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REVIEW ARTICLE

Placebo analgesia in physical and psychological interventions: Systematic review and meta-analysis of three-armed trials

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Abstract

Background: The magnitude of placebo effects from physical and psychological 'sham' is unknown but could impact efficacy trials and treatment understanding. To quantify placebo effects, this systematic review of three-armed randomised controlled trials (RCTs) of physical and psychological interventions for pain compared outcomes in 'sham' control intervention and non-exposure arms.

Methods: RCTs with treatment, 'sham' control intervention, and non-exposure groups were included, enrolling adults with any pain. A protocol was pre-registered (PROSPERO: CRD42023413324), and twelve databases searched from 2008 to July 2023. Trial methods and blinding were analysed descriptively and risk of bias assessed. Meta-analysis of pain measures at short-, medium- and long-term was performed with random-effects models of standardised mean differences (SMD).Studies were sub-grouped according to control intervention type.

Results: Seventeen RCTs were included. The average short-term placebo effect was small (0.21 SMD, 0.1–0.33 95% CI, $p = 0.0002$, 1440 participants). It showed no heterogeneity ($Tau^2 = 0.1$, $I^2 = 11\%$, $p = 0.3$), preventing meta-regression analyses

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of effect modifiers. However, sub-group analyses revealed larger placebo effects in manual control interventions compared to disabled devices and miscellaneous control interventions. Overall, placebo analgesia accounted for 39% of treatments' short-term effectiveness. No placebo effects were found at medium-term (7 RCTs, 381 participants) or long-term follow-up (3 RCTs, 173 participants).

Conclusions: The observed placebo analgesia has mechanistic and methodological implications, though its clinical importance may be limited. Control intervention design affects placebo effects, highlighting the importance of considering methodology in RCT interpretation. Review limitations include a small number of long-term studies and sample heterogeneity.

Significance: This systematic review directly quantifies placebo effects from physical and psychological 'sham' control interventions and compares them to treatments' overall effectiveness. By doing so, the review enhances our understanding of placebo effects, their relative contribution in clinical trials, and their susceptibly to trial design. It poses further questions regarding the influence of blinding, participant expectations, and features of the therapeutic context. Overall, the insights provided by this review carry methodological significance and are important for the interpretation and synthesis of efficacy trials in this field.

1 | BACKGROUND

Explanatory trials test the efficacy of interventions under ideal conditions (Haynes, 1999). A main objective of such trials is the reduction of bias, thereby increasing confidence in the validity of conclusions about treatment efficacy (Keefe et al., 2022). The use of specifically designed control interventions in efficacy trials ('placebo', 'sham' or 'attention' controls) aims to control for placebo effects (expectancy and learning-related benefits from treatment contexts (Evers et al., 2018)) and facilitate participant blinding (Hohenschurz-Schmidt, Vase, et al., 2023). These control interventions can also be used to investigate treatment mechanisms.

Recommendations for control interventions in efficacy trials of physical, psychological and self-management (PPS) interventions for people with pain rely on several assumptions: For example, we have recently shown that the degree of similarity between control interventions and the tested treatments influences not only pain-related trial outcomes but also blinding effectiveness and participant attrition (Hohenschurz-Schmidt, Draper-Rodi, et al., 2023). This supports earlier calls for 'structural equivalence' between control and test interventions (Baskin et al., 2003) and is reflected in recent guidance (Hohenschurz-Schmidt, Vase, et al., 2023). However, the assumption that there are potentially large placebo effects to be controlled for is only supported indirectly: Mechanistic experiments (Benedetti, 2020) and meta-analytical work from other fields (Meissner et al., 2013) certainly suggest considerable placebo effects in context-rich clinical encounters such as PPS (Bialosky et al., 2017; Rossettini et al., 2020), and when patient-reported outcomes such as pain are assessed (Hróbjartsson & Gøtzsche, 2010)—but high-quality evidence syntheses are lacking. The open question of how large placebo effects in PPS trials are impinges on the relevance of placebo-controlled trials; and whether placebo effects are dependent on blinding impinges on the importance of blinding, about which there is currently much debate (Anand et al., 2020) and conflicting evidence (Moustgaard et al., 2020; Savovic et al., 2018). Finally, better understanding the contribution of placebo effects to clinical effectiveness of non-pharmacological interventions will help specify current models of treatment mechanisms (Bialosky et al., 2009, 2017; Cuijpers et al., 2019).

Placebo *responses* refer to any symptom change after the administration of a placebo. Measured without a control group and thus including other mechanisms such as regression phenomena and natural symptom fluctuations, placebo *responses* must be distinguished from placebo *effects* (Evers et al., 2018). Three-armed trials with 'sham' and non-exposure groups offer the unique opportunity to assess placebo *effects* by using non-exposure groups to account for regression and natural history effects (Hróbjartsson, 2002). Drawing their samples from a single population and treated under the normal circumstances of clinical trials, such pair-wise analysis also avoids the unreliability of indirect comparisons, as in reviews with two-armed RCTs (Hróbjartsson & Gøtzsche, 2010) and network meta-analyses (Jansen

& Naci, 2013). However, three-armed trials are rare (Karjalainen et al., 2022).

Focusing on manual therapy for pain, a recent review (Lavazza et al., 2021) found only four trials with both a 'sham' control intervention and a non-exposure arm, three of which could be meta-analysed. Pooled differences between non-exposure and controls were insignificant. Both this and a previous review (Cerritelli et al., 2016) used highly specific inclusion criteria, reducing the pool of potential studies.

Here, we conducted a systematic review and meta-analysis of three-arm trials of PPS interventions for any pain population to investigate the magnitude of placebo effects (more specifically, placebo analgesia), as defined as the difference in outcomes between 'sham' and no-treatment arm. We also strove to examine a potential temporal development of placebo effects in the eligible studies, the influence of potential modulators of placebo effects and their proportionate contribution to overall clinical effectiveness of interventions.

2 | METHODS

A systematic review of methods and meta-analysis of placebo effects was conducted.

2.1 | Protocol and registration

This review is reported in accordance with the 2020 Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). A detailed protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, Registration ID CRD42023413324) prior to commencing data extraction (Booth et al., 2012), including a detailed a priori plan of review methods and analysis methods.

2.2 | Eligibility criteria

This review included RCTs of PPS interventions for adults living with pain, irrespective of gender, underlying pathology or pain severity and duration. At least one pain-related primary outcome measure had to be reported. The PPS umbrella includes all forms of manual and physical therapy, exercise and rehabilitation therapy, conversation-based and psychological therapies, body–mind, spiritual, religious, other non-material healing practices, web-based therapies, relaxation and educational interventions (the latter two are classified as 'self-management' here) (Hohenschurz-Schmidt, Draper-Rodi, et al., 2023).

Eligible RCTs were of a parallel-group or cross-over design. Only trials were eligible that did not add additional interventions to the sham control intervention, other than usual care (i.e. trials had to follow the design: intervention vs. sham vs. non-exposure; not intervention A plus intervention B vs. intervention A plus sham vs. non-exposure).

To be eligible, trials had to employ a control intervention as typically employed in efficacy trials with the objective to facilitate participant blinding or control for expectancy effects (also known as 'sham', 'attention' or 'placebo control') (Hohenschurz-Schmidt, Vase, et al., 2023), as well as a non-exposure group. Eligible non-exposure groups could be described as usual care, standard care, best-available care, treatment as usual, waiting list or no-treatment groups, and potentially others – the primary criterion for inclusion being that no trial-related intervention was provided.

