Pain sensitivity is reduced by exercise training : evidence from a systematic review and meta-analysis

Pain sensitivity is reduced by exercise training: Evidence from a systematic review and meta-analysis.

*Daniel L Belavy [1] PhD, Jessica Van Oosterwijck [2-5] PhD, Matthew Clarkson [6] PhD, Evy Dhondt [2,5] MSc, Niamh L Mundell [6] MAppSc(ExRehab), Clint T Miller [6] PhD, Patrick J Owen [1] PhD

[1] Deakin University, Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Geelong, Australia.

[2] Ghent University, SPINE Research Unit Ghent, Department of Rehabilitation Sciences, Faculty of Medicine and Health Sciences, Ghent, Belgium.

[3] University of Antwerp, Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, Belgium.

[4] Research Foundation – Flanders (FWO), Brussels, Belgium.

[5] Pain in Motion international research group, www.paininmotion.be

[6] Deakin University, School of Exercise and Nutrition Sciences, Geelong, Australia.

*Corresponding author: A/Prof Daniel L Belavy, PhD; Deakin University, Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, 221 Burwood Highway, Burwood, Victoria, 3125, Australia. Tel: +61 3 9244 6606; Fax: +61 3 9244 6017; E-mail: d.belavy@deakin.edu.au, belavy@gmail.com

Email addresses: belavy@gmail.com; d.belavy@deakin.edu.au; jessica.vanoosterwijck@ugent.be; matthew.c@deakin.edu.au; evyl.dhondt@ugent.be; niamh.mundell@deakin.edu.au; c.miller@deakin.edu.au; p.owen@deakin.edu.au

Highlights

- Exercise leads to increased pressure pain thresholds
- Exercise improves pain sensitivity more than non-exercise interventions
- Exercise effects are greater locally at the site of pain than at remote regions

Abstract

BELAVY, D. L., J. Van Oosterwijck, M. Clarkson, E. Dhondt, N. L. Mundell, C. Miller and P. J. Owen. NEUROSCI BIOBEHAV REV 21(1) XXX-XXX, 2020. Exercise training is capable of reducing pain in chronic pain syndromes, yet its mechanisms are less well established. One mechanism may be via the impact of exercise on increasing a person's pain threshold. Here we show, via meta-analysis of fifteen exercise training studies in pain syndromes that exercise training leads to increased pressure pain thresholds (low to moderate quality evidence). We also find low to moderate quality evidence exists that exercise training was more effective than non-exercise interventions, such as pain education, massage and stress management for improving pain sensitivity. Further, the effect of exercise was greater locally at the site of pain and less so at remote regions. These finding suggest that adaptations in central inhibition occur over time with exercise training and, more widely, add to the mechanistic understanding of how effective interventions can improve pain in chronic pain syndromes.

Keywords: chronic pain ; nociceptive ; hypersensitivity ; hyperalgesia ; randomized controlled trial ; movement

INTRODUCTION

Musculoskeletal conditions impose great societal and economic burden[1]. In the European Union, they have been estimated to cause an equivalent of two percentage point loss of gross domestic product[2]. Musculoskeletal pain (i.e. the tissue source of pain is muscle, ligament, tendon, joint, cartilage or discogenic) is driven by a number of factors[3], including, yet not limited to: nociceptive pain drivers, nervous system dysfunction, comorbidity drivers and cognitive-emotional drivers. In chronic pain, alterations in the normal processing of pain occur. For example, a meta-analysis[4] showed inhibition of pain via the experience of pain (conditioned pain modulation) is impaired in chronic pain. Evidence from another meta-analysis[5] found increased activation of specific brain regions (e.g. left putamin, right middle frontal gyrus and insula) in chronic pain. Meta-analyses have also shown that pain sensitization (i.e. a structural and sensory maladaptive response to stimuli) is present in chronic pain conditions such as knee osteoarthritis[6], with pressure pain thresholds being reduced both locally and remote to the site of pain[7]. Finally, an association exists between pain thresholds and reported pain and disability in spinal pain, albeit the correlation is weak[8,9].

Exercise training is an important and effective treatment strategy for managing pain and disability for adults with chronic pain conditions[10]. Exercise training can reduce pain in people with chronic pain conditions[11]. Whilst exercise training traditionally focused on improving, for example, strength and endurance, it is likely that the mechanism of action of exercise in improving chronic pain is not due to these musculoskeletal factors alone[12]. Factors such as self-efficacy, and central nervous system adaptation likely play a role. Prior meta-analysis[13] provided evidence that a conservative treatment such as spinal manipulation is able to reduce pain sensitivity, at local as well as remote sites. We are not aware of similar meta-analytic review of the effect of exercise training on pain sensitivity.

Prior randomised controlled trials (RCTs) provided[14] evidence that exercise can reduce pain sensitivity. This study therefore aimed to systematically review, and conduct meta-analysis of, the literature to examine whether exercise training interventions used as a standalone conservative treatment were effective in reducing peripheral and/or central pain sensitisation compared to no exercise training or to other conservative, non-exercise training interventions. Our hypothesis was that exercise training would result in a decrease in pain sensitivity. Our secondary hypothesis was that exercise in localised (e.g. neck) pain would have a greater impact on pain sensitivity at the painful site, but not at remote regions.

METHODS

This review was completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15]. The review was registered prospectively with PROSPERO (CRD42019143478).

Information sources and search strategy

Six online databases (MEDLINE, SPORTDiscus, CINAHL, PsycINFO, EMBASE and CENTRAL) were electronically searched for research published from database inception to 22nd August 2019. The search terms and strategy can be found in Supplementary Table 1. The search strategy was developed on the basis of current guidelines for the design of systematic reviews, our prior experience with systematic reviews and input from content experts. The search had the following limits: MEDLINE (Nil), CINAHL (exclude MEDLINE records), SPORTDiscus (Nil), PyschINFO (Nil), EMBASE (exclude MEDLINE records) and CENTRAL (exclude MEDLINE and EMBASE records). Trial registrations (N=1760) in CENTRAL (i.e. where the author is a clinical trial registry) were removed prior to screening. To locate additional publication, we searched for previously published systematic reviews identified via the Cochrane Database of Systematic Reviews (search terms: peripheral central sensitisation exercise; limits: none) and GoogleScholar (search terms: 'systematic review' peripheral central sensitisation exercise; limits: previous 10 years) and the reference lists of the included studies were checked for potentially relevant articles.

