Boosting treatment outcomes via the patient-practitioner relationship, treatment-beliefs or therapeutic setting. A systematic review with meta-analysis of contextual effects in chronic musculoskeletal pain.

Authors:

Tobias Saueressig (TS), PT, Dipl.-Vw.[1]

Dr Patrick J Owen (PO), PhD[2]

Hugo Pedder (HP), PhD[3]

Nitin Kumar Arora PT (NKA), MPT[4,5]

Marieke Simons (MS), Physiotherapy student[4]

Svenja Kaczorowski (SK), PT, MSc[4]

Dr Clint T Miller, PhD (CM)[2]

Prof Lars Donath (LD), PhD[5]

Prof Daniel L Belavy (DB), PhD[4]

[1] Physio Meets Science GmbH, Johannes Reidel Str. 19, 69181 Leimen; Germany

[2] Deakin University, Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Geelong VIC 3220, Australia

[3] University of Bristol, Population Health Sciences, Bristol Medical School, UK;

[4] (Hochschule für Gesundheit [University of Applied Sciences], Department of Applied Health Sciences, Division of Physiotherapy, Bochum,

[5] German Sport University, Department of Intervention Research in Exercise Training, Cologne, Germany

Twitter: @PhysioMeScience, @PatrickOwenPhD, @BelavyProf, @hugopedder @_clintmiller @nitintarika

Address all correspondence to Tobias Saueressig at: t.saueressig@gmx.de

Address: Physio Meets Science GmbH, Johannes Reidel Str. 19, 69181 Leimen; Germany.

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Abstract

Objective: To ascertain whether manipulating contextual effects (e.g. interaction with patients, or beliefs about treatments) boosted the outcomes of non-pharmacological and non-surgicaltreatments for chronic primary musculoskeletal pain.

Design: Systematic review of randomized controlled trials

Data Sources: We searched for trials in six databases, citation tracking, and clinical trials registers. We included trials that compared treatments with enhanced contextual effects with the same treatments without enhancement in adults with chronic primary musculoskeletal pain.

Data synthesis: The outcomes of interest were pain intensity, physical functioning, global ratings of improvement, quality of life, depression, anxiety, and sleep. We evaluated risk of bias and certainty of the evidence using Cochrane Risk of Bias tool 2.0 and the GRADE approach, respectively.

Results: Of 17637 records, we included 10 trials with 990 participants and identified 5 ongoing trials. The treatments were acupuncture, education, exercise training, and physical therapy. The contextual effects that were improved in the enhanced treatments were patient-practitioner relationship, patient beliefs and characteristics, therapeutic setting/environment, and treatment characteristics. Our analysis showed that improving contextual effects in non-pharmacological and non-surgical treatments may not make much difference on pain intensity (mean difference [MD] : -1.77, 95%-CI: [-8.71; 5.16], k = 7 trials, N = 719 participants, Scale: 0-100, GRADE: Low)) or physical functioning (MD: -0.27, 95%-CI: [-1.02; 0.49], 95%-PI: [-2.04; 1.51], k = 6 , N = 567, Scale: 0-10, GRADE: Low) in the short-term and at later follow-ups. Sensitivity analyses revealed similar findings.

Conclusion: Whilst evidence gaps exist, per current evidence it may not be possible to achieve meaningful benefit for patients with chronic musculoskeletal pain by manipulating the context of non-pharmacological and non-surgical treatments.

Trial Registration: This systematic review was prospectively registered in PROSPERO (registration number: CRD42023391601)

Keywords: pain, physiotherapy, review, placebo effects.

Introduction

Musculoskeletal pain, affecting 16% of the global population, caused 121,300 deaths and 138.7 million disability adjusted life years in 2017,[47] impacting workability,[4] quality of life,[23] and mental and physical well-being.[24] Non-pharmacological treatments for musculoskeletal pain offer moderate benefits,[3] but improving treatment outcomes is crucial as global burden grows.[47,49]

Contextual effects,[9] including environmental, psychological, social, and cultural elements, can alter the experiences of individuals with musculoskeletal conditions beyond specific treatment.[8,18] These factors, including patient expectations, beliefs, previous experiences, and therapeutic relationships, can influence treatment outcomes.[10,55]

Manipulating contextual effects to improve treatment outcomes in musculoskeletal pain conditions could be a cost-effective and a low-resource alternative.[18,50] However, the literature on systematic assessments of contextual effects' impact on musculoskeletal conditions is limited. Only one recent systematic review[50] assessed the impact of contextual effects on clinical outcomes in patients with low back pain. The review was limited because it included differing comparators and used vote-counting for synthesis, which is not recommended.[29]

We focus on non-pharmacological interventions for chronic primary musculoskeletal pain. These treatments are often the first line of management due to their potential to minimize the risks associated with pharmacological treatments or surgical interventions.[33] Enhancing contextual effects could improve treatment effects, patient satisfaction, help allocate resources, and inform policy and practice. Our objective was to investigate the impact of contextual effects on managing musculoskeletal pain.

Methods

Our review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[2,45] and was prospectively registered in PROSPERO (CRD42023391601). Data and statistical code are available at the Open Science Framework online repository (https://osf.io/xzv92/).

Patient involvement

There was no patient or public involvement.

Search strategy

The whole search strategy is presented in Supplement 1. The electronic databases of MEDLINE, EMBASE, CINAHL, Web of Science Core Collection, CENTRAL, and SPORTDiscus were searched. The search terms were combined using the 'AND' operator to capture relevant trials across all domains. The search strategy was partially based on one systematic review identified in the literature.[50]

The search was limited to trials that were published from inception up to December 15, 2022. Unpublished and ongoing trials were searched through the WHO International Clinical Trials Registry Platform (http:// www.who.int/ictrp/en/) and the US National Institutes of Health ClinicalTrials.gov (https://clinicaltrials.gov/). A search for prior systematic reviews was conducted using the Cochrane Database of Systematic Reviews and GoogleScholar (https://scholar.google.de/) (see Supplement 1). We also performed forward and backward citation tracking in Web of Science on March, 28, 2023 for the included trials and relevant systematic reviews.

Eligibility criteria

The inclusion criteria followed the Participants, Interventions, Comparators, Outcomes, and Study design (PICOS) framework.[45]

Participants: Adults (≥18 years) experiencing primary chronic musculoskeletal pain.[56] Chronic primary pain, as per the ICD-11, is pain persisting for more than three months in one or more body regions, accompanied by significant emotional distress or functional disability, and not attributable to another chronic condition.[46] Chronic pain was defined as pain duration at baseline ≥ 3 months. There were no restrictions based on sex or race.

Interventions: An enhanced intervention was defined as any intervention designed to change or modify one or more known contextual effects of the health encounter/clinical consultation or experimental condition.[50] Possible contextual effects could be the ones described by previous authors[18] and entail: 1) patient beliefs and characteristics (e.g., medical history, illness and treatment beliefs, expectations, or prior experiences); 2) practitioner beliefs and characteristics (e.g., professional reputation, attire, empathy, professional training and prior experiences, and beliefs about treatment effectiveness); 3) patient-practitioner relationship (e.g., therapeutic alliance, trust, verbal or non-verbal communication, reassurance); 4) therapeutic setting/environment (e.g., setting, layout, décor, interior design); and 5) treatment characteristics (e.g., continuity of care, labelling, visual cues, sham/dummy treatment, variations in touch or stimulus conditions).[50] The intervention encompassed any non-pharmacological intervention as defined in Supplement 2.

