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Effectiveness of Osteopathic Interventions in Chronic Non-Specific Low Back Pain: a Systematic Review and Meta-Analysis

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HIGHLIGHTS

- Osteopathic interventions improves pain levels and functional status in patients with chronic non-specific low back pain.
- Myofascial release shows better levels of evidence for pain improvement if compared to other osteopathic modalities.
- Osteopathic interventions shows "low" or "very low" levels of evidence for functional status improvement.
- Findings of this review represent an integration of the 2016 American Osteopathic Association Guidelines for Osteopathic Manipulative Treatment in LBP.

ABSTRACT

Background
Chronic low back pain (CLBP) is a frequent cause of disability and it represents a medical, social and economic burden globally. Therefore, we assessed effectiveness of osteopathic interventions in the management of CLBP for pain and functional status.
Methods
A systematic review and meta-analysis were conducted. Findings were reported following the PRISMA statement. Six databases were searched for RCTs. Studies were independently assessed using a standardized form. Each article was assessed using the Cochrane risk of bias (RoB) tool. Effect size (ES) were calculated at post-treatment and at 12 weeks' follow up. We used GRADE to assess quality of evidence.
Results
10 articles were included. Studies investigated osteopathic manipulative treatment (OMT, n=6), myofascial release (MFR, n=2), craniosacral treatment (CST, n=1) and osteopathic visceral manipulation (OVM, n=1). None of the study was completely judged at low RoB. Osteopathy revealed to be more effective than control interventions in pain reduction (ES: -0.59; 95% CI: -0.81, -0.36; P<0.00001) and in improving functional status (ES: -0.42; 95% 95% CI: -0.68, -0.15; P=0.002). Moderate-quality evidence suggested that MFR is more effective than control treatments in pain reduction (ES: -0.69; 95% CI: -1.05, -0.33; P=0.0002), even at follow-up (ES: -0.73; 95% CI:

-1.09, -0.37; P<0.0001). Low-quality evidence suggested superiority of OMT in pain reduction (ES: -0.57; 95% CI: -0.90, -0.25; P=0.001) and in changing functional status (ES: -0.34; 95% CI: -0.65, -0.03; P=0.001). Very low-quality evidence suggested that MFR is more effective than control interventions in functional improvements (ES: -0.73; 95% CI: -1.25, -0.21; P=0.006).

Conclusion

Results strengthen evidence that osteopathy is effective in pain levels and functional status improvements in CLBP patients. MFR reported better level of evidence for pain reduction if compared to other interventions. Further high-quality RCTs, comparing different osteopathic modalities, are recommended to produce better-quality evidence.

Keywords: Chronic low back pain, Osteopathic manipulative treatment, Manipulation, Myofascial release, Systematic review

DECLARATIONS

Submission: this research has not been published previously and it is not under consideration for publication elsewhere.

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INTRODUCTION

Low back pain (LBP) is one of the most common musculoskeletal health problem with the highest prevalence in the adult population; globally, it represents a relevant cause of medical, social and economic burden[1,2]. Non-specific chronic low back pain (NS-CLBP) is defined as lumbar pain persisting for longer than three months, in absence of a suspected pathology (red flag conditions such as e.g. tumor, infection or fracture). Patients typically report physical disabilities and psychological distress concurrently with the pain[3]. Prevalence varies from 4% to 20% , increasing linearly from the third decade until the 60 years of age and stabilizing in the seventh decade; it is more relevant in women (approximately 1,5:1)[4].

Since NS-CLBP pathophysiology remains partially unclear, several authors tried to explain it considering the problem as a result of interactions of biological, psychological, and social factors [5]. Central sensitization is considered one of the key-aspects in the NS-CLBP[6]; neuroimaging research showed how some brain areas, activated by nociception stimuli, can also be influenced by emotions and behaviors. This process could induce mood alterations, depression and maladaptive coping[7]. These findings probably explain the reason why pharmacological treatments (NSAIDs, steroids and opioids) are not particularly recommended in NS-CLBP, also considering their potential adverse effects[8]. Conversely, active interventions including exercise, cognitive-behavioral therapy or multidisciplinary rehabilitation represent more consistent therapeutic recommendations[9]. However, due to the persistence of symptoms, many people refer to complementary approaches as part of their

pain management strategy[10]. Among these, there are several manual and manipulative therapies to consider in the management of CLBP, such as chiropractic and osteopathy, including spinal manipulation and mobilization[11,12].
Osteopathy is a health approach based on manual contact for diagnosis and treatment of the somatic dysfunction (SD)[13]. Its therapeutic aim is specifically oriented to improve physiological function and support homeostasis altered by SD[14,15,16]. Osteopathic manipulative treatment (OMT) typically involve a wide range of manual techniques, which may include soft tissue stretching, joints manipulation, resisted isometric 'muscle energy' stretching, myofascial release (MFR), craniosacral treatment (CST) and visceral manipulations (OVM); each of these modalities can be applied alone or in combination. Treatment is characterized by a whole-body approach, and it may be applied to many body regions, sometimes remote from the symptomatic area[17]. Recently neuroimaging research regarding the therapeutic mechanisms underlying OMT is growing[18,19]. On the basis of these studies, some authors assumed that OMT could act on the interoceptive ways, thus having a beneficial role towards the sensitization process[20]. However, further research is needed in this field.
Since now, three systematic reviews had been conducted to investigate the effectiveness of osteopathy in LBP[21,22,23]. In 2005 Licciardone et al.[21] considered in a meta-analysis six studies, concluding that OMT significantly reduces pain levels within three months; however, inclusion criteria comprised not exclusively pure osteopathic approaches (e.g. spinal manipulative therapy); in addition, both specific and non-specific LBP were combined in the study. For all these reasons, authors' conclusions remain questionable. In Orrock's review[22] only two studies, with methodological issues and relevant study design differences, met inclusion criteria; thus, a quantitative analysis was not possible. However, authors concluded that no superiority of OMT in comparison to sham intervention, physiotherapy and exercise exists. In 2014 Franke and colleagues[23] reported clinically relevant effects in reducing pain and improving functional status, even if they pointed out the lack of robust, high-quality randomized controlled trials among the included studies. Nevertheless, authors considered in their review simultaneously acute and chronic pain, and they did not exclude some peculiar conditions such as pregnancy and post-partum. On the basis of these partial evidence, in 2016 the American Osteopathic Association provided guidelines for OMT in LBP, focusing on the necessity to identify SD as the more probable cause of pain[24].
To date, in light of the abovementioned issues, complete and updated information concerning effectiveness of osteopathic interventions in NS-CLBP is needed. Hence, we performed a systematic review and meta-analysis pursuing three main objectives: to assess the effectiveness of osteopathic interventions in decreasing pain levels and improving functional status in NS-CLBP; to specifically evaluate the impact of each different osteopathic modality; to assess the effectiveness over a medium- or long-term period.

METHODS

Protocol Registration

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[25].
A "PICO" approach was applied to formulate the research question[26] and the "2015 Updated Guideline for Systematic Reviews in the Cochrane Back and Neck Group"[27] were considered to perform the methodological steps of this study.
The protocol of the current review had been regularly approved and recorded on PROSPERO (https://www.crd.york.ac.uk/prospero/ registration number: CRD42018117518).

Search Process

A literature search was conducted to investigate the effectiveness of OMT on pain and disability in patients with NS-CLBP. Literature was searched up to April 2020, using the following database: PubMed, Cochrane CENTRAL, Embase, PEDro and Scopus. Gray literature was also considered using Google web searching and ClinicalTrials.gov. Cross referencing was used in order to search any other possible missing study and authors were contacted if supplementary information was needed.

Multiple search terms were used, such as “Osteopathic Medicine”, “Osteopathic Manipulative Treatment”, “Visceral Manipulation”, “Myofascial release”, “Craniosacral”, “Low Back Pain”, “Non-specific pain” and “Chronic pain”. These terms were combined in different forms and modalities; details on the search strategy are provided in the Appendix.

Eligibility

Inclusion criteria for the research was based on papers responding to the following features: randomized controlled clinical trials (RCTs) with parallel or cross-over design and feasibility or pilot RCTs studies; testing the effectiveness and/or efficacy of an osteopathic intervention compared to other interventions or no intervention; considering a study condition of NS-CLBP (pain lasting from at least three months, no specific cause of pain). Additional inclusion criteria were: adult subjects (age 18-70), any type of osteopathic modality as intervention and English language; due to the intrinsic variability of manual techniques, no dosage limitations in terms of time and frequencies were applied.

