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Original citation & hyperlink:
Seed, SA, Harwood, AE, Sinclair, J, Pymer, S, Caldow, E, Ingle, L, Egun, A & Birkett, ST 2021, 'A Systematic Review of Exercise Prescription in Patients with Intermittent Claudication: Does Pain Matter?', Annals of Vascular Surgery, vol. 77, pp. 315-323. https://dx.doi.org/10.1016/j.avsg.2021.06.025

DOI 10.1016/j.avsg.2021.06.025
ISSN 0890-5096
ESSN 1615-5947

Publisher: Elsevier

A Systematic Review of Exercise Prescription in Patients with Intermittent Claudication: Does Pain Matter?

Sally A Seed[1], Amy E Harwood[2], Jonathan Sinclair[1], Sean Pymer[3], Edward Caldow[4], Lee Ingle[5], Anselm Egun[6], Stefan T Birkett[1]

[1]School of Sport and Health Sciences, University of Central Lancashire, Preston, UK

[2]Centre for Sports, Exercise and Life Sciences, Coventry University, Coventry, UK

[3]Academic Vascular Surgical Unit, Hull York Medical School, Hull, UK

[4]School of Health and Society, University of Salford, Salford, UK

[5] Department of Sport, Health and Exercise Science, University of Hull, Hull, UK

[6] Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK

Corresponding Author:

Sally Seed
School of Sport and Health Sciences
University of Central Lancashire
Fylde Road
Preston
PR1 2HE
saseed@uclan.ac.uk
07702654335

Declaration of Interests: None.

ABSTRACT

Background: Current guidelines for intermittent claudication advocate exercise at moderate to maximal claudication pain. However, adherence rates to supervised exercise programmes (SEP) remain poor and claudication pain is a contributing factor. Limited evidence suggests that moderate or pain-free exercise may be just as beneficial and may be better tolerated. However, it remains unclear what 'level' of claudication pain is optimal for improving functional outcomes. We therefore conducted a systematic review to synthesise the evidence for exercise prescribed at different levels of claudication pain.

Methods: The CENTRAL, MEDLINE, Embase and CINAHL databases were searched up to October 2020. Randomised controlled trials (RCTs) that directly compared at least two different intensities of claudication pain were included. Outcome measures included walking performance, adherence, quality of life and vascular function.

Results: Of 1,543 search results, two studies were included. Maximal walking distance improved by 100-128% in the moderate-pain SEP groups, and by 77-90% in the pain-free SEP groups. Importantly, there were no significant differences between the moderate-pain and pain-free SEP groups in either study for improvements in walking performance, though comparison to a maximal-pain SEP group was not made.

Conclusions: The efficacy of SEPs for patients with intermittent claudication is irrefutable, though there is no consensus on the optimal level of pain. Therefore, adequately powered RCTs are required to compare the effect of pain-free SEPs,

moderate-pain SEPs and maximal-pain SEPs on functional outcomes. (PROSPERO ID: CRD42020213684).

1.1 INTRODUCTION

Peripheral artery disease (PAD) is a chronic disease characterised by atherosclerotic lesions in the lower limbs,[1] affecting over 236 million people worldwide.[2] A classic symptom of PAD is intermittent claudication (IC), characterised by reproducible cramping, ischaemic muscle pain, precipitated by exertion and relieved by rest.[3] This symptom arises due to the imbalance of oxygen supply and demand in the working muscles, secondary to atherosclerosis.[4] IC can reduce an individual's quality of life by significantly impairing walking ability and functional capacity.[5, 6]

National and international guidelines[7, 8] recommend supervised exercise programmes (SEP) as first line treatment for patients with IC and there is overwhelming evidence for the benefit of SEPs including improvements in maximal and pain-free walking distance.[9] Despite these benefits, recruitment and adherence rates are poor,[10] with only one third of patients eligible and willing to undertake a SEP.[11] One potential reason for this, may be because of the exercise-related pain. Indeed, it has been demonstrated that completion rates were higher when exercise was performed at a low, rather than high, pain threshold.[12, 13] Indeed, exercising to a high level of pain may have adverse effects, such as pro-inflammatory response and muscle catabolism.[14] Furthermore, limited evidence has also shown that exercising up to the point of onset or mild claudication pain improves walking ability.[15, 16]

