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Exercise for intermittent claudication (Review)

Lane R, Harwood A, Watson L, Leng GC

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[Intervention Review]

Exercise for intermittent claudication

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ABSTRACT

Background

Exercise programmes are a relatively inexpensive, low-risk option compared with other, more invasive therapies for treatment of leg pain on walking (intermittent claudication (IC)). This is the fourth update of a review first published in 1998.

Objectives

Our goal was to determine whether an exercise programme was effective in alleviating symptoms and increasing walking treadmill distances and walking times in people with intermittent claudication. Secondary objectives were to determine whether exercise was effective in preventing deterioration of underlying disease, reducing cardiovascular events, and improving quality of life.

Search methods

For this update, the Cochrane Vascular Information Specialist searched the Specialised Register (last searched 15 November 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10) via the Cochrane Register of Studies Online, along with trials registries.

Selection criteria

Randomised controlled trials of an exercise regimen versus control or versus medical therapy for people with IC due to peripheral arterial disease (PAD). We included any exercise programme or regimen used for treatment of IC, such as walking, skipping, and running. Inclusion of trials was not affected by duration, frequency, or intensity of the exercise programme. Outcome measures collected included treadmill walking distance (time to onset of pain or pain-free walking distance and maximum walking time or maximum walking distance), ankle brachial index (ABI), quality of life, morbidity, or amputation; if none of these was reported, we did not include the trial in this review.

Data collection and analysis

For this update (2017), RAL and AH selected trials and extracted data independently. We assessed study quality by using the Cochrane 'Risk of bias' tool. We analysed continuous data by determining mean differences (MDs) and 95% confidence intervals (CIs), and dichotomous data by determining risk ratios (RRs) and 95% CIs. We pooled data using a fixed-effect model unless we identified significant heterogeneity, in which case we used a random-effects model. We used the GRADE approach to assess the overall quality of evidence supporting the outcomes assessed in this review.

Main results

We included two new studies in this update and identified additional publications for previously included studies, bringing the total number of studies meeting the inclusion criteria to 32, and involving a total of 1835 participants with stable leg pain. The follow-up period ranged from two weeks to two years. Types of exercise varied from strength training to polestriding and upper or lower limb exercises; supervised sessions were generally held at least twice a week. Most trials used a treadmill walking test for one of the primary outcome measures. The methodological quality of included trials was moderate, mainly owing to absence of relevant information. Most trials were small and included 20 to 49 participants. Twenty-seven trials compared exercise versus usual care or placebo, and the five remaining trials compared exercise versus medication (pentoxifylline, iloprost, antiplatelet agents, and vitamin E) or pneumatic calf compression; we generally excluded people with various medical conditions or other pre-existing limitations to their exercise capacity.

Meta-analysis from nine studies with 391 participants showed overall improvement in pain-free walking distance in the exercise group compared with the no exercise group (MD 82.11 m, 95% CI 71.73 to 92.48, P < 0.00001, high-quality evidence). Data also showed benefit from exercise in improved maximum walking distance (MD 120.36 m, 95% CI 50.79 to 189.92, P < 0.0007, high-quality evidence), as revealed by pooling data from 10 studies with 500 participants. Improvements were seen for up to two years.

Exercise did not improve the ABI (MD 0.04, 95% CI 0.00 to 0.08, 13 trials, 570 participants, moderate-quality evidence). Limited data were available for the outcomes of mortality and amputation; trials provided no evidence of an effect of exercise, when compared with placebo or usual care, on mortality (RR 0.92, 95% CI 0.39 to 2.17, 5 trials, 540 participants, moderate-quality evidence) or amputation (RR 0.20, 95% CI 0.01 to 4.15, 1 trial, 177 participants, low-quality evidence).

Researchers measured quality of life using Short Form (SF)-36 at three and six months. At three months, the domains 'physical function', 'vitality', and 'role physical' improved with exercise; however this was a limited finding, as it was reported by only two trials. At six months, meta-analysis showed improvement in 'physical summary score' (MD 2.15, 95% CI 1.26 to 3.04, P = 0.02, 5 trials, 429 participants, moderate-quality evidence) and in 'mental summary score' (MD 3.76, 95% CI 2.70 to 4.82, P < 0.01, 4 trials, 343 participants, moderate-quality evidence) secondary to exercise. Two trials reported the remaining domains of the SF-36. Data showed improvements secondary to exercise in 'physical function' and 'general health'. The other domains - 'role physical', 'bodily pain', 'vitality', 'social', 'role emotional', and 'mental health' - did not show improvement at six months.

Evidence was generally limited in trials comparing exercise versus antiplatelet therapy, pentoxifylline, iloprost, vitamin E, and pneumatic foot and calf compression owing to small numbers of trials and participants.

Review authors used GRADE to assess the evidence presented in this review and determined that quality was moderate to high. Although results showed significant heterogeneity between trials, populations and outcomes were comparable overall, with findings relevant to the claudicant population. Results were pooled for large sample sizes - over 300 participants for most outcomes - using reproducible methods.

Authors' conclusions

High-quality evidence shows that exercise programmes provided important benefit compared with placebo or usual care in improving both pain-free and maximum walking distance in people with leg pain from IC who were considered to be fit for exercise intervention. Exercise did not improve ABI, and we found no evidence of an effect of exercise on amputation or mortality. Exercise may improve quality of life when compared with placebo or usual care. As time has progressed, the trials undertaken have begun to include exercise versus exercise or other modalities; therefore we can include fewer of the new trials in this update.

PLAIN LANGUAGE SUMMARY

Exercise for reducing intermittent claudication symptoms

Background

Intermittent claudication is a cramping leg pain that develops when walking and is relieved with rest. It is caused by inadequate blood flow to the leg muscles caused by atherosclerosis (fatty deposits restricting blood flow through the arteries). People with mild to moderate claudication are advised to keep walking, stop smoking, and reduce cardiovascular risk factors. Other treatments include antiplatelet therapy, pentoxifylline or cilostazol, angioplasty (inserting a balloon into the artery to open it up), and bypass surgery.

Studies and key results

Review authors identified 32 controlled trials that randomised 1835 adults with stable leg pain to exercise, usual care or placebo, or other interventions (current until November 2016). Researchers measured outcomes at times ranging from two weeks to two years. Types of exercise varied from strength training to polestriding and upper or lower limb exercises; in general, supervised sessions were held at least twice a week. The quality of included trials was moderate, mainly because of absence of relevant information. Ten trials reported that in the exercise groups, pain-free walking distance and the maximum distance that participants could walk was increased. Improvements were seen for up to two years. Exercise did not improve ankle to brachial blood pressure index. No evidence of an effect of exercise was seen on death or need for amputation because data were limited. Researchers assessed quality of life using the SF-36 Questionnaire at three and six months. At three months, indicators of quality of life - 'physical function', 'vitality', and 'role physical' - had all improved with exercise, but these data are limited, as only two trials reported this. Five studies reported improved 'physical summary score' and four studies reported improved 'mental health score' following exercise at six months, with two trials also reporting improvements in 'physical function' and 'general health'. All other domains showed no improvement at six months following exercise.

Comparisons of exercise with antiplatelet therapy, pentoxifylline, iloprost, vitamin E, and pneumatic foot and calf compression were limited because numbers of identified trials and participants were small.

Quality of the evidence

The present review shows that exercise programmes appear to improve walking distance for people considered fit for exercise regimens. This benefit appears to be sustained over two years. Evidence presented in this review was of moderate to high quality. Although differences between trials were evident, populations and outcomes were comparable overall, and findings were relevant to people with intermittent claudication. Combined results were derived from large sample sizes - over 300 participants for most outcomes - using reproducible methods.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Exercise compared with no exercise for intermittent claudication

Patient or population: adults with intermittent claudication
Settings: hospital or community-based physical therapy exercise programmes
Intervention: exercise[a]
Comparison: no exercise (previously known as usual care)

Outcomes	Illustrative comparative risks* (95% CI)[b]		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No exercise	Exercise[a]				
Pain-free walking distance (m) follow-up: 6 weeks to 24 months	Mean pain-free walking distance ranged across control groups from 63.3 m to 253 m.	Mean pain-free walking distance (m) in exercise groups ranged from 116 m to 413 m. MD was **82.11 m further** in the exercise group. (95% CI 71.73 to 92.48)		391 (9 RCTs)	⊕⊕⊕⊕ **high**[c]	4/9 studies (Cucato 2013; Gardner 2002; Jansen 1991 and Mika 2005) reported a clear improvement.
Maximum walking distance (m) follow-up: 6 weeks to 24 months	Mean maximum walking distance ranged across control groups from 122 m to 771 m	Mean maximum walking distance (m) in exercise groups ranged from 136 m to 1100 m. MD was **120.36 m further** in the exercise group. (95% CI 50.79 to 189.92)		500 (10 RCTs)	⊕⊕⊕⊕ **high**[d]	5/10 studies (Cucato 2013; Gardner 2002; Jansen 1991; Tew 2015; Zwierska 2005) reported a clear improvement.

Ankle brachial index follow-up: 3 to 12 months	Mean ABI ranged across control groups from 0.32 to 0.89.	Mean ABI in exercise groups ranged from 0.34 to 0.96. MD was **0.04 higher** in the exercise group. (95% CI 0.00 to 0.08)		570 (13 RCTs)	⊕⊕⊕◯ **moderate**[e]	A change in ABI of 0.04 is of limited clinical significance.
Mortality: all-cause deaths follow-up: 3 to 12 months	A total of 9/273 deaths occurred in the no exercise group.	A total of 8/267 deaths occurred in the exercise group.	RR 0.92 (0.39 to 2.17)	540 (5 RCTs)	⊕⊕⊕◯ **moderate**[f]	
Amputation follow-up: 12 months	A total of 2/88 amputations occurred in the no exercise group	No amputations occurred in the exercise group (0/89).	RR 0.20 (0.01 to 4.15)	177 (1 RCT)	⊕⊕◯◯ **low**[g]	
Quality of Life SF-36 Physical Summary score (scale 0 to 100, higher score indicates better quality of life) follow-up: 6 months	Mean physical summary score ranged across control groups from 34.2 to 47.1.	Mean Physical Summary score in exercise groups ranged from 41 to 54.1. MD score was **2.15** **higher** in the exercise group. (95% CI 1.26 to 3.04)		429 (5 RCTs)	⊕⊕⊕◯ **moderate**[h]	
Quality of Life SF-36 Mental Summary score (scale 0 to 100, higher score indicates better quality of life) follow-up: 6 months	Mean Mental Summary score ranged across control groups from 38.8 to 62.0.	Mean Mental Summary score in exercise groups ranged from 39.6 to 67. MD score was **3.76** **higher** in the exercise group. (95% CI 2.7 to 4.82)		343 (4 RCTs)	⊕⊕⊕◯ **moderate**[i]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ABI: ankle brachial index; CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio; SF: Short Form

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Variability in type, duration, and frequency of exercise programmes as prescribed. Exercise programmes included a duration of six weeks up to one year, generally twice or three times a week, varying in length between 30 minutes and one hour.

[b] When possible, the no exercise (control) groups results were measured at the same time point and were used in the meta-analysis to calculate assumed risk.

[c] The level of evidence was high, as most trials were of high quality.

[d] The level of evidence was high, as most trials were of high quality. Heterogeneity was significant (P = 0.01, I^2 = 89%), and CIs were broad (50.79 to 189.92). However further research is unlikely to change this.

[e] We downgraded by one step owing to significant heterogeneity (P $\leq$ 0.01, I^2 = 64%); however CIs were narrow (0.00 to 0.09). Given the size of the data set, it is unlikely that further data will demonstrate a difference between the two groups.

[f] We downgraded the evidence by one step, as analysis included only five small studies (of which one was underpowered) and showed wide confidence intervals (imprecision).

[g] We downgraded the evidence by two steps, as data are from a single study with wide CIs (imprecision) and events were few overall.

[h] We downgraded owing to heterogeneity (P = 0.02, I^2 = 66%), narrow CI (1.26 to 3.04), and a symmetrical distribution on funnel plot. Other quality of life measures were used and have been described more fully in the additional Table 1. Improvement was also seen in the following domains: vitality and role physical at three months, physical function, and general health at six months.

[i] We downgraded owing to heterogeneity (P < 0.01, I^2 = 87%), narrow CI (2.70 to 4.82), and a symmetrical distribution on funnel plot. Additional improvements in other domains may be seen in the future as more studies report their outcomes for quality of life scores.

BACKGROUND

Peripheral arterial disease is an important cause of morbidity and mortality for people in many Western countries. It is estimated that most adults have some degree of atherosclerosis by the time they reach middle age, and approximately 4% will develop intermittent claudication (Leng 1993). As the population ages, the prevalence of claudication will increase. Risk factors for development of lower limb arterial disease are similar to those for coronary heart disease, and include smoking, raised cholesterol levels, hypertension, and diabetes.

Several epidemiological studies have demonstrated an association between sedentary habits, functional decline, and worsening claudication (McDermott 2006; McDermott 2011). The impact of exercise therapy on physical functional ability, muscle strength, and walking times has drawn increased focus since a review was prepared in 2013 (Parmenter 2013). Over the past few years, further research into calf muscle strength has supported known changes in muscle architecture while enhancing focus on the impact of these changes in relation to walking distance and physical function. Researchers have described reduction in myofibre cross-sectional area, enzymes, and power (Clyne 1985; Dahllof 1974; King 2015; Koutakis 2015), along with alterations in gait (Gommans 2016; King 2012), among patients with intermittent claudication.

Description of the condition

Peripheral arterial disease covers a spectrum ranging from asymptomatic disease through to claudication, critical limb ischaemia, and finally limb loss. Within this spectrum, most people have relatively stable disease, termed 'claudication'. Intermittent claudication occurs secondary to atherosclerosis of the lower limb arteries, resulting from impaired blood flow. Whether at rest or when walking slowly, this reduction may go unnoticed; however during periods of exercise or walking with additional loads, for example, carrying while shopping, a cycle of pain requiring short rests occurs. This muscular, cramp-like tightening of the calf, the buttocks, or the foot on walking is known as 'claudication'.

Description of the intervention

Treatment options for intermittent claudication include bypass surgery, angioplasty, and drug therapy, but the mainstay of treatment for many patients with mild to moderate claudication remains advice to 'stop smoking and keep walking' (Housley 1988; NCGC 2012) while modifying cardiovascular risk factors.

Exercise therapy or programmes usually require a regular weekly commitment, lasting from six weeks to a year. In general, programmes are run twice or three times per week. Duration can vary; usually a minimum of 30 minutes is required per session.

How the intervention might work

Researchers have conducted numerous studies of exercise therapy using various regimens that differ in duration and intensity; many of these studies suggest that exercise can prove beneficial for individuals with intermittent claudication (Ernst 1992). Underlying mechanisms through which exercise may effect improvement include increased and more effective distribution of blood flow to the legs (Ernst 1987a), improved rheological characteristics of the blood (Ernst 1987), less reliance on anaerobic metabolism (Ruell 1984), and greater use of oxygen (Dahllof 1974).

A systematic review of the effect of exercise on lower limb haemodynamics in individuals with mild to moderate claudication identified 33 trials. In these trials, investigators reported no change when comparing effects of control versus exercise therapy on resting ankle brachial index (ABI), postexercise ABI, resting calf arterial blood flow, reactive hyperaemic blood flow post ischaemia, and resting toe systolic pressure (Parmenter 2011). An extensive non-systematic review of the literature focussed on exercise training in people with claudication and physiological changes associated with exercise (Haas 2012). This review discussed how regular exercise improves endothelial flow-mediated dilatation (FMD). Exercise training also improves FMD in those with claudication.

Exercise is proposed to improve walking among claudicants through angiogenesis. Underlying biomechanisms by which this may occur include ischaemia, sheer stress secondary to exercise, and remodelling of skeletal muscle (Hiatt 1994; Regensteiner 1993). Researchers have done extensive work on the changes that occur in skeletal muscle secondary to claudication. These changes can be summarised as a change in capillary density (Clyne 1985), as a ratio of type I to type II fibres (Clyne 1985; Hiatt 1994; Sjöström 1982), or as increases in arteriogenesis and mitochondrial activity. Trialists have described subsequent changes in skeletal muscle that can occur with training in humans (Lundgren 1989a; Terjung 1988; Wang 2009), as well as in animal models with artificial hindlimb stenoses (Yang 1991).

More recently, researchers have explored changes secondary to differing exercise programmes, while focussing on calpain activity, which has been associated with muscle atrophy in animal models. When trial authors explored effects of walking regimens versus strength training combined with walking, they noted that neither was seen to alter calpain activity (Delaney 2014).

The impact of peripheral arterial disease (PAD) on lower limb skeletal muscle becomes apparent when focussing on daily tasks or measuring strength. Individuals with PAD have reduced lower limb strength and ability or endurance for performing lower limb tasks, that is, knee flexion, dorsiflexion, or plantar flexion, when compared with healthy controls (Câmara 2012). In addition, people with PAD and reduced muscle density are more likely to have higher all-cause and cardiovascular disease mortality (McDermott 2012).

Clinicians have identified reduced muscle strength (Câmara 2012; Gohil 2013a; Parmenter 2013a), decreased walking distances

(Parmenter 2013a), greater imbalance (Gohil 2013; Mockford 2014), and alterations in gait (King 2012; Koutakis 2010), secondary to PAD.

Why it is important to do this review

A meta-analysis of exercise rehabilitation programmes for claudication pain showed that exercise training to near-maximal pain for at least six months was beneficial in improving claudication (Gardner 1995). That review provided good evidence for the best type of exercise therapy but did not compare findings with non-exercised control groups. The present Cochrane review focusses on randomised controlled trials only and encompasses additional endpoints. The National Institute for Health and Care Excellence (NICE) (NCGC 2012) currently advocates that all patients with PAD should undergo an exercise programme as first-line treatment. Numerous other studies have echoed this advice (Haas 2012; Lauret 2012; Willigendael 2005). However, uptake remains low across the UK. This review aims to add weight to the current body of available evidence recommending exercise, while demonstrating effects of different durations of exercise on walking distance and quality of life.

OBJECTIVES

Our goal was to determine whether an exercise programme was effective in alleviating symptoms and increasing walking treadmill distances and walking times in people with intermittent claudication. Secondary objectives were to determine whether exercise was effective in preventing deterioration of underlying disease, reducing cardiovascular events and improving quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) of an exercise regimen versus control, or versus medical therapy. We excluded trials that used alternation (e.g. allocation by date of birth or days of the week). We included trials that did not perform intention-to-treat analysis, provided all randomised participants were accounted for. We excluded trials for which numerical data were not available in a usable format, despite contact with study authors, but that were otherwise suitable.

We included studies in this review if they focussed on exercise versus usual care or other medical interventions. We excluded studies focussing on exercise compared with other forms of exercise, unsupervised exercise, angioplasty, or surgery, to prevent overlap with other Cochrane reviews (Antoniou 2017; Fakhry 2013; Fokkenrood 2013; Fowkes 1998). We excluded studies in which usual care included walking advice or suggestions to increase daily exercise, as this advice constitutes unsupervised exercise. Although the exclusion of walking advice as part of usual care may be deemed controversial, this has been undertaken according to what has been reported by the trialists in the study papers.

Types of participants

We included trials involving participants with symptomatic intermittent claudication due to atherosclerotic disease. Intermittent claudication may be diagnosed objectively by an ABI < 0.9 or evidence of PAD on Doppler ultrasound or angiography, or both, or by questionnaire or clinically if objective measures such as ABI or imaging were not used or reported. We excluded studies of participants with asymptomatic lower limb atherosclerosis that was identified by testing.

Types of interventions

We included any exercise programme used for treatment of patients with intermittent claudication, such as walking, skipping, and running, and home-based therapies provided researchers compared treatment against placebo or no therapy. Inclusion of trials was not affected by duration, frequency, or intensity of the exercise programme, but these issues were taken into account in the meta-analysis. This review did not consider supervised versus unsupervised exercise because this is the topic of another Cochrane review (Fokkenrood 2013). Walking advice provided by consultants in clinic can be seen as the best medical treatment or control. However, this may also be deemed unsupervised exercise. Therefore, we excluded from this review all studies that provided best medical treatment, which includes walking advice.

To avoid overlap with other Cochrane reviews (Antoniou 2017; Fakhry 2013; Fowkes 1998), this review excluded all modalities by which exercise can be compared with percutaneous transluminal angioplasty (PTA) or surgery. We therefore reviewed studies originally included in this review comparing exercise versus PTA or surgery, and excluded them when appropriate.

Types of outcome measures

We included only studies that reported one or more of the following outcome measures: treadmill walking distance (time to onset of pain or pain-free walking distance and maximum walking time or maximum walking distance), ABI, quality of life, morbidity, or amputation.

Primary outcomes

- Treadmill walking distance (time to onset of pain or pain-free walking distance and maximum walking time or maximum walking distance)

Secondary outcomes

- ABI
- Mortality
- Amputation
- Quality of life (includes QoL measured by the Short Form (SF)-36 Questionnaire and other validated measurements such as the EuroQoL Group Quality of Life Questionnaire based on five dimensions (EQ-5D), the Vascular Quality of Life Questionnaire (VascuQol), and the Intermittent Claudication Questionnaire)
- Peak exercise blood flow
- Cardiovascular events

Search methods for identification of studies

Electronic searches

For this update, the Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials.

- Cochrane Vascular Specialised Register (15 November 2016).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10) via the Cochrane Register of Studies Online.

See Appendix 1 for details of the search strategy used to search CENTRAL.

The CIS maintains the Cochrane Vascular Specialised Register, which is constructed from weekly electronic searches of MEDLINE Ovid, Embase, Ovid, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Allied and Complementary Medicine Database (AMED), and through handsearching of relevant journals. The full list of databases, journals, and conference proceedings searched, as well as the search strategies used, is presented in the Specialised Register section of the Cochrane Vascular Module in the Cochrane Library (www.cochranelibrary.com).

The CIS searched the following trial registries for details of ongoing and unpublished studies.

- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch).
- ISRCTN Register (www.isrctn.com/).

See Appendix 2.

Searching other resources

We checked the reference lists of relevant studies retrieved via electronic searches.

Data collection and analysis

Selection of studies

For this update, one of the review authors (RAL) independently identified relevant trials and determined their eligibility for inclusion in the review; another review author (AH) checked this work. We resolved disagreements by discussion or by consultation with a third review author (GL); however this was not required. As necessary, we sought additional information from authors of all trials that appeared to meet the inclusion criteria.

Data extraction and management

Two review authors (RAL and AH) independently extracted data. Review authors resolved disagreements by discussion and included the final results in the review.

