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ORIGINAL ARTICLE



# Inequity in exercise-based interventions for adults with intermittent claudication due to peripheral arterial disease: a systematic review

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**ABSTRACT**

**Purpose:** To determine the equity in access to trials of exercise interventions for adults with intermittent claudication due to peripheral arterial disease.

**Methods:** Systematic electronic database searches of MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Clinical Trials, PEDRO, Opengrey, ISRCTN and ClinincalTrials.gov for randomised controlled trials of exercise interventions for adults with intermittent claudication were conducted. Data extraction was informed by Cochrane's PROGRESS-Plus framework.

**Results:** Searches identified 6412 records. Following the screening of 262 full texts, 49 trials including 3695 participants were included. All trials excluded potential participants on at least one equity factor. This comprised place of residence, language, sex, personal characteristics (e.g., age and disability), features of relationships (e.g., familial risk factors) and time-dependent factors, (e.g., time since revascularisation). Overall, 1839 of 7567 potential participants (24.3%) were excluded based on equity factors. Disability was the most frequently reported factor for exclusions.

**Conclusion:** Trialists endeavour to enrol a representative sample in exercise trials whilst preserving the safety profile of the intervention. This review highlights that these efforts can inadvertently lead to inequities in access as all trials excluded potential participants on at least one equity factor. Future exercise trials should optimise participation to maximise generalisability of findings.

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**KEYWORDS**
Intermittent claudication; peripheral arterial disease (PAD); exercise therapy; inequity; systematic review; disability

**➤ IMPLICATIONS FOR REHABILITATION**

- Equity factors influence health opportunities and outcomes.
- All trials of exercise for people with intermittent claudication excluded adults on at least one equity factor.
- Disability was the predominant factor for exclusions from trials.
- Trials should optimise participation to maximise generalisability of results as these findings are used to inform treatment and service design.

## Introduction

Access to healthcare is defined as the opportunity or ease with which people can use appropriate services in proportion to their needs [1]. Intermittent claudication (ischaemic leg pain) is a common symptom of peripheral arterial disease, an age-related atherosclerotic condition. Exercise therapy is a recommended first-line treatment [2,3] yet, access to exercise therapy is highly variable due to social, environmental and/or health-related factors [4–6]. Addressing such systematic inequities in access to appropriate services is a public health priority [7].

Healthcare services are commissioned based on evidence of clinical efficacy and cost-effectiveness, often from randomised controlled trials or meta-analyses of several trials. However, less than a quarter of people with intermittent claudication screened for eligibility take part in exercise trials [4,5]. Subgroups of the population who do not participate in trials may respond differently to exercise therapy due to differences in equity factors related to social, environmental, physiology or disease states. The PROGRESS-Plus guidance framework (place of residence, race/ethnicity, occupation, gender, religion, education, social capital, socioeconomic status and other factors such as personal characteristics (e.g., disability), features of relationships and time-dependent relationships [8]) offers a framework for summarising factors that influence health opportunities and outcomes such as the chance to participate in exercise interventions [8,9]. Once subgroups have been identified, a failure to describe them in the baseline characteristics of trial participants or as trial subgroup analyses means clinicians and decision-makers lack evidence for appropriate management or service commissioning [10,11]. This may inadvertently

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perpetuate inequity of access to exercise interventions and health outcomes in adults with intermittent claudication.

Therefore, the primary objective of this study was to describe the extent to which PROGRESS-Plus equity factors were considered in the eligibility criteria of trials of exercise interventions for adults with intermittent claudication. Secondary objectives were to describe the extent to which equity factors were considered in baseline characteristics and sub-group analyses in trials of exercise interventions for intermittent claudication.

## Methods

The protocol was registered on the International Register of Systematic Reviews (PROSPERO: CRD42020189965) [12] and reported in adherence to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols equity extension [13,14].

### *Search strategy*

An electronic database search for published (MEDLINE, Embase, CINAHL, PEDRO, Cochrane Central Register of Controlled Clinical Trials (CENTRAL)), unpublished (Opengrey) and registered ongoing studies (ISRCTN, ClinincalTrials.gov) was conducted from January 1st 2010 to 24th July 2020 (see Supplementary File 1). The search strategy was based on the study population (adults with intermittent claudication caused by peripheral arterial disease), intervention (exercise-based) and study design (randomised controlled trials). Reference lists of relevant systematic reviews [15–18] and included trials were hands searched for additional eligible studies. Authors were contacted for further information if required.