Despite this, current UK guidelines[8] recommend exercise to maximal claudication pain, with international guidelines and meta-analyses advocating that exercise should be

performed at moderate to maximal pain to improve walking ability.[17] As such, conflicting evidence exists, with inconsistencies between guidelines as to what level of pain exercise is prescribed at. Therefore, it remains unclear which claudication pain prescription is optimal for improving functional outcomes. Furthermore, a recent scientific statement from the American Heart Association[18] recommended further research to consider the role of exercising at different pain levels as identifying the optimal pain-based prescription may improve patient adherence.[12]

Therefore, the primary aim of this systematic review was to assess interventions that have directly compared exercise prescription at differing levels of claudication pain on walking performance in patients with IC. A secondary aim was to access the level of claudication pain on vascular function and quality of life (QoL).

1.2 METHODS

This review adhered to the PRISMA guidelines[19] and was prospectively registered on PROSPERO (CRD42020213684).

1.2.1 Search Strategy and Inclusion Criteria

Potential studies were identified from database inception to 9th October 2020. The CENTRAL, MEDLINE, Embase and CINAHL databases were searched. Only full text articles published in the English language were included and duplicate articles were

removed. Key search terms were developed by SS and reviewed by SB and AH. The search strategy combined key words including "peripheral artery disease" [OR] "intermittent claudication" [AND] "pain free" [OR] "moderate pain" [OR] "maximal pain". All titles and abstracts were independently screened by two assessors (SS and SB), and a third reviewer was consulted to discuss any disagreements (AH). Full text manuscripts of potentially eligible articles were then independently screened using the inclusion/exclusion criteria. Reference lists of full texts were also hand searched.[20, 21] We included randomised control trials (RCTs) that employed any mode of prescribed structured exercise for the treatment of IC, comparing at least two different intensities of IC pain. Exercise interventions had to be ≥4 weeks in duration and studies that included patients with critical limb ischaemia or asymptomatic PAD were excluded. Studies were also excluded if patients were <18 years old or the programme used other interventions (e.g., surgery) in addition to exercise.

1.2.2 Data Extraction

Data were extracted and inputted into a Microsoft Excel database (Microsoft Excel, Redmond, USA). Data extraction included the primary outcome measure of maximal walking distance/time (MWD/T). MWT where reported was converted to MWD to allow between study comparison (walking time in seconds (s) x treadmill speed (m/s)). Other outcomes included pain-free walking distance/time (PFWD/T), recruitment and adherence, flow mediated dilation (FMD), ankle brachial pressure index (ABPI), and QoL

data. Study characteristics such as sample size, intervention components and inclusion/exclusion criteria were also extracted to assess the quality of the study.

1.2.3 Risk of bias and Quality assessment

RCTs that met our inclusion criteria were assessed by two reviewers (SS and AH) for risk of bias using the Cochrane risk of bias tool[22]. Quality assessment was also performed using the physiotherapy evidence database (PEDro) scale.[23] Points were awarded when a criterion was clearly satisfied generating an overall score of the study out of 10 (Table II).

1.3 RESULTS

The PRISMA flow diagram[23] is shown in Figure 1. Our search generated 1,543 results and four full-text articles were retrieved after screening titles and abstracts. Two articles were then excluded[24,25] due to the exercise intensity prescription based on percentage of heart rate on maximal capacity. Two articles[20, 21] were retained for the review.

Figure 1 here

1.3.1 *Included trials*

The total number of patients included in the analysis was 96. Of those, 84 were allocated to a SEP and 12 were allocated to the control (non-exercise) group. *Mika et al (2013)*[20]

randomised 27 patients (59% males and 41% female, mean age of 64.8 ± 7.2) to the moderate-pain SEP group and 25 patients (64% males and 36% females, mean age of 65.2 ± 8.0) to the pain-free SEP group. *Novakovic et al (2019)*[21] randomised 10 patients to the moderate-pain SEP group (60% male and 40% female, mean age 65.1 ± 7.6), 11 patients to the pain-free SEP group (82% male and 18% female, mean age 65.6 ± 11.0) and 8 patients to the control group (75% male and 25% female ,mean age 62.0 ± 8.3). *Novakovic et al (2019)*[21] also used a control group that did not attend a SEP and was advised to continue with secondary preventative activities such as walking, as recommended by a vascular surgeon or other vascular medicine specialist. Medications included aspirin (acetylsalicylic acid), clopidogrel, β-blockade, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics and statins. MWD/T was measured using either a graded[20] or constant load treadmill protocol[21] and was determined as the point at which patients reached a level of 5 on the 1-5 pain scale, where 1 = no pain. ABPI and FMD were measured via established techniques.