Study selection

All results of the search were screened to exclude duplicates. Independent screening of the titles and abstracts of the remaining studies considering predetermined eligibility criteria was completed by two independent reviewers (MC and ED) who were blinded for each other's assessment. The full-text reports of articles which seemed eligible after this first screening, were screened once again using the previously mentioned inclusion and exclusion criteria. Any disagreements were adjudicated by PJO and discussed with project team if necessary.

Eligibility criteria

Inclusion criteria followed the Participants, Interventions, Comparators, Outcomes and Study design (PICOS) framework[15]. No restrictions based on participant (P) population, sex, or race were made. Similarly, no restriction on diseases state was made, allowing the inclusion of studies performed on pain-free population, as well as population suffering from pain disorders. Included interventions (I) prescribed exercise training alone (i.e. programs including one or more of the following exercise modes: resistance, stabilisation/motor control, Pilates, yoga, McKenzie, flexion, aerobic, water-based or stretching[16] without the addition of other treatments (e.g. massage, electrotherapies, cognitive behavioural therapy, pain education). Only studies which compared (C) an exercise training intervention to a no-intervention control or treatments that involved passive treatment by a therapist (e.g. manual therapy, chiropractic, passive physiotherapy, osteopathic, massage or acupuncture) and treatments that involved practitioner interaction only (e.g. general practitioner management, education or psychological interventions) were considered. Studies were required to include either an outcome (O) measure of peripheral pain sensitivity and/or central pain sensitivity. Peripheral sensitisation is an increase in localised nociceptor response to tissue damage, with reduced afferent threshold for conduction at the sensory neuron peripherally[17,18]. Central

sensitisation is defined as a dysfunctional enhancement in nociceptor responsiveness to either normal or subthreshold afferent input within the central nervous system (CNS), causing pain sensitivity which may be disproportionate to noxious, or innocuous stimuli[17]. Studies which measured the expression of peripheral and/or central sensitisation via quantitative sensory testing (QST) were included. Studies using additional measures of mechanisms contributing to central sensitization such as temporal summation of pain, spatial summation of pain, conditioned pain modulation, offset analgesia, exercise induced hypoalgesia, and/or the flexor withdrawal response were also included[17]. Studies that solely report the effects of exercise on self-report pain (e.g. VAS, NRS, pain questionnaires) were not eligible for study inclusion. In regard to the study design (S) only full text articles reports of analytical studies were considered for inclusion. Studies published in a peer-reviewed journal (i.e. grey literature excluded) with a parallel arm (individual- or cluster-designed) randomised controlled or clinical trial design were eligible. No restrictions were placed on language for inclusion.

Data collection and data items

Data extraction was completed by two independent assessors (MC and ED) and a Kappa statistic of 0.866 was achieved across all duplicate decisions, which signifies almost perfect agreement[19]. Extracted information included relevant publication information (i.e. author, title, year, journal), study design, number of participants, participant characteristics (e.g. population [e.g. pain free, chronic pain], age and sex, numbers), intervention details (e.g. duration, type, frequency) and outcome measures. Extracted outcome data were pre- and post-intervention mean and standard deviation (SD). Data presented as median (interquartile range) or alternate measures of variance were converted to mean and SD using established

formulae. Where data were presented as pre-intervention mean (SD) and mean (SD) change with intervention only, the pre intervention SD was utilised for the post-intervention mean based on Cochrane guidelines[20]. When data were presented in figures only, rather than numerical data within text, data were extracted by generating a screenshot, loading this in ImageJ (version 1.48v https://imagej.nih.gov/ij/) to then measure the length (in pixels) of the axes to calibrate, and then the length in pixels of the data points of interest[21]. In all instances where data required for meta-analysis were not available, authors were contacted a minimum of three times over a four-week period to request the information. Similarity between extracted data from the two independent assessors (MC and ED) was evaluated through Covidence (Veritas Health Innovation, Melbourne, Australia; https://www.covidence.org). Any discrepancies were discussed by MC and ED with disagreements adjudicated by PJO similarly as described in the section study selection.

Risk of bias in individual studies

The Cochrane Collaboration Risk of Bias Tool[22] was used to examine potential selection bias (random sequence generation and allocation concealment), performance bias (blinding of patients and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias. This assessment was completed independently by MC and ED. Studies were classified as having a low, high or unclear (when reporting was not adequate to rate a specific domain) risk for each type of bias. In line with previous work[16], participant blinding is not feasible in exercise training studies and thus participant blinding was rated as having a high risk of bias for all studies, unless an RCT explicitly implemented a sham-exercise treatment with blinding of participants. Any disagreements for the risk of bias were adjudicated by PJO.

Synthesis of results

The evidence synthesis for this review was conducted in accordance with, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines[23].

Statistical analysis

Pairwise random-effects meta-analysis was conducted in Stata 16.0 (Stata Corp, College Station TX, USA). As all outcomes of interest were continuous, yet possibly subject to small sample bias, Hedges' g, rather than Cohen's d, was used as the effect estimate[24]. In line with Cochrane guidelines, individual study groups were pooled when a study investigated multiple groups defined as exercise training to avoid overlapping samples[20]. The main analysis investigated pooled exercise training versus non-exercise comparators on pain sensitivity. Sub-group analyses were performed for: (1) exercise training vs non-exercise treatment interventions (i.e. excluding no intervention ['true' control] or wait-list control), (2) resistance exercise training, (3) aerobic exercise training, (4) multimodal exercise training, (5) fibromyalgia populations with widespread pain, and (6) neck/upper quadrant pain populations. Heterogeneity was assessed for all pairwise comparisons via the I^2 statistic[20] and publication bias via visual inspection of funnel plots in addition to calculating P-value of Egger's test. An alpha level of 0.05 was taken for statistical significance. Sensitivity meta-regressions were performed for: (1) participant baseline pain intensity, (2) participate baseline age, (3) intervention frequency (days/week), (4) intervention duration (weeks), (5) weekly training load (frequency [day/week] x session duration [minutes]), and (6) total training load (weekly training load [minutes/week] x study duration [weeks]). Subsequent sub-group

analyses were performed for participant baseline pain intensity and age. Outlier analyses were performed in R (www.r-project.org) using the packages 'meta' and 'dmetar'.

