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Effects of manual osteopathic interventions on psychometric and psychophysiological indicators of anxiety, depression and stress in adults: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objectives To evaluate whether osteopathic and related manual interventions improve adult mental health (depression, anxiety, stress) and psychophysiological measures (eg, heart rate variability, skin conductance).

Design Systematic review and meta-analysis of randomised controlled trials (RCTs).

Data sources PubMed, MEDLINE (Ovid), Scopus, Cochrane, and AMED, searched through September 2024.

Eligibility criteria English-language RCTs with ≥30 participants investigating osteopathic or related manual therapies (eg, myofascial release, high-velocity low-amplitude thrusts) delivered by qualified practitioners, compared with no treatment or sham, and reporting immediate postintervention mental health or psychophysiological outcomes.

Data extraction and synthesis Full-text screening, risk-of-bias assessment and data extraction were conducted independently by multiple reviewers using a standardised Joanna Briggs Institute (JBI) Extraction Form. Risk of bias was assessed using the JBI Critical Appraisal Checklist. For meta-analyses, Hedges' g (with 95% CIs) was calculated from postintervention means and SD. Random-effects models accounted for heterogeneity, and prediction intervals were calculated to assess uncertainty in effect estimates.

Results 20 RCTs were included. Osteopathic interventions reduced depression (Hedges' g=−0.47, 95% CI: −0.86 to −0.09, p=0.02) and increased skin conductance (Hedges' g=0.67, 95% CI: 0.00 to 1.34, p=0.05). Depression improvements were greater in pain populations (Hedges' g=−0.61, 95% CI: −1.06 to −0.17, p=0.01). However, wide prediction intervals and moderate heterogeneity indicate uncertainty in true effect sizes, and limited studies and sample sizes restrict assessment of publication bias.

Conclusions Osteopathic and related manual therapies may reduce depression and influence certain psychophysiological markers, particularly in pain populations, but uncertainty and heterogeneity limit confidence. More rigorous, larger, and longitudinal RCTs are needed.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Only randomised controlled trials with clear randomisation procedures and sufficient sample sizes (≥30 participants) were included to ensure study quality.
⇒ Full-text screening, risk of bias and data extraction were done by multiple independent reviewers to increase precision.
⇒ This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was preregistered on the Open Science Framework, ensuring transparency and replicability.
⇒ The review only considered studies in English and those published in peer-reviewed journals, potentially introducing language and publication bias, limiting the comprehensiveness of the evidence.
⇒ The analysis only considered immediate postintervention outcomes, restricting insights into long-term effects.

Trial registration number This meta-analysis was not formally registered, though the protocol and search strategy can be found at Open Science Framework, registration identification: https://osf.io/jrtpx/.

INTRODUCTION

Mental health issues such as anxiety and depression affect approximately one in eight people globally, with even higher rates in the UK, where one in six individuals report ongoing symptoms.[1 2] The COVID-19 pandemic has exacerbated these problems, leading to a 28% increase in both anxiety and depression worldwide.[3–5] Beyond personal suffering, mental health issues contribute to problematic behaviours like substance abuse, self-harm and suicidal ideation,[5] and impose a significant economic burden. In the UK alone, mental health problems cost the economy around £118 billion annually, primarily due to lost productivity.[6]

Traditional treatments like psychotherapy and psychopharmacology are effective but have limitations. Pharmacological treatments can cause adverse effects such as dizziness, emotional blunting and even suicidal thoughts.[7–9] Psychotherapy faces barriers including mental health stigma and patient apathy due to depression-related lack of motivation.[1 10–12] Additionally, increasing demand and limited resources strain access to these services, potentially limiting individuals' access to qualified psychological therapists.[1 13]

One approach to address these challenges is to explore integrative therapies as part of primary care.[14–17] Osteopathic manipulative treatment (OMT) is a promising method that has shown potential in reducing symptoms of anxiety and depression.[18–22] Osteopathy is an Allied Health Profession regulated by the General Osteopathic Council (https://www.osteopathy.org.uk/home/) in the UK, requiring practitioners to be registered by law. Osteopathic practices are evidence-informed, employing manual therapy (MT) techniques such as myofascial release, lymphatic drainage and high-velocity low-amplitude (HVLA) thrusts to modulate pain and improve function. Other manual therapies, such as general physiotherapy or chiropractic, typically focus on alleviating specific symptoms like joint pain or muscle tension. In contrast, osteopathy targets the underlying somatic dysfunction, aiming for improved systemic health and self-regulation[23 24]

By applying these techniques, osteopaths can influence the patient's autonomic nervous system (ANS), promoting relaxation, increasing motion and reducing pain.[16 25] Emerging evidence suggests that OMT affects brain regions involved in emotional regulation, such as the amygdala, insular cortex and prefrontal cortex, all critical for processing stress and anxiety.[26 27] These regions are also implicated in modulating the body's stress responses, and their modulation via OMT might explain reductions in stress and anxiety observed in clinical outcomes.[25 28]

OMT has been shown to enhance parasympathetic activity, as reflected in increased heart rate variability (HRV), suggesting improved vagal tone and reduced sympathetic activation.[29–31] This vagal enhancement, coupled with changes in neurophysiological markers such as cortisol levels and ANS balance, provides a mechanistic basis for observed mental health improvements.[32 33] Additionally, these treatments can alter other physiological responses, such as interoception, blood flow and electrodermal activity (EDA), which are linked to emotional regulation and stress responses.[25 34 35] These physiological changes may underpin the mental health benefits that researchers have observed in osteopathy.[18–22]

HRV measures the variation between consecutive heartbeats and is associated with mental health and emotional regulation.[36–40] Higher HRV indicates increased parasympathetic activation and relaxation, while lower HRV suggests increased sympathetic activation and stress.[41–44] Similarly, EDA, commonly measured through skin conductance (SC), reflects changes in sympathetic nervous system activity and is frequently used as a marker of autonomic arousal.[45] Previous research into the effects of osteopathic techniques has found that an immediate increase in sympathetic nervous system activity, as reflected by the galvanic skin response, may be associated with autonomic regulation and a reduction in the experience of pain and may therefore also reflect a beneficial effect of osteopathic treatment.[46] Such autonomic shifts may influence emotional states, suggesting a complex interaction between sympathetic activation and psychological outcomes.

Interoception, the perception of internal bodily sensations, plays a role in emotional awareness and regulation.[38 47 48] Mindfully oriented changes in interoceptive awareness can lead to positive outcomes, such as increased emotional regulation and positive states of mind.[49 50] Conversely, maladaptive alterations in interoception have been associated with various mental health issues, including anxiety disorders, depression and reduced psychological flexibility.[48 51 52] Therefore, the mental health benefits observed from osteopathy may involve processes like mindful enhancement of interoception or decreased sympathetic arousal measured through HRV.

Previous systematic reviews have highlighted the potential benefits of osteopathic interventions on both autonomic function and psychosocial outcomes. One review identified positive effects of osteopathic treatment on ANS regulation, particularly through HVLA techniques, but noted inconsistent results across varying techniques and body regions.[25] Another review found that osteopathic treatments may reduce psychological symptoms and enhance the quality of life in persistent pain populations.[18] However, neither review conducted a meta-analysis of randomised controlled trials (RCTs), nor did they examine the effects of osteopathic interventions on mental health outcomes beyond pain-specific populations. This meta-analysis addresses these gaps, synthesising evidence from rigorously designed RCTs to assess osteopathy's psychophysiological impacts across a broader range of mental health contexts.

Given this body of evidence, the present systematic review and meta-analysis has three main objectives. First, we will specifically focus on the effects of osteopathic and related manual therapies on mental health, justified by evidence supporting positive outcomes in this area.[18–22] For the purpose of this review, osteopathic interventions include treatments delivered by qualified practitioners using techniques commonly employed in osteopathic practice, such as HVLA thrusts, myofascial release, craniosacral therapy and other manual therapies consistent with osteopathic principles. Second, we will include only RCTs as they are considered the gold standard for establishing the effectiveness of an intervention, and a meta-analysis requires data from RCTs.[53] Specifically, any studies where the randomisation procedure is unclear will not warrant inclusion in the final synthesis. To ensure methodological rigour, any studies with unclear randomisation procedures will be excluded from the final synthesis. Finally, this review will address both psychometric measures and psychophysiological indicators relevant to mental health, including factors known to reflect ANS activity or psychophysiological bodily states, such as HRV, SC and interoception. This focus is justified by evidence suggesting that osteopathy can alter these psychophysiological measures related to mental health.[18–22 34]

The primary research question therefore being addressed is: 'Are osteopathic and related manual interventions effective for improving psychophysiological indicators and psychological psychometric outcomes relating to mental health in adult populations?'

METHODS

This systematic review and meta-analysis has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[54] (see online supplemental checklist). The protocol was preregistered via the Open Science Framework (registration identification osf.io/jrtpx).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Eligibility criteria

The eligibility was determined using the Population, Intervention, Comparison, Outcome, and Study-type framework.[55] This systematic review and meta-analysis included RCTs that explored the effectiveness of MT interventions for improving related psychophysiological and mental health psychometric outcomes in adults. The eligibility criteria are described in table 1.

