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Title: Effect of High-Pain versus Low-Pain Structured Exercise on Walking Ability in people with Intermittent Claudication: A Systematic Review and Network Meta-analysis

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ABSTRACT

Aim: To determine the comparative benefits of structured high-pain exercise, structured low-pain exercise, and usual-care control, to identify which has the largest effect on walking ability in people with intermittent claudication (IC).

Methods and Results: We undertook a network meta-analysis to assess two outcomes; pain free walking ability (PFWA) and maximal walking ability (MWA). We searched nine electronic databases. Trials were included if they: were randomised controlled trials; involved adults with IC; had at least two of following arms structured low-pain exercise, structured-high pain exercise or a usual-care control; and a maximal or pain free treadmill walking outcome. Fourteen trials were included; results were pooled using SMD. Structured low-pain exercise had a significant large positive effect on MWA (SMD: 2.23; 95% CI: 1.11 to 3.35) and PFWA (2.26; 1.26 to 3.26) when compared to usual-care control. Structured high-pain exercise had a significant large positive effect on MWA (SMD: 0.95; 95% CI: 0.20 to 1.70) and a moderate positive effect on PFWA (0.77; 0.01 to 1.53) when compared to usual-care control. Structured low-pain exercise, compared to structured high-pain exercise showed a large positive effect in favour of low-pain exercise on MWA (SMD: 1.28, 95% CI: -0.07 to 2.62) and PFWA (1.50; 0.24 to 2.75); however only PFWA reached significance.

Conclusion: There is strong evidence in support of structured high-pain exercise, and some evidence in support of structured low-pain exercise, to improve walking ability in people with IC over usual-care control (unstructured exercise advice). Large head-to-head RCTs are needed.

INTRODUCTION

Intermittent claudication (IC) is the most common manifestation of peripheral artery disease (PAD),⁽¹⁾ and manifests itself as leg pain during exercise caused by ischaemia secondary to flow-limiting atherosclerosis in the arteries of the lower limbs.⁽²⁾ As severity increases, people with IC become progressively more sedentary with lower physical activity levels and poorer walking ability.⁽³⁻⁶⁾ People with IC who have low levels of physical activity have been associated with negative quality of life, depression, and elevated risk of all-cause mortality independent of disease severity and age.^(7, 8) Therefore, improving walking ability is viewed as one of the most important outcome measures of intervention to clinicians and patients, measures of which include pain free and maximum walking distances (or times) obtained during standardised walking assessments.⁽¹⁾

Walking ability can be improved via structured exercise (adhering to the Frequency, Intensity, Time and Type [FITT] principle^(9, 10)) in people with IC,⁽¹¹⁾ where pain is often prescribed in place of intensity. Furthermore, supervised exercise programs are more effective than home-based exercise programs which employ methods of observation.⁽¹²⁾ Though technological advancements, partially accelerated by the COVID-19 pandemic, may modify this relationship. The National Institute for Health and Care Excellence recommends structured exercise programs which involve walking to maximum claudication pain for 2 hours per week, for 12 weeks;⁽¹³⁾ these guidelines are similar internationally.⁽⁹⁾ Nevertheless, research suggests that improvements in walking ability are achievable across a range of exercise modalities, whether exercising to mild, moderate, or maximal claudication pain in people with PAD and IC^(14, 15) and the benefit of structured low-pain exercise may be overlooked.

Despite the benefits of low-pain exercise interventions, there is little published evidence of the comparative efficacy of low- and high-pain exercise interventions on walking ability in people with IC. When direct comparisons are lacking, a network meta-analysis allows for the comparison of multiple treatments when studies use a common comparator, such as a usual-care control group. To help clarify the evidence, we conducted a systematic review and network meta-analysis of randomised controlled trials (RCTs) to determine the comparative effects of structured high-pain exercise, structured low-pain exercise, and usual-care control (unstructured exercise advice only) to identify which has the largest effect on walking ability in people with IC.

METHODS

This meta-analysis was conducted and reported in line with Preferred Reporting In Systematic reviews and Meta-Analysis (PRISMA) guidelines (checklist reported in the Supplemental Material).⁽¹⁶⁾ Ethical approval was not required. Methods of the analysis were specified in advance and the protocol registered with PROSPERO (ID: CRD42020172421).