### *Eligibility criteria*

This review included reports and ongoing randomised controlled trials of exercise-based interventions that included adults (>18 years old) with stable symptomatic intermittent claudication (defined as Fontaine classification IIa and IIb/Rutherford classification 1–3 [19,20]) due to peripheral arterial disease published in English since January 1st, 2010. As the aim of this review was to describe the extent to which equity factors were considered in the eligibility criteria of exercise trials, a broad definition of the exercise was applied. An exercise-based intervention was defined as any supervised or unsupervised programme, conducted in an inpatient, outpatient, community or home-based setting, that included any kind of exercise training [21]. Randomised controlled trials were included irrespective of the comparator group or outcome. Non-randomised controlled studies and randomised controlled trials published before 2010 were excluded to reflect the period after the publication of the World Health Organisation reports and the Marmot review which focused on the implementation of action on social determinants of health [7,9]. The searches were limited to the English language because no translation was available.

### *Study selection*

Records were exported to Covidence for de-duplication and screening [22]. Two reviewers independently screened titles and abstracts based on the eligibility criteria (R2, R3). Disagreements were resolved by consensus and a third reviewer (R1) arbitrated, if necessary. Full texts of five potentially eligible randomised controlled trials were independently screened by two reviewers and consensus was confirmed (R2, R3). Disagreements were resolved by consensus and a third reviewer (R1) arbitrated if necessary. All other eligible randomised controlled trials were screened by one of the two reviewers (R2 or R3) and checked by the third reviewer (R1).

### *Data extraction*

Data from included randomised controlled trials were extracted by one of two reviewers (R2 or R3) into a template modified from published extraction templates [23,24]. Data were checked for accuracy by a third reviewer (R1). Extraction included: author name, publication year, location, study design, sample size, eligibility criteria, population characteristics, intervention, control and outcome details, and equity factors defined by the PROGRESS-Plus framework (Place of residence, Race/ethnicity/language/culture, Occupation, Gender, Religion, Education, Social Capital and Socioeconomic status and age, disability features of relationships and time-dependent relationships) reported in eligibility criteria, baseline characteristics and sub-group analysis [8,25]. When available, the count of potential participants excluded based on PROGRESS-plus factors and the justification for eligibility criteria were recorded.

### *Quality assessment*

All included randomised controlled trials were appraised by one of two reviewers (R2, R3) using the Cochrane Risk of Bias Tool 2.0 [26]. This tool assesses bias in five domains: bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and in the selection of the reported results. Data were checked for accuracy by a third reviewer (R1).

### *Data synthesis*

Data were summarised descriptively following a template from a previously published review [23]. PROGRESS-Plus factors reported in eligibility criteria, baseline characteristics and sub-group analysis were summarised with counts and proportions. Where reported, the count and proportion of eligible patients excluded for equity factors were calculated.

## Results

In total, 6412 records were identified after de-duplication. A total of 262 full texts were screened and 49 studies reported 38 published randomised controlled trials [27–64] and 11 registered ongoing randomised controlled trials included [65–75] (Figure 1).

### *Trial characteristics*

This review included 3695 participants and randomised controlled trials sample sizes ranged from seven [34] to 304 [53]. Randomised controlled trials were conducted in 16 countries: USA ($n = 11$) [31,32,38,41,42,52,63,64,70,74,75], Brazil ($n = 10$) [30,33,34,43,47,51,55,56,69,71], UK ($n = 6$) [40,49,58,60,72,73], Poland ($n = 4$) [29,50,57,61], The Netherlands ($n = 3$) [39,44,53], Slovenia ($n = 2$) [54,67], Norway ($n = 2$) [28,62], New Zealand ($n = 1$) [27], Ireland ($n = 1$) [45], Serbia ($n = 1$) [48], Italy ($n = 1$) [46], Austria ($n = 1$) [59], Australia ($n = 3$) [35–37], France ($n = 1$) [68], Sweden ($n = 1$) [66] and Canada ($n = 1$) [65].

Interventions were either (i) supervised and completed in a healthcare facility only ($n = 26$) [27–29,34–37,41–45,49–51,53–55,