Search strategy

We searched PubMed, MEDLINE via Ovid, Scopus, Cochrane and AMED from database inception to September 2024, applying a filter for English-language studies. Although our search was broad to capture various study designs, only RCTs were included in the final analysis per our inclusion criteria. We replaced PEDro with the Cochrane database to ensure broader coverage as PEDro does not include osteopathic studies with mental health outcomes. The full search strategy for each database is detailed in online supplemental material 1. We used a combination of MeSH terms and keywords, applying 'title and abstract fields only' and 'all fields' filters. Manual citation searching was conducted using Google Scholar's 'cited by' function, and reference lists of relevant systematic reviews were examined for additional studies.

Selection process

Search results were exported to Zotero (V.6.0.14) to remove duplicates, then imported into Rayyan, a web app for screening studies,[56] as Rayyan did not support automated duplicate removal at the time. Initial screening was independently conducted by both TCG and JH-B. Full-text PDFs were retrieved for studies meeting the initial criteria. Studies not published in English or unavailable through institutional or open access were excluded. Full-text screening was then conducted independently in duplicate by four blinded reviewers (TCG, JH-B, AM and DM). Studies were divided so that each half (50%) of the studies were screened independently by two reviewers (TCG and JH-B screened the first half; AM and DM screened the second half), ensuring that every study was assessed by two blinded reviewers. Discrepancies were resolved through discussion among the reviewers.

Risk of bias

Methodological quality was assessed independently in duplicate by three reviewers (JH-B, AM and DM) using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for RCTs (2017 version).[57] The JBI tool allows for subjective assessment of studies' trustworthiness, relevance and results. Studies lacking a clear randomisation process were deemed to have critical weaknesses and were excluded as randomisation ensures balanced participant characteristics and reduces potential biases.[53] As per our preregistered protocol, we included only studies with clearly reported methods. While the protocol allowed for contacting authors regarding missing data, this was not pursued for randomisation details as the focus was on studies with adequately reported methods to ensure transparency and reproducibility within the review timeline.

Data extraction

Data were collected using the standardised JBI Extraction Form (see online supplemental material 2). This included citation details such as authors, date of publication, journal name and country of origin. The study details included population characteristics (health status/diagnosis, age, sample size setting), intervention characteristics (technique used, duration, comparison), outcomes measured and procedures for randomisation and blinding. Data extraction was done in duplicate independently by three reviewers (JH-B, AM and DM) and simultaneous to the risk-of-bias assessment.

Meta-analysis

We extracted mean postintervention scores, SD and sample sizes to compute standardised mean differences using Hedges' *g*, as reported in other meta-analyses.[58–60] Effect sizes were calculated using postintervention scores as randomisation ensures baseline equivalence between groups. Pre-post comparisons could not be used because many of the included studies did not provide sufficient information for calculating change scores, including SD of the changes. Psychometric measures included mean scores for anxiety, stress and depression. Psychophysiological measures included postintervention HRV as measured by the time domain root mean square of

Table 1 The eligibility criteria used for decision-making about the inclusion of studies in this systematic review and meta-analysis

Population	The included populations were adults (18+) who were either (1) healthy individuals, defined as those without a diagnosed medical, psychological or chronic pain condition at the time of study enrolment, as reported by the study authors; (2) individuals without pain conditions but had either an official clinical diagnosis (by an accredited mental health practitioner) of ongoing anxiety, stress or depression, or where the papers had identified and reported some form of existing anxiety, stress or depression present through the mental health psychometric measures they employed or (3) individuals with pain conditions with corresponding anxiety, depression or stress-related difficulties. The corresponding mental health problems were again reported either as an official clinical diagnosis (by an accredited mental health practitioner) of ongoing anxiety, stress or depression, or where the papers had identified and reported some form of existing anxiety, stress or depression present through the mental health psychometric measures they employed. This was kept as open as possible and without specific psychometric cut-off scores as it is difficult to standardise cut-off scores between the many different types of mental health measures used. Populations were excluded in cases where their condition or treatments could confound the outcomes. This included populations with neurological conditions such as Alzheimer's disease, dementia, brain injury, as well as populations with ongoing cancer treatment and individuals who were pregnant.
Intervention	Studies using osteopathic interventions were included. Interventions had to be delivered by a qualified clinician (eg, osteopath, physiotherapist, massage therapist) using techniques commonly employed in osteopathic practice, such as high-velocity low-amplitude thrusts, myofascial release, craniosacral therapy and other manual therapies consistent with osteopathy. Studies that used techniques less commonly used by osteopaths were excluded. This included reflexology, acupressure, aromatherapy massage and Thai massage. Invasive techniques such as acupuncture were also excluded, as were electrical stimulation techniques. In addition, interventions that only reported using physical exercise or yoga were excluded as this does not constitute manual, *touch-based* therapy. Interventions that were solely self-administered and not by a practitioner were excluded. Interventions that had a significant psychotherapeutic element were excluded as this could be considered a confound with regards to mental health outcomes. Lastly, studies where patients received medication as part of the intervention were excluded.
Comparison	Eligible comparator groups included those where participants received either no intervention or a placebo (sham) intervention, such as light touch or relaxation techniques. While the preregistration allowed for any type of comparator, we limited our analysis to control, placebo or sham groups to ensure the specific effects of osteopathic interventions could be isolated and minimise the risk of confounding influences. Active treatment comparators, such as thermotherapy or electrical stimulation, were excluded to maintain methodological rigour and consistency across the included studies.
Outcome	Both psychophysiological and mental health psychometric outcomes were of interest as outcome measures. Psychophysiological indicators of autonomic nervous system activity were included such as heart rate variability, galvanic skin conductance, as well as bodily interoception, and cortisol measurements. Additionally, studies using psychometrics assessing outcomes of depression, anxiety and stress were also included. Outcomes that were excluded involved measures that did not directly assess mental health as a psychometric outcome, such as quality of life scales, sleep quality and studies that only measured heart rate. Although positive affect and psychological flexibility were included as outcomes in the preregistration, they were later excluded for similar reasons as they were considered indirect measures of mental health. Outcome measurements reflect immediate postintervention effects, with no follow-up data included. The decision to exclude follow-up assessments was based on inconsistencies in timing and availability across studies, which would complicate meaningful synthesis and interpretation.
Study	Only full randomised controlled trials (RCTs) were included, studies labelled as a pilot RCT or had 30 participants or less in total were excluded. 30 participants were selected as an arbitrary cut-off to remove very small sample RCTs that may not be labelled as a pilot study but clearly were. This arbitrary cut-off was selected because 30 participants are typically selected in many pilot RCT studies.[114–117] Additional criteria included the availability of full-text papers and reports had to be written in English. Published data were used where possible; however, authors of published data were also contacted in the case where data had been reported as collected but not reported in a way that could be usefully applied to a meta-analysis.

successive differences of normal heartbeats (RMSSD), and the frequency-domain sympathovagal balance of the low-frequency/high-frequency (LF/HF) ratio, as well as EDA as measured by SC.

Meta-analyses were conducted using the Comprehensive Meta-Analysis software (CMA, V.4)[61] for outcomes where at least two studies could be meaningfully combined.[62] CMA was chosen over Revman, as initially specified in our protocol, for its capabilities for calculating prediction intervals and assessing heterogeneity. The analyses considered the overall effect (computed as Hedges' *g*) of the osteopathic interventions versus control group for psychophysiological and psychological psychometric measures independently. The data were entered into the analyses as continuous outcomes and Hedges' *g* was computed with 95% CI, SE. A random-effects model was used to account for the clinical and methodological heterogeneity among the studies.[63] In addition, we assessed the certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[64] This method evaluates the risk of bias, inconsistency, indirectness and imprecision to categorise the evidence into high, moderate, low or very low certainty.

Inclusion in meta-analysis

Studies were included in the meta-analyses when at least two studies measured the same outcome. For one outcome measure (perceived stress), only a single eligible study was identified;[65] therefore, it could not be compared in a meta-analysis. Studies deemed to have a high risk of bias were excluded to maintain the methodological rigour of the meta-analysis, in line with our prespecified eligibility criteria. One indicator of high risk of bias was the presence of significant baseline imbalances in key outcome measures, as such imbalances can confound treatment effects and undermine the validity of between-group comparisons.[66 67] For example, Castro-Sanchez *et al*[68] demonstrated substantial baseline differences in RMSSD—a primary outcome—raising concerns that postintervention effects could reflect pre-existing group differences rather than the intervention itself. While sensitivity analyses are often used to test the robustness of findings, by including studies with methodological concerns, this approach assumes that the identified issues, such as baseline imbalances, have a minimal impact on results.[69] In cases where primary outcomes are directly compromised, as in Castro-Sanchez *et al*, sensitivity analyses are inappropriate because the potential for bias cannot be sufficiently mitigated.[70]

Crossover RCTs were excluded due to the high likelihood of carry-over effects, as per Cochrane guidelines.[71] While first-period data can sometimes be used to mitigate carry-over bias,[72] none of the included crossover studies[34 73–75] sufficiently reported first-period outcomes for analysis. Also, as the maximum washout period across these studies was only 1 week, the risk off carry-over bias remained high. Therefore, crossover trials included in the systematic review were excluded from the quantitative meta-analysis.