Comparators: The same intervention without enhancement of contextual effects.

Outcomes: The choice of outcome measures were influenced by Dworkin's core outcome measures set.[20] The primary outcomes of interest included measures of pain intensity and physical functioning. Secondary outcomes encompassed global ratings of improvement, health-related quality of life, depression, anxiety, and sleep impairment. The follow-up time points were categorized as immediate (<1 day), short-term (≥1 day but <3 months), intermediate-term (≥3 months but <12 months), and long-term (≥12 months). A 10-point between-group difference was established as a range of equivalence for pain on a 0- to 100- numeric pain rating (NRS) scale.[44] The range of equivalence for outcomes with standardized mean differences (SMD) was set at a value of SD=0.50,[42] indicating situations where differences between interventions are not clinically significant.[41]The range of equivalence was transformed to the original scale by multiplying with the corresponding reference SD.

Study design: Randomized trials (individual or cluster or cross-over) conducted in English or German. The trials compared a contextually "enhanced" intervention with the same intervention without enhancement. Only full-text articles were considered.

The exclusion criteria are listed in Supplement 3.

Data extraction

Two independent assessors (NKA, TS) screened and extracted data using custom data extraction sheets, resolving disagreements through a third reviewer (PO). Extracted information included publication details, study design, demographics, main results, and follow-up duration. Mean and standard deviation (SD) were extracted for main results, with missing SD imputed using regression. Guidelines for handling randomized cross-over and cluster randomized trials were followed.[29] Multiple groups within a trial were combined when possible, and outcomes on different scales were standardized and combined using appropriate methods.[12] Data from figures were extracted using

GetData Graph Digitizer.[25] Any discrepancies in extracted data were resolved through discussion among assessors, with adjudication by a third researcher if needed (Supplement 4).

Risk of bias assessment and GRADE

The revised Cochrane Collaboration Risk of Bias Tool (RoB 2) was used to assess potential biases in both individually and cluster randomized trials.[29,52] Each source of bias was classified as having a low risk, some concerns, or high risk. Current guidelines from the Cochrane Collaboration[21] provide no definite guidance on how many outcomes and how many follow-up time-points should be assessed. All included outcomes were self-reported by the included participants. To prioritise workload, the assessment of the risk of bias was based on the results obtained at the last follow-up time point of the study. One subjective outcome (pain intensity) was rated.[29,52] Two independent assessors (NKA, TS) performed the ratings. A third adjudicator (DB) resolved disagreements as required.

The quality of evidence for pairwise comparisons was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[27] The criteria from Confidence in Network Meta-Analysis (CINeMA) evaluated imprecision, inconsistency, and publication bias.[41] For a detailed overview of our approach see Supplement 5. We used custom-made analysis R code to semi-automatically assess the GRADE criteria. Results of this ratings were double checked by two adjudicators (TS, SK).

Statistical analysis

We employed a lumping approach in our meta-analyses to test for the existence of intervention effects.[19,26] When pre- and post-treatment SD correlation was unavailable, we used $\rho = 0.59$, with sensitivity analysis at $\rho = 0.40$ and 0.81.[6] Effect sizes were MD for pain scales (converted to a 100-

point NRS) and SMD with an internal reference SD[17] for other outcomes, interpreted as small (≥ 0.2 SD), moderate (≥ 0.5 SD), and large (≥ 0.8 SD) following Cohen.[15] SMD for physical function and quality of life were back converted to original scales (for further details see Supplement 6). Reverse-scaled trials were adjusted by multiplying means by -1. Random-effects meta-analysis was conducted with REML estimation, and confidence intervals were calculated using Knapp-Hartung method. Heterogeneity was assessed with Cochrane Q, chi-squared statistic, I^2, and 95% prediction intervals when the number of trials was ≥ 5 and tau > 0. Funnel plots and Egger's test assessed small study effects and publication bias only if ≥ 10 trials were available.[53] Meta-regression was performed only if ≥ 10 trials were available.[11] Analyses were conducted in R (version 4.3.1) using Meta and metafor packages.[5,57] Conclusions were drawn based on the guidelines in the Cochrane Handbook.[29]

Subgroup Analysis

If the number of available trials was ≥ 10, we planned subgroup analyses and/or random effects meta-regression on: pain condition (e.g. low back pain, hip pain, etc.), type of intervention, risk of bias, usage of intention-to-treat analysis or per protocol analysis.

Sensitivity Analysis

Sensitivity analysis was performed via outlier identification and influence analysis if there were more than 10 trials in the analysis.[58] The impact of the choice of correlational values for calculating the SD of the change-from-baseline was assessed. We performed meta-analysis with unrestricted weighted least squares (UWLS) to account for small-study effects and high heterogeneity.[51] We planned to perform a sensitivity analysis for missing participant data if the percentage of missing

data was over 30% for the corresponding meta-analytic outcome but this analysis was not conducted as the missing data was always less than 30%.[60]

Results

We identified 17,637 reports. After removing duplicates and screening titles and abstracts of all remaining unique reports, 177 full-text reports were assessed for eligibility. We included 10 trials with 10 study reports (Figure 1).[28] Literature sources and reasons for exclusion of ineligible trials are in Supplement 7. We identified 5 ongoing trials potentially relevant for this review (Supplement 8).[13,16,38–40]

Study characteristics

The characteristics of the 10 included trials are shown in Table 1. Sample size ranged from 12 to 127 participants (mean: n=49.7; total: n=994). Mean (SD) age of participants was 47.8 (11.1) years. The median (range) intervention duration was 3 (0.14-8) weeks. The duration of complaints was median (range) 205.15 (16.25-747.5) weeks. The chronic MSK conditions were: knee osteoarthritis (n=1),[32] knee and-hip osteoarthritis (n=1),[48] lateral epicondylalgia (n=1),[35] plantar heel pain (n=1),[37] rotator cuff-related shoulder pain (n=1),[1] and low back pain (n=5).[7,22,34,36,59] Interventions were classified as acupuncture (n=2),[7,32] aids and devices (n=1),[1] education (n=1),[36] electrophysical agents (n=2),[22,37] exercise training (n=1),[48] manual therapies (n=1),[35] and physical therapy treatment (n=2).[34,59]

Six trials[7,22,32,34,36,48] were funded by governmental organizations, three trials[35,37,59] did not report their funding source, and one trial[1] reported no funding. Six trials[1,7,35,36,48,59] stated no conflict of interest, two trials[32,34] declared a conflict of interest, and two trials[22,37] did not report their conflict of interest. Trials were assigned to the following enhancement categories (Table 2): patient-

practitioner relationship (n=4),[22,34,36,59] patient´s beliefs and characteristics (n=4),[1,7,32,35] therapeutic setting/environment (n=1),[48] and treatment characteristics (n=1).[37]

Risk of bias

We assessed the outcome pain intensity at the longest follow-up time-point available in the trial. Two trial outcomes were rated as low RoB overall.[34,48] The other trial outcomes were either rated with some concerns (k=7)[1,7,22,35–37,59] or a high RoB overall (k = 1)[32] (Supplement 9). One trial was assessed with the ROB tool 2.0 for cluster RCTs.[34]

Data handling and synthesis

All data transformations (i.e. conversion of CI to SD, conversion of medians to means and SD) can be retraced via our analysis code which is openly available on the Open Science Framework (https://osf.io/xzv92/). One trial reported medians and interquartile range which were transformed to a mean with a corresponding SD.[35] In one trial, data were extracted from figures.[37] The included cluster RCT[34] did not need adjustment of the standard error because the trial reported adjusted results for clustering. No SDs were imputed.