Treadmill walking was the mode of exercise for both interventions. Methods of exercise prescription differed between studies. *Novakovic et al (2019)*[21] set the initial treadmill speed based on an intensity of 70% of predicted maximum heart rate (HR_{max}) with the gradient set at 0%. When heart rate during walking reduced to <65% HR_{max} the treadmill speed was increased by 0.3 km/h. For the moderate-pain SEP, patients walked until they reported a score of three to four on the five-point pain scale. For the pain-free SEP, patients walked up to two-thirds of their PFWD measured at baseline. *Mika et al (2013)*[20]

set the treadmill speed at 3.2 km/h and the grade was individually determined for each patient so that it would induce claudication pain within three to five minutes. The moderate-pain SEP group walked until they reported a score of four on the pain scale, whilst the pain-free SEP group stopped at the onset of claudication, (a score of two on the pain scale).

SEP delivery varied between studies, one study used an exercise bike for active recovery to allow leg pain to subside,[21] whilst the other allowed patients to rest until the claudication pain had abated.[20] Training frequency and duration varied from two to three times per week for up to 35 to 60 minutes per session, for a period of 12 weeks. Study characteristics are shown in Table I.

Table I here

1.3.2 *Risk of bias*

Risk of bias is shown in Figure 2 and study quality in Table II. The mean score on the PEDro scale was 6.5. One study stated that outcome assessors were blinded and an intention to treat analysis was not used in either study.

Figure 2 here

Table II here

1.3.3 *Walking performance and adherence*

MWD/T

One study reported MWD in meters[21] and one reported MWT in seconds.[20] *Novakovic et al (2019)*[21] found that the moderate-pain SEP group improved by 128% (median change 109m, range 85m to 194m, p <0.005) and the pain-free SEP group improved by 77% (median change 71m, range 92m to 163m, p <0.003). There was no improvement in MWD for the control group. *Mika et al (2013)*[20] found that the moderate-pain SEP group improved by 100% (mean change 440 ± 262 seconds, p <0.001, converted to 392 ± 233m) and the pain-free SEP group improved by 98% (mean change 479 ± 333 seconds, p <0.001, converted to 426 ± 296m). There were no significant differences between the moderate-pain and pain-free SEP groups in either study, for improvements in MWD (Table I).

PFWT

Novakovic et al (2019)[21] found that PFWD improved by 114% (median change 57m, range 50m to 107m, p <.005) in the moderate-pain SEP group, and by 141% (median change 75m, range 53 to 128m, p <0.003) in the pain-free SEP group. There was no significant improvement in the control group.[21] *Mika et al (2013)*[20] found comparable results as PFWT improved by 119% (mean change 167 ± 158 seconds, p <0.001, converted to 149 ± 141m) in the moderate-pain SEP group and by 93% in the pain-free SEP group (mean change 157 ± 117 seconds, p <0.001, converted to 140 ± 104m). There

were no significant differences between the moderate-pain and pain-free SEP groups in either study, for improvements in PFWD (Table I).

1.3.4 *QoL*

QoL was considered in one study,[21] using the short-form 36. Following the 12-week programme, the moderate-pain SEP group showed significant improvements in the physical component summary (p =0.004) but not the mental component summary. The moderate-pain SEP noted improvements in several physical single domains including physical functioning and bodily pain, whilst the pain-free SEP group had significant improvements in the single domains of physical role and bodily pain (Table I).