Assessment of risk of bias in included studies

For this update (2017), two review authors (RAL and AH) independently performed risk of bias assessments. We discussed discrepancies, and we planned that if we could not reach agreement, we would ask a third review author (GL) to assess the trial. Risk of bias assessment comprises seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and the additional option of assessing any other aspects deemed to produce bias.

Measures of treatment effect

When appropriate, we pooled trial results in a statistical meta-analysis using guidelines published by Cochrane Vascular. We analysed continuous data by determining mean differences (MDs) and 95% confidence intervals (CIs) using a fixed-effect model. When significant heterogeneity was present, we used a random-effects model. We analysed dichotomous data by determining risk ratios (RRs) and 95% CIs using a fixed-effect model, unless we suspected heterogeneity. In addition, for the primary outcome measure treadmill walking distance (time to onset of pain or pain-free walking distance and maximum walking time or maximum walking distance), we also analysed percentage change by using the 95% CI.

Unit of analysis issues

We analysed all data by using means and standard deviations. When original study papers did not provide these, we calculated them using the method recommended by the statistician for Cochrane Vascular. The unit of analysis was the individual participant.

Dealing with missing data

When data were not available from the original study paper, we contacted study authors to request the relevant data. If these were not available, we excluded the paper from the review. If data for at least one predefined outcome of the review were available, we included the study and examined available data in the meta-analysis.

Assessment of heterogeneity

We subjectively tested heterogeneity between trial results by using clinical judgement of differences in patient populations, interventions (including type, duration, and intensity of exercise programmes), and outcome assessments. We assessed heterogeneity statistically by using the Chi^2 test and the I^2 statistic. We deemed heterogeneity as significant if the P value of the Chi^2 test was less than 0.01, or if I^2 was greater than 70%. An I^2 of 50% to 70% equated to moderate heterogeneity.

Assessment of reporting biases

When we identified sufficient studies (> 10), we assessed publication bias using a funnel plot. For meta-analyses, when the number of studies was less than 10, we did not use funnel plots, as this would have led to reduced power and inability to differentiate artefactual from true asymmetry.

Data synthesis

For this update, two review authors (RAL and AH) independently collected and pooled data, provided agreement was met. We then uploaded data into Review Manager 5 (RevMan 2014) software for analysis. We performed meta-analysis by using a fixed-effect model unless we detected heterogeneity (Chi^2 test P < 0.01); we used a random-effects model in the analysis if heterogeneity was present.

Subgroup analysis and investigation of heterogeneity

Owing to the numerous domains associated with assessment of quality of life as per the Medical Outcomes Study (MOS) Short Form (SF)-36, we analysed all domains by performing subgroup analysis. When possible, we also analysed and presented data by subgroups for usual care and placebo.

Sensitivity analysis

Exercise programmes consisted of 12-week interventions or 24-week interventions. In one case, the duration of the programme was two years. In view of the variable length of programmes, we separated and analysed data as two separate analyses - one for 12 weeks and one for 24 weeks.

'Summary of findings' table

For this update we included a table summarising the findings presented by this review for our main comparison of exercise versus no exercise in adults with symptomatic intermittent claudication. The study population continues to be at low risk with regards to their claudication; however, this is only one aspect of a progressive debilitating disease that can lead to limb loss and is accompanied by the coexistent risk of cardiovascular disease. We selected for inclusion in Summary of findings for the main comparison the most important and clinically relevant outcomes thought to be essential for decision-making. We described these under Types of outcome measures; they include pain-free walking distance, maximum walking distance, ABI, mortality, amputation, and quality of life. We calculated assumed control intervention risks by using the mean number of events in control groups of selected studies for each outcome. We used the system developed by the GRADE Working Group in grading the quality of evidence as high, moderate, low, or very low, on the basis of within-study risk of bias, directness of evidence, heterogeneity, precision of effects estimates, and risk of publication bias (GRADE 2004). We used GRADEpro GDT (GRADEpro GDT 2015) software to create Summary of findings for the main comparison.

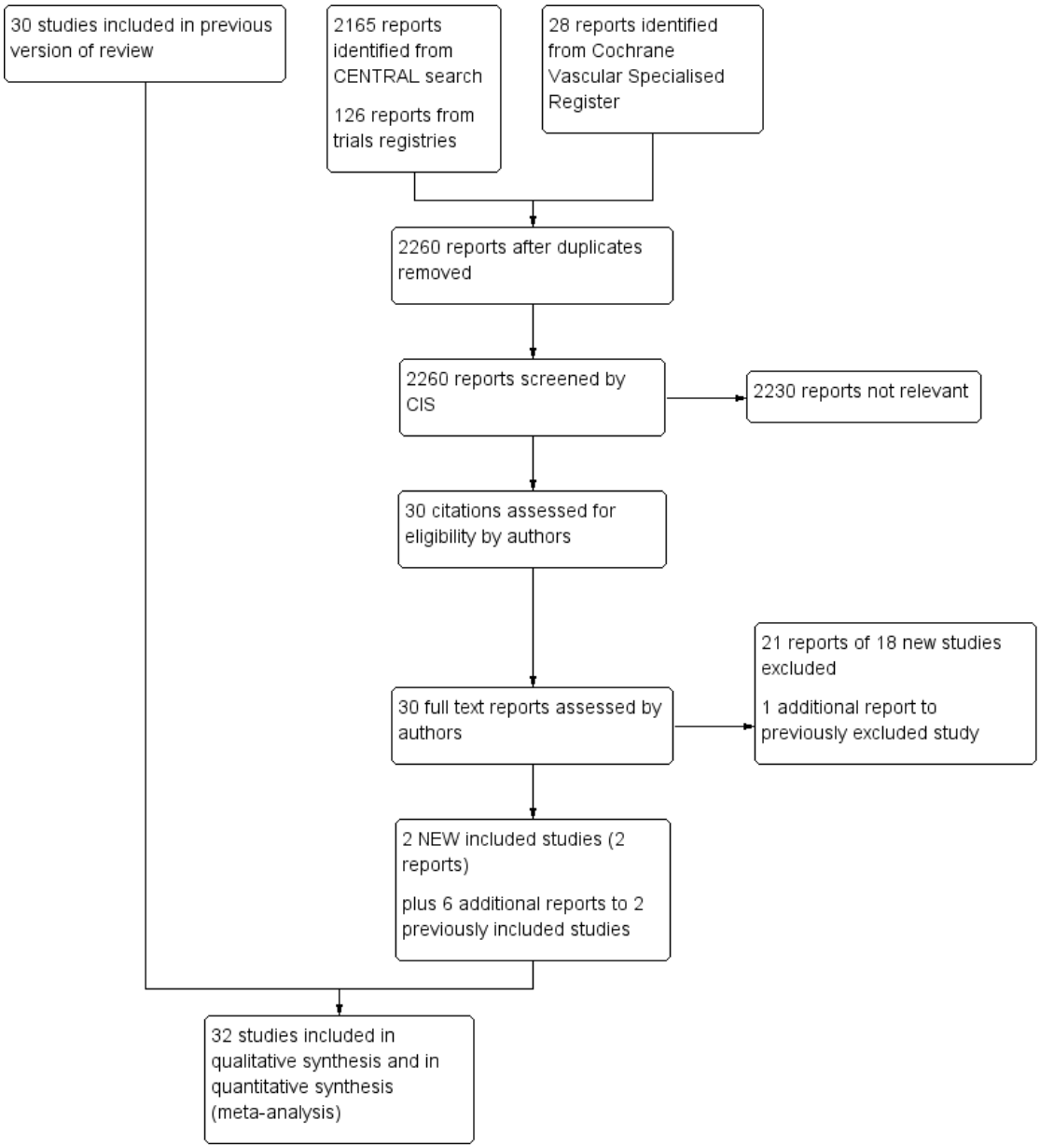
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies.

We included two additional trials for this update (McGuigan 2001; Tew 2015). We also included five publications related to the previously included GOALS 2013 trial (McDermott 2013; McDermott 2013a; McDermott 2014; McDermott 2014a; Rejeski 2014). However only one of these publications provided data (on mortality at six months) that could be included within the results section (McDermott 2014a). This brings the total number of included studies to 32 (Arosio 2001; Castro-Sanchez 2013; Ciuffetti 1994; Collins 2005; Crowther 2012; Cucato 2013; Dahllof 1974; Gardner 2002; Gelin 2001; GOALS 2013; Guidon 2010; Hiatt 1990; Hiatt 1994; Hobbs 2005; Jansen 1991; Kakkos 2005; Larsen 1966; Leicht 2011; Mannarino 1991; McDermott 2008; McGuigan 2001; Mika 2005; Mika 2006; Mika 2011; Sanderson 2006; Schlager 2011; Tew 2009; Tew 2015; Tisi 1997; Tsai 2002; Wood 2006; Zwierska 2005) and the total number of participants to 1835.

Eighteen trials included fewer than 50 participants (Arosio 2001; Ciuffetti 1994; Crowther 2012; Cucato 2013; Dahllof 1974; Guidon 2010; Hiatt 1990; Hiatt 1994; Hobbs 2005; Jansen 1991; Kakkos 2005; Larsen 1966; Leicht 2011; Mannarino 1991; McGuigan 2001; Sanderson 2006; Schlager 2011; Wood 2006), ten between 50 and 100 participants (Castro-Sanchez 2013; Collins 2005; Gardner 2002; Mika 2005; Mika 2006; Mika 2011; Tew 2009; Tew 2015; Tisi 1997; Tsai 2002), three over 100 participants (GOALS 2013; McDermott 2008; Zwierska 2005), and one over 200 participants (Gelin 2001).

Researchers compared exercise versus six different modes of treatment, the most common being usual care or placebo. Two early trials compared exercise versus placebo tablets (Dahllof 1974; Larsen 1966), but in more recent studies, trial authors used usual care as the control comparator (Collins 2005; Crowther 2012; Gardner 2002; Gelin 2001; GOALS 2013; Guidon 2010; Hiatt 1990; Hiatt 1994; Jansen 1991; Leicht 2011; McDermott 2008; McGuigan 2001; Mika 2005; Mika 2006; Mika 2011; Sanderson 2006; Schlager 2011; Tew 2009; Tew 2015; Tisi 1997; Tsai 2002; Wood 2006; Zwierska 2005). Investigators compared exercise with the following drug therapies: antiplatelet agents (Mannarino 1991), pentoxifylline (Ciuffetti 1994), iloprost (Arosio 2001), and vitamin E (Collins 2005). One study compared exercise versus pneumatic foot and calf compression (Kakkos 2005); one used a placebo treatment protocol of disconnected ultrasound electrotherapy (Castro-Sanchez 2013); and one used a 'stretching class' as usual care (Cucato 2013).

Inclusion and exclusion criteria of the included studies varied widely, but usually excluded people with serious comorbidities that would compromise an exercise programme, or would make it impractical.

We noted some variation in the exercise regimens used, although all recommended at least two sessions weekly. All specified some element of supervision, except the earliest trial (Larsen 1966), in which participants were simply advised to exercise at home and were given some training or walking regimen. Types of exercise varied from strength training to polestriding, cycling, and upper or lower limb exercises. We did not identify studies that included skipping or running. Duration of treatment generally fell within 3 to 12 months. Trialists measured outcomes at times ranging from 14 days to 2 years and reported variable compliance with exercise. Nearly all trials used a treadmill walking test to assess one of the outcome measures, but results show considerable variation in outcomes. Some reported walking distance, and others reported walking times. Trial authors reported calf blood flow and ABI and often provided haematological and biochemical measures. Trialists provided little information about mortality, amputations, and fatal or non-fatal cardiovascular events. Eleven studies reported quality of life measures (Collins 2005; Gardner 2002; Gelin 2001; GOALS 2013; Guidon 2010; Kakkos 2005; McDermott 2008; Tew 2015; Tisi 1997; Tsai 2002; Zwierska 2005). As trials increasingly used the Short Form (SF)-36 Questionnaire, we have combined these results for meta-analysis in this review. We did not include in the meta-analysis trials that used an alternative quality of life assessment; we provided individual study findings in Table 1.

We sought additional information from trialists in most of the included studies for the updated version of this review.

Excluded studies

See Characteristics of excluded studies.

For this update (2017), we excluded 18 additional studies (Aruna 2015; Cucato 2015; Dantas 2016; Gardner 2014; Gardner 2014a; Gibbs 2013; Guidon 2013; Guirro 2015; Kono 2013; LIFE Study; Mays 2015; NCT02075502; NCT02879019; PROPEL study; Rodrigues 2014; Schlager 2011a; Sonaglia 2013; Ventura 1984). We added one publication to a previously excluded study (EXITPAD 2010).

We excluded a total of 111 studies from the current review.

We excluded studies from this review because they compared percutaneous transluminal angioplasty versus exercise (CLEVER 2009; Creasy 1990; Greenhalgh 2008; Hobbs 2006; Kruidenier 2011; Mazari 2010; Spronk 2009; SUPER study), surgery versus exercise (Lundgren 1989), different exercise regimens (Allen 2010; Andreozzi 2008; Beutel 1985; Buchwalsky 1974; Cachovan 1999; Cheetham 2004; Choi 2012; Collins 2012; Cucato 2011; Cucato 2011a; Cucato 2015; Dedes 2010; Degischer 2002; Fakhry 2011; Gardner 2005; Gardner 2012; Gardner 2014; Gardner 2014a; Gottstein 1987; Jones 1996; Kiesewetter 1987; Labs 1999;

Martinez 2009; Nawaz 1999; Nawaz 2001; NCT01241747; NCT02879019; Nicolai 2010; Nielsen 1977; Parr 2009; Patterson 1997; Pinto 1997; Riebe 2001; Ritti-Dias 2010; Rodrigues 2014; Saleem 2011; Savage 2001; Scheffler 1991; Slordahl 2005; Sonaglia 2013; Thomson 1999; Zwierska 2004), and exercise versus walking advice as the form of conservative best medical treatment (Bronas 2011; Crowther 2008; EXERT 2009; EXITPAD 2010; Gardner 2011; Gardner 2012; Hodges 2008; Mays 2015; Nawaz 1999; NCT02075502; Nordanstig 2011; Parr 2009; Stewart 2008; Wang 2008). We excluded nine studies because relevant suitable numerical data were not available despite attempts to contact study authors (Collins 2010; Fowler 2002; Gibbellini 2000; Holm 1973; Maejima 2005; Schlager 2011a; Streminski 1992; Tebbutt 2011; Ventura 1984). We excluded the remainder of excluded studies because they did not fit the inclusion criteria (e.g. participants did not have intermittent claudication, not an RCT, insufficient evidence of randomly allocated population, no non-exercise control group) (Aruna 2015; Brotons 2011; Bulling 1991; Carmeli 2004; Cina 1996; Cunningham 2012; Dahllof 1976; Dantas 2016; Dittmar 1977; Ericsson 1970; Ernst 1987; Ernst 1990; Fitzgerald 1971; Gibbs 2013; Guidon 2013; Guirro 2015; Kono 2013; Krause 1976; Lee 2007; Leon 2005; Lepantalo 1984; LIFE Study; Mannarino 1988; Mannarino 1989; McDermott 2004; NCT01065740; Necker 2003; Presern-Strukelj 200; PROPEL study; Riccioni 2010; Richardson 1991; Schoneberger 1994; Silvestro 2002; Snabl 1958; Taft 2004; Treat-Jacobson 2012; Walker 2000; Waller 1988; Wang 2008; Winterfeld 1983).

Ongoing studies

We included within the ongoing studies section two studies that are still awaiting data: NCT01231360 (completed 2014) and NCT01822457 (completed August 2016). See Characteristics of ongoing studies.

Risk of bias in included studies

Figure 2 and Figure 3 provide an overall summary of bias present within each of the included studies (see also Characteristics of included studies). The high level of unclear bias was due to unclear reporting about sequence generation and allocation. We have expanded upon these aspects below.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

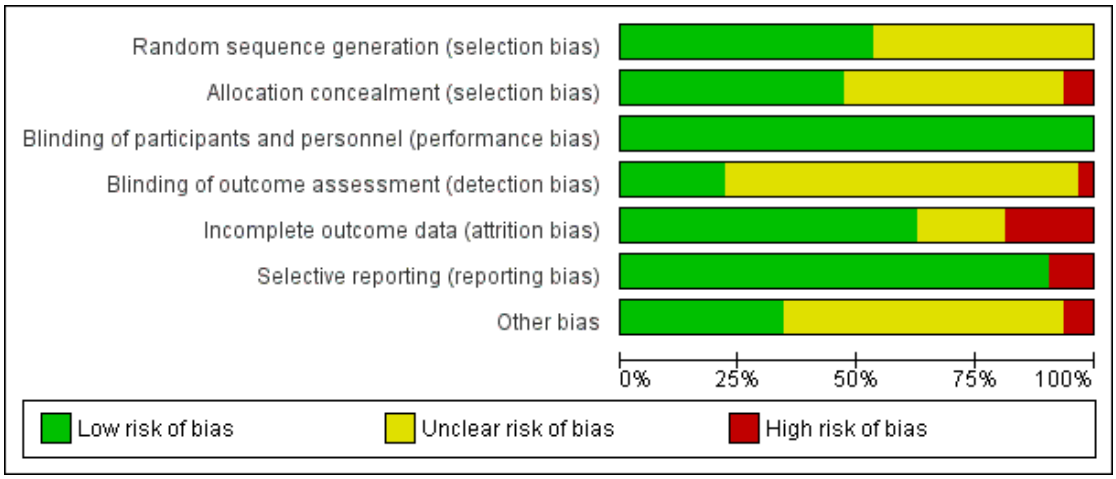
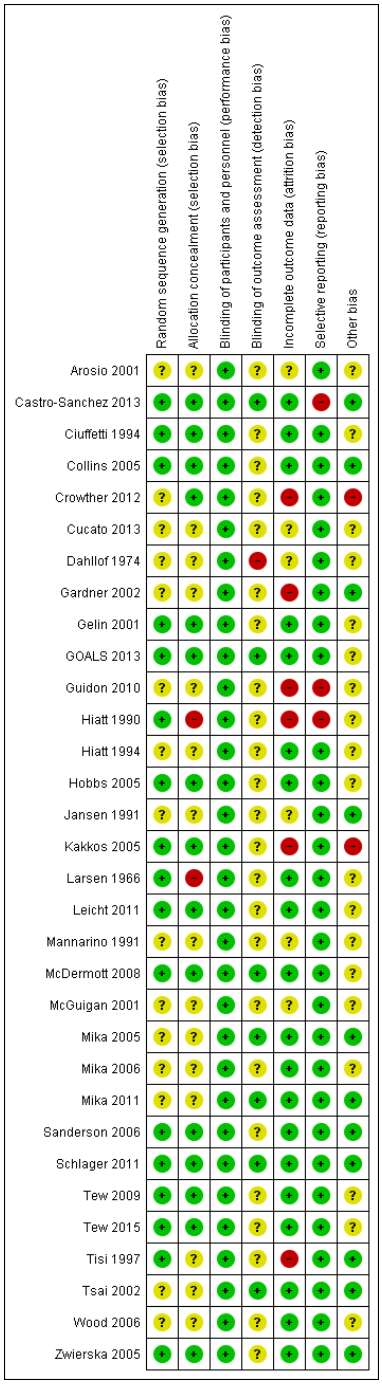


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies were RCTs, but many reports provided no details on random sequence generation other than a statement of 'randomised' (Arosio 2001; Crowther 2012; Cucato 2013; Dahllof 1974; Gardner 2002; Guidon 2010; Hiatt 1994; Jansen 1991; Mannarino 1991; McGuigan 2001; Mika 2005; Mika 2006; Mika 2011; Tsai 2002; Wood 2006). See Figure 3. To ensure that all trials were dealt with fairly, we deemed that any described as 'randomised' with no explanation as to how this was done had unclear risk of bias. We deemed that the remaining studies were at low risk of bias for random sequence generation.

A total of 15 studies did not report details of allocation concealment (Arosio 2001; Cucato 2013; Dahllof 1974; Gardner 2002; Guidon 2010; Hiatt 1994; Jansen 1991; Mannarino 1991; McGuigan 2001; Mika 2005; Mika 2006; Mika 2011; Tisi 1997; Tsai 2002; Wood 2006); we deemed these studies to be at unclear risk of selection bias. We deemed two studies to be at high risk of bias because the randomisation procedure was not blinded (Hiatt 1990; Larsen 1966). The remaining studies provided details of allocation concealment, and we judged them to be at low risk of bias.

Blinding

As the nature of exercise-based studies involved an activity versus standard care, medication, or an intervention, review authors deemed that blinding of participants was not possible. To ensure that all trials used a standardised approach, we scored all as having low risk of bias secondary to participant blinding. Inevitably in trials of exercise, blinding was not possible; therefore significant placebo responses may have occurred in trials comparing exercise versus usual care.

Blinding of participants was not possible, and included trials have additional risk of bias as outcome assessors may not be blinded to the group to which a participant was randomised. Seven studies did specify that outcome assessors were blinded; we judged these to be at low risk of bias (Castro-Sanchez 2013; GOALS 2013; McDermott 2008; Mika 2005; Mika 2011; Schlager 2011; Tsai 2002). For some, however, blinding involved a separate aspect of the trial that was not focused on exercise, that is, vitamin E in Collins 2005, or carnitine analysis in Hiatt 1990; we judged these studies as having unclear risk. We deemed Dahllof 1974 to be at high risk of bias because the outcome assessor was not blinded to treatment groups. We judged the remainder of the included studies to be at unclear risk of bias owing to lack of reporting on blinding of outcome assessors.

Incomplete outcome data

Most trials reported no or minimal losses to follow-up (Arosio 2001; Castro-Sanchez 2013; Ciuffetti 1994; Collins 2005; Cucato 2013; Dahllof 1974; Gelin 2001; GOALS 2013; Hiatt 1994; Hobbs 2005; Jansen 1991; Larsen 1966; Leicht 2011; Mannarino 1991; McDermott 2008; Mika 2005; Mika 2006; Mika 2011; Sanderson 2006; Schlager 2011; Tew 2009; Tew 2015; Tsai 2002; Wood 2006; Zwierska 2005). We judged studies that had an attrition rate of 20% or more to be associated with higher risk of bias (Crowther 2012; Gardner 2002; Guidon 2010; Hiatt 1990; Kakkos 2005; McGuigan 2001; Tisi 1997).