All meta-analysis outcomes are reported in Table 2 and figures 2-5. SMD analyses of physical function and quality of life are shown in Supplement 10. The internal reference SD for standardization can be found in Supplement 11. All individual trial outcomes can be found in Supplement 12.

Primary Outcomes

Pain Intensity

All trials (k = 10) reported on the outcome pain intensity (Figure 2).[1,7,22,32,34–37,48,59]

At immediate follow-up, 2 trials reported on pain intensity.[1,22] A (MD: -7.99, 95%-CI: [-77.46; 61.47], k = 2 , N = 125, GRADE: Very Low) with very uncertain evidence was estimated. Short-term results for pain intensity were reported in 7 trials.[7,32,35–37,48,59] In our analysis, we observed a small effect favoring the intervention group (MD: -1.77, 95%-CI: [-8.71; 5.16], 95%-PI: [-19.51; 15.96], k = 7 , N = 719, GRADE: Low) in the short-term. For the intermediate-term, 5 trials reported on pain intensity.[7,34,36,37] A small effect in favour of the intervention group was estimated (MD: -0.81, 95%-CI: [-6; 4.38], k = 5 , N = 238, GRADE: High). Long-term results for pain intensity were reported in 2 trials.[36,37] A small effect (MD: -0.49, 95%-CI: [-6.37; 5.4], k = 2 , N = 616, GRADE: High) was estimated for pain intensity in the long-term. All three estimated outcomes did not translate into clinically meaningful differences in outcomes.

Physical Functioning

Eight trials examined the effect of contextual enhancement on physical function outcomes (Figure 3).[1,32,34–37,48,59] The results are on the patient-specific functional scale which ranges from 0-10.

One trial[1] reported immediate-term outcomes and found a moderate effect (MD: 1.2, 95%-CI: [0.65; 1.75], k = 1 , N = 66, GRADE: High) in favour of the control group. Six trials reported short-term outcomes and showed a small effect (MD: -0.27, 95%-CI: [-1.02; 0.49], 95%-PI: [-2.04; 1.51], k = 6 , N = 567, GRADE: Low) which may make no difference.[32,35–37,48,59] Four trials reported intermediate-term outcomes and revealed a small effect (MD: -0.1, 95%-CI: [-1.08; 0.88], k = 4 , N = 238, GRADE: Moderate) in favor of the enhancement group which likely makes no clinically significant difference in outcomes.[34,36,37] Two trials reported long-term outcomes and found a small effect (MD: -0.9, 95%-CI: [-8.32; 6.55], k = 2 , N = 464, GRADE: Low) which may make a slight difference in results.[36,37]

Secondary Outcomes

Global Ratings of Improvement

Three trials examined the effect of contextual enhancement on global ratings of improvement (GROC) outcomes (Figure 4).[34,36,48]

For short-term outcomes, 2 trials reported a small effect (SMD: 0.18, 95%-CI: [-2.16; 2.52], k = 2 , N = 148, GRADE: Low) in favour of the control group which may result in little or no difference in outcomes.[36,48] For intermediate-term outcomes, 2 trials reported a small effect (SMD: -0.13, 95%-CI: [-0.93; 0.67], k = 2 , N = 401, GRADE: Low) in favor of the enhancement group which may result in little or no difference in outcomes.[34,36] For long-term outcomes, one trial revealed a small effect (SMD: -0.39, 95%-CI: [-0.77; -0.01], k = 1 , N = 230, GRADE: High) in favor of the enhancement group.[36]

Health-related quality of life

Three trials investigated the impact of contextual enhancement on health-related quality of life outcomes at different time-points (Figure 5).[32,34,48] The results are on the SF-36 mental component scale, which ranges from 0-100.

For short-term outcomes, 2 strials reported a very uncertain effect (MD: 0.31, 95%-CI: [-37.64; 38.15], k = 2 , N = 253, GRADE: Very Low) in favor of the control group.[32,48]

For intermediate-term outcomes, one trial found no effect of contextual enhancement on health-related quality of life (MD: 1.43, 95%-CI: [-1.94; 4.79], k = 1 , N = 126, GRADE: High) in favor of the control group.[34]

Other Outcomes

The outcomes “self-reported depression”, “self-reported anxiety”, and “sleep impairment” were not reported in any of the included trials.

Subgroup Analysis

We performed an a posteriori subgroup analysis for trials that included low back pain patients (Supplement 13). Subgroup analyses for both outcomes showed no substantial difference in comparison to the main analyses

Sensitivity Analysis

We did not perform outlier identification and influence analysis due to the low number of trials included in each analysis. A sensitivity analysis for missing participant data was not performed as the percentage of missing data was never over 30% for any meta-analyses. The impact of imputed SD was not assessed as we did not impute any SD and only converted one trial from median to mean and SD. The results for the UWLS analysis to account for small-study effects and high heterogeneity can be found in Supplement 14.

Sensitivity analysis showed differences for the outcome global rating of change in the short and intermediate term. The estimates reversed their direction favouring the control group in the short-term and favouring the intervention group in the intermediate term for the UWLS analyses. The precision of the estimates was lower for the UWLS analyses compared to the main analyses. The sensitivity analyses for different correlational values for the imputation of the change from baseline SD did not show any important differences in results (Supplement 15). We also performed an a posteriori sensitivity analysis where we changed the time-frame for the immediate follow-up to

one week (Supplement 16). No important differences were noted in comparison to our pre-specified analysis.

Certainty of evidence

Main reasons for downgrading the evidence were imprecision and inconsistency. We did not grade down due to publication bias in accordance with our pre-specified criteria as we found no empirical evidence for publication bias in the literature and we performed extensive searches to rule out missing trials in our search. Indirectness was not downgraded.

Reporting Biases

We did not assume that reporting bias was present because we performed a comprehensive search, and identified no empirical evidence for publication bias. Statistical evidence could not be assessed as there were not enoughtrials to get reliable test results.

Amendments to information provided at registration

The amendments to our protocol are in supplement 18.

Discussion

Enhancing contextual effects in non-pharmacological and non-surgical interventions for chronic primary, musculoskeletal pain did result in little to no differences between the enhancement group and the control group for pain intensity (very low to high certainty evidence) and physical functioning (low to high certainty evidence) outcomes across immediate-term, short-term, intermediate-term, and long-term follow-up time-points. Short-term and intermediate-term global ratings of improvement showed no substantial differences, while the long-term outcome favored the enhancement group which showed a small effect favoring the enhancement group (low to high

certainty evidence). The impact on health-related quality of life outcomes was uncertain (very low to high certainty evidence), with no substantial differences in the short-term. In the intermediate-term there was evidence of no effect for the enhancement of interventions. Findings from meta-analysis in the subgroup of trials including only patients with low back pain were consistent with the wider meta-analyses.