RESULTS

Study selection

A summary of the systematic review process is shown in Figure 1. There were 3,435 studies (after removal of 590 duplicates) included in initial title and abstract screening. Following the completion of the title and abstract screening there were 49 studies included in the full-text screening. The examination of full-texts resulted in 31 studies being excluded (Supplementary Table 2) and 18 studies[25–42] being included for qualitative analysis (Supplementary Table 3). Of these, 15 studies were eligible for meta-analysis[25,27–33,35,37–42]; three studies[26,34,36] could not be included in quantitative synthesis as the end intervention SD was not available and the contacted authors could not provide data. For one study[31], data were extracted from an image.

Study characteristics

The details of each included study (n=18; participants n=1,121)[25–40] are shown in Supplementary Table 3. The sample size of individual groups in the included studies varied from 9 to 64 participants and mean age ranged from 25 to 60 years. The length of intervention ranged from 4 to 16 weeks. Of the included studies, one[26] investigated healthy populations, eight[27,28,32,35,37,38,40,42] examined fibromyalgia, seven studied upper quadrant pain (three[29,30,34] with neck pain, three[25,36,39] with neck and shoulder pain, one[31] with trapezius muscle pain), one[41] assessed type 2 diabetes and one[33] included people with Achilles tendon pain.

Considering the exercise interventions trialled, nine studies[25–27,30,31,33,36,39,42] implemented a form of resistance exercise training, seven studies[26,29,31,32,35–37] implemented aerobic exercise training, five studies[26,34,38,40,41] implemented a group with more than one mode of exercise training, one study[28] implemented Pilates exercise training, one study[27] examined stretching exercise training and one study[36] a form of balance and proprioception/sensorimotor exercise training.

Considering the control interventions, seven studies[25,26,29,34,38,41,42] implemented true control (i.e. no intervention), three studies implemented education[30,31,39], one implemented hyperbaric oxygen therapy[42] and two implemented massage[28,33]. Two studies each implemented usual care[27,35] and stress management[35,36]. One study each implemented placebo transcutaneous electrical nerve stimulation (TENS[32]), monthly group meetings[37] or non-exercise based pool therapy[40]. All studies examined pressure-pain thresholds or a related form of testing (e.g. 'algometric score'[40] or dolorimetry[35,37]).

Risk of bias within individual studies

A summary of the risk of bias assessment for each study is shown in Supplementary Table 4. When examining the studies overall, there was low risk of bias (Figure 2) for random sequence generation for 61% of studies, allocation concealment for 56% of studies, 0% of studies for blinding of patients and personnel (a known limitation of exercise-based interventions), 44% for blinding of outcome assessment, 67% for incomplete outcome data, 89% for selective outcome reporting and 100% for other bias. In our pre-planned methodology we did not include blinding of patients and personnel in the overall assessment

of risk of bias; therefore, four of 18[30,33,37,42] included studies were considered low risk of bias on all of the remaining domains.

Quantitative analysis

Fifteen studies (n=926) were eligible for quantitative analysis[25,27–33,35,37–40]. The primary pairwise meta-analysis (exercise [all] versus control [all]), showed that exercise training was effective for reducing pain sensitivity (increasing pressure pain thresholds; g[95%CI]: 0.551[0.222, 0.879], P=0.001, I^2=80.7%, studies: n=15; Figure 3; Table 1). There was no evidence of publication bias within the comparison (P=0.680; Supplementary Figure 1). The overall GRADE quality was considered low (Table 1). When comparing exercise training (all) to comparators where a non-exercise treatment/intervention was performed, there was a significantly greater impact of exercise training (g[95%CI]: 0.603[0.159, 1.046], P=0.008, I^2=86.6%, studies: n=10, GRADE: low; Figure 3; Table 1). Moreover, exercise training (all) compared to control (all) was effective for reducing pain sensitivity in people with fibromyalgia (g[95%CI]: 0.551[0.098, 1.004], P=0.017, I^2=79.7%, studies: n=8, GRADE: very low) and neck/upper quadrant pain (g[95%CI]: 0.666[0.014, 1.1317], P=0.045, I^2=87.3%, studies: n=5, GRADE: low; Table 1; Supplementary Figure 2). The effect sizes of resistance, aerobic and multimodal exercise training did not reach statistical significance (Table 1; Supplementary Figure 2).

Three studies[25,31,39] investigated populations with pain in a specific region (neck/upper quadrant; n=267) and assessed pain sensitivity locally (trapezius) and remotely (tibialis anterior). Whilst the effect size of exercise training on pain sensitivity was larger in magnitude local to the pain region than remotely (g[95%CI]: 0.429[0.173, 0.686] versus

0.245[-0.090, 0.580]), the effects were statistically significant at the local site (P=0.001), yet not the remote site (P=0.151; Table 2).

Two studies, Sencan et al. [32] and Li et al. [30], did not state what kind of measure of spread was presented in their results sections. Notably, these two studies showed the greatest effect sizes (2.21 and 1.97 respectively) of all included studies. Contacting the authors did not yield further information for Sencan et al. [32] but Li et al. [30] responded that the measure of spread presented was the standard deviation. Outlier analysis (Supplementary Figure 3) indicated that Sencan et al. [32] and Li et al. [30] were potential outliers. We repeated the analyses presented in Table 1 excluding these two studies (see Supplementary Table 5). With these studies excluded, the main findings remained, albeit with smaller effect size estimates, but lower heterogeneity and GRADE improved to 'moderate' (exercise versus all types of control g[95%CI]: 0.344[0.196-0.492], P=0.001, I^2=0.0%, studies: n=13, GRADE: moderate; exercise versus non-exercise treatment/intervention g[95%CI]: 0.316[0.133-0.499], P<0.001, I^2=10.7%, studies: n=9, GRADE: moderate).

Exploratory meta-regressions for participant and exercise intervention features were performed to investigate heterogeneity (Supplementary Table 6). Sub-group meta-analyses were conducted for age (Supplementary Figure 4) and intervention duration (Supplementary Figure 5) given these moderators may contribute to the heterogeneity observed.

DISCUSSION

This systematic review and meta-analysis found that exercise training may be effective for reducing pain sensitivity when compared to non-exercise training comparators. This effect persisted when compared to treatments that involved practitioner interaction only without exercise. Further, exercise was also effective in fibromyalgia and in neck/shoulder pain. Notably, the evidence was low to very-low quality overall, as assessed by the GRADE criteria.