Excluded were studies where pharmacological or drug interventions formed the mainstay of treatment and studies of surgical or otherwise invasive interventions. Furthermore, all therapies relying on the permanent introduction of some form of matter into the body were excluded. Due to specific considerations and solutions to the sham control problem in device and needle-based therapies (Boutron et al., 2007; Braithwaite et al., 2018, 2020; Vase, Baram, et al., 2015), studies from these categories were also not eligible. Implanted and externally applied devices, all acupuncture modalities and therapies based on assumed reflex points or energy meridians were excluded. Also excluded were non-randomized studies, observational studies, cross-sectional studies, case–control, case-series and case report studies to reduce selection and allocation bias. Pilot or feasibility RCTs were excluded due to larger inherent risk of bias.

The first reporting guideline for non-pharmacological therapy trials was published in February 2008 (Boutron et al., 2008). Therefore, this review systematically assessed studies published from 2008 onwards. Eligibility criteria are presented in tabular form in the Table S1.

2.3 | Data sources

The following databases were searched from 1 January 2008 to 7 July 2023: MEDLINE®, EMBASE, PsychInfo, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), NIH Clinicaltrials.gov, AMED (Allied and Complementary Medicine), CINAHL (nursing and allied health), the Physiotherapy evidence database (pedro.org.au), ostmed.dr (ostmed-dr.oclc.org), osteopathic research web (osteo

pathic-research.com) and the index to chiropractic literature (chiroindex.org).

2.4 | Search strategy

The search strategy was built around the following keywords, developed based on existing literature and with database experts, and is provided in full for each database in the digital supplement:

(Pain OR painful conditions) AND Physical, Psychological, Self-management therapies (specific therapy and technique names) AND (placebo control OR sham control OR attention control) AND controlled clinical trials.

2.5 | Study selection

Eligibility screening was performed on Covidence.org in duplicate by two independent reviewers drawn from a pool of specifically trained research contributors. Disagreements were resolved by discussion or a third reviewer if needed. The screening was first performed based on study title and abstract. Full-text eligibility was assessed in a second step.

2.6 | Data extraction

Data were extracted from primary and all associated trial reports. Trial protocols were consulted for additional method information, where available.

The data extraction process was also conducted in duplicate by two independent reviewers. Discrepancies were resolved through discussion or by a third independent reviewer.

Data extraction was trialled using a sample of potentially eligible studies. All reviewers received training in systematic review methods, trial design and the use of online platforms provided by the lead investigator (DHS) prior to starting data extraction. Results of the pilot testing informed the final approach to data extraction, with detailed annotations for extraction items available to reviewers, and reliability was monitored throughout (Higgins et al., 2019).

Data extraction domains were as follows: Bibliographic data, general study design, control intervention methods and blinding-related information, the nature and content of non-exposure arms, trial outcomes and risk of bias. Funding information was not extracted as not deemed relevant due to limited industry interests in PPS interventions.

2.7 | Trial outcomes

Pain-related outcome measures were extracted for treatment, control intervention and non-exposure groups. Pain-related outcomes can be unidimensional (usually pain intensity rating scales) or multidimensional (e.g. questionnaires assessing disease-related function, pain interference or quality of life) (Turk et al., 2003). Our previous analysis showed the former to be more susceptible to aspects of control intervention design and thus potentially placebo effects (Hohenschurz-Schmidt, Draper-Rodi, et al., 2023). For the present review, we therefore only extracted unidimensional measures of pain intensity, such as visual or numeric rating scale data.

Outcome data were extracted for baseline, short-term (closest to the end of treatment, no longer than 4 weeks), medium-term (closest to 8 weeks, but within 4–12 weeks) and long-term time points (closest to 26 weeks and >12 weeks).

Where necessary, data were extracted from figures using the Adobe Reader measurement tool. Authors were contacted via email if data were missing that were required for the calculation of effect sizes, if data appeared erroneous and if methodological clarification was required. Data were converted into means and standard deviations if required and possible, and direction of effect was considered (Higgins et al., 2019).

The number of participants lost to follow-up was calculated based on sample sizes at the above time points. Reports of adverse events were extracted as per Lavazza et al. (2021). Where reported, information about blinding effectiveness was extracted as per Hohenschurz-Schmidt, Draper-Rodi, et al. (2023).

2.8 | Data analysis

2.8.1 | Descriptive analysis

The following information is provided at trial level and for the entire sample of included studies, where reported:

- Publication year
- Country of study conduct
- Participant description (index condition/pain descriptor, duration of pain experience in sample, age, gender or sex)
- Sample size in total and per group at randomization
- Investigational treatment (including therapy complexity as simple vs. complex, and content)
- Nature and classification of control intervention
- Amount of exposure to control intervention and providers as part of control intervention

- Reports of supposed blinding status of participants in the control intervention arm
- Reports of blinding effectiveness and control intervention credibility or satisfaction
- Nature and classification of non-exposure groups
- Pain-related outcome measures as extracted
- Risk-of-bias assessment (Sterne et al., 2019)

2.8.2 | Meta-analysis of placebo effects (primary analysis) and subgrouping

All eligible trials were used for the primary analysis if change scores and their variance could be calculated or were reported. Placebo effects were calculated as between-group differences in change scores between control intervention and non-exposure groups, treatment efficacy as the difference between investigational treatment and control intervention groups, and effectiveness as investigational treatment versus non-exposure group changes. To illustrate natural disease history and regression phenomena in our sample, changes from baseline to follow-up in non-exposure arms were also calculated, and in control intervention arms to show the placebo *response* (not placebo *effect*) (Evers et al., 2018).

Sensitivity analyses were conducted to exclude trials of less than 20 participants per arm at randomization. We had also planned to conduct sensitivity analyses to exclude trials with overall high risk of bias, and/or outliers according to pre-defined criteria, but these could not be performed as most studies had high risk of bias and due to the absence of outliers. For secondary meta-analyses, we only subgrouped according to control intervention type and not investigational treatment type due to the preponderance of manual therapy interventions. An aggregate effect was calculated as per below as primary analysis.

Trials that could not be pooled were analysed descriptively (see Table S2). Criteria for non-pooling were cancer-related pain and studies with patients who had no pain at study outset (pain interventions during or immediately after surgery).

Within-group effects were calculated as mean changes from baseline to short-, medium- and long-term follow-up after the end of the treatment period (where available). Standard deviations for change scores were obtained by pooling baseline and follow-up standard deviations and correcting them for an assumed moderate correlation between baseline and follow-up (0.5 correlation coefficient). Natural history and placebo responses were calculated as Hedge's g by dividing change scores by pooled standard deviations and calculating standard errors (Borenstein et al., 2021; Higgins et al., 2019; Lipsey & Wilson, 2000). Between-group effects (i.e. placebo effects and treatment effectiveness and efficacy) were calculated from non-standardized change scores during meta-analysis as per below. Meta-analyses of between-group differences were performed as aggregate across the entire sample and per control intervention type subgroup. This was done separately for all available time points; the primary time point of interest being immediately after the end of the treatment period ('short-term'). For the overall effect and each subgroup, summary effects were calculated using random effects models weighted by the inverse of the variance and plotted as forest plots using RevMan 5 software (The Cochrane Collaboration, 2020). The heterogeneity of overall effects was estimated using Tau^2 (T^2) and I^2 statistics and tested for significance using Z statistics (Borenstein et al., 2021). Data are presented in forest plots for individual time points.