Some individual trials showed beneficial and relevant effects. These findings highlight the varying effects of different interventions on pain intensity, physical functioning, and global ratings of improvement, emphasizing the need for further research in these areas to inform clinical practice and enhance patient outcomes. A small trial[22] demonstrated a moderate immediate decrease in pain intensity through enhanced therapeutic interaction, while another[36] found no short-term effect of therapeutic alliance. Kong et al.[32] showed a significant short-term reduction in pain intensity using "boosted acupuncture" with expectancy manipulation, whereas Barth et al.[7] did not. For physical functioning, Kong et al.[32] reported a significant short-term improvement for "boosted acupuncture", but with a high risk of bias and small sample size. Morral et al.[37] found no significant effect in the short term but observed a beneficial effect in the long term for physical function for a shockwave device with a more sophisticated design. Martínez-Cervera et al.[35] reported a moderate non-significant effect on physical functioning with a small sample for manual therapy with enhanced patient expectations. In terms of global ratings of improvement, Miyamoto et al.[36] found little difference in short-term and intermediate-term outcomes but demonstrated a moderate effect in the long term for enhancing therapeutic alliance.

Results in context of other evidence

Our findings have implications for existing literature and current clinical practices. The lack of considerable differences in all outcomes suggests that enhancing contextual effects may not have

a substantial impact in the treatment of chronic primary musculoskeletal pain. Some trials suggested that enhancing treatment expectations could improve treatment outcomes. Nevertheless, our findings do not align with previous research[18,50] that concludes that leveraging contextual effects could improve patient-reported outcomes.

We reached a different conclusion to the most recent systematic review.[50] There are a few explanations: first, we focused exclusively on non-pharmacological and non-surgical interventions for chronic primary musculoskeletal pain, whereas Sherriff et al.[50] included only treatments for chronic low back pain. Sherriff et al.[50] included a broader range of treatment comparisons, which included interventions that differed not only in the contextual effects but also in the specific treatment components (e.g., cognitive functional therapy vs. exercise training + manual therapy). Including diverse treatment comparisons may introduce bias and makes it challenging to isolate and estimate the specific effect of enhancing contextual effects alone. Consequently, it is difficult to draw definitive conclusions regarding the impact of enhancing contextual effects on the outcomes of interest from the prior review. In contrast to the Sherriff review[50] , we used a quantitative approach via meta-analysis. By avoiding vote counting and conducting a comprehensive synthesis of data, we provided a more robust and reliable evaluation of the effects of enhancing contextual effects in non-pharmacological and non-surgical interventions for chronic primary musculoskeletal pain.

We employed a comprehensive search strategy that included forward and backward citation tracking, and a search of trial registries, minimising the risk of missing important evidence. Additionally, we assessed the certainty of the evidence using the GRADE framework, allowing for a systematic and transparent evaluation of the quality and confidence in the findings.

Enhancing contextual effects when treating chronic primary musculoskeletal pain had a generally small or trivial effect on outcomes. While there may be some minor effects, they may not have substantial clinical significance in terms of pain intensity, physical functioning, global ratings of improvement, or self-reported quality of life. Clinicians should consider these findings when weighing the potential benefits of enhancing contextual effects against other treatment options and patient preferences—there is likely limited impact of enhancing contextual effects.

While previous research has emphasized the importance of patient expectations, communication, and environmental factors in influencing treatment outcomes, our review suggests that enhancing these factors alone may not substantially improve outcomes. We underscore the need for a multi-modal and individualized approach to managing chronic musculoskeletal pain that incorporates a range of strategies beyond contextual enhancements. We urge clinicians to avoid overemphasizing the role of enhancing contextual effects for chronic primary musculoskeletal pain. Instead, we suggest focus on treatment approach that integrates various evidence-based interventions. Patient-centered care and shared decision-making remain crucial in tailoring treatment plans to individual needs and preferences.[30] From a healthcare policy perspective, these findings suggest the importance of allocating resources towards interventions that have demonstrated more robust and clinically significant effects on pain management and functional improvement in chronic primary musculoskeletal pain.[3,33]

Limitations

Other factors such as patient subgroups, pain duration, contextual enhancement type could affect the outcomes and moderate the effects of enhancing contextual effects. Therefore, definitive conclusions about the role of contextual effects in enhancing treatment efficacy for musculoskeletal pain cannot be drawn from this study alone. We only included randomized clinical trials (RCTs)

written in German or English language, although adding non-English trials does not significantly impact effect size estimates.[43] Risk of bias was rated only for one outcome and the last follow-up time-point. A limitation of subgroup analyses with such a low number of trials ($k \leq 4$ per subgroup) is their very low power to detect an effect.[29]Future research should aim to improve the quality and rigor of the trials on this topic, by using factorial designs that can isolate and manipulate different contextual effects, increasing sample size to achieve adequate statistical power, and enhancing patient expectations through more elaborate interventions similar to open-label placebo trials .[14,31,54] In addition, it would be interesting to explore whether some individuals are more responsive to placebo effects or contextual influences than others, and what are the underlying mechanisms for this variability. This could be related to psychological factors such as personality traits, beliefs, or emotions, or biological factors such as genetic variations or neurobiological responses. This is an important area for future research that could have implications for personalized medicine and how treatment is delivered.

The trials included in the analysis showed variations in design, interventions, and outcome measures, causing heterogeneity, and potentially impacting the comparability of results. The limited number of trials prevented further exploration of heterogeneity through meta-regression or subgrouping. Assigning individual trial interventions to specific enhancement categories involves subjective judgment. The chosen route or execution of enhancing an intervention may not be adequate. The challenge of determining universally applicable values for thresholds of clinical relevance in the analysis could be improved by considering lower ranges of equivalence. However, the lack of smallest-worthwhile-effect (SWE) studies hinders establishing specific lower thresholds. Further exploration and discussion are needed to refine these thresholds based on context-specific considerations.

Conclusion

Enhancing contextual effects in non-pharmacological and non-surgical interventions for chronic primary musculoskeletal pain likely has limited clinical application. Although some individual trials reported larger effects, the findings were based on small sample sizes and were susceptible to bias.

435 **Table 1 - Study descriptions**

Author Year	Primary Musculoskeletal Condition	Duration Of Complaints (weeks)	Study Design	Population Enrolled (N)	Mean Age (Sd)	Female (N)	Intervention Duration (weeks)	Intervention Label	Enhancement Category	Group Label	Total Number Of Arms	Outcome	Follow-Up (weeks)	Scale Information	Study Funding	Competing Interest
Akbaba 2018	Rotator Cuff-related Shoulder Pain	55	Parallel RCT	33	50.03 (10.22)	22	0.14	Aids & devices	None	CON	3	Pain intensity; Physical functioning	0.07; 0.14	VAS-Rest; VAS-Activity; VAS-night; DASH; ASES	no support	state no conflict of interest
Akbaba 2018	Rotator Cuff-related Shoulder Pain	40	Parallel RCT	33	48.86 (10.3)	17	0.14	Aids & devices	Patient's beliefs and characteristics	INT	3	Pain intensity; Physical functioning	0.07; 0.14	VAS-Rest; VAS-Activity; VAS-night; DASH; ASES	no support	state no conflict of interest
Barth 2021	Low Back Pain	457.4	Parallel RCT	75	39.1 (12)	51	4	Acupuncture	None	CON	2	Pain intensity	4; 26	NRS or NPRS	government	state no conflict of interest
Barth 2021	Low Back Pain	381.3	Parallel RCT	77	40 (13.1)	49	4	Acupuncture	Patient's beliefs and characteristics	INT	2	Pain intensity	4; 26	NRS or NPRS	government	state no conflict of interest