An acute bout of exercise (one session) is known to reduce pain sensitivity and increase pain thresholds in healthy people[11], yet in chronic pain populations, this effect is less consistent[43]. The current study adds that exercise training (i.e. exercise performed over a number of sessions) can result in a reduction of pain sensitivity (increased pressure pain thresholds). An acute bout of exercise may alter pain processing by increasing cerebral perfusion and cortical inhibition, moderating inflammatory and immune response to perceived or actual harm[12]. Chronic exercise training promotes central neuroplastic changes theorised to alter pain processing, while regional musculoskeletal adaptations can reduce pain by reducing associated dysfunction[12]. Multiple domains can contribute to pain and disability in pain conditions[3]: beyond pain sensitivity and other CNS adaptations (e.g. brain network alterations), tissue damage and mental health status (e.g. depressive symptoms, reduced self-efficacy) can play a role. Further, fear-avoidance behaviors can lead to physical deconditioning, reduced self-efficacy and a sedentary lifestyle, further exacerbating the likelihood of continued pain[44,45]. Prior meta-analysis has shown that exercise can improve mental health status[46] and that physical therapy can effect a slight improvement in central sensitization related variables[47]. A systematic review concluded, based on two non-

randomised studies, that there was preliminary evidence of brain adaptation with exercise in people with pain syndromes[48]. Overall, whilst we show exercise impacts on pain sensitivity, it can also impact on other domains of the pain experience.

Three studies[25,31,39] assessed pain sensitivity changes over time in response to exercise training local to the pain region and remote to it. Our analysis showed that the effect size of pain sensitivity locally to the pain region was larger in magnitude than remote regions, and only the effects locally were statistically significant (very low quality evidence). This finding was in studies[25,31,39] of people with upper quadrant pain where the exercises were performed targeted the same region. This may suggest that possible adaptations in central inhibition may occur over time with exercise training, however there are currently no studies to our knowledge to have evaluated this type of training response. Cross sectional studies do show that athletes who perform strenuous exercise training have increased conditioned pain modulation when compared to non-athletes[49,50]. The three studies included in this review performed resistance training to volitional fatigue which can generate temporary fatigue-related muscle discomfort at the end of each set. However, the training stimulus in these studies are unlikely to compare to the exercise training methods commonly performed by athletes. It remains unclear whether conditioned pain modulation and CNS adaptations in response to an exercise program in people with chronic pain are possible. Further research to understand the CNS mechanisms of pain sensitivity in response to exercise training in populations with chronic pain are required.

The current study found that, in comparison to non-exercise treatments (i.e. where an intervention other than exercise was provided), the effect size favoured exercise. On face value, this implies that exercise training may be better for reducing pain sensitivity than non-

exercise treatments. However, the quality of evidence was low according to GRADE criteria. Also, various non-exercise interventions were included as comparators for the analysis, including 'education'. Often 'education' is used as a control group where participants do not receive the primary intervention and are aware of this[51]; potentially influencing outcomes[52]. Further higher quality studies are needed with rigorous comparator interventions (e.g. cognitive behaviour therapy versus exercise training) to determine whether exercise is indeed superior to non-exercise interventions for reducing pain sensitivity.

Our findings suggest that, in clinical application, exercise training could be preferenced as a therapeutic tool to reduce pain sensitivity over passive modalities. However, the optimal exercise prescription required to achieve reductions in pain sensitivity is unclear. Interventions ranged between 4-16 weeks in duration, nine studies[25–27,30,31,33,37–39] described prescription parameters (frequency, intensity, duration, modality and progression), whereas seven studies[28,29,32,34–36,40] omitted at least one of these variables. One study[36] reported habitual physical activity levels extraneous to the intervention. Further work is needed to identify appropriate exercise prescription variables (e.g. duration of intervention, frequency of exercise, and frequency of practitioner contact) for improving pain sensitivity in chronic pain populations.

It is appropriate to consider the strengths and limitations of the current work. One strength is that we focussed solely on exercise training to understand its effect on pain sensitivity. This is important as systematic reviews evaluating exercise may sometimes include studies which mix non-exercise interventions in with exercise. This may mask the true effect of 'exercise' by confounding it with other intervention forms. It is a strength of the current work that all studies examined pressure pain sensitivity or a closely related measure (e.g. algometric

score); reducing the heterogeneity of the outcomes examined. In terms of limitations, no RCTs assessed heat, electrical or chemical sensitivity. We also noted that no studies examined underlying mechanisms such as conditioned pain modulation or the nociceptive flexion reflex; such examinations would give deeper insight. Thus, these domains could not be included in the current meta-analysis and limit our ability to comment on the effect of exercise on these aspects of pain sensitivity. Further, we assessed control interventions that were either 'no intervention' control, or conservative interventions existing of passive treatment by a therapist, or treatments that involved practitioner interaction only (e.g. general practitioner management, education or psychological interventions). Consequently, interventions with medication or surgery were not included as comparators. Therefore, our analysis cannot comment on efficacy of exercise training versus analgesic or psychoactive medications. Notably, we did not exclude studies that examined pain sensitivity as a secondary outcome; hence, individual studies included in our analyses may have not achieved adequate statistical power to detect an effect. Heterogeneity was high and subsequent sensitivity analyses suggest that whilst exercise duration and participant age may play a role in heterogeneity, it is more likely that two studies [30,32], which by coincidence did not state in the original publication what kind of measure of spread they reported, were responsible for this heterogeneity. This further underscores the need for consistent reporting of studies. Importantly, there were few RCTs of low risk of bias and the overall quality of the evidence according to GRADE criteria was low.

In conclusion, the results of this systematic review and meta-analysis provided low to very low quality evidence that exercise training alone may be an effective treatment for reducing pain sensitivity in adults, as well as those with fibromyalgia or neck/upper quadrant pain specifically. Furthermore, there was low quality evidence that exercise training was more

effective than non-exercise treatments for reducing pain sensitivity. Few studies with low risk of bias is a limitation. To better understand the mechanism of effect of exercise training on pain and disability, and thus guide treatment prescription, in patient populations, future RCTs should consider assessing multiple domains that contribute to the pain experience and consider implementing rigorous non-exercise interventions using rigorous, low risk of bias, designs.

Funding:

Jessica Van Oosterwijck was funded by the Research Foundation – Flanders [grant number 12L5616N]. No other funding was received for the conduct of this work.

