

BMJ Open Effect of osteopathic manipulative treatment on comorbid depressive symptoms in patients with chronic low back pain: study protocol for a randomised controlled trial

Lucas Bohlen ^{1,2}, Michael Eggart,³ Bruno Müller-Oerlinghausen,^{4,5} Jürgen Lorenz ⁶, Robert Schleip,^{7,8} Torsten Liem,^{1,9} Francesco Cerritelli ^{10,11}, Jorge E Esteves,^{10,12} Meike Shedden-Mora ^{13,14}, Tobias Schmidt^{1,15}

To cite: Bohlen L, Eggart M, Müller-Oerlinghausen B, *et al.* Effect of osteopathic manipulative treatment on comorbid depressive symptoms in patients with chronic low back pain: study protocol for a randomised controlled trial. *BMJ Open* 2025;**15**:e094747. doi:10.1136/bmjopen-2024-094747

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2024-094747>).

Received 08 October 2024
Accepted 30 June 2025



© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to

Lucas Bohlen;
lbohlen@osteopathie-schule.de

ABSTRACT

Introduction Chronic low back pain (CLBP) and depressive symptoms (DS) are highly prevalent, burdensome, costly and comorbid health conditions. Osteopathic manipulative treatment (OMT) was shown to improve pain and disability in patients with CLBP; however, the effect on comorbid DS remains less certain. Interestingly, CLBP and DS seem to be associated with changes in interoception, which may be reversed by OMT.

Methods and analysis The study protocol proposes a single-blinded, parallel-group, randomised controlled trial to investigate the effect of OMT on clinical symptoms (depression, pain and disability) and interoceptive functions (interoceptive accuracy, sensibility and awareness) in patients with CLBP and comorbid DS. A sample of 60 adult subjects with CLBP and comorbid DS shall be recruited from osteopathic, orthopaedic and physiotherapeutic practices and educational institutes for osteopathy, sports science, psychology and medicine in Hamburg, Germany. Participants will be randomly allocated (1:1 ratio) to receive six 45 min treatment sessions of either OMT (standard-OMT group) or sham treatment imitating OMT (sham-OMT group). Primarily, symptoms of depression, pain and disability will be assessed with the Beck's Depression Inventory, Second Edition (BDI-II), Numeric Rating Scale (NRS) and Oswestry Disability Index (ODI). Secondarily, interoceptive accuracy, sensibility and awareness will be evaluated using the Heartbeat Tracking Task (HTT), Multidimensional Assessment of Interoceptive Awareness (MAIA-2) and confidence-accuracy correspondence (CAC). Ancillary, the therapeutic alliance will be investigated with the Helping Alliance Questionnaire. Data will be collected at baseline (t_0), the first, third and sixth treatment sessions (t_1 , t_3 , t_6) and at 3 months follow-up (t_7). The findings will be analysed for between-group differences using descriptive (mean and SD) and inductive statistics (mixed analysis of variance). It is hypothesised that standard-OMT, compared with sham-OMT, will reduce depression, pain and disability (BDI-II, NRS, ODI) and increase interoceptive accuracy, sensibility and awareness (HTT, MAIA-2, CAC) in patients with CLBP and comorbid DS.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ First trial investigating the effect of osteopathic treatment on the symptoms and interoception of patients with chronic low back pain and comorbid depressive symptoms.
- ⇒ A randomised controlled trial will be implemented, and the sample size has been calculated, which represents the gold standard.
- ⇒ Osteopathic and sham treatments are based on previous literature and reported according to established guidelines.
- ⇒ The study will be single-blinded as manual therapists cannot be adequately blinded.
- ⇒ Eligibility and harms must be precisely defined and closely monitored to ensure patient safety.

Ethics and dissemination The study was approved by the ethics committee of the Medical School Hamburg (MSH-2023/288). The anonymised dataset will be published in an online repository, and the results will be published in peer-reviewed scientific journals.

Trial registration number DRKS00031694.

INTRODUCTION

Background

Low back pain and major depressive disorder

Low back pain (LBP) and major depressive disorder (MDD) are highly prevalent, burdensome and costly conditions that contribute substantially to the global disease burden.^{1–4} Across the world, LBP was estimated to account for 568.4million prevalent cases and 63.7million years lived with disability,¹ whereas MDD seems to account for 246million prevalent cases and 49.4million disability-adjusted life-years.² LBP and MDD are among the most expensive health conditions, accounting for healthcare spending of US\$134.5 and US\$67.5billion, respectively,

in the USA alone.⁴ While these conditions are major health problems on their own, they frequently co-occur. LBP and MDD seem to show a bidirectional comorbidity, as evidenced by the longitudinal prospective association reported between these conditions (LBP was prospectively associated with MDD and vice versa).⁵ For example, patients with LBP have a higher risk and prevalence of depressive symptoms (DS),^{6,7} which were associated with higher pain and disability levels as well as lower recovery rates.⁸ In terms of treatments, patients with LBP or MDD will likely receive physical or mental health interventions, respectively. Among others, LBP can be treated with physical and manual therapies (eg, exercise), whereas MDD can be treated with psychological and pharmacological therapies (eg, psychotherapy).^{9,10} Still, the available treatment approaches are (mostly) moderately effective. In patients with LBP, the effect sizes for improvements of pain are large for exercise therapy (standardised mean difference (SMD): 1.40) and moderate for manual therapy (SMD: 0.72), whereas the effect sizes for improvements of disability are moderate for both exercise therapy (SMD: 0.71) and manual therapy (SMD: 0.52).¹¹ In patients with MDD, the effect sizes for the improvement of DS are small for antidepressants (SMD: 0.17–0.48),¹² and small to large for psychotherapies (SMD: 0.32–0.81).¹³ Despite available and effective treatments for LBP and MDD, many patients do not respond to therapy^{14,15} and the burden of these conditions has only increased during the past decades.^{16,17} However, interestingly, it was shown that exercise interventions commonly applied to patients with LBP may also improve MDD,¹⁸ whereas psychological interventions commonly applied to patients with MDD may also improve LBP.¹⁹ Hence, to reduce the high prevalence, burden and comorbidity of LBP and MDD, it was proposed to initiate multidisciplinary collaborations between physical and mental healthcare specialists.²⁰ Recently, osteopathy was proposed as a potential therapeutic approach to complement these multidisciplinary collaborations.²¹

Osteopathy

Osteopathy is a person-centred healthcare approach that combines manual treatment and informed advice.²² Patients primarily consult osteopaths for musculoskeletal pain conditions like LBP,²³ which are manually treated with osteopathic manipulative treatment (OMT).²⁴ OMT was shown to be safe and effective for patients with musculoskeletal disorders.^{25,26} Specifically, osteopathic care seems to improve spinal pain conditions.²⁷ For example, OMT was shown to reduce pain and disability in patients with chronic LBP (CLBP).^{28–30} However, although most original studies report reduced pain and improved function in patients with CLBP after OMT,^{31–37} a recent high-quality clinical trial reported smaller changes and scrutinised the clinical meaningfulness of these effects.³⁸ Furthermore, the literature is limited by small sample sizes, no long-term follow-ups and heterogeneity between studies (regarding the interventions, controls and measures).²⁸

In contrast, the effect of OMT on DS remains less certain. While an earlier systematic review found mixed evidence for the effect of OMT on DS in patients with chronic pain,³⁹ a recent meta-analysis reported improved DS after OMT, particularly in pain populations.⁴⁰ However, these reviews were mostly based on clinical trials that applied diverse manual therapy approaches, which were not clearly defined as OMT.^{39,40} Regarding OMT, some original studies reported no effect of OMT on DS,^{41–47} while others showed significant improvements,^{48–50} which may differ between single osteopathic techniques.⁵¹ Particularly in patients with CLBP, OMT was shown to reduce DS.^{35,52,53} Nonetheless, patients with CLBP and comorbid DS seem to respond less to OMT (in terms of pain reduction and functional improvement) than patients with CLBP showing no comorbid DS.⁵⁴ In sum, the literature remains limited, partially inconsistent and heterogeneous.^{39,40} Thus, future research is required,⁴⁰ particularly on the effect of OMT on comorbid DS in patients with CLBP.²² Conceptually, this research avenue appears reasonable because both CLBP and DS seem to be associated with changes in interoception,^{55,56} whereas the effects of OMT (on DS) might be mediated by (the effects on) interoception.^{21,40}

Interoception

In recent years, the role of interoception in health conditions has been increasingly recognised⁵⁷ as abnormalities in interoception seem to underlie both mental health and chronic pain conditions.^{55,58} Specifically, the current literature shows that patients with chronic pain conditions (like LBP) and mental health conditions (like MDD) show reduced interoceptive accuracy compared with healthy controls.^{55,56} Consequently, it has been suggested that treatment approaches targeting interoception may benefit physical and mental health conditions.^{59,60} Among others, an approach that seems to affect interoceptive pathways is affective touch, which activates C-tactile (CT) fibres.⁶¹ Interestingly, the stimulation of CT fibres may improve chronic pain (preliminary evidence) and DS (theoretical perspective) via interoceptive mechanisms.^{62,63} For example, massage therapies have demonstrated an antidepressant effect,^{64,65} specifically, in patients with chronic back pain who receive massage using gentle touch to activate CT-fibres.^{66,67} Hence, it was speculated that therapeutic approaches that use touch, such as OMT, may benefit physical and mental health conditions showing interoceptive dysfunctions by activating CT fibres and modulating interoceptive pathways.^{21,68–70} Indeed, OMT produces hyper-parasympathetic and anti-inflammatory effects, which seem to be mediated by interoception.^{68,71,72} More specifically, osteopathic treatment might modulate interoceptive pathways by activating CT fibres through touch.^{73–76} Beyond theoretical perspectives, it has been shown that osteopathic treatments influence interoceptive brain areas in healthy subjects and patients with CLBP.^{71,72,77} However, the effect of OMT on interoceptive outcomes remains mixed. While some studies

showed either no effect,⁷⁸ a non-significant increase⁷⁹ or a significant increase⁸⁰ in interoceptive accuracy of healthy subjects after diverse osteopathic techniques, another study reported increased interoceptive accuracy after OMT in patients with CLBP.⁷² In turn, interoceptive sensibility in patients with pain was not changed by a single session of OMT.⁸¹ Hence, further research on the effects of OMT on interoceptive accuracy and sensibility is needed, and pilot trials have already been run.⁵¹