Author Year	Primary Musculoskeletal Condition	Duration Of Complaints (weeks)	Study Design	Population Enrolled (N)	Mean Age (Sd)	Female (N)	Intervention Duration (weeks)	Intervention Label	Enhancement Category	Group Label	Total Number Of Arms	Outcome	Follow-Up (weeks)	Scale Information	Study Funding	Competing Interest
Fuentes 2014	Low Back Pain	197	Parallel RCT	30	30.5 (10.26)	18	0.14	Electrophysical agents	None	CON	4	Pain intensity	0.14	NRS or NPRS	government	NR
Fuentes 2014	Low Back Pain	222.6	Parallel RCT	29	29.7 (11.33)	19	0.14	Electrophysical agents	Patient-practitioner relationship	INT	4	Pain intensity	0.14	NRS or NPRS	government	NR
Kong 2018	Knee Osteoarthritis	NR	Parallel RCT	20	61.2 (7.7)	10	4	Acupuncture	None	CON	3	Pain intensity; Physical functioning; Self-reported quality of life	4	KOOS Pain subscale VAS-Rest	government	one author declares possible COI
Kong 2018	Knee Osteoarthritis	NR	Parallel RCT	24	61.3 (6.9)	9	4	Acupuncture	Patient's beliefs and characteristics	INT	3	Pain intensity; Physical functioning; Self-reported quality of life	4	KOOS Pain subscale VAS-Rest	government	one author declares possible COI
Lonsdale 2017	Low Back Pain	NR	Cluster RCT	122	46.71 (13.48)	64	NR	Physical therapy	None	CON	2	Global rating of improvement; Pain intensity; Physical	24	Perception of Recovery Scale; NRS or NPRS ;	government	one author declares

Author Year	Primary Musculoskeletal Condition	Duration Of Complaints (weeks)	Study Design	Population Enrolled (N)	Mean Age (Sd)	Female (N)	Intervention Duration (weeks)	Intervention Label	Enhancement Category	Group Label	Total Number Of Arms	Outcome	Follow-Up (weeks)	Scale Information	Study Funding	Competing Interest
												functioning; Self-reported quality of life		European Quality of Life Questionaire EurQoL		possible COI
Lonsdale 2017	Low Back Pain	NR	Cluster RCT	131	44.11 (12.96)	73	NR	Physical therapy	Patient-practitioner relationship	INT	2	Global rating of improvement; Pain intensity; Physical functioning; Self-reported quality of life	24	Perception of Recovery Scale; NRS or NPRS ; European Quality of Life Questionaire EurQoL	government	one author declares possible COI
Martínez-Cervera 2017	Lateral Epicondylalgia	18	Parallel RCT	12	55.03 (8.09)	7	1	Manual therapies and manipulation	None	CON	2	Pain intensity; Physical functioning	1	VAS ; DASH	NR	state no conflict of interest
Martínez-Cervera 2017	Lateral Epicondylalgia	14.5	Parallel RCT	12	48.08 (11.25)	6	1	Manual therapies and manipulation	Patient's beliefs and characteristics	INT	2	Pain intensity; Physical functioning	1	VAS ; DASH	NR	state no conflict of

Author Year	Primary Musculoskeletal Condition	Duration Of Complaints (weeks)	Study Design	Population Enrolled (N)	Mean Age (Sd)	Female (N)	Intervention Duration (weeks)	Intervention Label	Enhancement Category	Group Label	Total Number Of Arms	Outcome	Follow-Up (weeks)	Scale Information	Study Funding	Competing Interest
																interest
Miyamoto 2021	Low Back Pain	345.67	Parallel RCT	74	47.2 (14.8)	38	2	Education	None	CON	3	Global rating of improvement; Pain intensity; Physical functioning	4.34; 26; 52	Global perceived effect	government	state no conflict of interest
Miyamoto 2021	Low Back Pain	368.28	Parallel RCT	74	46 (14.7)	46	2	Education	Patient-practitioner relationship	INT	3	Global rating of improvement; Pain intensity; Physical functioning	4.34; 26; 52	Global perceived effect	government	state no conflict of interest
Morral 2019	Plantar Heel Pain	57.7	Parallel RCT	45	48.27 (9.96)	15	3	Electrophysical agents	None	CON	3	Pain intensity; Physical functioning	4; 8; 17; 60	VAS - pain with the first weight-bearing step in the morning; VAS - pain during	NR	NR

Author Year	Primary Musculoskeletal Condition	Duration Of Complaints (weeks)	Study Design	Population Enrolled (N)	Mean Age (Sd)	Female (N)	Intervention Duration (weeks)	Intervention Label	Enhancement Category	Group Label	Total Number Of Arms	Outcome	Follow-Up (weeks)	Scale Information	Study Funding	Competing Interest
														the day; FFI		
Morral 2019	Plantar Heel Pain	65	Parallel RCT	45	52.51 (12.28)	27	3	Electrophysical agents	Treatment characteristics	INT	3	Pain intensity; Physical functioning	4; 8; 17; 60	VAS - pain with the first weight-bearing step in the morning; VAS - pain during the day; FFI	NR	NR
Sandal 2019	Hip and Knee Osteoarthritis	765	Parallel RCT	40	57.6 (9.8)	25	8	Exercise	None	CON	3	Global rating of improvement; Pain intensity; Physical functioning; Self-reported quality of life	8	Global Perceived Effect	government	state no conflict of interest
Sandal 2019	Hip and Knee Osteoarthritis	730	Parallel RCT	42	59.6 (10.9)	25	8	Exercise	Therapeutic setting/environment	INT	3	Global rating of improvement; Pain	8	Global Perceived Effect	government	state no conflict of

Author Year	Primary Musculoskeletal Condition	Duration Of Complaints (weeks)	Study Design	Population Enrolled (N)	Mean Age (Sd)	Female (N)	Intervention Duration (weeks)	Intervention Label	Enhancement Category	Group Label	Total Number Of Arms	Outcome	Follow-Up (weeks)	Scale Information	Study Funding	Competing Interest
												intensity; Physical functioning; Self-reported quality of life				interest
Vong 2011	Low Back Pain	221	Parallel RCT	38	45.1 (10.7)	26	8	Physical therapy	None	CON	2	Pain intensity; Physical functioning	8; 12	VAS	NR	state no conflict of interest
Vong 2011	Low Back Pain	180	Parallel RCT	38	44.6 (11.2)	22	8	Physical therapy	Patient-practitioner relationship	INT	2	Pain intensity; Physical functioning	8; 12	VAS	NR	state no conflict of interest

436 NR: Not reported.

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Table 2: Detailed description of enhancement categories

Author Year	Primary Musculoskeletal Condition	Intervention Label	Enhancement Category	Enhancement Description
Akbaba 2018	Rotator Cuff-related Shoulder Pain	Aids & devices—Orthotics, tapes, braces, collars, insoles and other support devices	Patient's beliefs and characteristics (e.g., medical history, illness and treatment beliefs, expectations, or prior experiences)	Group 3: Received standardized therapeutic kinesiotape application. Group 3 received verbal input that there is evidence of excellent effectiveness (positive).
Akbaba 2018	Rotator Cuff-related Shoulder Pain	Aids & devices—Orthotics, tapes, braces, collars, insoles and other support devices	None	Group 1: Received standardized therapeutic kinesiotape application. Group 1 received verbal input that there is no evidence that kinesiotaping is effective (nocebo). Group 2: Received standardized therapeutic kinesiotape application. Group 2 received neutral verbal input that there is limited evidence of effectiveness (neutral).
Barth 2021	Low Back Pain	Acupuncture	Patient's beliefs and characteristics (e.g., medical history, illness and treatment beliefs, expectations, or prior experiences)	Received standardized intervention consisting of 2 oral briefing sessions and written materials delivered by a single physician, followed by 2 booster emails after acupuncture sessions 3 and 6. Received minimal acupuncture for free (8 sessions, 2 times per week for 45 minutes) delivered by 3 specially trained treatment practitioners. Could use nonsteroidal anti-inflammatory drugs but were asked to document this in a medication diary. High expectation group, emphasis was placed on the clinically relevant difference between acupuncture and usual care (responder rates, 48%vs 27%) based on the findings of an earlier study.
Barth 2021	Low Back Pain	Acupuncture	None	Received standardized intervention consisting of 2 oral briefing sessions and written materials delivered by a single physician, followed by 2 booster emails after acupuncture sessions 3 and 6. Received minimal acupuncture for free (8 sessions, 2 times per week for 45 minutes)