2.8.3 | Secondary meta-analyses: Blinding effectiveness, blinding indices, treatment expectations and differential attrition

We could not perform a meta-analysis on blinding index ratio because studies that provided an indication as to the effectiveness of the employed blinding methods did not report in a manner that enabled Bang's blinding index to be calculated (Bang et al., 2004; Colagiuri et al., 2019). Descriptive results of blinding effectiveness are provided. In addition, we identified trials that measured participant expectancy or related concepts (treatment credibility and satisfaction). Again, data pooling and meta-analysis of expectancy measures were not possible. As an indirect marker of study acceptability, the number of participants lost from control intervention and non-exposure groups was extracted for all available time points. Subgroup analyses were conducted to test for differences in percentual attrition depending on the control intervention type.

2.8.4 | Multiple meta-regression analysis: The role of control intervention types, provider contact and exposure time in predicting placebo effects

We had intended to assess the potential relationship between placebo effects and the features of the control interventions by means of meta-regression analyses (Borenstein et al., 2021; Wilson, 2005). Surprisingly, the meta-analysis of placebo effects revealed low statistical heterogeneity ($I^2 = 11\%$), so meta-regression analyses were not possible.

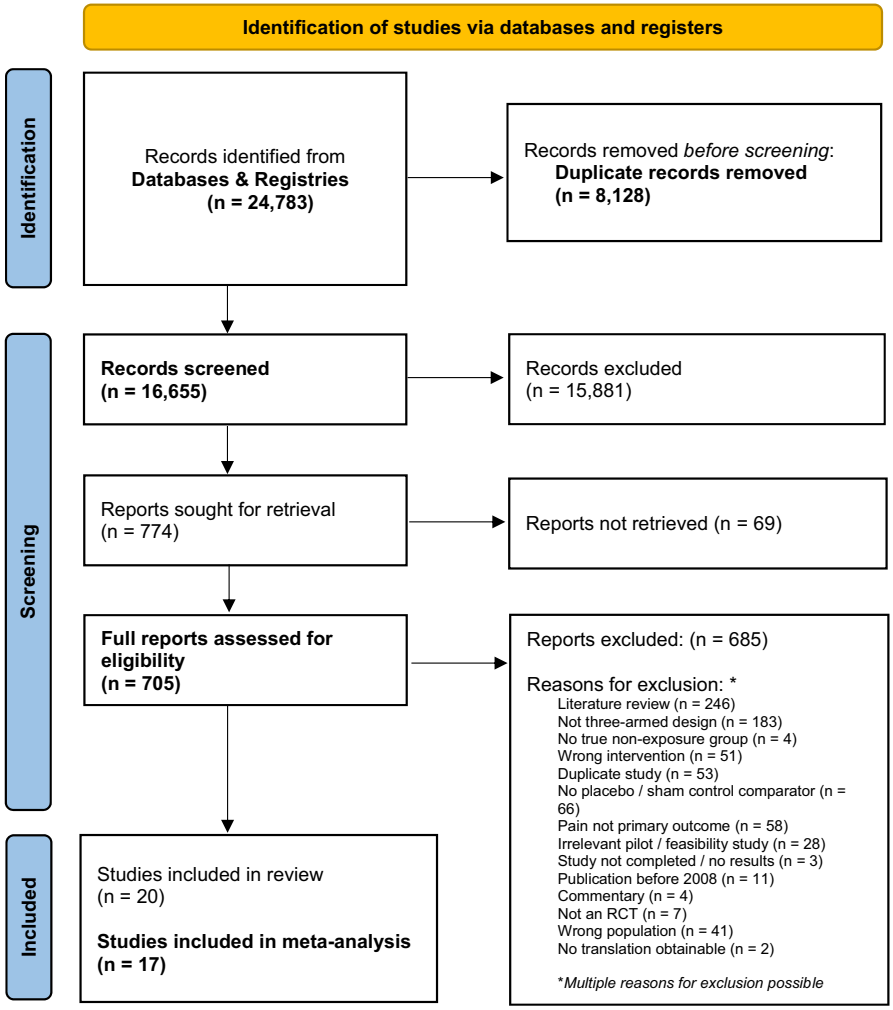

FIGURE 1 PRISMA flow diagram of the systematic search and selection process.

Meta-subgrouping according to investigational treatment type was not possible due to small subgroup numbers.

3 | RESULTS

3.1 | Search results

Having screened 16,655 records and 705 full-text articles, 20 three-armed RCTs were found eligible. Seventeen trials were included in the analysis as three author groups (Aghabati et al., 2010; Gercek et al., 2023; Tabatabaee et al., 2016) did not provide outcome data suitable for meta-analysis. A PRISMA flow diagram with exclusion reasons for all studies is provided in Figure 1.

3.2 | Sample description

All 20 eligible trials are described at study level in Table S2. The characteristics of the 17 meta-analysed studies are summarized in Table 1 and the text below. One trial (Paulo et al., 2021) was a cross-over design, all others were parallel-group RCTs. Most trials (84%) were single-centre trials.

3.2.1 | Patient populations

Patients mainly experienced musculoskeletal pain (n of studies = 5, 29%, e.g. back, neck pain or peripheral joint pain) or diffuse/widespread chronic pain (n = 5, 29%; e.g. diagnosed with fibromyalgia). Patients with headaches (n = 3), pregnancy-related pain (n = 2), visceral and post-surgical pain (n = 1 each) were also studied. Most patient populations (n = 13, 77%) had pain or painful conditions lasting for over 3 months (median duration 9.3 years, Q1,3 = 0.5, 13.6 years). The average number of participants per study arm at randomization was 52 (median 35, Q1,3 = 27, 59).

3.2.2 | Investigational treatments

Most trials investigated manual therapy interventions (n = 10, 59%) (Bialosky et al., 2014; Cerritelli et al., 2015;

TABLE 1 Study characteristics.

Therapy types	***n* of studies**	**%**
Manual therapy with spinal manipulation[a]	3	17.6
Craniosacral manual therapy and gentle myofascial release[a]	1	5.9
Other manual therapy (e.g. joint articulation or massage)[a]	6	35.3
Mindfulness/relaxation	3	17.6
Rehabilitation/physiotherapy	1	5.9
Self-management	1	5.9
Cognitive-behavioural and other psychotherapy	1	5.9
Spiritual/energetic/esoteric healing (Reiki)	1	5.9
Intervention complexity	***n***	**%**
Simple	8	47.1
Complex	9	52.9
Treatment dosage (investigational treatment)	Median	Q1/Q3
Duration of treatment period (weeks)	4	2/10.5
Number of treatment sessions	7	6/10.5
Pain descriptor	***n***	**%**
Musculoskeletal pain	5	29.4
Diffuse chronic pain	5	29.4
Headaches	3	17.6
Pregnancy-related pain	2	11.8
Visceral pain	1	5.9
Postsurgical	1	5.9
Neuropathic pain	0	0.0
Cancer-related pain	0[b]	0.0
Pain duration	***n***	**%**
Chronic (>3 months)	13	76.5
Acute (<3 months on average)	1	5.9
Not reported	3	17.6
Sample size at randomization	**Median**	**Q1/Q3**
Overall sample size (all trial arms combined)	105	69/184
Sample size per trial arm (only groups included in review)	35	27/59
Registered trial protocol available	***n***	**%**
Registered	16	94.1
Group design		
Parallel group	15	94.1
Cross-over	1	5.9
Number of study settings	***n***	**%**
1 (single-centre)	14	82.4
2	0	0.0
3	2	11.8
Home-based intervention	1	5.9
Number of study conditions per trial	***n***	**%**
3	15	88.2
4	2	11.8

(Continues)

TABLE 1 (Continued)

Nature of 'sham' control intervention	***n***	**%**
Disabled ultrasound device	5	29.4
Manual, simulated manoeuvre[a]	4	33.3
Manual, soft touch[a]	1	5.9
Other (educational attention control, simulated hands-off manoeuvre, multicomponent therapist interaction, mimicked patient body positioning, floatation tank with altered settings, white noise and saline injection)	7	41.2
Reported participant blinding status in control intervention arms	***n***	**%**
Blinded to group allocation	9	52.9
Not blinded	5	29.4
Not reported	3	17.6
Nature of non-exposure arm	***n***	**%**
Usual care continuation[c]	12	70.6
No treatment as part of the trial, but usual care continuation unclear	3	17.6
True no-treatment control	1	5.9
Waitlist	1	5.9
Additional comparators used (apart from 'sham' control intervention)	***n***	**%**
Active comparator (comparative effectiveness)	1	5.9
'Enhanced' sham/placebo[d]	1	5.9

Note: This table provides an overview of the studied therapies and patient populations, and the main design features of the meta-analysed studies ($n = 17$).

