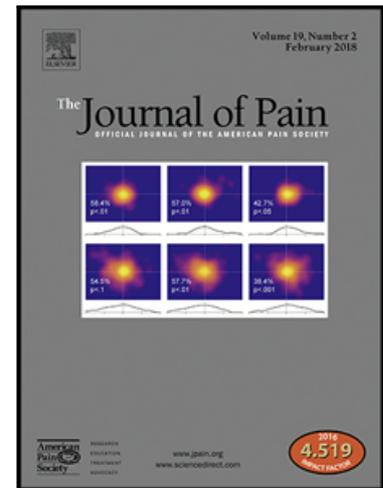


## Journal Pre-proof

Exercise-induced hypoalgesia in healthy individuals and people with chronic musculoskeletal pain: a systematic review and meta-analysis

Michael A. Wewege , Matthew D. Jones

PII: S1526-5900(20)30042-0  
DOI: <https://doi.org/10.1016/j.jpain.2020.04.003>  
Reference: YJPAI 3865



To appear in: *Journal of Pain*

Received date: 12 July 2019  
Revised date: 6 April 2020  
Accepted date: 26 April 2020

Please cite this article as: Michael A. Wewege , Matthew D. Jones , Exercise-induced hypoalgesia in healthy individuals and people with chronic musculoskeletal pain: a systematic review and meta-analysis, *Journal of Pain* (2020), doi: <https://doi.org/10.1016/j.jpain.2020.04.003>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© Published by Elsevier Inc. on behalf of United States Association for the Study of Pain, Inc.

Review Article

**Exercise-induced hypoalgesia in healthy individuals and people with chronic musculoskeletal pain: a systematic review and meta-analysis**

Michael A. Wewege<sup>a,b</sup>, Matthew D. Jones<sup>a,b</sup>

<sup>a</sup>School of Medical Sciences, University of New South Wales, Sydney, Australia

<sup>b</sup>Neuroscience Research Australia, Sydney, Australia

**Corresponding Author**

Dr Matthew Jones

School of Medical Sciences, University of New South Wales

Kensington 2052

Sydney, Australia

[matthew.jones@unsw.edu.au](mailto:matthew.jones@unsw.edu.au)

**Disclosures**

The authors declare no actual or potential conflicts of interest that could influence this work. Michael Wewege was supported by an Australian Government Research Training Program Scholarship and a University Postgraduate Award from the University of New South Wales.

## Abstract

Exercise-induced hypoalgesia (EIH) is a reduction in pain that occurs during or following exercise. Randomised controlled studies published from 1980 to January 2020 that examined experimentally induced pain before and during/following a single bout of exercise in healthy individuals or people with chronic musculoskeletal pain were systematically reviewed. Data were analysed using random-effects meta-analyses and studies were appraised using the Cochrane Risk of Bias tool and GRADE. 5829 records were screened, with 13 studies ultimately included. In healthy individuals, aerobic exercise caused large EIH (7 studies, 236 participants;  $g = -0.85 [-1.58, -0.13]$ ), dynamic resistance exercise caused small EIH (2 studies, 23 participants;  $g = -0.45 [-0.69, -0.22]$ ), and isometric exercise did not cause EIH (3 studies, 177 participants;  $g = -0.16 [-0.36, 0.05]$ ). In chronic musculoskeletal pain, isometric exercise did not cause EIH (3 studies, 114 participants;  $g = -0.41 [-1.08, 0.25]$ ); aerobic (0 studies) and dynamic resistance (1 study) exercise were not analysed. We conclude that, based on small studies with unclear risk of bias, aerobic and dynamic resistance exercise reduce experimental pain in healthy individuals. Further research is needed to determine whether EIH exists for experimental and clinical pain in people with chronic musculoskeletal pain.

**Registration:** PROSPERO ID: CRD42018085886.

**Perspective**

Based on low-quality data from small samples, a single bout of aerobic exercise reduces experimental pain in healthy individuals. The evidence is unclear in people with chronic musculoskeletal pain but warrants further investigation due to the limited number of studies in these populations.

**Keywords:** exercise-induced hypoalgesia; chronic musculoskeletal pain; pain threshold

**Highlights:**

- The effect of a single bout of exercise on experimental pain was meta-analysed
- Exercise had varying effects on reducing pain in healthy individuals
- Exercise did not reduce pain in people with chronic pain

## Introduction

Exercise-induced hypoalgesia (EIH) is a reduction in pain that occurs during or following a single bout of exercise. This phenomenon has been studied for almost 40 years with diverse methodology<sup>3,16</sup>. The magnitude of EIH appears to vary according to the modality, dose, and intensity of exercise performed<sup>23,24,32</sup>, the type of noxious stimulus used to evoke pain<sup>39</sup>, the method used to quantify pain (e.g. threshold, tolerance, rating)<sup>39</sup>, the site of pain assessment (e.g. over an exercised or non-exercised area and over bone or muscle)<sup>28,37,53</sup>, and the timing of pain assessment (e.g. during or following exercise)<sup>9,29,30</sup>. That is, EIH is usually greater after higher intensity exercise, when pain is assessed over an exercised site during or immediately following exercise, and when noxious pressure is used to induce pain. Other factors intrinsic to the participant such as their age<sup>40</sup>, sex<sup>13</sup>, and the presence and severity of chronic pain<sup>39,54,58</sup> can also influence EIH, whereby EIH is typically smaller or absent in those with pain.

Early narrative reviews<sup>31,32</sup> of EIH in humans concluded that a single bout of exercise causes a reduction in experimental pain in healthy individuals. In people with chronic pain however, where the effects of exercise training on pain are better established<sup>14,43</sup>, the effect of a single

bout of exercise on reducing pain is more variable and is frequently impaired<sup>39,44</sup>. To date, only one meta-analysis has investigated the effect of a single bout of exercise on pain in healthy individuals and people with chronic pain<sup>39</sup>. In healthy individuals, the hypoalgesic effects of aerobic exercise were small to moderate (Cohen's  $d = -0.41$  to  $-0.59$ ) and the hypoalgesic effects of isometric exercise ( $d = -0.72$  to  $-1.02$ ) and dynamic resistance exercise ( $d = -0.75$  to  $-0.83$ ) were moderate to large<sup>39</sup>. In people with chronic pain, effect sizes were highly variable within and across exercise modes ( $d = -0.43$  to  $1.92$ ), ranging from hypoalgesia to hyperalgesia (more pain). A limitation to this previous meta-analysis is that uncontrolled, single arm studies were included. This study design (e.g. single arm, within-group, pre-post design) is typical of the majority of the EIH literature, whereby experimentally induced pain is measured before and after a single bout of exercise without comparison to a control condition. This study design does not account for well-documented phenomena like regression to the mean, participant expectation, or habituation to the painful stimulus and is prone to bias<sup>6</sup>. Randomised trials are the preferred study design to establish the causal effect of an intervention because they attempt to remove systematic differences and confounding, which allows the investigator to attribute any difference in effect solely due to the intervention<sup>17</sup>.