All outcome measurements were assessed immediately post intervention, aligning with the available data from included studies. No follow-up assessments were included in this meta-analysis due to limited consistent follow-up data across studies. Studies containing multiple treatment/control groups or data collection timepoints were assessed to determine which scores were most relevant for comparison in the meta-analysis. In the two cases where studies contained two treatment groups involving osteopathic manual therapy (OMT),[76 77] groups scores (n, M, SD) were combined using a formula described and recommended by Cochrane[78] before being compared with the control group. There were three cases in which a study used two controls;[22 79 80] for Sherman *et al*[22] we opted to exclude the thermotherapy control group as it was considered likely to influence psychometric and psychophysiological results.[81] In the other two cases,[79 80] the placebo interventions data were excluded in favour of the no-treatment controls (ie, these were not combined). This decision was made on the basis that the inclusion of the placebo intervention introduced excessive heterogeneity to the analysis (I^2>75.0), and therefore was considered to limit the validity of our calculated effect size which should be avoided.[82]

Heterogeneity

Statistical heterogeneity was assessed using the I^2 statistic and *Q*-value (χ^2 test). I^2 values of 0–24% indicate low heterogeneity, 25–49% low, 50–74% moderate and >75% high heterogeneity.[83 84] A significant *Q*-value (p<0.05) suggests true heterogeneity in effect estimates.[55] To enhance homogeneity, we compared outcomes reported at the same or at similar timepoints. For depression outcomes, two studies did not report immediate postintervention outcomes and instead reported outcomes at 5 weeks[85] and 14 weeks,[22] while one study only reported immediate outcomes.[21] In order to ensure homogeneity of timepoints in line with Cochrane guidelines section 9.3.4 (ie, to maximise data available),[78] the closest timepoints to the 5 weeks and 14 weeks were chosen, and hence compared with scores taken at 12 weeks[86] and 4 weeks.[87] In the analyses of anxiety, RMSSD, LF/HF ratio and SC outcomes, all studies reported immediate postintervention outcomes, which were subsequently used in the following meta-analyses.

RESULTS

After full-text screening, 41 studies were selected for the risk-of-bias assessment and data extraction (see figure 1). Following risk-of-bias assessment, 18 studies were excluded due to unclear randomisation procedures, leading to questions about their status as RCTs. An additional four studies were excluded for other reasons, including lack of a control group, absence of relevant postintervention outcome measures and use of a device-delivered intervention (see online supplemental material 3). The included studies demonstrated clear randomisation procedures and often included blinding, particularly with outcome assessment. Although blinding is challenging in MT studies, the included studies were considered at low risk of bias despite some design limitations (see online supplemental material 4).

A total of 20 studies were included, focusing on psychological outcomes such as depression, anxiety, stress or general well-being (n = 6), and psychophysiological outcomes like HRV and SC (n = 14). Where possible, individual study effect sizes are reported.

Psychometric mental health outcomes

The studies examining psychometric mental health outcomes are summarised in table 2. Two studies included

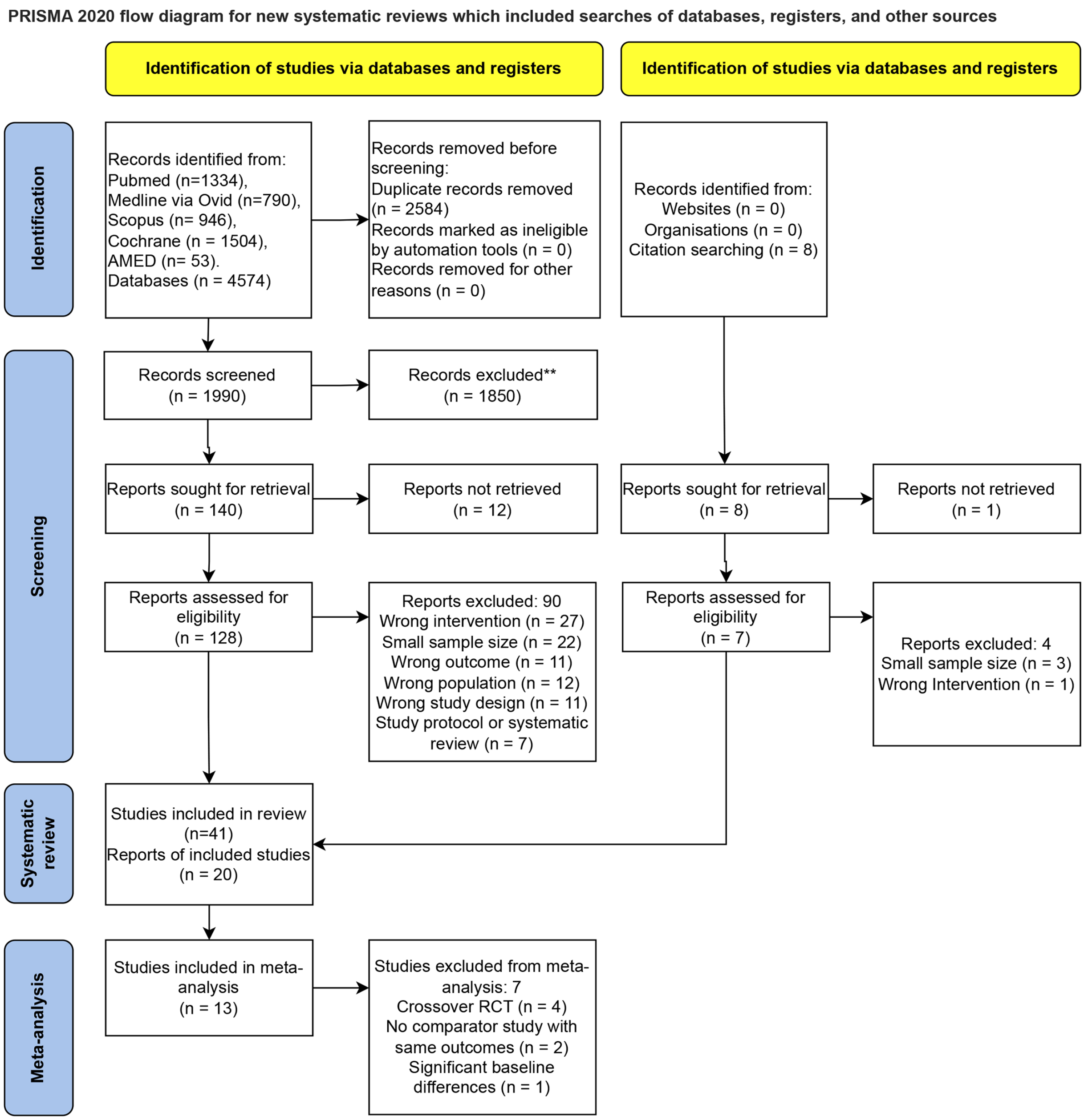

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of screening process and papers excluded at each stage. RCT, randomised controlled trial.

depression only as an outcome,[85 86] one study included anxiety as an outcome,[22] two studies included both depression and anxiety as outcomes[21 87] and one study included a general psychological well-being outcome and perceived stress as an outcome.[65] The measures used for depression included the Beck Depression Inventory (BDI)[88] (n=2), the Hamilton Depression Rating Scale[89] (HDRS) (n=1), the Patient Health Questionnaire[90] (n=1) and the Centre for Epidemiologic Studies Depression Scale (CES-D)[91] (n=1). Measures of anxiety included the State-Trait Anxiety Inventory (STAI)[92] (n=2) and the Hamilton Anxiety Rating Scale (HARS)[93] (n=2). Studies examining stress used the Perceived Stress Scale (PSS)[94] (n=1) and as a general measure of psychological well-being, the General Well-Being Schedule (GWB)[95] was used (n=1). Three of the studies[21 22 86] reported that the manual therapeutic interventions had clinically relevant effects on the psychological outcomes.

Depression

Two studies examined depression as a primary outcome of MT,[85 86] with both finding significant improvements following treatment. Baumgart *et al*[86] compared psychoregulatory massage therapy (PRMT) to classical massage in women with chronic lower back pain. The results suggested that those in the PRMT group significantly reduced depression scores over time, while the control group did not. The authors noted that the severity of depression in the PRMT condition was reduced by 56% from moderate to minimal levels post intervention.