[a]Grouped together as 'manual' interventions or control interventions.

[b]One study investigated diffuse chronic pain in cancer patients, but pain was not directly cancer related.

[c]Ince et al. (2023) recruited only patients who were taking medication for fibromyalgia, but drug regimens did not change significantly during the study.

[d]Data not used for this review.

Chaibi et al., 2017; Hasuo et al., 2022; Hensel et al., 2015; Ince et al., 2023; Licciardone et al., 2010; Moraska et al., 2017; Ozgul et al., 2023; Paulo et al., 2021), followed by mindfulness and other relaxation interventions ($n = 3$, 18%) (Amirova et al., 2017; Loose et al., 2021; Schmidt et al., 2011). One trial each investigated pain self-management programmes (Allen et al., 2010), cognitive-behavioural therapy (Ashar et al., 2022), exercises (Krauß et al., 2014) and Reiki (Sisman & Arslan, 2022).

Half the study interventions were classified as 'simple' (consisting of individual techniques or a few simple steps) and half as 'complex' (47 and 53%, respectively). The average duration of treatment periods was 9 weeks (Median 4, Q1,3 = 2, 11).

3.2.3 | Control interventions and blinding

'Sham' control interventions were grouped as 'disabled devices', 'manual' or hands-on control interventions, and 'other' (Table 1). Detuned ultrasound devices were used in five cases (31%), controlling for manual therapy interventions (Hensel et al., 2015; Licciardone et al., 2010; Moraska et al., 2017; Ozgul et al., 2023) or exercise (Krauß et al., 2014). Manual control interventions were also used five times; in the form of simulated manoeuvres (Bialosky et al., 2014; Chaibi et al., 2017; Hasuo et al., 2022; Ince et al., 2023), controlling mainly for spinal manipulation therapy, or soft touch application controlling for craniosacral therapy (Cerritelli et al., 2015). The remaining control interventions classed as 'other' included educational attention controls used in a pain self-management trial (Allen et al., 2010), open-label saline injection in a cognitive-behavioural trial (Ashar et al., 2022), patient positioning on a treatment bench without further manipulation, used in a myofascial release study (Paulo et al., 2021) and simulated hands-off Reiki (Sisman & Arslan, 2022). The three trials of relaxation or mindfulness interventions used white noise provision over headphones (Amirova et al., 2017), multicomponent therapist interaction with educational and social support components (Schmidt et al., 2011) and a modified floatation tank (Loose et al., 2021).

Participants were reported as supposed to be blinded to group allocation in nine control intervention arms (53%) (Amirova et al., 2017; Bialosky et al., 2014; Cerritelli et al., 2015; Chaibi et al., 2017; Ince et al., 2023; Loose et al., 2021; Moraska et al., 2017; Schmidt et al., 2011; Sisman & Arslan, 2022). Blinding was not an objective in

five control intervention arms (29%) (Ashar et al., 2022; Hasuo et al., 2022; Krauß et al., 2014; Ozgul et al., 2023; Paulo et al., 2021), one of which only blinded participants to another active comparator, not the main investigational treatment (Krauß et al., 2014). Blinding information could not be obtained for another three trials (18%) (Allen et al., 2010; Hensel et al., 2015; Licciardone et al., 2010). The supposed blinding status did not differ between trials with different types of control interventions (as categorized above; $Chi^2 = 3.69$, df = 4, $p = 0.45$).

Blinding effectiveness was assessed and reported in five studies (29%) (Bialosky et al., 2014; Cerritelli et al., 2015; Chaibi et al., 2017; Ince et al., 2023; Loose et al., 2021), all of which reported successful blinding based on participants' allocation guesses. Three trials examined the credibility of the control intervention (Amirova et al., 2017), participant expectations (Bialosky et al., 2014) or both (Loose et al., 2021).

The amount of therapeutic exposure was matched between investigational and control intervention arms in 14 trials (87.5%), with the remaining two studies (Ashar et al., 2022; Krauß et al., 2014) providing considerably shorter and fewer sessions to participants in the control intervention arm.

3.2.4 | Non-exposure arms

Of the non-exposure arms, most patients continued their usual care ($n = 12$, 71%), although only one study specified the usual care content (Ince et al., 2023). In three further trials, no treatment was received as part of the trial, but the permissibility of other treatments was unclear (Bialosky et al., 2014; Moraska et al., 2017; Ozgul et al., 2023). One study employed a waitlist control with patients expecting treatment at a later time point (Schmidt et al., 2011). Only one non-exposure arm was classified as a true no-treatment comparator where no healthcare interaction occurred throughout the course of the study; however, this was only possible in a study of a single technique application with non-exposure patients being re-examined after a 5-minute waiting period (Paulo et al., 2021). No therapeutic attention or interaction with providers was reported for any of the non-exposure arms.

The blinding status of patients in non-exposure arms was unclear in all cases, although it is unlikely that participants were effectively blinded if they had full information about the studies' design.

3.2.5 | Intervention reporting

Assessing compliance with relevant CONSORT (Boutron et al., 2017) and TIDieR-Placebo (Howick et al., 2020) items, the reporting of intervention content was judged sufficient for replication for 16 test interventions (94%), 16 control interventions (94%) and 13 non-exposure arms (76%).

3.3 | Study results

3.3.1 | Outcome measures

The extracted outcome measures were mainly pain intensity (usually measured by visual or numerical rating scales) ($n = 13$, 76%). These being not available, pain-related compound scores were extracted from two trials (13%) (Krauß et al., 2014; Schmidt et al., 2011), 'bothersomeness' of pain from another (Schmidt et al., 2011) and the number of headache days per month from another (Chaibi et al., 2017). The extracted outcome measures were the declared primary outcomes in 12 trials (71%).

3.3.2 | Time points of outcome assessment

While all trials provided outcome data immediately or within 4 weeks after the end of the treatment period ('short term'), only seven sampled follow-up data 4–12 weeks later ('medium term') (Ashar et al., 2022; Chaibi et al., 2017; Ince et al., 2023; Loose et al., 2021; Moraska et al., 2017; Ozgul et al., 2023; Schmidt et al., 2011), and only three did so at a time point more than 12 weeks after the end of the treatment ('long term') (Ashar et al., 2022; Chaibi et al., 2017; Loose et al., 2021). Most trials assessed short-term outcomes immediately after the end of the treatment period, with two trials (Ince et al., 2023; Ozgul et al., 2023) following up 1 week later.