No restrictions regarding types of control were considered, except for active manipulative interventions (e.g: comparison with different osteopathic techniques/modalities); comparison included usual care, sham therapy (both manual and through devices) and other treatments (pharmacological or non-pharmacological). We also considered standardized, semi-standardized or patients’ need based treatments on any anatomical region, without considering the types of technique used, alone or in conjunction with other treatments. Trials using other forms of manual and manipulative therapies (e.g. chiropractic, physiotherapy) applied to the experimental group were excluded.

Study Selection and Data Collection

Titles, abstracts and, secondly, full texts were screened independently by two reviewers (FDF, RGR) to identify studies potentially eligible. Records were managed using “Rayyan QCRI”[28].

Any disagreement was resolved through a discussion with a third reviewer (AB), until consensus was reached.

Steps of the studies selection are detailed in a PRISMA flow diagram (Fig. 1).

A standardized form was used to extract the main characteristics from the included studies, reporting: the article source, objective and outcomes, sample size, mean age of participants, percentage of men/women, the main intervention characteristics (dose, frequency, length) and allocation. Another standardized form was used to better detail the type of intervention and to specifically describe the results.

This was done independently by the two main reviewers; discrepancies were identified and resolved through discussion with a third author.

For missing data, investigators were contacted by e-mail.

Outcomes

Primary outcomes of the present review were pain levels and functional status (disability), measured at post-intervention and follow-up.

Secondary outcomes were "safety" (in terms of 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.

Assessment of Risk of Bias

Two reviewers independently assessed the methodological quality of the included RCTs using the 13-item tool, based on the updated version of the Cochrane Collaboration Risk of Bias tool (RoB) in RCTs[29]. This tool considers six different domains: selection bias (criteria 1, 2 and 9), performance bias (criteria 3, 4, 10 and 11), attrition bias (criteria 6 and 7), detection bias (criteria 5 and 12), reporting bias (criterion 8) and other sources of bias (criterion 13). RoB was assessed for each domain, according to a three-point scale: low, unclear, and high RoB. In case of disagreement, consensus was reached with a third investigator.

Measures and Synthesis of Results

As measurements of treatment effect, we reported results and differences among groups in a descriptive way. Data were reported as mean ± standard deviation (SD), mean and 95% confidence interval (CI) for continuous data and relative risk (RR) and 95% CI for dichotomous data; if osteopathic treatment was protective compared to control group, the RR was smaller than one. The VAS scores[30] from included studies were converted to a 100-point scale. If data were presented as median and interquartile range (IQR), median was assimilated to mean and SD was calculated considering the rate between IQR and SD (approximately 1.35:1)[31].

A meta-analysis was performed using "Review Manager v 5.3.5" (The Nordic Cochrane Centre, http://ims.cochrane.org/revman). At first, authors determined the overall effect of osteopathic treatments versus no control interventions both for pain and for functional status outcomes. Then, subgroup analyses were considered for the same end-points and data were pooled only when at least two studies for each category of osteopathic intervention were present. In this case, subgroup analyses was thought to be a valuable tool to show potential differences between single osteopathic modalities (e.g MFR, CST, OVM) and a more general semi-standardized approach based on practitioner assessment (OMT); thus, these analyses allowed us to evaluate the strength of the evidence for different osteopathic interventions. Alpha level was set at 0.05 to test for overall effect.

For continuous outcomes (pain levels, functional status), standardized mean difference (SMD or Hedges' *g*) with 95% CI was calculated using a random effects model to acknowledge the clinical and methodological diversity among included studies. For this reason, in case of different measures used across studies to assess the same outcome (e.g.: ODI and RMDQ for functional status), data were pooled together or adjusted with a "-1 conversion" when the scales were divergent. An effect size (ES) ranging from 0.2 to 0.49 is considered "small", from 0.5 to 0.79 "moderate", and a value of 0.8 or above is to consider large.

Heterogeneity was measured through I^2 statistics and explains how much of the variation between studies is due to heterogeneity rather than to chance. Values included between 0% and 40% may suggest "no important" heterogeneity, range 30% - 60% indicates "moderate" levels, 50% to 90% may represents "substantial" and 75% - 100% suggests "considerable" heterogeneity[27].

The overall quality of evidence for each category of intervention was assessed through the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach[32], as recommended by the updated Cochrane Back Review Group method guidelines[25]. This approach allows authors to downgrade the evidence from "high" to "moderate", "low" or "very low" on the basis of 5 key-domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.

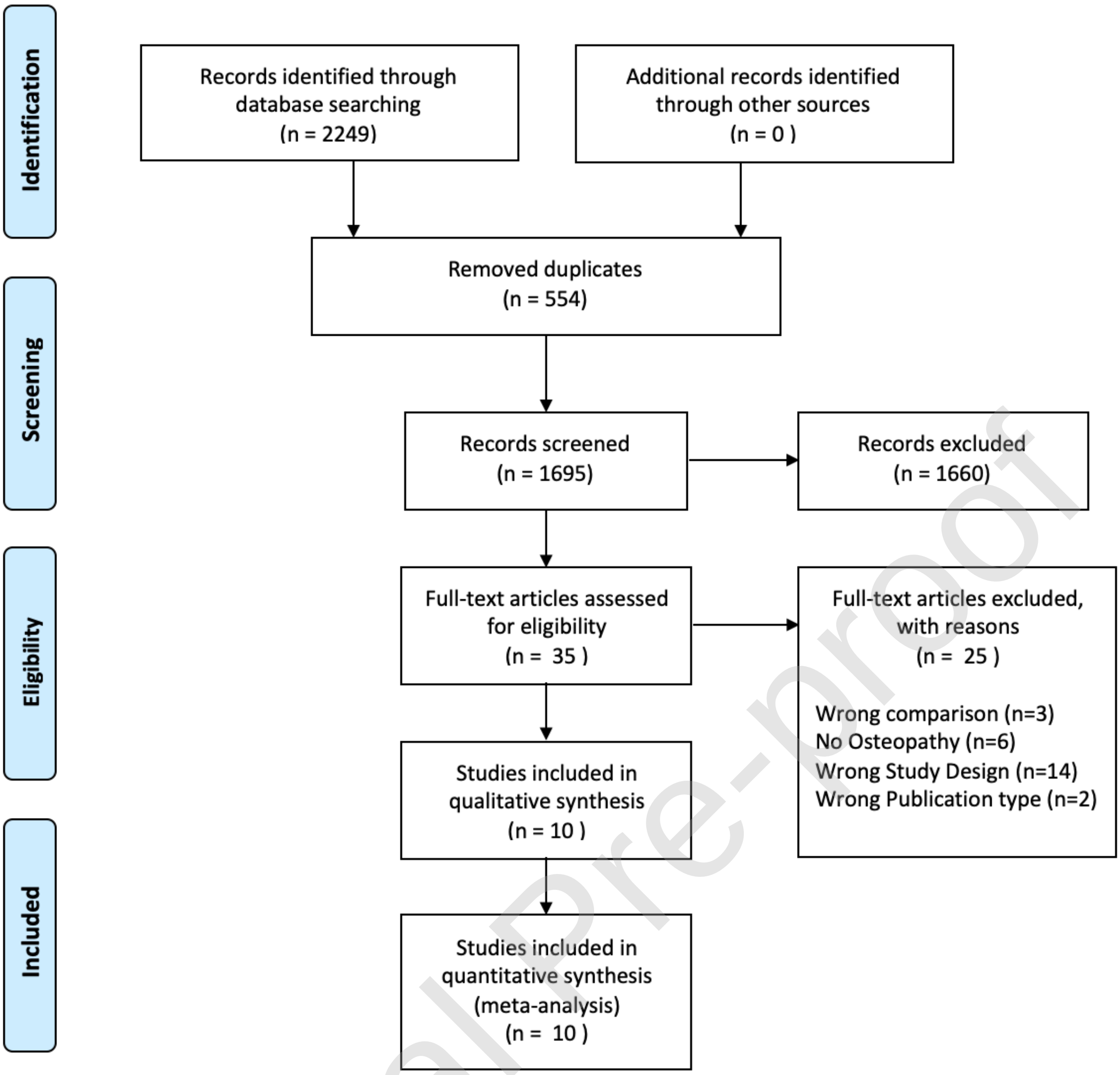

Fig. 1. Flow diagram based on PRISMA statement (www.prisma-statement.org**)**

RESULTS

Studies Selection

The search strategy identified a total of 2,249 results, 554 of which represented duplicates and were consequently deleted. Other 1660 records were rejected after reading title and abstract. A total of 35 full-text articles were assessed for eligibility. Finally, 25 studies were excluded with reasons (for details see Fig. 1). To notice that two of these trials[33,34] effectively investigated osteopathic intervention in NS-CLBP (respectively OMT plus specific diaphragm technique and OVM); however, the comparison was done versus other types of osteopathic manipulation and this issue was not in accordance with the inclusion criteria of the present review.
Finally, 10 studies[35-36] were included both in the qualitative and in the quantitative analysis (Fig. 1). The aggregate number of subjects in the included studies is 1160, even if great differences among trials were detected (sample size range: 20– 455).