Rationale

Taken together, OMT was shown to be effective for patients with CLBP. However, the evidence is less certain regarding the effect of OMT on DS. Both LBP and DS seem to be associated with altered interoception. In turn, OMT seems to modulate interoceptive pathways. Thus, we hypothesise that OMT may improve CLBP and comorbid DS by restoring interoceptive dysfunctions. The theoretical basis for these assumptions was derived from the fields of predictive coding and active inference. Specifically, it has been proposed that chronic pain^{82–84} and depression^{85–87} are characterised by (high precision) prior interoceptive predictions (beliefs), which are not updated when confronted with (low precision) actual interoceptive information (likelihood) that disconfirms

the expectations; instead, the beliefs are confirmed through active inference (producing the expected sensations through autonomic activity).²¹ In turn, we speculated that OMT may produce interoceptive information that mismatches interoceptive expectations (ie, prediction errors), which will be minimised by perceptual inference (updating prior beliefs based on actual information), thereby reducing the symptoms.^{21 88} In sum, we speculate that CLBP and DS are associated with active inference processes that produce the expected symptoms (due to strong prior beliefs predicting pain and depression), whereas OMT may initiate perceptual inference processes that update these prior beliefs (by providing strong sensory information that contradicts prior beliefs), thus alleviating the symptoms (figure 1).²¹

Objectives

Against this background, we aim to investigate the effect of OMT (standard-OMT group), compared with sham treatment imitating OMT (sham-OMT group), on the clinical symptoms (depression, pain and disability) and interoceptive functions (interoceptive accuracy, sensibility and awareness) of patients with CLBP and comorbid DS. It is hypothesised that standard-OMT will significantly improve (1) DS (decrease Beck's Depression Inventory,

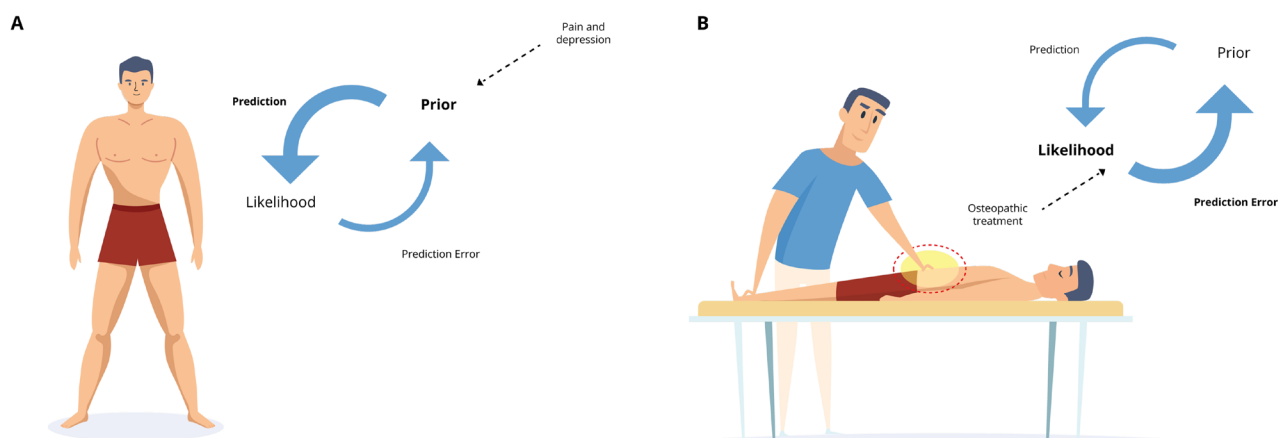


Figure 1 An embodied, predictive and interoceptive framework to osteopathy and mental health (based on Bohlen *et al*²¹). (A) A patient with chronic pain and comorbid depressive symptoms through the lens of active inference. Due to past experiences with pain and depression, the patient's generative model has produced a belief (prior) that predicts physical and mental states associated with pain and depression as the likely causes of uncertain, and even harmless, interoceptive information (likelihood). The resulting mismatch (prediction error) between expected and actual (eg, harmful and harmless) interoceptive information will likely be minimised using active inference. Thus, the expected interoceptive information is produced through action (eg, of the autonomic nervous system) to make the prediction of interoceptive information associated with pain and depression come true. Hence, the generative model affords high precision (confidence) to the belief (prior and prediction), and low precision to the sensory information (likelihood and prediction error), thereby shifting perception towards expectation (putatively maintaining symptoms through active inference). (B) An osteopathic treatment for a patient with chronic pain and comorbid depressive symptoms through the lens of perceptual inference. The osteopathic treatment provides surprising and harmless interoceptive information (likelihood), which is not linked to physical and mental states associated with pain and depression, thereby contradicting the belief (prior). The resulting mismatch (prediction error) between expected and actual (eg, harmful and harmless) interoceptive information will likely be minimised using perceptual inference. Thus, the belief (prior) is updated based on the actual interoceptive information (likelihood) provided during osteopathic treatment, thus revising future predictions to not expect interoceptive information associated with pain and depression. Hence, the generative model affords high precision (confidence) to the sensory information (likelihood and prediction error), and low precision to the belief (prior and prediction), thereby shifting perception away from expectation (putatively alleviating symptoms through perceptual inference).

Second Edition, (BDI-II) score), (2) pain (decrease Numeric Rating Scale (NRS) score) and (3) disability (decrease Oswestry Disability Index (ODI) score) as well as (4) interoceptive accuracy (increase Heartbeat Tracking Task (HTT) score), (5) interoceptive sensibility (increase Multidimensional Assessment of Interoceptive Awareness (MAIA-2) score) and (6) interoceptive awareness (increase confidence-accuracy correspondence (CAC) score) compared with sham-OMT.

Trial design

This study protocol proposes a randomised controlled trial (RCT) with a parallel-group design (1:1 allocation ratio), which represents the gold standard for trials investigating the effect of healthcare interventions.⁸⁹ The research proposal is reported according to the Standard Protocol Items: Recommendations for Interventional Trials statement, and the checklist can be found in the online supplemental material 4.1.⁹⁰

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The study will be conducted in the university outpatient clinic for sports and exercise medicine of the Medical School Hamburg (MSH) in Hamburg, Germany. The study started on 15 July 2024 and is aimed to end on 31 December 2025.

Eligibility criteria

The study will recruit female and male adults with CLBP and comorbid DS. To be eligible, subjects must report pain in the lumbar region (International Classification of Diseases, 10th revision (ICD-10), F.54.5) for ≥ 3 months (chronic) without a recognised underlying pathology (non-specific) and with comorbid DS.⁹¹ More specifically, participants must demonstrate clinically relevant baseline levels of depression (BDI-II: ≥ 7), pain (NRS: ≥ 3) and disability (ODI: ≥ 15).^{92 93} The minimal BDI-II score was chosen because patients with CLBP show mean BDI-II scores of 7.8 ± 6.06 ⁹⁴ and the cut-off value for clinically relevant DS in medical conditions ranges between 7 and 20.^{93 95} The minimal NRS and ODI scores were chosen because they reflect threshold values that are commonly used as inclusion criteria in LBP trials.⁹² To ensure that subjects do not fulfil the diagnosis of a moderate or severe major depression or bipolar affective disorder (based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)), a structured diagnostic interview (Diagnostic Interview for Mental Disorders (DIPS)) will be conducted at baseline (online supplemental materials 2.19 and 2.20).⁹⁶ The DIPS was shown to be reliable⁹⁷ and valid.⁹⁸ The interviews will be conducted by trained personnel closely supervised by a licensed psychological psychotherapist and professor for clinical psychology and psychotherapy (MS-M). Based on the DIPS, participants will be included if they are diagnosed with subclinical DS, mild depressive episode (ICD-10, F.32.0), or

recurrent depressive disorder with a current mild depressive episode (ICD-10, F.33.0), and excluded if they are diagnosed with moderate or severe depressive episode (ICD-10, F.32.1–3) or bipolar affective disorder (ICD-10, F.31). Participants who will be diagnosed with moderate, severe or bipolar depression at baseline cannot participate in the trial. They will receive feedback on their diagnosis, followed by brief guideline-based information on treatment options.⁹⁹ If they wish, they will be referred to the university outpatient clinic for psychotherapy at the MSH for further diagnosis and treatment. Notably, if the DS deteriorates during the study (defined as BDI-II score > 20), a new DIPS will be conducted, and the subject will be excluded from participation if a moderate, severe or bipolar depressive disorder is diagnosed (termination criteria). Furthermore, children/adolescents (< 18 years) and older adults (> 60 years) will be excluded¹⁰⁰ due to differences in the symptomatology of CLBP and DS between age groups.^{101 102} Subjects will be prohibited from participation if they report: (1) pregnancy, (2) malignancy, (3) obesity (body mass index (BMI): > 30), (4) trauma, surgeries or diseases of the spine (eg, fractures, spinal fusion or spondylolisthesis), (5) mental disorders (other than depression), (6) substance abuse/dependence, (7) active suicidal ideation, (8) short duration of DS (< 2 weeks), (9) systemic conditions (eg, inflammatory, immunological or rheumatological diseases) or (10) an inability to provide informed consent (eg, due to insufficient language skills).^{92 103} Regarding substance abuse/dependence, subjects with diagnosed substance use disorders (current or in past 12 months), including alcohol use disorder, are not eligible to participate in this study. Still, caffeine and tobacco consumption are permitted, whereas alcohol consumption of more than two drinks a day for men and one drink a day for women is not permitted (based on recommendations from¹⁰⁴).