Data Sources and Searches

Records, without language restriction and published from database inception to January 21st 2021, were identified by an experienced clinical librarian (C.J.P.) on MEDLINE, Embase, Emcare, Cochrane Library, Cochrane Central Register of Controlled Trials, PEDro, OpenGrey, ClinicalTrials.gov and The Cumulative Index to Nursing and Allied Health Literature (CINAHL) bibliographic databases. We limited the MEDLINE, Embase, Emcare and CINAHL searches to randomised control trials using validated filters.⁽¹⁷⁻¹⁹⁾ Search terms for intermittent claudication and exercise were defined in part using strategies from two systematic reviews^(14, 20) and a Cochrane review,⁽¹²⁾ with an additional cluster for walking assessment. Additional trials were identified by hand-searching bibliographies from included studies, relevant reviews and meta-analyses. Results from each database were combined using EndNote (version X9 for Windows, Clarivate Analytics, Philadelphia, PA, USA). The MEDLINE search strategy is presented in the Expanded Methods in the Supplemental Material.

Study Selection

Following removal of duplicates, article titles and abstracts were reviewed independently by two authors (J.P. and A.N.). Potentially eligible articles were retrieved for full-text review where possible and any disagreements were resolved by discussion and consensus (J.P. and

A.N. or C.P.). Studies were included if they met the following criteria: 1) adult male and female individuals with intermittent claudication (Fontaine stage ≤ 2 or Rutherford ≤ 3 ; or exercise induced aching/cramping, pain affecting the lower limbs or buttocks, which subsides with rest; or IC confirmed by validated questionnaire; and ankle-brachial pressure index (ABPI) $< 0.9-1.00$ or > 1.4 at rest or $> 20\%$ decrease post exercise); 2) RCTs with at least two of the following arms: structured exercise which is prescribed at low-pain; structured exercise which is prescribed at high-pain; or usual-care control (unstructured exercise advice only). For the purpose of this review, levels of pain either achieved or prescribed in the exercise interventions were used to classify studies into low pain ($< 50\%$ on a claudication pain scale) or high pain ($> 50\%$ on an even scale. Studies which used a scale with an odd number of scale points, the mid-point fell outside of classification, and studies were classified in the same way 3) completed measures of pain free or maximal walking time or distance pre- and post-intervention measured using treadmill test, reported or retrieved as mean \pm standard deviation (SD) or standard error (SE); 4) structured exercise adhering to FITT.^(9, 10) For two studies^(21, 22) with multiple publications using the same cohort, one follow-up study was excluded⁽²¹⁾ as there was a subgroup of participants from the original study;⁽²³⁾ while another was excluded as the follow-up was shorter (6 vs 12 months).⁽²²⁾

Data Extraction and Quality Assessment

Data extraction was completed independently by two researchers (J.P. and C.P.) using a customised Microsoft Excel spreadsheet and checked for agreement. Data extracted for each eligible trial included bibliographic information (author, publication year), baseline and post-intervention measures of maximal walking distance or time (maximal walking ability; MWA) or pain free walking distance or time (pain free walking ability; PFWA) (mean \pm SD or SE), sample characteristics (age, number in each trial arm), and details of interventions

(intervention length, supervision, treadmill test, claudication pain level and scale, training modality, control group activities, exercise frequency and volume). The assumptions of transitivity and consistency were assessed comparing Patient/Population, Intervention, Comparator, Outcomes (PICO) across the included studies. If the required data was not reported in the article, the corresponding authors were contacted for further information; if the data was still unavailable, mean \pm SD or SE values were extracted using ImageJ image analysis software by two independent investigators (J.P. and C.P.).⁽²⁴⁾ To ensure accuracy of this method, validity was assessed by comparing extracted values from published figures to known true values. Reliability was assessed by analysing each published figure three times, recalibrating the software each time. Inter-rater reliability (IRR) was then assessed using a two-way mixed, absolute agreement, average-measures model to assess the degree of consistency between researchers using IRR package⁽²⁵⁾ in RKWard, a graphical front end to R.⁽²⁶⁾ For the assessment of validity and reliability using ImageJ software, investigators displayed excellent validity and reliability (J.P., ICC = 1.00, r = 1.00, and C.P., ICC = 0.99, r = 1.00). The investigators also displayed excellent inter-rater reliability (ICC = 0.99). Thus, it is very likely that only a minimal error (if any) was introduced using this method. Risk of bias was assessed by at least 2 authors (J.P. and J.H. or A.N.) using the Cochrane Risk of Bias Tool 2.0; any disagreement was resolved by consensus.