Table 1. Overview of included studies

Author/year	Objective	Outcomes	Population	Interventions	Comparison
Licciardone 2003	Efficacy of OMT as a complementary treatment for NS-CLBP	1)Quality of life (SF 36) 2)Pain intensity (VAS) 3)Disability (RMDQ) 4)Lost work days 5)Satisfaction (Likert Scale)	N=91 Male= 35% Age: 50+/-12 years	OMT (n=48) *Description:* 7 sessions; duration: 15 to 30 min each session, over 5 months.	1)Sham OMT (n=23) *Description:* 7 sessions; duration: 15 to 30 min each session, over 5 months. 2)No intervention (n=20) *Description:* UC and co-treatments permitted.
Chown 2008	Difference between Exercise, physiotherapy or OMT in patients with NS-CLBP	1)Disability (ODI)* 2)Health Status (VAS) 3)Quality of life (EQ-5D) 4)Walking endurance (SWT) 5)Life and Care satisfaction (Likert Scale)	N=239 Male: 42% Age: 43.5 years	OMT (n=79) *Description:* 5 treatment sessions within a 3-month period; duration: 30 min each session	1)Physiotherapy (n=80) 2)Group Exercise (n=80) *Description:* 5 treatment sessions within a 3-month period; duration: 30 min each session
Mandara 2008	Effectiveness of OMT in NS-CLBP	1)Disability (ODI) 2)Pain Intensity (VAS)	N=94 Male: NA Age: NA	OMT + UC (n=44) *Description:* treatments over 6 months	Sham OMT + UC (n=50) *Description:* treatments over 6 months
Vismara 2012	Effectiveness of OMT plus SE in obese patients with NS-CLBP	1)Kinematic Analysis* 2)Pain Intensity (VAS) 3)Disability (RMDQ, ODI)	N=21 Male: 0% Age: 43.7	OMT + SE (n=10) *Description:* 1OMT + 10 SE sessions; duration: (45 min + 45 min) each session	SE (n=11) *Description:* 10 sessions; duration: 45min
Ajimsha 2013	Effectiveness of MFR plus SE in nursing professionals with NS-CLBP	1)Pain Experience (MPQ)* 2)Disability (QBPDS)*	N= 80 Male: NA Age: 20-40	MFR + SE (n= 38) *Description:* interventions 3 times weekly, for 8 weeks; duration: 60 min each session (40 min MFR + 20 min SE)	Sham MFR + SE (n=36) *Description: :* interventions 3 times weekly, for 8 weeks; duration: 60 min each session (40 min Sham MFR + 20 min SE)
Licciardone 2013	Efficacy of OMT and ultrasound therapy for NS-CLBP	1)Pain Intensity (VAS)* 2)Disability (RMDQ) 3)Quality of life (SF 36) 4)Satisfaction (Likert Scale)	N=455 Male: 38% Age (median): 41 (29-51)	OMT (n=230) *Description:* 6 sessions over 8 weeks.	Sham OMT (n=225) *Description:* 6 sessions over 8 weeks.
Castro-Sanchez 2016	Effects of CST in patients with NS-CLBP	1)Disability (RMDQ*, ODI) 2)Pain Intensity (NRS) 3)Kinesiophobia (TSK)	N=64 Male: 34% Age: 50+/-12 years	CST (n=32) *Description:* 10 sessions, once per week, over 10 weeks; duration:	Classic massage (n=32) *Description:* 10 sessions, once per week, over 10 weeks; duration:

		4)Trunk Muscle Endurance (McQuade Test) 5)Lumbar mobility (finger-to-floor distance) 6)Blood, pressure, biochemical measures		50 min each session.	30 min each session.
Arguisuelas 2017	Effects of MFR protocol in NS-CLBP	1)Pain Experience and Pain Intensity (SF-MPQ*, VAS*) 2)Disability (RMDQ) 3)Fear-Avoidance Beliefs (FABQ)	N=54 Male: 39% Age: 46.5	MFR (n=27) *Description:* 4 sessions, twice a week for 2 weeks; duration: 40 min each session.	Sham MFR (n=27) *Description:* 4 sessions, twice a week for 2 weeks; duration: 40 min each session.
De Oliveira Meirelles 2019	Efficacy of OMT for NS-CLBP	1)Pain Intensity (VAS*) 2)Disability (ODI) 3)Kinesiophobia (TSK) 4)Depression (BDI)	N=42 Male: 26% Age: 48 +/- 10	OMT (n=20) *Description:* 5 sessions carried out over 5 weeks; duration: 30 to 45 min each session.	ACG (n=18) *Description:* 10 treatment sessions, twice per week, for 5 weeks.
Santos 2019	Short-term effects of OVM associated with physical therapy in people with NS-CLBP	1)Pain Intensity (VAS*) 2)Lumbar spine mobility (Schober Test) 3)Disability (RMDQ, PSFS)	N= 20 Male: 5% Age:41	Conventional PT + OVM (n=10) *Description:* 5 sessions over 5 weeks, once per week; duration: 50 min each session (40 min PT + 10 min OVM)	Conventional PT + Placebo OVM (n=10) *Description:* 5 sessions over 5 weeks, once per week; duration: 50 min each session (40 min PT + 10 min placebo OVM)

*: primary outcome
N: sample size

Abbreviations: ACG Active control group, OMT Osteopathic manipulative treatment, NS-CLBP Non-specific chronic low back pain, SF-36 Short-Form Health Survey 36 domains, VAS Visual analogical scale, RMDQ Roland and Morris disability questionnaire, UC Usual care, ODI Oswestry disability index, EQ-5D Euro-qol 5 domains, SWT Shuttle walking test, SE Standard exercise, MFR Myofascial release, MPQ McGill Pain Questionnaire, SF-MPQ Short-form MPQ, QBPDS Quebec Pain Disability Scale, CST Craniosacral treatment, NRS Numerical rating scale, TSK Tampa scale of Kinesiophobia, FABQ Fear avoidance beliefs questionnaire, BDI Back depression index, PSFS Patient specific functional scale, PT Physical therapy, OVM Osteopathic visceral manipulation

Description of the Studies

All the included studies (n= 10) were RCTs, nine[35-39,41-44] (90%) with a parallel design, and one[40] (10%) had a "2 x 2 factorial" design. Five trials[35,37,40,42,44] (50%) had no active treatment as comparison (sham therapy or no intervention), and the other five[36,38,39,41,43] (50%) had an active control group (standard exercise, classic massage). Six trials[35,36,39-42] (60%), including 983 subjects, reported a follow-up assessment, varying from 4 to 24 weeks depending on the study. Dropout rate was extremely various (range: 0%-77%). The mean of the sample size was 116 +/- 134,5 with a total of 1160 NS-CLBP participants (age, 43.3 +/- 7.7 years; mean 0-100 cm VAS score: approx. 52.45 +/- 14.18). Five studies[39,40,42-44] (50%) had "pain levels reduction" as a primary outcome, three[36,39,41] (30%) considered the "functional status", one[38] (10%) kinematic analysis, in two trials[35,37] (20%) no information had been provided by authors. Interventions tested in the included studies were heterogeneous: OMT sessions, interpreted as a semi-standardized protocol based on combination of osteopathic techniques, were applied in six trials[35-38,40,43] (60%); the other four studies investigated single osteopathic modalities, predominantly focused on specific technicism applied on a unique body area: in two protocols[39,42] (20%) MFR was considered, in one study[41] (10%) CST and in another one[44] (10%) OVM. The total number of osteopathic sessions differed among studies (range, 1 – 24, mean: 8.7 +/- 5.8), the treatment period ranged from 2 to 24 weeks (mean: 9.9 +/- 7.04) and the duration of each sessions varied from a minimum of 15 min to 60 min, at most (mode: 45 min); also frequency of treatments were different for each trial, varying from two per week to one per month. Further details are shown in Table 1.