We judged five studies to be at unclear risk of bias (Arosio 2001; Cucato 2013; Dahllof 1974; Jansen 1991; Mannarino 1991); Arosio 2001, Dahllof 1974, Jansen 1991, and Mannarino 1991 because investigators did not mention whether all enrolled participants completed the studies, and Cucato 2013 because only participants from the exercise group were lost to follow-up.

Selective reporting

All studies reported their prespecified outcome measures and were at low risk of reporting bias. Guidon 2010 discussed results of the Walking Impairment Questionnaire (WIQ) and the Intermittent Claudication Questionnaire (ICQ) for 30 of 44 randomised participants; therefore, we judged this study to be at high risk of selective reporting bias. Castro-Sanchez 2013 did not report on intermittent claudication distance; we therefore classified it as having high risk. Hiatt 1990 did not specifically report on maximum walking distance or intermittent claudication in the treatment group but correlated it with treadmill performance; therefore, we classified this study as having high risk of reporting bias.

Other potential sources of bias

We initially labelled studies as having high risk of bias when they failed to meet sample size calculations (Kakkos 2005; McDermott 2008; McGuigan 2001). Kakkos 2005 reported an attrition rate of 26% (8 of 34 discontinued); we therefore kept it at high risk. However, we reclassified McDermott 2008 to unclear risk of bias, as the attrition rate was low; according to power calculations, 50 were needed in each group, and 50 completed the supervised exercise therapy (SET) whilst 48 in the control group completed the study. We also reclassified McGuigan 2001 to unclear risk of bias as the reported attrition rate was low.

Reporting of treatment group numbers varied in the results section of Crowther 2012; effects on outcomes were unclear. We therefore judged the study to be at high risk of bias.

Eleven studies were at low risk of bias (Castro-Sanchez 2013; Collins 2005; Gardner 2002; Jansen 1991; Mika 2005; Mika 2011; Sanderson 2006; Schlager 2011; Tisi 1997; Tsai 2002; Zwierska 2005).

Eleven studies included small sample sizes; we therefore deemed these studies to be at unclear risk of bias (Arosio 2001; Ciuffetti 1994; Cucato 2013; Dahllof 1974; Hiatt 1990; Hiatt 1994; Hobbs 2005; Larsen 1966; Leicht 2011; Mannarino 1991; Wood 2006). We deemed the remaining six studies to be at unclear risk of bias for a variety of other reasons (Gelin 2001; GOALS 2013; Guidon 2010; Mika 2006; Tew 2009; Tew 2015). Please see the risk of bias tables for additional details.

Effects of interventions

See: **Summary of findings for the main comparison** Is exercise an effective intervention in intermittent claudication?

Exercise regimen compared with placebo or usual care

Overall outcomes

The wide range of reported time points meant that the overall analysis includes the last data time point at which data were presented in the study publications. This section shows a high degree of heterogeneity, with low heterogeneity noted in Analysis 1.2 and Analysis 1.8.

Maximum walking distance

(Analysis 1.1)
Ten trials with 500 participants reported this outcome and showed significant statistical heterogeneity (I^2 = 89%, P < 0.00001) therefore we used a random-effects model (Cucato 2013; Gardner 2002; Gelin 2001; Hobbs 2005; Jansen 1991; Leicht 2011; Schlager 2011; Tew 2009; Tew 2015; Zwierska 2005). The exercise group showed overall improvement in maximum walking distance (MD 120.36 metres, 95% CI 50.79 to 189.92, P < 0.00007, high quality of evidence as assessed via GRADE).

Pain-free walking distance

(Analysis 1.2)
Nine trials with a total of 391 participants reported on this outcome (Cucato 2013; Gardner 2002; Hobbs 2005; Jansen 1991; Leicht 2011; Mika 2005; Tew 2009; Tew 2015; Zwierska 2005) and noted improvement in pain-free walking distance in the exercise group (MD 82.11 metres, 95% CI 71.73 to 92.48, P < 0.00001, low quality of evidence as assessed via GRADE). Trials showed no significant heterogeneity (I^2 = 41%, P = 0.1) therefore a fixed-effect model was used.

Maximum walking time

(Analysis 1.3)
Twelve studies with a total of 577 participants reported on maximum walking time (Collins 2005; Crowther 2012; GOALS 2013; Hiatt 1990; Hiatt 1994; Larsen 1966; McDermott 2008; Mika 2006; Mika 2011; Sanderson 2006; Tsai 2002; Wood 2006). Data show overall improvement in walking time for those who underwent exercise (MD 4.51 minutes, 95% CI 3.11 to 5.92, P < 0.00001, high-quality evidence). Heterogeneity between studies was found to be significant (I^2 = 82%, P < 0.00001) therefore a random-effects model was used. Walking time improved in eight trials (Crowther 2012; Hiatt 1990; Hiatt 1994; Larsen 1966; McDermott 2008; Mika 2006; Mika 2011; Tsai 2002), which demonstrated exercise to be effective.

Pain-free walking time

(Analysis 1.4)
Eleven studies with a total of 534 participants reported on pain-free walking time (Collins 2005; Crowther 2012; GOALS 2013; Hiatt 1994; Larsen 1966; McDermott 2008; Mika 2006; Mika 2011; Sanderson 2006; Tsai 2002; Wood 2006). Meta-analysis demonstrated improvement in pain-free walking time for the exercise groups (MD 2.93 minutes, 95% CI 1.77 to 4.09, P < 0.0001, high-quality evidence). Heterogeneity between studies was found to be significant (I^2 = 89%, P < 0.00001) therefore a random-effects model was used. Heterogeneity was most likely secondary to differences in reporting times and variable length of exercise programmes. Data show 100% improvement in pain-free walking time, which was likely to be of clinical significance. Only two of the studies found no real improvement with exercise (Sanderson 2006; Wood 2006).

Percentage change in maximum walking distance or time

(Analysis 1.5)
We calculated the percentage change in maximum walking distance or time for 15 studies with a total of 656 participants (Arosio 2001; Crowther 2012; Cucato 2013; Gardner 2002; GOALS 2013; Hiatt 1990; Hiatt 1994; Kakkos 2005; Leicht 2011; Mannarino 1991; McDermott 2008; Mika 2006; Tisi 1997; Tsai 2002; Wood 2006). Meta-analysis reported overall improvement in maximum walking distance or time for those who underwent exercise (MD 40.25%, 95% CI 28.64 to 51.86, P < 0.00001). Heterogeneity between these studies was found to be significant (P < 0.00001, I^2 = 93%) therefore a random-effects model was used.

Percentage change in pain-free walking distance (intermittent claudication distance (ICD)) or time (ICT)

(Analysis 1.6)

We calculated the percentage change in ICD or ICT for 15 studies with 703 participants (Arosio 2001; Collins 2005; Crowther 2012; Cucato 2013; Gardner 2002; GOALS 2013; Kakkos 2005; Mannarino 1991; McDermott 2008; Mika 2005; Mika 2006; Sanderson 2006; Tew 2009; Tsai 2002; Wood 2006). Results showed overall improvement in percentage change for ICD or ICT in favour of exercise (MD 58.42%, 95% CI 44.20 to 72.64, P < 0.00001). Heterogeneity between studies was found to be significant (P < 0.001, I^2 = 70%) when a random-effects model was used.

Ankle brachial index (ABI)

(Analysis 1.7)

Thirteen trials with a total of 570 participants reported this outcome (Castro-Sanchez 2013; Collins 2005; Crowther 2012; Gardner 2002; Gelin 2001; Hiatt 1990; Hiatt 1994; Hobbs 2005; Leicht 2011; McGuigan 2001; Schlager 2011; Tew 2009; Tisi 1997). Meta-analysis showed a small change in ABI (MD 0.04, 95% CI 0.00 to 0.08, P = 0.06, moderate-quality evidence), which was supported by three studies (Castro-Sanchez 2013; Crowther 2012; Schlager 2011). Studies showed significant statistical heterogeneity (P = 0.002, I^2 = 63%) therefore a random-effects model was used. Heterogeneity may be attributed to variations in exercise programme type or duration. Of note, as the number of trials included in updates has increased, the significance of change in ABI with exercise has diminished to show no improvement.

Mortality

(Analysis 1.8)

Five studies with 540 participants reported on mortality (Gelin 2001; GOALS 2013; McDermott 2008; Schlager 2011; Tew 2009). Results show no differences in effect between groups (risk ratio (RR) 0.92, 95% CI 0.39 to 2.17, P = 0.85, moderate-quality evidence). We updated these figures for this update, as recent published data included mortality figures for GOALS 2013. We noted no significant heterogeneity between trials (I^2 = 0%, P = 0.76).

Amputation

(Analysis 1.9)

Only Gelin 2001 reported on amputation. Two amputations occurred in the usual care group, and none in the exercise group (RR 0.20, 95% CI 0.01 to 4.15, P = 0.3, low-quality evidence).

Quality of life

Overall, researchers reported quality of life (QoL) in numerous different ways (see Table 1). SF-36 provided the only consistently reported outcome for QoL, but this was reported at three and six months, rather than at one year. We have reported below results at these time points.

Other QoL questionnaires included the ICD Questionnaire (Tew 2015; Guidon 2010; Kakkos 2005), the Nottingham Health Profile (NHP) (Tisi 1997), and the Intermittent Claudication-Specific Sickness Impact Profile (SIP) scale (SIPIC) (Gelin 2001). Tew 2015 used the ICD Questionnaire to assess changes between zero and six weeks. Data show no differences between intervention and control groups in EQ-5D score at six weeks, but improvement in ICD score in the intervention group (ICD score -10.6, 95% CI -18.9 to - 2.3, P < 0.05) (see Table 1).

Cardiovascular events

None of the included studies reported on non-fatal cardiovascular events. We have examined all-cause mortality in Analysis 1.8.

Peak exercise calf blood flow

(Analysis 1.10)

We included in the meta-analysis for this outcome four studies with a total of 103 participants (Dahllof 1974; Gardner 2002; Hiatt 1990; Larsen 1966). Results show no significant overall improvement in blood flow between groups (MD 0.94 mL/100 mL/min, 95% CI -0.81 to 2.69, P = 0.29, low-quality evidence) (I^2 = 59%, P = 0.06, moderate heterogeneity between trials). We downgraded the evidence owing to small sample size and wide confidence intervals.

Three-monthly outcomes

Seven trials provided one or more outcomes at the three-month time point for exercise compared with placebo or usual care (Collins 2005; Hiatt 1990; Hiatt 1994; Mika 2011; Schlager 2011; Tew 2009; Tsai 2002).

Maximum walking distance

(Analysis 2.1)

Three studies with 116 participants reported outcomes for maximum walking distance at the three-month time point (Cucato 2013; Schlager 2011; Tew 2009). Results showed no clear differences in distance between groups (MD 104.46 metres, 95% CI -64.33 to 273.24, P = 0.23) along with significant heterogeneity (P = 0.008, I^2 = 79%) between studies when a random-effects model was used.

Pain-free walking distance

(Analysis 2.2)

Three trials with 156 participants provided pain-free walking distance outcomes at three months (Cucato 2013; Mika 2005; Tew 2009). Data showed significant improvement in the exercise group (MD 88.70 metres, 95% CI 58.25 to 119.15, P < 0.00001) (I^2 = 16, P = 0.3, no significant heterogeneity).

Maximum walking time

(Analysis 2.3)
Meta-analysis of five trials with 172 participants reporting maximum walking time at three months (Collins 2005; Hiatt 1990; Hiatt 1994; Mika 2011; Tsai 2002) showed improvement with exercise (MD 6.05 minutes, 95% CI 5.47 to 6.62, P < 0.00001) and no significant heterogeneity (P = 0.62, I^2 = 0%).

Pain-free walking time

(Analysis 2.4)
Three trials with 132 participants provided data on pain-free walking time at three months (Hiatt 1994; Mika 2011; Tsai 2002). Meta-analysis demonstrated improvement in the exercise group (MD 4.95 minutes, 95% CI 4.38 to 5.53, P < 0.00001) and significant heterogeneity between trials (P = 0.02, I^2 = 73%).

Ankle brachial index (ABI)

(Analysis 2.5)
Four studies with a total of 130 participants reported on ABI outcomes at the three-month time point (Hiatt 1990; McGuigan 2001; Schlager 2011; Tew 2009). In contrast to the overall analysis, data show small differences in ABI between groups (MD 0.06, 95% CI 0.01 to 0.11, P = 0.02) (P = 0.06, I^2 = 61%, moderate heterogeneity).

Mortality

(Analysis 2.6)
Tew 2009 and GOALS 2013 reported on this outcome for a total of 229 participants. No deaths occurred in either group in GOALS 2013, and Tew 2009 reported one death in the control group compared with none in the exercise group (RR 0.30, 95% CI 0.01 to 6.98).

Quality of life

(Analysis 2.7)
Tsai 2002 and Guidon 2010 reported a quality of life analysis for the SF-36 at three months. Domains found to improve secondary to exercise included 'physical function' (MD 6.60, 95% CI 2.37 to 10.83), 'vitality' (MD 5.55, 95% CI 1.54 to 9.56), and 'role physical' (MD 10.31, 95% CI 3.64 to 16.98). A random-effects model applied to assess for any variation revealed that the domain 'vitality' continued to show improvement secondary to exercise, but significance was lost for 'role physical' (MD 16.06, 95% CI -8.41 to 40.53) and 'physical function' (MD 5.95, 95% CI-2.45 to 14.34).

Peak exercise calf blood flow

(Analysis 2.8)
Only Hiatt 1990 reported on this outcome at three months and included 19 participants. Results show no clear differences between exercise and control groups at the end of the study (MD 2.50 mL/100 mL/min, 95% CI -1.49 to 6.49).

Six-monthly outcomes

Maximum walking distance

(Analysis 3.1)
Three studies with a total of 156 participants reported maximum walking distance at six months (Gardner 2002; Schlager 2011; Zwierska 2005). Results showed an increase in the exercise group (MD 138.36 metres, 95% CI 22.39 to 254.34, P = 0.02) and significant heterogeneity between studies (P = 0.002, I^2 = 84%) when a random-effects model was used.

Pain-free walking distance

(Analysis 3.2)
Two studies with 116 participants reported on pain-free walking distance at six months (Gardner 2002; Zwierska 2005), noting improvement in the exercise group (MD 52.14 metres, 95% CI 6.83 to 97.45, P = 0.02) (I^2= 79%, P = 0.03, high heterogeneity).

Maximum walking time

(Analysis 3.3)
Four studies with a total of 295 participants reported outcomes for maximum walking time at six months (Crowther 2012; GOALS 2013; Larsen 1966; McDermott 2008). Meta-analysis showed improvement in favour of exercise (MD 3.20 minutes, 95% CI 2.04 to 4.36, P < 0.00001) and high heterogeneity (P = 0.01, I^2 = 72%).

Pain-free walking time

(Analysis 3.4)
Five trials with 292 participants provided pain-free walking time outcomes at six months (Collins 2005; Crowther 2012; GOALS 2013; Larsen 1966; McDermott 2008), showing improvement with exercise (MD 2.32 minutes, 95% CI 0.91 to 3.74, P < 0.001) and significant heterogeneity between studies (P = 0.005, I^2 = 73%) when a random-effects model was used.

Ankle brachial index (ABI)

(Analysis 3.5)
Six studies with 240 participants reported on ABI at six months (Castro-Sanchez 2013; Collins 2005; Crowther 2012; Gardner

2002; McGuigan 2001; Schlager 2011). Data showed no clear differences in ABI between the two groups (MD 0.05, 95% CI -0.01 to 0.11, P = 0.07) and significant heterogeneity (P = 0.007, I^2 = 69%) between studies when a random-effects model was used.

Mortality

(Analysis 3.6)

Only GOALS 2013 provided mortality data for the six-month time point. Overall data show no clear difference in mortality between exercise and non-exercise groups at the six-month time period (RR 0.51, 95% CI 0.05 to 5.54, P = 0.58).

Quality of life

(Analysis 3.7)

Five studies with a total of 429 participants provided outcomes for the SF-36 generic quality of life measure (Collins 2005; Gardner 2002; GOALS 2013; McDermott 2008; Zwierska 2005), which showed improvement in quality of life secondary to exercise in certain domains, namely, 'physical summary score' (MD 2.15, 95% CI 1.26 to 3.04, P < 0.00001, moderate-quality evidence; supported with a random-effects model) and 'mental summary score' (MD 3.76, 95% CI 2.70 to 4.82, P < 0.00001, 4 studies, 343 participants, moderate-quality evidence). The 'mental summary score' no longer showed improvement when a random-effects model was applied (MD 2.85, 95% CI -1.01 to -6.71). Heterogeneity was significant (87%) for 'mental summary score'. Only two studies (43 participants) gave details on all domains; 'physical function' (MD 9.78, 95% CI 0.82 to 18.74) and 'general health' (MD 10.19, 95% CI 1.83 to 18.55) improved with exercise (Collins 2005; Zwierska 2005); this was supported again when a random-effects model was used. The other domains - 'role physical', 'bodily pain', 'vitality', 'social function', 'role emotional', and 'mental health' - did not show improvement.

Peak exercise calf blood flow

(Analysis 3.8)

Two studies with 66 participants reported on blood flow measurements at six months (Gardner 2002; Larsen 1966). As with overall and three-month analyses, six-month blood flow measurements showed no differences between groups (MD 3.79 mL/100 mL/min, 95% CI 0.51 to 7.07, P = 0.02). Results showed no significant heterogeneity (P = 0.33, I^2 = 0%) between studies when a fixed-effect model was used.

Publication bias

We assessed overall publication bias using a funnel plot in three meta-analyses (Analysis 1.3; Analysis 1.4; Analysis 1.7) (see Figure 4; Figure 5; and Figure 6).

Figure 4. Funnel plot of comparison: 1 Overall outcomes: exercise regimen compared with placebo or usual care, outcome: 1.1 Maximum walking time (min).

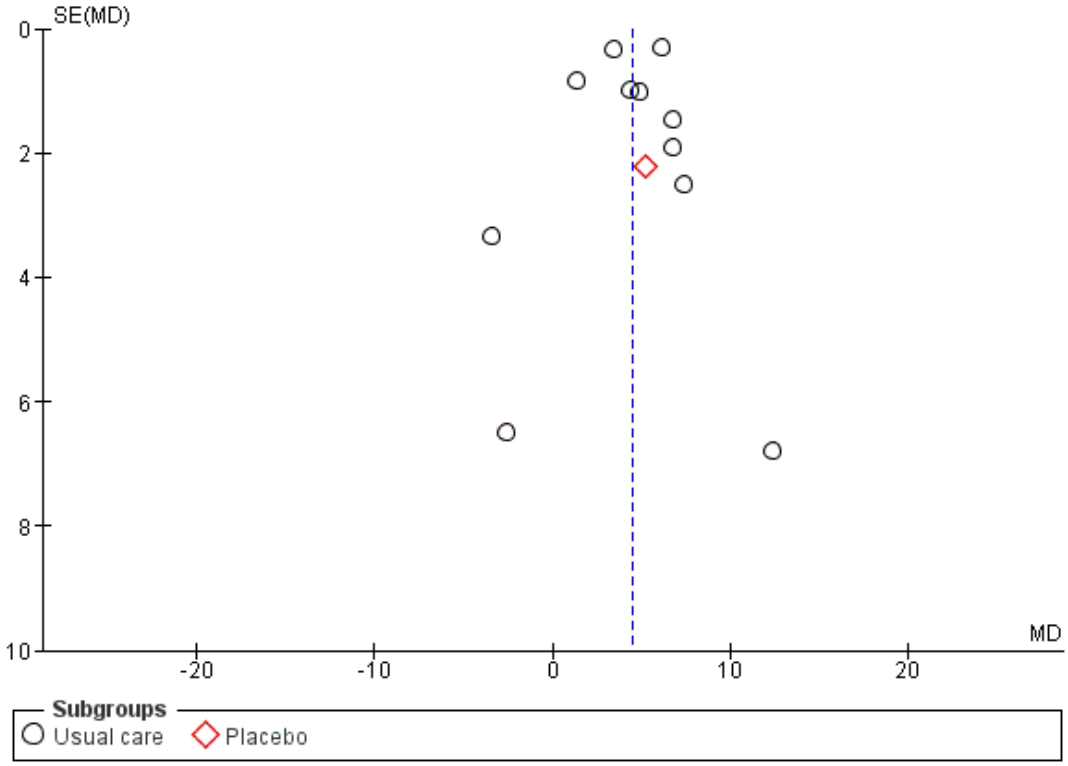


Figure 5. Funnel plot of comparison: 1 Overall outcomes: exercise regimen compared with placebo or usual care, outcome: 1.4 Pain-free walking time (min).