Interventions

Participants will be randomly allocated into an intervention group and a control group. Both groups will receive six treatment sessions applied once weekly for 45 min in the same facility. The interventions in both groups will be delivered individually and face-to-face (without equipment). In the intervention group, OMT will be provided, which refers to the individualised application of manual osteopathic techniques to alleviate somatic dysfunctions (standard-OMT group). In the control group, sham treatment will be provided, which refers to the standardised application of light touch to imitate OMT (sham-OMT group). The interventions are reported according to the Template for Intervention Description and Replication (TIDieR) and Recommendations for the Development, Implementation and Reporting of Control Interventions in Efficacy and Mechanistic Trials of Physical, Psychological and Self-Management Therapies (CoPPS) statements, and a checklist combining both statements can be found in the online supplemental material 4.2.^{105 106} Both groups will undergo an anamnesis, inspection and

manual diagnosis. However, the diagnostic findings will only be treated individualised with OMT in the standard-OMT group, whereas the sham-OMT group will receive standardised light touch independent of the diagnostic findings. Further information about the anamnesis, inspection and diagnosis is provided in the online supplemental material 1.2. Eight osteopaths (all treat both groups) with similar characteristics (ie, age, training and experience) will apply the osteopathic and sham treatments. Each subject will receive treatment from the same practitioner over the course of the study (to enable a solid patient-therapist relationship). The therapists will be instructed to establish a similar therapeutic relationship with participants from both groups,⁷¹ by adhering to factors that are essential for an advantageous therapeutic alliance (eg, empathy, positive esteem and consensus on goals).¹⁰⁷ Personal interactions (eg, small talk) and patient management approaches (eg, advice) will be allowed in both groups (and should not differ). More specifically, patient management approaches commonly used in osteopathy will be individually tailored to the participants (and their conditions) of both groups, including advice on nutrition, exercise and lifestyle. Importantly, the anamnesis, inspection, diagnosis, treatment plan, interventions (standard-OMT and sham-OMT), and patient management approaches will be documented using a form that can be found in the online supplemental material 2.1. Furthermore, non-adherence of participants with the interventions and modifications to the interventions will be documented by the therapists. In contrast, the adherence and fidelity of providers with the interventions will not be recorded. A consensus training will be conducted before the study. The control group (treated with sham-OMT) will be offered a single session of OMT after the trial (undocumented and free of charge) to improve recruitment and retention rates. Further information about the interventions (ie, similarities and differences) is provided in online supplemental material 1.3.

Standard-OMT

The intervention group will receive an individualised osteopathic treatment, which refers to the application of 'OMT' to alleviate somatic dysfunctions (standard-OMT group). In general, OMT can be defined as a manual treatment approach that applies touch and manual forces.^{21 108} It comprises various manual techniques like manipulation, mobilisation, massage and stretching.¹⁰⁹ Furthermore, verbal communication may be used in conjunction with touch to reinterpret sensory information (and update prior beliefs).¹¹⁰ Beyond manual approaches, osteopathic care involves patient management approaches, including advice on nutrition, exercise and lifestyle.²² Further information about osteopathy is provided in online supplemental material 1.1. In this study, standard-OMT will be individualised for each participant. This person-centred approach was chosen, although it cannot be adequately controlled, because it reflects the real-world application of OMT¹¹¹ and adheres

to clinical recommendations for chronic pain and depression.^{112 113} More specifically, the osteopath will choose freely which manual treatment and patient management approaches to apply for each subject. Standard-OMT may comprise all types of osteopathic techniques defined by the Glossary of Osteopathic Terminology, including manipulation, mobilisation, myofascial release, muscle energy, soft tissue, counterstrain, lymphatic pump, balanced ligamentous tension, stretching, massage, cranial and visceral techniques.¹⁰⁸ These manual techniques aim to alleviate somatic dysfunctions (ICD-10, M99.0),¹¹⁴ which are characterised by palpable signs of tissue texture abnormalities, asymmetry, restricted range of motion and tenderness (TART).¹¹⁵ Thus, OMT will be applied to peripheral tissues manually diagnosed with somatic dysfunction (based on TART), which could be linked to the patient's condition (eg, in LBP) based on clinical reasoning.²⁴ Although the manual treatment of somatic dysfunctions will vary individually, the specific osteopathic techniques used should largely be outlined in established textbooks.^{116–119}

Sham-OMT

The control group will receive a standardised sham treatment, which refers to the application of 'light touch' to imitate OMT (sham-OMT group). In general, sham conditions in manual therapy trials are difficult to implement due to challenges like the impossibility of double-blinding.¹²⁰ It is particularly challenging to identify the active ingredient of complex interventions like osteopathy and to provide comparable treatment to both groups (except for the component under investigation).^{105 121} Indeed, active and sham interventions show limited similarity in manual therapy trials.¹²² Still, recent proposals and guidelines provide novel and valuable resources.^{105 121} In this study, sham-OMT comprises the standardised application of light manual touch to predefined (not based on palpatory findings) bodily areas (including the feet, legs, knees, thighs, pelvis, abdomen, chest, shoulder, arm, elbows, forearms, hands, lumbar and thoracic spine, neck and head)³⁸ without using specific techniques, procedures or treatment intention.⁷¹ The sham treatment procedure was developed by Nguyen *et al.*³⁸ Therein, light touch will be applied for five seconds per body region (to prevent tissue response to the mechanical stimulus) using spread-out hands (to reduce focalisation of force).³⁸ The sham treatment aims to mimic the characteristics of OMT in terms of the area and time of contact, the positioning of the patient as well as the type of touch, pressure and movement as far as possible. Except for the application of OMT, the sham-OMT group should receive identical care (in terms of anamnesis, inspection, diagnosis, verbal communication and patient management approaches) compared with the standard-OMT group. The standardised sham-OMT procedure, as developed and reported by Nguyen *et al.*,³⁸ is outlined in online supplemental material 1.4.

Concomitant care

Participants are permitted to receive concomitant care for CLBP and/or DS, which may include pharmacological, non-pharmacological and psychotherapeutic interventions (eg, pain killers, antidepressants, physical therapy and cognitive-behavioural therapy). The type and duration of the therapeutic interventions each participant receives will be reported at enrolment (together with the demographic data) using a form that can be found in online supplemental material 2.2. Moreover, the dosage of these interventions must remain constant throughout the trial and will be monitored before each trial session. Subjects showing variation in the dosage of concomitant care during the trial will be excluded from participation.

Outcomes

Symptoms (primary outcomes)

The primary outcomes (DS, pain and disability) are listed in order of their relevance, as previous studies have called for further research on the effect of OMT on DS,^{39 40} while the effect of OMT on pain and disability in patients with CLBP is relatively well researched (but still requires further high-quality studies).²⁸ The English and German versions of the primary outcome measures can be found in online supplemental materials 2.3-2.8.

Depressive symptoms

DS will be measured (at t_0 , t_1 , t_3 , t_6 and t_7) with the BDI-II, which is a 21-item self-report questionnaire (with a 4-point Likert scale) that ranges from 0–13 (minimal depression), 14–19 (mild depression), 20–28 (moderate depression) and 29–63 (severe depression).¹²³ The German version of the BDI-II will be used, which showed high internal consistency, test–retest reliability, convergence validity (with the PHQ-9) and discriminant validity (between patients in remission and non-remission).¹²⁴ The BDI-II was chosen to measure comorbid DS in patients with CLBP because it is widely used, corresponds to diagnostic (DSM) criteria, and assesses cognitive, affective, somatic and vegetative symptoms of depression.¹²⁵ The minimally clinically important difference (MCID) for DS on the BDI-II ranges between 5 and 11 points⁹³ and will be ≥ 5 in this study.¹²⁵

Pain

Pain will be measured (at t_0 , t_1 , t_3 , t_6 and t_7) with the NRS, which is an 11-point self-report scale ranging from 0 (no pain) to 10 (worst pain imaginable).¹²⁶ The NRS showed excellent test–retest reliability and high construct validity (with the Visual Analogue Scale (VAS)) in patients with chronic pain.¹²⁷ The NRS was recommended to evaluate pain intensity in LBP, despite inconsistent findings for test–retest reliability and construct validity in this population, because other measures lack superiority over the NRS.¹²⁸ The MCID for the NRS in LBP was defined to be ≥ 2 ,¹²⁹ which will be used in this study.

Disability

Disability will be measured (at t_0 , t_1 , t_3 , t_6 and t_7) using the ODI, which is a 10-item self-report questionnaire (with a 6-point Likert scale) that ranges between 0 (no disability) and 100 (worst disability).¹³⁰ The German version of the ODI will be used, which showed excellent internal consistency, excellent test–retest reliability and good convergent validity (with the Roland Morris Disability Questionnaire (RMDQ)) in patients with CLBP.¹³¹ However, there is no compelling reason to prefer the ODI over other common measures for LBP-specific disability like the RMDQ, which shows lower reliability but higher validity.¹³² The MCID for LBP on the ODI ranges between 4 and 16 points¹³⁰ and will be ≥ 10 in this study.¹³³

Interoception (secondary outcomes)

The secondary outcomes (interoceptive accuracy, sensibility and awareness) are listed in order of their relevance, as previous studies have primarily investigated interoceptive accuracy (higher objectivity and comparability),^{72 78–80} and (to a lesser extent) interoceptive sensibility (lower objectivity and comparability),⁸¹ while interoceptive awareness has not been investigated in the field of osteopathy. The English and German versions of the secondary outcome measures can be found in online supplemental materials 2.9-2.14.