Outcomes

All the included trials assessed pain levels and functional status, considered as the primary outcomes in the current review.

As regards pain, eight studies assessed it through VAS[37], one used NRS[38] while in another one McGill Pain Questionnaire (MGPQ)[39] was preferred. Disability was measured in five studies by using Oswestry Disability Index (ODI)[40], in four trials through Roland and Morris Disability Questionnaire (RMDQ)[41] and in one case Quebec Pain Disability Scale (QBPDS)[42] was utilized. Pain levels were considered as primary outcome in five studies, whereas in other three studies the change in functional status was considered. Every included trial also considered secondary outcomes that literature reports as potentially of interest for NS-CLBP, such as: quality of life, walking endurance, kinematic and mobility analysis, fear-avoidance beliefs, kinesiophobia, depression, number of adverse events and level of care satisfaction. However, these outcomes were assessed only in few cases and with different tools, so that a synthesis was not possible; detailed results for each single trial are reported in Table 2.

Table 2. Description of interventions and main results of the included studies

Authors/Year	Description of Interventions	Main Results
Licciardone 2003	*OMT: MFR, strain-counterstrain, MET, soft tissue, HVLA, CST. Techniques applied in the low back or adjacent areas Sham OMT: ROM activities, light touch, simulated OMT. All the groups allowed to receive usual care and co-treatments except for other OMT or chiropractic manipulation	At 1 Month: OMT group reported more improvement in SF 36 physical functioning (P=0.03) and mental health (P=0.04) than the no-intervention control subjects. At 1, 3 and 6 months: both OMT and Sham OMT groups reported greater VAS improvements (diff. btw gr: -0.5, P=0.01 and -0.6, P=0.003) than no intervention; RMDQ: no differences among groups. Greater satisfaction for both OMT (P=0.001) and Sham OMT (P=0.02).
Chown 2008	*OMT: soft tissue, articulation, HVLA, functional, exercise, education, psychological issues. Physiotherapy: education, joint mobilization, McKenzie, mobility and stabilization exercise, postural correction. Exercise: home stretching exercise, basic pathophysiology, question and answer session.	At 6 weeks. No significant changes between groups. Reduction in ODI score for the three groups (OMT: -5.0 +/- 10.5; Physio: -4.1 +/- 8.0; Exercise: -4.5 +/- 8.4 P<0.05); improvement in EQ-5D for Physiotherapy and OMT (P<0.05); significant change in VAS (OMT: -4.0 +/- 19.9; Physio: -4.8 +/-11.5; Exercise: -2.8 +/- 17.2 P<0.05). At 12 months after discharge.

		No significant change detected in mean ODI score.
Mandara 2008	*OMT: further details not available Sham OMT: further details not available	At 6 months: OMT significantly decreased pain and disability compared to Sham OMT; significant interaction (group x time) for both VAS (P<0.01) and for ODI (p<0.01) *Diff. between groups not available.*
Vismara 2012	*OMT + SE: HVLA, CST, MFR + SE. SE: combined back school and cognitive behavioural approach.	At post treatment: OMT + SE group showed a significant improvement in thoracic ROM. VAS, RMDQ, ODI changed significantly in both groups, higher improvements in OMT + SE group (diff. btw. gr. respectively -15.52; -4.14; -5.68; P<0.05).
Ajimsha 2013	*MFR + SE: MFR of thoracolumbar fascia, gluteus maximus, posterior hip and piriformis, deeper back muscles + specific back exercise program. Sham MFR + SE: gentle pressure of the hand over the areas treated in MFR group + specific back exercise program.	At week 8 and 12: Significant reduction in MPQ and QBPDS in favour of experimental group (diff. btw. gr. respectively: -6.2 and -5.8 at week 8; -5.2 and -3.8 at week 12; P<0.001).
Licciardone 2013	*OMT: lumbosacral, iliac and pubic regions targeted using HVLA, MVMA, soft tissue, MFR, treatment of tender points, MET. Sham OMT: hand contact, active and passive ROM, simulated OMT (light touch, improper patient position, misdirected movements, diminished physician force). Applied to the same anatomical areas.	At post treatment and at 12 weeks: VAS significant reduction in OMT group compared to sham OMT (P=0.02) *Diff. between groups not available.* At week 12 (VAS): moderate improvement reported for OMT patients (RR: 1.38, 95% CI: 1.16-1.64); substantial improvement reported for OMT patients (RR: 1.41, 95% CI: 1.13-1.76). Greater satisfaction for OMT group in comparison to Sham OMT (P<0.01).
Castro-Sanchez 2016	*CST: pelvic and respiratory diaphragm release, thoracic inlet release, hyoid release, L5-sacrum technique, CV4 induction. Classic massage: soft tissue massage on the low back.	Post treatment and 1-month follow-up: No significant difference between groups for RMDQ, ODI, TSK, McQuade Test, finger to floor distance. VAS: Significant difference between groups at post treatment (diff. btw. gr. -1.03, P=0.008) and at follow-up (diff. btw. gr. -1.0, P=0.009). in favor of craniosacral. Significant difference over time for the all endpoints, except for TSK.

Arguisuelas 2017	*MFR: longitudinal sliding of lumbar paravertebral muscles, release of: thoracolumbar fascia, quadratus lumborum, psoas muscle. Sham MFR: delicate placing of the hands over the same areas.	At 2 weeks (post treatment): significant difference between group in FABQ total score in favor of MFR group. At 12 weeks (follow-up): Significant difference between group in SF-MPQ (-7.8, P<0.05), SF-MPQ sensorial domain (-6.1, P<0.05), RMDQ (-3.7, P<0.05), FABQ total score.
De Oliveira Meirelles 2019	*OMT: articulation and myofascial techniques ACG: therapeutic exercise	At 5 weeks: Significant pre-post reduction in VAS, ODI, TSK and BDI (P<0.05) Statistically significant difference between groups in VAS and ODI in favor of OMT (diff. btw. gr. respectively: -5.0 and -8.0, P<0.05).
Santos 2019	For both groups: conventional PT consisted of strengthening, mobilizing and stabilizing exercises. *OVM: active Visceral Manipulation: cardias, pylorus, Oddi sphincter, duodenojejunal valve, ileocecal valve, sigmoid colon, liver, global hemodynamic maneuver. Placebo OVM: light touch over the same spots, without therapeutic intention.	At 5 weeks: significant pre-post improvement in VAS (diff. -4.0, P<0.001); statistically significant improvement between group in Schober Test and PSFS (p<0.05).

*: experimental intervention
p: p-value (significance level)
Abbreviations: HVLA High velocity low amplitude, MVMA Medium velocity medium amplitude, CV-4 Compression of fourth ventricle, ROM Range of motion, MET Muscle-energy technique

Risk of Bias

Risk of bias was assessed in the 10 included studies. No study showed low Rob in all the 13 items. Since interventions relate to manual therapies, all the trials were judged to be intrinsically at high risk for blinding of personnel (criterion 4). 50% of studies were supposed to be at high risk for selection bias because of no mention about blinding of participants (criterion 3), in one case this risk was judged as unclear. In 30 % of included RCTs, authors estimated high risk for attrition bias, since intention-to-treat analysis was not observed or declared; in two trials this judgement remained uncertain (criterion 7) and in two cases it was unclear since no drop-outs information were provided (criterion 6). One trial was judged at high Rob for allocation concealment (criterion 2) and for outcome reporting (criterion 8), even if most of the included papers did not show any protocol registration number. Six out of 10 studies were judged to be at unclear risk for baseline comparability (criterion 9): authors referred no baseline differences between groups, but no statistical data in this regard was found in the article. Finally, all the trials appeared to be at low Rob for cointerventions' management, treatment compliance, timing of outcome assessment and for other possible sources (criteria 10, 11, 12, 13). Results of this evaluation and specific judgement for each study are shown in in Fig. 2 and Fig. 3

Fig. 2. Risk of Bias assessment graph for the included studies.