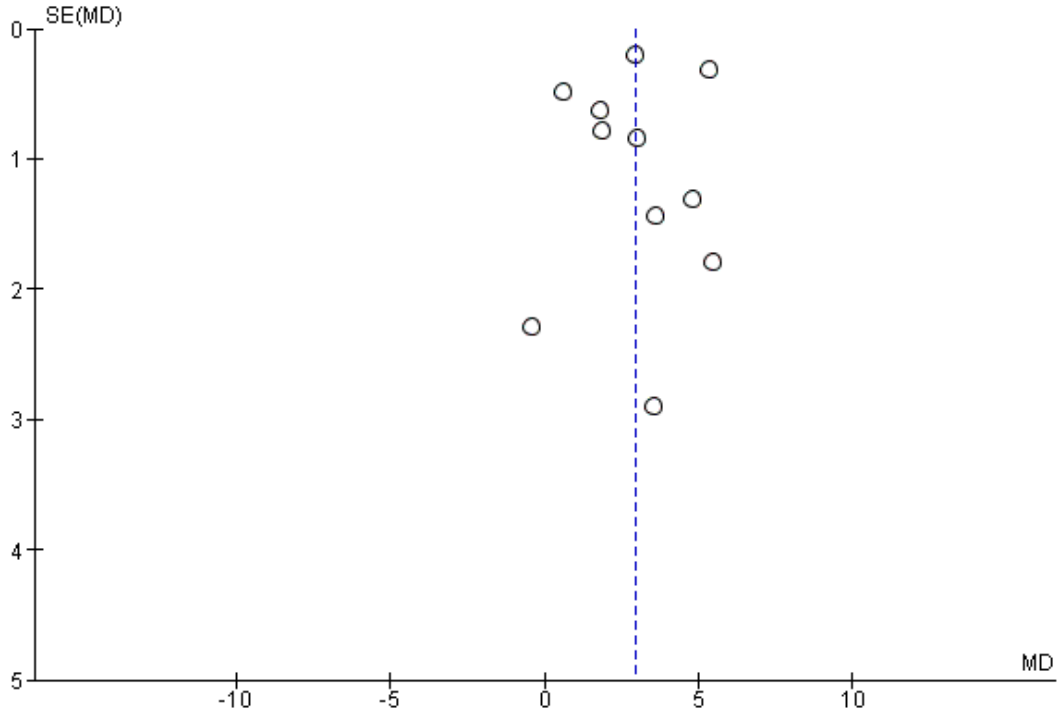
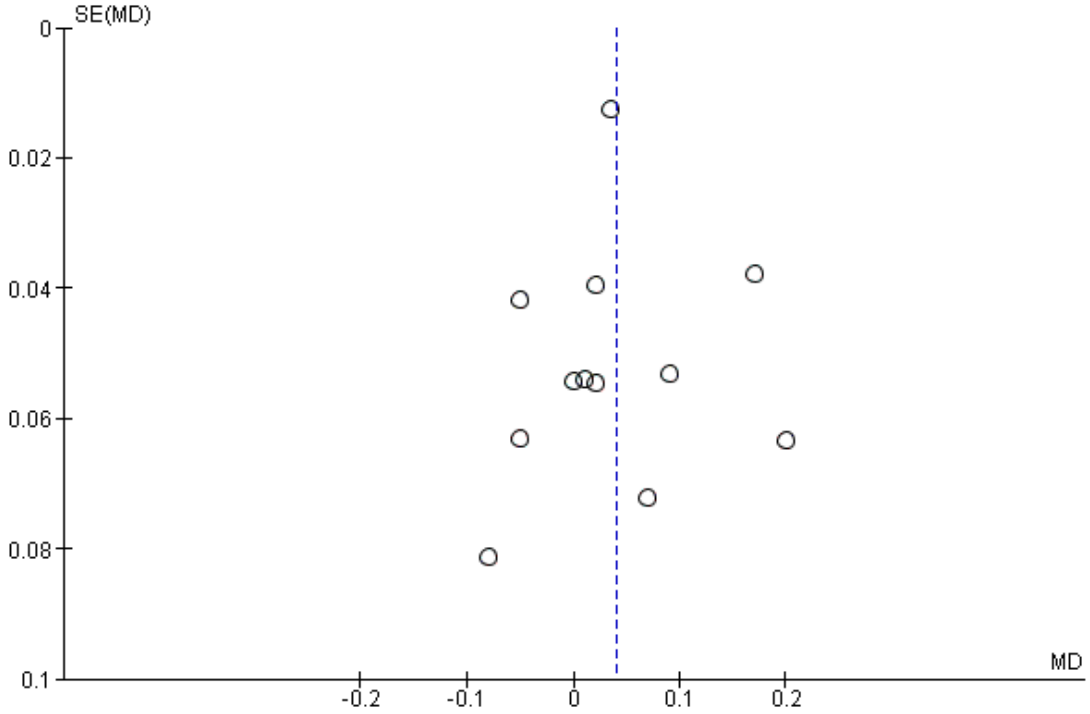


Figure 6. Funnel plot of comparison: 1 Overall outcomes: Exercise regimen compared with placebo or usual care, outcome: 1.5 Ankle brachial index.



The funnel plot in Figure 4 shows that 10 studies were within the 95% CI, and two were outside this range. Overall plot data were symmetrical, suggesting no evidence of publication bias or asymmetry secondary to the presence of smaller studies.

The funnel plot in Figure 5 indicates that seven studies were within the 95% CI, and three were outside this range. Overall plot data were asymmetrical, suggesting bias, possibly attributed to the presence of smaller studies.

The funnel plot in Figure 6 revealed that nine studies were within the 95% CI, and three were outside this range. Overall plot data were asymmetrical, suggesting bias, possibly attributed to the presence of smaller studies.

Exercise regimen compared with antiplatelet therapy

One trial involving 10 participants compared exercise with antiplatelet therapy (Mannarino 1991) and reported the following results.

Maximum walking time

(Analysis 4.1)

After six months of treatment, maximum walking time was improved in the exercise group compared with the group treated with antiplatelet therapy (MD 1.06 minutes, 95% CI 0.15 to 1.97). Maximum walking time was increased by 86% in the exercise group and by 38% in antiplatelet therapy group.

Ankle brachial index (ABI)

(Analysis 4.2)

Results show no differences between exercise and antiplatelet therapy groups at the end of the trial (MD 0.00, 95% CI -0.22 to 0.22).

Peak exercise calf blood flow

(Analysis 4.3)

Results show no clear differences in calf blood flow between antiplatelet therapy and exercise groups after six months, although flow tended to be higher in the exercise group (MD 2.18 mL/100 mL/min, 95% CI -0.28 to 4.64).

Mannarino 1991 did not report the remaining outcomes of this review.

Exercise regimen compared with pentoxifylline

One trial involving 30 participants compared exercise versus pentoxifylline (Ciuffetti 1994) and reported the following results.

Maximum walking time

(Analysis 5.1)
After 13 weeks of therapy, maximum walking time was greater in the pentoxifylline group than in the exercise group (MD -0.45 minutes, 95% CI -0.66 to -0.24). Walking distance increased by 62% in the exercise group and by 88% in pentoxifylline group.

Adverse events

Two participants experienced gastroenteritis during treatment with pentoxifylline, but investigators did not consider this to be a side effect of study treatments.
Ciuffetti 1994 did not report the remaining outcomes of this review.

Exercise regimen compared with iloprost therapy

One study with 24 participants compared iloprost versus exercise (Arosio 2001) and reported the following results.

Pain-free walking distance

(Analysis 6.2)
Data showed improvement in pain-free walking distance in the exercise group at two weeks (MD 188.7 metres, 95% CI 15.38 to 362.02).

Maximum walking distance

(Analysis 6.1)
Data showed no clear effect on maximum walking distance in the exercise group at two weeks (MD 196.80 metres, 95% CI -83.8 to 477.40).
Arosio 2001 did not report the remaining outcomes of this review.

Exercise regimen compared with pneumatic foot and calf compression

One study with 25 participants compared exercise versus pneumatic foot and calf compression (Kakkos 2005).

Pain-free walking distance

(Analysis 7.2)
Data showed no clear effect on pain-free walking distance in the pneumatic compression group compared with the exercise group (MD -160.30 metres, 95% CI -438.88 to 118.28).

Maximum walking distance

(Analysis 7.1)
Data showed no clear effect on maximum walking distance in the pneumatic compression group compared with the exercise group (MD -61.90 metres, 95% CI -391.59 to 267.79).

Mortality

(Analysis 7.3)
One death occurred within the pneumatic calf compression group, and no deaths occurred in the exercise group (odds ratio (OR) 3.52, 95% CI 0.13 to 95.09).
Kakkos 2005 did not report the remaining outcomes of this review.

Exercise regimen compared with vitamin E

One study involving 24 participants compared effects of vitamin E and exercise (Collins 2005).

Maximum walking time

(Analysis 8.1; Analysis 8.2)
Collins 2005 demonstrated improvement secondary to exercise, which was greater than with vitamin E alone, at three and six months, respectively (MD 15.22 minutes, 95% CI 2.38 to 28.05; MD 22.60 minutes, 95% CI 8.05 to 37.15).

Ankle brachial index (ABI)

(Analysis 8.3; Analysis 8.4)
ABI was unchanged at three and six months, respectively (MD -0.03, 95% CI -0.21 to 0.15; MD 0.10, 95% CI -0.09 to 0.29).
Collins 2005 did not report the remaining outcomes of this review.

DISCUSSION

Summary of main results

The data presented in this update generally confirm the findings of previous versions of this review - that exercise has a significant positive effect on walking times and walking distances in people considered to be fit for exercise intervention, compared with placebo or usual care. Although most studies examined outcomes at three or six months, it is important to note that this benefit would appear to be sustained for up to two years (Jansen 1991). Of note, however, data show improvement in maximum walking distance at six months but not at three months.
Mean improvements in walking distance and walking time with exercise were clinically and statistically significant; however in most cases, the data were not normally distributed. Some individuals

responded with improvement of considerably larger magnitude than the mean, whereas others responded less well, which may reflect varying compliance with exercise programmes. Successful programmes generally comprised physiotherapy with supervised exercise two or three times per week for 30 to 60 minutes, often with walking, leg exercises, or treadmill training. Some programmes encouraged additional home exercise.

We used percentage change from baseline to allow a more holistic understanding of change in walking ability. These additional parameters have demonstrated an increase in both initial claudication and maximum walking percentage changes, in keeping with changes documented for initial claudication walking distance and time, as well as for maximum walking distance and time. Of note, use of combined data allowed inclusion of 15 studies and a larger cohort of participants in the analysis.

Data related to ankle brachial index (ABI) and to other important outcomes are sparse. Investigators provided no data on non-fatal cardiovascular events and inconclusive data regarding mortality and amputation.

Antiplatelet therapy was less effective than exercise in improving walking distance and other measures of lower limb function, but researchers presented no data pertaining to fatal and non-fatal cardiovascular events. A previous meta-analysis has shown that antiplatelet agents reduce the incidence of cardiovascular events in people with claudication (Trialists 1994). Therefore, aspirin should be of benefit despite lack of effect on the lower limb.

The single small trial comparing pentoxifylline with exercise showed that participants on drug therapy had significantly longer walking distances after three months than those on exercise therapy (Ciuffetti 1994). Investigators reported no cardiovascular or adverse events among those on pentoxifylline, but disadvantages of drug treatment might include cost and lack of general cardiovascular improvement. Arosio 2001 showed that exercise improved pain-free walking time significantly more than iloprost, but this was a small study (24 participants).

Pneumatic foot and calf compression showed no clear effect on walking distances compared with exercise, again in a small trial (Kakkos 2005). However, alternatives for improving blood flow among those with poor mobility represent an important area for future research in those who are unsuitable for exercise programmes. Therefore further research into such avenues may yield more certain results and may therefore be of interest.

Researchers reported quality of life data on a range of scales, which made it difficult to incorporate this information into a meta-analysis. Results were variable depending on the comparisons made; this is a topic for future research.

Overall completeness and applicability of evidence

Overall, it is not contested that exercise may provide benefit for individuals with intermittent claudication. However, the overall benefit and duration of exercise programmes differ. A standardised approach with a minimum duration of six months appears to confer benefit and would improve both pain-free and maximum walking distance. Review authors found scant data on the benefits of a six-month programme compared with a three-month programme when measured outcomes focused on quality of life, mortality, or amputation risk. The general assumption is that exercise training is safe in peripheral arterial disease, but the data presented are often focussed on mortality and limb loss. Other cardiovascular morbidity appears to be under-reported, and additional details on safety data within exercise studies would be of value.

Criteria for participant selection resulted in exclusion of many individuals with stable claudication for whom exercise was not practical or safe owing to pre-existing medical conditions. As most people with intermittent claudication are elderly, comorbidities are common. For up to a third of people, exercise may not be a suitable option. Other research trials and reviews have examined optimum modes of exercise for people with intermittent claudication, for example, a Cochrane review explored supervised versus unsupervised exercise for intermittent claudication (Fokkenrood 2013). The present review cannot resolve uncertainties about different exercise regimens.

This review did not investigate the issue of non-compliance, which has a large impact on the use of supervised exercise classes and how funding should be allocated for this treatment as advocated by the National Institute for Health and Care Excellence (NICE) (NCGC 2012). Further information on the cost-effectiveness of exercise programmes is needed.

Quality of the evidence

We the review authors continue to believe that the quality of evidence is high in supporting exercise as first-line treatment for symptomatic claudicants. See Summary of findings for the main comparison. In this review update, we have added only two studies that support the body of literature already presented.

Compared with the previous version of this review, the evidence presented has improved in quality, as reporting criteria have become more stringent. In general, the bias present within papers was often difficult to assess owing to absence of relevant information. In these cases, we marked risk of bias as unclear, as evidence on which to base a judgement was insufficient. Overall, included studies were of moderate methodological quality.

Pooled outcomes for walking distance and maximum walking distance at all time points demonstrated significant heterogeneity. This most likely was secondary to pooling of walking times from some studies at two years and reporting of outcomes after three months in other studies. When possible we addressed this heterogeneity by analysing data at specific time points, such as three and six months post intervention. Regardless of this, data showed improvement in initial walking distance and time at three months, and in maximum walking distance and time by six months.

Publication bias remains an additional confounding factor for the quality of evidence pooled within this review. Older studies have been reported more poorly, as journal reporting criteria were previously less rigorous, resulting in greater inherent bias.

Potential biases in the review process

We searched the Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) for new publications about exercise in patients with intermittent claudication. Two review authors independently assessed all new studies in keeping with recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The main cause of bias within this review is that walking advice provided by consultants in clinics is now seen as the best medical advice but may also be deemed as unsupervised exercise. Therefore this review excluded all studies that reported best medical treatment, which includes walking advice, as we believe this would overlap with the Cochrane review on supervised versus unsupervised exercise (Fokkenrood 2013). It remains possible that usual care included walking advice, but this was not explicitly stated by trialists in their study papers, suggesting one possible aspect of reporting bias within studies.

It is the review authors' feeling that as claudication research develops, a usual care non-exercise control group will cease to exist, as its inclusion will be deemed unethical.

Finally, earlier studies used treadmill walking distance as the primary outcome measure, and this has continued to serve as a method for assessment of improvement in claudication. Whilst treadmill distances remain a reliable means of assessment, this method is being superseded by other functional and subjective assessments. Newer assessment tools to assess changes in walking distance include GPS tracking, six-minute walks, subjective reporting, and assessments based on the Walking Impairment Questionnaire (WIQ). It is important that future reviews consider inclusion of these as outcome measures (Cucato 2013b; Tew 2013).

Agreements and disagreements with other studies or reviews

This review is consistent with previous versions (Lane 2014; Leng 2000; Watson 2008) and adds to the body of available evidence supporting exercise for people with intermittent claudication. This evidence is also in line with NICE guidelines, which recommend that exercise should be provided as first-line treatment for people with intermittent claudication (NCGC 2012). Other meta-analyses such as Parmenter 2011 and other reviews such as Lauret 2012 and Lauret 2012a also support this finding.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides high-quality evidence showing that exercise therapy should play an important part in the care of selected patients with intermittent claudication, to improve walking times and distances. Effects were demonstrated following three months of supervised exercise, although some programmes lasted longer than one year. Limited data suggest that an effect is sustained for up to two years. Exercise did not improve ankle brachial index (ABI), and investigators detected no differences in the effect of exercise between groups in terms of amputation or mortality. Exercise may improve quality of life when compared with placebo or usual care.

Antiplatelet agents were less effective than exercise in improving walking distance but should continue to be used because of benefits in reducing cardiovascular events and death. In contrast, pentoxifylline was more effective than exercise but may have fewer beneficial effects on the cardiovascular system in general. Iloprost led to less improvement in walking time than exercise. Data show no clear effect on walking distances when pneumatic foot and calf compression was compared with exercise. However the number of participants in these studies is small and data are limited.

Implications for research

Important questions involve the degree of supervision required in any exercise regimen and how long any change in exercise habits can be expected to last. Therefore, a trial with long follow-up - of five years - is needed to compare the effectiveness of different supervised and unsupervised regimens in terms of changing long-term exercise patterns. Behavioural changes and attitudes towards exercise have been items of key interest in areas such as cardiovascular rehabilitation (Jolly 2009). More recent studies have demonstrated that brief psychological interventions may play a key role in improving walking distances among patients with intermittent claudication up to one year (Cunningham 2012). A telling aspect of research into claudicants' beliefs is their poor overall understanding of the disease and of why walking is recommended (Cunningham 2014). Future holistic exercise programmes, which may include cognitive-behavioural therapy and lifestyle and risk factor modification, could provide great benefit in encouraging people to start and maintain a better overall lifestyle.

Future research should also focus on compliance with exercise and how this could be improved. Outcome measures should include fatal and non-fatal cardiovascular events. In addition, expansion of this review to assess the benefit of exercise for asymptomatic patients and its impact on cardiovascular morbidity is an important goal.

Further cost-effectiveness analysis is required to determine whether the cost of supervised sessions might offset the cost of deterioration in terms of surgery or occupation of in-patient beds for complications such as myocardial infarction.

A trial is needed to compare exercise treatment with pentoxifylline to determine whether the benefit of drug treatment is sustained over a longer period, and whether data show any differences in cardiovascular events. Further investigation of pneumatic foot and calf compression for treatment of individuals with intermittent claudication is also needed. Consistency in use of quality of life measures among different trials would be helpful in linking outcomes to patient-assessed improvements.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Arosio 2001

Methods	Study design: RCT Method of randomisation: 'randomly divided' Exclusions post randomisation: not reported Losses to follow-up: not reported
Participants	Country: Italy Setting: hospital No. of participants: 24 Age: mean 65 years; 64.5 (55 to 69) years in exercise group; 66.4 (57 to 72) years in iloprost group Sex: all male Inclusion criteria: Fontaine stage II PAD with IC during past 4 to 6 years, confirmed by Doppler ultrasound, angiography, and ABI Exclusion criteria: not clearly stated but inferred to be smoking, severe hypertension, stroke, ischaemic attack, cerebrovascular disease, any drugs for PAD or other disease except transdermal clonidine for mild to moderate hypertension
Interventions	Intervention 1: physical exercise (n = 10) - walking, running, squat thrusts, 2 × day for 30 min, cycle ergometer for 30 min, plus 30 min constant load treadmill (2 mph, slope 0%) Intervention 2: iloprost (0.5 to 2 ng/kg/min) (n = 10) Duration: 14 days
Outcomes	Endogenous NO products Neutrophil adhesion ICD (m) and ACD (m) from constant load treadmill test (2 mph, slope 0%)
Notes	Exercise was interrupted at onset of pain, participant rested for 3 min, or until pain had gone, then resumed activity until each 30-min block

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomisation method provided. Simply stated, 'the groups were randomly divided in two treatment regimens'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants

Arosio 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether all enrolled completed the study
Selective reporting (reporting bias)	Low risk	Prespecified outcome measures reported
Other bias	Unclear risk	Small numbers (n = 10 per treatment arm) and duration for only 14 days

Castro-Sanchez 2013

Methods	Study design: RCT Method of randomisation: randomised balanced (stratified) selection process Groups were balanced for type of medication received and Leriche-Fontaine stage (I or IIa), via a stratification system that generates a sequence of letters (from a table of correlatively ordered permutations) for each category and combination of categories Exclusions post randomisation: 5; 3 in placebo (reasons: working hours, care for grandparents, and sprained ankle) and 2 in the physical therapy modality (reasons: terminally ill husband, and bed rest) Losses to follow-up: not reported
Participants	Country: Spain Setting: healthcare district No. of participants: 68 Age: mean (SD) age, 53 (12) years; range, 41 to 65 years Sex: 30 women and 38 men Inclusion criteria: diagnosis of type 2 diabetes, postexercise ABI of 0.6 to 0.9, HbA1c of 7% to 13%, BMI of 25 to 40, and sedentary lifestyle Exclusion criteria: other stages of PAD; peripheral venous insufficiency; cardiac, renal, or hepatic insufficiency; a cardiovascular event in the previous year; arterial pressure > 160/90 mmHg; LDL cholesterol > 160 mg/dL; an active smoking habit (in 3 previous years); and the presence of walking disorder, impaired skin integrity, or psychological or neurological disorder
Interventions	Intervention 1: Exercise group (n = 34) performed a session of 3 physical therapy modalities 2 times/d at home Intervention 2: Placebo group (n = 34) received a treatment protocol 1 day/week with disconnected ultrasound electrotherapy equipment in dorsal and lumbar regions (15 minutes per region); these patients were instructed on the use of ultrasound equipment and were unaware that it was switched off Duration: 20 weeks
Outcomes	Initial claudication walking distance (not reported in results); constant load treadmill test (3 km/h, 10% grade) Blood parameters: fibrinogen (mg/dL), haemoglobin (g/dL), glucose (mg/dL), choles-

	terol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), LDL cholesterol (mg/dL), triglycerides (mg/dL), and HbA1c (%) Doppler flow velocity ABPI Cardiovascular risk score Heart rate during exercise test Assessments at 3 time points: baseline (before treatments), immediately after the final treatment session, and at 6 months after the conclusion of treatment
Notes	Home exercise protocol described by Boutroux 1980

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised balanced (stratified) selection process
Allocation concealment (selection bias)	Low risk	Groups were balanced for type of medication received and Leriche-Fontaine stage (I or IIa) via a stratification system that generates a sequence of letters (from a table of correlatively ordered permutations) for each category and combination of categories
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to the treatment group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five dropouts were reported and excluded.
Selective reporting (reporting bias)	High risk	All outcomes stated - with the exception of initial claudication walking distance
Other bias	Low risk	No evidence of other bias

Ciuffetti 1994

Methods	Study design: RCT Method of randomisation: allocated by predetermined computer code. Not blinded Exclusions post randomisation: not reported Losses to follow-up: no dropouts reported
Participants	Country: Italy Setting: hospital No. of participants: 30 Age: 48 to 64 years Sex: male and female Inclusion criteria: stable maximal walking time (90 to 130 s) at 2 previous 6-monthly checks, plus stage II PAD confirmed by velocimetry and angiography Exclusion criteria: no h/o vascular surgery, coronary or cerebrovascular disease, DM; no factors affecting oxygen demand (e.g. anaemias); recent infection; treatment with vasodilators, antiplatelets, anticoagulants, or drugs affecting haemorrheological parameters for previous 1 month
Interventions	Treatment: 1 h exercise at home daily plus twice-weekly supervision as out-patients. Home regimen: week 1, 500 m in 20 min; week 2, 1000 m in 40 min; week 3, 2000 m in 60 min on the flat Control: pentoxifylline 800 mg tds Duration: 3 months
Outcomes	Primary: treadmill test maximal walking distance (2 km/h on 12° slope)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised by means of a predetermined computer code
Allocation concealment (selection bias)	Low risk	Predetermined computer code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in paper
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All outcomes stated

Ciuffetti 1994 (*Continued*)

Other bias	Unclear risk	n = 15 per group; small numbers; groups matched for baseline gender and age