Interoceptive accuracy

Interoceptive accuracy will be measured (at t_1 , t_3 , t_6 and t_7) using the HTT, which evaluates how accurately subjects can detect their own heartbeat by comparing actual and perceived heartbeats.¹³⁴ Specifically, subjects will be instructed to count their heartbeats (without manual palpation) over a period of 25, 30, 35, 40, 45 and 50 s (in random order, with 30 s of rest between trials) and report them verbally to the investigators.¹³⁵ Simultaneously, heartbeats will be measured objectively using electrocardiography (with CardioSecur).¹³⁶ Based on the subjective and objective assessment of heartbeats, the interoceptive accuracy scores will be calculated as follows: $1 - (nbeats_{real} - nbeats_{reported}) / (nbeats_{real} + nbeats_{reported}) / 2$, and the six trials will be averaged (scores range between 0 and 1, with higher scores indicating higher accuracy).^{135 136} Although questions about the validity of the HTT remain, the measure is commonly used and provides comparable results.^{137 138}

Interoceptive sensibility

Interoceptive sensibility will be measured (at t_1 , t_3 , t_6 and t_7) using the MAIA-2 questionnaire, which is a 37-item self-report questionnaire with 8 subscales that are rated on a 6-point Likert scale.¹³⁹ Scores will be calculated for each of the subscales (higher scores indicate higher interoceptive sensibility): (1) Noticing (eg, “When I am tense, I notice where the tension is located in my body”); (2) Not-distracting (eg, “I ignore physical tension or discomfort until they become more severe”); (3) Not-worrying (eg, “When I feel physical pain, I become

upset"); (4) Attention regulation (eg, "I can pay attention to my breath without being distracted by things happening around me"); (5) Emotional awareness (eg, "I notice how my body changes when I am angry"); (6) Self-regulation (eg, "When I feel overwhelmed, I can find a calm place inside"); (7) Body listening (eg, "I listen for information from my body about my emotional state") and (8) Trusting (eg, "I trust my body sensations").¹⁴⁰ In this study, we will use the German version of the MAIA-2, which was validated in a sample of patients with MDD and showed acceptable internal consistency for the subscales.¹⁴¹ Similarly, there are different MCIDs for each subscale, and we will adhere to these values outlined in Eggart *et al.*¹⁴¹

Interoceptive awareness

Interoceptive awareness will be evaluated (at t_1 , t_3 , t_6 and t_7) by calculating the CAC. Specifically, participants will rate their confidence for the HTT (perceived accuracy of the response) on an 11-point scale (for each of the six trials) ranging from 0 (not confident, total guess) to 10 (very confident, full perception).¹³⁵ Additionally, the interoceptive measures may be used to model interoceptive prediction errors by calculating the discrepancy between the (1) HTT and MAIA-2 (interoceptive (trait) prediction error) and (2) HTT and CAC (interoceptive (state) prediction error).¹⁴²

Clinical and demographic data (additional outcomes)

At baseline (t_0), clinical and demographic data will be collected from participants. This will include information about the subject's age, sex, height, weight, education, employment, smoking and prior experience with OMT as well as the duration of symptoms (CLBP and DS), concomitant care and medication. The clinical and demographic data will be recorded with a form that can be found in the online supplemental material 2.2.

Therapeutic alliance (ancillary outcome)

Ancillary, the therapeutic alliance will be measured (at t_3 and t_6) using the Helping Alliance Questionnaire (HAQ), which is an 11-item self-report questionnaire (with a 6-point Likert scale).¹⁴³ There are two subscales, which are informative of the 'satisfaction with therapeutic outcome' (items: 2, 3, 4, 5, 11), and the 'relation to the therapist' (items: 1, 6, 7, 8, 9, 10).¹⁴⁴ The German version of the HAQ will be used, which showed high internal consistency but low convergent validity (with the Inventory of Interpersonal Problems) in patients with persistent depressive disorder.¹⁴⁴ In this study, the HAQ for patients (not therapists) will be used and no MCID will be defined. This is because we aim to detect putative differences in the therapeutic alliance between groups to determine if contextual factors may be responsible for potential between-group differences. The English and German versions of the HAQ can be found in online supplemental materials 2.15 and 2.16.

Feasibility (pilot outcomes)

In a pilot run with twenty subjects (ten per group), the feasibility of the trial will be investigated by means of the retention of the subjects, safety of the interventions and satisfaction of the subjects with the interventions. The safety of the interventions will be investigated by dividing the number of adverse events that occurred until follow-up through the number of subjects at follow-up (per group) and multiplying the resulting number by 100.¹⁴⁵ This adverse events rate (in percentage) must be $\leq 6\%$ to be considered feasible.³³ The retention of participants in the trial will be assessed by dividing the number of subjects at baseline by the number of subjects at follow-up and multiplying the resulting number by 100.¹⁴⁵ This retention rate (in percentage) must be $\geq 80\%$ to be considered feasible.¹⁴⁶ The patient satisfaction with the interventions will be evaluated (at t_7) by asking participants the following question at follow-up: "How satisfied are you with the treatment?" The participants will be asked to rate their overall satisfaction with the treatment on an 11-point scale ranging from 0 (extremely dissatisfied) to 10 (extremely satisfied).¹⁴⁷ To be feasible, the average satisfaction score must not be < 4 in both groups. The English and German versions of the forms to assess adverse events and patient satisfaction can be found in online supplemental materials 2.17, 2.18 and 2.23, 2.24.

Participant timeline

The schedule for the enrolment, interventions and assessments is depicted in [table 1](#). All measurements are performed before the interventions.

Sample size

A prospective power analysis was carried out to determine the sample size for this RCT.¹⁴⁸ The required sample size was calculated with G*Power.^{149 150} Therefore, a trial investigating the effect of massage on depression in subjects with back pain was used.⁶⁷ The analysis used BDI-II scores. Based on an assumed type I error level of 0.05, a statistical power of 95%, a mean difference of -11.04 (intervention group) and -0.29 (control group), a pooled SD of 10.06, and using a two-tailed test, a total sample size of 48 participants was calculated. Considering an estimated drop-out of 20%, the sample size for a future RCT was determined to be 58 participants. Hence, a sample of 30 subjects per group (N=60) should be recruited.

Recruitment

Participants will be recruited through posters and flyers, which will be posted at various osteopathic, orthopaedic and physiotherapeutic practices as well as educational institutes for osteopathy, sports science, psychology and medicine in Hamburg, Germany. Furthermore, the posters will be shared on social media and websites. It is expected that a sufficient sample of subjects with CLBP and DS will be recruited from these facilities because

Table 1 Participant timeline

		Baseline	First session	Second session	Third session	Fourth session	Fifth session	Sixth session	Follow-up
		t ₀	t ₁	t ₂	t ₃	t ₄	t ₅	t ₆	t ₇
Enrolment	Screening	X							
	Consent	X							
	Randomisation	X							
	Demographics	X							
	DIPS	X							
Interventions	Standard-OMT		X	X	X	X	X	X	
	Sham-OMT		X	X	X	X	X	X	
Outcomes	BDI-II, NRS, ODI	X	X		X			X	X
	HTT, MAIA-2, CAC		X		X			X	X
	HAQ				X			X	
	AEs		X	X	X	X	X	X	X
	BC, PS								X

AEs, adverse events; BC, blinding concealment; BDI-II, Beck's Depression Inventory, Second Edition; CAC, confidence-accuracy correspondence; DIPS, Diagnostic Interview for Mental Disorders; HAQ, Helping Alliance Questionnaire; HTT, Heartbeat Tracking Task; MAIA-2, Multidimensional Assessment of Interoceptive Awareness-2; NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; OMT, osteopathic manipulative treatment; PS, patient satisfaction; Sham-OMT, Control Group receiving Sham Treatment; Standard-OMT, Intervention Group receiving Osteopathic Treatment.

patients frequently consult osteopaths for LBP²³ and use complementary therapies for DS.¹⁵¹

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.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation

Sequence generation

Simple randomisation will be used to allocate subjects into an intervention group (standard-OMT) and a control group (sham-OMT) (1:1 ratio, n=30). The allocation schedule will be based on random computer-generated numbers (<http://www.randomization.com>). Notably, this approach is at risk of generating an unbalanced sample and investigators must closely monitor the distribution across groups.¹⁵²

Allocation concealment mechanism

The group allocation (as determined by randomisation) will be concealed from subjects, outcome assessors and statisticians. Therefore, sealed envelopes will be used to inform the therapists about the group allocation of the participants.

Implementation

The randomisation sequence and allocation concealment will be generated and ensured by a principal investigator (TS), while the outcome assessors and statisticians will be blinded to the process.

Blinding

The trial will be single-blinded. The participants, statisticians and outcome assessors will be blind to the conditions. However, the therapists will not be blinded because of the recognised impossibility of blinding manual therapists in clinical trials (ie, practitioners must always be aware of the manual approaches they apply with their hands).¹²⁰ Participants will be asked at follow-up (t₇) if they think they were part of the intervention or control group (to assess blinding concealment). More specifically, participants will be asked: “*Did you think you received the osteopathic or sham treatment?*”. For both groups, the number of subjects that guessed the condition incorrectly will be divided by the total number of subjects, which will then be multiplied by 100.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection methods

Participants will provide informed consent, demographic (age, sex, height, weight, education, employment, smoking and prior experience with OMT as well as the duration of CLBP and DS, concomitant care and medication), and clinical data (BDI-II, NRS and ODI) at the baseline (t₀) to determine eligibility and evaluate intergroup comparability. The trial will be carried out over 18 weeks, comprising a 6-week trial (with one treatment session per week) and a 3-month follow-up.³⁸ Primary and secondary outcomes will be collected before treatment at the first, third and sixth session (t₁, t₃ and t₆) and at follow-up 3 months after the sixth session (t₇), while the ancillary outcome will be collected before treatment at the third and sixth session (t₃ and t₆) and the pilot outcomes will be

collected before treatment at all sessions (t_1 – t_6) and/or at follow-up (t_7) (table 1).

Data management

All data will be stored electronically at the university and will be secured by password protection. Confidentiality will be ensured as the data will be pseudonymised and a coding list will be stored separately (on paper in a lockable cabinet). Only the principal investigator (LB) will have access to the coding list. After 5 years, the coding list will be destroyed, and all data will be anonymised. Storing the coding list for 5 years enables the researchers to contact the participants in case of abnormal findings or for recruitment in future studies. Data sharing will follow the FAIR Data Principles (Findable, Accessible, Interoperable and Reusable).¹⁵³ The anonymised data will be published permanently in the online repository 'Open Science Framework' (<https://osf.io>).