Table 2 Summary of included studies measuring psychometric outcomes

Author	Population	Intervention	Duration	Control group	Outcome measures	Results	Inclusion in meta-analysis
Baumgart *et al*[86]	Patients with chronic back pain (n=57; 57 females; mean age not specified)	Psycho-regulatory massage therapy (PRMT) (n=28) by licensed therapist; clinic setting	10 sessions 30–60 min, twice a week	Classical massage therapy (n=29)	Beck Depression Inventory (BDI)	Significant reduction in BDI-II scores for PRMT group (55.69% reduction vs 3.1% in CMT). Effect size Z=−4.41, p=0.001. Dropout: ~20%. CI not specified.	Yes
Castro-Sanchez *et al*[85]	Patients with fibromyalgia (n=89; 48 females, 41 males; mean age 54, SD=8)	Manual therapy (variety of techniques: suboccipital release, release of the pectoral region, diaphragm release, lumbosacral decompression, release of the psoas fascia and thoracic spine extension manipulation in prone (high-velocity low-amplitude) (n=45); delivered by a physiotherapist; clinic setting	Five weekly sessions of 45 min each	No-intervention control (NIC) (n=44)	Centre for Epidemiologic Studies Depressive Symptoms Scale (CES-D)	Significant improvement in CES-D scores for the manual therapy group (F(1, 87) = 23.93, p<0.001). Dropout: not specified. CI not provided.	Yes
Espí-López *et al*[87]	Patients with tension-type headache (n=84; 68 females, 16 males; mean age 39.7, SD=11.38)	1. Suboccipital soft tissue treatment (n=20) 2. Articulatory techniques (n=20) 3. Combined techniques (n=20); delivered by physiotherapists; primary healthcare centres	Four weekly sessions of 20 min each	NIC (n=24)	State-Trait Anxiety Inventory (STAI), BDI	Significant improvement in BDI (Cohen's *f*=0.35, F(3, 80) = 2.75, p<0.05). For anxiety, chronic TTH participants in the articulatory technique group had lower state anxiety scores (Cohen's *f*=0.35, F(3, 80) = 3.12, p<0.05). Dropout: 5%. CIs not specified.	Yes
Rapaport *et al*[21]	Adults with generalised anxiety disorder (GAD) (n=40; 30 females, 10 males; mean age 36.0, SD=13.8)	Swedish massage therapy (n=20); delivered by a licensed massage therapist; healthcare institute setting	12 sessions of 45 min each, over 6 weeks	Light touch intervention (n=20)	Psychiatrist assessed with Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating Scale (HDRS) Participants self-reported STAI, Quick Inventory of Depressive Symptomatology-Self-Report and Profile of Mood States	Swedish massage reduced HARS by 11.67 (SEM=1.09) vs 8.41 (SEM=1.01) in light touch (effect size=−0.69, 95% CI: −1.33 to −0.05, p=0.030). QID-SR: effect size=−0.96 (95% CI: −1.52 to −0.02, p=0.003). HDRS: effect size=−0.84 (95% CI: −1.44 to −0.24, p=0.027). Dropout: two in light touch.	Yes
Sharpe *et al*[65]	Older adults 60+ (n=54; 18 females, 36 males; mean age 68.0, SD=5.7)	Massage therapy (n=25; techniques: Swedish, neuromuscular and myofascial) delivered by licensed therapists; university campus setting	Two weekly sessions of 50 min each for 4 weeks	Guided relaxation (n=24)	General Well-being Schedule (GWB), Perceived Stress Scale (PSS)	Improvement in GWB (F(1, 52) = 3.56, p=0.07) and significant improvement in PSS (F(1, 52) = 4.65, p=0.04) for massage group vs guided relaxation. Dropout: 9%. CIs not provided.	No (only study reporting this outcome)
Sherman *et al*[22]	Adults with GAD (n=68; 21 females, 47 males; mean age 41.3, SD=13.0)	Therapeutic massage (n=23) delivered by licensed massage therapist; clinical setting	10 sessions of 60 min each, over 12 weeks	1. Thermotherapy control (n=22) 2. Relaxation control (n=23)	HARS, Penn State Worry Q, Patient Health Questionnaire and Sheehan Disability Scale	Clinically meaningful reduction in HARS across all groups (adjusted mean change: −12.5; 95% CI: −15.0 to −10.0), with no significant differences between groups. Dropout: low, with similar rates across groups but specific figures not reported.	Yes

Castro-Sánchez[85] evaluated an MT intervention comprising various techniques (eg, suboccipital release, diaphragm release, lumbosacral decompression) in patients with fibromyalgia, compared with a no-intervention control. The intervention significantly reduced depression scores (CES-D) compared with control for both men (effect size *d*=0.97) and women (*d*=0.40), with males showing greater improvements.

Anxiety

One study measured anxiety as a primary outcome. Sherman *et al*[22] assessed the effectiveness of massage therapy, including myofascial and Swedish massage, in adults with generalised anxiety disorder (GAD), compared with thermotherapy and relaxation controls. All three groups showed significant improvements in anxiety symptoms (HARS scores) over time, with no significant differences between groups. Approximately 59% of participants in the massage group experienced at least a 50% improvement in anxiety scores at 12 weeks, with similar significant improvements in anxiety scores of the thermotherapy (57.1%) and relaxing room (61.9%) conditions.

Anxiety and depression

Two studies measured both anxiety and depression as primary outcomes following manual interventions. Rapaport *et al*[21] evaluated Swedish massage therapy in adults with GAD compared with a light-touch control. Participants received weekly sessions for 12 weeks, and outcomes were assessed using the HARS and HDRS. The massage group showed significant reductions in both anxiety and depression scores compared with the control group. Specifically, the massage group had a greater mean reduction in HARS scores, indicating significant improvement in anxiety symptoms. Similar significant reductions were observed in HDRS scores for depression. The effect sizes were *d*=–0.69 for anxiety and *d*=–0.96 for depression, indicating medium to large effects. Clinically significant improvements (≥50% reduction on HARS) were observed in 57.1% of massage participants versus 35.3% in controls, although this difference did not reach statistical significance.

Espí-López *et al*[87] examined MT combining soft tissue techniques (STs) and articulatory techniques (ATs) in patients with tension-type headaches. Four groups were compared: STs, ATs, combination therapy (MT) and a no-intervention control. Significant improvements in depression (BDI scores) were observed in the AT group compared with control. Results did, however, show that those treated with ATs significantly improved symptoms of depression compared with the control.

General psychological well-being and stress

One study measured general psychological well-being and stress as primary outcome measures. Sharpe *et al*[65] examined the effects of various massage techniques (Swedish, neuromuscular, myofascial) in older adults (60+). The massage group showed significant improvements on GWB subscales, including anxiety, depression, positive well-being, vitality and general health, and reduced PSS scores compared with a relaxation control. As participants had baseline distress scores below clinical levels, the intervention may offer preventive benefits. (Note: this was the only study examining GWB and stress, so it was not included in the meta-analysis.)

Mental health psychometric interventions summary

Overall, the six studies examining psychometric mental health outcomes indicate that MT interventions, particularly massage-based therapies, are associated with significant improvements in depression and general psychological well-being. Three out of four massage studies reported significant reductions in depression symptoms or enhancements in well-being compared with controls. Additionally, manual therapies combining STs and ATs demonstrated significant benefits in reducing depression among patients with conditions like fibromyalgia and tension-type headaches. However, the effects on anxiety were mixed, with some studies showing significant improvements while others found no significant differences compared with controls. These findings suggest that MT may be more consistently effective for alleviating depression than anxiety.

Physiological outcomes

14 of the included studies examined psychophysiological outcomes and are summarised in table 3. Four studies included HRV as a primary outcome,[68 77 96 97] three studies included SC as a primary outcome[79 80 98] and one study included interoception as an outcome.[99] The remaining seven studies measured a variety of psychophysiological outcomes, which included a combination of HRV and SC[76]; a combination of SC, skin temperature (ST), breathing rate (BR) and heart rate (HR)[100]; a combination of HRV, SC and ST[73]; a combination of SC and ST[75]; a combination of thermal imaging, SC and HRV,[99] interoceptive accuracy and HRV[34]; a combination of HRV and salivary alpha-amylase[101]; and a combination of HRV and blood pressure variability.[74]

Heart rate variability

Four studies measured HRV as a primary outcome.[68 77 96 97] Of these studies, only one found a significant result. This was Seifert *et al*,[97] who examined the effect of rhythmical massage therapy (RMT) on HRV in healthy female adults. This consisted of two RMT groups (one with aromatic oil and one without oil) compared with a sham control group. The results demonstrated that both RMT groups significantly increased HRV from pre- to post intervention, and that this was significant relative to the control group. They also found that aromatic oil did not seem to offer any advantage over RMT without aromatic oil in this context.