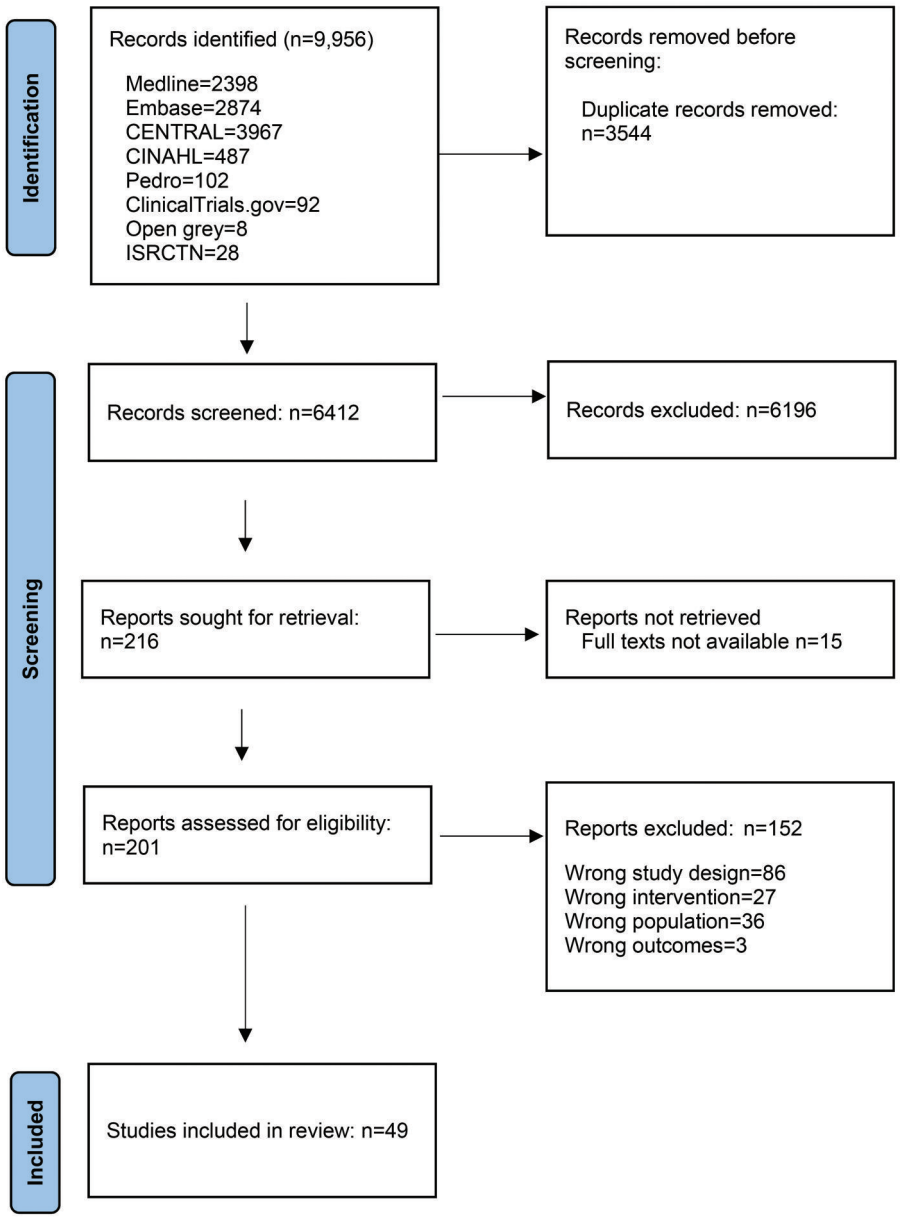


**Figure 1.** Flow diagram for a systematic review of equity factors in randomized controlled trials of exercise interventions for adults with intermittent claudication.

57–59,63,70,72] (ii) supervised at a healthcare facility and also at home by telephone ($n = 3$) [32,52,64], (iii) supervised at a healthcare facility and unsupervised at home ($n = 6$) [30,39,66,71,73,75] (iv) supervised remotely at home only($n = 2$) [38,40] or (v) unsupervised at home ($n = 3$) [46,60,72]. Nine studies did not specify the intervention setting [31,33,48,56,61,62,67–69]

Interventions included treadmill training ($n = 16$) [29,33,35–37,39,41,42,44,50,52,54,57,63,69,75], outdoor walking programmes ($n = 13$) [30,32,40,46,48,61,64,65,67,70,71,73,75], resistance training ($n = 5$) [43,47,55,56,62], aerobic training ($n = 4$) [28,45,51,58], Nordic pole walking ($n = 3$) [31,60,72], circuit training ($n = 2$) [49], tai chuan ($n = 1$) [34], walking and circuit training ($n = 1$) [27], a personalised exercise digital health programme ($n = 1$) [38], and unspecified exercise training ($n = 3$) [53,59,66].

### *Risk of bias*

The risk of bias assignments for completed randomised controlled trials is displayed in Supplementary File 2. Twenty-two randomised controlled trials had an overall high risk of bias [27,29–32,35,38,39,41,42,44–49,51,54,55,60–62], 16 randomised controlled trials had some concerns [28,33,34,36,37,40,43,50,52,53,56–59,63,64] and no randomised controlled trials were graded as low risk of bias. The most common reasons for high risk of bias were a deviation from intended intervention ($n = 18$) and measurement of outcome ($n = 11$), other reasons for high risk of bias included randomisation process ($n = 3$) and selection of reported results ($n = 2$).