3.3.3 | Adverse events

No information about adverse events was reported in eight trials (47%), and no adverse events occurred in another eight trials (47%); only one study of spinal manipulation therapy for migraines (Chaibi et al., 2017) reported the occasional occurrence of local tenderness and tiredness after treatments, significantly more so in the test intervention compared to the control intervention group.

3.3.4 | Attrition

In the control intervention groups, an average of 10.9% of participants were lost to short-term follow-up (median 4.6%, 0.0–13.7% IQR, $n = 17$ studies) and 27.4% to medium-term (median 23.2%, 1.3–47.4% IQR, $n = 8$ studies).

In the three studies with long-term follow-up, an average of 37.3% of participants were lost from control intervention groups (median 37.8%, 25.9–48.0% IQR). There was no significant difference in percentual attrition between types of control interventions at short-term (manual, disabled devices or other; one-way ANOVA: $F(2,13) = 0.41$, $p = 0.67$) or medium-term follow-up ($F(2,5) = 5.06$, $p = 0.06$).

In non-exposure arms, percentual attrition was 9.2% at short-term (median 0.0%, 0.0–14.3% IQR, $n = 17$ studies), 20.7% at medium-term (median 12.7%, 0.0–36.5% IQR, $n = 8$ studies) and 29.9% at long-term follow-up (median 31.6%, 20.0–38.1% IQR). Subgrouping according to the type of non-exposure arm was not possible due to insufficient variability (most arms described as 'usual care', Table 1).

3.4 | Risk of bias

All but three studies were judged as overall high risk of bias for the meta-analysed pain-related outcome measure, considering the comparison between investigational and control interventions. Concerns arose mainly regarding the assessment of outcomes, with many studies not clarifying the patients' supposed blinding status. Also commonly, pre-registered analysis plans were rarely identified, leading to concerns in the final domain of the Cochrane Risk-of-bias tool 2 (Sterne et al., 2019) (See Figure 2 for an overview of the RoB assessment, and Table S3 for risk of bias at study level).

3.5 | Meta-analysis

Meta-analyses included 17 studies with short-term outcomes, with 882 participants randomized to the investigational treatment arms, 882 to control intervention arms and 865 to non-exposure arms.

We here present the comparative meta-analysis of changes in control interventions compared to non-exposure arms (i.e. the placebo *effect*), and treatment arms against non-exposure or control intervention groups (i.e. treatment effectiveness and efficacy, respectively).

Also analysed were changes within non-exposure groups (illustrating the natural history of symptoms and regression effects) and within control intervention groups (i.e. the placebo *response* (Evers et al., 2018)), presented in the (Figures S1 and S2).

For meta-analyses, studies were subgrouped according to the type of control intervention employed. Subgrouping according to investigational treatments was not possible due to small numbers in non-manual therapy groups.

3.5.1 | Placebo effects

Comparing 'sham' control interventions to non-exposure arms, a small effect of placebo analgesia was found across studies at the short term (−0.21 SMD, −0.33 to −0.1 95% CI, $p = 0.0002$) and low heterogeneity ($T^2 = 0.01$, $I^2 = 11\%$, participants = 1440, studies = 17; Figure 3). The five studies employing hands-on (manual) control interventions showed a significantly larger placebo effect than the other two groups (−0.54 SMD, compared to −0.16 in trials using disabled devices and −0.11 in studies with other types of control interventions; $\text{Chi}^2 = 9.27$, df = 2, $p = 0.01$; Figure 3).

In medium term and with data from seven RCTs, there was no placebo effect (−0.11 SMD, −0.31 to 0.09 95% CI, $p = 0.28$, $T^2 = 0.0$, $I^2 = 0\%$, participants = 381). There were no subgroup differences ($\text{Chi}^2 = 2.12$, df = 2, $p = 0.35$; Figure S3).

Long-term data from three trials also showed no effect (−0.23 SMD, −0.53 to 0.07 95% CI, $p = 0.13$, $T^2 = 0.0$, $I^2 = 0\%$, participants = 173) and no subgroup differences ($\text{Chi}^2 = 0.25$, df = 1, $p = 0.62$).

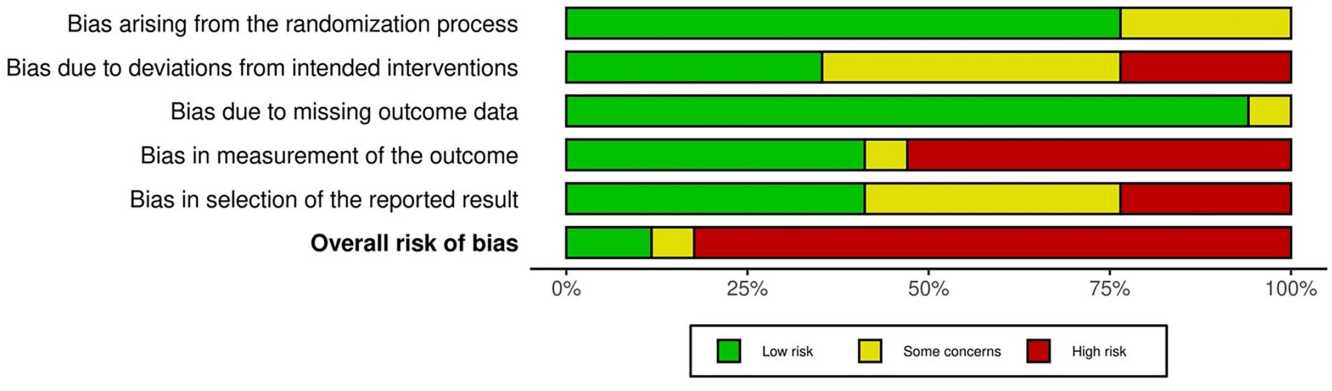

FIGURE 2 Risk of bias in meta-analysed sample. $N = 17$; Figure created with the *robvis* tool by McGuinness and Higgins (2020).