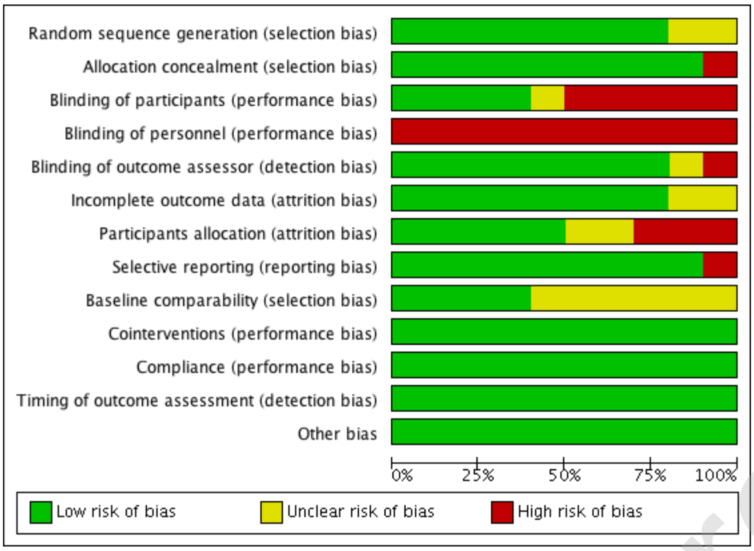

Fig 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Description of results

Osteopathic interventions resulted substantially safe: seven studies[35-38,41-43] (70%) did not report any adverse effect, Ajimsha and coll.[39] reported an increasing of pain in 10 subjects during the first week of MFR treatment, Licciardone's 2013 study[40] indicated "increased back muscle spasticity" in one occasion; Santos et al.[44] did not collect any data.

Effects of osteopathic interventions for pain and disability reduction have been estimated through a meta-analysis reported in the following sections. To notice that seven[37-43] out of 10 studies reported significant pain and disability improvements in favor of osteopathic intervention: among these, OMT (4), MFR (2), CST (1) were applied. Six studies assessed pain through VAS, reporting a significative mean difference between-groups ranging from -15.52 to -1.03 points; one trial[39] measured the same outcome through MGPQ founding a significant between-groups difference of -6.2 ($P<0.05$). As regards functional status, one study[38] reported significant RMDQ between groups change (-4.14, $P<0.05$) and three studies founded significant differences in ODI (range: -8.0; -5.68, $P<0.05$). Ajimsha[39] noted a significant improvement in disability by using QBPDS (-5.8, $P<0.001$).

Only 3 RCTs[35,36,44] did not show any improvements in the primary outcomes of the present review (OMT: 2; OVM: 1). Four RCTs[36,39,40,42] provided data at three months follow-up; two[40,42] (OMT: 1; MFR: 1) reported significant results in favor of osteopathy for functional status: Arguisuelas[42] reported a between-groups RMDQ score of -3.7 (P<0.05). Two studies[39,41] (MFR: 2) demonstrated significant effect also for pain reduction (respectively -7.8 and -5.2 between-groups MGPQ change score).

Three trials[41-43] also investigated psychological profiles. Specifically, Castro-Sanchez[41] (CST) did not report any significant change in kinesiophobia, de Oliveira Merelles[43] (OMT) found improvement only in pre-post comparison in favor of osteopathy. Arguisuelas[42] (MFR) showed significative changes for intervention group in FABQ (fear-avoidance beliefs), both at post and over 12 weeks follow-up.

Three RCTs[35,36,40] assessed levels of patients' care satisfaction; in all the measurements OMT was appreciated, only in one occasion[40] significantly in respect of control (sham OMT).

Other indicators (e.g work disability, kinematics, co-treatments) resulted sporadic and details are provided in Tab. 2.

Effect of interventions

Osteopathy versus control interventions for Pain

Overall Effect

All the included RCTs[35-44] (n = 10, 12 comparisons) were considered in the meta-analysis, with a total of 1049 participants. Two[35,36] of these studies had two comparison groups. In five cases[39,40,42-44] pain was considered as a primary outcome, in three studies[36,39,41] it was secondary and in three others[35,37,38] no details were provided. As shown in the forest plot (Fig. 4), seven RCTs[37-43] reported a significant effect in favor of osteopathy, in three studies[35,36,44] this result was not significant, and in one case[35] the control intervention revealed not significantly superior in comparison to osteopathy. The quantitative synthesis showed an overall effect in favor of osteopathic interventions (ES = -0.59 [-0.81, -0.36]; P < 0.00001). Heterogeneity was moderate-to-substantial and significant (I^2 = 59%; P = 0.005).

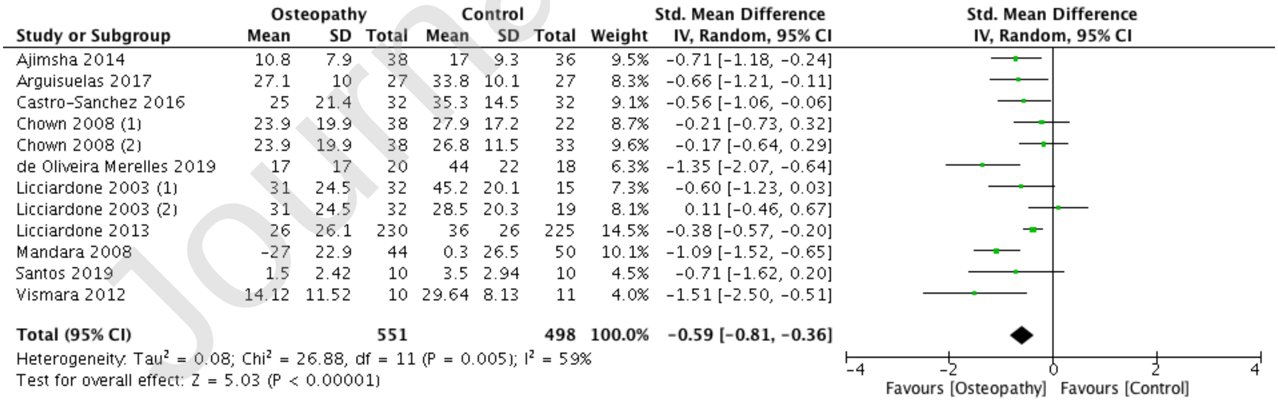

Figure 4: Forest plot of comparison: Overall effect of Osteopathy vs. Control interventions for Chronic Low Back Pain. Outcome: pain. Abbreviations: CI, confidence interval; SD, standard deviation.

Subgroup Analysis

Eight[35-40,42,43] of 10 RCTs (10 comparisons) were included in a subgroup analysis (Fig. 5), with an aggregate sample of 965 subjects. Two trials[41,44] were excluded since they were the only investigating CST and OVM. Subgroup analysis involved MFR (n = 2) and OMT (n = 6). In the first analysis both studies[39,42] reported a significant effect in favor of MFR, in the second comparison four trials[37,38,40,44] showed relevant effects for OMT; in three comparisons[35,36] the effect was not significative and in one case[35] a non-significant superiority of control intervention was detected.

Pooled ES was significant for both groups (respectively: ES: – 0.69 [–1.05, –0.33]; P = 0.0002) and ES: –0.57 [–0.90; –0.25]; P = 0.0006]. Evidence of MFR for NS-CLBP was rated as of "moderate-quality", whereas evidence of OMT for NS-CLBP was judged as "low" (see Tab. 3 for further details).