Skin conductance

Three studies measured SC as a primary outcome following MT treatment.[79 80 98] Only one of these studies

Table 3 Summary of included studies measuring physiological outcomes

Author	Population	Intervention	Duration	Control/sham group	Outcome measures	Results	Inclusion in meta-analysis
de Araujo *et al*[77]	Healthy participants (n=57; 31 males, 26 females; mean age 22.6, SD=4.1)	1. Posterior-to-anterior rotatory thoracic passive accessory intervertebral mobilisation (PAIVM) (n=18) 2. Unilateral posterior-to-anterior in slump position (n=19) (these experimental groups were combined as per Cochrane suggestions); delivered by a physiotherapist in a controlled lab setting	One session, approximately 6 min	Placebo intervention (mimicking PAIVM with minimal pressure and no oscillation) (n=20)	Heart rate variability (HRV) (root mean square of successive differences of normal heartbeats (RMSSD) and low-frequency/high-frequency (LF/HF) ratio)	No significant difference in HRV (RMSSD, LF/HF ratio) for PAIVM vs placebo (F(2, 57) = 1.30, p=0.28, 95% CI: −1.39 to 1.03). Dropout: 5%.	Yes
Arienti *et al*[76]	Healthy participants (n=32; 23 females, 9 males; mean age 33.9, SD=14)	1. Fourth ventricle compression (CV4) (n=16) 2. Rib-raising techniques (n=10) (these experimental groups were combined as per Cochrane suggestions); delivered by an osteopath in a clinical setting	One session, 5 min	Placebo intervention (light touch without any osteopathic technique) (n=6)	HRV and skin conductance (SC)	LF/HF ratio significantly lower in CV4 vs placebo (F(2, 29) = 3.44, p=0.042, 95% CI: −0.21 to −0.02). Dropout: not specified.	Yes
Castro-Sanchez *et al*[68]	Patients with fibromyalgia (n=92; 46 females, 46 males; mean age 53.9, SD=10.1)	Craniosacral therapy (n=46), delivered by a trained craniosacral therapist; clinical setting	Two weekly 1 hour sessions over 20 weeks	Placebo intervention with disconnected magnetotherapy equipment (n=46)	HRV (RMSSD)	Placebo group had higher RMSSD at 1 year follow-up (p=0.047, 95% CI: 0.01 to 0.09). No significant within-group differences over time. Dropout: 15%.	No (significant baseline differences)
Cerritelli *et al*[99]	Patients with chronic lower back pain (n=29; 18 males, 11 females; mean age 41.8, SD=6.6)	Osteopathic manipulative treatment (OMT), including balanced-ligamentous tension, balanced-membranous and fluidic techniques (n=16); delivered by an osteopath in a clinical rehabilitation setting	Four weekly sessions of 30 min each	Placebo intervention (light touch without any osteopathic technique) (n=13)	Heartbeat tracking (interoceptive accuracy (IA)), auditive tracking (exteroceptive accuracy (EA)), and fMRI of brain areas associated with interoceptive pathways	OMT significantly improved IA with fewer errors (t=−3.69, p<0.001, effect size d=1.01, 95% CI: −1.50 to −0.43); no significant effect on exteroceptive accuracy. Dropout: not specified.	No (only study reporting this outcome)
Cerritelli *et al*[73]	Healthy adults (n=37; 14 males, 23 females; mean age 27, SD=5)	OMT, including balance-ligamentous, balance-membranous and cranio-sacral techniques (n=18); delivered by an osteopath in a controlled lab setting	Two weekly sessions of 60 min each	Placebo intervention (light touch without any osteopathic technique) (n=19)	HRV (LF/HF ratio), SC and skin temperature (ST)	Significant increases in HF HRV (p<0.001, effect size d=0.7, 95% CI: 0.15 to 0.30), SC (p<0.01, 95% CI: 0.10 to 0.25), and ST (p<0.01, 95% CI: 0.08 to 0.20) in OMT vs placebo. Dropout: not specified.	No (crossover design randomised controlled trial (RCT))

Continued

Table 3 Continued

Author	Population	Intervention	Duration	Control/sham group	Outcome measures	Results	Inclusion in meta-analysis
Edwards *et al*[34]	Healthy participants (n=35; 35 males; mean age 21, SD=4)	OMT, osteopathic mobilisation of temporomandibular joint (n=35); delivered by an osteopath; lab setting	One session, approximately 90 s	1. Deep touch (DT) (n=35) 2. No-intervention (n=35)	HRV (RMSSD) and IA	RMSSD increased significantly in deep-touch group (p<0.01, 95% CI: 0.05 to 0.20). IA increased significantly in both deep-touch and OMT groups (p<0.04, effect size *d*=0.5, 95% CI: 0.02 to 0.15). Dropout: not specified.	No (crossover design RCT)
Galaasen Bakken *et al*[96]	Participants with neck pain (n=131; 73 females, 58 males; mean age 57, SD=13.9)	Spinal manipulative therapy and home stretching (n=66); provided by chiropractors and physiotherapists in a primary care clinical setting	Five sessions	Home stretching only (n=65)	HRV (RMSSD and LF/HF ratio)	No significant effects on HRV (RMSSD, LF/HF ratio) between SMT+ stretching vs stretching alone (B=0.4, p=0.9, 95% CI: −0.12 to 0.15). Dropout rate: 7%.	Yes
Honguten *et al*[101]	Healthy participants (n=66; 8 males, 58 females; mean age 52.4, SD=10.8)	Lymphatic drainage therapy (n=33); delivered by a physiotherapist; clinical setting	One session, 45 min	Rest (n=33)	H-reflex, HRV, salivary alpha-amylase (sAA), straight leg raise (SLR)	Significant reduction in H-reflex (p<0.05, 95% CI: −0.30 to −0.05) and SLR muscle tension; no significant HRV or sAA differences. Dropout: 5%.	No (significant baseline differences)
Jowsey and Perry[98]	Healthy participants (n=36; 20 males, 16 females; mean age 27.5, SD=6.1)	Grade 3 postero-anterior rotatory mobilisation technique applied to T4 (n=18); delivered by a physiotherapist; lab setting	One session, approximately 6 min	Placebo intervention (mimicking treatment with no oscillation applied) (n=18)	SC	SC significantly increased in the right hand (F(1, 34) = 4.888, p=0.034, 95% CI: 0.05 to 0.25) and trend-level increase in the left (F(1, 34) = 4.072, p=0.052). Dropout: not specified.	Yes
La Touche *et al*[100]	Patients with cervico-craniofacial pain (n=32; 14 males, 18 females; mean age 44, SD=7)	Anterior-posterior upper cervical mobilisation (n=16); delivered by a physiotherapist; clinical setting	Three sessions approximately 7 min over 2 weeks	Placebo intervention (mimicking treatment with no mobilisation applied) (n=16)	SC, ST, heart rate (HR), breathing rate (BR)	Significant increase in SC (p<0.001, effect size *d*=0.5, 95% CI: 0.18 to 0.32) and BR (p=0.02, 95% CI: 0.04 to 0.15) in the treatment group. HR increased in both conditions; no significant ST differences. Dropout: 6%.	Yes

Continued

Table 3 Continued

Author	Population	Intervention	Duration	Control/sham group	Outcome measures	Results	Inclusion in meta-analysis
Moutzouri *et al*[80]	Healthy participants (n=45; 12 males, 33 females; mean age 29, SD=3.5)	Sustained natural apophyseal glide (SNAG) on L4 with active lumbar flexion (n=15); delivered by a physiotherapist; lab setting	One session, 3 min	1. Placebo intervention (mimicking treatment with no mobilisation applied) (n=15) 2. No-intervention (n=15) (the no-intervention was selected as the comparator due to the high level of heterogeneity when combined)	SC	SNAG intervention increased SC compared with no-intervention control on the right leg (mean difference=9.43%, 95% CI 0.18 to 18.69), p=0.04) and left leg (mean difference=12.05%, 95% CI 3.29 to 20.81), p<0.01). No significant difference compared with placebo. Dropout: 0%.	Yes
Picchiottino *et al*[74]	Healthy first-year chiropractic students (n=41; 22 females, 19 males; mean age 19.9, SD=3.5)	Thoracic HVLA spinal manipulation (n=41), delivered by a licensed chiropractor; laboratory setting	One session	Placebo intervention (mimicking treatment without applying OMT technique) (n=41)	HRV and blood pressure variability (BPV)	No significant effects on HRV indices (eg, RMSSD, LF/HF ratio) between HVLA and sham groups (eg, LF/HF mean difference=0.2, 95% CI −0.5 to 0.9), p=0.498). Dropout rate: 20%.	No (crossover design RCT)
Seifert *et al*[97]	Healthy adults (n=44; 44 females; mean age 26.2, SD=4.7)	1. Rhythmical massage therapy with aromatic oil (RMT-A) (n=17) 2. RMT without aromatic oil (n=13); delivered by certified rhythmic massage therapists in a university hospital setting	One session, 20–30 min	Placebo intervention (sham massage involving touch with no oscillation) (n=14)	HRV (LF/HF ratio)	RMT significantly increased HRV (LF/HF ratio) in both RMT groups compared with sham (mean difference=0.15, p<0.001). Dropout rate: 0%. CIs not specified.	Yes
Sterling *et al*[75]	Adults with chronic cervical spine pain (n=30; 16 females, 14 males; mean age 35.8, SD=14.9)	Unilateral grade 3 cervical mobilisation on C5/6 (n=10); performed by a trained physiotherapist in a controlled lab setting	One session, 6 min	1. Placebo intervention (mimicking treatment with no movement of vertebral segment) (n=10) 2. No-intervention (n=10)	SC and ST	SC and ST significantly increased post-cervical mobilisation compared with both control and placebo (SC mean difference~16%, p=0.05; ST mean difference~2%, p=0.05). Dropout rate: 0%.	No (crossover design RCT)
Tsirakis and Perry[79]	Healthy male participants (n=45; mean age 23.6, SD=4.6)	Spinal mobilisation with leg movement (SMWLM) (n=15); performed by a physiotherapist; university lab setting	One session	1. Placebo intervention (mimicking treatment with no mobilisation applied) (n=15) 2. No-Intervention the no-intervention was selected as the comparator due to the high level of heterogeneity when combined) (n=15)	SC	SC increased significantly during SMWLM intervention compared with both placebo and control (30% increase on the treated side, p=0.045), but no significant difference post intervention. Dropout: 0%. CIs not reported.	Yes

found a significant effect. Jowsey and Perry[98] examined the effects of a rotatory mobilisation technique on SC as an outcome in healthy adults compared with a placebo treatment. They found that the experimental (MT) group demonstrated a significant sympathoexcitatory response compared with the control. Moutzouri *et al*[80] found significant increases in SC during the intervention compared with baseline that consisted of a sustained natural apophyseal glide (SNAG), but there were no significant differences between SNAG and the controls at post intervention. Tsirakis and Perry[79] found a similar finding, that is, increases in SC for the treatment group (spinal mobilisation with leg movement) compared with the control groups during the intervention but not at post intervention.