### *Eligibility criteria*

All 49 randomised controlled trials excluded participants based on at least one PROGRESS-Plus factor. Potential participants were excluded from randomised controlled trials based on PROGRESS-Plus factor – place of residence ($n = 21$, 42.9%) [27,28,30,33–37,39,45,46,48–51,55,58–62], race/ethnicity/culture/language ($n = 4$, 8.1%) [53,64,66,70], sex ($n = 3$, 6.1%) [30,33,74], personal characteristics – age ($n = 26$, 53.1%) [27,30–32,34,40,43,46,47,50,51,54,57,61,63–65,67–75], personal characteristics – disability ($n = 48$, 98%) [27–65,67–75], features of relationships ($n = 2$, 4.0%) [64].

Table 1. Contribution of PROGRESS-Plus equity factors to eligibility criteria, reporting of baseline characteristics and subgroup analyses in randomized controlled trials of exercise for adults with peripheral arterial disease.

| PROGRESS-Plus factor | Eligibility criteria *n* (%) | Baseline characteristics *n* (%) | Subgroup analysis *n* (%) |
|---|---|---|---|
| Place of residence | | | |
| Outside trial catchment area | *n* = 21 (42.9%) [27,28,30,33–37,39,45,46,48–51,55,58–62] | | |
| Race/ethnicity/culture/language | | | |
| Language barrier | *n* = 4 (8.2%) [53,64,66,70] | *n* = 9 (18.4%) [31,32,35,38,40–42,63,64] | |
| Racial/ethnic background | | | *n* = 1 (2%) [64] |
| Occupation | | | |
| Sex | *n* = 3 (6.1%) [30,33,74] | *n* = 34 (69.4%) [27–29,31,32,35–60,62–64] | *n* = 1 (2%) [64] |
| Religion | | | |
| Education | | *n* = 2 (4.1%) [28,32] | |
| Socioeconomic status | | | |
| Social capital | | | |
| Plus: Personal characteristics | | | |
| • Age | *n* = 26 (53.1%) [27,30–32,34,40,43,46,47,50,51,54,57,61,63–65,67–75] | *n* = 37 (75.6%) [27–60,62–64] | *n* = 1 (2%) [64] |
| • Minimum age | *n* = 26 (53.1%) [27,30–32,34,40,43,46,47,50,51,54,57,61,63–65,67–75] | | |
| • Maximum age | *n* = 11 (22.4%) [43,46,50,57,65,67–69,72,74,75] | | |
| • Disability (see Table 2) | *n* = 48 (98%) [27–65,67–75] | *n* = 37 (75.5%) [27–56,58–60,62–64] | *n* = 2 (4%) [62,64] |
| Plus: Features of relationships | | | |
| • Presence of risk factors in family history | *n* = 1 (2%)[46] | *n* = 1 (2%) [46] | |
| • Enrolled on another trial | *n* = 1 (2%) [64] | | |
| Plus: Time dependent factors | | | |
| • Time since diagnosis | *n* = 5 (10.2%) [45,55,58,59,72] | *n* = 4 (8.2%) [40,45,48,58] | |
| • Time until vascular intervention | *n* = 3 (6.1%) [40,64,66] | | |
| • *Time* since vascular intervention | *n* = 21 (42.9%) [29,32–38,42,45,47,49,50,55,58,60–62,64,66,72] | | |
| • Time since participation in exercise programme | *n* = 7 (14.3%) [31,47,51,53,56,71,73] | | |
| • Availability for duration of intervention | *n* = 2 (4.1%) [28,29] | | |

And time dependent relationships (*n* = 38). These included the time since diagnosis of peripheral arterial disease (*n* = 5, 10.2%) [45,55,58,59,72], time to upcoming revascularisation (*n* = 3, 6.1%) [40,64,66], time since revascularisation (*n* = 21, 42.9%) [29,32–38,42,45,47,49,50,55,58,60–62,64,66,72], time since participation in exercise programme (*n* = 7, 14.3%) [31,47,51,53,56,71,73] and availability for duration of intervention (*n* = 2, 4.1%) [28,29]. No potential participants were excluded based on occupation, religion, education, socioeconomic status or social capital (Tables 1 and 2, Figure 2).

Seventeen randomised controlled trials provided counts with reasons for excluding potential participants [28,31,32,35–37,39,40,43,45,49,51,54,55,58,63,64]. Of 7567 potential participants, 1839 (24.3%) were excluded due to disability [28,31,32,35–37,39,40,43,45,49,51,54,55,58,63,64]. One randomised controlled trial also excluded four of a possible 54 participants based on place of residence (outside catchment area) [51] and another randomised controlled trial excluded 14 of a possible 1756 participants based on minimum age (people aged <40 years) [32]. One randomised controlled trial excluded seven of a possible 94 participants based on Plus Factor-time dependent relationships (upcoming revascularisation) [40]. Another randomised controlled trial excluded one of a possible 503 participants based on Plus Factor-features of relationships (already enrolled in another trial) [64].