Author Year	Primary Musculoskeletal Condition	Intervention Label	Enhancement Category	Enhancement Description
				delivered by 3 specially trained treatment practitioners. Could use nonsteroidal anti-inflammatory drugs but were asked to document this in a medication diary. Low expectation group, emphasis was placed on the small difference between acupuncture and sham acupuncture (responder rates, 48%vs 44%) based on the findings of an earlier study.
Fuentes 2014	Low Back Pain	Electrophysical agents	Patient-practitioner relationship (e.g., therapeutic alliance, trust, verbal or non-verbal communication, reassurance)	Group 1: Active IFC for 30 minutes with enhanced therapeutic interaction [During the first 10 minutes, each participant was questioned about his or her symptoms and lifestyle and about the cause of his or her condition. The therapeutic interaction was enhanced through verbal behaviors, including active listening (ie, repeating the patient's words, asking for clarifications), tone of voice, nonverbal behaviors (ie, eye contact, physical touch), and empathy (such as saying, "I can understand how difficult LBP must be for you."). This intervention model aimed to create an optimal patientclinician relationship. The therapist then stayed in the room during the entire treatment and during the measurement of outcomes. During this time, verbal interaction between the therapist and participant was encouraged. Finally, at the end of the session, few words of encouragement were given.]
Fuentes 2014	Low Back Pain	Electrophysical agents	None	Group 2: Active IFC for 30 minutes [The limited interaction included about 5 minutes during which the therapist introduced herself and explained the purpose of the treatment. In addition, participants were told that this was a "scientific study" in which the therapist had been instructed not to converse with participants.],

Author Year	Primary Musculoskeletal Condition	Intervention Label	Enhancement Category	Enhancement Description
				Group 3: Sham IFC with enhanced therapeutic interaction, Group 4: Sham IFC with limited therapeutic interaction
Kong 2018	Knee Osteoarthritis	Acupuncture	Patient's beliefs and characteristics (e.g., medical history, illness and treatment beliefs, expectations, or prior experiences)	Intervention Group (boosted acupuncture): 4 weeks acupuncture treatment (2 times/week for first 2 weeks, then 1 time/week for last 2 weeks) 13 study visits including baseline training, clinical assessment, fMRI scan sessions, acupuncture treatments, and clinical assessments (midpoint and final) Expectancy manipulation during fMRI scan sessions to enhance positive expectation of pain reduction with acupuncture treatment
Kong 2018	Knee Osteoarthritis	Acupuncture	None	Control Group 1 : (Standard Acupuncture Group) 4 weeks acupuncture treatment (2 times/week for first 2 weeks, then 1 time/week for last 2 weeks), 13 study visits including baseline training, clinical assessment, fMRI scan sessions, acupuncture treatments, and clinical assessments (midpoint and final), No expectancy manipulation, Control Group 2 (No treatment): 5 visits including baseline training, clinical assessment, fMRI scan sessions, midpoint assessment, and final assessment, No treatment
Lonsdale 2017	Low Back Pain	Physical therapy (otherwise not falling into specific treatment combination)	Patient-practitioner relationship (e.g., therapeutic alliance, trust, verbal or non-verbal communication, reassurance)	Group 1: one-hour refresher workshop on evidence-based physiotherapy care for chronic low back pain for physiotherapist + eight hours of communication skills training
Lonsdale 2017	Low Back Pain	Physical therapy (otherwise not falling into specific treatment combination)	None	Group 2: care was delivered by a physiotherapist who had completed a 1-hour workshop on evidence-based chronic low back pain management.

Author Year	Primary Musculoskeletal Condition	Intervention Label	Enhancement Category	Enhancement Description
Martínez-Cervera 2017	Lateral Epicondylalgia	Manual therapies and manipulation	Patient's beliefs and characteristics (e.g., medical history, illness and treatment beliefs, expectations, or prior experiences)	Group 1: Mobilization with movement + "The technique that you will receive is very effective for the treatment of lateral epicondylalgia, so we expect that it will reduce your perception of pain". (positive)
Martínez-Cervera 2017	Lateral Epicondylalgia	Manual therapies and manipulation	None	Group 2: Mobilization with movement + "The technique that you will receive is used to treat lateral epicondylalgia, but its effect in pain perception is unknown". (neutral)#
Miyamoto 2021	Low Back Pain	Education	Patient-practitioner relationship (e.g., therapeutic alliance, trust, verbal or non-verbal communication, reassurance)	Intervention Group: The education-plus-TA group received two 60-minute individual treatment sessions with structured sessions aimed at increasing TA and empathy, along with education intervention sessions related to return to daily activities, advice on coping with pain, and a clear explanation of signs and symptoms.
Miyamoto 2021	Low Back Pain	Education	None	Control Group 1 (Education-Only Group): Participants received the same education intervention sessions related to return to daily activities, advice on coping with pain, and a clear explanation of signs and symptoms, but without any emphasis on enhancing the quality of the patient-therapist relationship. Control Group 2 (No-Education Group): Participants received no intervention and were advised not to seek treatment in the first month after randomization.
Morral 2019	Plantar Heel Pain	Electrophysical agents	Treatment characteristics (e.g., continuity of care, labelling, visual cues, sham/dummy treatment, variations in touch or stimulus conditions)	Group 2: standard radial extracorporeal shock wave device modified to give a more sophisticated appearance

Author Year	Primary Musculoskeletal Condition	Intervention Label	Enhancement Category	Enhancement Description
Morral 2019	Plantar Heel Pain	Electrophysical agents	None	Group 1: standard radial extracorporeal shock wave device, Group 3: standard radial extracorporeal shock wave device modified to give a more austere and unattractive, low-tech appearance.
Sandal 2019	Other	Exercise	Therapeutic setting/environment (e.g., setting, layout, décor, interior design)	Group 1: NEMEX (Exercise programm) + Physically enhanced environment [The exercise environment is located in a newly built facility on the second floor and has a vista over a sport and recreational park. The room is a designated exercise room. It appears clean and new, with rubberised floors, smooth concrete walls. Decoration includes pictures of landscapes. It is equipped with state of the art exercise equipment.]
Sandal 2019	Other	Exercise	None	Group 2: NEMEX (Exercise Programm) + Standard environment [The exercise environment is marked by years of use and resembles many existing exercise facilities at hospitals and rehabilitation clinics. It is located in the basement of an older campus building and has no windows. Access through a series of staircases and dark hallways. The room appears used with polished wooden floors, wall bars, bare, unadorned concrete walls.] Group 3: Waitlist
Vong 2011	Low Back Pain	Physical therapy (otherwise not falling into specific treatment combination)	Patient-practitioner relationship (e.g., therapeutic alliance, trust, verbal or non-verbal communication, reassurance)	Group 1: Conventional PT [Ten 30-minute sessions in 8 weeks, Interferential Therapy, Exercise Program Home Exercise Program] + Treatment is with PT's that were specifically training in Motivational Enhancement Therapy (MET) [Motivational-Enhanced Therapy (MET) is a therapeutic approach that integrates motivational interviewing (MI) techniques and psychosocial