Acknowledgments:

The authors thank Associate Professor of Biostatistics Steven J Bowe (Deakin Biostatistics Unit) for advice on the 'meta' command within Stata and Tobias Saueressig for assistance with the outlier analysis.

REFERENCES

1. Briggs, A. M. *et al.* Reducing the global burden of musculoskeletal conditions. *Bull World Health Organ* 96, 366–368 (2018).
2. Bevan, S. Economic impact of musculoskeletal disorders (MSDs) on work in Europe. *Best Pr. Res Clin Rheumatol* 29, 356–373 (2015).
3. Tousignant-Laflamme, Y., Martel, M. O., Joshi, A. B. & Cook, C. E. Rehabilitation management of low back pain - it's time to pull it all together! *J. Pain Res.* 10, 2373–2385 (2017).
4. Lewis, G. N., Rice, D. A. & McNair, P. J. Conditioned Pain Modulation in Populations With Chronic Pain: A Systematic Review and Meta-Analysis. *J. Pain* 13, 936–944 (2012).
5. Tanasescu, R., Cottam, W. J., Condon, L., Tench, C. R. & Auer, D. P. Functional reorganisation in chronic pain and neural correlates of pain sensitisation: A coordinate based meta-analysis of 266 cutaneous pain fMRI studies. *Neurosci. Biobehav. Rev.* 68, 120–133 (2016).
6. Fingleton, C., Smart, K., Moloney, N., Fullen, B. M. & Doody, C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 23, 1043–1056 (2015).
7. Suokas, A. K. *et al.* Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 20, 1075–1085 (2012).
8. den Bandt, H. L. *et al.* Pain Mechanisms in Low Back Pain: A Systematic Review With Meta-analysis of Mechanical Quantitative Sensory Testing Outcomes in People With Nonspecific Low Back Pain. *J. Orthop. Sports Phys. Ther.* 49, 698–715 (2019).

9. Hübscher, M. *et al.* Relationship between quantitative sensory testing and pain or disability in people with spinal pain—A systematic review and meta-analysis: *Pain* 154, 1497–1504 (2013).
10. Ambrose, K. R. & Golightly, Y. M. Physical exercise as non-pharmacological treatment of chronic pain: Why and when. *Best Pract. Res. Clin. Rheumatol.* 29, 120–130 (2015).
11. Naugle, K. M., Fillingim, R. B. & Riley, J. L. A Meta-Analytic Review of the Hypoalgesic Effects of Exercise. *J. Pain* 13, 1139–1150 (2012).
12. Sluka, K. A., Frey-Law, L. & Hoeger Bement, M. Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. *Pain* 159 Suppl 1, S91–S97 (2018).
13. Coronado, R. A. *et al.* Changes in pain sensitivity following spinal manipulation: A systematic review and meta-analysis. *J. Electromyogr. Kinesiol.* 22, 752–767 (2012).
14. Henriksen, M. *et al.* Association of Exercise Therapy and Reduction of Pain Sensitivity in Patients With Knee Osteoarthritis: A Randomized Controlled Trial: Effects of Exercise on Pressure-Pain Sensitivity in Knee OA. *Arthritis Care Res.* 66, 1836–1843 (2014).
15. Liberati, A. *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J. Clin. Epidemiol.* 62, e1-34 (2009).
16. Owen, P. J. *et al.* Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis. *Br. J. Sports Med.* in press (2019) doi:10.1136/bjsports-2019-100886.
17. Latremoliere, A. & Woolf, C. J. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J. Pain* 10, 895–926 (2009).
18. Gangadharan, V. & Kuner, R. Pain hypersensitivity mechanisms at a glance. *Dis. Model. Mech.* 6, 889–895 (2013).

19. McHugh, M. L. Interrater reliability: the kappa statistic. *Biochem. Medica* 22, 276–82 (2012).

20. *Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019).* (Cochrane, 2019).

21. Vucic, K., Jelicic Kadic, A. & Puljak, L. Survey of Cochrane protocols found methods for data extraction from figures not mentioned or unclear. *J. Clin. Epidemiol.* 68, 1161–1164 (2015).

22. Higgins, J. *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343, d5928 (2011).

23. Guyatt, G. *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J. Clin. Epidemiol.* 64, 383–394 (2011).

24. Borenstein, M., Hedges, L. V., Higgins, J. P. T. & Rothstein, H. R. *Introduction to meta-analysis*. (John Wiley & Sons, 2011).

25. Andersen, C. H., Andersen, L. L., Zebis, M. K. & Sjøgaard, G. Effect of scapular function training on chronic pain in the neck/shoulder region: a randomized controlled trial. *J. Occup. Rehabil.* 24, 316–324 (2014).

26. Anshel, M. H. & Russell, K. G. Effect of aerobic and strength training on pain tolerance, pain appraisal and mood of unfit males as a function of pain location. *J. Sports Sci.* 12, 535–547 (1994).

27. Assumpção, A. *et al.* Muscle stretching exercises and resistance training in fibromyalgia: which is better? A three-arm randomized controlled trial. *Eur. J. Phys. Rehabil. Med.* 54, 663–670 (2018).

28. Ekici, G. *et al.* Effects of active/passive interventions on pain, anxiety, and quality of life in women with fibromyalgia: Randomized controlled pilot trial. *Women Health* 57, 88–107 (2017).

29. Kocur, P. *et al.* The effects of Nordic Walking training on selected upper-body muscle groups in female-office workers: A randomized trial. *Work Read. Mass* 56, 277–283 (2017).

30. Li, X. *et al.* Comparison of the effectiveness of resistance training in women with chronic computer-related neck pain: a randomized controlled study. *Int. Arch. Occup. Environ. Health* 90, 673–683 (2017).

31. Nielsen, P. K. *et al.* Effect of physical training on pain sensitivity and trapezius muscle morphology. *Muscle Nerve* 41, 836–844 (2010).

32. Sencan, S. *et al.* A study to compare the therapeutic efficacy of aerobic exercise and paroxetine in fibromyalgia syndrome. *J. Back Musculoskelet. Rehabil.* 17, 57–61 (2004).

33. Stefansson, S. H., Brandsson, S., Langberg, H. & Arnason, A. Using Pressure Massage for Achilles Tendinopathy: A Single-Blind, Randomized Controlled Trial Comparing a Novel Treatment Versus an Eccentric Exercise Protocol. *Orthop. J. Sports Med.* 7, 2325967119834284 (2019).