Statistical methods

Data will be analysed with descriptive and inductive statistics using IBM SPSS Statistics (V.28.0.1.1). Descriptive statistics for all outcomes, groups and time points will be presented by mean and SD. Furthermore, the BMI will be calculated, using the participants' weight (kilogram (kg)) and height (metres (m)), as follows: $BMI = kg/m^2$. Inductive statistics will use the outcomes as dependent, and interventions as independent, variables. The significance level will be set at $p < 0.05$. Baseline data (clinical and demographic characteristics) will be tested for between-group differences (intergroup comparability) using descriptive statistics. Outcome data (symptoms and interoception) will be tested for between-group differences using a mixed analysis of variance. In detail, the primary (BDI-II, NRS and ODI) and secondary outcomes (HTT, MAIA-2 and CAC) will be assessed for between-group differences at t_1 , t_3 , t_6 and t_7 . The ancillary outcome (HAQ) will be evaluated for between-group differences at t_3 and t_6 . No subgroup analyses are planned, and missing data will be omitted (listwise deletion).¹⁵⁴

METHODS: MONITORING

Data monitoring

A data monitoring committee will not be implemented, because they are not needed for early-stage trials assessing symptom relief.¹⁵⁵ The trial will be stopped and terminated if serious adverse events arise in more than three participants, or mild and moderate adverse events arise in more than a quarter of the participants. Notably, active and acute suicidality represents a serious adverse event and termination criteria, leading to the termination of the subject's trial participation. The handling of adverse events is outlined below.

Harms

There are risks to the participants (due to the interventions) that need to be considered. On the one

hand, OMT appears to be safe for people with CLBP as adverse events are mostly mild or moderate (eg, short-lived musculoskeletal complaints like pain in the treatment area, bruising, headache, fatigue and stiffness) and serious side effects are rare (eg, discs herniation, cauda equina syndrome, arterial wall dissection, neurological impairment, stroke or death).^{25 156 157} On the other hand, the harms of OMT for people with DS are largely unclear. Hence, in this study, safety protocols will be implemented to detect and manage adverse events. Subjects will be asked about harms to their physical and mental health before each trial session and at follow-up. The investigators will assess and report any adverse events (including the type, location, severity, onset, functional limitation and actions taken and needed) using a designated form that can be found in online supplemental materials 2.17 and 2.18 (including English and German versions). Additionally, participants will be instructed to report harms that occur outside the trial sessions (and up to 3 months after the trial) by email or telephone (pending their severity). Importantly, subjects will have an emergency telephone number to communicate harms to the investigators and receive immediate care for physical or mental adverse events that may arise. In detail, the emergency number for adverse events will be available for the entire trial, including the follow-up (18 weeks), during standard working hours (Monday to Friday between 9:00 and 17:00 hours). The emergency number will be operated by a listed general practitioner (TS). For physical adverse events, the general practitioner (TS) will assess the participants. If mild or moderate physical adverse events occur, the physician will offer medical or osteopathic treatment. If severe physical adverse events occur, the participant will be referred to further medical or emergency care. For psychological adverse events, the general practitioner (TS) will forward the participant by telephone to a psychological psychotherapist (MS-M) using a different telephone number. If mild or moderate psychological adverse events occur, the psychotherapist will offer psychological treatment. If severe psychological adverse events occur, the participant will be referred to psychiatric or emergency care. If a participant reports suicidal ideation or attempted suicide during the study, the investigators and therapists will follow the Standard Operating Procedure for suicidality of the MSH (online supplemental materials 2.21 and 2.22).

Auditing

Not applicable.

ETHICS AND DISSEMINATION

Research ethics approval

This study protocol was approved by the ethics committee of the MSH (MSH-2023/288). Further, the trial will adhere to the 'Declaration of Helsinki'.¹⁵⁸

Protocol amendments

Important modifications of the study protocol after trial registration, ethical approval and/or publication of the

study protocol will be documented and reported in the publication of the trial results. In general, changes to the study protocol can be tracked via the protocol version identifier.

Consent or assent

Informed consent will be obtained from voluntary participants before the trial by the principal investigators (LB and TS). Participants will be briefed about the scope of the research and the requirements and risks associated with participation (in lay language, until the information is understood).¹⁵⁹ Further, it will be ensured that subjects can revoke their consent for participation at any time without negative consequences.¹⁶⁰ Data will only be used for the purposes outlined in the information sheets. However, the anonymised data will be published in the online repository 'Open Science Framework' (<https://osf.io>) and might therefore be reused or reanalysed in the future. Model sheets for the 'Participant Informed Consent Form' and the 'Participant Information Sheet' can be found in online supplemental materials 3.1–3.4 (including English and German versions).

Confidentiality

Confidentiality will be ensured by pseudonymisation and subsequent anonymisation of the collected data. In other words, identifying information from participants will be stored separately from the research data to secure the privacy of participants.¹⁶¹ Only a principal investigator (LB) will have access to the identifying information of participants. After 5 years, the coding list will be deleted, and all data will be anonymised. Data will only be published in anonymised form.

Access to data

All investigators will have access to the pseudonymised dataset during the trial and the public will have access to the anonymised dataset after trial completion; however, the identifying information can only be accessed by one of the principal investigators (LB). Furthermore, the trial will adhere to the general data protection regulation¹⁶² and participants will retain ownership of the data they provide and can request its deletion or anonymisation¹⁶³ until the completion of the trial, after which the data will be anonymised and published in the online repository 'Open Science Framework' (<https://osf.io>).

Ancillary and post-trial care

After the study, the control group (treated with sham-OMT) will be offered a single session of OMT to improve recruitment and retention rates.

Dissemination policy

The results of the trial will be published in peer-reviewed scientific journals. The data will be made accessible in the online repository 'Open Science Framework' (<https://osf.io>) after trial completion. The contributors to this study protocol will be authors

of the publication. Other investigators may join the study and team of authors if they make significant contributions to the implementation of the study and/or preparation of the manuscript.

Author affiliations

- ¹Research Department, Osteopathie Schule Deutschland, Hamburg, Germany
- ²Institute of Interdisciplinary Exercise Science and Sports Medicine & Institute for Clinical Psychology and Psychotherapy, Medical School Hamburg, Hamburg, Germany
- ³Center for Mental Health, Immanuel Hospital Rüdersdorf, Brandenburg Medical School Theodor Fontane, Rüdersdorf, Germany
- ⁴Charité University Medicine Berlin, Berlin, Germany
- ⁵Faculty of Medicine and Psychology, Brandenburg Medical School Theodor Fontane, Neuruppin, Germany
- ⁶Department of Biomedical Engineering, Faculty of Life Science, University of Applied Sciences, Hamburg, Germany
- ⁷Professorship of Conservative and Rehabilitative Orthopaedics, TUM School of Medicine and Health, Technical University of Munich, Munich, Germany
- ⁸DIPLOMA Hochschule, Bad Sooden-Allendorf, Germany
- ⁹Liem Institut for Psychosomatic Osteopathy, Hamburg, Germany
- ¹⁰Clinical-Based Human Research Department, Foundation COME Collaboration, Pescara, Italy
- ¹¹College of Osteopathic Medicine, New York Institute of Technology, Old Westbury, New York, USA
- ¹²Escola Superior de Saúde Atlântica, Barcarena, Portugal
- ¹³Institute for Clinical Psychology and Psychotherapy & Department of Psychology, Medical School Hamburg, Hamburg, Germany
- ¹⁴Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
- ¹⁵Institute of Interdisciplinary Exercise Science and Sports Medicine, Medical School Hamburg, Hamburg, Germany

Acknowledgements The authors would like to acknowledge that a funding proposal has been submitted to a private foundation funding osteopathy-related research projects.

Contributors LB: conceptualisation, methodology, writing—original draft, investigation, project administration; ME, BM-O, FC and JEE: conceptualisation, methodology, writing—review and editing; JL, RS and TL: writing—review and editing; MS-M and TS: conceptualisation, methodology, resources, investigation, writing—review and editing. All authors provided substantial contributions to the conception or design of the work, drafted the work or revised it critically for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LB is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

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.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Lucas Bohlen <http://orcid.org/0000-0002-8267-7546>