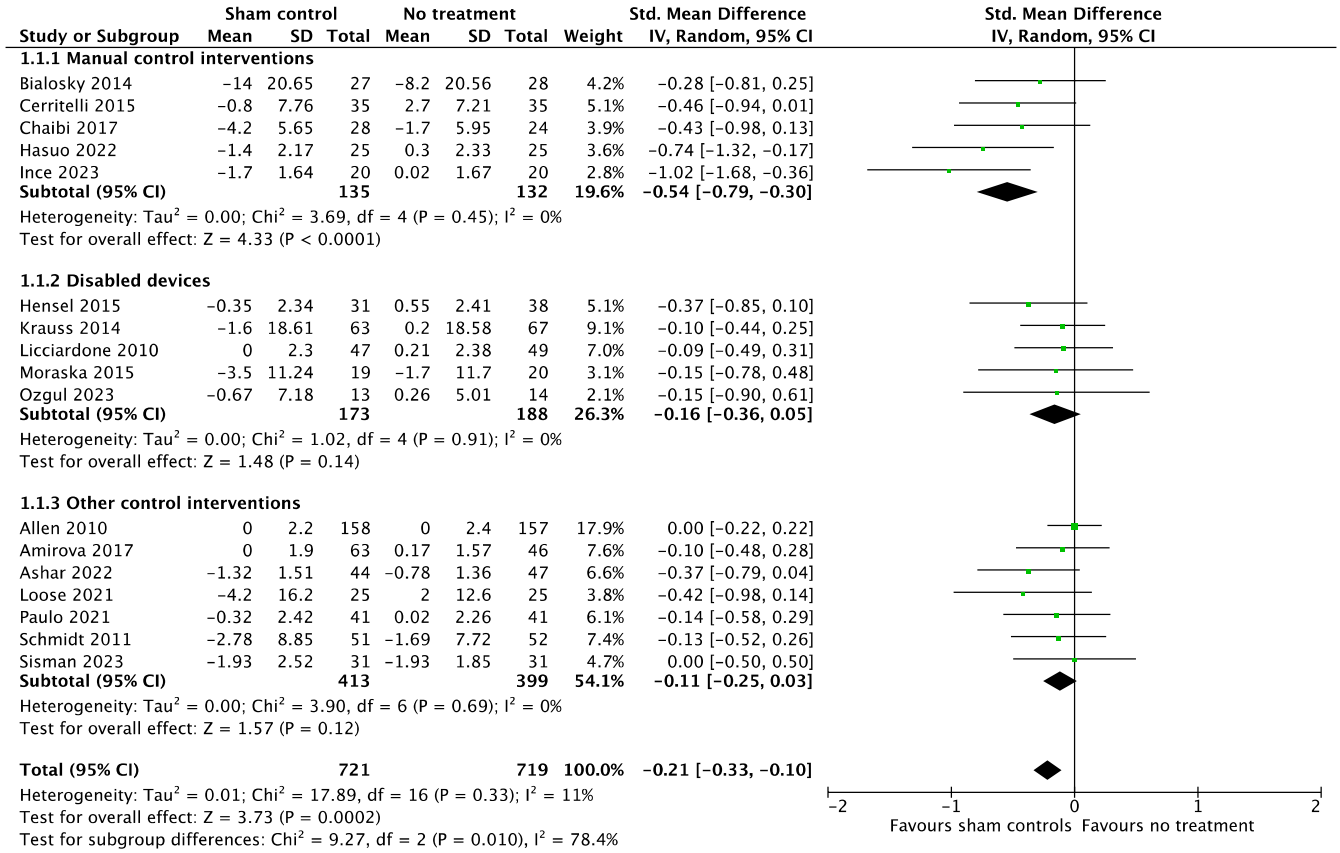

FIGURE 3 Placebo effects at short-term follow-up. Meta-analysis illustrated as forest plot, comparing changes in control intervention groups to non-exposure groups, subgrouped according to the type of control intervention employed.

3.5.2 | Treatment effectiveness and efficacy

Compared to no treatment, participants in the investigational treatment arms experienced medium-sized short-term pain relief (SMD = −0.54, −0.76 to −0.31 95% CI, $p < 0.00001$, $T^2 = 0.16$, $I^2 = 75\%$, participants = 1426; studies = 17; Figures S4 and S5). Between-study heterogeneity of treatment effectiveness was considerable. At medium term, the standardized mean difference was −0.31 (−0.55 to −0.08 95% CI, $p = 0.01$, $T^2 = 0.02$, $I^2 = 22\%$, participants = 382; studies = 7; result not reported in figure), and −0.46 but not significant at long-term follow-up (−1.27 to 0.35 95% CI, $p = 0.26$, $T^2 = 0.44$, $I^2 = 86\%$, participants = 179; studies = 3; result not reported in figure).

Compared to 'sham' control interventions, investigational treatments resulted in an aggregate small benefit ('efficacy') of −0.25 in the short term, with considerable between-study heterogeneity (−0.44 to −0.05 95% CI, $p = 0.01$, $T^2 = 0.11$, $I^2 = 68\%$, participants = 1427; studies = 17; Figure 4). Grouping the studies according to the type of control intervention employed showed that there was no significant difference between studies that employed manual control interventions, disabled devices or other control interventions (Figure 4); although only the subgroup with 'other' control interventions showed significant efficacy.

At medium-term follow-up, interventions had a summary efficacy of −0.35 compared to control interventions and there was moderate between-study heterogeneity in effects (−0.64 to −0.05 95% CI, $p = 0.02$, $T^2 = 0.07$, $I^2 = 48\%$, studies = 7, participants = 375). There was again no significant difference between subgroups ($Chi^2 = 0.06$, df = 2 $p = 0.97$). At long-term follow-up, combined treatments from three studies showed no efficacy (−0.19, SMD -0.87 to 0.49 95% CI, $p = 0.59$, $T^2 = 0.29$, $I^2 = 81\%$, participants = 184; test for subgroup differences: $Chi^2 = 0.83$, df = 1, $p = 0.36$).

3.5.3 | Sensitivity analyses

Meta-analysis results were not changed notably by excluding two trials with less than 20 participants per group at randomization (Moraska et al., 2017; Ozgul et al., 2023) (both using disabled ultrasound devices as control intervention) (Figures S6–S8 for forest plots of efficacy, effectiveness and placebo effect sensitivity analyses at short term). Sensitivity analyses with only low risk-of-bias

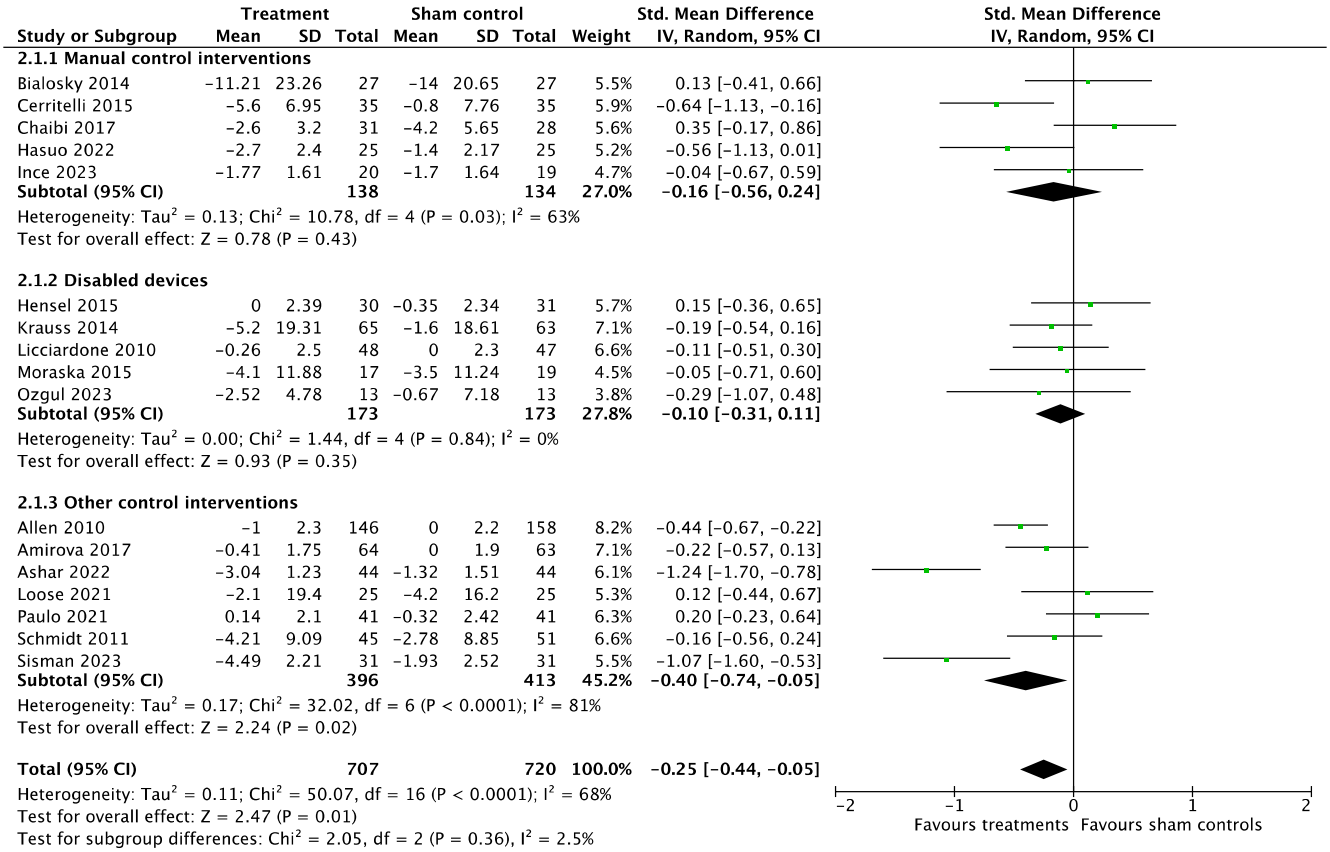

FIGURE 4 Short-term treatment efficacy. Forest plot of changes in investigational treatments compared to control interventions, showing an aggregate effect and subgrouped according to the type of control interventions employed.

studies were not possible due to their small number ($n = 3$). Outliers were not present.