34. Takala, E. P., Viikari-Juntura, E. & Tynkkynen, E. M. Does group gymnastics at the workplace help in neck pain? A controlled study. *Scand. J. Rehabil. Med.* 26, 17–20 (1994).

35. Wigers, S. H., Stiles, T. C. & Vogel, P. A. Effects of aerobic exercise versus stress management treatment in fibromyalgia. A 4.5 year prospective study. *Scand. J. Rheumatol.* 25, 77–86 (1996).

36. Waling, K., Sundelin, G., Ahlgren, C. & Järvholm, B. Perceived pain before and after three exercise programs--a controlled clinical trial of women with work-related trapezius myalgia. *Pain* 85, 201–207 (2000).

37. Schachter, C. L., Busch, A. J., Peloso, P. M. & Sheppard, M. S. Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: a randomized controlled trial. *Phys. Ther.* 83, 340–358 (2003).

38. Munguía-Izquierdo, D. & Legaz-Arrese, A. Exercise in warm water decreases pain and improves cognitive function in middle-aged women with fibromyalgia. *Clin. Exp. Rheumatol.* 25, 823–830 (2007).

39. Andersen, L. L. *et al.* Central adaptation of pain perception in response to rehabilitation of musculoskeletal pain: randomized controlled trial. *Pain Physician* 15, 385–394 (2012).

40. Altan, L., Bingöl, U., Aykaç, M., Koç, Z. & Yurtkuran, M. Investigation of the effects of pool-based exercise on fibromyalgia syndrome. *Rheumatol. Int.* 24, 272–277 (2004).

41. Cox, E. R., Gajanand, T., Burton, N. W., Coombes, J. S. & Coombes, B. K. Effect of different exercise training intensities on musculoskeletal and neuropathic pain in inactive individuals with type 2 diabetes – Preliminary randomised controlled trial. *Diabetes Res Clin Pr.* 164, (2020).

42. Izquierdo-Alventosa, R. *et al.* Comparative study of the effectiveness of a low-pressure hyperbaric oxygen treatment and physical exercise in women with fibromyalgia: randomized clinical trial. *Ther Adv Musculoskal Dis* 12, 1–14 (2020).

43. Rice, D. *et al.* Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. *J. Pain* 20, 1249–1266 (2019).

44. Booth, J. *et al.* Exercise for chronic musculoskeletal pain: A biopsychosocial approach. *Musculoskeletal Care* 15, 413–421 (2017).

45. Leeuw, M. *et al.* The Fear-Avoidance Model of Musculoskeletal Pain: Current State of Scientific Evidence. *J. Behav. Med.* 30, 77–94 (2007).

46. Miller, K. J. *et al.* Comparative effectiveness of three exercise types to treat clinical depression in older adults: A systematic review and network meta-analysis of randomised controlled trials. *Ageing Res. Rev.* 58, 100999 (2020).

47. Arribas-Romano, A., Fernández-Carnero, J., Molina-Rueda, F., Angulo-Diaz-Parreño, S. & Navarro-Santana, M. J. Efficacy of Physical Therapy on Nociceptive Pain Processing Alterations in Patients with Chronic Musculoskeletal Pain: A Systematic Review and Meta-analysis. *Pain Med.* (2020) doi:10.1093/pm/pnz366.

48. Kregel, J. *et al.* Does Conservative Treatment Change the Brain in Patients with Chronic Musculoskeletal Pain? A Systematic Review. *Pain Physician* 20, 139–154 (2017).

49. Assa, T., Geva, N., Zarkh, Y. & Defrin, R. The type of sport matters: Pain perception of endurance athletes versus strength athletes. *Eur. J. Pain* 23, 686–696 (2019).

50. Flood, A., Waddington, G., Thompson, K. & Cathcart, S. Increased conditioned pain modulation in athletes. *J. Sports Sci.* 35, 1066–1072 (2017).

51. Ainpradub, K., Sitthipornvorakul, E., Janwantanakul, P. & van der Beek, A. J. Effect of education on non-specific neck and low back pain: A meta-analysis of randomized controlled trials. *Man. Ther.* 22, 31–41 (2016).

52. Hróbjartsson, A., Emanuelsson, F., Skou Thomsen, A. S., Hilden, J. & Brorson, S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *Int. J. Epidemiol.* 43, 1272–1283 (2014).

53. Lin, L. & Chu, H. Quantifying publication bias in meta-analysis. *Biometrics* 74, 785–794 (2018).

FIGURE TEXT

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram of the study screening process.

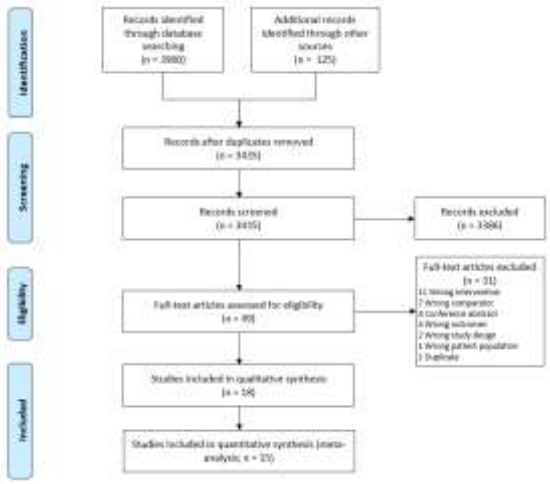


Figure 2. Percentage of studies examining the efficacy of exercise training for reducing pain sensitivity beliefs with low, unclear and high risk of bias for each aspect of the Cochrane Risk of Bias Tool (revised version). See Supplementary Table 4 for the assessment for each individual study. The use of exercise training makes it not possible to truly blind patients to treatment allocation, therefore, this was not considered in the overall risk of bias assessment of each study.