Therefore, our aim was to investigate whether exercise causes a reduction in experimentally induced pain in healthy individuals and people with chronic musculoskeletal pain by comparing the effect of exercise to a non-exercise control condition.

## **Methods**

### ***Protocol, registration, and data availability***

A systematic review and meta-analysis of randomised controlled trials of EIH was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement<sup>38</sup>. The review was registered on PROSPERO on 6<sup>th</sup> February 2018 (ID: CRD42018085886). The data and analysis codes used in the meta-analyses are available on the Open Science Framework ([osf.io/73b6t](https://osf.io/73b6t)).

### ***Deviations from protocol***

This review originally included all studies of EIH that examined experimentally induced pain. However, on the advice of peers that the causal nature of EIH is best inferred from randomised controlled studies (crossover or parallel), we limited our review to these study designs. This necessitated a change in the risk of bias tool used, which was swapped from the Effective Practice Public Health Project quality assessment tool for quantitative studies to the Cochrane Risk of Bias tool for parallel

studies and an adapted version for crossover designs. The Grades of Recommendation, Assessment, Development and Evaluations (GRADE) approach was then used to grade the quality of the evidence<sup>15</sup>. We also updated our database search to include MEDLINE. We initially planned to pool data across exercise modes (e.g. calculate the aggregate effect of aerobic and resistance exercise) but again, on the advice of peers, analysis was instead only conducted within exercise modes. Each of these decisions restricted the *a priori* planned sub-analyses that were to be performed (e.g. the influence of age, sex, type and timing of pain assessment, and the effect of exercise type and intensity on EIH), none of which were subsequently done.

### ***Eligibility criteria***

*Population:* 1) apparently healthy individuals of any age or ethnicity free from current pain or chronic disease; or 2) individuals of any age or ethnicity with local or widespread chronic musculoskeletal pain. Studies that examined individuals with acute or sub-acute pain, or pain attributed to non-musculoskeletal pathologies (e.g. neuropathic pain or cancer-related pain), were excluded.

*Intervention:* A standardised single bout of exercise. Studies that did not adequately quantify the duration and intensity of exercise or used exercise in conjunction with another intervention (e.g. drugs, education,

electrical stimulation) were excluded. Studies where exercise was used to induce delayed-onset muscle soreness were also excluded.

*Comparator.* A control condition (e.g. quiet rest or sham exercise).

Appropriate control conditions were determined by consensus by the authors during study screening.

*Outcomes:* Sensitivity to experimentally induced pain measured using a quantitative sensory test (e.g. pressure pain threshold, cold pressor pain tolerance, heat pain intensity etc). Studies that quantified pain sensitivity using other methods (e.g. clinical pain or muscle pain during exercise) were excluded.

*Study design:* Crossover or parallel randomised controlled trials with pain assessed within 60 minutes prior to the start of exercise/control and again during exercise or within 60 minutes following exercise.

### ***Information sources***

The literature search was initially conducted on February 6<sup>th</sup>, 2018 and was updated on 28<sup>th</sup> January, 2020. Six electronic databases (Scopus, EMBASE, PsycINFO, CINAHL, SPORTDiscus, and MEDLINE) were searched from 1980 to the abovementioned dates using terms related to EIH. The full search strategy for Scopus is available in Supplementary Table 1. Searches were restricted to human studies published in English. Additional articles were identified through examining the

reference sections of published studies that met the inclusion criteria.

Results of the literature searches were uploaded into Endnote (EndNote X8, Thomson Reuters, NY, USA).

### ***Study selection***

Authors M.J. & M.W. independently screened each article via title and abstract for potential eligibility. The remaining studies were collated and the full text of each was independently screened by M.J. & M.W. for adherence to the eligibility criteria. Discrepancies were resolved via discussion.

### ***Data extraction and collation***

Data was extracted in duplicate by authors M.J. and M.W., with discrepancies resolved via discussion. Participant characteristics (healthy cohort: sample size, age, sex, number of dropouts; chronic pain cohort: sample size, age, sex, pain condition, duration and severity of symptoms, number of dropouts), exercise modality and dose (duration and intensity), control condition, and the method, site and, timing of pain assessment(s) for each included study were extracted into an electronic spreadsheet.

The primary outcome was the change in experimental pain following exercise compared to control, indicated by the pre- to during/post- mean difference and standard deviation (SD) of difference ( $SD_{diff}$ ). When available, these measures were extracted. The direction of the mean difference was adjusted, when necessary, so that a reduction in pain after exercise or control was signified by a *negative* effect. If the mean difference and  $SD_{diff}$  were not reported, the mean and SD at pre- and during/post- exercise or control were used to calculate them using formulae for paired-samples outlined by the Cochrane Handbook for Interventions<sup>22</sup> and Borenstein et al.<sup>4</sup>. We used a conservative paired-samples correlation of 0.85 for both exercise and control conditions, which was based on data from six published studies (range = 0.87 to 0.95 for exercise and 0.87 to 0.96 for rest)<sup>13,26,27,45,52,56</sup>.

To calculate Hedges'  $g$  for crossover designs, the mean difference and  $SD_{diff}$  for exercise and control, as well as the sample size and a correlation between related values for repeated measures, were entered<sup>4</sup>. Crossover correlation ( $r$ ) values were not reported in any included studies so they were estimated from previous studies from our group that utilised a similar design<sup>26,27</sup>. Both these studies observed strong correlations between post-rest and post-exercise values ( $r = 0.92$

and 0.97, respectively), while correlations between change scores were low ( $r = 0.24$  and  $0.33$ , respectively). Therefore, we conducted analyses with a range of  $r$  values (0.9, 0.5, 0). No correlation was required for parallel-group designs.

If no data were available, the study's corresponding author was emailed to request the data, with a second email sent two weeks later if no reply had been received. In the instances where authors did not respond, or when a response was received but the authors were unable to provide the data (e.g. due to the age of the data), the mean and SD were estimated from the study's figures using the data extraction software GRABIT (MATLAB version R2016b, MA, USA). This software enables the user to select specific points on a figure (e.g., the mean and error bars) and export them as numerical values based on their X and Y coordinates. Data extracted from GRABIT as mean (standard error), mean (95% confidence interval) and/or median (interquartile range) were converted to mean (SD) using standard equations<sup>21,59</sup>.