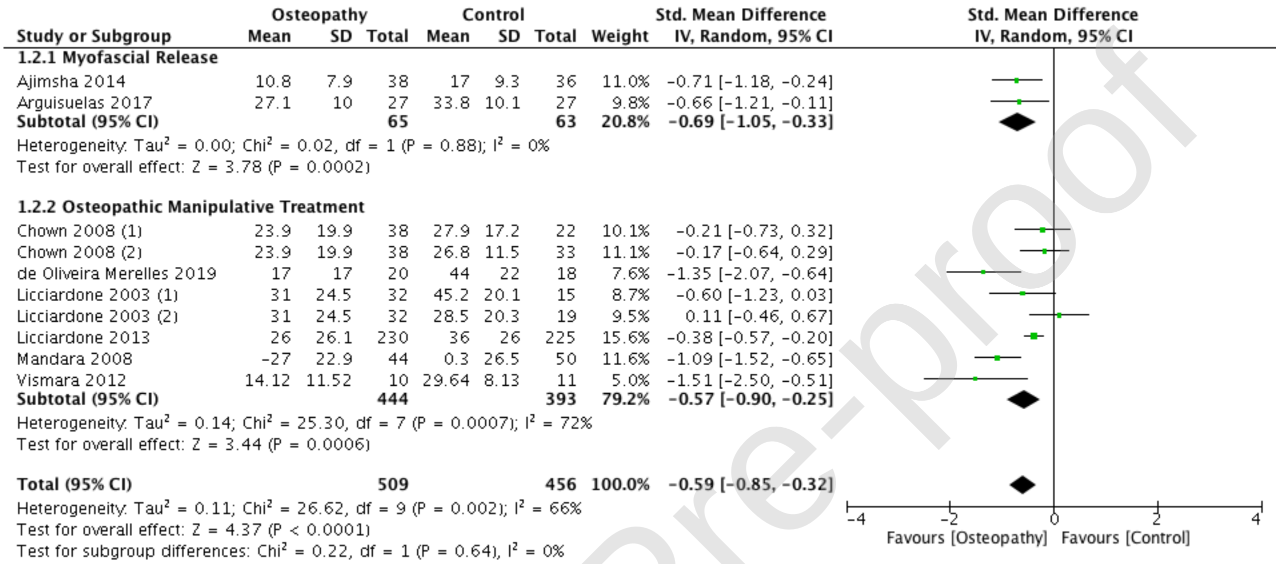

Figure 5. Forest plot of comparison: Subgroup analysis (category of intervention) comparing the effect of Osteopathy vs Control interventions for Chronic Low Back Pain. Outcome: pain. Abbreviations: CI, confidence interval; SD, standard deviation.

Osteopathy versus control interventions for functional status

Overall Effect

All the trials (12 comparisons) were included in the analysis, with an aggregate of 1055 participants. Change in functional status was considered the primary outcome in three studies[36,39,41]. Forest plot shown in Fig. 6 indicates that osteopathic interventions effects resulted statistically significant in six trials[37-39,41-43] when compared to control treatment. One study[36], reported data in favor of osteopathy, without significant effect; in two cases[35,40] the two interventions resulted totally indifferent and two trials[35,44] reported results in favor of control group without statistical significance. An overall effect in favor of osteopathy was estimated (ES = –0.42 [–0.68, –0.15]; P = 0.002. Heterogeneity was substantial and significant (I^2 = 72%; P <0.0001).

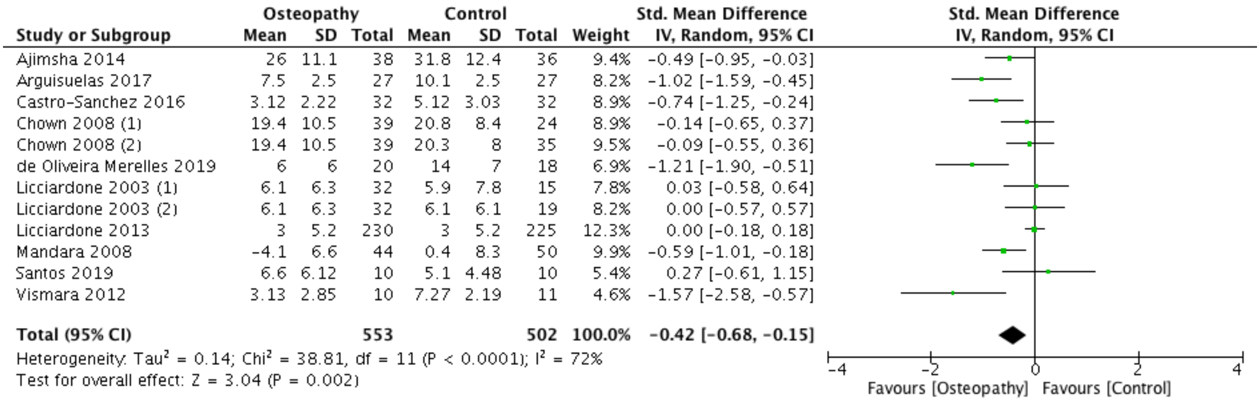

Figure 6. Forest plot of comparison: Overall effect of Osteopathy vs Control interventions for Chronic Low Back Pain. Outcome: functional status. Abbreviations: CI, confidence interval; SD, standard deviation

Subgroup Analysis

Subgroups considered for the outcome "functional status" were the same of the precedent analysis. Concerning MFR (128 participants), the two included RCTs[39,42] reported significant effect in favor of the osteopathic intervention compared to control groups; pooled data showed a significant ES: (– 0.73 [–1.25, –0.21]; P = 0.006). Also OMT group revealed a significant result in comparison to control interventions (ES= –0.33 [–0.65, –0.01]; P = 0.04); as forest plot shows, in this comparison three studies[37,38,43] demonstrated a significative difference in favor of OMT, in one case[36] this difference was not significative, two trials reported indifference in results[35,40] and in one comparison[35] non-significant results in favor of control group was detected (Fig. 7).

The GRADE level of evidence was rated as "very low" for MFR and "low" for OMT. (see Tab. 3 for further details).

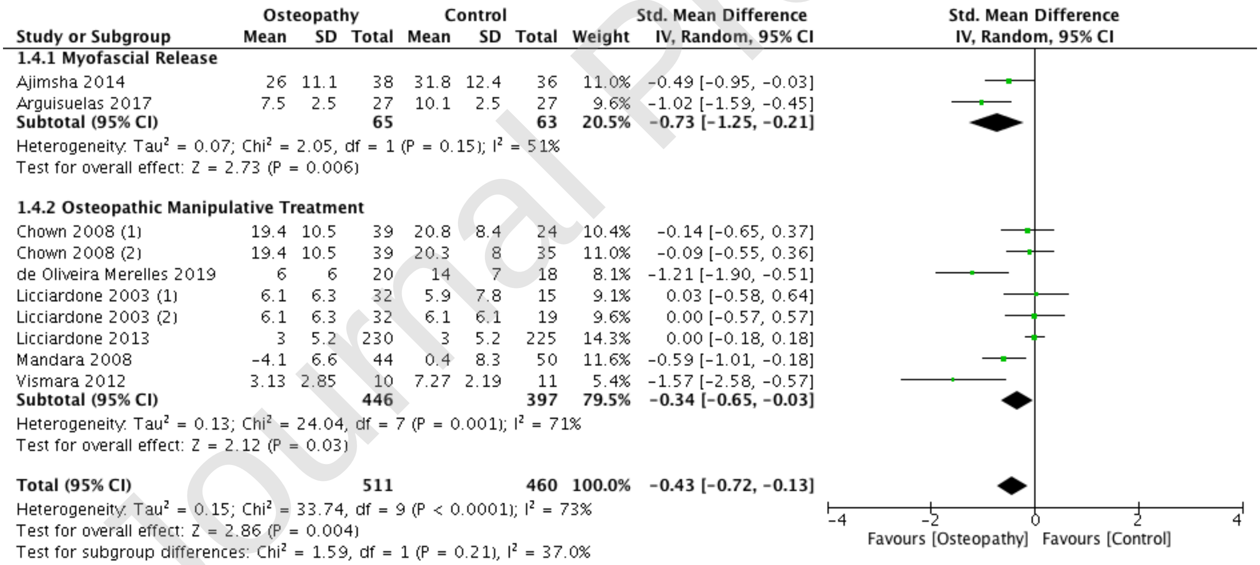

Figure 7. Forest plot of comparison: Subgroup analysis (category of intervention) and overall effect analysis comparing the effect of Osteopathy vs Control for Chronic Low Back Pain. Outcome: functional status. Abbreviations: CI, confidence interval; SD, standard deviation.