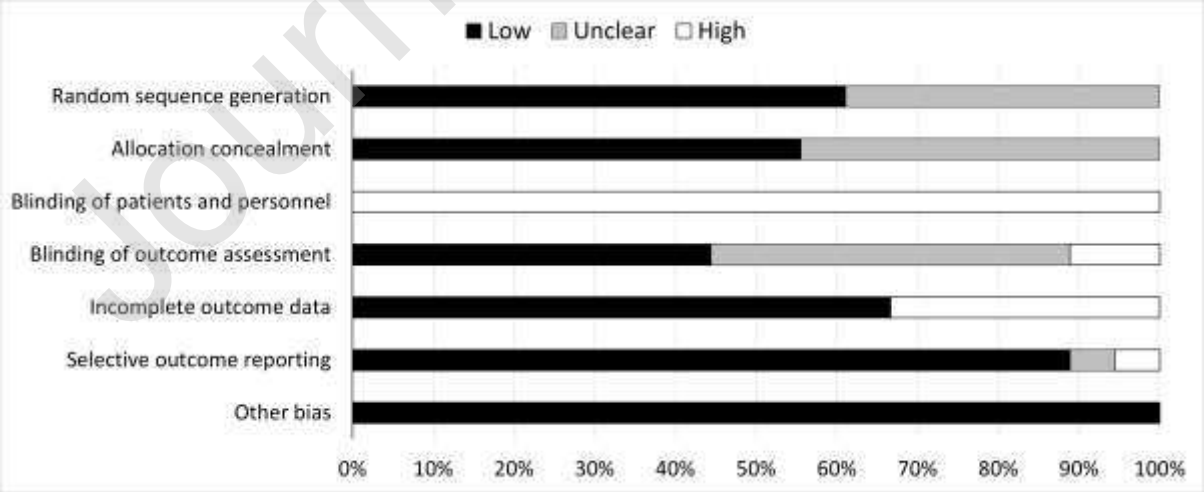


Figure 3. Forest plot for the meta-analyses investigating the effectiveness of exercise training versus all non-exercise comparators (top) and non-exercise treatments (bottom) for reducing pain sensitivity.

See also Table 1 for more detail. Funnel plots are presented in Supplementary Figure 1. Sencan et al. [32] and Li et al. [30], did not state what kind of measure of spread was presented and notably showed the greatest effect sizes. See also the outlier analysis presented in Supplementary Figure 3. Excluding these two studies from meta-analysis (see sensitivity analyses in Supplementary Table 5) did not impact the findings of the main meta-analyses, but yielded lower heterogeneity, higher GRADE and lower effect size estimates (see Results text for more detail).

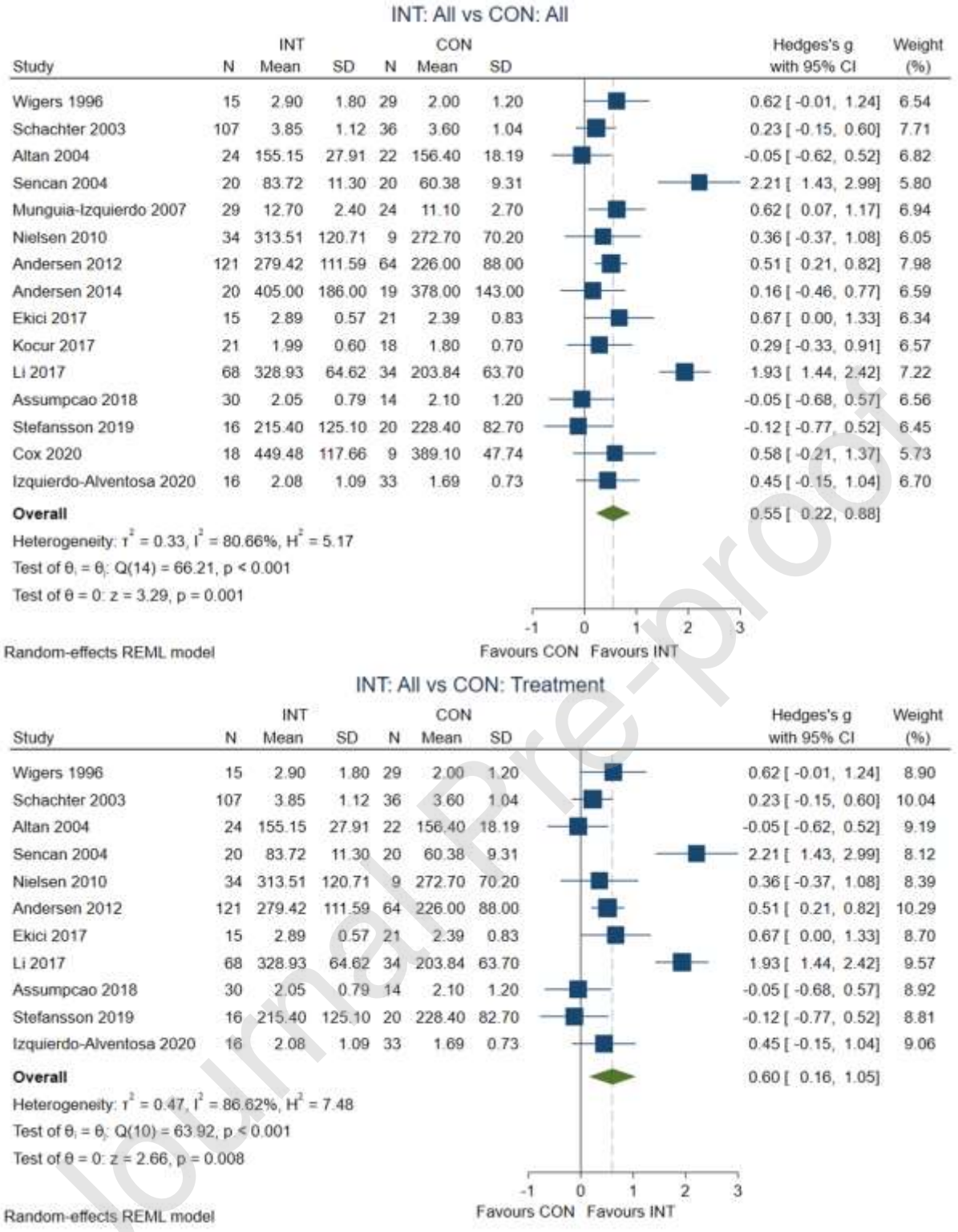
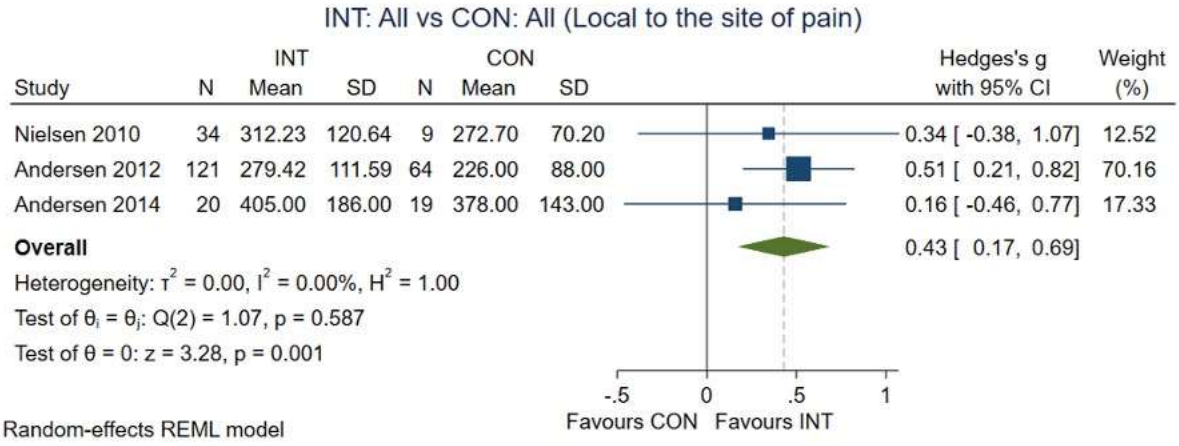