### ***Statistical analysis***

Meta-analyses were performed in R using the "metafor" package<sup>50,57</sup>. We conducted all analyses using a random-effects model and "restricted

maximum-likelihood estimator” method to calculate summary effect sizes (Hedges’ *g*) with 95% confidence intervals.

To ensure independence of observations, only one measure of EIH was taken from each mode of exercise per study to contribute to the primary meta-analysis. The measure to be taken was specified *a priori*, as follows:

- exercise dose – the highest dose of exercise was used;
- exercise intensity – the highest intensity of exercise was used;
- site of pain assessment – the most exercised site was used, determined by the authors as the site most likely to have performed the most work during exercise;
- noxious stimulus – pressure was the preferred method of pain induction. If pressure was not used, then other noxious stimuli were preferred in the following order: thermal heat, thermal cold, electrical, ischemic, chemical;
- method of pain assessment – pain threshold was the preferred method of pain assessment. If pain threshold was not measured, then other measures of pain were preferred in the following order: intensity, unpleasantness, tolerance, temporal summation, conditioned pain modulation, offset analgesia, evoked potentials;

- timing of pain assessment – the first post-exercise assessment of pain was used. If pain was assessed during but not following exercise, the pain assessment made closest to the end of exercise was used.

Effects from the meta-analysis were deemed negligible ( $< 0.2$ ), small ( $0.2-0.49$ ), moderate ( $0.5-0.79$ ) or large ( $\geq 0.8$ ). Heterogeneity was quantified using the  $I^2$  statistic and was deemed small ( $< 25\%$ ) moderate ( $25\%-74\%$ ) or large ( $\geq 75\%$ ). The threshold for statistical significance was set at  $p < 0.05$ . Publication bias was assessed using contour-enhanced funnel plots and Egger's regression test.<sup>10</sup> The threshold for statistically significant asymmetry was set at  $p < 0.2$ .<sup>19</sup>

### ***Risk of bias***

Risk of bias was assessed independently by authors M.J. and M.W., with discrepancies resolved via discussion. We used the Cochrane Risk of Bias tool for parallel studies and an adapted version for crossover designs to assess internal study validity and risk of bias.<sup>8,20</sup> Seven domains from the original tool for parallel designs were applied to all studies: random sequence generation; allocation concealment; blinding of participants/researchers; blinding of outcome assessment; incomplete outcome data; selective reporting; and other potential biases. In addition,

crossover designs were assessed for three other domains: appropriate crossover design (which considered (1) the condition of the participants, (2) the temporary effect of the intervention, and (3) the potential for carry over effect); evaluation of the carry over effect; and unbiased data presentation. The overall quality of evidence was assessed using the GRADE approach<sup>15</sup>.

## Results

### *Description of included studies*

The PRISMA flow diagram for the literature search is illustrated in Figure 1. Thirteen studies were included; ten studies of healthy individuals (423 adults in 15 groups [55% males]) and three studies of people with chronic pain (114 adults in 4 groups [40% males]). No studies examined both population groups. GRABIT was used to extract some or all data from four studies of healthy individuals.<sup>1,12,33,34</sup> Table 1 outlines the characteristics of the included studies. In chronic musculoskeletal pain, only one study examined dynamic resistance exercise<sup>45</sup> and no studies examined aerobic exercise. Only two studies (both in chronic musculoskeletal pain) reported on the presence/absence of adverse events<sup>5,41</sup>; no adverse events were reported in these studies.

***Risk of bias and quality of included studies***

Egger's regression test indicated significant asymmetry in healthy individuals for all correlations ( $r = 0.9$ :  $z = -2.44$ ,  $p = 0.0146$ ;  $r = 0.5$ :  $z = -4.29$ ,  $p < 0.0001$ ;  $r = 0.0$ :  $z = -3.62$ ,  $p = 0.0003$ ). We did not conduct this statistical test in people with chronic musculoskeletal pain due to the limited number of included studies. The contour-enhanced funnel plots for healthy individuals indicated skewness towards significant findings in favour of EIH in healthy individuals, particularly a lack of smaller studies with null findings (Supplementary Figure 1)<sup>49</sup>. We refrain from comment about skewness in people with chronic musculoskeletal pain due to the limited number of studies (Supplementary Figure 2).

The risk of bias summary is presented in Figure 2 and the individual scores are available in Supplementary Table 2. In the categories unique to crossover designs, we considered all nine crossover studies (100%) to be of low risk of bias for "Appropriate crossover design" as they all examined a stable condition, examined a temporary effect, and allowed sufficient time for washout (all randomised sessions were separated by at least 24-48 hours). We considered 100% of crossover studies to be at low risk of bias for "Unbiased data" as they presented data for all experimental periods in their respective studies. We judged one crossover study (11%) to be at low risk of bias for "Carry over effect" as

it conducted a statistical assessment of intervention washout; 89% were at unclear risk of bias.

Considering the risk of bias categories applicable to both parallel and crossover designs, we deemed four studies (31%) to be of low risk of bias in “Random sequence generation” for thoroughly describing the randomisation method; we considered 69% unclear. Allocation concealment was thoroughly described and therefore at low risk of bias in two studies (15%), and unclear in 85%. We considered two studies (15%) to be at low risk of performance bias for blinding assessors, with the rest considered unclear (although we do acknowledge that one study attempted to blind participants to the hypothesis of the study). All studies were unclear for outcome blinding as no studies described attempts to implement it. Six studies (46%) were considered at low risk of bias for incomplete outcome data for fully describing patient flow through the trial. One study (8%) was considered at low risk of reporting bias because it was prospectively registered with a clinical trial registry and outcomes were also fully reported in the publication. We considered all studies (100%) to be at low risk of other potential biases.

The overall quality of evidence for the effect of a single bout of exercise on pain was rated as very low (Supplementary Table 3). The evidence

was downgraded due to limitations in study design (unclear risk of bias), inconsistency of results (considerable heterogeneity –  $I^2$  greater than 75% for almost all outcomes), imprecision (small sample sizes limiting precision of measurement) and high probability of publication bias (especially in studies of healthy individuals).

### **Healthy individuals**

Figure 3 illustrates the summary effects of EIH with correlation set at 0.9.