1.3.5 *Vascular function*

FMD

Both trials reported the effect of exercise on FMD, measured at the brachial artery. *Novakovic et al (2019)*[21] found that the moderate-pain SEP group had a significant improvement in FMD, whilst the pain-free SEP group did not (4.4% to 8.0%; p =0.002 vs pain-free: 4.6% to 6.9%; p =0.066). *Mika et al (2013)*[20] found that both SEP groups had a significant improvement in FMD (moderate-pain: 4.59% to 6.27%; p <0.001 vs pain-free: 3.98% to 6.22%; p <0.001; Table I).

ABPI

Novakovic et al (2019)[21] reported that neither SEP group had a significant improvement in ABPI. *Mika et al (2013)*[20] however, reported a significant improvement in ABPI (0.06 ± 0.12 p <0.05) in the moderate-pain SEP group, but not the pain-free SEP group (Table I).

1.3.6 *Adherence*

Completion of the exercise interventions varied between studies, ranging from 80%[21] to 87%.[20] Reasons for non-completion included surgery, ulcers, transportation problems, personal reasons and loss to follow-up. Only one study[21] reported adherence rates which were similar between groups (93% vs 95%; p =0.645).

1.4 DISCUSSION

Current recommendations state that patients with IC should exercise at moderate to maximal pain to obtain optimal improvements in MWD, though evidence comparing different pain intensities is lacking.[8, 17, 26] We aimed to consider the evidence for exercise prescribed at different levels of claudication pain. Whilst there were only two RCTs identified, the findings indicate that pain-free exercise may be as beneficial as exercise prescribed at moderate levels of claudication pain for improving walking performance. Importantly, neither study included a maximum pain SEP group.

1.4.1 *Walking performance and adherence*

Both studies showed significant improvements in walking performance, there was no statistical difference between training conditions, with similar improvements shown in the pain-free SEP group and the moderate-pain SEP group. This supports previous evidence that pain-free exercise improves walking performance to a similar extent as moderate-pain exercise.[15, 16] Indeed, prescribing exercise to the point of strong pain has been described as behaviourally counterintuitive,[27] however a recent study showed that exercise at a high pain threshold was significantly more effective at improving walking performance versus pain-free exercise.[28] Despite this, no trial has directly compared a pain-free SEP, to a moderate-pain SEP and maximal-pain SEP.[18] Consequently, conclusions cannot be drawn as to which method provides the most effective outcomes. Further investigation is therefore warranted, which has the potential to inform future guidelines and clinical practice, as long as it is well-designed and adequately powered.

This further work is important, given that the level of pain prescribed can have a significant impact on patient adherence to SEPs.[29] Indeed, Harwood et al (2016)[11] highlighted that SEP participation rates remain low, with claudication pain being a contributable factor. Likewise, a recent systematic review[10] found that completion rates were significantly higher in those prescribed low claudication pain exercise (93.4% adherence) versus exercise prescribed to high pain (77.0% adherence). In addition, completion rates were higher in the low pain groups, with patients in these groups being 1.5 times more likely to complete the intervention. This is further supported by a recent study that found significantly lower levels of fidelity to the desired intensity when

exercise was prescribed at maximal pain[28]. Therefore, whilst low and moderate pain exercise may elicit similar improvements in walking, low pain exercise could encourage a higher compliance and be more likely to result in long lasting behaviour change.

One major concern with regards to exercise prescription is the inconsistency between guidelines. For instance, UK guidelines state that patients should exercise to the point of maximal pain,[8] whereas the American College of Sports Medicine guidelines advocate exercising to the point of moderate pain.[17] Moreover, the American Heart Association guidelines state that patients should walk to moderate-maximal pain[30] whilst several other guidelines do not provide a specific recommendation.[31, 32] Consequently, this could cause confusion for clinicians and exercise professionals, who may be unsure which guidelines to adhere to, leading to some patients receiving suboptimal care. These findings indicate that a universal and consistent guideline is required for exercise prescription in patients with IC.