Author Year	Primary Musculoskeletal Condition	Intervention Label	Enhancement Category	Enhancement Description
				components to enhance patients' motivation to engage in treatment and make appropriate behavioral changes. Some of the key psychosocial factors relevant to the motivational approach include proxy efficacy, treatment expectancy, and working alliance.]
Vong 2011	Low Back Pain	Physical therapy (otherwise not falling into specific treatment combination)	None	Group 2: Conventional PT [Ten 30-minute sessions in 8 weeks, Interferential Therapy, Exercise Program Home Exercise Program]

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Table 3 - Results with GRADE ratings

Outcome	Analysis Timepoint	Number Of Trials	Trials Included In Analysis	Number Of Participants (Dropouts)	Estimate (MD/ SMD)	Prediction Interval (PI)	Tau	I^2	Final Grade Rating
Pain Intensity	immediate	2	Akbaba 2018; Fuentes 2014	125 (4)	MD: -7.99, 95%CI: [-77.46; 61.47]		7.02	0.82, 95%-CI: [0.23; 0.96]	Very Low,f,g
Pain Intensity	short-term	7	Barth 2021; Kong 2018; Martínez-Cervera 2017; Miyamoto 2021; Morral 2019; Sandal 2019; Vong 2011	719 (67)	MD: -1.77, 95%CI: [-8.71; 5.16]	95%-PI: [-19.51; 15.96]	6.29	0.69, 95%-CI: [0.32; 0.86]	Low,h
Pain Intensity	intermediate-term	5	Barth 2021; Lonsdale 2017; Miyamoto 2021; Morral 2019; Vong 2011	238 (22)	MD: -0.81, 95%CI: [-6; 4.38]	95%-PI: [-6.76; 5.14]	0.00	0.07, 95%-CI: [0; 0.81]	High
Pain Intensity	long-term	2	Miyamoto 2021; Morral 2019	616 (21)	MD: -0.49, 95%CI: [-6.37; 5.4]		0.00		High
Physical Function	immediate	1	Akbaba 2018	66 (7)	MD: 1.2, 95%-CI: [0.65; 1.75]				High
Physical Function	short-term	6	Kong 2018; Martínez-Cervera 2017; Miyamoto 2021; Morral 2019; Sandal 2019; Vong 2011	567 (67)	MD: -0.27, 95%-CI: [-1.02; 0.49]	95%-PI: [-2.04; 1.51]	0.57	0.68, 95%-CI: [0.25; 0.87]	Low,h
Physical Function	intermediate-term	4	Lonsdale 2017; Miyamoto 2021; Morral 2019; Vong 2011	238 (22)	MD: -0.1, 95%-CI: [-1.08; 0.88]		0.47	0.57, 95%-CI: [0; 0.86]	Moderate,e
Physical Function	long-term	2	Miyamoto 2021; Morral 2019	464 (21)	MD: -0.9, 95%-CI: [-8.32; 6.55]		0.73	0.78, 95%-CI: [0.02; 0.95]	Low,f
Global Rating of Change	short-term	2	Miyamoto 2021; Sandal 2019	148 (19)	SMD: 0.18, 95%-CI: [-2.16; 2.52]		0.16		Low,f

Outcome	Analysis Timepoint	Number Of Trials	Trials Included In Analysis	Number Of Participants (Dropouts)	Estimate (MD/ SMD)	Prediction Interval (PI)	Tau	I^2	Final Grade Rating
Global Rating of Change	intermediate-term	2	Lonsdale 2017; Miyamoto 2021	401 (64)	SMD: -0.13, 95%-CI: [-0.93; 0.67]		0.00		Low,f
Global Rating of Change	long-term	1	Miyamoto 2021	230 (12)	SMD: -0.39, 95%-CI: [-0.77; -0.01]				High
Quality of Life	short-term	2	Kong 2018; Sandal 2019	253 (46)	MD: 0.31, 95%-CI: [-37.64; 38.15]		3.67	0.74, 95%-CI: [0; 0.94]	Very Low a,f
Quality of Life	intermediate-term	1	Lonsdale 2017	126 (7)	MD: 1.43, 95%-CI: [-1.94; 4.79]				High

a or b : Downgraded by one or two levels due to risk of bias; c or d: Downgraded by one or two levels due to indirectness; e or f: Downgraded by one or two levels due to imprecision; g or h: Downgraded by one or two levels due to inconsistency; i or j Downgraded by one or two levels due to publication bias.