Aerobic exercise caused large EIH with high heterogeneity (7 studies<sup>25,34,36,40,47,48,55</sup>, 236 participants;  $g = -0.85 [-1.58, -0.13]$ ,  $I^2 = 99\%$ ), dynamic resistance exercise caused small EIH with no heterogeneity (2 studies<sup>33,36</sup>, 23 participants;  $g = -0.45 [-0.69, -0.22]$ ,  $I^2 = 0\%$ ), and isometric exercise did not cause EIH with high heterogeneity (3 studies<sup>1,12,40</sup>, 207 participants;  $g = -0.16 [-0.36, 0.05]$ ,  $I^2 = 98\%$ ). When the correlation was reduced to 0.5 (Supplementary Figure 3), aerobic exercise caused large EIH with high heterogeneity ( $g = -0.82 [-1.47, -0.16]$ ,  $I^2 = 94\%$ ), dynamic resistance exercise did not cause EIH with no heterogeneity ( $g = -0.46 [-0.94, 0.03]$ ,  $I^2 = 0\%$ ), and isometric did not cause EIH with no heterogeneity ( $g = -0.18 [-0.36, 0.01]$ ,  $I^2 = 0\%$ ).

Similar effects were observed when the correlation was reduced to 0 for aerobic exercise ( $g = -0.75 [-1.33, -0.17]$ ,  $I^2 = 85\%$ ), dynamic resistance exercise ( $g = -0.46 [-1.09, 0.18]$ ,  $I^2 = 0\%$ ) and isometric exercise ( $g = -$

0.17 [-0.40, 0.06],  $I^2 = 0\%$ ; Supplementary Figure 4). All these findings are based on very low quality evidence with an unclear risk of bias.

### ***Chronic musculoskeletal pain***

Figure 4 illustrates the summary effects of EIH with correlation set at 0.9. Isometric exercise did not cause EIH with high heterogeneity (3 studies<sup>5,41,45</sup>, 114 participants;  $g = -0.41$  [-1.08, 0.25],  $I^2 = 95\%$ ). This remained true when the correlation was reduced to 0.5 ( $g = -0.44$  [-1.13, 0.24],  $I^2 = 87\%$ ; Supplementary Figure 5) or 0 ( $g = -0.47$  [-1.18, 0.24],  $I^2 = 80\%$ ; Supplementary Figure 6). The effect of aerobic and dynamic resistance exercise on EIH in people with chronic musculoskeletal pain could not be meta-analysed due to an insufficient number of studies. The one study of dynamic resistance exercise found no effect ( $g = -0.12$  [-1.31, 0.07],  $I^2 = 0\%$ ; Figure 4). All these findings are based on very low quality evidence with an unclear risk of bias.

### **Discussion**

This systematic review and meta-analysis found varied effects of a single bout of exercise on experimental pain in healthy individuals and no effect in people with chronic musculoskeletal pain. Only randomised controlled trials were included, however the limited number of small

studies that were mostly of an unclear risk of bias and of very low quality means the results must be interpreted with caution.

In healthy individuals, aerobic exercise caused large EIH, which was robust to different correlations used in sensitivity analyses. The inclusion of randomised controlled trials provides a more accurate estimate of the causal nature of EIH which contrasts the previous review and meta-analysis<sup>39</sup>, and vast majority of published EIH literature, where single group pre-post designs were used. These study designs are more prone to bias and do not account for other factors such as habituation to the noxious stimulus or statistical phenomena such as regression to the mean. However, our finding is limited by the small number of included studies, many of which had small numbers of participants. As smaller trials usually find larger effect sizes<sup>7</sup>, the effects found in our review are probably an overestimate of the true magnitude of EIH.

We identified minimal or no effects for isometric exercise and dynamic resistance exercise in healthy individuals, both of which displayed the largest effects in the previous meta-analysis<sup>39</sup>. This discrepancy is likely due to methodological differences. Our decision to only include randomised controlled studies greatly limited the number of studies

included in this review but provides a more accurate representation of the causal nature of EIH, which we infer is smaller than previously observed. Many studies ( $n > 100$ ) were excluded from this review because they did not use a randomised controlled trial design, and several studies were excluded because they did not randomise the order of exercise and rest<sup>11,13,51,52,56</sup> which can introduce bias in the estimate of EIH. We recommend that future studies of EIH utilise control conditions as part of parallel-group or crossover designs. Random allocation to, or order of, exercise and control are essential. Quiet rest, sham exercise and/or light activity may all be appropriate controls<sup>12,26,46</sup>. Future studies using these designs would give a clearer indication of the causal effect of a single bout of exercise on experimental pain.

Three studies of people with chronic musculoskeletal pain were included in this review. The meta-analysis of the isometric exercise studies demonstrated no hypoalgesic effect, and the one study of dynamic resistance exercise (which could not be meta-analysed) found no effect. As resistance exercise is a guideline recommendation for many chronic musculoskeletal pain states (e.g. osteoarthritis, chronic low back pain, fibromyalgia)<sup>2,18,42</sup>, investigations of EIH after resistance exercise are of clinical importance. Aerobic exercise is similarly recommended by many guidelines<sup>2,18,42</sup>. However, despite being the most investigated exercise

mode in healthy individuals, no aerobic EIH studies in people with chronic musculoskeletal pain were included in this review. Admittedly, the abovementioned guidelines refer to the effect of exercise training whereas our review was limited to the effect of a single bout of exercise. Nonetheless, it may be important to determine how a single bout of exercise affects clinical pain in people with chronic pain as this may influence their adherence to exercise training. Therefore, there is a need for larger, higher quality studies of EIH on clinical pain in people with chronic pain following aerobic and resistance exercise which are commonly used in the clinical setting.

#### *Quality of evidence and risk of bias*

The overall quality of the evidence according to GRADE was rated as very low due to issues with inconsistency, imprecision, publication bias and risk of bias. Although we judged some categories to be at low risk of bias, most categories were generally considered unclear, which casts doubt about the strength of evidentiary support for the findings in this review. Some key elements for reducing risk of bias in these trials include more thorough descriptions of randomisation and allocation concealment, attempting researcher blinding (particularly because it is difficult to blind participants), and accurately reporting all data in a manuscript. Lee *et al.*<sup>35</sup> recently suggested preregistration, registered

reports, data sharing, and greater adherence to reporting guidelines as areas for improvement in clinical pain research<sup>35</sup>. Studies of EIH would benefit from adopting these recommendations.

### *Limitations*

Several limitations impact the strength of our findings. First, pre-post correlations were rarely reported, so they were estimated based on limited available data. Although the correlations used did not have substantial impact on aerobic exercise in healthy individuals, reducing correlations did render the effect of dynamic exercise non-significant. As we cannot be sure that the correlation used was truly reflective of all included studies, the effect sizes must be interpreted with caution. Second, most of the meta-analyses showed moderate-high heterogeneity, which presents difficulty determining the true effect. Third, small studies may have influenced the effect size, whereby smaller trials (as included in this review) find larger effects<sup>7</sup>. Fourth, all but one study used noxious pressure to induce pain, so the findings may not be generalisable to other types of experimental pain (e.g. thermal or electrical). Related to this, as we only included studies investigating EIH for experimental pain, the findings are not generalizable to clinical pain<sup>7</sup>. Finally, Egger's regression test indicated significant asymmetry for healthy individuals. This does not confirm publication bias *per se*,

however the possibility of positive publication bias cannot be ruled out, particularly seeing as our systematic literature search did not include grey literature. For these reasons, the results of this systematic review and meta-analysis, although a better estimate of the causal nature of EIH, must be interpreted with caution.