1.4.2 *QoL*

IC is strongly associated with reduced QoL,[33] however only one study[21] in this review investigated the impact on QoL as a consequence of exercise prescribed at different pain thresholds. Exercise prescribed to moderate claudication pain led to improvements in the physical component summary of the SF-36, and several single domains including physical functioning and bodily pain, whilst pain-free exercise led to improvements in the single domains of role physical and bodily pain. Neither intervention found

improvements in the mental component summary. These results are in agreement with previous studies, by which exercise training improved physical functioning and bodily pain.[34, 35] However there is a general paucity of data considering the effects of exercise training on QoL.[36] In addition, it is likely that the trials included in this review would be underpowered to detect meaningful change in QoL. Therefore, adequately powered trials that directly compare a pain-free SEP, a moderate-pain SEP, and a maximal-pain SEP are required to investigate if the level of pain is associated with changes in QoL.

1.4.3 *Vascular function*

Increases in FMD may lead to improvements in walking performance.[37] *Mika et al (2013)*[20] demonstrated an improvement in FMD in both SEP groups. This supports previous findings which have shown an improvement in FMD following a SEP[38, 39], although this finding is not consistent across different studies.[40] In contrast, *Novakovic et al (2019)*[21] only found a significant improvement in FMD in the moderate-pain SEP group, suggesting changes may be intensity driven, with exercise prescribed at higher pain thresholds providing an adequate stimulus for physiological adaptations. Indeed this is supported by previous evidence, though even higher intensities (maximal claudication pain) may be needed to consistently elicit positive changes in FMD.[41] However, exercising to maximal pain may impair vascular function due to an increase oxidative stress which inactivates endothelium derived nitric oxide, thus exacerbating the condition.[41] However, this effect is relatively short lived with a gradual four hour post-exercise recovery.[42] Clearly, there are inconsistencies in the evidence as to which pain

threshold is required to promote changes in FMD in patients with IC, with no trial directly comparing a pain-free SEP, a moderate-pain SEP and a maximal-pain SEP. This warrants further investigation.

Novakovic et al (2019)[21] reported no change in ABPI in either SEP group and this finding is supported by a recent Cochrane review which found that SEPs do not elicit changes in ABPI.[36] In contrast, *Mika et al (2013)*[20] found a significant change in ABPI in the moderate training group, but not the pain-free group, with the authors suggesting that the ischaemic stimulus from this level of pain was a contributing factor. However, there was a lack of correlation between walking performance and ABPI, increasing the possibility of this finding being due to a type I error.

1.5 LIMITATIONS

This review is not without limitations. Firstly, we were unable to directly compare pain-free and moderate exercise with exercise prescribed at a maximal pain threshold. Secondly, both studies had an unclear risk of bias for a number of criteria and had small sample sizes, with only one adequately powered to detect change in MWD[21]. Thirdly, both studies used treadmill walking as the form of exercise, meaning the results cannot be generalised to different forms of SEP such as a circuit format.[43] Finally, the studies adopted different claudication pain scales, as such the number that represents moderate (3/5 vs. 4/5) or severe (4/5 vs. 5/5) differs. Future studies should familiarise patients with the pain scale to enable accurate reporting.

1.6 CONCLUSIONS

Evidence suggests that pain-free SEPs and moderate-pain SEPs elicit similar improvements in walking performance for patients with IC. However, no trial has directly compared the level of pain at different thresholds; pain-free; moderate intensity; maximal pain; despite a maximal pain prescription being recommended in most clinical guidelines. Adequately powered RCTs are therefore required to compare all three pain thresholds, which may affect patient adherence to SEPs, and directly impact upon future exercise training guidelines in patients with IC.

1.7 FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Tables

Table I**. Summary of findings**

Study (country and design)	**Sample**	**Description of Intervention**	**Outcome measures, follow-up**	**Main findings**
Novakovic et al, 2019[21] (Slovenia) Randomised trial	Total *n* = 36. Patients with diagnosed PAD, Fontaine II classification. Patients with unstable CVD, hospitalisation (< 3 months) and any comorbidities were excluded.	Three groups – moderate-pain SEP, pain-free SEP and control group (1:1:1 ratio) 36 sessions – 2/3 times per week for 60 minutes, walking on a treadmill, followed by AR on an exercise bike	PFWD, MWD, ABPI, FMD, biomarkers, HRV and health related QoL, SF-36 questionnaire Measures performed twice at baseline and after the intervention (12 weeks)	Both moderate-pain and pain-free SEP improved walking capacity (Moderate; PFWD p = .005, MWD p = .005) (Pain-Free; PFWD p = .003, AWD p = .003) There were no improvement in PFWD and MWD with the control group The moderate pain SEP significantly improved FMD (p = .002) whereas the pain-free SEP did not. Neither condition significantly changed ABPI/HRV/biomarkers