Collins 2005

Methods	Study design: RCT Method of randomisation: participants randomised after baseline testing completed; 4 groups, randomised 2 × 2 factorial analysis, permuted blocks: computer generated for vit E, sealed envelopes for exercise Exclusions post randomisation: none Losses to follow-up: 6 (4 polestriding group, 2 control group)
Participants	Country: USA Setting: community No. of participants: 52 (49 analysed) Age: 65.8 ± 7.1 years polestriding group; 68.0 ± 8.6 control group Sex: 51 M, 1 F Inclusion criteria: history of IC, ABI < 0.95 at rest or < 0.85 after exercise, IC pain a factor for arrested walking Exclusion criteria: vascular surgery, angioplasty in previous 6 months; other comorbid conditions that would interfere with participation in an exercise programme; currently taking vit E, warfarin, or pentoxifylline; unable to give informed consent
Interventions	Treatment: polestriding (n = 27), supervised training 3 times per week for 4 weeks, twice weekly for 8 weeks, once weekly for 4 weeks, biweekly for 4 weeks, unsupervised for 4 weeks Control: no exercise (n = 25), usual care. Seen biweekly for 3 months and monthly thereafter Duration: 24 weeks
Outcomes	Primary: ABI, maximum walking distance, oxygen uptake Secondary: health-related quality of life
Notes	All participants given $6 travel for each visit and $5 for each test battery completed, starting at $25 Secondary analysis of the 2 × 2 factorial design of Collins 2003; because results showed no influence of vit E on exercise, researchers combined exercise groups and compared findings with those of the non-exercise groups The treadmill protocol began at a speed of 1.8 meter per hour (mph) and 0% grade. After the first 6 minutes, speed increased by 0.2 mph every 3 minutes. Per cent grade increased by 0.5% every 30 seconds

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Collins 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Participants randomised after baseline testing completed; 4 groups, randomised 2 × 2 factorial analysis, permuted blocks, computer generated
Allocation concealment (selection bias)	Low risk	Randomised 2 × 2 factorial analysis, permuted blocks, computer generated for vit E. For exercise: sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded to tablets, but not to exercise
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessors blinded to serum vit E levels
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data clearly reported
Selective reporting (reporting bias)	Low risk	All outcomes stated
Other bias	Low risk	Controlled for additional visits by making it fair across all 4 groups

Crowther 2012

Methods	Study design: RCT Method of randomisation: "randomly allocated using a blinded protocol" Exclusions post randomisation: nil stated Losses to follow-up: For personal reasons, 6 participants (n = 5 CPAD-IC, and n = 1 TPAD-IC) withdrew over the course of the research study
Participants	Country: Australia Setting: hospital No. of participants: N = 22; control (CPAD-IC, n = 11) or treatment (TPAD-IC, n = 11) group Age: CPAD-IC group: 67.1 (± 6.8), TPAD-IC group: 71.3 (± 8.5) Sex: 50% male Inclusion criteria: symptoms of IC, appropriate history of IC, imaging confirmation of PAD on lower limb duplex or CTA, and ability and willingness to attend for regular supervised exercise Exclusion criteria: selection for surgical or endovascular intervention (n = 30), patient preference (n = 20) and requirement for mobility aids, obvious gait abnormalities (e.g. steppage, vaulting, circumduction, hip hiking), and medical conditions that influenced gait (e.g. orthopaedic conditions, neurological impairment)

Crowther 2012 (*Continued*)

Interventions	Treatment: 6-month supervised exercise programme Control: standard medical treatment as outlined in the Trans-Atlantic Inter-Society Consensus (TASC II) guidelines Duration: 6 months
Outcomes	Primary: submaximal walking economy and walking performance during a graded treadmill exercise test Secondary: body composition; resting ABI
Notes	Exercise programme initially consisted of intermittent supervised treadmill walking 3 days per week for a total time of 25 minutes at 3.2 km/h (0.88 m/s). Participants were required to walk until the pain level was perceived as 3 or 4 on the CPS. Exercise intensity (via treadmill grade and walking speed) and duration (25 minutes up to a maximum of 40 minutes) were progressively increased once the participant could walk continuously for 25 minutes at a level below 3 on the CPS. This exercise progression strategy was continued over the 6-month period of the study The graded treadmill walking protocol consisted of a constant speed of 3.2 km/h (0.88 m/s) at an incline of 0% for the first 2 min, which was then increased by 2% every 2 minutes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Description of randomisation limited to: "Participants were randomly allocated using a blinded protocol"
Allocation concealment (selection bias)	Low risk	Blinded protocol; no further details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	6 participants lost to follow-up. Groups left uneven. However baseline data for the 2 groups were similar after participants who dropped out were excluded
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	In Results section, numbers in CPAD and TPAD groups alternate. In Table 1, CPAD (n = 6), TPAD (n = 10); Table 2, CPAD (n

Crowther 2012 (*Continued*)

		= 10), TPAD (n = 6)

Cucato 2013

Methods	Study design: RCT Method of randomisation: randomised; nil else stated Exclusions post randomisation: nil stated Losses to follow-up: 4 from the walking group (reason: personal reasons)
Participants	Country: Brazil Setting: hospital No. of participants: 29 Age: control 61 ± 8 years; walking training 64 ± 6 years Sex: male Inclusion criteria: Stable symptoms of IC were recruited from a tertiary centre specialising in vascular disease. Male patients with Fontaine stage II symptoms of IC for longer than 6 months, an ABI < 0.90 at rest in 1 or 2 legs, and who were able to walk for at least 2 min at 3.2 km/h on a treadmill were invited to participate Exclusion criteria: obesity (BMI < 30 kg/m^2); use of beta-blockers, non-dihydropyridine calcium channel blockers, or peripheral vasodilators; inability to obtain the ABI; exercise tolerance limited by factors other than claudication (i.e. arrhythmias, cardiac symptoms, or exaggerated blood pressure rise); electrocardiogram response suggestive of myocardial ischaemia, and h/o revascularisation in the previous year
Interventions	Treatment: 15 × 2-min walking bouts, with 2-min intermittent rest periods. Exercise intensity was adjusted to maintain heart rate within 4 bpm above or below the heart rate of claudication pain onset (e.g. if the patient reported claudication pain onset in the maximal treadmill test at 100 bpm, the heart rate exercise zone was set at 96 to 104 bpm). Treadmill speed was set at 3.2 km/h, while the grade was adjusted to achieve the target heart rate Twice-weekly 12-week walking exercise training programme Control: stretching exercise classes Duration: 12 weeks
Outcomes	Primary: to analyse the pain, cardiovascular and metabolic responses experienced by patients during walking exercise performed at the heart rate corresponding to claudication pain onset, and to investigate the effects of a 12-week walking training programme at this intensity on walking capacity in patients with IC Secondary: to determine whether low-volume walking exercise training programme at this intensity would induce walking performance improvements in this patient group Graded treadmill test: PFWD, MWD
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Cucato 2013 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Randomised into 2 groups
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants given the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants from exercise group lost to follow-up only. Baseline demographics between 2 groups matched in spite of attrition
Selective reporting (reporting bias)	Low risk	All stated
Other bias	Unclear risk	Small numbers

Dahllof 1974

Methods	Study design: RCT Method of randomisation: states "randomised". Not blinded Exclusions post randomisation: not stated Losses to follow-up: not stated
Participants	Country: Sweden Setting: not stated No. of participants: 18 Age: 54 to 71 years Sex: male and female Inclusion criteria: IC for > 1 year Exclusion criteria: DM or IHD
Interventions	Treatment: 30-min training sessions 3 times weekly, supervised by a physiotherapist, including dynamic leg exercises beyond the appearance of pain Control: placebo tablets Duration: 6 months
Outcomes	Primary: treadmill test pain-free and maximal walking distance (max 1000 m), at 4 km/h Secondary: calf blood flow - venous occlusion plethysmography after ischaemic foot exercises
Notes	

Dahllof 1974 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, nil else reported
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded to tablets, but not to exercise
Blinding of outcome assessment (detection bias) All outcomes	High risk	Physiotherapist ran exercise aspect.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether all enrolled completed the study
Selective reporting (reporting bias)	Low risk	All outcomes stated
Other bias	Unclear risk	Small numbers (n = 18)

Gardner 2002

Methods	Study design: RCT Method of randomisation: not described Exclusions post randomisation: nil Losses to follow-up: 3 in treatment group, 6 in control group dropped out. More at 18 months. 31 remained
Participants	Country: USA Setting: vascular clinics, newspaper and radio adverts No. of participants: 61 originally, 31 remained at 18 months Age: over 60 years Sex: 90% male Inclusion criteria: Fontaine II PAD Rose Questionnaire. ABI < 0.97 at rest. IC limiting factor on treadmill Exclusion criteria: other significant medical conditions limiting exercise tolerance, poorly controlled DM
Interventions	Treatment: 30-min training sessions 3 times weekly for 6 months, then twice weekly for 12 months Control: usual care Duration: 6 months and 18 months

Gardner 2002 (*Continued*)

Outcomes	Treadmill distance to claudication Maximum claudication distance ABI Peak oxygen uptake Walking economy Six-minute walking test distance Accelerometer-derived physical activity Walking Impairment Questionnaire Calf blood flow Health-related quality of life on SF-36 Self-perceived ambulatory measures
Notes	Participants performed a progressive, graded treadmill protocol (2 mph, 0% grade with 2% increase every 2 minutes) until maximal claudication pain. Distance walked to onset of claudication pain, distance walked to maximal claudication pain, time to relief of claudication pain after the test, and peak oxygen uptake were measured

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation not specified
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants given the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in paper
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers for attrition provided for all outcomes except the HRQoL, but reasons not stated 61 originally, 31 remained at 18 months: high loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported on
Other bias	Low risk	No evidence of other bias

Gelin 2001

Methods	Study design: RCT Method of randomisation: block, computer Exclusions post randomisation: nil stated Losses to follow-up: 39 (13 control, 15 training, 11 invasive therapy) did not complete evaluation at 1 year. A total of 90 patients did not complete treatment as allocated, although analysis was based on intention to treat. 15 were unsuitable for surgery and 17 received angioplasty in surgery arm. 25 withdrew from quality of life section
Participants	Country: Sweden Setting: vascular out-patients No. of participants: 253 Age: mean 67 (range 45 to 81) years Sex: 67% male Inclusion criteria: stable IC for > 6 months, ABI < 0.6 Maximum postischaemic blood flow < 25 mL/min/100 g, willing to undergo operations Exclusion criteria: contraindication to surgery; other disorder limiting treadmill walking
Interventions	Treatment: • Supervised exercise training 30 min 3 times per week for 6 months, then 6 to 12 months 2 sessions per week • Invasive surgery/endovascular procedure, based on angiographic findings Control: observation only Duration: 1 year
Outcomes	Primary: mortality, ABI, amputation, treadmill distance; max postischaemic calf blood flow, big toe systolic pressure Secondary: blood pressure, haemoglobin, cholesterol, triglycerides, creatine, quality of life
Notes	Quality of life (data for 171 only, 18 changed group but were analysed in original) Randomised before pretreatment investigations. Low compliance in exercise group but classes offered for longer than most studies Results for ABI omitted standard deviations. Walking test was performed on a treadmill with a progressively inclinating slope from 0° to 12°, simulating a gradually increasing workload

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised into 3 groups 'utilising a computer based algorithm, taking 21 assumed long-term prognostic variables into account'
Allocation concealment (selection bias)	Low risk	Randomisation performed by an independent nurse, who communicated the allocation group to the responsible physician

Gelin 2001 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in paper
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data clearly reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	No competing interests declared. Funding transparent. High number of cross-overs described and discussed. However, greater degree of treatment dropouts in the exercise group; total numbers for this section (58%); has the potential to bias reported outcomes (PTA/surgery 80%)

GOALS 2013

Methods	Study design: RCT Method of randomisation: parallel-design randomised controlled clinical trial Exclusions post randomisation: 5 lost interest (control), 8 lost interest in exercise group Losses to follow-up: in CONSORT diagram; 3 deaths overall
Participants	Country: USA Setting: community No. of participants: 194 Age: 69.3 (9.5) exercise group; 71.0 (9.6) control group Sex: 49 (50.5%) men in exercise group; 48 (49.5%) in control group Inclusion criteria: ABI $\leq$ 0.90 in either leg. Individuals with a resting ABI $\geq$ 0.91 to $\leq$ 1.00 at baseline were eligible if their ABI dropped by at least 20% after a heel-rise test. Individuals with a resting ABI > 0.90 were eligible if they provided medical record documentation of lower extremity revascularisation or evidence of PAD from an accredited vascular laboratory Exclusion criteria: potential participants with a below- or above-knee amputation; wheelchair confinement; inability to walk at least 50 feet without stopping; use of a walking aid other than a cane; inability to attend weekly sessions; walking impairment for a reason other than PAD, foot ulcer, or critical limb ischaemia; significant visual or hearing impairment; non-completion of the study run-in (attendance at 2 weekly health education sessions over a 3-week period); major surgery or lower extremity revascularisation during the previous 3 months or planned during the next 12 months; major medical illness including cancer treatment during the prior 12 months; current participation in another clinical trial or in another exercise trial within the past 3 months; completion of cardiac rehabilitation during the past 3 months; Parkinson disease; requirement

	of oxygen with activity or exercise; determination that exercise may be unsafe including having more than a class II New York Heart Association level of heart failure or angina; an increase in angina pectoris during the prior 6 months; an abnormal baseline exercise stress test; an exercise level similar to that targeted in the intervention at the time of recruitment; and a Mini-Mental State Examination score of < 23 at baseline
Interventions	Treatment: Our intervention applied principles from social cognitive theory, the group dynamics literature, and research on self-regulation to motivate participants to adhere to home-based walking exercise. Participants met once weekly for 90 minutes in a group with other PAD participants for the entire 6 months of the intervention. Forty-five minutes was devoted to facilitator-led discussions and 45 minutes to walking around an indoor track Control: The health education control group attended weekly 60-minute group sessions with other PAD participants. Physicians and other healthcare professionals provided lectures on topics including managing hypertension, cancer screening, and vaccinations Control group attended weekly lectures about topics not related to exercise. Duration: 6 months
Outcomes	Primary: 6-minute walk test Secondary: maximal treadmill walking time, pain-free treadmill walking time, physical activity, Walking Impairment Questionnaire (WIQ) scores, and Physical Health Composite Score (PCS) and Mental Health Composite Score (MCS) from the 12-item Medical Outcomes Study Short-Form Health Survey (SF-12)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	RCT: parallel-design randomised controlled clinical trial randomised by computer via a randomly permuted block method
Allocation concealment (selection bias)	Low risk	Eligible participants were randomised by computer via a randomly permuted block method, stratifying by baseline 6-minute walk performance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcomes were measured before randomisation and at 6-month follow-up by assessors unaware of participants' group assignment

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up rates were 90.7% and 92.8% in the intervention and control groups. After exclusion of 3 participants who died before follow-up testing, follow-up rates were 91.7% and 94.7%
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Multiple imputation was used by study authors to account for missing data at 6-month follow-up, including additional analyses in which a value of zero was assigned for missing 6-month follow-up data for decedents

Guidon 2010

Methods	Study design: RCT Method of randomisation: "randomly allocated" Exclusions post randomisation: nil stated Losses to follow-up: 13 withdrew before follow-up
Participants	Country: Ireland Setting: not stated No. of participants: 44 initially randomised, 30 completed study Age: 67 ± 8.12 years Sex: 70.5% male Inclusion criteria: IC with ABI < 0.9 Exclusion criteria: nil stated
Interventions	Treatment: twice-weekly supervised exercise programme for 12 weeks Control: usual care Duration: 12 weeks
Outcomes	Walking Impairment Questionnaire Intermittent Claudication Questionnaire SF-36
Notes	RCT performed by School of Physiotherapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"; no further information available
Allocation concealment (selection bias)	Unclear risk	Not stated

Guidon 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	25% lost to follow-up
Selective reporting (reporting bias)	High risk	Only WIQ and ICQ discussed for 30/44 participants
Other bias	Unclear risk	RCT performed by School of Physiotherapy: who will require funding and may therefore be undertaking the study to provide weight for sustaining or undertaking additional classes

Hiatt 1990

Methods	Study design: RCT Method of randomisation: randomised in pairs by coin toss Exclusions post randomisation: 6 were discontinued from the study. 4 treated participants were discontinued: 3 for non-compliance with exercise training sessions and 1 for development of medical problems unrelated to PAD. Two control participants were discontinued: 1 for medical problems not due to PAD and the second for progression of arterial disease, as previously defined Losses to follow-up: nil
Participants	Country: USA Setting: not stated No. of participants: 19 (25 enrolled, 6 discontinued); 10 treatment and 9 control Age: mean 61 years (treatment), 59 years (control) Sex: all male Inclusion criteria: IC due to PAD (ABI < 0.95 at rest or < 0.85 after exercise) Exclusion criteria: critical limb ischaemia; resting ankle blood pressure < 50 mmHg; unable to walk on the treadmill at a speed of 2 mph or an exercise capacity limited by angina, congestive heart failure, COPD, or arthritis; DM; vascular intervention in previous year; treatment with beta-blockers or pentoxifylline
Interventions	Treatment: programme of exercise 3 times each week (5 min warm up, 50 min intermittent isotonic resistive exercise, 5 min cool down) Control: maintain usual level of exercise Duration: 12 weeks

Hiatt 1990 (*Continued*)

Outcomes	Primary: treadmill test maximal walking time (2 mph at 0% slope, with a subsequent 3.5% increase in slope every 3 min until forced to stop) Secondary: calf blood flow venous occlusion plethysmography, concentration of plasma carnitine at rest Subjective indicators: perceived pain during exercise; walking-limited distance
Notes	Hiatt 1990 included distance walked and claudication pain. Unfortunately these results were not reported by treatment group but simply correlated with treadmill performance. The correlation was good; therefore it may be assumed that significant improvement was experienced by those receiving exercise therapy Treadmill test: graded treadmill test (2 mph 0% grade, with a subsequent 3.5% increase in grade every 3 minutes)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Coin toss
Allocation concealment (selection bias)	High risk	Coin toss
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only for the carnitine analysis
Incomplete outcome data (attrition bias) All outcomes	High risk	All outcome data clearly reported. 25 enrolled, 6 discontinued (24% lost)
Selective reporting (reporting bias)	High risk	Maximum walking distance and claudication pain not reported for individual treatment group but correlated with treadmill performance
Other bias	Unclear risk	Small numbers (n = 19)

Hiatt 1994

Methods	Study design: RCT Method of randomisation: not stated Exclusions post randomisation: 3 did not consent for muscle biopsy Losses to follow-up: 2 in control group
Participants	Country: USA Setting: not stated No. of participants: 29 Age: mean 67 years ± 6 years Sex: male only Inclusion criteria: 3-month h/o stable IC (Rose Questionnaire) limiting exercise sufficiently to affect ability to perform routine activity; ABI < 0.94 at rest, < 0.73 after exercise Exclusion criteria: rest pain, ulcer, gangrene; inability to walk on treadmill at > 2 mph; exercise limited by angina, CHF, COAD, or arthritis; no DM, vascular surgery, or PTA in previous year
Interventions	Treatment: supervised treadmill walking exercise (n = 10) or strength training (n = 9) and encouraged to walk alone for 2 days each week (treadmill 1 h 3 times a week, walking until moderate pain, then rest) Control: maintain usual level of activity (n = 10) Duration: 12 weeks
Outcomes	Primary: treadmill test pain-free and maximal walking distance (2 mph, 0% slope, with a subsequent 3.5% increase in slope every 3 min until forced to stop) ABI (resting and post exercise)
Notes	Trial continued after 12 weeks without a control group; therefore later results not included Strength training was less effective than treadmill exercise; only the latter was included in the meta-analysis for statistical reasons

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data reported

Hiatt 1994 (*Continued*)

Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Small numbers

Hobbs 2005

Methods	Study design: RCT Method of randomisation: 2 × 2 factorial design, random number table Exclusions post randomisation: not reported Losses to follow-up: 4 of original 38 withdrew
Participants	Country: UK Setting: university department of vascular surgery, patients referred to IC clinic from primary or secondary care No. of participants: 34 Age: median 67 (63 to 72) years Sex: 27 men, 7 women Inclusion criteria: IC diagnosed by Edinburgh Claudication Questionnaire and reduced ABI < 0.9, reviewed after 3 to 6 months; max walking distance 20 to 500 m Exclusion criteria: significant aorto-iliac disease, inability to complete treadmill distance to absolute claudication distance, MI, transient ischaemic attack, stroke or PTA in past 3 months, CHF, bleeding diathesis, glomerular filtration rate < 20 mL/min, CYP3A4 or CYP2C19 inhibitor use
Interventions	Treatment: • Supervised exercise: 3-month, twice-weekly 1-hour physiotherapist-led exercise programme. Given videotape of programme and encouraged to take log of exercise at home • Cilostazol 100 mg twice daily, if side effects dosing halved for 1 week • Exercise as above plus cilostazol Control: best medical therapy Duration: 6 months
Outcomes	MWD Pain-free MWD ABI Thrombin antithrombin complex Prothrombin fragments 1 and 2 Plasminogen activator inhibitor Tissue plasminogen activator
Notes	Study authors contacted for means and SDs - received for BMT and supervised exercise groups Treadmill test: 3 km/h, 10% incline to MWD or 1000 m

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hobbs 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	2 × 2 factorial design randomisation, random number table
Allocation concealment (selection bias)	Low risk	Eligible participants were randomised in a 2 × 2 factorial design to continue BMT only or to receive BMT + supervised exercise, BMT+ cilostazol, or BMT + supervised exercise + cilostazol. The 2 × 2 factorial design is well recognised as one of the most robust study designs and allows for greater interrogation of the data, as well as allowing interaction of different treatments to be assessed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in paper
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data clearly reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Small numbers

Jansen 1991

Methods	Study design: RCT Method of randomisation: not described Exclusions post randomisation: not described Losses to follow-up: not described
Participants	Country: Germany Setting: community No. of participants: 48 Age: not described Sex: not described Inclusion criteria: PAD stage II Exclusion criteria: not stated
Interventions	Treatment: training on treadmill 3.5 km/h 10% slope for 2 hours twice per week under medical/physiotherapy supervision Control: no training Duration: 2 years

Jansen 1991 (*Continued*)

Outcomes	Primary: treadmill walking distance, pain-free and maximum Secondary: ultrasound Doppler of arm and leg arteries	
Notes	Treadmill test: 3.5 km/h, 10% incline Translated from German	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised; no further information available
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether all enrolled completed the study
Selective reporting (reporting bias)	Low risk	All prespecified outcomes stated
Other bias	Low risk	No evidence of other bias