443 # Figures

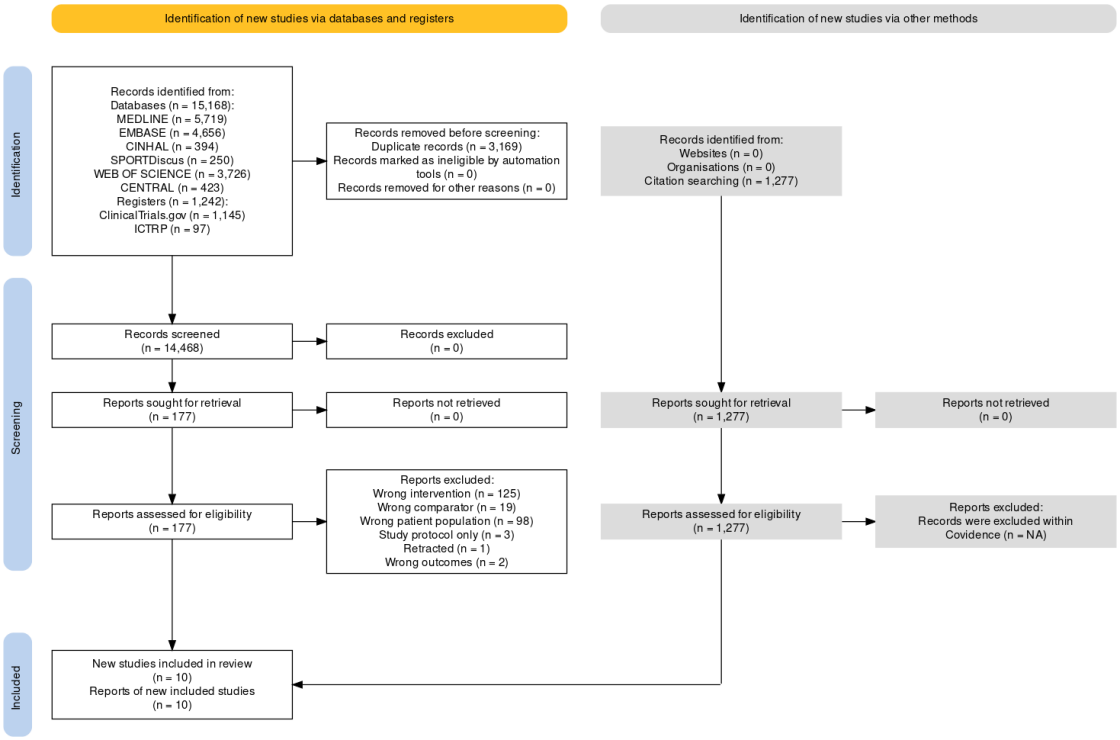

Figure 1: PRISMA Flow Chart

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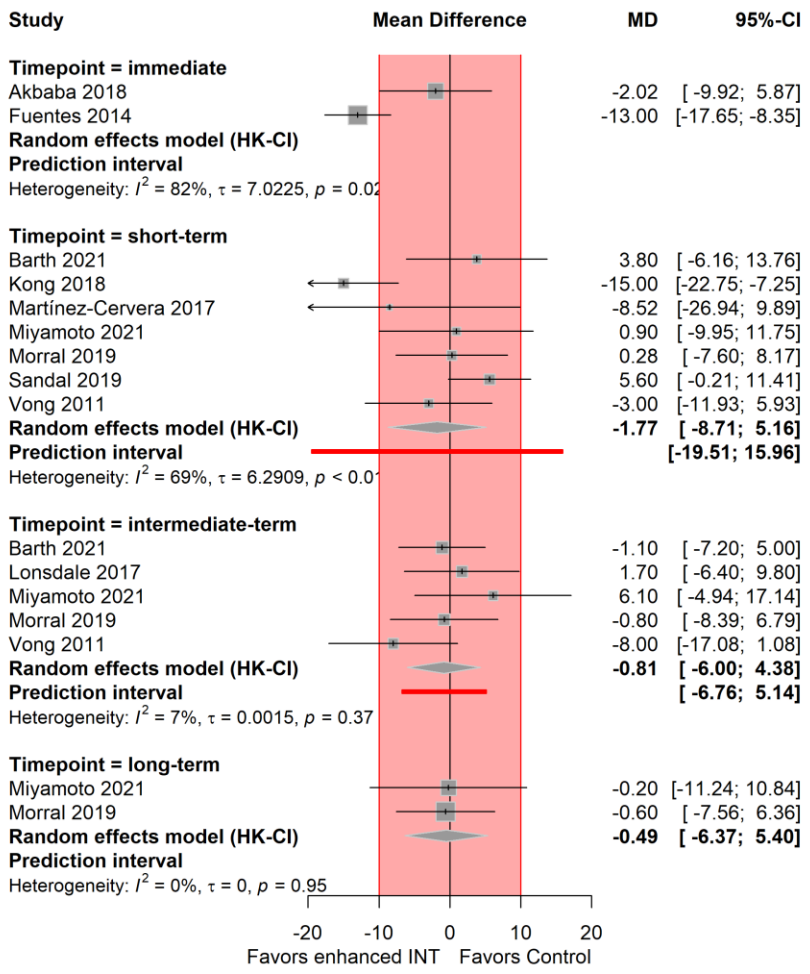

Figure 2: Forest Plot - Pain Intensity (0-100 scale), summary estimate for the time-point "immediate" not shown because of very wide CI, ([MD] : -7.99, 95%-CI: [-77.46; 61.47])

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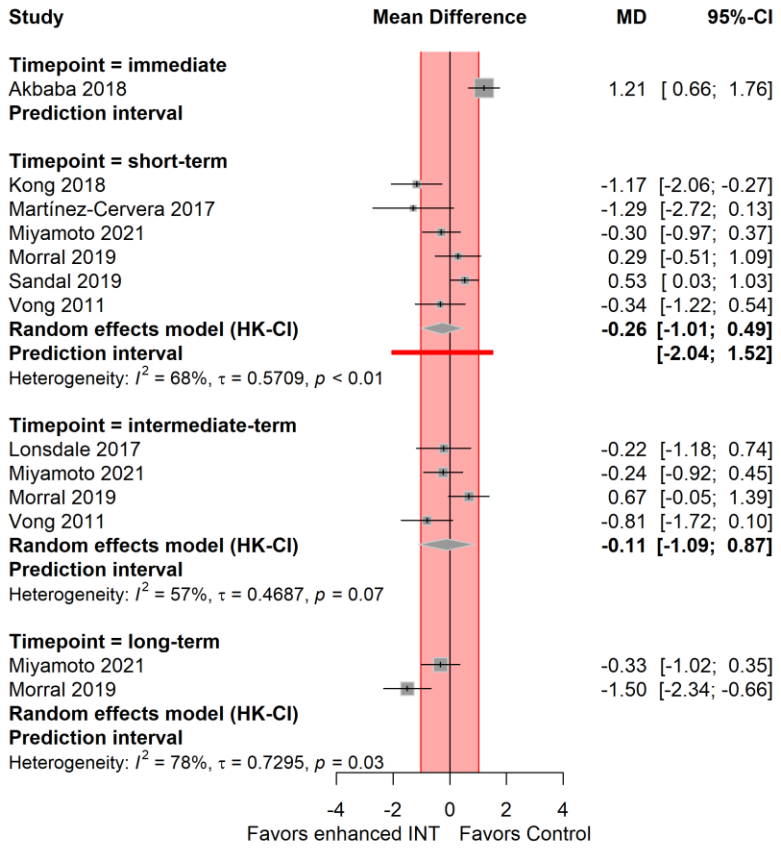

Figure 3: Forest Plot - Physical Function (0-10 scale), summary estimate for the time-point "long-term" not shown because of very wide CI, (MD: , 95%-CI: [;])

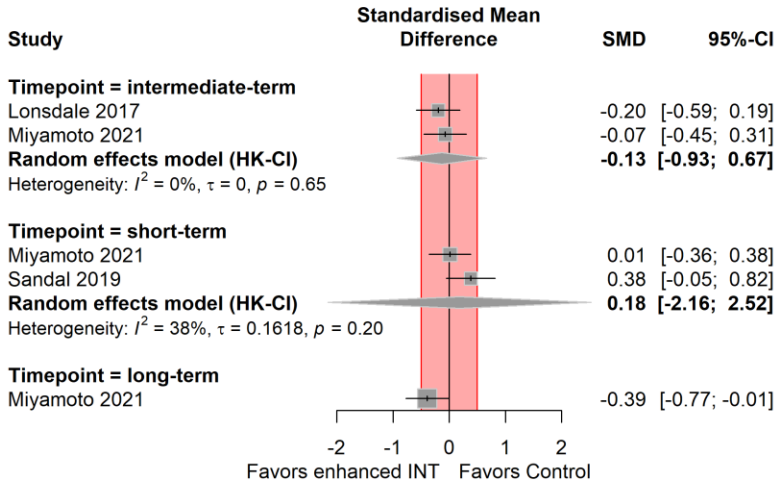

Figure 4: Forest Plot - Global Rating of Change (SMD scale)

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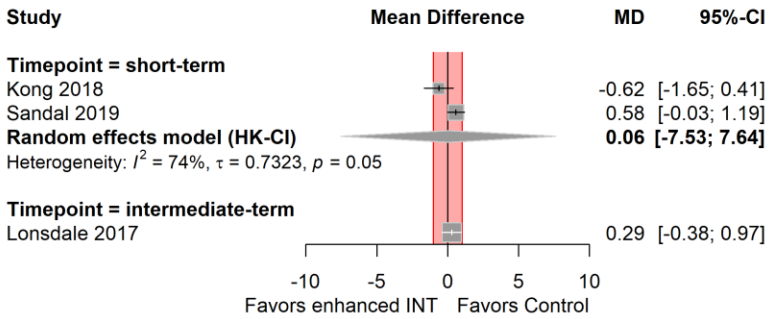

Figure 5: Forest Plot - Quality of Life (0-100 scale)

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