Data Synthesis and Analysis

Data for exercise and usual-care control groups were extracted at baseline (pre-intervention) and follow-up (post-intervention) as mean \pm SD or SE for two outcomes: MWA and PFWA. We used this information, alongside the sample size, to estimate the standard deviation of the within-arm mean difference with correlation coefficients (r) of 0.1, 0.5, and 0.9, as suggested in Cochrane Handbook for Systematic Reviews of Interventions (chapter 6.5.2.8).⁽²⁷⁾ This

analytical approach was used because, within each arm, the standard deviations of the difference were not available as they were reported for MWA or PFWA only before and after the intervention. For both outcomes, maximal walking ability and pain free walking ability (either time or distance), we estimated the effect of the intervention as standardised mean difference (SMD) calculated as Hedges g :⁽²⁸⁾ effects were considered trivial if <0.2 , small if $0.2-0.5$, moderate if $0.5-0.8$, and large at >0.8 in relation to the common thresholds applied when interpreting Hedge's g .⁽²⁹⁾ In one study, two high-pain arms reported MWA and PFWA, a fixed-effect meta-analysis was used to combine effect sizes across the two arms.⁽³⁰⁾

We firstly performed random effects pairwise meta-analyses (using restricted maximum likelihood and r of 0.5) for MWA and PFWA, presented as Hedge's g , 95% confidence intervals (CI) and 95% prediction intervals (PI); and quantified heterogeneity using I^2 statistic: I^2 of 25%, 50%, and 75%, which are generally considered as indicative of low, moderate, and high heterogeneity, respectively.⁽³¹⁾ Despite the low number of studies, funnel plots were produced to assess the risk of small-study effect, which was formally tested using Egger's regression test, and a possible publication bias.

We then conducted a random-effects network meta-analysis with a frequentist approach, which is based on multivariate random-effects meta-analysis or meta-regression.⁽³²⁾ Network plots were drawn to determine the network of comparisons, with thickness of lines between nodes and size of the nodes based on the number of studies in each comparison and treatment, respectively. Comparisons across the three interventions are presented as Hedge's g , 95% CI separately for MWA and PFWA, using within-arm estimates for r of 0.5.

Sensitivity analyses using values of r of 0.1 and 0.9 were also performed and are presented in the same way.

All analyses were conducted using Stata version 16.1 (StataCorp, College Station, TX).

RESULTS

Study Characteristics

Electronic searches yielded 7379 records and an additional 24 articles were identified from manual searches of bibliographies of relevant reviews, meta-analyses, and other article publications (Figure 1). After removal of duplicates, 1419 titles and abstracts were screened for eligibility, and 82 articles were reviewed in full. A total of 14 studies were included in the analysis, with a combined sample size of 657 patients. The final analysis included the comparison of 9 high-pain arms,^(23, 30, 33-39) 4 low-pain arms,⁽⁴⁰⁻⁴³⁾ and 13 usual-care control arms^(23, 30, 33-43) for MWA; and 7 high-pain arms,^(23, 30, 33, 35, 37-39) 4 low-pain arms^{(41),(42-44)} and 11 usual-care control^{(23, 30, 33, 35, 37-39, 41),(42-44)} for PFWA.

Characteristics of studies are presented in Supplemental Table 5. Ten out of 14 of these studies had an intervention length 12-14 weeks, two were 6 months and two were 12 months. All studies used walking as a training modality and utilised a treadmill walking test to measure maximal and pain free walking ability. Twelve studies reported use of a progressive treadmill test to measure walking outcomes. Two studies used a single stage treadmill test. Most studies fully supervised the intervention. Eleven of the interventions implemented an exercise frequency of 3x·week with a duration of up to 60 minutes per session. One study implemented an exercise frequency of 5x·week with undisclosed session durations, one study implemented an exercise frequency of 2x·week with 30 minute sessions, and another one implemented an exercise frequency of 2-3x·week with 60 minute sessions.

Risk of Bias

Ten studies were deemed to have a high risk of bias.^(23, 34, 35, 37, 39-44) Only three studies^(30, 33, 36) met intention to treat principles in line with Consolidated Standards of Reporting Trials

(CONSORT) guidelines.⁽⁴⁵⁾ Eleven studies that had not included participant data for dropouts, and those lost to follow-up post-randomisation in the main analysis, were considered per-protocol analyses with most of these studies at high risk of bias due to missing outcome data for this reason.^(23, 34, 35, 37-44) Furthermore, there were some concerns with risk of bias due to blinding procedures not being stated in nine studies,^(23, 33-36, 38-40, 43) and a high risk of bias from assessor non-blinding in one study.⁽³⁷⁾ All studies in this review showed either some concerns^(23, 30, 33-38, 40-42, 44) or a high risk of bias,^(39, 43) with the selection of the reported result particularly due to the lack of available pre-specified statistical analysis plans. The details for these assessments are presented in Supplemental Table 1 and Supplemental Table 2.