To conclude, based on a limited number of small, very low quality studies with an unclear risk of bias, a single bout of aerobic exercise causes large EIH in healthy individuals and dynamic resistance exercise may have a small hypoalgesic effect on experimental pain. However, these are likely overestimates due to the small studies on which they were based. There is insufficient evidence to support any mode of exercise causing EIH to experimental pain in people with chronic musculoskeletal pain and again, this conclusion is based mostly on small, very low quality studies with an unclear risk of bias. Future studies of EIH should employ more rigorous methodology to determine causal effects of a single bout of exercise in populations with chronic musculoskeletal pain, particularly for clinical pain as opposed to experimental pain.

## **Acknowledgements**

We would like to thank all the researchers who provided data from their studies to be included in our analysis.

Journal Pre-proof

## References

1. Alsouhibani A, Vaegter HB, Hoeger Bement M. Systemic Exercise-Induced Hypoalgesia Following Isometric Exercise Reduces Conditioned Pain Modulation. *Pain Med.* 20:180-190, 2019
2. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, Blanco FJ, Espinosa R, Haugen IK, Lin J, Mandl LA, Moilanen E, Nakamura N, Snyder-Mackler L, Trojian T, Underwood M, McAlindon TE. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage.* 27:1578-1589, 2019
3. Black J, Chesher GB, Starmer GA, Egger G. The painlessness of the long distance runner. *Med J Aust.* 1:522-523, 1979
4. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR: Part 2: Effect size and precision. In: *Introduction to Meta-Analysis*, Wiley, Chinchester, UK, 2009, pp. 17-60.
5. Coombes BK, Wiebusch M, Heales L, Stephenson A, Vicenzino B. Isometric Exercise above but not below an Individual's Pain Threshold Influences Pain Perception in People with Lateral Epicondylalgia. *Clinical Journal of Pain.* 32:1069-1075, 2016

6. Cuijpers P, Weitz E, Cristea IA, Twisk J. Pre-post effect sizes should be avoided in meta-analyses. *Epidemiol Psychiatr Sci.* 26:364-368, 2017
7. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *Bmj.* 346:f2304, 2013. doi:10.1136/bmj.f2304
8. Ding H, Hu GL, Zheng XY, Chen Q, Threapleton DE, Zhou ZH. The method quality of cross-over studies involved in Cochrane Systematic Reviews. *PloS one.* 10:e0120519-e0120519, 2015
9. Drury DG, Greenwood K, Stuempfle KJ, Koltyn KF. Changes in pain perception in women during and following an exhaustive incremental cycling exercise. *J Sports Sci Med.* 4:215-222, 2005
10. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 315:629-634, 1997
11. Ellingson LD, Stegner AJ, Schwabacher IJ, Koltyn KF, Cook DB. Exercise strengthens central nervous system modulation of pain in fibromyalgia. *Brain Sci.* 6:8, 2016. doi:10.3390/brainsci6010008
12. Foxen-Craft E, Dahlquist LM. Brief submaximal isometric exercise improves cold pressor pain tolerance. *J Behav Med.* 40:1-12, 2017
13. Gajjar H, Titze C, Hasenbring MI, Vaegter HB. Isometric back exercise has different effects on pressure pain thresholds in healthy men and women. *Pain Med.* 18:917-923, 2017

14. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 4:Cd011279, 2017
15. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj.* 336:924-926, 2008
16. Haier RJ, Quaid K, Mills JC. Naloxone alters pain perception after jogging. *Psychiatry Res.* 5:231-232, 1981
17. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *Bjog.* 125:1716, 2018. doi:10.1111/1471-0528.15199
18. Hauser W, Ablin J, Perrot S, Fitzcharles MA. Management of fibromyalgia: practical guides from recent evidence-based guidelines. *Pol Arch Intern Med.* 127:47-56, 2017
19. Hayashino Y, Noguchi Y, Fukui T. Systematic evaluation and comparison of statistical tests for publication bias. *J Epidemiol.* 15:235-243, 2005
20. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JAC. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 343:d5928, 2011. doi:10.1136/bmj.d5298

21. Higgins JPT, Deeks JJ, (editors): Part 2, Chapter 7, Section 7.7.3.3  
Obtaining standard deviations from standard errors, confidence intervals, t values and P values for differences in means. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011), The Cochrane Collaboration, 2011.
22. Higgins JPT, Deeks JJ, Altman DG, (editors): Part 3, Chapter 16: Special topics in statistics. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011), The Cochrane Collaboration, 2011.
23. Hoeger Bement MK, Dicapo J, Rasiarmos R, Hunter SK. Dose response of isometric contractions on pain perception in healthy adults. *Med Sci Sports Exerc.* 40:1880-1889, 2008
24. Hoffman MD, Shepanski MA, Ruble SB, Valic Z, Buckwalter JB, Clifford PS. Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain. *Arch Phys Med Rehabil.* 85:1183-1187, 2004
25. Hviid JT, Thorlund JB, Vaegter HB. Walking increases pain tolerance in humans an experimental cross-over study. *Scand J Pain.* 2019.  
doi:10.1515/sjpain-2019/0070

26. Jones MD, Nuzzo JL, Taylor JL, Barry BK. Aerobic exercise reduces pressure more than heat pain sensitivity in healthy adults. *Pain Med.* 20(8): 1534-1546, 2019. doi:10.1093/pm/pny1289, 2019
27. Jones MD, Taylor JL, Barry BK. Occlusion of blood flow attenuates exercise-induced hypoalgesia in the occluded limb of healthy adults. *J Appl Physiol (1985).* 122:1284-1291, 2017
28. Jones MD, Taylor JL, Booth J, Barry BK. Exploring the mechanisms of exercise-induced hypoalgesia using somatosensory and laser evoked potentials. *Front Physiol.* 7:581, 2016. doi:10.3389/fphys.2016.00581
29. Kempainen P, Hamalainen O, Kononen M. Different effects of physical exercise on cold pain sensitivity in fighter pilots with and without history of acute in-flight neck pain. *Med Sci Sports Exerc.* 30:577-582, 1998
30. Kempainen P, Pertovaara A, Huopaniemi T, Johansson G, Karonen SL. Modification of dental pain and cutaneous thermal sensitivity by physical exercise in man. *Brain Res.* 360:33-40, 1985
31. Koltyn KF. Analgesia following exercise: a review. *Sports Med.* 29:85-98, 2000
32. Koltyn KF. Exercise-induced hypoalgesia and intensity of exercise. *Sports Med.* 32:477-487, 2002

