Mandara 2008	94	Papa 2012	72		
Peters 2006	57					Schwerla 2008	37	Peters 2006	57
Grundemann 2013	41					Stepnik 2018	31	Gundemann 2013	41
Recknagle 2007	39			De Oliveira 2019	38			Recknagle 2007	39
Vismara 2012	21	Vismara 2012	21	Vismara 2012	21				
Anderson 1999	155								
Adorjàn - Schaumann 1999	57								
Heinze 2006	60								
Cruser 2012	60								
Schwerla 2012	80								
Trials 15	**TP 1502**	**Trials 5**	**TP 278**	**Trials 6**	**TP 739**	**Trials 7**	**TP 759**	**Trials 8**	**TP 858**

TP, Total participants. *OMT group counted twice and considered exercise group even if drop-out are >40%, **participants at 6 months, OMT counted twice.

Supplementary Table 4. Traffic light and overall traffic light evidence for each condition.

MUSCULOSCHELETAL CONDITIONS	First author, year	GRADE	Effect size	Traffic light evidence	Downgrade	Overall traffic light evidence $
1. ANSLBP/CNSLBP §						
Pain	Franke, 2014[25]	moderate	medium		Least favourable assessment from new RoB	
	Dal Farra, 2020[27]	low	medium		Low GRADE	
Functional status	Franke, 2014[25]	moderate	small		Least favourable assessment from new RoB	
	Dal Farra, 2020[27]	low	medium		Low GRADE	
2. CNSLBP §						
Pain	Franke, 2014[25]	moderate	small		Least favourable assessment from new RoB	
	Dal Farra, 2020[27]	low	medium		Low GRADE	
Functional status	Franke, 2014[25]	high	small		Least favourable assessment from new RoB	
	Dal Farra, 2020[27]	low	small		Low GRADE	
3. NSLBP in Pregnancy §						
Pain	Franke, 2014[25]	low	medium		Low GRADE	
	Franke, 2017[26]	moderate	medium		Least favourable assessment from new RoB	
Functional status	Franke, 2014[25]	low	medium		Low GRADE	
	Franke, 2017[26]	moderate	small		Least favourable assessment from new RoB	
4. NSLBP in PP						
Pain	Franke, 2014[25]	moderate	large		Least favourable assessment from new RoB	
	Franke, 2017[26]	low	large		Low GRADE	
Functional status	Franke, 2014[25]	moderate	small		Least favourable assessment from new RoB	
	Franke, 2017[26]	low	small		Low GRADE	
5. LBP WITH SCIATICA						
Pain	De Oliveira, 2013[24]	NP	NP		Critically low SR	
6. LBP with MENOPAUSAL SYMPTOMS						
Pain	De Oliveira, 2013[24]	NP	NP		Critically low SR	
7. CNSNP						
Pain	Franke, 2015[28]	moderate	medium		Least favourable assessment from new RoB	
Functional status	Franke, 2015[28]	moderate	small		Least favourable assessment from new RoB	
8. CNCP						
Pain	Rehman, 2020[29]	moderate	small		No judgement for imprecision	
Disabiliy	Rehman, 2020[29]	moderate	small		No judgement for imprecision	
Quality of life	Rehman, 2020[29]	moderate	medium		No judgement for imprecision	
PAEDIATRIC CONDITIONS						
*Outcomes for different conditions **	Posadzky, 2013[30]	NP	NP		High risk of bias and critically low quality of SR	
NEUROLOGICAL CONDITIONS						
*Outcomes for migraine and tension type headache***	Cerritelli, 2017[31]	NP	NP		High risk of bias and low quality of SR	
VISCERAL CONDITION						
*Outcomes for IBS****	Muller, 2014[32]	NP	NP		High risk of bias and low quality of SR	

Traffic light evidence: Green light, MAs indicated intervention effectiveness (Effect size any level). Downgrade for GRADE low (or GRADE moderate/high in which judgement for some domains was not performed by the authors or our use of the new RoB version was the least favorable assessment) or for a low/critically low quality of the SRs; **Yellow light**, MA was not performed, conflicting results from RCTs or only one RCT. Downgrade for high risk of bias (from SR authors or our assessment) or low/critically low quality of SR; **Red light**, MA indicated that the intervention was ineffective or less effective than comparator. § SR from De Oliveira was not considered as for this condition all RCTs were included in more recent SRs with MAs.

Overall traffic light evidence: Green light, high quality evidence from MAs indicates intervention effectiveness; **Yellow light**, promising evidence suggests possible effectiveness, but more research would increase the confidence in the estimate of the effect; **Red light**, limited or inconclusive evidence.
ANSLBP: acute non-specific low back pain, CNCP: chronic non-cancer pain, CNSLBP: chronic non-specific low back pain, CNSNP: chronic non-specific neck pain, IBS: irritable bowel syndrome, LBP: low back pain, MA: meta analysis, NP: not performed, NSLBP: non-specific low back pain, PP: postpartum, RCT: randomized controlled trial, RoB: risk of bias, SR: systematic review.
*Different conditions were considered. It's not possible to evaluate the single outcome for each condition, **pain, work disability, headache frequency, quality of life, ***pain, constipation, quality of life.

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
Title			
	#1	Identify the report as an overview of systematic reviews.	1
Abstract			
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	2-3

Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	4
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	4-5
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, and date last searched.	5
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 Appendix
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the overview).	5
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	5-6
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	6. This is an overview therefore we used the AMSTAR-2 tool.
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7

Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	6-7. Meta-analysis was not performed
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a This is an overview
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a. However, an overlapping analysis of the primary clinical trial was performed. 6
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, Figure 1, Supplementary Table 1.
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	8-13 Table 1
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	This is an overview therefore we used the AMSTAR-2 tool. 13-14 Table 4
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals.	Tables 2 and 3
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	8-14 Meta-analysis was not performed
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a. This is an overview

Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplementary Tables 2 and 3
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	14-16
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	17