Pairwise Comparisons

In pairwise comparisons, the standardised mean differences for structured low-pain exercise vs. usual-care control were: 2.18 (95% PI: -7.474 to 11.832; 95% CI: 0.16 to 4.19; I^2 , 94.8%) across four studies for MWA,⁽⁴⁰⁻⁴³⁾ and 2.21 (-5.866 to 10.285; 0.51 to 3.91; I^2 , 93.4%) across four studies for PFWA^{(41),(42-44)} (Figure 2 and Figure 3). Corresponding estimates for structured high-pain exercise vs. usual-care control were: 0.85 (95% PI: 0.58 to 1.11; 95% CI: 0.63 to 1.07; I^2 , 0%) across nine studies for MWA,^(23, 30, 33-39) (Figure 2) and 0.70 (0.396 to 1.008; 0.47 to 0.94; I^2 , 0%) across seven studies for PFWA^(23, 30, 33, 35, 37-39) (Figure 2 and Figure 3).

The investigation for small-study effects suggested no evidence of publication bias for the comparison of high-pain exercise vs control for MWA ($p = 0.356$; Supplemental Figure 1) and PFWA ($p = 0.505$; Supplemental Figure 2) outcome. Conversely, there was evidence of

publication bias for the comparison of low-pain exercise vs control for both MWA ($p < 0.001$; Supplemental Figure 1) and PFWA ($p = 0.044$; Supplemental Figure 2) outcome.

Network Meta-Analysis

Treatments were grouped into common nodes based on high-pain, low-pain, and usual-care control. Network of included trials were connected at C (usual-care control) and A (structured high-pain exercise) or B (structured low-pain exercise) for MWA and PFWA. There were nine high-pain arms, five low-pain arms, and 14 usual-care control arms in total. No studies compared high-pain with low-pain exercise, therefore quantitative tests of inconsistency were not possible (Supplemental Figure 3 and Supplemental Figure 4).

The network meta-analysis showed a large positive effect of structured low-pain exercise vs. usual-care control on MWA (Hedges g : 2.23; 95% CI: 1.11 to 3.35; Figure 4) and PFWA (Hedges g : 2.26; 1.26 to 3.26; Figure 5) in favour of low-pain exercise. For the effect of high-pain exercise vs. usual-care control, there was a large positive effect on MWA (Hedges g : 0.95; 95% CI: 0.20 to 1.70; Figure 4) and a moderate positive effect on PFWA (Hedges g : 0.77; 0.01 to 1.53; Figure 5) in favour of high-pain exercise. Furthermore, for the effect of low-pain exercise vs. high-pain exercise there was a large positive effect on both MWA (Hedges g : 1.28; 95% CI: -0.07 to 2.62; Figure 4) and PFWA (Hedges g : 1.50; 0.24 to 2.75; Figure 5) in favour of low-pain exercise; however only PFWA reached significance.

Network meta-analysis results were consistent in sensitivity analysis with r 0.1 and 0.9 (Supplemental Figure 5 and Supplemental Figure 6). For the comparison of structured high-pain exercise vs. control, there was a moderate to large positive effect on MWA in favour of high-pain exercise and a small to large positive effect on PFWA in favour of high-pain exercise. For the comparison of structured low-pain exercise vs. control, there was large positive effect on MWA and PFWA in favour of low-pain exercise. Lastly, for the

comparison of low-pain exercise vs. high-pain exercise, there was a large positive effect in favour of low-pain exercise for both outcomes.

DISCUSSION

This systematic review and network meta-analysis aimed to determine the comparative benefits of structured high-pain exercise, structured low-pain exercise, and usual-care control (unstructured exercise advice only) to identify which has the largest effect on walking ability in people with IC. Our analysis of RCTs revealed three important findings: 1) there is an overall positive effect of both low- and high-pain structured exercise on MWA and PFWA when compared to usual-care control in people with IC; 2) that structured low-pain exercise has a larger positive effect than structured high-pain exercise for MWA and PFWA when compared to usual-care control; 3) the comparison of structured low-pain to high-pain exercise reveals a large positive effect in favour of low-pain exercise on walking ability in people with IC, although there is a level of uncertainty with only PFWA reaching statistical significance and wide prediction intervals which cross the null. With little published evidence on the comparative efficacy of low- and high-pain exercise interventions on walking ability in people with IC, this analysis provides the most robust estimate to date, and adds to a growing body of literature which supports structured low-pain exercise as a non-pharmacological treatment for IC.