Interoception

One study examined interoception as a primary outcome. Cerritelli *et al*[99] investigated the impact of OMT on interoceptive accuracy and brain activity in adults with chronic lower back pain compared with a sham therapy control. Participants received four weekly sessions of either OMT or sham therapy. Interoceptive accuracy was assessed using a heartbeat-tracking task, where participants counted their own heartbeats without feeling their pulse. The OMT group demonstrated significantly higher interoceptive accuracy than the control group immediately after the first session ($d = 1.02$) and after the fourth session ($d = 1.31$). Functional MRI scans showed changes in brain regions associated with interoception in the OMT group. These findings suggest that OMT may enhance interoceptive awareness and modulate related brain activity in individuals with chronic lower back pain. (Note: this was the only study examining interoception, so it was not included in the meta-analysis).

Multiple psychophysiological outcomes

Seven of the included studies examined multiple psychophysiological outcomes rather than a single primary outcome,[34 74–76 99–101] of which, four found a statistically significant effect. Arienti *et al*[76] measured HRV spectral components and SC in healthy participants following fourth ventricle compression (CV4). Both techniques significantly decreased the LF/HF ratio, indicating a parasympathetic shift (CV4 $\eta p^2=0.73$, $p<0.001$; rib-raising $\eta p^2=0.58$, $p<0.001$). The CV4 intervention also resulted in significant increases in SC from pre- to post intervention ($\eta p^2=0.179$, $p=0.04$), suggesting simultaneous sympathetic activation. La Touche *et al*[100] assessed SC, ST, BR and HR in patients with cervico-craniofacial pain following anterior-posterior upper cervical mobilisation compared with a placebo intervention. The experimental group showed significant increases in SC ($\eta p^2=0.26$, $p<0.001$), BR ($\eta p^2=0.13$, $p=0.02$) and HR ($\eta p^2=0.39$, $p<0.001$), indicating heightened sympathetic activity.

Sterling *et al*[75] explored the effect of spinal manipulative therapy on patients with cervical spine pain, measuring psychophysiological outcomes SC and ST. The results found that the treatment group significantly increased SC ($\eta p^2=0.23$) and decreased ST ($\eta p^2=0.13$) relative to a placebo condition involving physical contact but no vertebrae movement and no-intervention controls. Cerritelli *et al*[73] examined the effects of two OMT sessions compared with sham treatment involving light touch on healthy participants in terms of autonomic changes, as measured by temperature (thermal imaging), SC and HRV. The results showed significant increases in temperature, SC and high-frequency HRV (HF-HRV) in the experimental group compared with sham post intervention; however, no data relating to effect size were reported.

Edwards *et al*[34] measured the effects of osteopathic mobilisation for healthy students on interoceptive accuracy and HRV. The treatment was compared with a deep-touch condition and a no-intervention control. Interoceptive accuracy improved in the two experimental groups, but this was not significant compared with the control. Similarly, HRV increased in the deep-touch condition but no significant between-groups differences were observed. Honguten *et al*[101] measured HRV and salivary alpha-amylase following a lymphatic drainage treatment. These indicators increased in the experimental group but were not statistically significant and no between-group differences were observed. Lastly, Picchiottino *et al*[74] studied the effects of HVLA treatment on HRV and blood pressure variability compared with a sham control but found no statistically significant effects.

Psychophysiological interventions summary

To summarise, of the nine studies that measured HRV, five examined manipulation-based interventions.[73 74 76 77 96] Of these five studies, only two found that the intervention significantly increased HRV.[73 76] A further two studies used massage-based interventions[97 101] but only Seifert *et al* found that HRV significantly increased in the treatment groups compared with controls. Castro-Sanchez *et al*[68] used craniosacral therapy and found that at post intervention the experimental group had significantly lowered HRV as measured by RMSSD, 1 year post intervention. Lastly, Edwards *et al*[34] examined both OMT and deep touch (a form of head cradling). Deep touch was found to significantly increase HRV while OMT was not. The remaining seven studies explored mobilisation-based interventions as measured by SC as an outcome. Of these seven studies, four found significant increases in SC responses for the treatment group[73 75 98 100] and three did not.[76 79 80]

Meta-analysis

Five main meta-analyses were conducted for each of the following outcomes with one subgroup analyses for pain and non-pain patients (where this was possible with a minimum of two papers for each population type): (1) psychometric self-reported depression scores, (2) psychometric self-reported anxiety scores, (3) psychophysiological HRV (as measured by RMSSD), (4) psychophysiological HRV (as measured by LF/HF ratio) and (5) psychophysiological

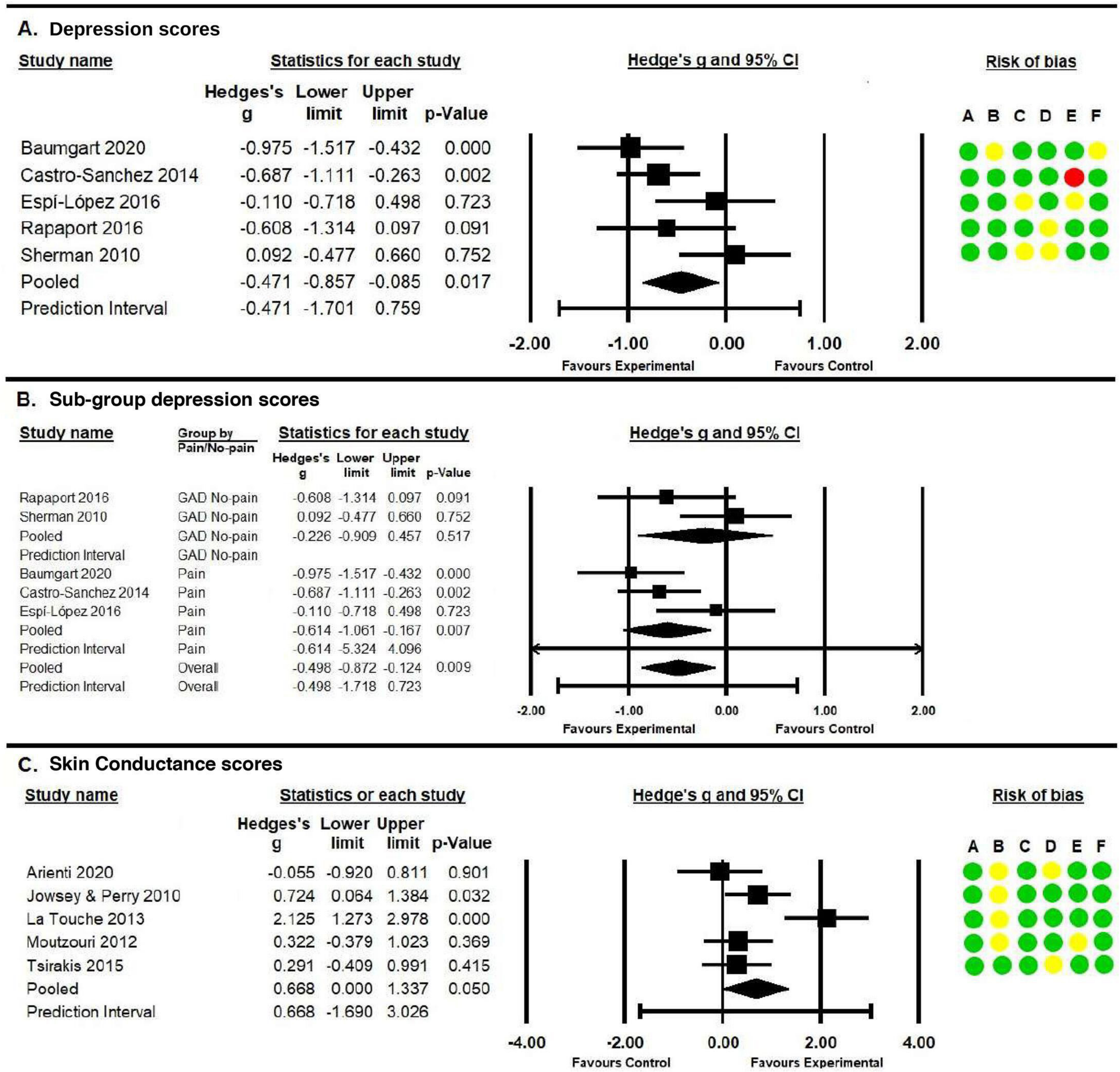

Figure 2 (A) Forest plot showing Hedge's *g* and 95% CIs for overall analyses of depression scores. (B) Forest plot showing Hedge's *g* and 95% CIs for subgroup analysis of depression scores. (C) Forest plot showing Hedge's *g* and 95% CIs for overall analysis of skin conductance (percentage change from baseline). (A, B) Lower scores=lower levels of depression, represented by studies left of the line of null effect. (C)Higher scores=greater skin conductance and therefore increased autonomic nervous system (ANS) activity, indicated by studies right of the line of null effect. Risk-of-bias key: A: Was true randomisation used for assignment of participants to treatment groups? B: Was allocation to treatment groups concealed? C: Were treatment groups similar at baseline? D: Were participants blind to treatment assignment? E: Were outcomes assessors blind to treatment assignment? F: Were treatment groups treated identically other than the intervention of interest? GAD, generalised anxiety disorder.