### *Justification for eligibility criteria*

Of the 49 randomised controlled trials, only two (4.1%) included justification for eligibility criteria [32,74]. Potential participants were excluded if they expressed a lack of intention to start exercising in the next 6 months as this may limit the intervention effect [32] or if they had a calf muscle skin fold too large for the outcome measurement to be taken [74]. Potential participants with contraindications to exercise were also excluded to minimise any adverse effects of the intervention [32,74].

### *Baseline characteristics*

Thirty-seven randomised controlled trials reported at least one PROGRESS-Plus factor in their baseline characteristics [27–56,58–60,62–64]. Place of residence, occupation, religion, socioeconomic status and social capital were not reported in baseline characteristics in any of the 49 included randomised controlled trials (Tables 1 and 2, Figure 2).

### *Subgroup analysis*

PROGRESS-Plus factors were explored in subgroup analyses of two randomised controlled trials (4.1%) [62,64]. One trial reported no differential effect in response to a structured home-based exercise programme according to sex (male versus female), race (black versus other racial groups), age (below 70 years versus 70 years and above), disability factors – diabetes (yes versus no) and smoking status (current smoker versus non-smoker) [64]. Another trial compared the characteristics of those participants who increased peak walking time after 8-weeks of exercise to those participants who decreased peak walking time. Those with a deterioration in peak walking time were more likely to have advanced disease severity and exhibited different physiological

**Table 2.** Contribution of PROGRESS-Plus equity factors to eligibility criteria, reporting of baseline characteristics and subgroup analyses in randomized controlled trials of exercise for adults with peripheral arterial disease.