Osteopathy versus control interventions for Pain (12 weeks follow-up)

Subgroup analysis

Only three studies[39,40,42], two[39,42] concerning MFR and one[40] applying OMT, assessed pain levels over a 12 weeks follow-up post intervention. Thus, a meta-analysis was possible only for trials regarding MFR.

Both included studies reported significant effect in favor of MFR compared to control intervention, with a pooled ES of –0.73 [–1.09, –0.37]; P < 0.0001 (Fig. 8). Evidence was rated as of "low-quality" (see Tab. 3 for further details).

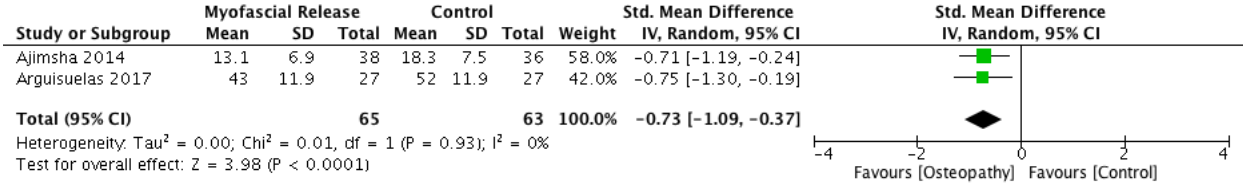

Figure 8. Forest plot of comparison: Overall effect of Myofascial Release vs Control for Chronic Low Back Pain at 12-weeks follow-up. Outcome: pain. Abbreviations: CI, confidence interval; SD, standard deviation.

Osteopathy versus control interventions for Functional Status (12 weeks follow-up)

Subgroup analysis

We considered four studies[36,39,40,42](five comparisons) that measured functional status outcome over a 12 weeks follow-up. Two studies[39,42] were relative to MFR intervention, two others[36,40] applied OMT.

Concerning the first group, only one trial[42] showed significant effect in favor of MFR; in Ajimsha's study[39] the same result was not supported by statistical significance. Pooled ES (–0.85 [–1.79, 0.10] P = 0.08) means not-significative effect in favor of MFR. The same result was observed in the OMT subgroup: Chown's trial[36] (two comparisons) shows a non-significant effect in favor of control intervention and Licciardone's study[40] report a statistical relevant result in favor of OMT. The pooled effect size was estimated as –0.14 [–0.31, 0.03]; P = 0.10, suggesting absence of significative effect (Fig. 9). Evidence for MFR was rated as of "very low-quality", for OMT was judged as of "low-quality" (see Tab. 3 for further details).

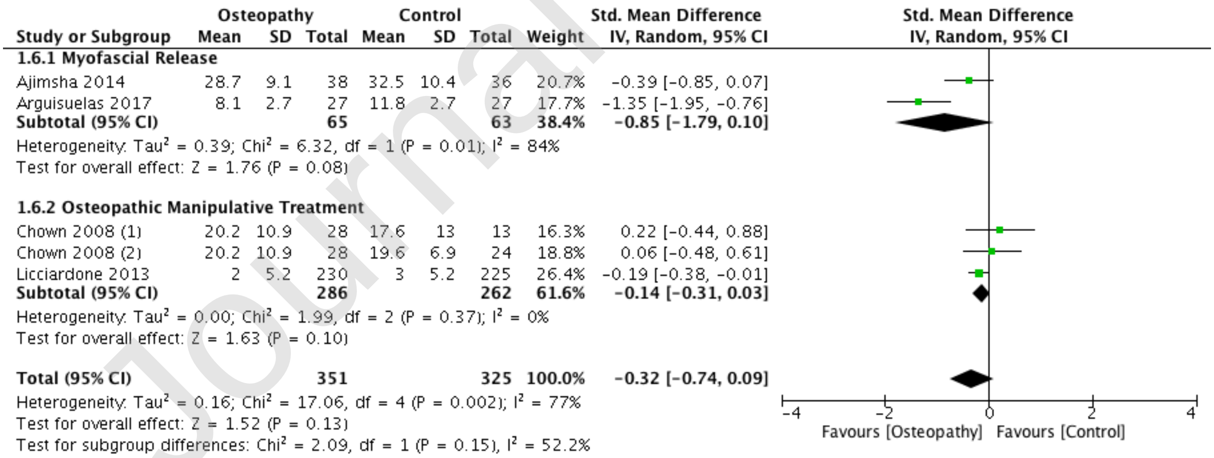

Figure 9. Forest plot of comparison: Overall effect of Myofascial Release vs Control for Chronic Low Back Pain at 12-weeks follow-up. Outcome: functional status. Abbreviations: CI, confidence interval; SD, standard deviation

Table 3. Quality of evidence based on GRADE criteria.

Imprecision: a = wide confidence interval;
Evidence downgraded for imprecision for wide confidence interval and/or sample size <100.

Outcome	SMD (95% CI)	N. of subjects (Studies)	Comments	Quality of Evidence
Pain: post-treatment Myofascial Release	-0.69 (-1.05; -0.33)	128 (2 RCT)	Downgraded by one level for risk of bias	⊕⊕⊕○ Moderate
Pain: post-treatment OMT	-0.57 (-0.90; -0.25)	837 (8 RCT)	Downgraded by one level for risk of bias Downgraded by one level for inconsistency (I^2 = 59%)	⊕⊕○○ Low
Functional status: post-treatment Myofascial Release	-0.73 (-1.25; -0.21)	128 (2 RCT)	Downgraded by one level for risk of bias Downgraded by one level for inconsistency (I^2 =51%) Downgraded by one level for imprecision[a]	⊕○○○ Very low
Functional status: post-treatment OMT	-0.34 (-0.65; -0.03)	843 (8 RCT)	Downgraded by one level for risk of bias Downgraded by one level for inconsistency (I^2 = 73%)	⊕⊕○○ Low
Pain: long-term effect Myofascial Release	-0.73 (-1.09; -0.37)	128 (2 RCT)	Downgraded by one level for risk of bias	⊕⊕⊕○ Moderate
Functional status: long-term effect Myofascial Release	-0.85 (-1.79; 0.10)	128 (2 RCT)	Downgraded by one level for risk of bias Downgraded by one level for inconsistency (I^2 =84%) Downgraded by one level for imprecision[a]	⊕○○○ Very low
Functional status: long-term effect OMT	-0.14 (-0.31; 0.03)	548 (3 RCT)	Downgraded by one level for risk of bias Downgraded by one level for imprecision[a]	⊕⊕○○ Low

GRADE criteria
High Quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility
that it is substantially different.
Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

DISCUSSION

Summary of Evidence

Specific aim of the current review was to analyze effects of different osteopathic interventions for chronic non-specific low back pain. For this reason, we decided to include not only OMT studies, but also trials focusing on single osteopathic modalities (MFR, CST, OVM) experimented alone and in comparison to other type of control intervention. To our knowledge, only one systematic review[21] conducted by Licciardone in 2003 pursued the same objective, with some methodological issues