SC. Significant results from the meta-analyses have been presented as forest plots (see figure 2) and corresponding funnel plots (see online supplemental materials 5 and 11). A concise risk-of-bias assessment diagram has been included for studies within each forest plot, covering items A, B, C, D, F and G. As none of the included studies reported double blinding, item E was omitted from the forest plot figures. For full transparency, the complete risk-of-bias assessment, including all items A to M, is available in online supplemental material 4.

Psychometric self-reported depression meta-analysis

Five studies were included in the meta-analysis of self-reported depression scores.[21 22 85–87] Postintervention depression scores were lower for participants (both pain and non-pain) in the experimental conditions relative to the controls involving light touch or no-intervention (Hedges' g=–0.47, –0.86 to –0.09; SE=0.197; p=0.02), indicating a small-to-moderate effect size (see figure 2A). However, the CI suggests that the true effect size could range from a large effect (−0.86) to a small effect (−0.09), reflecting some uncertainty about the exact magnitude of the effect. Additionally, prediction intervals suggest that future studies could show a wide range of effects, from beneficial (lowering depression scores) to potentially harmful outcomes. The lower bound of the prediction interval (−1.701) suggests the possibility of a large beneficial effect, while the upper bound (0.759) indicates the possibility of a small harmful effect. This highlights the considerable uncertainty in predicting the effect of osteopathic interventions on depression. The Q statistic was significant (Q=9.52, p=0.05), indicating that the observed heterogeneity across the studies is unlikely to be due to chance alone. This moderate heterogeneity is also reflected by the I^2 statistic (57.99%), suggesting that variability between the study results could be influenced by differences in study design or population characteristics, rather than random error.

Subgroup analyses were conducted to examine specific effects for studies of patients living with pain and studies of patients with GAD (see figure 2B). For the subgroup analysis studies of pain patients,[21 22] postintervention depression scores were lower in the intervention groups compared with the controls (Hedges' g=–0.61, –1.06 to –0.17; SE=0.23; p=0.01), indicating a moderate effect size. The CI suggests that the true effect size could range from a large effect (–1.06) to a small effect (–0.17), indicating some uncertainty. The prediction intervals for the pain subgroup (–5.324 to 4.096) are particularly wide, suggesting that future studies may observe highly variable effects, including the possibility of either strong beneficial or harmful impacts. The heterogeneity for this subgroup was moderate (I^2 =54.82%, Q=4.43, p=0.11), though it was not statistically significant, indicating that while there is variability between the studies, it could be due to chance.

For the subgroup analysis of studies with patients with GAD (non-pain),[85–87] postintervention depression scores were lower in the intervention groups compared with the controls, but this was not found to be statistically significant (Hedges' g=–0.23, –0.91 to 0.46; SE=0.35; p=0.52). The wide CI (–0.91 to 0.46) indicates considerable uncertainty about the true effect size. Heterogeneity for this subgroup was also moderate (I^2=56.41%, Q=2.29, p=0.13), but the non-significant p value similarly indicates that the variability across the studies could be due to chance rather than true differences between studies. The funnel plot (see online supplemental material 5) did not indicate publication bias for studies measuring depression. However, with fewer than 10 studies and similar sample sizes, the ability to detect publication bias through this method is limited,[102] so the possibility of bias cannot be ruled out.

Anxiety

Three studies were included in the meta-analysis for the anxiety outcome.[21 22 87] Subgroup analysis of pain/no-pain groups was not conducted, as it would require at least two studies containing each subgroup. Postintervention anxiety scores were lower for participants in the experimental conditions, but this was not found to be significant (Hedges' g=–0.15, –0.51 to 0.20; SE=0.18; p=0.40). The wide CI (–0.51 to 0.20) suggests a considerable range of potential effects, indicating uncertainty about the true size of the effect. See online supplemental material 6 for the overall forest plot of anxiety scores. No heterogeneity was observed in this analysis (I^2=0.00%, Q=1.04, p=0.60), indicating that the effect estimates were consistent across studies. The funnel plot (see online supplemental material 7) showed no clear evidence of publication bias for studies measuring anxiety. Nonetheless, due to the small number of studies and lack of variation in sample sizes, this method may not be sensitive enough to detect potential bias, and the results should be interpreted with caution.

Heart rate variability (RMSSD)

Two studies were included in the meta-analysis of HRV (RMSSD) outcomes,[77 96] meaning that additional subgroup analysis could not be conducted. Postintervention scores for HRV (RMSSD) were higher in the experimental groups relative to the control conditions (Hedges' g=0.11, –0.29 to 0.51; SE=0.20, p=0.57), although this result was not statistically significant. The CI (–0.29 to 0.51) reflects uncertainty as the true effect could be either positive or negative. Heterogeneity was low to moderate (I^2=38.79%, Q=1.63, p=0.20), and the non-significant p value suggests that the observed variability may be due to random chance. See online supplemental material 8 for the overall forest plot of HRV (RMSSD) scores.

Heart rate variability (LF/HF ratio)

Four studies were included in the meta-analysis for the HRV LF/HF ratio outcome measure.[76 77 96 97] Postintervention scores for HRV as measured by LF/HF ratio showed a small to moderate effect, where scores were lower for participants in the experimental conditions, but this was not significant (Hedges' g=–0.36, –0.80 to 0.08,; SE=0.23, p=0.11). The CI (–0.80 to 0.08) indicates uncertainty, with the effect potentially ranging from a moderate reduction to no effect. Moderate heterogeneity was observed (I^2=58.83%, Q=7.29, p=0.06), but the non-significant p value suggests that the observed variability may be due to chance. See online supplemental material 9 for the forest plot of HRV LF/HF ratio scores. The funnel plot (see online supplemental material 10) did not suggest the presence of publication bias for the included HRV (LF/HF ratio) studies. However, given the limited number of studies and their similar sample sizes, the funnel plot may not be fully reliable for detecting bias in this context.

Table 4 Heterogeneity statistics, Hedges' *g* effect sizes, *Z* score significance values* and certainty of evidence for meta-analyses

	Q	P value	I^2	Level of heterogeneity	Average sample size per group	Hedges' *g*	P value	Size of observed effect	Certainty of evidence
Depression									
Combination of all studies	9.52	0.05*	57.99	Moderate	26.3	0.47	0.02*	Small to moderate	Low
Pain studies	4.43	0.11	54.82	Moderate	31.0	0.61	0.007*	Moderate	Low
Non-pain studies	2.29	0.13	56.41	Moderate	18.5	0.23	0.52	Small	Very low
Anxiety									
Combination of all studies	1.04	0.60	0.00	None	19.5	0.15	0.40	Very small	Low
Heart rate variability (root mean square of successive differences of normal heartbeats)									
Combination of all studies	1.63	0.20	38.79	Low	45	0.11	0.57	Very small	Low
Heart rate variability (low-frequency/high-frequency ratio)									
Combination of all studies	7.29	0.06	58.83	Moderate	32	0.36	0.11	Small to moderate	Low
Skin conductance									
Combination of all studies	15.93	0.00*	74.90	Moderate	16	0.67	0.05*	Moderate	Very low

*p<0.05.

Skin conductance

Five studies were included in the meta-analysis for the SC outcome measure.[76 79 80 98 100] SC responses were significantly higher with a medium to large effect size in the experimental groups relative to the control groups (Hedges' *g*=0.67, 0.00 to 1.34; SE=0.34, p=0.05). The wide CI (0.00 to 1.34) suggests that while the result is significant, the true effect size could range from no effect to a large effect, indicating some uncertainty. Prediction intervals for SC (ranging from −1.690 to 3.026) indicate that future studies may yield varied outcomes, potentially showing either a large decrease or a large increase in SC. These wide intervals suggest that the evidence for the effect of osteopathic interventions on autonomic outcomes, like SC, remains highly uncertain. Substantial heterogeneity was also observed (I^2=74.90%, *Q*=15.93, p=0.00), indicating that the variability across studies was unlikely to be due to chance alone. Suggesting that the effect estimates may be influenced by differences in study characteristics or design. See figure 2C for the overall forest plot of SC scores. The funnel plot (see online supplemental material 11) did not reveal strong evidence of publication bias for SC studies. However, the small sample size and limited number of included studies make it difficult to conclusively assess the presence of bias using this method.