				Moderate-pain SEP significantly improved the physical component summary but no change in the mental component summary of the SF-36
Mika et al, 2013 [20] (Poland) Randomised trial	Total *n* = 60. Patients with PAD, Fontaine II classification ABPI < 0.9, able to walk 150m without pain, Pharmacological treatment was stable within 6 months and remained unchanged. Patients with CHD < 1 year, unable to walk 3.2 km/h and any comorbidities were excluded.	Two groups – moderate-pain SEP group (n=30) Pain-free SEPgroup (n=30) 12 weeks, 3 sessions per week Began at 35 minutes, progressively increasing by by 5 min every 2 weeks until 60 mins was completed.	PFWT, MWT, ABPI, FMD, biomarkers Measures performed twice at baseline and after the intervention (12 weeks)	Both moderate-pain and pain-free SEP significantly improved PFWT and MWT(p <0.001) Both groups showed a significant increase in resting and post-exercise FMD (Pain-free; p<0.01, moderate; p<0.001) Significant ABPI change observed only in the moderate training group after 12 weeks (p<0.05) Neither condition significantly changed biomarkers

PAD, peripheral artery disease; CVD, cardiovascular disease; PFWD, pain free walking distance; MWD, maximal walking distance; AR, Active Recovery; ABPI, ankle-brachial pressure index; FMD, flow mediated dilation; HRV, heart rate variability; QoL, quality of life; CHD, coronary heart disease; PFWT, pain-free walking time; MWT, maximal walking

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506 **Table II.** Quality assessment of included trials according to a Physiotherapy Evidence Database (PEDro) Scale

PEDro Scale	Novakovic (2019)	Mika (2013)
Eligibility criteria specified	1	1
Random Allocation	1	1
Concealed Allocation	1	1
Baseline similarity	1	1
Blinding of all subjects	0	0
Blinding of the therapists	0	0
Blinding of assessors	0	1
Measure of one outcome at least 85% subjects	1	1
Intention to treat analysis used	0	0
Between-group comparison performed	1	1
Measures of variability	1	1
Total	7	8
0, No; 1, yes. Score out of 10		