33. Koltyn KF, Arbogast RW. Perception of pain after resistance exercise. *Br J Sports Med.* 32:20-24, 1998
34. Koltyn KF, Garvin AW, Gardiner RL, Nelson TF. Perception of pain following aerobic exercise. *Med Sci Sports Exerc.* 28:1418-1421, 1996
35. Lee H, Lamb SE, Bagg MK, Toomey E, Cashin AG, Moseley GL. Reproducible and replicable pain research: a critical review. *Pain.* 159:1683-1689, 2018
36. Lee HS. The effects of aerobic exercise and strengthening exercise on pain pressure thresholds. *Journal of Physical Therapy Science.* 26:1107-1111, 2014
37. Micalos PS, Arendt-Nielsen L. Differential pain response at local and remote muscle sites following aerobic cycling exercise at mild and moderate intensity. *Springerplus.* 5:91, 2016. doi:10.1186/s40064-016-1721-8
38. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 339:b2535, 2009. doi:10.1136/bmj.b2535
39. Naugle KM, Fillingim RB, Riley JL, 3rd. A meta-analytic review of the hypoalgesic effects of exercise. *J Pain.* 13:1139-1150, 2012

40. Naugle KM, Naugle KE, Riley JL, 3rd. Reduced modulation of pain in older adults following isometric and aerobic exercise. *J Pain*. 17:719-728, 2016
41. Neelapala YVR, Nayak S, Sivalanka S, Cornelio R, Prajapati M. Influence of isometric exercise on pressure pain sensitivity in knee osteoarthritis. *Journal of Pain Management*. 11:361-367, 2018
42. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CC, Chenot JF, van Tulder M, Koes BW. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J*. 27:2791-2803, 2018
43. Polaski AM, Phelps AL, Kostek MC, Szucs KA, Kolber BJ. Exercise-induced hypoalgesia: A meta-analysis of exercise dosing for the treatment of chronic pain. *PLoS One*. 14:e0210418, 2019
44. Rice D, Nijs J, Kosek E, Wideman T, Hasenbring MI, Koltyn K, Graven-Nielsen T, Polli A. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. *J Pain*. 20:1249-1266, 2019
45. Riel H, Vicenzino B, Jensen MB, Olesen JL, Holden S, Rathleff MS. The effect of isometric exercise on pain in individuals with plantar fasciopathy: A randomized crossover trial. *Scandinavian Journal of Medicine and Science in Sports*. 28:2643-2650, 2018

46. Ring C, Edwards L, Kavussanu M. Effects of isometric exercise on pain are mediated by blood pressure. *Biol Psychol.* 78:123-128, 2008
47. Samuelli-Leichtag G, Kodesh E, Meckel Y, Weissman-Fogel I. A Fast Track to Hypoalgesia - The Anaerobic Exercise Effect on Pain Sensitivity. *Int J Sports Med.* 39:473-481, 2018
48. Schmitt A, Wallat D, Stangier C, Martin JA, Schlesinger-Irsch U, Boecker H. Effects of Fitness Level and Exercise Intensity on Pain and Mood Responses. *Eur J Pain.* 24: 568-579, 2019.
49. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP.  
Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ.* 343:d4002, 2011
50. Team RC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2018
51. Vaegter HB, Bjerregaard LK, Redin M-M, Rasmussen SH, Graven-Nielsen T. Hypoalgesia after bicycling at lactate threshold is reliable between sessions. *European Journal of Applied Physiology.* 119:91-102, 2019

52. Vaegter HB, Dorge DB, Schmidt KS, Jensen AH, Graven-Nielsen T. Test-Retest Reliability of Exercise-Induced Hypoalgesia After Aerobic Exercise. *Pain Med.* 19:2212-2222, 2018
53. Vaegter HB, Handberg G, Graven-Nielsen T. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain.* 155:158-167, 2014
54. Vaegter HB, Handberg G, Graven-Nielsen T, Edwards R. Hypoalgesia after exercise and cold pressor test are reduced in chronic musculoskeletal pain patients with high pain sensitivity. *Clin J Pain.* 32:58-69, 2016
55. Vaegter HB, Handberg G, Jorgensen MN, Kinly A, Graven-Nielsen T. Aerobic exercise and cold pressor test induce hypoalgesia in active and inactive men and women. *Pain Med.* 16:923-933, 2015
56. Vaegter HB, Lyng KD, Yttereng FW, Christensen MH, Sorensen MB, Graven-Nielsen T. Exercise-Induced Hypoalgesia After Isometric Wall Squat Exercise: A Test-Retest Reliability Study. *Pain Med.* 20:129-137, 2019
57. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *2010.* 36:48, 2010
58. Vierck CJ, Jr., Staud R, Price DD, Cannon RL, Mauderli AP, Martin AD. The effect of maximal exercise on temporal summation of second pain

(windup) in patients with fibromyalgia syndrome. *J Pain*. 2:334-344, 2001

59. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 14:135, 2014. doi:10.1186/1471-2288-14-135

Journal Pre-proof

## Figure Legends

**Figure 1.** PRISMA flow diagram.

**Figure 2.** Risk of bias summary for crossover and parallel studies.

**Figure 3.** Forest plot of exercise-induced hypoalgesia for healthy individuals (correlation = 0.9).

**Figure 4.** Forest plot of exercise-induced hypoalgesia for patients with chronic musculoskeletal pain (correlation = 0.9).