Kakkos 2005

Methods	Study design: RCT Method of randomisation: "blind block telephone procedure" by means of computer Exclusions post randomisation: 2 participants in the IPC group withdrew their consent before their 6 weekly appointments Losses to follow-up: 4 in supervised exercise group; 4 in IPC group
Participants	Country: England Setting: vascular out-patient clinic No. of participants: 34 Age: median and IQR: 66 (10.5) unsupervised exercise (USE) group; 69 (11.8) supervised exercise (SE) group; 66 (7) intermittent pneumatic compression (IPC) group Sex: 27 M in total; 8 M USE group, 11 M SE group, 8 M IPC group Inclusion criteria: stable IC for > 6 months due to superficial femoral artery occlusion of ≥ 6 cm in length on ultrasound and/or angiogram Exclusion criteria: duration of symptoms < 6 months, previous angioplasty or arterial surgery to symptomatic leg, MI within previous 6 months, inability to manage treadmill

Kakkos 2005 (*Continued*)

	or training, any psychiatric illness or other reason making follow-up difficult, ischaemic rest pain, gangrene, ischaemic ulceration, inability to attend supervised programme, severe peripheral neuropathy, ABI > 0.9 at enrolment, non-compressible calf arteries, iliac occlusions or stenoses amenable to surgery or angioplasty, femoral artery occlusion < 6 cm; exercise capacity limited by angina, congestive heart failure, COPD, disease of spinal column, venous disease, neurological disease, mental illness, or arthritis
Interventions	Treatment: • Supervised (n = 12): 5-minute warm-up, 50-minute intermittent exercise, 5-minute cool-down. Attendance was 3 times a week for 6 months • Unsupervised exercise (n = 9); advised to walk for approximately 45 minutes each day • Pneumatic foot compression (n = 13); to be used daily for 3-hour periods Duration: 6-month treatment period plus further follow-up at 12 months after treatment began (exercise advice given for second 6-month period)
Outcomes	Primary: ICD, ACD, ABI Secondary: SF-36, WIQ, IC Questionnaire
Notes	Study authors were successfully contacted for means and SDs. Treadmill test: 3.5 km/h, 10% incline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised: blind, block telephone computer generated randomisation, undertaken by Clinical Trials and Evaluation Unit
Allocation concealment (selection bias)	Low risk	Independent allocation A blind, block 'telephone' randomisation procedure was performed by means of a computer Randomisation was performed by the Clinical Trials and Evaluation Unit at the Royal Brompton Hospital in London
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	8 of 34 discontinued at 6 months (attrition rate of 26%)

Kakkos 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	All data reported
Other bias	High risk	n = 8 per group. Power calculation required 15 participants per group

Larsen 1966

Methods	Study design: RCT Method of randomisation: randomised in pairs matched by age and disease, not blinded Exclusions post randomisation: 0 Losses to follow-up: 0
Participants	Country: Denmark Setting: not stated No. of participants: 14 Age: 44 to 65 years Sex: male and female Inclusion criteria: typical IC, stable for > 6 months Exclusion criteria: none stated
Interventions	Treatment: instructed to walk daily, in addition to normal activities Control: 1 placebo (lactose) tablet bd Duration: 6 months
Outcomes	Primary: treadmill test MWD (4.6 km/h, elevation of 0, 8, or 16 cm/m) Secondary: calf blood flow xenon clearance method
Notes	Treadmill test differed for each participant.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised in pairs matched by age and disease. Not blinded
Allocation concealment (selection bias)	High risk	Not blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants to exercise
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes stated

Larsen 1966 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Treadmill test different for each participant, small numbers (n = 14)

Leicht 2011

Methods	Study design: RCT Method of randomisation: (info from study author) Consecutive IC patients were randomly allocated to each group via sealed envelopes that were developed by a researcher not associated with the study Exclusions post randomisation: nil stated Losses to follow-up: described in detail in CONSORT chart (Leicht 2011)
Participants	Country: Australia Setting: local hospital and university centre No. of participants: 25 PAD, 24 healthy age-matched controls Age: 66.9 years (± 8 years) Sex: 14 male (56%) Inclusion criteria: PAD was confirmed based on absence of lower limb peripheral pulses, lower limb artery stenosis, or occlusion on duplex or computed tomographic angiography, and ankle brachial index (ABI) < 0.94 Exclusion criteria: inability to attend potential regular supervised exercise (n = 48), selected for surgical or endovascular intervention (n = 30), declined (n = 20), other medical condition influencing gait (n = 20), exhibited significant ectopy at rest (n = 3)
Interventions	• Conservative medical treatment (n = 13) • Supervised exercise (n = 12) consisted of treadmill walking 3 days per week for 25 to 40 minutes per day at a workload that induced intense to maximal claudication pain Control: healthy age-matched controls (n = 24) Duration: 12 months
Outcomes	Primary: to compare heart rate variability (HRV) in patients with IC and in age-matched healthy adults Secondary: to examine the influence of an intense long-term (12-month) exercise programme on HRV in patients with IC PFWD, MWD, ABI
Notes	Treadmill test: 3.2 km/h and incline of 0%. The incline increased by 2% every 2 minutes until voluntary exhaustion or a maximum time of 25 minutes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised, consecutive IC patients were randomly allocated to each group via sealed envelopes that were developed by a re-

Leicht 2011 (*Continued*)

		searcher not associated with the study
Allocation concealment (selection bias)	Low risk	Consecutive IC patients were randomly allocated to each group via sealed envelopes that were developed by a researcher not associated with the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data reported
Selective reporting (reporting bias)	Low risk	All outcome data reported
Other bias	Unclear risk	Small numbers

Mannarino 1991

Methods	Study design: RCT Method of randomisation: states random. Not blinded Exclusions post randomisation: not stated Losses to follow-up: none
Participants	Country: Italy Setting: not stated No. of participants: 20 Age: 48 to 75 years Sex: male and female Inclusion criteria: IC for > 2 years, stable for past 3 months, pain-free walking distance < 300 m Exclusion criteria: h/o angina, recent MI, or stroke; vascular surgery or PTA in previous 6 months; impaired cardiac or lung function; major liver, kidney, or metabolic disorders; infection; cancer; peptic ulcer
Interventions	Treatment: 1 h home exercises daily supervised via out-patients. Week 1: 500 m in 20 min; week 2: 1000 m in 40 min; week 3: 2000 m in 60 min Control: dipyridamole 75 mg tds plus aspirin 330 mg od Duration: 6 months
Outcomes	Primary: treadmill test pain-free and maximal walking time (2 km/h on 12° slope), ABI Secondary: calf blood flow strain-gauge plethysmography

Mannarino 1991 (*Continued*)

Notes	A third group of 10 participants received antiplatelet treatment and exercise. These results are discussed but are not formally included in a meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised; no further information available
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in paper
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether all enrolled completed the study
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Small numbers

McDermott 2008

Methods	Study design: RCT Method of randomisation: parallel assignment by computer via a randomly permuted block method; outcome assessor blinded Exclusions post randomisation: not described Losses to follow-up: described in flow chart (McDermott 2008)
Participants	Country: Chicago Setting: urban academic medical centre No. of participants: 156 Age: 70.6 ± 10.3 years Sex: male and female Inclusion criteria: 150 peripheral arterial disease patients with and without IC Exclusion criteria: above or below knee amputation, wheelchair confinement, inability to walk on a treadmill or perform progressive resistance training, inability to attend 3 times a week for 6 months, Class II NYHA heart failure or angina at rest or on minimal exertion, silent coronary ischaemia (ST depression of 1 mm) during baseline exercise test, ST-T wave changes or LBBB on baseline ECG, walking impairment not attributed to PAD, planned lower extremity revascularisation or major surgery within 12 months, MI or CABG during previous 3 months, current foot ulcer, ABI > 0.95, life expectancy

	< 12 months, does not speak English, dementia, poorly controlled BP, treated for cancer in the past 12 months, current significant exercise
Interventions	Treatment group 1: supervised treadmill exercise (6 months, 3 times a week; followed by a 6-month home-based programme). Initially 15 minutes of exercise, increased to 40 minutes by week 8. Initial treadmill walking speed 2.0 mph. Between weeks 8 and 24, intensity was increased weekly; either by grade or by speed, n = 51 Treatment group 2: lower extremity resistance training (6 months, 3 times a week; followed by a 6-month home-based programme). Participants performed 3 sets of 8 repetitions of knee extensions, leg press, leg curl exercises. Weights adjusted monthly until lifting 80% of 1 maximum repetition. 3 sets of 8 repetitions of squat and toe rises were also performed, n = 52 (1 dropped out) Control: usual care with diet and nutrition advice (11 sessions lasting 1 hour each over 6 months), n = 53 (1 dropped out) Duration: 6 months
Outcomes	6-Minute walking test distance Short physical performance battery Brachial artery flow-mediated dilatation Treadmill walking performance distance WIQ SF-36 physical functioning score
Notes	Treadmill test: Gardner Skinner Protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised parallel assignment by computer via a randomly permuted block method
Allocation concealment (selection bias)	Low risk	Parallel assignment by computer via a randomly permuted block method
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examiners were blinded to participant group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data clearly reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

McDermott 2008 (*Continued*)

Other bias	Unclear risk	Underpowered. Power calculations assumed that 50 people in each group would complete 6-month follow-up, and that 2 separate 2-sample t-tests using a 2-sided alpha of 0.05 would be conducted. The study was designed to have 80% power to detect a difference of 30 meters change in 6-minute walk distance and a difference of 0.97 change in the SPPB between baseline and 6-month follow-up between each exercise and control group Only 50 completed the SET; 48 were in the control group, and 46 were in the lower extremity resistance group

McGuigan 2001

Methods	Study design: RCT Method of randomisation: randomly assigned to either of the 2 experimental groups Exclusions post randomisation: 2 participants from the training group and 2 from the control group withdrew from the study because of circumstances unrelated to the investigation Losses to follow-up: not stated
Participants	Country: Australia Setting: not stated No. of participants: 20 (sample size of 18 needed) Age: not stated Sex: male and female Inclusion criteria: ABI < 0.94 at rest that decreased to < 0.73 after exercise Exclusion criteria: • Leg pain at rest • Ischaemic ulceration or gangrene • Inability to walk at least 2 km/h on a treadmill • Limited exercise capacity by factors other than IC (e.g. symptoms of angina, CCF, COPD, arthritis) • Vascular surgery or angioplasty undergone within the previous year • Smoking
Interventions	Treatment: n = 11. Resistance training program 3 days per week throughout the 24-week period. Minimum of 48 hours between sessions Control: n = 9 Duration: 24 weeks
Outcomes	Aims: to investigate effects of resistance training on walking performance, strength, and skeletal muscle adaptation Primary: fibre area and shifts in MHC isoforms Secondary:

McGuigan 2001 (*Continued*)

	• Graded treadmill protocol - initially 3 km/h at 0% for 2 min, then increased 2% every 2 min with speed constant • Rate of perceived pain (scale 0 to 10) • Time in seconds to onset of claudication pain or maximal claudication pain • 6-minute walk • ABI • Fibre type and distribution • Muscle capillarisation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated. Randomly assigned to either of the 2 experimental groups
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two participants from the training group and 2 from the control group withdrew from the study because of circumstances unrelated to the investigation Unclear what total numbers were
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Sample size was 18, which was not met, as 4 withdrew.

Mika 2005

Methods	Study design: RCT Method of randomisation: not described Exclusions post randomisation: not described Losses to follow-up: 18 withdrew (10 control, 8 exercise)
Participants	Country: Poland Setting: university department out-patient clinics No. of participants: 98

Mika 2005 (*Continued*)

	Age: 50 to 70 years Sex: male and female Inclusion criteria: PAD and IC (Fontaine stage II) stable for 3 months, PFWD 50 to 200 m at 3.2 km/h Exclusion criteria: angina, recent MI, vascular surgery in past 3 months, impaired cardiac or lung function, DM, cancer, kidney and liver disease, arthritis limiting walking, other contraindication to walking, those taking beta-blockers, pentoxifylline or other haemorheologically active drugs
Interventions	Treatment: 12-week programme of supervised pain-free treadmill exercise, 1 hour per day 3 times a week of repetitive walking exercise Control: usual care Duration: 3 months
Outcomes	PFWD Total leukocyte count Neutrophil count Microalbuminuria
Notes	Treadmill test: 3.2 km/h, 12% incline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised; no further details available
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded assessor. Testing and analyses were conducted by qualified medical staff blinded to participants' group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data clearly reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No evidence of other bias

Mika 2006

Methods	Study design: RCT Method of randomisation: not described Exclusions post randomisation: not described Losses to follow-up: 5
Participants	Country: Poland Setting: university department clinics No. of participants: 60 Age: 50 to 70 years Sex: male and female Inclusion criteria: Fontaine stage II PAD, IC limiting walking and stable for 3 months, ABI < 0.9 Exclusion criteria: angina; recent MI; vascular surgery in past 3 months; impaired cardiac or lung function; DM; cancer, kidney, and liver disease; arthritis limiting walking; inability to walk at 3.2 km/h; taking beta-blockers, pentoxifylline, or other haemorheologically active drugs
Interventions	Treatment: 12-week programme of supervised pain-free MD treadmill exercise, 1 hour per day 3 times a week of repetitive walking exercise Control: usual care, to maintain normal activity level Duration: 3 months
Outcomes	Pain-free walking time Maximum walking time Red cell deformability - erythrocyte elongation index
Notes	Treadmill test: 3.2 km/h 0% for 3 minutes followed by an increase in grade of 3.5% every 3 minutes (speed remained constant)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised; no further details available
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 lost to follow-up (3 in exercise group, 2 in control group). All data on remaining 55 reported

Mika 2006 (*Continued*)

Selective reporting (reporting bias)	Low risk	All data on remaining 55 reported
Other bias	Unclear risk	Patients who were unable to walk on the treadmill at a speed of at least 3.2 km/h were also excluded

Mika 2011

Methods	Study design: RCT Method of randomisation: not stated Exclusions post randomisation: not stated Losses to follow-up: 7 dropped out
Participants	Country: Poland Setting: hospital; vascular out-patient clinic No. of participants: 68 Age: 63.5 years (training group), 62.1 years (control group) 60 male, 8 female Inclusion criteria: PAD and IC - Fontaine stage II, aged 50 to 70 years, ABI < 0.9 at rest and 0.75 after exercise. All included patients had stable claudication distance and were able to walk no less than 150 m without pain Exclusion criteria: rest pain, gangrene, ulceration, history of angina pectoris, recent MI or vascular surgery within the previous year, impaired cardiac or lung function, DM, cancer, or kidney and liver disease. Also, patients with arthritis who were unable to walk on the treadmill at a speed of at least 3.2 km/h. Additionally, women in menopausal status and those taking oestrogen were excluded because of the possible effects of these factors on HDL cholesterol level. None of the participants in the study was taking beta-blockers
Interventions	Treatment: 12-week SEP, sessions conducted in the morning, 3 times per week Repetitive walking exercise with 3-min resting intervals. During each session, after 5 min of warm-up activities (free cycling on a stationary cycle ergometer), participants walked on the treadmill at a speed of 3.2 km/h at a grade that induced claudication pain within approximately 3 to 5 min Control: no change in physical activity All study participants were encouraged to stop smoking. Their diet was neither controlled nor modified throughout the study period Duration: 3 months
Outcomes	Pain-free walking time (PFWT) Maximal walking time Haematocrit Plasma lipoproteins
Notes	Graded treadmill protocol (Gardner protocol): 3.2 km/h throughout the test, but the inclination from 0% (during initial stage) was raised by 2% every 2 min until maximal claudication pain occurred; without handrail

Mika 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned to either an intervention group (n = 34) or a control group (n = 34)
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treadmill testing and biochemical analyses were conducted by medical staff blinded to participants' group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 dropouts discussed; rest of data complete
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	During an initial visit, participants were familiarised with treadmill walking (speed 3.2 km/h, 0% inclination) for 10 min. The treadmill test was repeated on the next day, and the mean of 2 measurements was used in data analysis. The treadmill was calibrated before each testing. Participants were instructed not to use handrail support during the test

Sanderson 2006

Methods	Study design: RCT Method of randomisation: closed envelope system Exclusions post randomisation: nil Losses to follow-up: 1 in treadmill group
Participants	Country: Australia Setting: not stated No. of participants: 42 Age: mean 63 years Inclusion criteria: claudication lasting > 1 year, ABI < 0.9 Exclusion criteria: reduced cardiac function, rest pain, recent surgery or cardiac event, other medical conditions rendering exercise unsuitable

Sanderson 2006 (*Continued*)

Interventions	Treatment: • Treadmill exercise • Cycling Both groups exercised 3 times a week for 6 weeks Control: no exercise Duration: 6 weeks
Outcomes	MWD and PFWD and cycling tests Submaximal and peak physiological response ABI
Notes	Stratified by gender, presence of diabetes, then randomised Results given as mean differences The maximal graded walking test was performed on a motorised treadmill (TrackMaster TMX425CP, Newton, Kan) at a constant speed of 2.7 km/h. The treadmill gradient was set at 0% for the first 5 minutes of the test, then it was increased by 2% every 3 min until the participant failed to sustain the task

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Closed envelope system
Allocation concealment (selection bias)	Low risk	Closed envelope system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in paper
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data clearly reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No evidence of other bias

Schlager 2011

Methods	Study design: RCT single centre Method of randomisation: computer-generated random digits in sealed envelopes (block-wise randomisation by 2) Exclusions post randomisation: nil Losses to follow-up: 1 (MI 3 months after study inclusion)
Participants	Country: Austria Setting: single-centre hospital No. of participants: 40 Age: mean age of 69.1 years (standard deviation of ± 9.5 years) Inclusion criteria: symptomatic PAD (Rutherford category I to III), diagnosed by clinical evaluation, oscillometric pulse wave measurements, ABI, duplex sonography, and or CT or MR angiography Exclusion criteria: asymptomatic PAD, critical limb ischaemia and reduced exercise tolerance caused by other limitations than claudication (coronary artery disease, congestive heart failure, dyspnoea, uncontrolled blood pressure, any kind of restriction of the musculoskeletal system, which might have an influence on the efficiency of exercise training)
Interventions	Treatment: SEP with BMT (twice-weekly programme for 6 months). Warm-up period of 5 to 10 min; initial duration included 35 min of intermittent walking, which was increased by 5 min each session until 50 min of intermittent walking was accomplished. The workload of exercise training was set to a walking speed that elicited claudication symptoms within 3 to 5 min Control: BMT Duration: 12 months
Outcomes	Endothelial progenitor cells (CD34+, CD133+, KDR+) Plasma levels of vascular endothelial growth factor (VEGF), asymmetrical dimethylarginine (ADMA), stromal cell derived factor-1 (SDF-1) Maximum walking distance
Notes	Treadmill test: 3.2 km/h, 12% incline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random digits in sealed envelopes (block-wise randomisation by 2)
Allocation concealment (selection bias)	Low risk	Computer-generated random digits in sealed envelopes (block-wise randomisation by 2)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants

Schlager 2011 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treadmill exercise tests were routinely performed by 2 experienced medical technical assistants, who were blinded to the assigned treatment arm and otherwise were not involved in the study. Participants were instructed to report all symptoms and discomforts (claudication and other than claudication) occurring during the test, but assistants refrained from encouraging participants during treadmill exercise tests
Incomplete outcome data (attrition bias) All outcomes	Low risk	One out of 40 participants did not complete the study.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No evidence of other bias

Tew 2009

Methods	Study design: RCT Method of randomisation: computer programme (nQuery Advisor 6.0 Statistical solutions) Not blinded Exclusions post randomisation: none Losses to follow-up: 2 withdrew from the exercise group, and 4 withdrew from the control group; 1 participant died of a heart attack, 1 developed a lower limb ulcer that required revascularisation surgery, 1 was identified as having a popliteal artery aneurysm, and 1 returned to full-time employment. The remaining 2 participants cited lack of time as their reason for withdrawal
Participants	Country: England Setting: single-centre hospital No. of participants: 57 Age: 69 ± 9 years Sex: male and female Inclusion criteria: Fontaine stage II PAD, 12-month history of stable IC, ambulation limited by IC, resting ABI < 0.90 or ABPI drop > 15 mmHg post maximal walking exercise Exclusion criteria: absence of PAD, ABI unobtainable owing to incompressible vessels, Fontaine I or III, exercise limited by cause other than IC, history of IC < 12 months, revascularisation/other major surgery within past 12 months, pharmacological therapy specifically for IC (e.g. cilostazol)
Interventions	Treatment: • Arm crank exercise (twice-weekly exercise programme for 12 weeks at an intensity of 60% to 70% of the peak work rate achieved of the initial arm crank assessment. Patients trained in cycles of 2-minute exercise at 50 rev/min followed by 2 min of rest for a total

	of 40 min/session) Control: • Non-exercise group Duration: 3 months
Outcomes	Primary: lower limb oxygen delivery Secondary: NIRS, peak VO_2 kinetics
Notes	Treadmill test: 3.2 km/h, 0% grade with 1% increase every 1 min

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised via a computer programme (nQuery Advisor 6.0; Statistical Solutions)
Allocation concealment (selection bias)	Low risk	Computer programme (nQuery Advisor 6. 0; Statistical Solutions)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 from the exercise group and 4 from the control group
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Methodological limitations need to be considered: NIRS data;exact contribution of intracellular myoglobin to the StO2 signal is unclear, and subcutaneous fat thickness changes might have influenced findings No relationship exists between calf skinfold and calf muscle StO2 during walking in patients with IC

Tew 2015

Methods	Study design: RCT Method of randomisation: randomised ratio 2:3. Achieved via a block randomisation sequence (block size 10) generated before recruitment Exclusions post randomisation: none Losses to follow-up: 1 lost to follow-up, all accounted for within CONSORT diagram
Participants	Country: UK Setting: not stated No. of participants: 23 Age: > 18 Sex: men and women Inclusion criteria: age > 18 years and stable IC for > 3 months Exclusion criteria: CLI, planned or previous lower-limb revascularisation, presence of contraindications to exercise (e.g. unstable angina) or co-morbidities that limited walking to a greater extent than the IC (e.g. severe arthritis); major surgery, MI, or CVA in the previous 6 months
Interventions	Treatment: usual care + SEDRIC (structured education for rehabilitation in intermittent claudication programme that promotes self-managed walking in people with IC) Control: usual care (included a brief info leaflet on PAD) Duration: 6 weeks
Outcomes	Mean daily step count Pain-free and maximum walking distances 6-min walking distance WELCH questionnaire, WIQ, EQ-5D, Intermittent Claudication Questionnaire
Notes	Gardner incremental treadmill test: 3.2 km/h, 0% grade, with 2% increase every 2 min

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised ratio 2:3. Achieved via a block randomisation sequence (block size 10) generated before recruitment
Allocation concealment (selection bias)	Low risk	Implemented by an individual who was not involved in recruitment or data gathering processes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Group allocation was concealed from participants while baseline information was gathered
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Tew 2015 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All stated
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Baseline data showed that the intervention group had slightly higher levels of physical activity, walking capacity, and quality of life than the control group