Figure 4. Forest plot for the meta-analyses investigating the effectiveness of exercise training on local (at site of pain; top) and remote (bottom) pain sensitivity.

See also Table 2 for more detail. Funnel plots are presented in Supplementary Figure 1.



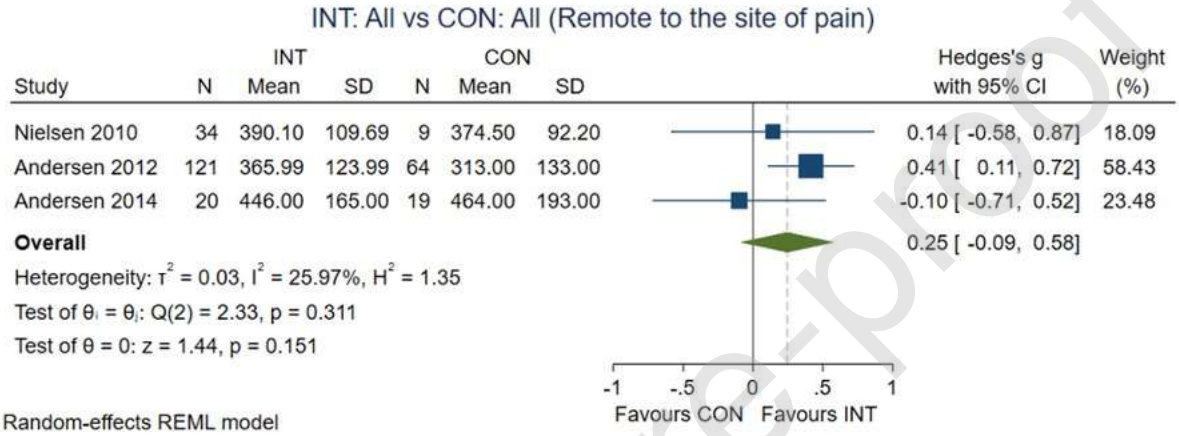


Table 1. Overview of results from meta-analyses

Group 1	Group 2	Studies	n	Hedges' g (95%CI)	P-value	I^2 (%)	Low ROB (%)	Egger's P	GRADE*
All studies[25,27–33,35,37–42]									
INT: All	CON: All	15	926	0.551 (0.222, 0.879)	**0.001**	80.7%	27%	0.680	Low (a, b)
INT: All	CON: Treatment	11	768	0.603 (0.159, 1.046)	**0.008**	86.6%	36%	0.607	Low (a, b)
INT: Resistance	CON: All	7	468	0.491 (-0.043, 1.024)	0.071	84.8%	43%	0.337	Low (a, b)
INT: Aerobic	CON: All	5	291	0.695 (-0.011, 1.402)	0.054	85.1%	20%	0.307	Very low (a, b, c)
INT: Multimodal	CON: All	5	235	0.270 (-0.019, 0.558)	0.068	12.5%	20%	0.815	Low (a, c)
Fibromyalgia only[27,28,32,35,37,38,40,42]									
INT: All	CON: All	8	455	0.551 (0.098, 1.004)	**0.017**	79.7%	25%	**0.047**	Very low (a, b, d)
Neck or upper quadrant pain only [25,29–31,39]									
INT: All	CON: All	5	408	0.666 (0.014, 1.317)	**0.045**	87.3%	20%	0.576	Low (a, b)

CON: control, INT: sole exercise training intervention, 95%CI: 95% Confidence Intervals, ROB: risk of bias (percentage of studies with low). All: all types of intervention or control; Treatment: where comparator groups involved treatment (i.e. excluding no-intervention control). Only clinical populations were included in the main meta-analyses as the one study[26] on healthy populations could not be included in quantitative synthesis due to missing standard deviation data. GRADE certainty ratings: very low- the true effect is likely markedly different from the estimated effect, low- the true effect might be markedly different from the estimated effect, moderate- the true effect is likely close to the estimated effect, high- the true effect is likely similar to the estimated effect. *a: certainty rated down one grade based on risk of bias, b: certainty rated down one grade based on inconsistency, c: certainty rated down

one grade based on imprecision, d: certainty rated down one grade based on publication bias. Egger's P was used for the assessment of publication bias[53].

Table 2: Meta-analysis of the effect of exercise on pain sensitivity local and remote to the site of pain.

Group 1	Group 2	Studies	n	SMD (95%CI)	P-value	I^2 (%)	Low ROB (%)	Egger's P	GRADE*
Local									
INT: All	CON: All	3	267	0.429 (0.173, 0.686)	**0.001**	0.0%	0%	0.381	Very low (a, b)
Remote									
INT: All	CON: All	3	267	0.245 (-0.090, 0.580)	0.151	26.0%	0%	0.182	Very low (a, b)

Three studies[25,31,39] examined neck/upper quadrant pain. Local site was at the trapezius muscle in all studies, remote site was tibialis anterior in all studies. Exercises performed targeted the upper quadrant. CON: control, INT: sole exercise training intervention, SMD: standardised mean difference, 95%CI: 95% Confidence Intervals, ROB: risk of bias (percentage of studies with low). *a: certainty rated down two grades based on risk of bias, b: certainty rated down one grade based on imprecision. Egger's P was used for the assessment of publication bias[53].