3.6 | Subgroup analyses

3.6.1 | Modulators of the placebo effect

Meta-regression analyses were not possible due to the lack of statistical heterogeneity in the overserved placebo effects ($I^2 = 11\%$, Figure 3) and limited reporting or variance in potential test variables. For example, the number of studies that assessed participants' expectations of treatment effect was limited ($n = 2$) and reported data in different ways (further discussed in the next paragraph). Studies assessing blinding effectiveness ($n = 5$) only reported successful blinding, not only preventing meta-regression but also qualitative comparisons. In addition, the content of non-exposure groups was often insufficiently reported, again making subgroup analyses impossible. The same limitation applies to the reporting of behaviour of participants in these study arms (e.g. seeking medical care outside of the trial).

Only Bialosky et al. (2014) and Loose et al. (2021) assessed the expectations of participants (See Table S2). Bialosky did so with a clinical question for expected symptom change after the first intervention session, finding no difference in expectations between the non-exposure group and the control intervention meta-analysed here (the 'standard' sham spinal manipulation); but more participants expected pain relief from the intervention than from the 'standard' control and non-exposure conditions. However, differences in expectations were not associated with clinical outcomes. Loose et al. (2021) asked how certain participants felt that interventions could ameliorate their symptoms—but only in the intervention and control intervention groups. Overall, a lack of information about expectancy in non-exposure and control intervention arms prevented any comparison of placebo effects between studies in the context of participant expectations.

As a potential proxy of expectations, the credibility of control interventions was assessed by Amirova et al. (2017) and Loose et al. (2021), both reporting no differences in the credibility of test and control interventions. Asking for the credibility of non-exposure arms as 'real treatments' is clearly meaningless, so this was not performed in any study.

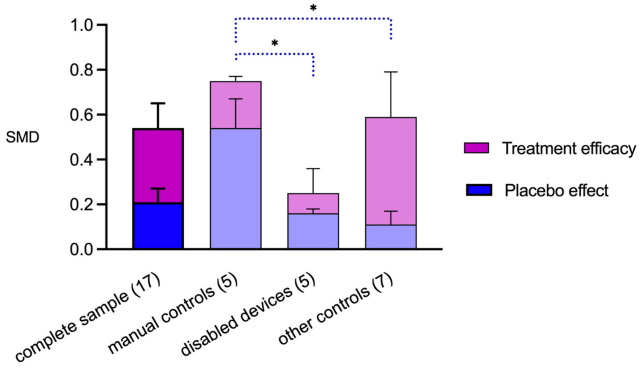

FIGURE 5 Direct comparison of the placebo effect to the overall effect observed in treatment arms at short-term follow-up. The number of studies per category is provided in brackets and further detail is found in respective forest plots in this publication. Dotted brackets indicate significant subgroup differences in the magnitude of the placebo effect (blue bars). SMD, standardized mean difference.

3.6.2 | Contribution of placebo effects to treatment effectiveness

To illustrate the proportionate contribution of placebo effects to treatment effectiveness in our sample and subgroups, we plotted the respective effect sizes (Figure 5). In the overall sample, the placebo effect made up 39% of the overall effectiveness of investigational treatments. Note that placebo and 'specific' effects may not be additive, despite what this graph may imply (Atlas et al., 2012; Lund et al., 2014).

4 | DISCUSSION

This review meta-analysed 17 three-armed RCTs of physical, psychological and self-management interventions for pain, enabling us to directly compare investigational treatments, 'sham' control interventions and non-exposure arms. By comparing clinical changes within the intervention and control intervention groups against changes in non-exposure groups, we were able to quantify and compare the total effectiveness of treatments and the placebo effect.

In our sample, the average placebo effect at short-term follow-up was 0.21 SMD (0.1–0.33 95% CI), typically classified as a small effect. Given a total treatment effectiveness of 0.54 (0.31–0.76 95% CI), placebo analgesia made up over a third (39%) of the overall effectiveness of treatments (Figure 5). The observed average placebo analgesic effect is similar to the placebo effects calculated by earlier reviews of physical control interventions (Hu et al., 2022; van Lennep et al., 2021) and drug trials (Vase et al., 2002) but considerably smaller than what is typically measured in laboratory experiments (Blythe et al., 2023; Forsberg et al., 2017; Peerdeman et al., 2018). The average placebo *response* measured here is also similar to previous studies, noting large heterogeneity of our and available comparison analyses (Hu et al., 2022; Vase, Vollert, et al., 2015). We did not observe placebo analgesia beyond the short term, but the number of studies available for longer-term analyses was limited.

Two interpretations of this main finding are possible: It may be that placebo effects are indeed less powerful than often suspected. However, the small average effect in this sample may also be due to methodological challenges present across all included RCTs, and placebo effects clearly varied in magnitude in our sample. Participants in non-exposure groups were not blinded and only half the trials indicated that participants in 'sham' control intervention arms were supposed to be blinded. Even in these studies, participants' actual blinding status was rarely reported, and the same is true for participants' expectations of benefit. Thus, if many of the participants suspected they were receiving a 'sham' treatment, this may have lowered the placebo effect (Forsberg et al., 2017; Vase et al., 2009). Further uncertainty is introduced by the differences in employed control intervention methods and the sparse reporting of protocol compliance and other potentially relevant information. These various factors, along with the fact that RCTs generally aim to boost treatment effects and avoid placebo responses, may have led to an underestimation of placebo effects here.

As for the factors influencing results in control intervention arms, our subgroup analyses suggested a larger placebo effect from hands-on (manual) control interventions than the placebo analgesia obtained with disabled devices such as ultrasound or with other miscellaneous control interventions, such as one-off saline injections, educational attention controls or white noise (Figures 3 and 5). This finding is aligned with other studies showing that interactive, personalized and higher-intensity control interventions produce larger effects (Benedetti, 2020; Hohenschurz-Schmidt, Draper-Rodi, et al., 2023; Howe et al., 2017; Meissner et al., 2013; Meissner & Linde, 2018; Rossettini et al., 2020; Sandra et al., 2023; Vase, Vollert, et al., 2015), possibly because they are perceived as more credible. Further assessment of potential effect modifiers was, however, not possible. Relevant features that will require further study include not only blinding effectiveness, expectancy and features of the therapeutic context and relationship but also the nature and duration of painful conditions and participant demographics (for an analysis of some of these factors, see Vase, Vollert, et al., 2015; Hohenschurz-Schmidt, Draper-Rodi, et al., 2023). Indeed, while expectations and learning are the main mechanisms of placebo effects (Evers et al., 2018), these factors are

likely influenced by contextual factors such as the interaction between therapist and patient, emotional responses, changes in knowledge and cognition and behaviour change (Ciechanowski, 2012; Enck & Zipfel, 2019; Wager & Atlas, 2015). However, reporting of such factors is poor (Hohenschurz-Schmidt, Draper-Rodi, et al., 2023), and it remains unclear how these factors interact with expectancy and learning-related ('placebo') effects and 'specific' therapeutic effects (Atlas et al., 2012; Lund et al., 2014). Nonetheless, the larger placebo effects in the manual controls subgroup suggest that control interventions' credibility and methodological aspects of trial design were influential, and the finding demonstrates that placebo effects can be variable and situation specific. This subgroup analysis is nonetheless limited by its sample size (267 participants from 5 studies) and the studies' overall high risk of bias. The warranted further study of factors influencing placebo effects in RCTs will only be possible through standardization of control intervention methods and enhanced reporting, discussed below.