Jürgen Lorenz <http://orcid.org/0000-0002-8561-6714>

Francesco Cerritelli <http://orcid.org/0000-0002-2963-9620>

Meike Shedden-Mora <http://orcid.org/0000-0003-2023-3824>

REFERENCES

- Chen S, Chen M, Wu X, *et al*. Global, regional and national burden of low back pain 1990–2019: A systematic analysis of the Global Burden of Disease study 2019. *J Orthop Translat* 2022;32:49–58.
- Santomauro DF, Mantilla Herrera AM, Shadid J, *et al*. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *The Lancet* 2021;398:1700–12.
- Vos T, Lim SS, Abbafati C, *et al*. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020;396:1204–22.
- Dieleman JL, Cao J, Chapin A, *et al*. US Health Care Spending by Payer and Health Condition, 1996–2016. *JAMA* 2020;323:863.
- Yang H, Hurwitz EL, Li J, *et al*. Bidirectional Comorbid Associations between Back Pain and Major Depression in US Adults. *IJERPH* 2023;20:4217.
- Amiri S, Behnezhad S, Azad E. Back pain and depressive symptoms: A systematic review and meta-analysis. *Int J Psychiatry Med* 2020;1–15.
- He C, Chen H, Guo L, *et al*. Prevalence and factors associated with comorbid depressive symptoms among people with low back pain in China: A cross-sectional study. *Front Psychiatry* 2022;13.
- Wong JJ, Tricco AC, Côté P, *et al*. Association Between Depressive Symptoms or Depression and Health Outcomes for Low Back Pain: a Systematic Review and Meta-analysis. *J Gen Intern Med* 2022;37:1233–46.
- Cuijpers P, Noma H, Karyotaki E, *et al*. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry* 2020;19:92–107.
- George SZ, Fritz JM, Silfies SP, *et al*. Interventions for the Management of Acute and Chronic Low Back Pain: Revision 2021. *J Orthop Sports Phys Ther* 2021;51:CPG1–60.
- Gianola S, Barger S, Del Castillo G, *et al*. Effectiveness of treatments for acute and subacute mechanical non-specific low back pain: a systematic review with network meta-analysis. *Br J Sports Med* 2022;56:41–50.
- Cipriani A, Furukawa TA, Salanti G, *et al*. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet* 2018;391:1357–66.
- Cuijpers P, Quero S, Noma H, *et al*. Psychotherapies for depression: a network meta-analysis covering efficacy, acceptability and long-term outcomes of all main treatment types. *World Psychiatry* 2021;20:283–93.
- Cuijpers P, Stringaris A, Wolpert M. Treatment outcomes for depression: challenges and opportunities. *Lancet Psychiatry* 2020;7:925–7.
- Mauck MC, Aylward AF, Barton CE, *et al*. Evidence-based interventions to treat chronic low back pain: treatment selection for a personalized medicine approach. *Pain Rep* 2022;7:e1019.
- Foster NE, Anema JR, Cherkid D, *et al*. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *The Lancet* 2018;391:2368–83.
- Ormel J, Hollon SD, Kessler RC, *et al*. More treatment but no less depression: The treatment-prevalence paradox. *Clin Psychol Rev* 2022;91:102111.
- Heissel A, Heinen D, Brokmeier LL, *et al*. Exercise as medicine for depressive symptoms? A systematic review and meta-analysis with meta-regression. *Br J Sports Med* 2023;57:1049–57.
- Ho EK-Y, Chen L, Simic M, *et al*. Psychological interventions for chronic, non-specific low back pain: systematic review with network meta-analysis. *BMJ* 2022;376:e067718.
- Tyrovoulas S, Moneta V, Giné Vázquez I, *et al*. Mental Disorders, Musculoskeletal Disorders and Income-Driven Patterns: Evidence from the Global Burden of Disease Study 2017. *J Clin Med* 2020;9:2189.
- Bohlen L, Shaw R, Cerritelli F, *et al*. Osteopathy and Mental Health: An Embodied, Predictive, and Interoceptive Framework. *Front Psychol* 2021;12:767005.
- Bohlen L, Schwarze J, Richter J, *et al*. Effect of osteopathic techniques on human resting muscle tone in healthy subjects using myotonometry: a factorial randomized trial. *Sci Rep* 2022;12:16953.
- Johnson JC, Degenhardt BF. Who Uses Osteopathic Manipulative Treatment? A Prospective, Observational Study Conducted by DO-Touch.NET. *J Am Osteopath Assoc* 2019;119:802–12.
- Snow RJ, Seffinger MA, Hensel KL. American Osteopathic Association Guidelines for Osteopathic Manipulative Treatment (OMT) for Patients With Low Back Pain. *J Am Osteopath Assoc* 2016;116:536–49.
- Bagagiolo D, Rosa D, Borrelli F. Efficacy and safety of osteopathic manipulative treatment: an overview of systematic reviews. *BMJ Open* 2022;12:e053468.
- Zipp CR, Semlitsch T, Tögel G, *et al*. An overview of systematic reviews on the efficacy and safety of osteopathic techniques. *J Bodyw Mov Ther* 2025;42:1186–97.
- Verhaeghe N, Schepers J, van Dun P, *et al*. Osteopathic care for spinal complaints: A systematic literature review. *PLoS ONE* 2018;13:e0206284.
- Dal Farra F, Risio RG, Vismara L, *et al*. Effectiveness of osteopathic interventions in chronic non-specific low back pain: A systematic review and meta-analysis. *Complement Ther Med* 2021;56:102616.
- Franke H, Franke JD, Fryer G. Osteopathic manipulative treatment for nonspecific low back pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord* 2014;15:286.
- Licciardone JC, Brimhall AK, King LN. Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials. *BMC Musculoskelet Disord* 2005;6:43:1–12.
- Vismara L, Cimolin V, Menegoni F, *et al*. Osteopathic manipulative treatment in obese patients with chronic low back pain: a pilot study. *Man Ther* 2012;17:451–5.
- Ajimsa MS, Daniel B, Chithra S. Effectiveness of myofascial release in the management of chronic low back pain in nursing professionals. *J Bodyw Mov Ther* 2014;18:273–81.
- Licciardone JC, Minotti DE, Gatchel RJ, *et al*. Osteopathic manual treatment and ultrasound therapy for chronic low back pain: a randomized controlled trial. *Ann Fam Med* 2013;11:122–9.
- Arguisuelas MD, Lisón JF, Sánchez-Zuriaga D, *et al*. Effects of Myofascial Release in Nonspecific Chronic Low Back Pain. *Spine (Phila Pa 1986)* 2017;42:627–34.
- de Oliveira Meirelles F, de Oliveira Muniz Cunha JC, da Silva EB. Osteopathic manipulation treatment versus therapeutic exercises in patients with chronic nonspecific low back pain: A randomized, controlled and double-blind study. *BMJ* 2019;33:367–77.
- Castro-Sánchez AM, Lara-Palomo IC, Matarán-Peñarocha GA, *et al*. Benefits of Craniosacral Therapy in Patients with Chronic Low Back Pain: A Randomized Controlled Trial. *J Altern Complement Med* 2016;22:650–7.
- Villalta Santos L, Lisboa Córdoba L, Benite Palma Lopes J, *et al*. Active Visceral Manipulation Associated With Conventional Physiotherapy in People With Chronic Low Back Pain and Visceral Dysfunction: A Preliminary, Randomized, Controlled, Double-Blind Clinical Trial. *J Chiropr Med* 2019;18:79–89.
- Nguyen C, Boutron I, Zegarra-Parodi R, *et al*. Effect of Osteopathic Manipulative Treatment vs Sham Treatment on Activity Limitations in Patients With Nonspecific Subacute and Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA Intern Med* 2021;181:620–30.
- Saracutu M, Rance J, Davies H, *et al*. The effects of osteopathic treatment on psychosocial factors in people with persistent pain: A systematic review. *Int J Osteopath Med* 2018;27:23–33.
- Gordon TC, Hope-Bell J, Draper-Rodi J, *et al*. 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. *BMJ Open* 2025;15:e095933.
- Davis SE, Hendryx J, Menezes C, *et al*. Weekly Osteopathic Manipulative Treatment to Improve Measures of Sympathetic Tone in Women With Polycystic Ovary Syndrome: A Randomized, Controlled Pilot Study. *J Am Osteopath Assoc* 2020;120:310–21.
- Espí-López GV, Inglés M, Soliva-Cazabán I, *et al*. Effect of the soft-tissue techniques in the quality of life in patients with Crohn's disease. *Medicine (Baltimore)* 2018;97:e13811.
- Attali T, Bouchoucha M, Benamouzig R. Treatment of refractory irritable bowel syndrome with visceral osteopathy: Short-term and long-term results of a randomized trial. *J of Digest Diseases* 2013;14:654–61.