Comparison with other studies

Our review adds to contrasting findings in the literature exploring the effect of low-and high-pain exercise on walking ability in people with PAD and IC. An earlier systematic review reported that improvements in walking ability and $\dot{V}O_{2peak}$ were achievable when exercising to varied levels of claudication pain.⁽¹⁵⁾ By comparison, a recent RCT in people with PAD showed high-intensity exercise (moderate-severe pain) to have superior walking ability outcomes compared to low-intensity exercise (no-pain); and those in the low-intensity

exercise group performed no better than those in the control group; despite participants in the low-intensity group reporting greater adherence than those in the high-intensity group.⁽⁴⁶⁾ However, it is worth highlighting that fewer than 20% of the participants in this study experienced classic claudication symptoms and the prescription of pain in the high-pain group would not be classified as high-pain according to the pain scale cut-off points used in our review. In addition, data for treadmill walking distance were not available in the claudication subgroup; therefore, this study was not included in our meta-analysis.

A recent systematic review reported greater adherence rates of low-pain exercise interventions (overall adherence rate: 93.4%; range: 80-100%) compared to high-pain exercise interventions (77%; 57.1%-100%; $p = 0.004$) in people with IC.⁽²⁰⁾ Greater program adherence to low-pain exercise may coincide with greater cumulative exercise volume over the intervention and thus a greater effect on walking ability when compared to structured high-pain exercise and usual-care control. Ultimately, in our analysis it was not possible to pool results by adherence owing to only one low-pain study reporting this outcome,⁽⁴⁰⁾ yet this is an interesting possibility and requires further research. Furthermore, a study by Murrow and colleagues compared the effect of traditional walking exercise (walk to pain), and walking exercise which attained a 15% reduction in skeletal muscle oxygenation which was less painful than pain-guided exercise (range: 1-6.5 on a 10 point pain scale), on walking ability and mitochondrial oxidative capacity.⁽⁴⁷⁾ The study found both training programs improved PFWA and mitochondrial oxidative capacity, which supports the notion that a repeated ischemic stimulus, however modest, may contribute to improvements in walking ability and mitochondrial oxidative capacity in people with PAD and IC. However, there was a significant interaction in favour of traditional walking (which was more painful) for mitochondrial oxidative capacity, and adherence was similar between groups. This suggests the most ischaemic stimulus may be superior at improving PFWA when adherence is held

constant. Nevertheless, only 50% of the randomised cohort completed the trial suggesting that these results may be underpowered. If heterogeneity in walking ability outcomes following exercise training are influenced by levels of ischaemia reached, and adherence to exercise, more research is needed to confirm whether structured low-pain exercise may be a viable alternative to high-pain exercise.

Whilst the large effect size estimates in our review suggest low-pain exercise has a greater effect compared to high-pain exercise on walking ability, there is a level of uncertainty. Using the network to compare low-pain to high-pain exercise indirectly, the SMD crosses the zero threshold in the MWA comparison (Hedges g : 1.28; 95% CI: -0.07 to 2.62; Figure 4); although there is a trend towards significance. The overall effect size for structured low-pain exercise is highly influenced by two studies in particular, which had a low standard deviation and large mean difference, inflating the effect size estimate.^(41, 42) Alongside this, there are wide PI which cross the null for the pairwise comparison of structured low-pain exercise to control. The estimates are imprecise as only a few small studies could be included in the analysis, and when calculating PI, there is an assumption that τ^2 and the study effects are normally distributed.⁽⁴⁸⁾ Nevertheless, structured low-pain exercise appears to be superior to unstructured exercise advice only. Therefore, we encourage further research into the potential use of structured low-pain exercise as a non-pharmacological treatment for IC.