| Disability factor | Eligibility criteria *n* (%) | Baseline characteristics *n* (%) | Subgroup analysis *n* (%) |
|---|---|---|---|
| Patient related factors | | | |
| Smoking status | *n* = 1 (2.0%) [69] | *n* = 31 (63.3%) [28,30–38,40–56,58–60,62] | *n* = 1 (2.0%) [64] |
| Medication | *n* = 12 (24.5%) [27,30,33,34,41, 42,50,56,59,63,70] | *n* = 16 (32.7%) [28,32–35,43,46,47,51, 52,54–56,59,60,62] | |
| Unsuccessful percutaneous transluminal angioplasty | *n* = 1 (2.0%) [28] | | |
| History of coronary bypass surgery | *n* = 3 (6.1%) [27,61,70] | *n* = 1(2%) [52] | |
| Suitability for revascularization | *n* = 1 (2.0%) [60] | | |
| Exercise tolerance limited by factors other than claudication | *n* = 23 46.9%) [28,32,33,35–37,40–44,46, 49,52,55,58–60,62,63,69,70,73] | | *n* = 1 (2.0%) [62] |
| Dizziness/balance limitation | *n* = 1 (2.0%) [32] | | |
| Other conditions or co-morbidities | | | |
| Hemodynamic instability | *n* = 12 (24.5%) [29,30,32,34,42,47,51, 56,59,61,65,71] | *n* = 22 (44.9%) [27,29,30,32–38,40–43, 45–49,52,55,56] | |
| Blood status | | *n* = 14 (28.6%) [27–30,33,35–38,40–43, | |
| Lipids* | | 46,48,52,59] | |
| Other blood characteristics# | | *n* = 2 (4%) [52,59] | |
| Cognitive dysfunction/dementia | *n* = 5 (10.2%) [45,61,65,74,75] | | |
| Pregnancy | *n* = 3 (6.1%) [54,67,70] | | |
| Obesity/body mass index | *n* = 2 (4.0%) [33,56] | *n* = 16 (32.7%) [27,29,30,34,38,41–43,51, 52,54–56,59,60,62] | |
| Chronic venous insufficiency/leg ulcers | *n* = 1 (2.0%) [61] | *n* = 2 (4.0%) [29,51] | |
| | *n* = 6 (12.2%) [29,31,38,61,64,70] | *n* = 1 (2.0%) [27] | |
| Acute illness | *n* = 1 (2.0%) [54] | | |
| Buerger's disease | *n* = 1 (2.0%) [61] | | |
| Incapacitating systemic disease | *n* = 1 (2.0%) [49] | | |
| Unstable chronic disease | *n* = 1 (2.0%) [46] | | |
| Diabetes/HbA1c status | *n* = 9 (18.4%) [27,29,30,42,45,51,61,62,71] | *n* = 24 (48.9%) [27–30,33–38,40,42–49, 51–53,55,58,60] | *n* = 1 (2.0%) [64] |
| Severe peripheral neuropathy | *n* = 1 (2.0%) [38] | | |
| Cancer | *n* = 9 (18.3%) [32,41,42,45,50,59,61,62,75] | | |
| Kidney or liver disease | *n* = 7 (14.3%) [41,45,50,61,62,75] | *n* = 2 (4.0%) [29,32] | |
| Heart failure | *n* = 5 (10.2%) [51,59,64,70,71] | *n* = 1 (2.0%) [38] | |
| Myocardial infarction | *n* = 18 (36.7%) [27,29,30,32–34, 42,45,47,50, 54–56,63,70,74,75] | *n* = 5 (10.2%) [27,28,46,52,58] | |
| Exercise limiting/incapacitating angina | *n* = 9 (18.4%) [27,38,42,50,51,58,71,74,75] | *n* = 3 (6.1%) [48,52,58] | |
| Cardiovascular disease/coronary artery disease | *n* = 11 (12.2%) [31,38,39,44,46,50, 54,59,61,62,67] | *n* = 12 (24.5%) [27,29,35–38,40,44,46,53,55,59] | |
| Cardiovascular autonomic neuropathy | *n* = 1 (2.0%) [30] | | |
| Aortic aneurysm | *n* = 5 (10.2%) [39,45,46,61,68] | | |
| Intellectual developmental disorder | *n* = 2 (4.0%) [54,67] | | |
| Neurological disease | *n* = 4 (8.2%) [46,63,64,70] | *n* = 2 (4.0%) [27,28] | |
| Chronic musculoskeletal disease/arthritis | *n* = 6 (%) [31,46,50,58,61,68] | *n* = 4 (8.2%) [29,44,53,60] | |
| Chronic obstructive airways disease/Chronic lung disease | *n* = 3 (6.1%) [32,55,70] | *n* = 6 (12.2%) [28,38,44,48,53,60] | |
| Unspecified co-morbidities | *n* = 1 (2.0%) [45] | *n* = 2 (4.0%) [31,64] | |
| Peripheral arterial disease-related factors | | | |
| Disease severity | | | |
| Critical limb ischaemia | *n* = 13 (26.5%) [29,32,35–38,49, 52,59,62–64,70] | | |
| Peripheral arterial disease – Fontaine 1,3 or 4 | *n* = 12 (24.5%) [28,44,45,48,49,53, 55,57,59,62,74,75] | | |
| Ankle brachial pressure index | *n* = 2 (4.0%) [71,72] | *n* = 9 (18.4%) [29,30,38,43,50,56,59,60,62] | *n* = 1 (2.0%) [64] |
| Vascular stenosis | *n* = 1 (2.0%) [46] | | |
| Isolated lower limb artery disease | *n* = 1 (2.0%) [39] | | |
| Lower limb amputation | *n* = 5 (10.2%) [31,32,63,64,70] | | |
| Symptom related | | | |
| Pain at rest | *n* = 2 (4.0%) [40,42] | | |
| Unstable claudication | *n* = 3 (6.1%) [46,49,73] | | |

*Total cholesterol; high-density lipoprotein; low-density lipoprotein; Triglycerides. #Fibrinogen; Platelets; Red blood cell count; white blood cell count; C-reactive protein.

responses to exercise compared with those with improved peak walking time [62] (Tables 1 and 2, Figure 2).

## Discussion

This review described equity in randomised controlled trials of exercise interventions in people with intermittent claudication due to peripheral arterial disease. All trials were graded as having some concerns or a high risk of bias. All included randomised controlled trials excluded potential participants on at least one equity factor. These comprised place of residence, language, gender, personal characteristics including age and disability and time-dependent factors, particularly time since revascularisation. Where reported, this equated to exclusion of 1839 of 7567 people