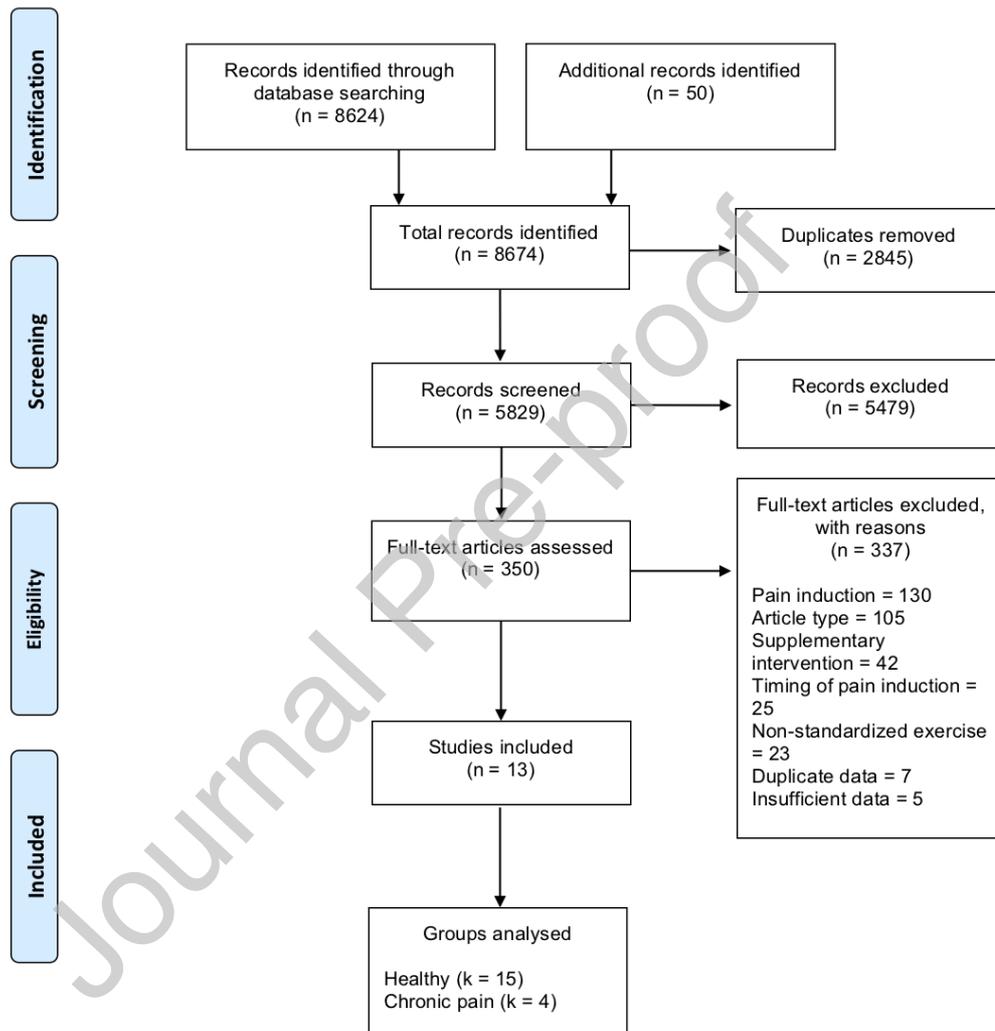
## Table Legends

**Table 1.** Characteristics of included studies.

Fig 1



## PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

Fig 2

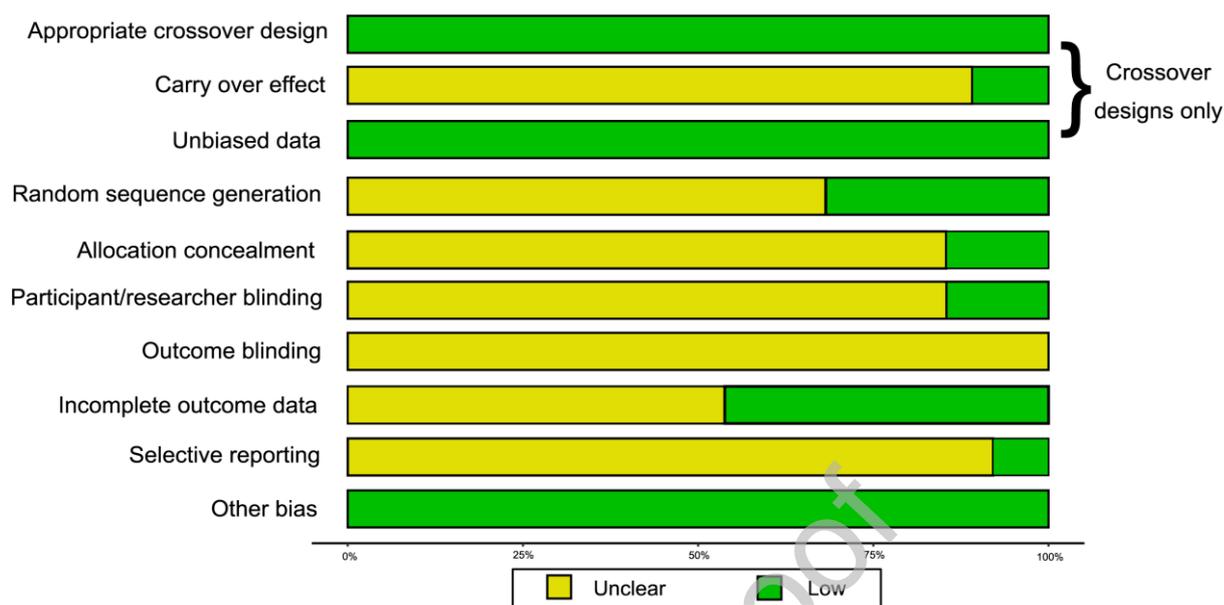


Fig 3

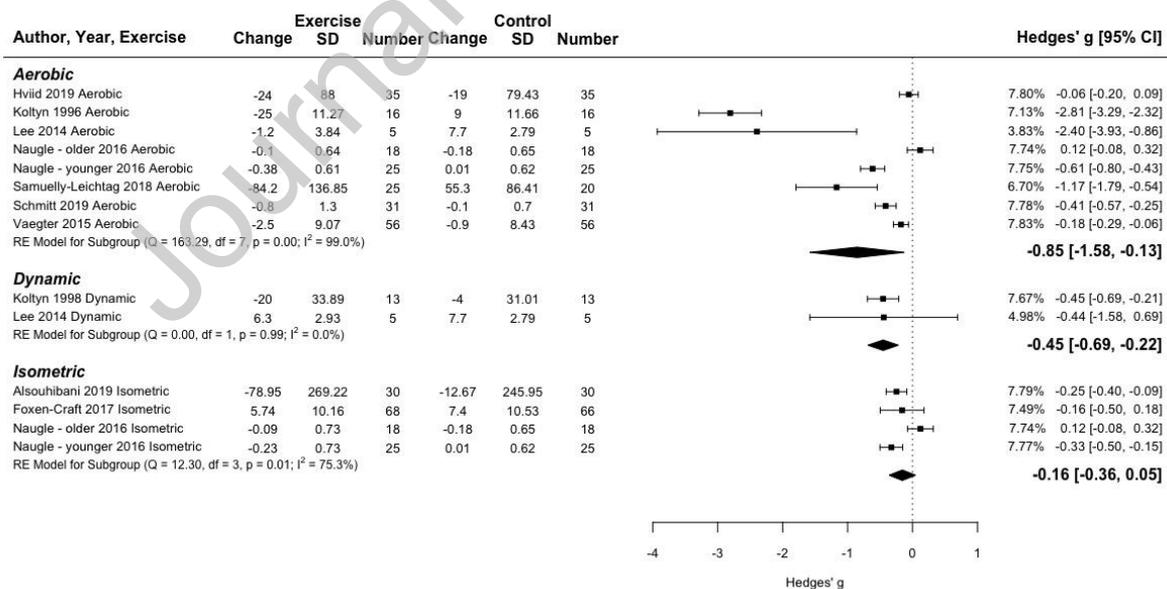
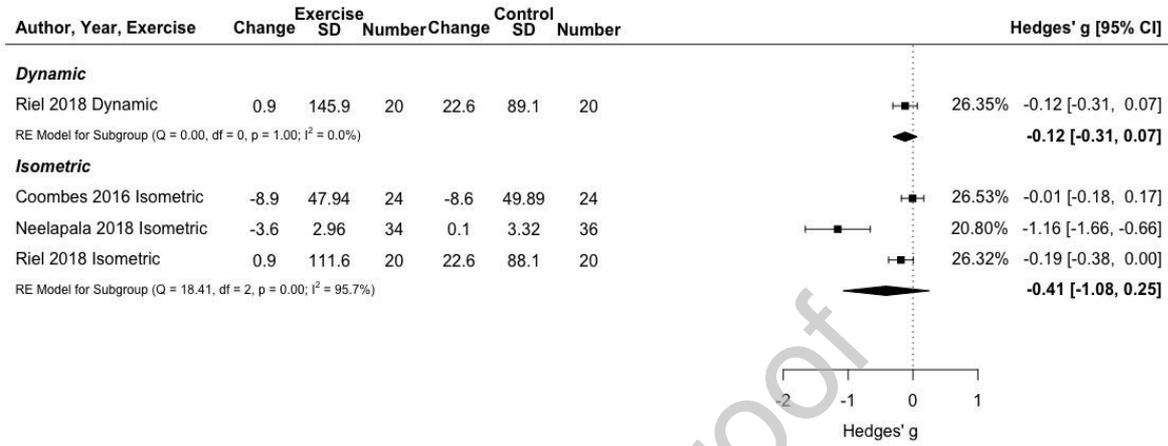


Fig. 4



**Table 1:** Characteristics of included studies.

First author (year)	Exercise mode	Population (mean age [years])	Study design	# participants (% males)	Exercise intervention	Control intervention	Pain stimulus
Hviid 2019	Aerobic	Healthy (26)	Crossover	35 (49)	6-minute walk test	6 min seated	Pressure pain threshold (quadriceps)
Koltyn (1996)	Aerobic	Healthy (29)	Crossover	16 (88)	Cycle ergometer, 30 min, 65-75% $\text{VO}_{2\text{peak}}$	30 min seated	Pressure pain threshold (index finger)
Lee (2014)	Aerobic	Healthy (25)	Parallel	10 (NA)	Treadmill, 40 min, 6.5 km/h	40 min seated	Pressure pain threshold (right trapezius)
Naugle (2016) - younger	Aerobic	Healthy (22)	Crossover	25 (48)	Cycle ergometer, 20 min, 70% HRR	25 min seated	Pressure pain threshold (forearm)
Naugle (2016) - older	Aerobic	Healthy (64)	Crossover	18 (50)	Cycle ergometer, 20 min, 70% HRR	25 min seated	Pressure pain threshold (forearm)
Samuelly-Leichtag (2018)	Aerobic	Healthy (25)	Parallel	50 (25)	Cycle ergometer, 30 s sprint	Rest in a seated position on the bike for 30 s	Pressure pain threshold (quadriceps)
Schmitt 2019	Aerobic	Healthy (26)	Crossover	31 (100)	Cycle ergometer, 20 min, 20% above lactate threshold	20 min seated	Heat pain threshold (forearm)
Vaegter (2015)	Aerobic	Healthy (22)	Crossover	56 (28)	Cycle ergometer, 15 min, 75% $\text{VO}_{2\text{peak}}$	Relax in a supine position for 15 min	Pressure pain threshold (quadriceps)
Koltyn (1998)	Dynamic	Healthy (23)	Crossover	13 (54)	4 exercises, 3 x 10, 75% 1RM, 45 min	45 min seated	Pressure pain threshold (middle finger)