already discussed in the introduction section. Since then, some new RCTs had been conducted in this field over years, allowing us to find favorable conditions to undertake a new systematic review.
Our results provide evidence that osteopathic interventions are effective in reducing pain and improving functional status in patients with NS-CLBP, in the short term. These overall results were obtained through a meta-analysis that involved all the RCTs included; this analysis was possible since all the studies assessed both outcome (pain and disability), even if primary outcomes and measure tools not always coincided. The effect was estimate as "moderate" for pain ($0.5 < ES < 0.79$) and "small" for functional status changes ($0.2 < ES < 0.49$), even if there is uncertainty regarding this last esteem. If this assumption was correct, it would suggest once again how pain and functional status are not necessary related in NS-CLBP patients, and respond differently to osteopathic manipulative interventions. These aspects find confirmation in literature: a recent prospective cohort study, for instance, demonstrated how disability can be influenced by various factors such as catastrophization, depression, fear of movement, and anxiety[43]. These statements should be considered in pain management, and osteopathic medicine should represent a single relevant component inside a wider treatment plan. In addition, findings of the current review are similar to Licciardone's[21] and Franke's[23] conclusions, whereas some discrepancies are visible in comparison to Orrock's[22] results: this fact could be explained in reason of different inclusion criteria that brought that study to include only two RCTs and to avoid meta-analysis.
Furthermore, in the qualitative synthesis of this review, we did not notice any substantial difference in terms of results when type of control was considered (active or sham); a subgroup analysis for different controls was avoided since low homogeneity in control groups was detected among studies. Results of this review probably strengthen the evidence that osteopathic interventions represent a therapeutic choice to consider in NS-CLBP, since they appear to be superior than standard care alone and a valuable option to associate with exercise. For this reason it's our opinion that, in future, osteopathic research should mainly focus on different manipulative modalities to better understand which type of intervention reveals to be superior than others. This could be done by performing high-quality RCT comparing different osteopathic manual approaches.
The included studies investigated different types of osteopathic interventions: OMT, MFR, OVM and CST. Variations and discrepancies were observed even inside the same typology of intervention. This aspect represents a limitation that will be discussed in the section below. However, it is important to consider that a certain degree of variability is predictable in manual interventions. This fact is even more notable in osteopathic medicine, where diagnosis and treatment process are completely based on palpatory findings (and not, for instance, on symptoms or instrumental examinations). In our opinion this aspect should not represent a methodological limit at all, since it elicits the person-centered model and the whole-body vision, typical of osteopathic medicine[17]. Nevertheless, it is important to remind how all the different osteopathic interventions are based on a common therapeutic aim: promoting optimal function of tissues to restore function of the body[16,17].
Such differences in terms of technicalities, dosage and length of treatment surely represent an obstacle to precisely estimate the therapeutic role of osteopathy, as well as a barrier to evaluate its cost-effectiveness. As already pointed out in a recent health economic review[44], there is need for appropriate osteopathic research that effectively reflect the person-centered system of care and provide data which can inform policy decisions within the healthcare system. Nowadays, despite some positive findings, authors concluded that data are of insufficient quality and quantity to inform policy and practice.

Evidence for different osteopathic interventions
A subgroup analysis was also performed to highlight the specific contribution of single interventions. This analysis showed significant results in favor of both MFR and OMT. MFR subgroup was composed of two only trials, with some differences in the control intervention; despite this, results were in the same direction. Four out of the six studies included in the OMT subgroup analysis reported

results in favor of osteopathy; among them, an important weight in the final result was given by Licciardone's 2013 trial[36], mainly due to its definitely large sample size (n = 225).
These findings are in line with current evidence; several RCTs and systematic reviews reported a significant beneficial role of osteopathy in chronic musculoskeletal conditions, especially regarding pain levels: some authors demonstrated efficacy of OMT in neck pain[45], in fibromyalgia[46,47,48] and in primary headache[49,50]. In addition, MFR had been investigated mainly in non-specific neck pain, appearing as an effective therapeutic choice[51,52]; beside this, systematic reviews reported encouraging (but still uncertain) results concerning its utility in chronic painful conditions[53,54]. Despite this, the therapeutic mechanisms underlying osteopathic manipulations are largely unknown and partly speculative. However, research about this topic is growing; Cerritelli and coll. recently highlighted, in a fMRI study involving NS-CLBP patients[17], the possible role of OMT in brain sensorial activity; based on these findings, their hypothesis is that OMT could act on the so-called "interoceptive ways"[55], thus modulating the sensitization process. In support, Tamburella et al.[16] demonstrated how osteopathic manipulation is able to change cerebral blood perfusion in healthy subjects; in a similar way, Ponzo and coll. provided support for the effects of the OMT on cortical plasticity[56]. In addition, D'Ippolito et al. founded osteopathic manipulation to be effective in reducing pain and improving mood disorders[57]. Differently, several authors continue to focus their attention on the mechanical effect that manipulation could provide on thoracolumbar fascia and tightly contiguous myofascial tissue[58,59,60]. In any case, these two visions are not necessary in contrast if mechanical and neurological aspects are thought to be coexisting, or even connected, as some authors suggested[61].
Finally, this review investigated effect of osteopathic interventions over a 12 weeks follow-up. Pooled data shows how MFR is statistically effective for pain reducing, on the contrary MFR and OMT did not give any certain effect in improving functional status. However, only few studies[30,33,34,36] with methodological differences were involved in this analysis and so, conclusions should be taken carefully.
Data related to CST and OVM studies were not pooled in any subgroup analysis, since these two trials[37,40] were the only applying these interventions. Considering encouraging reported results, further research should be done in these fields.

Quality of Evidence

As Tab. 3 shows, quality of evidence ranged from "very low" to "moderate". Reasons for downgrading were similar for each comparisons. Firstly, we downgraded all the evidence for serious risk of bias. No included study was completely safe from this risk, specifically regarding blinding procedures. Dealing with manual therapies, all the trials were intrinsically judged at high risk for "blinding of personnel"; five trials were also judged at high or unclear risk for "blinding of participants". In addition, even if low/unclear judgement was given to "blinding of assessor" item, we must consider how the majority of the assessments were completely self-reported; consequently, it becomes difficult to really intend this risk as "low". Beside this, intention-to-treat analysis was not always performed. All these issues are considerable of a critical importance for internal validity and led the authors to downgrade evidence by one level.
Secondly, in four cases we have downgraded for inconsistency; moderate or substantial levels of heterogeneity were found in the overall analyses and in some of the subgroup analyses. Conversely, no heterogeneity was present in MFR for pain analyses, even if the inclusion of two only RCTs invite to caution in interpreting these data.

Limitations

Some limitations are present in the current review and are worthy to be discussed.
Primarily, data were not always retrievable in the articles and, in some occasions, were not presented in a modality useful to perform meta-analysis. This fact regarded particularly Mandara's study[33], whose full text was not available. When possible authors were contacted via e-mail even if, in some

occasions, information remained partial.
The extreme variability of included studies protocols makes impossible, de facto, every type of generalization. Variability was observed in different manipulative approaches, even inside the same typology of intervention: dosage, length of sessions, duration of "in care" period, semi- or no standardized treatments, choice of techniques, operators' degree and levels of experience. A certain degree of heterogeneity was also observed in control interventions, causing difficulties in interpreting correctly data and relative conclusions.
In addition, the interpretation of the results might be affected by the inclusion of studies which investigated different osteopathic approaches; actually, if in OMT studies the treatment protocols were generally semi-standardized and the operators could partly decide which techniques were more appropriate, in trials applying single modalities the sessions were totally predetermined, thus bypassing any kind of osteopathic clinical reasoning. In our opinion this issue has profound implications and do not permit to understand the real effectiveness of osteopathic medicine in its complexity. From this point on, more efforts are required to better determine the real appropriateness of osteopathic assessment (e.g: reliability, validity) in the research field; at the same time, research should also focus on the biological mechanisms through which the different manipulations act. Only in the most recent period, some issues are emerging on these topics [62,63].
As discussed before, many studies reported high risk of bias in some critical methodological steps, such as blinding procedures or intention-to-treat analysis; for this reason, our conclusions should be interpreted with caution, since it is not possible to provide a precise esteem of these biases impact.
Even if Licciardone's 2013 trial[36] provided an important weight in meta-analyses in reason of a large number of participants, most of the other RCT's reported small sample sizes.
In addition, the majority of comparisons reported substantial levels of heterogeneity, which makes conclusions uncertain.
Finally, findings of this review could be influenced by publication bias; as known, there is no robust statistic tool able to precisely estimate it.

IMPLICATIONS

To our knowledge, this study represents an appropriate update of previous systematic reviews investigating effectiveness of different osteopathic interventions in NS-CLBP. Results confirms and strengthen evidence that osteopathy improves pain levels and functional status in patients with chronic non-specific low back pain over a short-term period. MFR approach reported better levels of evidence for pain improvement if compared to other osteopathic modalities. However, further research is necessary for confirmation. Encouraging data emerged for possible beneficial effect of osteopathic intervention over a three months follow-up even if, to date, results remain uncertain. Moreover, these findings could represent a source for an integration of the "2016 American Osteopathic Association Guidelines for Osteopathic Manipulative Treatment in LBP"[22].
In conclusion robust, high-quality and double-blinded RCTs, with a specific focus on technical approaches, safety, dosage of treatments and costs-effectiveness are necessary to produce higher-quality evidence, useful to correctly influence clinical practice and healthcare policies.

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