Strengths and weaknesses of the meta-analysis

Our findings are bolstered by the robust data extraction methods employed before conducting the analysis, results of which were confirmed in sensitivity investigations. A caveat to our conclusions is that we can have more confidence in our analysis of the high-pain studies. Our

analysis included more high-pain studies, which showed no evidence of heterogeneity among them. By comparison, high heterogeneity was present in the low-pain studies, likely driven by the small number of low-pain studies included in our analysis. A further limitation to our findings is the possible publication bias for low-pain studies; conversely, there was no evidence of publication bias for high-pain studies. In addition, there was a high-risk of other biases in most of the included studies, with only 3 studies adhering to CONSORT guidelines.⁽⁴⁵⁾ This is a weakness of the studies included in this review and in the literature as a whole. We also acknowledge that the objective cut-off points used to classify high and low pain exercise has potential limitations. In order to address these issues, large head-to-head RCTs which follow CONSORT guidelines are needed, to confirm the efficacy of different structured exercise programmes prescribed using pain, on walking ability in people with IC. This would also allow us to assess consistency in the estimates, as currently, for both outcomes, the networks were “tree-shaped” (i.e., without loops), hampering the possibility for this assessment.⁽⁴⁹⁾

Implications and conclusions

Current exercise guidelines for people with IC suggest exercising up to maximum claudication pain. Our analysis demonstrates that there is strong evidence in support of structured high-pain exercise, and some evidence in support of structured low-pain exercise, to improve walking ability in people with IC; with both performing better than usual-care control (unstructured exercise advice only). There is a clear lack of structured low-pain exercise studies available, despite some positive outcomes on walking ability in people with IC; as a result structured low-pain exercise may be overlooked in national guidelines. Large head to head RCTs which follow CONSORT guidelines are needed, to confirm the

superiority, or non-inferiority, of different structured exercise programmes prescribed using pain on walking ability in people with IC.

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DATA SHARING

The data underlying this article will be shared on reasonable request to the corresponding author.

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The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

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Figure 1. Study Selection Flow Diagram.

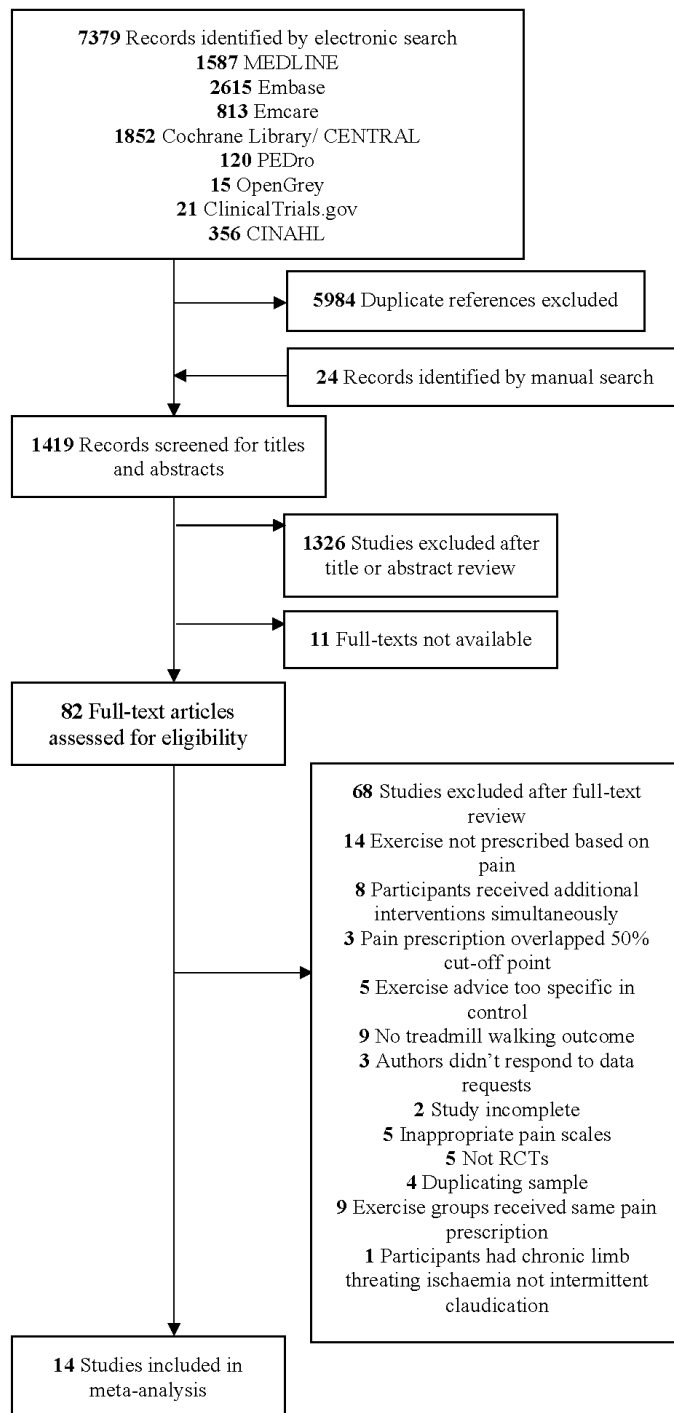


Figure 2. Pairwise Meta-Analysis High-Pain vs. Control and Low-Pain vs. Control Maximal Walking Ability.