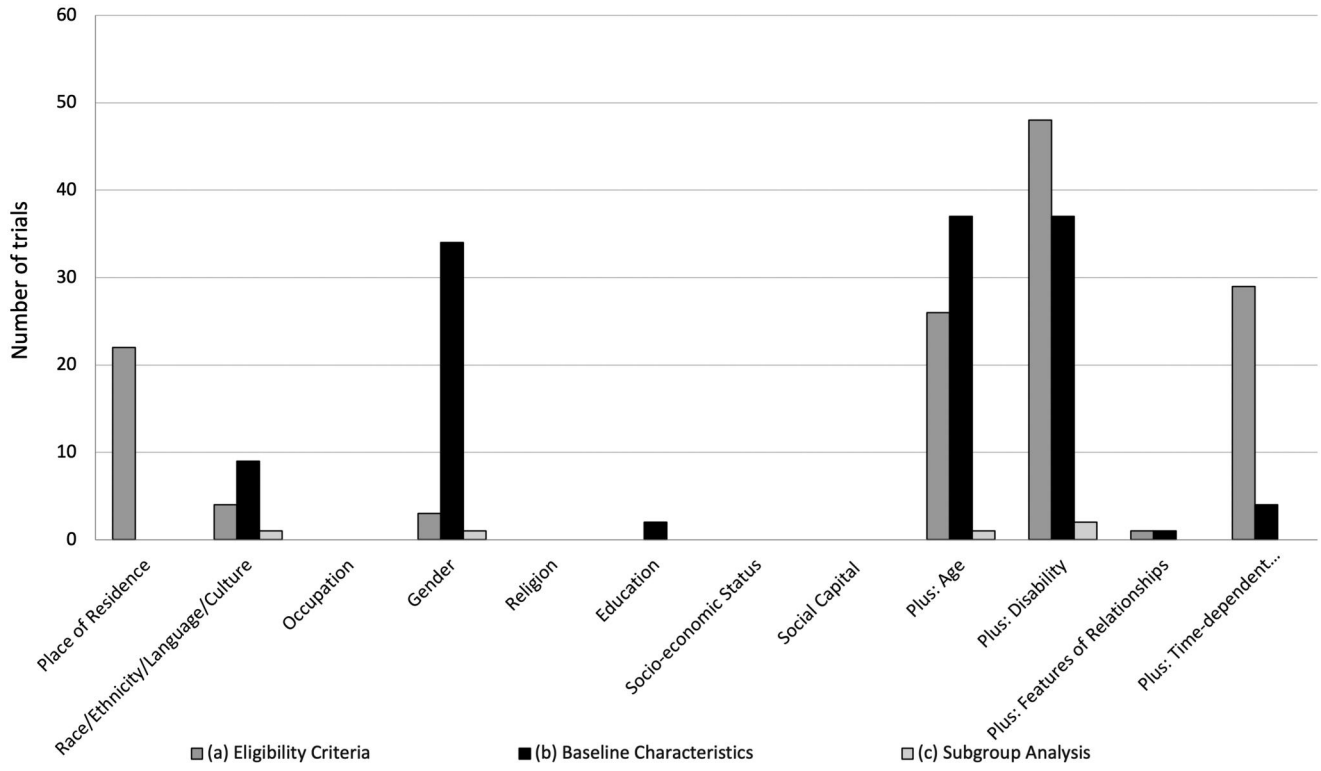


**Figure 2.** Contribution of equity factors to eligibility criteria, baseline characteristics and subgroup analyses in randomised controlled trials of exercise interventions in adults with peripheral arterial disease.

screened for eligibility based on equity factors. Disability was the dominant factor for exclusions.

Eligibility criteria are defined to optimise trial design and participant safety. International ethical guidelines for research involving human subjects [76] and the CONSORT and the SPIRIT statement require justification for the exclusion of study populations [77,78]. In this review, 48 trials (98%) excluded potential participants based on disability and/or co-morbid health conditions. Yet justification for excluding potential participants based on PROGRESS – Plus disability factors was seldom provided. This concurs with the findings from a previous review and could be due to limited potential for benefit or possible harm from an exercise intervention [79].

Careful consideration of trial and intervention design is required prior to exclusion based on a perceived lack of potential for benefit. One randomised controlled trial in the current review excluded people who were considered to have no intention to commence exercise because they may limit the intervention effect [32]. This means that potentially eligible people were not offered the opportunity to enrol into the trial based on screening of their intention to exercise, rather than the individual's refusal to participate. This exclusion may have led to an overestimation of the effect as the authors preferentially selected participants who were likely to adhere to the intervention. Moreover, it limits the generalisability of the findings as sedentary behaviour is common in people with intermittent claudication [80]. Should decision-makers commission services based on the findings of this trial, it may not yield the intended benefits for those who are at higher risk of poor outcome – widening inequities in access to care.