- 44 Florance B-M, Frin G, Dainese R, *et al.* Osteopathy improves the severity of irritable bowel syndrome: a pilot randomized sham-controlled study. *Eur J Gastroenterol Hepatol* 2012;24:944–9.
- 45 D'Ippolito M, Tramontano M, Buzzi MG. Effects of Osteopathic Manipulative Therapy on Pain and Mood Disorders in Patients With High-Frequency Migraine. *J Am Osteopath Assoc* 2017;117:365–9.
- 46 Wiegand S, Bianchi W, Quinn TA, *et al.* Osteopathic manipulative treatment for self-reported fatigue, stress, and depression in first-year osteopathic medical students. *J Am Osteopath Assoc* 2015;115:84–93.
- 47 Edwards DJ, Toutt C. An evaluation of osteopathic treatment on psychological outcomes with patients suffering from chronic pain: A prospective observational cohort study collected through a health and well-being academy. *Health Psychol Open* 2018;5:2055102918774684.
- 48 Cholewicki J, Popovich Jr JM, Reeves NP, *et al.* The effects of osteopathic manipulative treatment on pain and disability in patients with chronic neck pain: A single-blinded randomized controlled trial. *PM&R* 2022;14:1417–29.
- 49 Cordano C, Armezzani A, Veroni J, *et al.* Osteopathic Manipulative Therapy and Multiple Sclerosis: A Proof-of-Concept Study. *J Am Osteopath Assoc* 2018;118:531–6.
- 50 Miranda E, Giza J, Feketeova E, *et al.* Osteopathic Manipulative Treatment in Patients with Anxiety and Depression: A Pilot Study. *The AAO Journal* 2021;31:9–16.
- 51 Hope-Bell J, Draper-Rodi J, Edwards DJ. Applying an osteopathic intervention to improve mild to moderate mental health symptoms: a mixed-methods feasibility randomised trial. *Chiropr Man Therap* 2024;32.
- 52 Licciardone JC. Preventing progression from chronic to widespread pain and its impact on health-related quality of life: a historical cohort study of osteopathic medical care. *Journal of Osteopathic Medicine* 2021;122:21–9.
- 53 Martí-Salvador M, Hidalgo-Moreno L, Doménech-Fernández J, *et al.* Osteopathic Manipulative Treatment Including Specific Diaphragm Techniques Improves Pain and Disability in Chronic Nonspecific Low Back Pain: A Randomized Trial. *Arch Phys Med Rehabil* 2018;99:1720–9.
- 54 Licciardone JC, Gatchel RJ, Aryal S. Recovery From Chronic Low Back Pain After Osteopathic Manipulative Treatment: A Randomized Controlled Trial. *J Am Osteopath Assoc* 2016;116:144–55.
- 55 Di Lerna D, Serino S, Riva G. Pain in the body. Altered interoception in chronic pain conditions: A systematic review. *Neurosci Biobehav Rev* 2016;71:328–41.
- 56 Eggart M, Lange A, Binser MJ, *et al.* Major Depressive Disorder Is Associated with Impaired Interoceptive Accuracy: A Systematic Review. *Brain Sci* 2019;9:131.
- 57 Bonaz B, Lane RD, Oshinsky ML, *et al.* Diseases, Disorders, and Comorbidities of Interoception. *Trends Neurosci* 2021;44:39–51.
- 58 Khalsa SS, Adolphs R, Cameron OG, *et al.* Interoception and Mental Health: A Roadmap. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018;3:501–13.
- 59 Nord CL, Garfinkel SN. Interoceptive pathways to understand and treat mental health conditions. *Trends Cogn Sci* 2022;26:499–513.
- 60 Weng HY, Feldman JL, Leggio L, *et al.* Interventions and Manipulations of Interoception. *Trends Neurosci* 2021;44:52–62.
- 61 McGlone F, Wessberg J, Olsson H. Discriminative and affective touch: sensing and feeling. *Neuron* 2014;82:737–55.
- 62 Di Lerna D, Lacerenza M, Ainley V, *et al.* Altered Interoceptive Perception and the Effects of Interoceptive Analgesia in Musculoskeletal, Primary, and Neuropathic Chronic Pain Conditions. *J Pers Med* 2020;10:201.
- 63 Eggart M, Queri S, Müller-Oerlinghausen B. Are the antidepressive effects of massage therapy mediated by restoration of impaired interoceptive functioning? A novel hypothetical mechanism. *Med Hypotheses* 2019;128:28–32.
- 64 Field T. Massage therapy research review. *Complement Ther Clin Pract* 2016;24:19–31.
- 65 Moyer CA, Rounds J, Hannum JW. A meta-analysis of massage therapy research. *Psychol Bull* 2004;130:3–18.
- 66 Arnold MM, Müller-Oerlinghausen B, Hemrich N, *et al.* Effects of Psychoactive Massage in Outpatients with Depressive Disorders: A Randomized Controlled Mixed-Methods Study. *Brain Sci* 2020;10:676.
- 67 Baumgart S-E, Baumbach-Kraft A, Lorenz J. Effect of Psycho-Regulatory Massage Therapy on Pain and Depression in Women with Chronic and/or Somatoform Back Pain: A Randomized Controlled Trial. *Brain Sci* 2020;10:721.
- 68 D'Alessandro G, Cerritelli F, Cortelli P. Sensitization and Interoception as Key Neurological Concepts in Osteopathy and Other Manual Medicines. *Front Neurosci* 2016;10:100.
- 69 Casals-Gutiérrez S, Abbey H. Interoception, mindfulness and touch: A meta-review of functional MRI studies. *Int J Osteopath Med* 2020;35:22–33.
- 70 McGlone F, Uvnäs Moberg K, Norholt H, *et al.* Touch medicine: bridging the gap between recent insights from touch research and clinical medicine and its special significance for the treatment of affective disorders. *Front Psychiatry* 2024;15:1390673.
- 71 Cerritelli F, Chiacchiaretta P, Gambi F, *et al.* Osteopathy modulates brain-heart interaction in chronic pain patients: an ASL study. *Sci Rep* 2021;11:4556.
- 72 Cerritelli F, Chiacchiaretta P, Gambi F, *et al.* Effect of manual approaches with osteopathic modality on brain correlates of interoception: an fMRI study. *Sci Rep* 2020;10.
- 73 Manzotti A, Cerritelli F, Monzani E, *et al.* Dynamic touch induces autonomic changes in preterm infants as measured by changes in heart rate variability. *Brain Res* 2023;1799:148169.
- 74 McGlone F, Cerritelli F, Walker S, *et al.* The role of gentle touch in perinatal osteopathic manual therapy. *Neurosci Biobehav Rev* 2017;72:1–9.
- 75 Manzotti A, Cerritelli F, Esteves JE, *et al.* Dynamic touch reduces physiological arousal in preterm infants: A role for c-tactile afferents? *Dev Cogn Neurosci* 2019;39:100703.
- 76 Baroni F, Ruffini N, D'Alessandro G, *et al.* The role of touch in osteopathic practice: A narrative review and integrative hypothesis. *Complement Ther Clin Pract* 2021;42:101277.
- 77 Cerritelli F, Chiacchiaretta P, Gambi F, *et al.* Effect of Continuous Touch on Brain Functional Connectivity Is Modified by the Operator's Tactile Attention. *Front Hum Neurosci* 2017;11:368.
- 78 Griffiths FS, McSweeney T, Edwards DJ. Immediate effects and associations between interoceptive accuracy and range of motion after a HVLA thrust on the thoracolumbar junction: A randomised controlled trial. *J Bodyw Mov Ther* 2019;23:818–24.
- 79 Cathcart E, McSweeney T, Johnston R, *et al.* Immediate biomechanical, systemic, and interoceptive effects of myofascial release on the thoracic spine: A randomised controlled trial. *J Bodyw Mov Ther* 2019;23:74–81.
- 80 Edwards DJ, Young H, Cutis A, *et al.* The Immediate Effect of Therapeutic Touch and Deep Touch Pressure on Range of Motion, Interoceptive Accuracy and Heart Rate Variability: A Randomized Controlled Trial With Moderation Analysis. *Front Integr Neurosci* 2018;12:41.
- 81 Emmet DK, Davis G, Pierce-Talsma S, *et al.* Interoceptive bodily awareness in patients seeking pain relief with osteopathic manipulative treatment: an observational cohort pilot study. *J Osteopath Med* 2024;124:321–32.
- 82 Hechler T, Endres D, Thorwart A. Why Harmless Sensations Might Hurt in Individuals with Chronic Pain: About Heightened Prediction and Perception of Pain in the Mind. *Front Psychol* 2016;7:1638.
- 83 Kube T, Rozenkrantz L, Rief W, *et al.* Understanding persistent physical symptoms: Conceptual integration of psychological expectation models and predictive processing accounts. *Clin Psychol Rev* 2020;76:101829.
- 84 Van den Bergh O, Witthöft M, Petersen S, *et al.* Symptoms and the body: Taking the inferential leap. *Neurosci Biobehav Rev* 2017;74:185–203.
- 85 Kube T, Schwarting R, Rozenkrantz L, *et al.* Distorted Cognitive Processes in Major Depression: A Predictive Processing Perspective. *Biol Psychiatry* 2020;87:388–98.
- 86 Paulus MP, Feinstein JS, Khalsa SS. An Active Inference Approach to Interoceptive Psychopathology. *Annu Rev Clin Psychol* 2019;15:97–122.
- 87 Barrett LF, Quigley KS, Hamilton P. An active inference theory of allostasis and interoception in depression. *Phil Trans R Soc B* 2016;371:20160011.
- 88 Esteves JE, Cerritelli F, Kim J, *et al.* Osteopathic Care as (En)active Inference: A Theoretical Framework for Developing an Integrative Hypothesis in Osteopathy. *Front Psychol* 2022;13:1–19.
- 89 Schulz KF, Altman DG, Moher D, *et al.* CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
- 90 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- 91 Barrey CY, Le Huec J-C, French Society for Spine Surgery. Chronic low back pain: Relevance of a new classification based on the injury pattern. *Orthop Traumatol Surg Res* 2019;105:339–46.
- 92 Amundsen PA, Evans DW, Rajendran D, *et al.* Inclusion and exclusion criteria used in non-specific low back pain trials: a review of randomised controlled trials published between 2006 and 2012. *BMC Musculoskelet Disord* 2018;19:113.