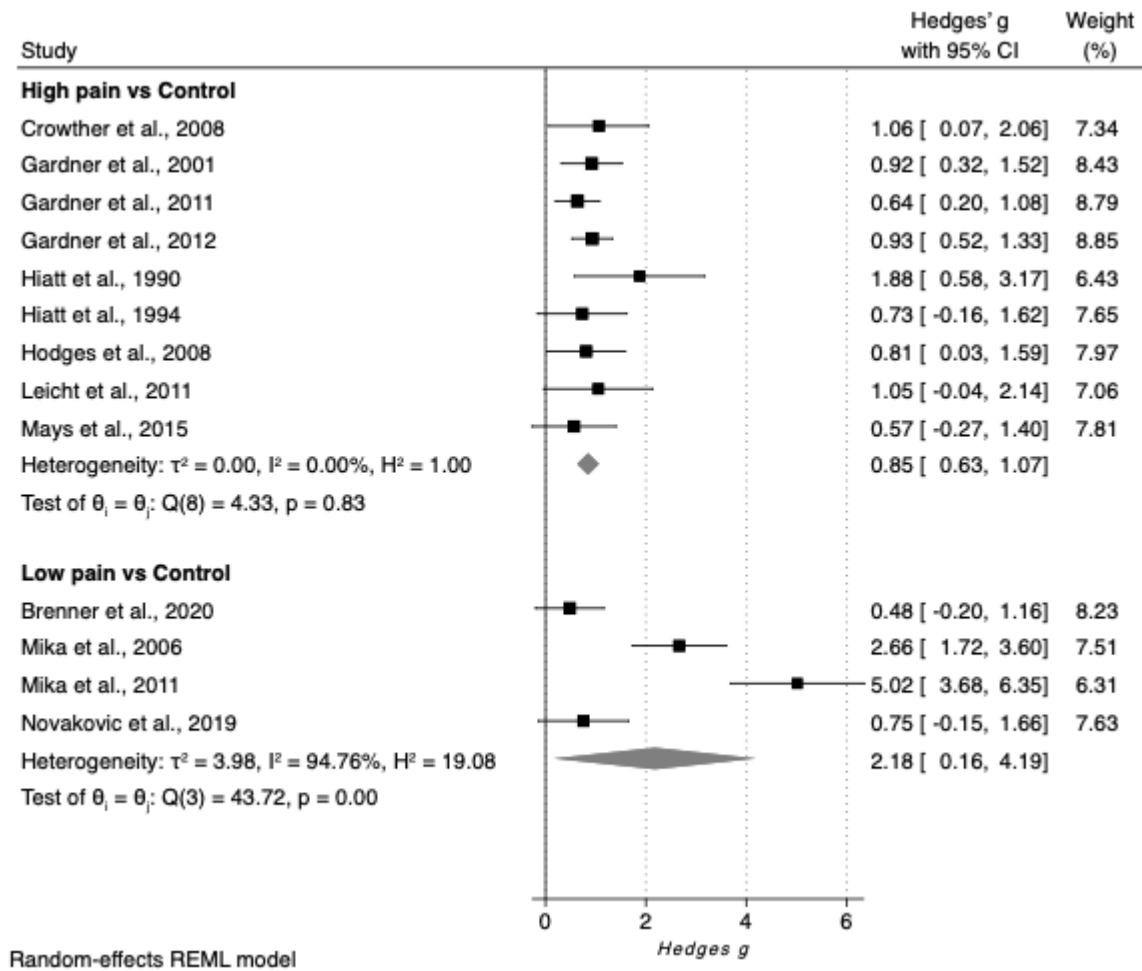


Figure 3. Pairwise Meta-Analysis High-Pain vs. Control and Low-Pain vs. Control Pain Free Walking Ability.