Table 4 displays a summary of study heterogeneity results, effect sizes as represented by Hedges' *g* and statistical significance as represented by p values for *Z* scores, as well as the certainty of evidence assessment for each outcome.

DISCUSSION

This review provides the first meta-analyses of high-quality RCT osteopathic interventions on mental health and psychophysiological factors. Significant overall effects were found for depression (Hedge's *g*=0.47, –0.86 to –0.09) and SC (Hedge's *g*=0.67, 0.00 to 1.34), suggesting that osteopathic interventions may improve these outcomes. However, the wide CIs highlight uncertainty about the true magnitude of these effects. For depression, the effect size could vary from large to small, while for SC, it could range from no effect to a large effect. Moderate heterogeneity was observed for depression (I^2=57.99%, p=0.05) and substantial heterogeneity for SC (I^2=74.90%, p=0.00), indicating variability between studies that may reflect differences in population characteristics or intervention protocols. Additionally, a subgroup analysis suggested that only pain studies demonstrated significantly lower depression scores for the intervention groups (Hedge's *g*=0.61, −1.06 to −0.17). However, the wide CI suggests that the true effect size could range from a large effect (−1.06) to a small effect (−0.17), indicating considerable uncertainty about the precise magnitude of the effect. Moderate heterogeneity was observed in the pain subgroup (I^2=54.82%, p=0.11), indicating that variability across these studies may be due to random chance or small differences in study characteristics. No significant effects were found in the meta-analyses of anxiety, RMSSD, and LF/HF ratio.

The review does however provide some useful findings about this specific evidence base. A sizeable number of controlled studies were found that have evaluated the use of manual interventions for improving anxiety, depression, stress and psychophysiological indicators of wellbeing. However, out of 41 studies, 18 of these did not clearly state their randomisation procedures, leading to questioning of their status as RCTs and therefore exclusion. To improve the quality and transparency of future trials, it would be beneficial for researchers to refer to the Consolidated Standards of Reporting Trials checklist,[103] which emphasises detailed reporting of randomisation methods to enhance reproducibility and rigour in clinical research.

Despite the meta-analyses finding limited effects, the narrative synthesis of this review can still be considered and placed in the context of existing evidence. For example, Saracutu *et al*[18] found that osteopathic interventions improved psychosocial factors such as anxiety, fear avoidance and quality of life in patients with chronic pain. Our review, by contrast, included a broader range of populations, such as asymptomatic individuals and those with mental health conditions. However, our meta-analysis for anxiety, which included only three studies, did not find significant effects. This contrasts with the findings of a recent systematic review by West and Huzij,[104] which reported significant reductions in anxiety symptoms following MT interventions, including OMT. The discrepancy between our results and those of West and Huzij may be explained by differences in the included studies, with their review incorporating a wider range of MT modalities and reporting significant heterogeneity across studies. These differences highlight the need for further rigorous research to clarify the effects of osteopathic and other manual therapies on anxiety symptoms.

This review included two studies in which participants had been diagnosed with GAD.[21 22] Both of which found that OMT improved symptoms of anxiety, but only Rapaport *et al*[21] found results that favoured the experimental group. It would therefore be useful for more studies to investigate the impact of OMT in populations diagnosed with mental health conditions as the evidence is limited. The current body of research on osteopathy and mental health outcomes has primarily been conducted with individuals living with chronic pain. This means that any improvements in mental health could be confounded by improvements in concomitant physical symptoms of pain. For this reason, we decided to conduct a subgroup analysis, grouping studies by samples with and without chronic pain conditions. However, we were only able to conduct a subgroup analysis for depression outcomes as it requires a minimum of two studies for each outcome of each sample group, which was not available for our analyses of anxiety, RMSSD, LF/HF or SC outcomes. More research targeting populations who do not have pain would provide more direct evidence for the impact of osteopathy on mental health and associated psychophysiological outcomes.

The significant effects observed for depression (Hedge's g=0.47) and SC (Hedge's g=0.67) suggest that osteopathic interventions may improve both psychological and autonomic outcomes, potentially through mechanisms involving pain regulation and autonomic adjustments. While increased SC typically reflects heightened sympathetic activity, it may also signal the body's engagement with pain modulation, which could explain the improvements in depression.[25] This might also explain why interventions tend to show stronger effects in pain groups, where the modulation of pain-related autonomic responses plays a central role. Non-pain groups may not experience the same shifts, resulting in smaller or non-significant changes in outcomes like HRV. On the other hand, the lack of significant effects for HRV measures (RMSSD, LF/HF ratio) and anxiety reflects the mixed findings in prior research on OMT's influence on parasympathetic activity.[29]

Additionally, the physiological effects of osteopathic interventions, particularly those related to autonomic regulation and psychophysiological outcomes, appear to be predominantly short-term. While several studies, such as Sterling *et al* and Edwards *et al*, reported significant changes immediately after the intervention (eg, increased HRV or SC), only a few, like Seifert *et al*, followed participants for up to 24 hours. These studies found that the effects tended to diminish over time, indicating a transient benefit. Therefore, current evidence suggests that osteopathic interventions may yield short-term autonomic changes, and more research is needed to determine the sustainability of these effects over longer periods. Overall, the combined results for depression and SC suggest that OMT may primarily target pain-related autonomic responses, which could indirectly impact mental health outcomes. Future research should explore the long-term effects of OMT on autonomic balance, particularly in populations without chronic pain, where there are fewer confounding factors.

In this review, seven studies examined the impact of osteopathy on healthy participants,[74 76 77 79 80 97 98] all measuring physiological outcomes such as HRV and SC. Our findings align with Rechberger *et al*,[25] who found mixed evidence for the effect of osteopathic interventions on the ANS, citing that the methodological quality of these studies is limited.

We also sought to include recent measures such as interoception, but only two studies assessed it.[34 99] One used a crossover design,[34] excluding it from our meta-analyses due to potential bias. Literature suggests interoception may predict mental well-being.[38 105] The role of interoception in manual therapies has been explored conceptually[32] and experimentally outside OMT. For example, Cazzato *et al*[106] found that CT-optimal touch was more pleasant and linked to emotional awareness. Lower emotional awareness and higher dysmorphic concerns correlated with a lower preference for CT-optimal touch, indicating impaired affective interoception processing. CT-targeted touch may help treat body image disturbances. Osteopathic interventions could similarly restore impaired interoceptive processing. Future research should explore whether interoception directly affects or mediates the effectiveness of osteopathic interventions on psychological outcomes, aiding in developing a clear model through interoceptive and predictive coding frameworks[39 107–110] to rationalise using osteopathic techniques for mental health.

This systematic review and meta-analysis has several limitations. First, restricting the search to English-language studies may have introduced language bias, potentially excluding relevant studies published in other languages, and excluding grey literature may limit the comprehensiveness of our findings. Additionally, the use of the 2017 version of the JBI risk of bias tool, rather than the updated 2023 version,[111] may have influenced bias assessments, although it allowed for consistency across studies available during the review period.

Significant variability among studies in participants, interventions and outcomes led to moderate to substantial heterogeneity in key outcomes like depression and SC. This heterogeneity, along with wide CIs, limits the precision of pooled estimates and highlights uncertainty about true effect sizes, necessitating cautious interpretation of results. Wide prediction intervals suggest that future studies could show results ranging from beneficial to potentially harmful effects, reinforcing this uncertainty. Certainty of evidence, assessed using the GRADE approach,[64] was low for depression, anxiety and HRV LF/HF ratio outcomes, and very low for HRV RMSSD and SC, reflecting issues with imprecision and inconsistency across studies. The absence of adverse event reporting and lack of follow-up data limit insights into the safety and long-term effects of osteopathic interventions. Additionally, none of the included studies used active comparators, limiting the assessment of osteopathic interventions' relative efficacy and generalisability. Most studies assessed only short-term outcomes, leaving gaps regarding long-term effects on mental health. The small number of studies in some analyses and similar sample sizes limited the detection of publication bias, thus, undetected bias cannot be ruled out, further emphasising cautious interpretation of the results.

Overall, it seems that it would be useful for more studies to examine both psychological *and* physiological outcomes following osteopathic interventions as suggested in recent work.[112] No such studies were included in this review. This would help determine whether any changes in psychological outcomes are associated with physiological changes that arise from therapeutic touch such as the possible mediating role of psychophysiology on mental health outcomes. Establishing processes through mediation is an important part of understanding how interventions function[113] and is much needed in osteopathic research, particularly as it seeks to develop a model and rationale for the investigation into its effects for mental health.

In conclusion, the results of this systematic review and meta-analysis indicate that osteopathic interventions may be useful in improving mental health outcomes such as depression, and increasing markers of autonomic activity such as SC. However, the moderate to substantial heterogeneity observed for these outcomes suggests that further research is needed to clarify the consistency of these effects across different populations and settings. This could mean that osteopathy could possibly in the future support mental health services as part of complimentary or even primary care. However, while this review included high-quality RCTs, there remains a need for additional studies that are larger in scale and longitudinal in design to further explore psychometric approaches to mental health reporting and related psychophysiological outcomes.

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