Lee (2014)	Dynamic	Healthy (26)	Parallel	10 (NA)	5 upper body exercises, based on perceived exertion, 40 min	40 min seated	Pressure pain threshold (right trapezius)
Riel (2018)	Dynamic	Plantar fasciopathy (49)	Crossover	20 (10)	Heel raise, 8RM, 8 reps x 4 sets with 2 mins between sets, total time 256 s	4 min walking at pace usually used at home	Pressure pain threshold (heel)
Alsouhibani (2019)	Isometric	Healthy (19)	Crossover	30 (50)	Knee extension, 30% MVC, 3 min	3 min seated	Pressure pain threshold (quadriceps)
Foxen-Craft (2017)	Isometric	Healthy (22)	Parallel	134 (39)	Handgrip, 25% MVC, 2 min	Hold dynamometer without handgrip contraction for 2 min	Cold pressor pain intensity
Naugle (2016) - younger	Isometric	Healthy (22)	Crossover	25 (48)	Handgrip, 25% MVC, 3 min	25 min seated	Pressure pain threshold (forearm)
Naugle (2016) - older	Isometric	Healthy (64)	Crossover	18 (50)	Handgrip, 25% MVC, 3 min	25 min seated	Pressure pain threshold (forearm)
Coombes (2016)	Isometric	Lateral epicondylalgia for 2 to 5 months (52)	Crossover	24 (54)	Wrist extension, 10 x 15 s at 120% "pain-free threshold", 15 s between reps	Seated with affected arm resting in apparatus for 4 min	Pressure pain threshold (lateral epicondyle)
Neelapala (2018)	Isometric	Knee osteoarthritis (62)	Parallel	70 (44)	Knee extension, 10 reps x 6 s, 5 min	5 min seated	Pressure pain threshold (knee)
Riel (2018)	Isometric	Plantar fasciopathy (49)	Crossover	20 (10)	Heel raise, as heavy as possible, 1 rep x 5 sets with 2 mins rest, total time 225 s	4 min walking at pace usually used at home	Pressure pain threshold (heel)

# = number; HRR = heart rate reserve; MVC = maximal voluntary contraction; RM = repetition maximum;  $\text{VO}_{2\text{peak}}$  = peak oxygen consumption.