History of a cardiac event, current cardiovascular disease and/or treatment, and cardiovascular risk factors were the most frequently reported disability-related exclusions. In the current review, only two trials justified these exclusions over concerns related to possible adverse consequences of exercise [62,64]. Cardiovascular disease is common in people with peripheral arterial disease, so whilst excluding people with this cardiovascular disease may seem understandable, it may leave uncertainty and expose people with intermittent claudication and comorbid cardiovascular disease to unintended harm from generalizing trial results. However, a systematic review of supervised exercise trials including 82 725 hours of exercise by 2876 people with intermittent claudication recorded only eight adverse events [81]. Whilst some randomised controlled trials included in the meta-analysis excluded participants based on limited exercise capacity due to comorbidities, the all-cause complication rate of one per 10 340 patient hours was low [81]. Home-based exercise programmes for people with intermittent claudication also have low adverse event rates (all-cause complication rate of one event per 36 953 exercise hours), even in trials without pre-enrolment cardiac screening [82]. The safety of exercise in people with cardiovascular disease is corroborated by the Functional Evaluation and Cardiac Rehabilitation Working Group evaluation of registry data on complications during cardiac rehabilitation, which reported a rate of one adverse event per 49 565 patient hours [83]. Carefully prescribed and monitored exercise interventions are safe in people with intermittent claudication and so exclusion based on exercise safety should be avoided, where possible [81].

An alternative reason for excluding potential participants may relate to the logistics of the delivery of randomised controlled trials. For example, randomised controlled trials included in the current review excluded participants (without justification) based on their place of residence. This exclusion may relate to known barriers to supervised exercise participation for adults with intermittent claudication such as location of healthcare facilities and transport access [4–6]. These challenges could be somewhat addressed by the implementation of remote exercise supervision. However, some trials of home-based exercise or interventions with minimal supervised exercise sessions also excluded eligible

participants due to their place of residence [30,46,60]. The identification of local trial sites, remote data collection or provision of funded transport for people who have limited mobility or resources may mitigate these constraints. These options may not be available as randomised controlled trials may need to limit eligibility to meet time and funding restrictions. Given randomised controlled trials are often publicly funded when time and funding constraints limit the generalisability of a randomised controlled trial, the potential cost-benefit of running the trial at all should be questioned. The recently commissioned INCLUDE project aims to develop a strategic guide to support researchers to address the needs of under-served groups in research [84]. Indeed, trial designs should optimise accessibility and acceptability to maximise participation and facilitate application to practice. This can only be achieved when the barriers are acknowledged and addressed by researchers, funders, and regulators.

Randomised controlled trials may define narrow, homogenous populations to reduce variance and the sample size needed. However, there appears to be a lack of agreement on which narrow homogenous population to target for exercise interventions for people with intermittent claudication. This uncertainty contributes to statistical heterogeneity between randomised controlled trials limiting the potential for care or service commissioning to be informed by meta-analysis. For example, in the current review 21 randomised controlled trials excluded potential participants due to the time since revascularisation while 28 trials did not. Exclusion based on time since revascularisation ranged from 3 months to 12 months and some trials excluded potential participants if they had ever had revascularisation [53,65]. Whilst it may be appropriate to delay exercise participation to allow healing of surgical incisions following revascularisation, the timeframe applied in eligibility criteria is heterogeneous and justification is seldom provided. Exclusions due to duration since revascularisation should be fully explained as people treated with combined therapy achieve greater functional benefits than those treated with revascularisation or supervised exercise training alone [85].

In the current review, only three randomised controlled trials reported excluding participants based on sex (one excluded males [74], two excluded females [30,33]). Yet, two-thirds of participants were male for the 34 randomised controlled trials which reported participant's sex in baseline characteristics. This is surprising because there is almost no sex difference in the prevalence of intermittent claudication and the trials which completed a subgroup analysis by sex reported no differential effect of exercise on walking capacity [64,86]. Females with intermittent claudication are at higher risk for poor outcomes and have a twofold higher mortality rate than males [87] and so should have equitable opportunities to participate in exercise trials. It is not clear why there were sex differences in participants recruited onto the randomised controlled trials identified by the current review, however, PROGRESS Plus factors often interact with each other i.e., inequities can occur at multiple levels (e.g., employment or financial status may be linked to sex). Careful thought should be given to eligibility criteria considering the potential implications of each exclusion on other equity factors.

The current review employed a comprehensive search strategy to capture published, unpublished and registered trials, with screening and appraisal completed by two authors independently, and the use of an established framework for evaluation of equity factors [8]. However, manuscripts not published in English, non-randomised studies and trials published before 1 January 2010 and after July 2020 were excluded which may have led to the omission of relevant randomised controlled trials [88] and an underestimation of the potential participants excluded from exercise trials due to equity factors.

## Conclusion

Trialists endeavour to enrol a representative sample of people with intermittent claudication in exercise trials whilst preserving the safety profile of the intervention. These efforts can inadvertently lead to inequities in access to randomised controlled trials as highlighted by the current review. Future trials of exercise therapy for adults with intermittent claudication should seek to optimise the opportunity for participation with particular attention to maximising generalisability of future findings as they relate to equity factors.

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