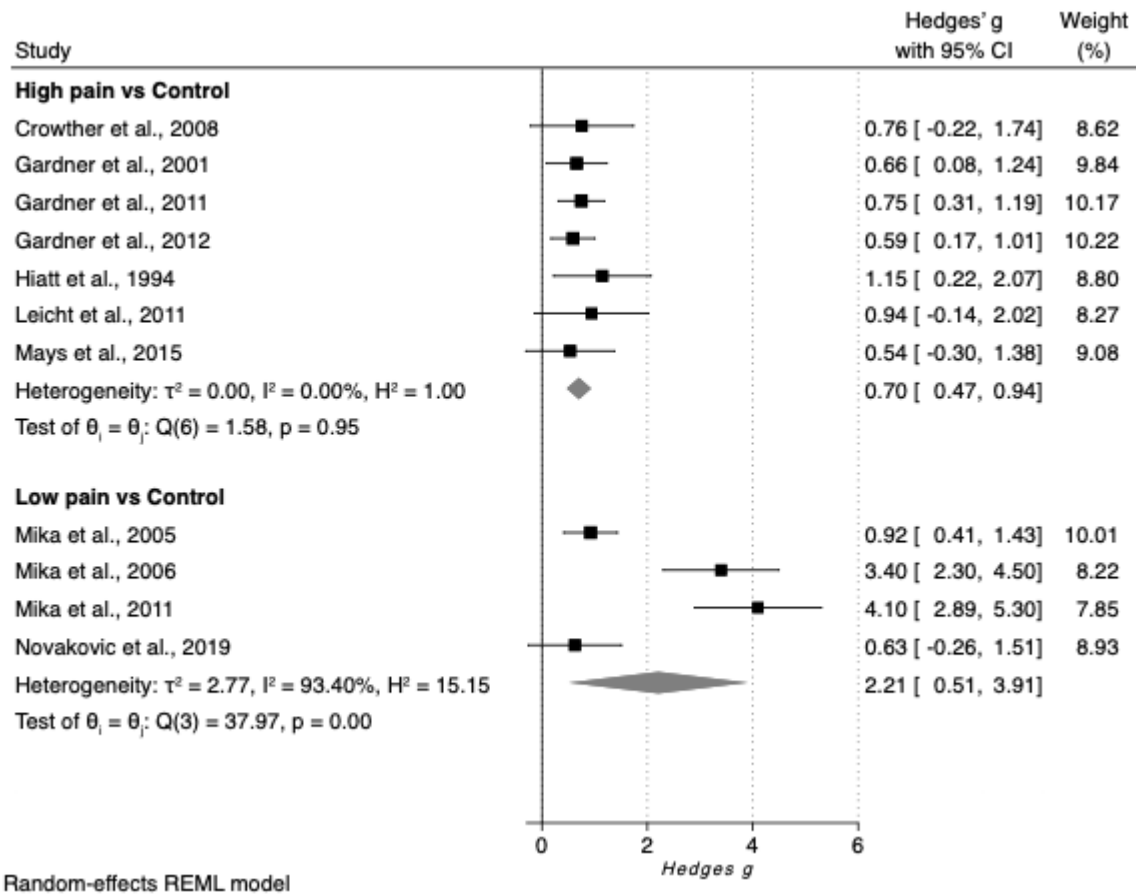


Figure 4. Summary of Network Meta-Analysis Maximal Walking ability. H: High-Pain, L: Low-Pain, C: Control. Effects were considered trivial at <0.2 , small at $0.2-0.5$, moderate at $0.5-0.8$, and large at >0.8 .

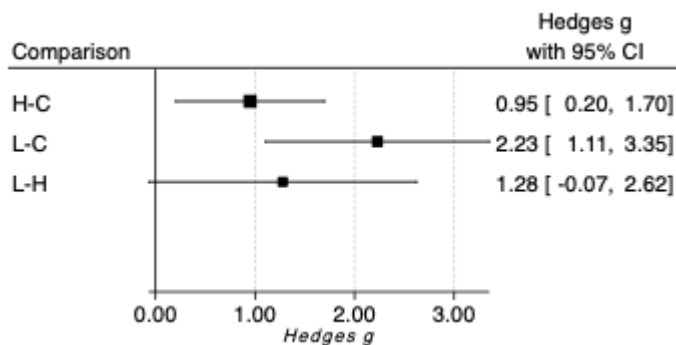


Figure 5. Summary of Network Meta-Analysis Pain Free Walking ability. H: High-Pain, L: Low-Pain, C: Control. Effects were considered trivial at <0.2 , small at $0.2-0.5$, moderate at $0.5-0.8$, and large at >0.8