Tisi 1997

Methods	Study design: RCT Method of randomisation: randomised by sealed envelope, weighted 70:40:40 (angioplasty:exercise:observation) 19/25 randomised to PTA had unsuitable lesions, and the technique failed in one other. Not blinded Intention-to-treat analysis Exclusions post randomisation: none stated Losses to follow-up: none stated
Participants	Country: England Setting: general hospital No. of participants: 67 Age: mean 69.3 years Sex: male and female Inclusion criteria: stable IC > 6 months, positive Edinburgh Claudication Questionnaire, ABI < 0.8 and > 3 0 mmHg drop in ankle systolic pressure on exercise, walking distance 50 to 250 m on treadmill (3 km/h, 10% gradient) Exclusion criteria: intervention for IC in past 6 months, exercise limited by other factors, concurrent medical disease, treatment with steroids, inability to complete assessment visits
Interventions	Treatment: • Exercise - series of active and passive leg exercises performed to the limit of exercise pain, supervised by a physiotherapist once weekly for 4 weeks. Also encouraged to exercise for 45 min daily at home, plus to walk 1 mile a day; n = 22 • PTA, n = 28 • Control: observation, plus advice given to all 3 groups (leaflet advising on weight loss, smoking, and exercise, plus 75 mg aspirin daily), n = 17 • Healthy controls, n = 15 Duration: 12 months
Outcomes	Primary: treadmill test - PFWD and MWD (3 km/h on 10% slope); ABI Secondary: Nottingham Health Profile

Tisi 1997 (*Continued*)

Notes	Results for the exercise versus angioplasty comparison have not been included in this review. Claudication and walking distance results not in usable format

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by sealed envelope, weighted 70:40:40 (angioplasty: exercise:observation)
Allocation concealment (selection bias)	Unclear risk	Randomised by sealed envelope, weighted 70:40:40 (angioplasty: exercise:observation); opacity of envelopes not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in paper
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 22 enrolled at baseline, 10 were present at 12 months in the exercise group. In the observation group, n = 17 at baseline, and n = 9 at 12 months. No reasons given for loss to F/U
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No evidence of other bias

Tsai 2002

Methods	Study design: RCT Method of randomisation: not described Exclusions post randomisation: not described Losses to follow-up: 11 - 5 in treatment group, 6 in control group
Participants	Country: Taiwan Setting: community No. of participants: 64 Age: 76 years ± 4 Sex: 81% male Inclusion criteria: Fontaine II PAD on Rose Questionnaire. ABI < 0.95

Tsai 2002 (*Continued*)

	Exclusion criteria: intervention for IC in past 3 months, exercise limited by other factors, rest pain, MI or unstable claudication in the past 3 months, history of angina on exertion
Interventions	Treatment: 12-week progressive rehabilitation programme, 3 times a week. Up to 30 minutes on the treadmill Control: usual care Duration: 12 weeks
Outcomes	Time to onset of pain Time to maximum pain 6-Minute walking test distance WIQ Physical function Bodily pain Role limitation physical and emotional General health Mental health Social function Vitality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised; no further details available
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data clearly reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No evidence of other bias

Wood 2006

Methods	Study design: RCT Method of randomisation: not stated by paper Not blinded Exclusions post randomisation: none stated Losses to follow-up: nil stated
Participants	Country: Australia Setting: vascular out-patient clinic at the Royal Brisbane and Women's Hospital No. of participants: 18 Age: 56 ± 9 control, 64 ± 6 treatment Sex: male and female Inclusion criteria: history (> 6 months) of stable PAD and IC Exclusion criteria: rest pain, unstable angina and/or uncontrolled hypertension, experienced loss of consciousness as a result of dizziness, had a bone or joint problem that could be exacerbated by exercise, had undergone vascular surgery within the past 6 months, had suffered a cerebrovascular or coronary event in the past 12 months, or resided more than 1 h by car from the laboratory. Patients not limited by claudication and those who experienced angina or demonstrated ischaemic ECG abnormalities during exercise were excluded from the study
Interventions	Treatment: • 6 weeks of treadmill walking training, three 40-min supervised walking training sessions/week (n = 7) Control: sedentary control (n = 6) Participants in both groups were asked to continue their normal daily activities Duration: 6 weeks
Outcomes	• To determine whether plasma vascular endothelial growth factor (VEGF) increases in response to acute exercise in patients with IC, given the potentially large hypoxic stimulus for VEGF release during exercise in this population • To determine whether this response is attenuated following 6 weeks of high-intensity exercise training
Notes	Treadmill test: 2.7 km/h, 0%, with grade increased 2% every 3 min

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"In part B participants were randomised to one of two study arms"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to bind participants

Wood 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	n = 6 for control and n = 7 for training. Nil lost to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Small numbers in each arm

Zwierska 2005

Methods	Study design: RCT Method of randomisation: Randomisation was undertaken via the fishbowl technique (Baumgartner 1998). This involved drawing patient names out of a 'hat' and allocating them to respective groups at random. Randomisation was undertaken by an independent academic based at another site in Sheffield Intention-to-treat analysis: yes Exclusions post randomisation: nil Losses to follow-up: 10
Participants	Country: UK Setting: not stated No. of participants: 104 Age: median 69 (50 to 89) Sex: 81% male in leg group, 78% in arm group, 73% in control group Inclusion criteria: stable symptomatic peripheral arterial disease Exclusion criteria: not stated
Interventions	Treatment: • Supervised upper limb aerobic exercise • Supervised lower limb aerobic exercise Control: no exercise Duration: 24 weeks
Outcomes	ICD MWD Peak heart rate Peak oxygen consumption Perceived exertion and pain Physical activity status
Notes	Results given as medians - study authors contacted successfully for more information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Zwierska 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomised Randomisation was undertaken via the fishbowl technique (Baumgartner and Strong 1998). This involved drawing patient names out of a 'hat' and allocating them to respective groups at random
Allocation concealment (selection bias)	Low risk	Randomisation was undertaken by an independent academic based at another site in Sheffield
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not possible to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessment of outcome measures was conducted by the same 2 staff members. Procedures were checked for consistency at random by the lead investigator at Sheffield Hallam University (J.S.), who was blinded to group assignment Blinding of the 2 staff members who assessed outcome measures was not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data clearly reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No evidence of other bias

ABI: ankle brachial index.
ABPI: ankle brachial pressure index.
ACD: absolute claudication distance (or maximum walking distance).
bd: twice a day.
BMI: body mass index.
BMT: best medical therapy.
bpm: beats per minute.
CABG: coronary artery bypass graft.
CCF: congestive cardiac failure.
CHF: congestive heart failure.
CLI: critical limb ischaemia.
COAD: chronic obstructive airways disease.
COPD: chronic obstructive pulmonary disease.
CPAD-IC: peripheral arterial disease with intermittent claudication control group.
CPS: composite pain scale.
CT: computed tomography.
CTA: computed tomographic angiography.

CVA: cerebrovascular accident.
DM: diabetes mellitus.
ECG: electrocardiography.
EQ-5D: EurQoL Group Quality of Life Questionnaire based on 5 dimensions.
HbA1c: glycated haemoglobin.
HDL: high-density lipoprotein.
h/o: history of.
HRQoL: health-related quality of life.
HRV: heart rate variability.
ICQ: Intermittent Claudication Questionnaire.
IQR: interquartile ratio.
LBBB: left bundle branch block.
LDL: low-density lipoprotein.
IC: intermittent claudication.
ICD: intermittent claudication distance.
IHD: ischaemic heart disease.
IPC: intermittent pneumatic compression.
MI: myocardial infarction.
min: minutes.
MR: magnetic resonance.
MWD: maximum or maximal walking distance.
NIRS: near-infrared spectroscopy.
NO: nitric oxide.
NYHA: New York Heart Association.
od: once a day.
PAD: peripheral arterial disease.
PFWD; pain-free walking distance.
PTA: percutaneous transluminal angioplasty.
RCT: randomised controlled trial.
SD: standard deviation.
SDF-1: stromal cell derived factor-1.
SE: supervised exercise.
SEP: supervised exercise programme.
SET: supervised exercise therapy.
SF-36: Short Form-36.
SPPB: Short Physical Performance Battery.
TASC: Trans-Atlantic Inter-Society Consensus.
tds: three times a day
TPAD-IC: peripheral arterial disease with intermittent claudication treatment group.
USE: unsupervised exercise.
VEGF: vascular endothelial growth factor.
vit E: vitamin E.
VO_2: maximum volume of oxygen.
WELCH: Walking Estimated-Limitation Calculated by History.
WIQ: Walking Impairment Questionnaire.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allen 2010	Compares home and supervised based programmes with a focus on nitrite flux
Andreozzi 2008	All 4 study arms utilised exercise.
Aruna 2015	Unclear whether symptomatic PAD. Methods state only that patients had type 2 diabetes mellitus for > 4 years and ABI between 0.90 and 0.40
Beutel 1985	Both groups included exercise; the RCT compared CO_2 mineral baths vs CO_2 gas baths.
Bronas 2011	The usual care group was provided with an exercise regimen that participants could decide whether to follow or not. Therefore, the study compares supervised vs non-supervised exercise. "Control participants also received written instructions on how to exercise independently if they so chose to do"
Brotons 2011	This RCT focussed on all patients with "a diagnosis of ischaemic heart disease, stroke or peripheral arterial disease", and the "primary endpoint was the combination of all-cause mortality and hospital cardiovascular readmission" Separate outcomes for each group were not provided.
Buchwalsky 1974	2 training groups
Bulling 1991	Comparison of exercise plus gingko biloba and exercise vs placebo. No non-exercise control group
Cachovan 1999	Comparison of 2 different sequences of exercise. No non-exercise control group
Carmeli 2004	Not randomised
Cheetham 2004	2 exercise groups and no non-exercise control group
Choi 2012	2 exercise groups and no non-exercise control group. "Controlled clinical trial with two intervention arms: calf ergometry and treadmill training"
Cina 1996	Comparison of physical training vs low-dose heparin and physical training and placebo. No non-exercise control group
CLEVER 2009	This study compares relative clinical and cost-effectiveness of invasive revascularisation with stents vs supervised exercise rehabilitation
Collins 2010	Satisfied inclusion criteria, but data not available in usable format despite attempt to contact trial author
Collins 2012	Comparison of 2 different sequences of exercise. No non-exercise control group. "Patients were randomized to a traditional walking program or walking with poles program of exercise training"
Creasy 1990	This study compared PTA vs supervised exercise therapy.
Crowther 2008	Supervised exercise vs usual care, which included exercise advice for both groups

(*Continued*)

Cucato 2011	Methodology not of an RCT: 8 participants randomly underwent 2 experimental sessions: a session of resistance exercise (6 exercises, 3 sets of 12, 10 and 8 repetitions with perceived exertion of 11 to 13 on the 15-grade Borg scale) and a control session (resting on exercise machines)
Cucato 2011a	The aim of this study was to compare effects of walking and strength training on cardiovascular responses assessed at rest and during exercise in patients with intermittent claudication
Cucato 2015	Participants with IC participated in 2 experimental sessions in a random order. Walking exercise (WE) (15 × 2-min bouts of WE interpolated with 2-min rest intervals) and control (standing rest on a treadmill for 60 min). BP, cardiac output (CO: CO_2 rebreathing), and cardiovascular autonomic modulation (spectral analysis of heart ratevariability) were assessed before and after both experimental sessions during supine rest, and stroke volume and systemic vascular resistance were calculated
Cunningham 2012	This trial assessed whether a brief psychological intervention could increase daily walking at 4 months. The control group received usual care plus researcher contact, and the treatment group received usual care and a brief psychological intervention to modify illness and walking beliefs and to develop a personalised walking action plan
Dahllof 1976	This trial was not fully randomised, as the first 10 of the 34 participants were allocated to exercise before randomisation was introduced. There were several differences between treatment and control groups, including significantly higher cholesterol levels and maximal calf blood flow in the control group. Treatment effects may also have been masked because many control participants spontaneously undertook increased exercise during the trial period
Dantas 2016	Randomised cross-over intervention study with outcome measures of systolic BP, diastolic BP, and heart rate
Dedes 2010	Compares calf ergometry vs standard treadmill training (both groups involve exercise)
Degischer 2002	Not a randomised trial, and both groups had exercise
Dittmar 1977	Exercise in addition to drug treatment
Ericsson 1970	This trial compared exercise with no treatment but was excluded from the review because of insufficient evidence that participants were randomised. The paper stated that participants were "divided into two groups", and trialists were approached to confirm the method of allocation. No reply was received; therefore it was decided to exclude results from the review, unless evidence to the contrary becomes available
Ernst 1987	This trial compared participants on an exercise programme with those not exercised, but allocation was not strictly randomised, as participants were "assigned according to space on the exercise programme"
Ernst 1990	Comparison of treadmill exercise plus pentoxifylline and treadmill exercise plus placebo. No non-exercise control group
EXERT 2009	Participants in the control group will continue to receive usual care from their regular doctor for treatment of PAD and will be provided with written exercise instructions
EXITPAD 2010	Both groups have compare supervised exercise vs walking advice

(*Continued*)

Fakhry 2011	Home-based exercise compared to supervised exercise
Fitzgerald 1971	This trial compared an exercise regimen with no treatment, but no evidence in the report indicates that the groups were randomly allocated. The quality of the trial appears generally poor, with variable periods of follow-up and inclusion of some patients who did not have intermittent claudication
Fowler 2002	Some patients were asymptomatic, and it was not possible to exclude them for data extraction purposes
Gardner 2005	2 exercise groups compared
Gardner 2011	Home-based exercise compared to supervised exercise, and third control group given walking advice
Gardner 2012	No exercise, usual care control group encouraged to walk more on their own but did not receive specific recommendations regarding an exercise programme during the study
Gardner 2014	80 participants were randomised to home-based and supervised exercise programmes. Both groups received training
Gardner 2014a	180 participants were randomised. The NEXT Step programme and the supervised exercise programme consisted of intermittent walking to mild to moderate claudication pain for 12 weeks, whereas controls performed light resistance training
Gibbellini 2000	Satisfied inclusion criteria but no usable data, despite attempts to contact trial authors. Results divided into asymptomatic and symptomatic groups, not aggregated
Gibbs 2013	This study is not focussed on patients with PAD. Participants (n = 140) with uncomplicated Type 2 Diabetes Mellitus, and without known cardiovascular disease or PAD, aged 40 to 65 years, were randomised to supervised aerobic and resistance training 3 times per week for 6 months, or to a usual care control group. ABI was measured before and after the intervention
Gottstein 1987	Both groups received training.
Greenhalgh 2008	Both groups included exercise with the addition of PTA as the modality being investigated
Guidon 2013	Focused on dropout rate of trials. Recruitment to clinical trials of exercise presents significant challenges in the PAD population owing to the presence of coexisting cardiovascular and cerebrovascular disease, reluctance to exercise due to leg pain, and acceptance of reduced mobility as part of ageing. Early identification in primary care before the onset of significant comorbidity may ameliorate some of these issues
Guirro 2015	A cross-over study was carried out with 1 session of each therapeutic resource (high-voltage electrical stimulation (HVES), continuous short-wave diathermy, or physical exercise), with a 7-day washout period between protocols
Hobbs 2006	This study compared exercise with angioplasty.
Hodges 2008	Groups were given supervised exercise or normal care, which included walking advice

(*Continued*)

Holm 1973	Suitable for review but no usable numerical data, despite attempt to contact trial author. Stated significant improvement in walking time in exercise group compared to placebo group
Jones 1996	Comparison of treadmill vs StairMaster. No non-exercise control group
Kiesewetter 1987	Both groups received intensive physical therapy. No non-exercise control group
Kono 2013	This study is not focussed on patients with PAD. An observer-blind randomised controlled trial that enrolled 70 patients (48 men, mean age 63.5 years) with acute non-cardioembolic mild ischaemic stroke. Participants were allocated in equal numbers to a lifestyle intervention group or a control group
Krause 1976	Combines exercise with drug
Kruidenier 2011	Treatment groups received angioplasty or exercise and angioplasty. A third group of exercise is required to make the trial eligible for inclusion in the review
Labs 1999	Comparison of constant-load and graded-load treadmill testing with and without beraprost sodium. No non-exercise control group
Lee 2007	Non-randomised (clinical and cost-effectiveness)
Leon 2005	Focussed on cardiovascular disease, not intermittent claudication
Lepantalo 1984	Comparison of exercise plus flunarizine and exercise plus placebo. No non-exercise control group
LIFE Study	Original study is a multi-centred RCT that compared the ability of a structured physical activity intervention vs a successful ageing intervention to prevent mobility disability in older sedentary people, not specifically those with PAD
Lundgren 1989	This study compared exercise vs surgical reconstruction.
Maejima 2005	Satisfied inclusion criteria, but no data available after attempt to contact trial authors. Reported improvement in walking time in exercise group at 12 weeks
Mannarino 1988	Controlled, not randomised
Mannarino 1989	This trial compared an exercise regimen with nothing (placebo tablets), but the report suggested that groups were not allocated by an acceptable randomisation method. Trialists have been approached to confirm the method of allocation; therefore it may become possible to include the trial at a later date
Martinez 2009	3 groups with different durations of a walking programme
Mays 2015	Participants with PAD randomised to a community-based walking exercise programme compared to usual care advice. Control group received verbal advice to exercise but no formal training
Mazari 2010	This trial compares PTA, a supervised exercise programme (SEP), and combined treatment (PTA plus SEP) for intermittent claudication

(*Continued*)

McDermott 2004	Participants did not have intermittent claudication.
Nawaz 1999	Both groups received exercise advice. No non-exercise control group
Nawaz 2001	Comparison of upper limb and lower limb exercise. Separate non-randomised control group
NCT01065740	Outcome measure of 6-minute walking distance, not treadmill walking distance
NCT01241747	Treadmill training vs light resistance training without any walking
NCT02075502	Participants with PAD randomised to an exercise programme in the community setting incorporating training, monitoring, and coaching compared with participants who received the standard of care (exercise advice)
NCT02879019	Both groups use exercise.
Necker 2003	Training after angioplasty
Nicolai 2010	This paper compared 4 different graded treadmill protocols in random order
Nielsen 1977	Both groups had exercise. No non-exercise control group
Nordanstig 2011	"All patients received verbal training advice and a written programme for IC. The patients were instructed to walk 1/hr day and up to MWD as often as possible" No arm received no exercise advice.
Parr 2009	All groups had exercise, no non-exercise control group. 3-armed trial of upper body strength training programme, conventional exercise programme, and walking advice for the control group
Patterson 1997	Comparison of supervised exercise programme plus lectures and home-based exercise plus lectures. No non-exercise control group
Pinto 1997	2 exercise regimens
Presern-Strukelj 200	Comparison of standard exercise alone and standard exercise plus electrostimulation in amputees with PAD
PROPEL study	Comparison between those with and without PAD. Looks at baseline data without exercise
Riccioni 2010	No mention of randomisation in methods
Richardson 1991	This compared rocker-bottomed shoes vs normal shoes with respect to walking distances
Riebe 2001	Comparison of 2 progressive treadmill tests. No non-exercise control group
Ritti-Dias 2010	No control arm; strength training vs walking

(*Continued*)

Rodrigues 2014	Randomised cross-over of participants with PAD who performed 2 experimental sessions: control (C) and resistance exercise (R). Both sessions were identical (8 exercises, 3 × 10 reps), except that R session was performed with intensity between 5 and 7 on the OMNI-RES scale, and the C session was performed without any load
Saleem 2011	Each group received exercise training. No non-exercise control group
Savage 2001	Compared supervised exercise vs home-based exercise. No non-exercise control group
Scheffler 1991	Each group received exercise training. No non-exercise control group
Schlager 2011a	Satisfied inclusion criteria but data not available in usable format despite attempt to contact trial author
Schoneberger 1994	Controlled study, not randomised
Silvestro 2002	Age-matched control group
Slordahl 2005	2 exercise groups
Snabl 1958	Not a randomised controlled trial
Sonaglia 2013	2 exercise groups. Eligible PAD La Fontaine IIa-IIb participants were randomised into 2 groups. Group A was treated with physical therapy plus oral pRLX, 20 ug b.i.d. for 12 weeks, and group B received physical therapy alone
Spronk 2009	This study compared endovascular revascularisation vs supervised exercise
Stewart 2008	Supervised exercise vs exercise advice. No control group
Streminski 1992	Satisfied inclusion criteria but data not available in usable format despite attempt to contact trial author. Actovegin vs exercise. Results given as mean change. Reported improvement in pain-free walking distance in exercise group
SUPER study	This study compared initial PTA vs initial supervised exercise therapy
Taft 2004	This study was not truly randomised and did not contain any outcomes of relevance to this review
Tebbutt 2011	Satisfied inclusion criteria but data not available in usable format despite attempt to contact trial author
Thomson 1999	2 exercise groups
Treat-Jacobson 2012	Participants with IC were assessed before and after a 12-week progressive, 3 times a week, supervised aerobic arm exercise training programme. No control arm
Ventura 1984	Satisfied inclusion criteria but data not available in usable format despite attempt to contact trial author
Walker 2000	The non-exercise group was not randomised.

(*Continued*)

Waller 1988	Comparison of exercise when participants had smoked immediately before treadmill test vs exercise when participants had not smoked before treadmill test
Wang 2008	Treatment: Plantar Flexion Ergometer, this occurred 3 times a week for 8 weeks. Each session lasted 40 minutes with equal time on each leg Control: received advice in accordance with existing exercise guidelines for PAD patients provided by the AHA
Wang 2010	The study design was that of a cross-over from control to exercise, not a randomised controlled trial
Winterfeld 1983	Not a randomised controlled trial
Zwierska 2004	Both groups had exercise. No non-exercise control group

ABI: ankle brachial index.
AHA: American Heart Association.
BP: blood pressure.
b.i.d.: twice daily.
CO_2: carbon dioxide.
IC: intermittent claudication.
MWD: maximum walking distance.
PAD: peripheral arterial disease.
PTA: percutaneous transluminal angioplasty.
RCT: randomised controlled trial.
SEP: supervised exercise programme.
WE: walking exercise.