While the observed placebo analgesia may not be clinically meaningful (Abdel Shaheed et al., 2023; Farrar et al., 2000), the effect and its differences between types of control interventions have mechanistic and methodological implications.

First, there was very little heterogeneity in placebo effects between studies, indicating that placebo analgesia is reliably produced by various control interventions, although of varying magnitude, possibly due to varying levels of perceived credibility or blinding. Placebo effects also contributed notably to moderate overall treatment effectiveness. Mechanistically, the on average larger placebo effect from manual control interventions may speak to the therapeutic potential inherent to human touch (McGlone et al., 2017) and/or to higher perceived credibility and expectations of benefits in these interventions (Benedetti, 2020; Meissner et al., 2013). This may inform mechanistic considerations for manual therapies (Bialosky et al., 2009) and experimental studies to determine effect modifiers or interactions with other therapy components. However, placebo effects may also be relevant in psychological and other non-pharmacological interventions, despite the smaller effect observed in our sample. Appreciating this requires the discussion of trial methodology: The smaller placebo effect in non-manual groups may simply be due to less rigorous control intervention design, for example, leading to lower participant expectations from non-credible control interventions (such as sham ultrasound or pre-recorded videos). Indeed, while common and often validated in spinal manipulation therapy, high-similarity control interventions (and efficacy trials in general) are rare in, for example, exercise interventions, psychotherapy research or pain self-management (Hohenschurz-Schmidt, Draper-Rodi, et al., 2023), making control intervention credibility a likely problem in this area. Further work on high-quality control interventions is required for these complex therapies, as well as to better understand treatment mechanisms.

Control intervention design and placebo effects may have important implications for the interpretation of trials. Illustrating this with our sample, the group of trials with miscellaneous control interventions was the only one that showed a significant level of *efficacy*, that is, benefit over 'sham' control interventions (SMD of 0.4 in this group vs. 0.16 in manually controlled trials; forest plot in Figure 4, and size of the pink areas in columns 2 and 4 in Figure 5). However, the *effectiveness* of the therapies with miscellaneous control interventions was similar to the effectiveness of trials using manual control interventions (SMD of 0.59 vs. 0.75; forest plot in Figure S4, and total size of columns 2 and 4 in Figure 5). Comparing the efficacy of these two groups without the ability to quantify placebo effects may thus be biased: in our sample, the magnitude of placebo effects was the only notable difference between these subgroups and may be based on considerable methodological differences in control intervention design. Conversely, only examining the effectiveness of interventions against non-exposure groups or other active comparators will leave important mechanistic and ethical questions unanswered (Hohenschurz-Schmidt, Cherkin, et al., 2023; Keefe et al., 2022) by not acknowledging the potential influence of placebo effects demonstrated in this review.

Finally, we do not yet know whether placebo and 'specific' treatment effects are additive or whether the relationship is largely non-linear (Atlas et al., 2012; Lund et al., 2014)—a possibility that requires further investigation and must be born in mind when inspecting Figure 5.

Our results regarding placebo effects are aligned with meta-analyses from other fields such as pain (Vase et al., 2002) and psychological outcomes in exercise interventions (Lindheimer et al., 2015) when trials were reviewed in which the purpose was to test interventions; but our results differ from experimental studies where the aim is to investigate placebo effects (Forsberg et al., 2017; Vase et al., 2002, 2009). Our results thereby underscore that there is not one but many placebo effects (Benedetti, 2020). Contrary to previous reviews in the PPS intervention field that could not conduct meta-analyses due to small samples (Cerritelli et al., 2016; Lavazza et al., 2021), our broader eligibility criteria led to important insights about placebo effects and the mechanisms of physical, psychological and self-management interventions (Box 1).

To address the challenges of adequate control intervention design, the recently published CoPPS Statement (Hohenschurz-Schmidt, Vase, et al., 2023) makes

BOX 1 Lessons learned from this systematic review with meta-analysis

1. Placebo effects
- This meta-analysis suggests that placebo effects from complex physical and psychological control interventions are on average small, although the role of blinding and expectancies requires further study.
- Placebo effects are reliably produced in clinical trials of physical, psychological and self-management interventions for pain, as illustrated by the negligible heterogeneity between studies.
- Different features of control interventions and trial design may, however, lead to larger or smaller average effects, but further study is required.
2. Mechanisms of PPS interventions
- Placebo effects appear to contribute considerably to the overall clinical effectiveness of PPS interventions.
3. Trial methods in PPS trials
- The design of control interventions influences the observed effect size in efficacy trials. Control interventions that employ hands-on manoeuvres may produce significantly larger placebo effects than detuned electrical devices or other types of control interventions.

recommendations for the development, implementation and reporting of control interventions in efficacy and mechanistic trials of physical, psychological and self-management therapies. CoPPS provides a highly structured approach to control intervention design, advocating for control interventions that are as similar as possible to the investigational treatment and only omit the treatment component of interest. With this recommendation, CoPPS aims to standardize the influence of placebo effects across studies (by matching contextual factors and enhancing credibility of control interventions) and improve the interpretability of trials. At the same time, and as supported by this and a previous review (Hohenschurz-Schmidt, et al., 2023), such high-similarity complex control interventions may contribute to smaller effect sizes in efficacy trials (Box 1, point 3); possibly also compared to drug trials. CoPPS therefore calls for the contextualized consideration of such smaller effects in the development of clinical practice guidelines and evidence synthesis. First and foremost, this requires appreciation of control intervention design and its implication for which intervention component is studied. Further research is required to compare effect sizes from high-quality PPS efficacy trials with other non-pharmacological and pharmacological trials.

AUTHOR CONTRIBUTIONS

All listed authors have contributed substantially to the project and fulfil ICMJE criteria. David Hohenschurz-Schmidt, Sigrid Juhl Lunde and Lene Vase made substantial contributions to the conception and design of this study; David Hohenschurz-Schmidt, Jessica Chan, Jules Phalip, Sigrid Juhl Lunde and Greta Gauhe to the acquisition of data; David Hohenschurz-Schmidt, Jan Vollert and Nadia Soliman to the analysis of the data; all authors made substantial contributions to the drafting or revising of the manuscript for important intellectual content, and all authors approved of the final manuscript version. Nobody who qualifies for authorship has been omitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest in relation to this work.

DATA AVAILABILITY STATEMENT

Upon publication, we will make any template data collection forms and data extracted from included studies freely and publicly available on the Open Science Framework.

STATEMENT OF ORIGINALITY

This manuscript contains original, unpublished work that is not being considered for publication elsewhere at the same time. Aspects of this work have been presented publicly as a poster at the 2023 Society for Interdisciplinary Placebo Studies Conference.

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