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514 **Figures**

515 Figure 1

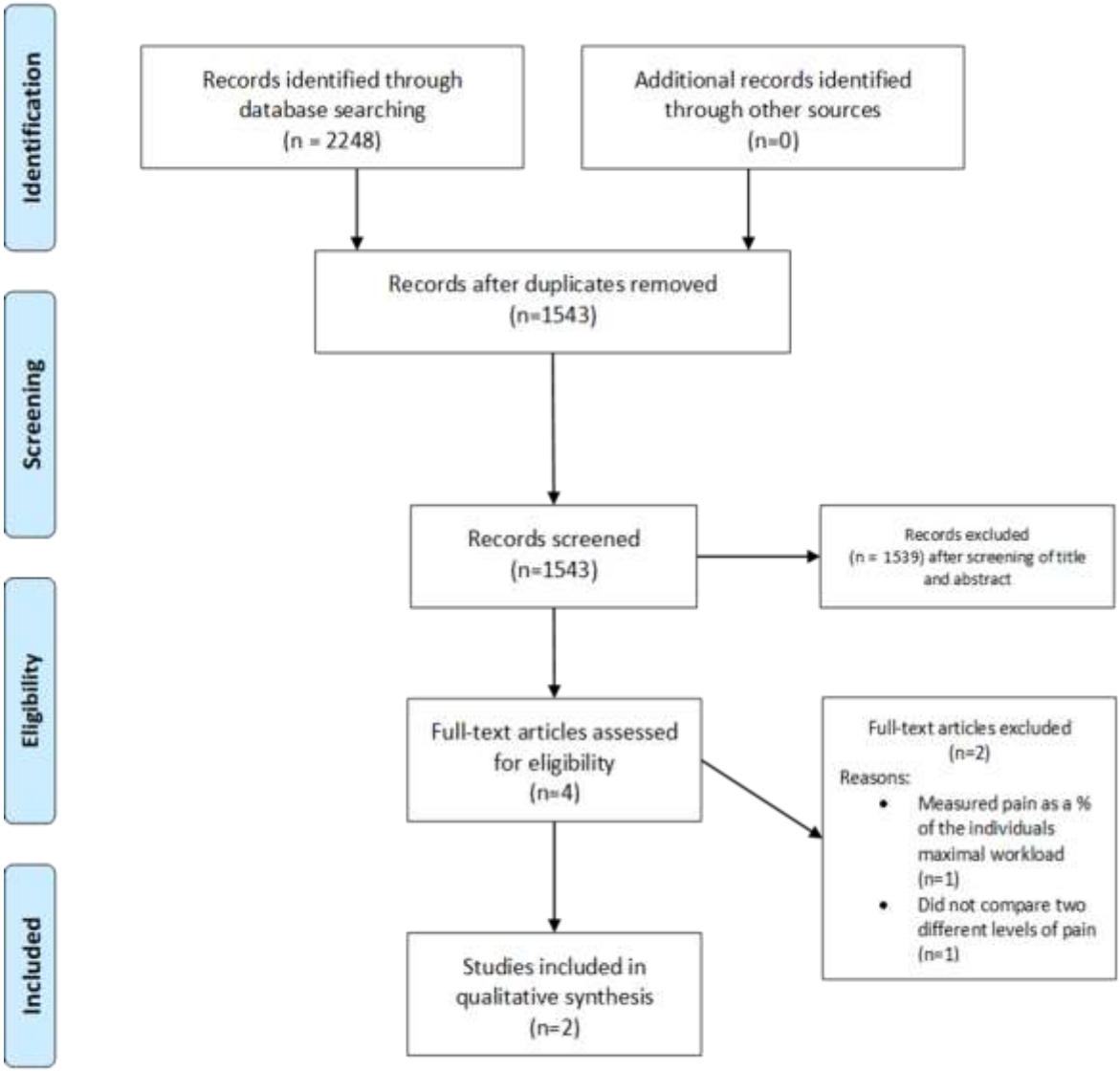

Figure 1. PRISMA flow chart of included studies

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518 Figure 2

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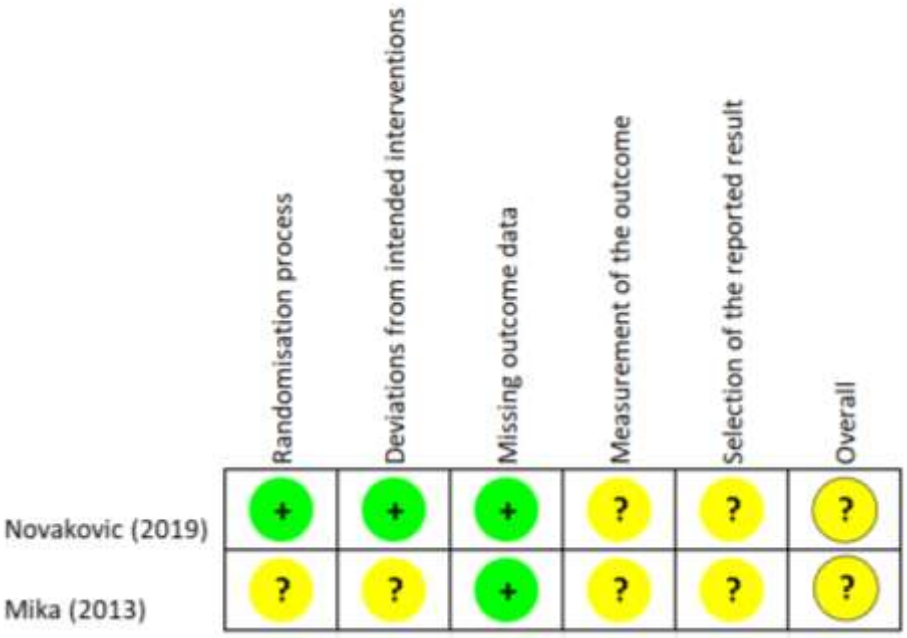

Figure 2. Risk of bias using the Cochrane collaboration tool.