Characteristics of ongoing studies *[ordered by study ID]*

NCT01231360

Trial name or title	The Effect of Exercise Training on Skeletal Muscle Metabolism in PAD
Methods	Allocation: randomised Intervention model: parallel assignment
Participants	Ages eligible for study: 40 years and older Genders eligible for study: both Accepts healthy volunteers: yes Inclusion criteria: • Claudication symptoms • ABI $\leq$ 0.9 in the symptomatic leg Exclusion criteria: • Diabetes • Impaired fasting glucose • Peripheral vascular intervention within prior 6 months

NCT01231360 (*Continued*)

	• Recent unstable angina • MI or stroke within prior 6 months • Changes to HMG-CoA reductase inhibitor (statin) within past 3 months • Changes to pentoxifylline and/or cilostazol regimen within past 3 months or anticipated to be necessary during the study • On Coumadin • Exercise limitations for reasons other than IC (such as congestive heart failure, angina, chronic lung disease, or other disorders affecting the limb such as arthritis or neuropathy) • Rest pain or ulcers due to CLI • Lower extremity amputation
Interventions	Active comparator: exercise training Participants randomised to exercise training will participate in a 3-month treadmill exercise programme in 1-h training sessions 3 times per week as previously described. After a 5-minute warm-up period, exercise is initiated at a low workload of 2 mph at 0% grade. Participants walk until moderate claudication severity develops, then rest until the discomfort resolves, repeating until the total exercise period is completed. The intensity of treadmill exercise is increased as tolerated by increasing walking speed by 0.5 to 1 mph and/or grade by 1% to 2%. Participants are encouraged to continue the walking programme at home for at least 30 minutes on 2 separate occasions each week Active comparator: normal routine Participants randomised to the routine activity control group will be asked to keep a log of their daily activities and return to the Vascular Research Center at weeks 4, 8, and 12, at which time they will be asked to return their log and undergo repeat treadmill testing and complete the 6-minute walking test
Outcomes	Specific aim 1: to test the hypothesis that subjects with PAD and IC have altered expression of genes that regulate skeletal muscle metabolism Specific aim 2: to test the hypothesis that exercise training improves calf skeletal muscle insulin resistance and genes that regulate skeletal muscle metabolic function in PAD patients with intermittent claudication
Starting date	Estimated enrolment: 75 Study start date: October 2010 Estimated study completion date: June 2013 Estimated primary completion date: December 2012 (final data collection date for primary outcome measure)
Contact information	Reena Pande, MD, Brigham and Women's Hospital skadivar@partners.org Contact: 617-732-6320
Notes	NCT01231360

NCT01822457

Trial name or title	Effect of Nike Fuel Band on Exercise and Function in Claudicants: A Randomised Controlled Trial
Methods	Allocation: randomised Intervention model: parallel assignment Masking: single-blind (outcomes assessor) Primary purpose: supportive care • Experimental: Nike Fuel Band (NFB). Participants will receive a Nike Fuel Band to encourage exercise.

NCT01822457 (*Continued*)

	• No intervention: control standard follow-up
Participants	Inclusion criteria: • Age 40 to 80 years • Referred to vascular rehabilitation service at St Mary's Hospital (UK) • IC involving the calf muscles • Clinical and duplex investigations indicate superficial femoral artery stenosis or occlusion Exclusion criteria: • Clinical and duplex investigations indicate iliac disease • Major joint disease in lower limb or lumbar spine/entrapment syndrome • Significant cardiopulmonary limitations (NYHA > 1) • MWD > 500 m • Hospital in-patient/living in a care home • *Unfamiliarity with required technology • History of dementia • Inability to mobilise independently (does not include walking aids) • IC not a limiting factor of mobilisation, limited by other medical problems • Inability to attend supervised exercise programme • Patient owns or uses any type of activity monitor • Uses a walking frame *Participants should be able to use the NFB technology with minimal assistance Gender: both Ages: 40 to 80 years
Interventions	Device: Nike Fuel Band (NFB). The NFB is a wrist-worn sensor with a built-in accelerometer for motion quantification. It is programmed to estimate the number of steps taken per day, and also to predict energy expenditure in units known as Nike Fuel. Accompanying software allows the user to set daily targets and monitor his or her activity through a graphical user interface
Outcomes	All outcomes assessed at 3 months Primary: MWD - standardised treadmill test Secondary: • PFWD - standardised treadmill test • Disease-specific quality of life via the VascuQol Questionnaire • Mood via the Hospital Anxiety and Depression Scale score
Starting date	August 2013
Contact information	Pasha Normahani: Pn106@imperial.ac.uk, Richard M Kwasnicki: rmk107@imperial.ac.uk
Notes	Estimated completion: February 2015 (final data collection date for primary outcome measure)

ABI: ankle brachial index.
CLI: critical limb ischaemia.
HMG-CoA: rate-controlling enzyme of the mevalonate pathway.
IC: intermittent claudication.
mph: miles per hour.
MI: myocardial infarction.

MWD: maximum walking distance.
NFB: Nike Fuel Band.
NYHA: New York Heart Association.
PAD: peripheral arterial disease.
PFWD: pain-free treadmill walking distance.

DATA AND ANALYSES

Comparison 1. Overall outcomes: exercise regimen compared with placebo or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking distance (m)	10	500	Mean Difference (IV, Random, 95% CI)	120.36 [50.79, 189.92]
2 Pain-free walking distance (m)	9	391	Mean Difference (IV, Fixed, 95% CI)	82.11 [71.73, 92.48]
3 Maximum walking time (min)	12	577	Mean Difference (IV, Random, 95% CI)	4.51 [3.11, 5.92]
3.1 Usual care	11	563	Mean Difference (IV, Random, 95% CI)	4.47 [3.00, 5.94]
3.2 Placebo	1	14	Mean Difference (IV, Random, 95% CI)	5.20 [0.88, 9.52]
4 Pain-free walking time (min)	11	534	Mean Difference (IV, Random, 95% CI)	2.93 [1.77, 4.09]
4.1 Usual care	10	520	Mean Difference (IV, Random, 95% CI)	3.08 [1.82, 4.34]
4.2 Placebo	1	14	Mean Difference (IV, Random, 95% CI)	1.77 [0.55, 2.99]
5 Change in MWD/T	15	656	Mean Difference (IV, Random, 95% CI)	40.25 [28.64, 51.86]
6 Change in ICD/T	15	703	Mean Difference (IV, Random, 95% CI)	58.42 [44.20, 72.64]
7 Ankle brachial index	13	570	Mean Difference (IV, Random, 95% CI)	0.04 [-0.00, 0.08]
8 Mortality	5	540	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.39, 2.17]
9 Amputation	1	177	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.15]
10 Peak exercise calf blood flow (mL/100 mL/min)	4	103	Mean Difference (IV, Fixed, 95% CI)	0.94 [-0.81, 2.69]
10.1 Usual care	2	71	Mean Difference (IV, Fixed, 95% CI)	2.83 [0.18, 5.49]
10.2 Placebo	2	32	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-2.85, 1.82]

Comparison 2. Three-monthly outcomes: exercise regimen compared with placebo or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking distance (m)	3	116	Mean Difference (IV, Random, 95% CI)	104.46 [-64.33, 273.24]
2 Pain-free walking distance (m)	3	156	Mean Difference (IV, Fixed, 95% CI)	88.70 [58.25, 119.15]
3 Maximum walking time (min)	5	172	Mean Difference (IV, Fixed, 95% CI)	6.05 [5.47, 6.62]
3.1 Usual care	5	172	Mean Difference (IV, Fixed, 95% CI)	6.05 [5.47, 6.62]
4 Pain-free walking time (min)	3	132	Mean Difference (IV, Fixed, 95% CI)	4.95 [4.38, 5.53]
5 Ankle brachial index	4	130	Mean Difference (IV, Fixed, 95% CI)	0.06 [0.01, 0.11]
6 Mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Quality of Life SF-36	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Physical function	2	82	Mean Difference (IV, Fixed, 95% CI)	6.60 [2.37, 10.83]
7.2 Bodily pain	2	82	Mean Difference (IV, Fixed, 95% CI)	3.89 [-1.91, 9.68]
7.3 General health	2	82	Mean Difference (IV, Fixed, 95% CI)	4.52 [-0.01, 9.04]
7.4 Mental health	2	82	Mean Difference (IV, Fixed, 95% CI)	1.44 [-0.93, 3.81]
7.5 Role emotional	2	82	Mean Difference (IV, Fixed, 95% CI)	1.26 [-4.84, 7.36]
7.6 Social function	2	82	Mean Difference (IV, Fixed, 95% CI)	1.49 [-4.16, 7.14]

7.7 Vitality	2	82	Mean Difference (IV, Fixed, 95% CI)	5.55 [1.54, 9.56]
7.8 Role physical	2	82	Mean Difference (IV, Fixed, 95% CI)	10.31 [3.64, 16.98]
7.9 Physical Summary Score	1	29	Mean Difference (IV, Fixed, 95% CI)	2.58 [-4.29, 9.45]
7.10 Mental Summary Score	1	29	Mean Difference (IV, Fixed, 95% CI)	2.05 [-4.73, 8.83]
8 Peak exercise calf blood flow (mL/100 mL/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 3. Six-monthly outcomes: exercise regimen compared with placebo or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking distance (m)	3	156	Mean Difference (IV, Random, 95% CI)	138.36 [22.39, 254.34]
2 Pain-free walking distance (m)	2	116	Mean Difference (IV, Fixed, 95% CI)	52.14 [6.83, 97.45]
3 Maximum walking time (min)	4	295	Mean Difference (IV, Fixed, 95% CI)	3.20 [2.04, 4.36]
3.1 Usual care	3	281	Mean Difference (IV, Fixed, 95% CI)	3.05 [1.84, 4.25]
3.2 Placebo	1	14	Mean Difference (IV, Fixed, 95% CI)	5.20 [0.88, 9.52]
4 Pain-free walking time (min)	5	292	Mean Difference (IV, Random, 95% CI)	2.32 [0.91, 3.74]
4.1 Usual care	4	278	Mean Difference (IV, Random, 95% CI)	2.72 [0.67, 4.77]
4.2 Placebo	1	14	Mean Difference (IV, Random, 95% CI)	1.77 [0.55, 3.00]
5 Ankle brachial index	6	240	Mean Difference (IV, Random, 95% CI)	0.05 [-0.01, 0.11]
6 Mortality	1	178	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.54]
7 Quality of Life SF-36	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Physical summary score	5	429	Mean Difference (IV, Fixed, 95% CI)	2.15 [1.26, 3.04]
7.2 Mental summary score	4	343	Mean Difference (IV, Fixed, 95% CI)	3.76 [2.70, 4.82]
7.3 Physical function	2	85	Mean Difference (IV, Fixed, 95% CI)	9.78 [0.82, 18.74]
7.4 Bodily pain	2	85	Mean Difference (IV, Fixed, 95% CI)	4.85 [-3.79, 13.50]
7.5 General health	2	85	Mean Difference (IV, Fixed, 95% CI)	10.19 [1.83, 18.55]
7.6 Mental health	2	85	Mean Difference (IV, Fixed, 95% CI)	1.82 [-5.28, 8.92]
7.7 Role emotional	2	85	Mean Difference (IV, Fixed, 95% CI)	4.90 [-7.15, 16.94]
7.8 Social function	2	85	Mean Difference (IV, Fixed, 95% CI)	3.48 [-6.74, 13.71]
7.9 Vitality	2	85	Mean Difference (IV, Fixed, 95% CI)	5.32 [-2.57, 13.22]
7.10 Role physical	2	85	Mean Difference (IV, Fixed, 95% CI)	8.55 [-2.69, 19.79]
8 Peak exercise calf blood flow (mL/100 mL/min)	2	66	Mean Difference (IV, Fixed, 95% CI)	3.79 [0.51, 7.07]
8.1 Usual care	1	52	Mean Difference (IV, Fixed, 95% CI)	3.10 [-0.46, 6.66]
8.2 Placebo	1	14	Mean Difference (IV, Fixed, 95% CI)	7.57 [-0.78, 15.92]

Comparison 4. Exercise regimen compared with antiplatelet therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking time (min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Ankle brachial index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Peak exercise calf blood flow (mL/100 mL/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 5. Exercise regimen compared with pentoxifylline therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking time (min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 6. Exercise regimen compared with iloprost therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking distance (m)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Pain-free walking distance (m)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 7. Exercise regimen compared with pneumatic foot and calf compression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximum walking distance (m)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Pain-free walking distance (m)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 8. Exercise regimen compared with vitamin E

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 3-monthly maximum walking time (min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 6-monthly maximum walking time (min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 3-monthly ABI	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 6-monthly ABI	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

ADDITIONAL TABLES

Table 1. Functional status and quality of life data (QoL) for all studies

Study	Measure reported	Effect reported
Collins 2005	Walking Impairment Questionnaire (WIQ) - perceived distance and walking speed	On the basis of analysis of change scores, the polestriding group reported significantly greater perceived ability to walk distance than the control group at 4 (P = 0.05), 12 (P = 0.001), and 24 (P = 0.002) weeks. Moreover, the polestriding group rated their perceived ability to walk faster to be significantly greater than the control group at 4 (P = 0.03), 12 (P = 0.19), and 24 (P = 0.02) weeks. The groups' ratings were equivalent at baseline (P > 0.05). In the polestriding group, polestriding aggregate scores for both distance and speed improved significantly between baseline and 12 weeks (P < 0.0001) and baseline and 24 weeks (P < 0.0001), but not between 12 and 24 weeks (P > 0.015). The perception of walking speed and distance did not improve in the control group
	Rand Short Form-36 (SF-36) - perceived physical function	Exercise significantly improved the Physical Component Summary score (PSS) of SF-36 when compared with usual care. Difference using the change score between polestriding and control groups for the PSS was significant; P = 0.03. There was no difference in the change on the Mental Component Summary score between groups
Gardner 2002	Health-related quality of life (QoL) assessed with the Medical Outcomes Study Short Form-36 (MOS SF-36)	Baseline measures of health-related QoL were comparable in both groups The physical and mental health composite scores of the MOS SF-36 were similar between the 2 groups and did not change during the study. Consequently, no analyses were performed on the individual subscales

Table 1. Functional status and quality of life data (QoL) for all studies (*Continued*)

	WIQ	No change in the WIQ was identified. Baseline scores on the 3 WIQ subscales ranged between 32% and 52%. Although the exercise group increased by 22% and 34% on the distance and speed subscales, respectively, these changes were not significant and did not differ from the changes in controls
Gelin 2001	Intermittent Claudication-specific Sickness Impact Profile (SIP) scale, SIPIC	Supervised physical training produced significant improvements from baseline in only 2 health-related quality of life (HRQoL) domains (SIP Recreation and pastimes ($P < 0.05$) and the single-item rating scale Physical Condition) and an ambiguous pattern of positive and negative trends in others. Unexpectedly, deterioration was most striking in functional health, where reductions appeared in 10 of 15 SIP categories. Compared with no treatment, physical training produced significantly greater improvement in only 1 HRQoL category: SIP recreation and pastimes. Improvement in this category, however, may possibly be accounted for by the opportunities for increased leisure activity afforded by participation in the ongoing training programme
	Health-related QoL, QoL overall	No significant improvement was observed between training and control groups. Training produced small SRMs (mean change between assessments divided by the standard deviation of change) (0.2 to < 0.5) on 4 HRQoL dimensions, of which 2 represented improvement
Guidon 2010	Medical Outcomes Study Short Form-36	No significant differences between groups were demonstrated for any of the MOS SF-36 scores over the 3 time points (baseline, 12 weeks, and 1 year). This study was not included in the meta-analysis, as the MOS SF-36 differs from the standard SF-36 Questionnaire
	Disease-specific QoL (ICQ)	Results show a statistically significant decrease ($P = 0.003$) in ICQ scores from baseline to 12-week follow-up (mean difference -9.74, 95% CI -3.76 to -15.71) in the exercise group, indicating improved quality of life. No significant difference was demonstrated in the control group
	WIQ	In the exercise group, increases were observed in all WIQ scores, with a statistically significant increase ($P = 0.015$) in the WIQ Distance score (mean difference 14.28, 95% CI 2.96 to 25.61). In the control group, scores for the WIQ Stair-climbing and Distance categories decreased, with a marginal increase in the WIQ Speed score. None of these changes were significant

Table 1. Functional status and quality of life data (QoL) for all studies (*Continued*)

Kakkos 2005	Short Form-36 (SF-36)	Score for the general health domain of the SF-36 was significantly improved at 1 year in individuals who used intermittent pneumatic compression (IPC). This study was not included in the meta-analysis, as the full dataset was not available in the study and could not be obtained from the study author
	WIQ	IPC improved speed score of WIQ significantly. WIQ scores for walking distance, walking speed, and stair climbing were reduced in the unsupervised exercise group, remained stable in the supervised exercise group, and were increased in the IPC group
	Intermittent Claudication Questionnaire (ICQ)	Supervised exercise and IPC reduced (improved) the ICQ score, but this was significant only in the IPC group
McDermott 2008	WIQ	Distance score improved (P = 0.02) in the treadmill group when compared to the control group. This was not apparent in the other 2 domains (speed and stair climbing)
	SF-36 physical functioning score	Improved (P = 0.04) in the treadmill group when compared to the control group
GOALS 2013	WIQ scores	Participants in the intervention group, when compared with those in the control group, improved their WIQ distance score (35.3 to 47.4 vs 33.3 to 34.4; mean difference 11.1, 95% CI 3.9 to 18.1; P = 0.003) and their WIQ speed score (36.1 to 47.7 vs 35.3 to 36.6; mean difference 10.4, 95% CI 3.4 to 17.4; P = 0.004) but not their WIQ stair-climbing score (48.9 to 57.3 vs 47.9 to 48.5; mean difference 7.9, 95% CI 0.00 to 15.8; P = 0.05)
	Physical Health Composite Score (PCS) and Mental Health Composite Score (MCS) scales from the 12-item Medical Outcomes Study Short Form Health Survey (SF-12)	Results show no between-group differences in change in the SF-12 PCS or MCS subscales
Tew 2015	Intermittent Claudication Questionnaire (ICD)	The intervention group demonstrated improvement in the ICD score of -10.6 (95% CI -18.9 to - 2.3)
Tisi 1997	Nottingham Health Profile (NHP)	A daily home exercise programme, supervised weekly by a physiotherapist for the first month, achieves good compliance, increased walking distances, and improved quality of life as assessed by the Nottingham Health Profile Questionnaire

Table 1. Functional status and quality of life data (QoL) for all studies (*Continued*)

Tsai 2002	WIQ	Improved speed (P < 0.001) and stairs (P < 0.001) in the exercise group when compared to the control group at 12 weeks. No significant difference in the distance domain
	SF-36 - version 1	Perception of QoL increased significantly in the exercise group compared to usual care for the domains of physical function, role limitation, bodily pain, general health, and vitality. This study was included in the 3-month meta-analysis; however the SF-36 version 1 differs from the standard SF-36 Questionnaire
Zwierska 2005	WIQ	Improvement in all 3 domains was seen in the upper limb group at 24 and 48 weeks when compared to the control group. The lower limb group improved in stair and speed domains at 24 and 48 weeks only when compared to the control group
	SF-36 - version 2	At 6 weeks, improvement in general health was seen in the lower-limb group when compared to the control group At 24 weeks, a significant improvement was seen in general health and vitality in the lower limb group when compared to the control group. The upper limb group significantly improved in physical function and mental health when compared to the control group

WHAT'S NEW

Last assessed as up-to-date: 15 November 2016.

Date	Event	Description
15 November 2016	New citation required but conclusions have not changed	Searches rerun, 2 new studies included, 18 additional studies excluded. New author (AH) joined the review team. Text updated to reflect current Cochrane standards. 'Summary of findings' table added. Conclusions not changed
15 November 2016	New search has been performed	Searches rerun, 2 new studies included, 18 additional studies excluded

HISTORY

Protocol first published: Issue 2, 1997

Review first published: Issue 1, 1998

Date	Event	Description
9 November 2013	New search has been performed	Searches rerun, 11 new studies included, 45 additional studies excluded
9 November 2013	New citation required but conclusions have not changed	New author (RAL) joined the review team. Searches rerun, 11 new studies included, 45 additional studies excluded. Risk of bias tables completed for all included studies In comparison with previous versions of this review, this version no longer focuses on supervised versus non-supervised exercise, or invasive interventions compared with exercise, as these are covered in other Cochrane reviews
18 June 2008	New search has been performed	12 new trials considered. Conclusions confirm findings of the previous review
29 April 2008	New citation required but conclusions have not changed	Two new review authors
8 April 2008	Amended	Converted to new review format
25 October 1999	New citation required but conclusions have not changed	Substantive updates made
17 June 1998	New citation required and minor changes	After consultation with GCL, original November 1997 version substituted for June 1998 'update', as latter was an incorrect version. Some phrasing changed in June 1998, no changes to figures, so earlier version more appropriate. Edited abstract added too (24.2.99)

CONTRIBUTIONS OF AUTHORS

Risha Lane (RL): selected trials, assessed quality, extracted data, and revised text for the third and fourth updates.

Amy Harwood (AH): selected trials, assessed quality, and extracted data for the fourth update.

Lorna Watson (LW): commented on content of the fourth update.

Gillian Leng (GCL): commented on content of the fourth update.

DECLARATIONS OF INTEREST

RL: none known.

AH: none known.

LW: none known.

GCL: I am responsible for the National Institute for Health and Care Excellence (NICE) Implementation programme and I am the Executive Director of NICE. I am a trustee of the Royal Society of Medicine and the Guidelines International Network.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the time of the original protocol, various changes have had to be instigated with regards to bias assessments. These have moved from the Schutlz assessment to Jadad and finally to the current Cochrane risk of bias assessment method (Higgins 2011). We have reassessed all trials to comply with the current bias scoring system.

The protocol itself has not been altered; however we have applied strict adherence to the protocol with regards to usual care. As walking advice has often been advocated as part of usual care, we have considered inclusion of only non-exercise control groups within this review. This has been clarified and searched for in each paper, as walking advice would constitute unsupervised exercise, which was not the focus of this review.

To avoid overlap with other existing Cochrane reviews (Antoniou 2017; Fowkes 1998), we removed from this review the comparisons exercise versus angioplasty and exercise versus surgery.

In addition to planned treadmill walking distance and walking time, we have presented the results as a percentage change.

In keeping with current Cochrane policy, this version includes a 'Summary of findings' table and GRADE assessment of the quality of evidence. We have amended secondary outcomes to reflect clinical relevance.

INDEX TERMS

Medical Subject Headings (MeSH)

Amputation [statistics & numerical data]; Ankle Brachial Index; Exercise Therapy [*methods]; Intermittent Claudication [*therapy]; Pain Management [methods]; Quality of Life; Randomized Controlled Trials as Topic; Time Factors; Walking

MeSH check words

Female; Humans; Male