- 93 Smarr KL, Keefer AL. Measures of Depression and Depressive Symptoms. *Arthritis Care Res (Hoboken)* 2020;72 Suppl 10:608–29.
- 94 Nduwimana I, Nindorera F, Sinzakayaye A, et al. Biopsychosocial factors associated with chronic low back pain-related activity limitations in Burundi. *S Afr J Physiother* 2022;78:1783.
- 95 Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Braz J Psychiatry* 2013;35:416–31.
- 96 Margraf J, Cwik JC, Pflug V, et al. Strukturierte klinische Interviews zur Erfassung psychischer Störungen über die Lebensspanne. *Zeitschrift Für Klinische Psychologie Und Psychotherapie* 2017;46:176–86.
- 97 Suppiger A, In-Albon T, Herren C, et al. Reliabilität des Diagnostischen Interviews bei Psychischen Störungen (DIPS für DSM-IV-TR) unter klinischen Routinebedingungen. *Verhaltenstherapie* 2008;18:237–44.
- 98 In-Albon T, Suppiger A, Schlup B, et al. Validität des Diagnostischen Interviews bei psychischen Störungen (DIPS für DSM-IV-TR). *Zeitschrift Für Klinische Psychologie Und Psychotherapie* 2008;37:33–42.
- 99 NVL. Nationale versorgungsleitlinie unipolare depression. 2022.
- 100 NIH. Age.National institutes of health. 2022. Available: <https://www.nih.gov.nih-style-guide/age>
- 101 Wagner S, Wollschläger D, Dreimüller N, et al. Effects of age on depressive symptomatology and response to antidepressant treatment in patients with major depressive disorder aged 18 to 65 years. *Compr Psychiatry* 2020;99:152170.
- 102 Manogharan S, Kongsted A, Ferreira ML, et al. Do older adults with chronic low back pain differ from younger adults in regards to baseline characteristics and prognosis? *Eur J Pain* 2017;21:866–73.
- 103 Zimmerman M, Holst CG, Clark HL, et al. The Psychiatric Inclusion and Exclusion Criteria in Placebo-Controlled Monotherapy Trials of Bipolar Depression: An Analysis of Studies of the Past 20 Years. *CNS Drugs* 2016;30:1209–18.
- 104 U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary guidelines for americans. 2020.
- 105 Hohenschurz-Schmidt D, Vase L, Scott W, et al. Recommendations for the development, implementation, and reporting of control interventions in efficacy and mechanistic trials of physical, psychological, and self-management therapies: the CoPPS Statement. *BMJ* 2023;381:e072108.
- 106 Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687.
- 107 Tschacher W, Haken H, Kyselo M. Alliance: a common factor of psychotherapy modeled by structural theory. *Front Psychol* 2015;6:1–11.
- 108 Hensel K, Will A, Giusti R, et al. *Glossary of osteopathic terminology*. 3rd edn. Chevy Chase: American Association of Colleges of Osteopathic Medicine, 2017.
- 109 NHS. Osteopathy: how it's performed. National Health Service; 2022. Available: <https://www.nhs.uk/conditions/osteopathy/what-happens/>
- 110 Kim J, Esteves JE, Cerritelli F, et al. An Active Inference Account of Touch and Verbal Communication in Therapy. *Front Psychol* 2022;13:1–17.
- 111 Alvarez G, Zegarar-Parodi R, Esteves JE. Person-centered versus body-centered approaches in osteopathic care for chronic pain conditions. *Ther Adv Musculoskelet Dis* 2021;13:1759720X211029417.
- 112 The Lancet. Ensuring care for people with depression. *The Lancet* 2022;399:885.
- 113 The Lancet. Rethinking chronic pain. *The Lancet* 2021;397:2023.
- 114 WHO. *International statistical classification of diseases and related health problems, 10th revision ICD-10*. 5th edn. 2016.
- 115 Consorti G, Castagna C, Tramontano M, et al. Reconceptualizing Somatic Dysfunction in the Light of a Neuroaesthetic Enactive Paradigm. *Healthcare (Basel)* 2023;11:479.
- 116 Liem T, Dobler TK. *Leitfaden Osteopathie: Parietale Techniken*. 4th edn. München: Elsevier, 2017.
- 117 Liem T, Dobler TK, Puylaert M. *Leitfaden Viszerale Osteopathie*. 3rd edn. Elsevier, 2020.
- 118 Liem T. *Kraniosakrale Osteopathie*. 7th edn. Thieme, 2018.
- 119 Liem T. *Praxis der kraniosakralen osteopathie*. 4th edn. Stuttgart, 2020. Available: <https://osteothek.thieme.de/10.1055/b-006-161640>
- 120 D'Alessandro G, Ruffini N, Iacopini A, et al. Five challenges for manual therapies trials with placebo controls: A proposal. *Int J Osteopath Med* 2022;46:55–9.
- 121 D'Alessandro G, Ruffini N, Iacopini A, et al. Overcoming placebo-related challenges in manual therapy trials: The 'whats and hows' and the 'touch equality assumption' proposals. *Int J Osteopath Med* 2021;42:5–10.
- 122 D'Alessandro G, Ruffini N, Aquino A, et al. Differences between experimental and placebo arms in manual therapy trials: a methodological review. *BMC Med Res Methodol* 2022;22:219.
- 123 Beck AT, Steer RA, Brown GK. *Manual for the beck depression inventory-II*. San Antonio, TX: Psychological Corporation, 1996.
- 124 Kühner C, Bürger C, Keller F, et al. Reliabilität und validität des revidierten Beck- Depressionsinventars (BDI-II). Befunde aus deutschsprachigen stichproben. *Nervenarzt* 2007;78:651–6.
- 125 Smarr KL, Keefer AL. Measures of depression and depressive symptoms: beck depression inventory-ii (bdi-ii), center for epidemiologic studies depression scale (CES-D). In: *Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire*. *Arthritis Care Res (Hoboken)*. 63. 2011: 454–66.
- 126 Boonstra AM, Stewart RE, Köke AJA, et al. Cut-Off Points for Mild, Moderate, and Severe Pain on the Numeric Rating Scale for Pain in Patients with Chronic Musculoskeletal Pain: Variability and Influence of Sex and Catastrophizing. *Front Psychol* 2016;7:1466.
- 127 Hawker GA, Mian S, Kendzerska T, et al. Measures of adult pain: visual analog scale for pain (vas pain). In: *Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS)*. 63. 2011: 240–52.
- 128 Chiarotto A, Maxwell LJ, Ostelo RW, et al. Measurement Properties of Visual Analogue Scale, Numeric Rating Scale, and Pain Severity Subscale of the Brief Pain Inventory in Patients With Low Back Pain: A Systematic Review. *J Pain* 2019;20:245–63.
- 129 Suzuki H, Aono S, Inoue S, et al. Clinically significant changes in pain along the Pain Intensity Numerical Rating Scale in patients with chronic low back pain. *PLoS One* 2020;15:e0229228.
- 130 Lauridsen HH, Hartvigsen J, Manniche C, et al. Responsiveness and minimal clinically important difference for pain and disability instruments in low back pain patients. *BMC Musculoskelet Disord* 2006;7:82:1–16.
- 131 Mannion AF, Junge A, Fairbank JCT, et al. Development of a German version of the Oswestry Disability Index. Part 1: cross-cultural adaptation, reliability, and validity. *Eur Spine J* 2006;15:55–65.
- 132 Chiarotto A, Maxwell LJ, Terwee CB, et al. Roland-Morris Disability Questionnaire and Oswestry Disability Index: Which Has Better Measurement Properties for Measuring Physical Functioning in Nonspecific Low Back Pain? Systematic Review and Meta-Analysis. *Phys Ther* 2016;96:1620–37.
- 133 Ostelo RWJG, de Vet HCW. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol* 2005;19:593–607.
- 134 Schandry R. Heart Beat Perception and Emotional Experience. *Psychophysiology* 1981;18:483–8.
- 135 Garfinkel SN, Seth AK, Barrett AB, et al. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biol Psychol* 2015;104:65–74.
- 136 Young HA, Williams C, Pink AE, et al. Getting to the heart of the matter: Does aberrant interoceptive processing contribute towards emotional eating? *PLoS ONE* 2017;12:e0186312.
- 137 Schulz A, Back SN, Schaan VK, et al. On the construct validity of interoceptive accuracy based on heartbeat counting: Cardiovascular determinants of absolute and tilt-induced change scores. *Biol Psychol* 2021;164:108168.
- 138 Desmedt O, Luminet O, Corneille O. The heartbeat counting task largely involves non-interoceptive processes: Evidence from both the original and an adapted counting task. *Biol Psychol* 2018;138:185–8.
- 139 Mehling WE, Acree M, Stewart A, et al. The Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2). *PLoS ONE* 2018;13:e0208034.
- 140 Todd J, Swami V, Aspell JE, et al. Are some interoceptive sensibility components more central than others? Using item pool visualisation to understand the psychometric representation of interoception. *PLoS One* 2022;17:e0277894.
- 141 Eggart M, Todd J, Valdés-Stauber J. Validation of the Multidimensional Assessment of Interoceptive Awareness (MAIA-2) questionnaire in hospitalized patients with major depressive disorder. *PLoS ONE* 2021;16:e0253913.
- 142 Koreki A, Garfinkel SN, Mula M, et al. Trait and state interoceptive abnormalities are associated with dissociation and seizure frequency in patients with functional seizures. *Epilepsia* 2020;61:1156–65.
- 143 Alexander LB, Luborsky L. The penn helping alliance scales. In: Greenberg LS, Pinsof W, eds. *The psychotherapeutic process: a research handbook*. New York: Guilford Press, 1986: 325–66.

- 144 Eich HS, Kriston L, Schramm E, *et al.* The German version of the helping alliance questionnaire: psychometric properties in patients with persistent depressive disorder. *BMC Psychiatry* 2018;18:107.
- 145 Liem T, Bohlen L, Jung A-M, *et al.* Does Osteopathic Heart-Focused Palpation Modify Heart Rate Variability in Stressed Participants with Musculoskeletal Pain? A Randomised Controlled Pilot Study. *Healthcare (Basel)* 2024;12:138.
- 146 Santiago RJ, Esteves JE, Baptista JS, *et al.* Results of a feasibility randomised controlled trial of osteopathy on neck-shoulder pain in computer users. *Complement Ther Clin Pract* 2022;46:101507.
- 147 de Steenwinkel M, Haagsma JA, van Berkel ECM, *et al.* Patient satisfaction, needs, and preferences concerning information dispensation at the emergency department: a cross-sectional observational study. *Int J Emerg Med* 2022;15:1–8.
- 148 Charles P, Giraudeau B, Dechartres A, *et al.* Reporting of sample size calculation in randomised controlled trials: review. *BMJ* 2009;338:b1732.
- 149 Faul F, Erdfelder E, Lang A-G, *et al.* G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.
- 150 HHU. G*Power: statistical power analyses for mac and windows. Heinrich-Heine-Universität; 2015. Available: <http://www.gpower.hhu.de/>
- 151 Haller H, Anheyer D, Cramer H, *et al.* Complementary therapies for clinical depression: an overview of systematic reviews. *BMJ Open* 2019;9:e028527.
- 152 Bepalov A, Wicke K, Castagné V. Blinding and Randomization. *Handb Exp Pharmacol* 2020;257:81–100.
- 153 Wilkinson MD, Dumontier M, Aalbersberg IJJ, *et al.* The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 2016;3:1–9.
- 154 Kang H. The prevention and handling of the missing data. *Korean J Anesthesiol* 2013;64:402.
- 155 U.S. Food and Drug Administration. Establishment and operation of clinical trial data monitoring committees: guidance for clinical trial sponsors. 2006. Available: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees>
- 156 Rubinstein SM, de Zoete A, van Middelkoop M, *et al.* Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2019;364:l689.
- 157 Carnes D, Mars TS, Mullinger B, *et al.* Adverse events and manual therapy: a systematic review. *Man Ther* 2010;15:355–63.
- 158 World Medical Association. World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.
- 159 Xu A, Baysari MT, Stocker SL, *et al.* Researchers' views on, and experiences with, the requirement to obtain informed consent in research involving human participants: a qualitative study. *BMC Med Ethics* 2020;21:93.
- 160 Fernandez Lynch H. The right to withdraw from controlled human infection studies: Justifications and avoidance. *Bioethics* 2020;34:833–48.
- 161 Kohlmayer F, Lautenschläger R, Prasser F. Pseudonymization for research data collection: is the juice worth the squeeze? *BMC Med Inform Decis Mak* 2019;19:178.
- 162 European Commission. General data protection regulation. 2022. Available: https://ec.europa.eu/info/law/law-topic/data-protection/reform/rules-business-and-organisations/dealing-citizens/do-we-always-have-delete-personal-data-if-person-asks_en
- 163 Politou E, Alepis E, Patsakis C. Forgetting personal data and revoking consent under the GDPR: Challenges and proposed solutions. *Journal of Cybersecurity* 2018;4:1–20.